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HSF1 and Its Role in Huntington's Disease Pathology

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Abstract

Purpose of review: Heat shock factor 1 (HSF1) is the master transcriptional regulator of the heat shock response (HSR) in mammalian cells and is a critical element in maintaining protein homeostasis. HSF1 functions at the center of many physiological processes like embryogenesis, metabolism, immune response, aging, cancer, and neurodegeneration. However, the mechanisms that allow HSF1 to control these different biological and pathophysiological processes are not fully understood. This review focuses on Huntington's disease (HD), a neurodegenerative disease characterized by severe protein aggregation of the huntingtin (HTT) protein. The aggregation of HTT, in turn, leads to a halt in the function of HSF1. Understanding the pathways that regulate HSF1 in different contexts like HD may hold the key to understanding the pathomechanisms underlying other proteinopathies. We provide the most current information on HSF1 structure, function, and regulation, emphasizing HD, and discussing its potential as a biological target for therapy.

Data sources: We performed PubMed search to find established and recent reports in HSF1, heat shock proteins (Hsp), HD, Hsp inhibitors, HSF1 activators, and HSF1 in aging, inflammation, cancer, brain development, mitochondria, synaptic plasticity, polyglutamine (polyQ) diseases, and HD.

Study selections: Research and review articles that described the mechanisms of action of HSF1 were selected based on terms used in PubMed search.

Results: HSF1 plays a crucial role in the progression of HD and other protein-misfolding related neurodegenerative diseases. Different animal models of HD, as well as postmortem brains of patients with HD, reveal a connection between the levels of HSF1 and HSF1 dysfunction to mutant HTT (mHTT)-induced toxicity and protein aggregation, dysregulation of the ubiquitin-proteasome system (UPS), oxidative stress, mitochondrial dysfunction, and disruption of the structural and functional integrity of synaptic connections, which eventually leads to neuronal loss. These features are shared with other neurodegenerative diseases (NDs). Currently, several inhibitors against negative regulators of HSF1, as well as HSF1 activators, are developed and hold promise to prevent neurodegeneration in HD and other NDs.

Conclusion: Understanding the role of HSF1 during protein aggregation and neurodegeneration in HD may help to develop therapeutic strategies that could be effective across different NDs.

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Keywords

Aggregation · Heat shock factor (HSF1) · Heat shock proteins (Hsp) · Huntington's diseases (HD) · Mitochondria

Abbreviations

17-AAG	17-allylamino-17-demethoxygeldanamycin
17-DMAG	17-dimethylaminoethylamino-17-demethoxygeldanamycin
8-OHDG	8-hydroxydeoxyguanosine
AD	Alzheimer's disease
AKT	Protein kinase B
ALFY	Autophagy-linked FYVE
ALS	Amyotrophic lateral sclerosis
AMPAR	α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor
AMPK	5′-AMP-activated protein kinase
AOO	Age of onset
AR	Androgen receptor
ATF3	Activating transcription factor 3
Atro	ATROPHIN-1
BAG3	BCL-2–associated athanogene 3
BAX	BCL2-associated X
BDNF	Brain-derived neurotrophic factor
CACNA1A	α1A subunit of the voltage-dependent calcium channel Cav2.1
caHSF1	Constitutive active form of HSF1
CCT	Chaperonin containing TCP-1
CHIP	C-terminus of HSC70-interacting protein
ChIP-seq	Chromatin immunoprecipitation followed by sequencing
CK2	Casein kinase holoenzyme
CK2α'	CK2 α prime
CRE	cAMP-response elements
DBD	DNA binding domain
Dclk1	Doublecortin-like kinase 1
DDL-1	DAF16-dependent longevity-1
DRP-1	Dynamin-related protein 1
DRPLA	Dentatorubral-pallidoluysian atrophy
EF3	Elongation factor 3
EMT	Epithelial-mesenchymal transition
ERK	Extracellular signal-regulated kinase
ETC	Electron transport chain
FBXW7	F-box and WD repeat domain containing 7
FILIP-1 L	Filamin A interacting protein 1-like
FRET	Fluorescence resonance energy transfer
FUS/TLS	Fused in sarcoma/translocated in liposarcoma
GCN5	General control non-repressed protein 5
GLT1	Glutamate transporter 1
GPX	Glutathione peroxidases
GSH	Glutathione
GSK3β	Glycogen synthase kinase 3β
HD	Huntington's disease
HDAC6	Histone deacetylase 6
HIF-1	Hypoxia-inducible factor 1
HMOX1	Heme oxygenase 1
HR-A/B	Heptad repeat-A/B
HSE	Heat shock element
HSFs	Heat shock transcription factors
Hsp	Heat shock protein(s)
HSR	Heat shock response
HTRA2/OMI	High-temperature requirement protein A2
HTT	Huntingtin
HuR	Hu-antigen R
IGF-1R	Insulin/insulin-like growth factor 1 receptor
IL-6	Interleukin-6
ILS	Insulin/insulin-like signaling
LZ	Leucine zipper domains
MEK	Mitogen-activated protein kinase kinase
MK2	MAPK-activated protein kinase 2
MMP	Mitochondrial membrane potential
MnSOD	Manganese-containing SOD
MPNST	Malignant peripheral nerve sheath tumor
mPTP	Mitochondrial permeability transition pore

MSNs	Medium-sized spiny neurons
N17	17-amino acid-long N-terminus
NDs	Neurodegenerative diseases
NEDD4	Neuronal precursor cell-expressed developmentally downregulated 4
NES	Nuclear export signal
NF1	Neurofibromatosis type 1
NF-IL6	Nuclear factor for interleukin-6
NLS	Nuclear localization sequence
NMDAR	N-methyl-D-aspartic acid receptor
NMP	Neuronal-specific 20S membrane proteasome complex
NOS	Nitric oxide synthase
NRF2	Nuclear factor E2-related factor 2
OD	Oligomerization domains
PD	Parkinson's disease
PGC-1α	Peroxisome proliferator-activated receptor-γ coactivator-1α
PIM2	Proviral integrations of Moloney virus 2
PLK1	Polo-like kinase 1
polyP	Polyproline
polyQ	Polyglutamine
PP2A	Protein phosphatase 2A
PR	Proteostasis regulators
PRDX	Peroxiredoxins
PSA-NCAM	Polysialylated-neural cell adhesion molecule
PTMs	Post-translational modifications
PUMA	p53 upregulated modulator of apoptosis
RD	Regulatory domain
RNS	ROS/reactive nitrogen species
ROS	Reactive oxygen species
SAE	SUMO-activating enzyme
SBMA	Spinal and bulbar muscular atrophy
SCAs	Spinocerebellar ataxias
SIRT1	Sirtuin 1
SOD	Superoxide dismutase
SQSTM1	Sequestosome 1
TAD	Transactivation domain
TARDBP	TAR DNA binding protein
TauT	Taurine transporter
TBP	TATA-box binding protein
TNF-α	Tumor necrosis factor-α
TOR1	Target of rapamycin 1
TPR	Translocated promoter region
TRiC	T-complex protein-1 ring complex
UPS	Ubiquitin proteasome system
USP19	Ubiquitin-specific protease 19
VCP	Valosin-containing protein
αB-crys	AlphaB-crystallin

1 Summary

Living organisms experience acute or chronic exposure to different endogenous and environmental insults during life, including elevated temperature, oxidative stress, and proteotoxic conditions. Cells have developed different self-defense mechanisms against such stressors to ensure cell survival. One of the most potent and successful mechanisms is the so-called heat shock response (HSR), characterized by the rapid induction of a group of molecular chaperones and heat shock proteins (Hsp) that fight the harmful effects of different stressors on proteins structure and function (Akerfelt et al. 2010; Anckar and Sistonen 2011). There is a regulation in the transcriptional activation of Hsp genes by a family of specialized heat shock transcription factors (HSFs) in eukaryotes. HSFs participate in many processes, including protein homeostasis, aging, innate immunity, and metabolism, and have a fundamental role in physiology and diseases like cancer and neurodegeneration. This chapter will focus on HSF1, the main HSF responsible for coordinating and executing the HSR in mammals. We will discuss fundamental features of HSF1, including structure, regulatory mechanisms, and physiological functions that go beyond the HSR, with particular emphasis on the neurodegenerative disease Huntington's disease (HD).

2 Introduction

HSF1 is a multifaceted factor, traditionally known for coordinating the cellular response to internal and external stimuli that disrupt cellular protein homeostasis (Akerfelt et al. 2010; Gomez-Pastor et al. 2018). This response is usually

mediated by the transcriptional regulation of several Hsp that have the task to prevent protein misfolding, refold misfolded proteins, and target damaged proteins for degradation (Ellis 2007). However, in the last few years, we have learned that HSF1 is much more complex, and it participates in numerous biological processes in both physiology and disease (Gomez-Pastor et al. 2018).

In unstressed cells, HSF1 exists as an inactive monomer in the cytoplasm due to the interaction by several regulatory proteins, including Hsp70, Hsp40, Hsp90, and the chaperonin complex TRiC (Gomez-Pastor et al. 2018). When cells encounter stress, HSF1 is released from its repressors and is activated. This activation process requires trimerization, several post-translational modifications (PTMs), and translocation to the nucleus where it binds to target genes. The transcriptional response elicited by HSF1 will then depend on the type of stress and the different protein-protein interactions in which HSF1 participates (Gomez-Pastor et al. 2018; Prince et al. 2020; Burchfiel et al. 2020). HSF1 recognizes a specific sequence in its target genes, composed of inverted repeats of a nGAAn sequence, called heat shock element (HSE) (Akerfelt et al. 2010; Vihervaara et al. 2013). Different studies conducting HSF1 chromatin immunoprecipitation followed by sequencing (ChIP-seq) revealed that numerous target genes contain HSE in their promoter and intergenic regions, but a subset of them do not (Korfanty et al. 2014; Riva et al. 2012; Vihervaara et al. 2017). However, it is important to note that the presence of an HSE within any given gene does not assure HSF1 binding. Another layer of complexity is that the expression of target genes of HSF1, with or without specific HSEs, can also be influenced by epigenetic modification of chromatin (Guertin and Lis 2010; Vihervaara et al. 2017). These studies imply that the regulatory events that control which set of genes are induced by HSF1 at any given time are much more complicated than we have previously anticipated. HSF1 is known for its role as a transcriptional activator. However, numerous studies confirmed its role in repressing transcription, i.e., interleukin-6 (IL-6) involved in inflammation and the microtubule-associated protein Tau involved in synaptic dysfunction in different tauopathies (Inouye et al. 2007; Kim et al. 2017).

HSF1 has been studied widely in the context of the HSR and proteotoxic stress, but its role is not limited to just regulating Hsp expression (Gomez-Pastor et al. 2018). Recent evidence now points to HSF1 influencing the expression of multiple genes that are essential for cell cycle regulation, glucose metabolism, inflammatory response, and development and maintenance of neuronal, reproductive, and sensory organs (Akerfelt et al. 2007; Nakai 2009; Page et al. 2006; Singh and Hasday 2013). Therefore, defects in the activity and levels of HSF1 result in devastating consequences. More studies now confirmed the role of HSF1 in age-related and neurodegenerative disorders like Alzheimer's (AD), Parkinson's (PD), and HD and its potential as a therapeutic target (Goetzl et al. 2015; Gomez-Pastor et al. 2017; Jiang et al. 2013; Khalsa 2015; Kim et al. 2016; Kozuki et al. 2011; Lee et al. 2014; Neef et al. 2010; Pierce et al. 2013; Soncin et al. 2003). Different molecules, i.e., Hsp90 inhibitors and proteotoxic stress inductors, have shown efficacy in activating HSF1 and ameliorating some neurodegeneration features in mouse models. Unfortunately, our incomplete understanding of the roles of HSF1 in the brain and the lack of direct activators of HSF1 that can penetrate the blood-brain barrier have negatively affected the translational potential of HSF1. Future studies need to address this need.

In this chapter, we have specifically focused on the pathological role of HSF1 in HD, a devastating neurodegenerative disease caused by a CAG repeat expansion in the HTT gene (Bates et al. 2015; MacDonald et al. 1993; Novak and Tabrizi 2010). A selective vulnerability characterizes HD with degeneration and death of medium spiny neurons (MSN) in the striatum (Gonitel et al. 2008; Goula et al. 2012; Kennedy et al. 2003; Lee et al. 2011; Mitchell and Griffiths 2003; Pickrell et al. 2011; Shelbourne et al. 2007) and deficits in behavioral, cognitive, and motor features (Group 1996; Kieburtz et al. 2001; Novak and Tabrizi 2010). Cumulative evidence

shows that HSF1 plays a crucial role in ameliorating disease progression in HD. Recent research has shown the inappropriate degradation of HSF1 in HD, exacerbates HTT aggregation and neuronal death (Gomez-Pastor et al. 2017). These studies also revealed a potential implication of HSF1 in regulating genes with synaptic functions and new avenues for controlling the levels of HSF1 in the brain.

Here, we will explore the fundamental features of HSF1, including the structure and regulatory mechanisms, and its implication in physiological and pathological conditions, mainly focusing on the role in the regulation of Hsp expression, proteasome-mediated degradation of abnormal proteins, oxidative stress, mitochondrial dysfunction, excitotoxicity, and synaptic function in HD.

3 Introduction to Heat Shock Factor 1

3.1 HSF1: Structure, Function, and Regulation

The human HSF family consists of six members: HSF1, HSF2, HSF4, HSF5, HSFX, and HSFY (Gomez-Pastor et al. 2018). Each of them possesses specialized tissue distribution, functions, and regulation. Among them, HSF1 is the most studied HSF due to its relevance during the stress response and cell survival (Akerfelt et al. 2010). The human HSF1 gene is located on chromosome 8q24 and is translated into 529 amino acids with a predicted molecular weight of 57 kDa. However, due to several PTMs (discussed below), the actual molecular size reaches approximately 75 kDa. HSF1 is composed of 4 functional domains distributed from N-terminus to C-terminus as follows: DNA binding domain (DBD), oligomerization domains (OD) composed of 4 leucine zipper domains (LZ1–3 and LZ4), regulatory domain (RD), and a transactivation domain (TAD) (Fig. 1).

The DBD, which is highly conserved within the human HSF family, binds to the major groove of the DNA by recognizing repeating units of a pentameric sequence motif (nGAAn, where n is any base) named HSE. Recent comprehensive ChIP-seq demonstrated that the architecture of HSEs is very diverse in the human genome, with deviations from the consensus sequence in the spacing, orientation, and extent of HSE repeats (Mahat et al. 2016; Pincus et al. 2018; Vihervaara et al. 2017; Vihervaara et al. 2013). These deviations can influence HSF1 DNA binding efficacy and the kinetics and magnitude of target gene expression. Several studies over the last decade have shown different types of HSE that can be classified as canonical and non-canonical HSE. Vihervaara et al. demonstrated that HSF1 prefers binding to triple inverted nGAAn pentamers (canonical HSE) in both mitotic and cycling human erythroleukemia K562 cells (Vihervaara et al. 2013). Studies in purified HSF1 using fluorescence polarization and thermal denaturation profiling showed that HSF1 prefers binding to extended HSE sequences. The HSE placement is on a head-to-head or tail-to-tail orientation (Jaeger et al. 2014). Studies from *S. cerevisiae* showed two types of non-canonical HSE, gap- and step-type HSE. In gap-type HSE, two nGAAn repeats are followed by a gap of 5 bp block and another repeat (nGAAnnTTCn(5 bp)nGAAn) (Morano et al. 2012), whereas, in step-type HSE, three of each nGAAn repeats are interrupted by 5-bp block (nGAAn(5 bp)nGAAn(5 bp)nGAAn) (Morano et al. 2012; Yamamoto et al. 2005). Recent studies using *C. albicans* found that GAAnnTTC and TTCn7TTC are another non-canonical binding site where HSF1 regulates virulence genes' expression (Leach et al. 2016). Different mechanisms can explain preferred binding to different HSEs, including sequence orientation and oligomerization with different HSFs (Jaeger et al. 2014, 2016; Korfanty et al. 2014). HSF1 and HSF2 can form heterotrimers in vitro and in vivo and cooperate under different stressful and physiological conditions to bind different HSEs (Jaeger et al. 2016; Korfanty et al. 2014; Sandqvist et al. 2009). However, the full implications of different HSF1-HSF2 oligomers' combination on tissue-specific genome regulation are still unknown.

The OD is composed of two amphiphilic helices, heptad repeat HR-A/B or leucine zipper

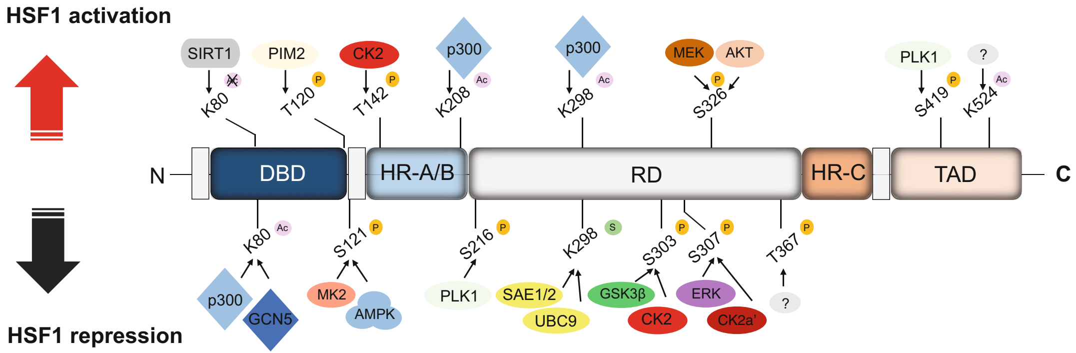


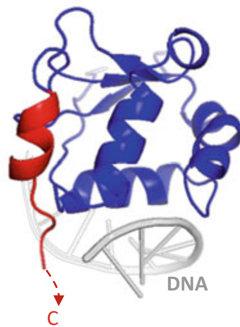
Fig. 1 Diagram of structural domains, regulatory enzymes, and PTMs of human HSF1. HSF1 can be divided into different structural domains: DBD (DNA binding domain), HR-A/B (heptad repeat-A/B), RD (regulatory domain), and TAD (transactivation domain). PTMs located at the top part of HSF1 are modifications with positive regulatory properties (red arrow), whereas PTMs located at the (bottom) represent modifications with repressive properties (black arrow). The different enzymes responsible for positive PTMs are SIRT1 (sirtuin 1), PIM2 (proviral integrations of Moloney virus 2, Pim-2 proto-oncogene, Ser/Thr kinase), CK2 (casein kinase holoenzyme), p300 (histone acetyltransferase p300), MEK (mitogen-activated protein kinase kinase), AKT (protein kinase B), and PLK1 (polo-like kinase 1). The enzymes responsive for the repressive PTMs are p300, GCN5 (general control non-repressed protein 5 histone acetyltransferase), MK2 (MAPK activated protein kinase 2), AMPK (5′-AMP-activated protein kinase), PLK1, SAE1/2 (SUMO-activating enzyme), UBC9 (RING-type E3 SUMO transferase), GSK3β (glycogen synthase kinase 3β), CK2, CK2α’ (catalytic subunit CK2 holoenzyme), and ERK (extracellular signal-regulated kinase). *Ac* acetylation, *P* phosphorylation, and *S* sumoylation

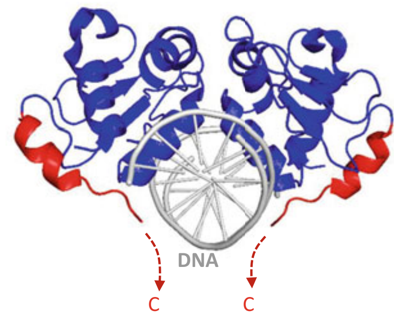
LZ1–3, which consist of a repeating pattern of seven hydrophobic and charged amino acid residues and it is critical in the activation of HSF1. HSF1 exists in monomeric and oligomeric (mostly trimer) states, and transitions between these two states are critical for HSF1 activation. Interactions between HR-A/B and other heptad repeats HR-C (or LZ4), located between the RD and TAD, regulate oligomerization of HSF1. Under non-stressful conditions, HR-A/B and HR-C are permanently bound by intramolecular coiled-coil interactions forcing the protein to be in a monomeric state (Chen et al. 1993; Nakai et al. 1997; Rabindran et al. 1993). Different conditions can disrupt the interaction between HR-A/B and HR-C, allowing HSF1 trimerization. Recent research has shown that HSF1 possesses an intrinsic capacity to sense temperature and that HSF1 monomers exposed to different temperatures can promote HR-A/B and HR-C dissociation (Hentze et al. 2016). However, other mechanisms described below have shown the ability to regulate oligomerization, such as PTMs and interactions with different regulatory proteins (reviewed in (Gomez-Pastor et al. 2018)). Trimerization is thought to be a prerequisite for the transcriptional activity of HSF1 and induction of Hsp (Farkas et al. 1998; Lu et al. 2008, 2009; Orosz et al. 1996). However, recent studies using a mutant form of HSF1 lacking the OD (HSF1Δ156–226) showed that, although HSF1 is unable to trimerize, this form was capable of protecting cells exposed to proteotoxic conditions (Qu et al. 2018; Verma et al. 2014), suggesting the existence of alternative mechanisms to control HSF1 activation not described yet.

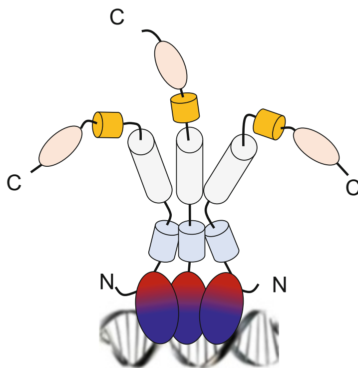
The RD is a highly unstructured domain targeted by many different PTMs (Green et al. 1995; Guo et al. 2001), which allow the RD to provide activating or repressing functions to HSF1 (Newton et al. 1996). Finally, the TAD located in the C-terminus is responsible for the transcriptional activation of target genes (Green et al. 1995; Newton et al. 1996). Recent HSF1 and HSF2 crystal structure studies have revolutionized the way we think about HSF binding to DNA and have opened the door for new

investigations regarding HSF DNA-binding regulation (Jaeger et al. 2016; Neudegger et al. 2016). Previous models suggested that the position of HSF1-DBD was so that the rest of the protein precluded access to the DBD once bound to the DNA, therefore limiting the interaction between the DBD and other potential regulatory proteins. Jaeger et al. and Neudegger et al. independently proposed a new HSF-DNA binding model in which the DBD wraps around the DNA, forcing the rest of the protein to be oriented in the opposite direction to the DBD and therefore leaving the DBD exposed for interaction with other potential regulators (Jaeger et al. 2016; Neudegger et al. 2016) (Fig. 2).

As stated above, the HSF1 activation/attenuation mechanism is highly influenced by its structural conformation and different protein-protein







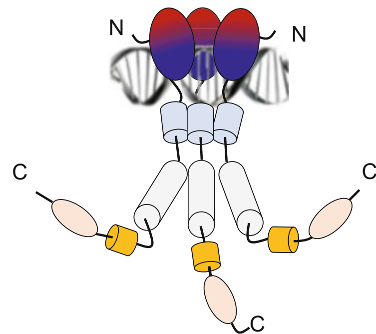


Fig. 2 Structural insights into HSF-DNA interaction topology. (**a**, **b**) Crystal structure of the DNA binding domain (DBD) of HSF1 and HSF2 bound to a two-site HSE as a dimer. These independently solved structures revealed that a previously unknown carboxy-terminal helix (red) that is conserved in both HSF1 and HSF2 directs these HSFs to wrap around the HSE DNA, resulting in a topology where the DBD and the remainder of the HSF1 protein (not present in the crystal structure) occupy opposite sides of the DNA. (**c**) A new model of the HSF-DNA interaction. Structural studies support a model in contrast with the previous model for the topology of DNA-bound HSF oligomers. In the old model (left), the oligomerization domains (light blue) were positioned on top of the DBD, such that the rest of the protein buried the free surface of the DBD (shown in red, in contrast to the DNA-bound portion of the DBD shown in blue). In the new model (right), this free surface of the DBD is solvent-exposed, making it available for interactions with regulatory proteins and accepting PTMs. (Figure adapted from (Gomez-Pastor et al. 2018) with authors' permission)

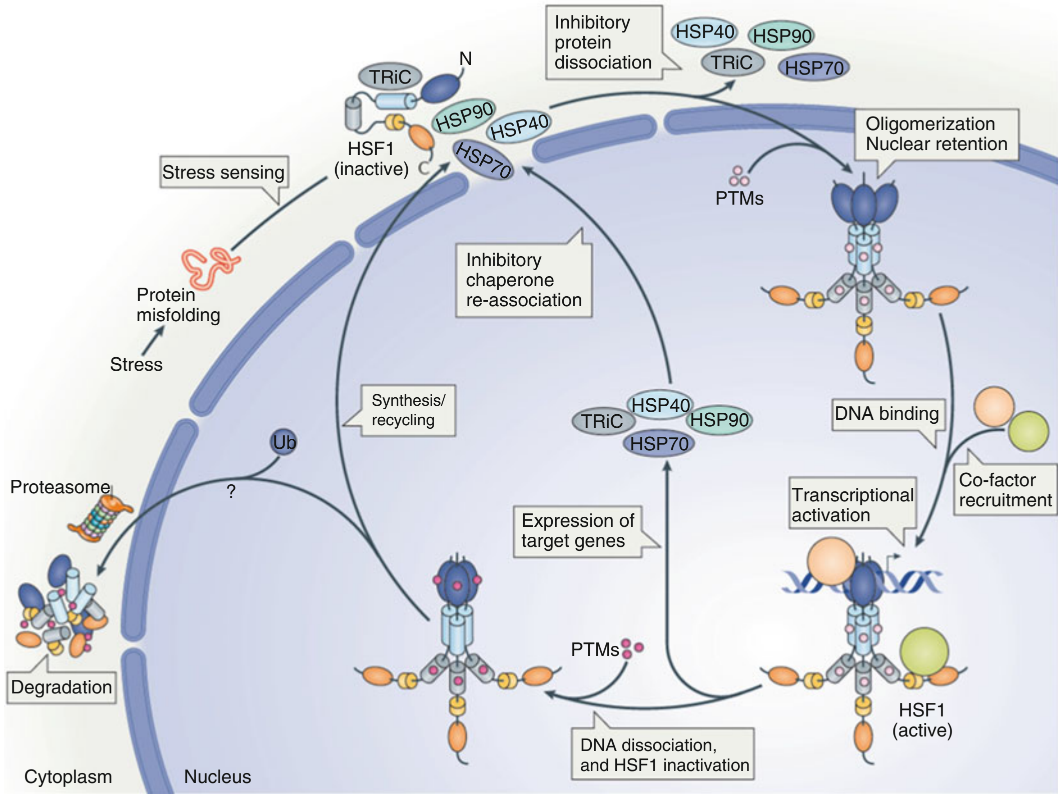


Fig. 3 HSF1 activation/attenuation cycle. In response to proteotoxic stress conditions, HSF1 is subject to a multi-step activation and attenuation cycle. Inactive HSF1 monomer is kept in the cytoplasm in a complex with regulatory proteins such as Hsp 40, 70, and 90, as well as the cytosolic chaperonin TCP1 ring complex (TRiC). Upon stress sensing, HSF1 is modified by several activating PTMs that promote DNA binding and transcriptional activation of target genes in concert with cofactor recruitment. HSF1 is then modified by different inhibitory PTMs and by p23 causing DNA dissociation, HSF1 inactivation, and HSF1 degradation (see Fig. 1) for PTMs details). It is currently unknown where HSF1 degradation occurs and the extent to which HSF1 is newly synthesized or recycled into the cytoplasm. Ultimately, after attenuation, HSF1 is maintained in the cytoplasm by an inhibitory protein complex in a negative feedback mechanism. Color code: DNA-binding domain (dark blue), leucine zipper oligomerization domain LZ1–3 (light blue), regulatory domain (gray-white), LZ4 (yellow), and activation domain (orange). (Figure adapted from (Gomez-Pastor et al. 2018) with authors' permission)

interactions (Fig. 3). Under non-stressful conditions, HSF1 exists in the cytoplasm as an inactive monomeric form due to intramolecular interactions between the HR-A/B and HR-C and direct protein-protein interactions with several inhibitory complexes. One of them is an auto-regulatory complex induced by HSF1-regulated proteins such as Hsp90, Hsp70, Hsp40, and T-complex protein-1 ring complex (TRiC)/ chaperonin containing TCP-1 (CCT) (Akerfelt et al. 2010; Anckar and Sistonen 2011; Neef et al. 2014; Zheng et al. 2016). Previous research has shown that Hsp90 can inhibit HSF1 oligomerization and DNA binding (Zou et al. 1998), whereas Hsp70 and its co-chaperone Hsp40 regulate HSF1 transactivation by interacting with the TAD (Gomez et al. 2008; Shi et al. 1998). The cytosolic chaperonin TRiC/ CCT also inhibits HSF1 activation by direct interaction with HSF1, although the exact mechanism by which TRiC/CCT inhibits HSF1 is not fully characterized (Akerfelt et al. 2010; Neef et al. 2014). Other repressive hetero-complexes include 14–3-3, histone deacetylase 6 (HDAC6), and the valosin-containing protein (VCP) that ultimately tune HSF1 activation (Pernet et al.

2014). Upon stress, there is a liberation of HSF1 from these repressive complexes allowing HSF1 trimerization and accumulation into the nucleus where HSF1 interacts with a different set of regulatory proteins that assist HSF1-DNA binding and transcriptional activation of its target genes (Amin et al. 1988; Pelham 1982; Sorger and Pelham 1988). HSF1 transcriptional activation results in increased levels of Hsp and other repressive proteins that hinder HSF1 activation by a negative feedback mechanism after the stress has subsided. Among these additional repressive proteins, filamin A interacting protein 1-like (FILIP-1 L) promotes HSF1 poly-ubiquitination and degradation by recruiting hHR23A, a ubiquitin receptor protein functioning as a transferrer of ubiquitinated proteins to the 19S proteasome (Hu and Mivechi 2011). In mammalian cells, FILIP-1 L forms complexes with HSF1 and Hsp72, and its ectopic overexpression reduces HSF1 protein levels leading to inhibition of HSF1-mediated transcription. However, the biological function of FILIP-1 L and the regulatory mechanisms responsible for HSF1-FILIP-1 L interaction are still unclear. Below we will discuss other regulatory events responsible for controlling HSF1 activity and stability in different contexts.

3.2 HSF1 PTMs: Pathophysiological Implications

The levels of HSF1 do not usually vary during stress-induced activation. In contrast, HSF1 undergoes numerous PTMs, including phosphorylation, sumoylation, and acetylation, that establish a complex code responsible for controlling every step of the HSF1 activation/attenuation cycle. Overall, HSF1-PTMs are classified into two main functions: positive and negative regulatory PTMs (Fig. 1). It is essential to mention that the enzymes responsible for HSF1 modifications and their effects are entirely dependent on the context. One example of the versatile-PTMs and the effects that they cause on HSF1 is led by polo-like kinase 1 (PLK1). During early mitosis, HSF1 is phosphorylated at Ser216 by PLK1, leading to HSF1 ubiquitin-dependent degradation by the SCFβTrCP E3 ligase (Lee et al. 2008). This event is critical to ensure mitosis progression. However, under heat shock conditions, PLK1 phosphorylates Ser419 and regulates HSF1 nuclear translocation. Similarly, protein kinase CK2 (casein kinase holoenzyme) regulates Thr142 phosphorylation and HSF1 DNA binding activation under heat shock conditions, but it controls phosphorylation of Ser303/307 and HSF1 degradation in the presence of pathogenic huntingtin (HTT) aggregates (Gomez-Pastor et al. 2017; Soncin et al. 2003).

Dozens of HSF1-PTM descriptions have been looked at under different experimental conditions, especially under heat shock. They have recently been reviewed in Gomez-Pastor et al. (2018), and their summaries can be seen in Fig. 1. This chapter will focus on some of those HSF1 PTMs that have relevance in pathophysiological stages. A fundamental set of PTMs that seem to control HSF1 activity and stability in different pathological conditions is Ser303 and Ser307 phosphorylation. In many cancer cells, there is a dramatic alteration in the levels of HSF1, contributing to cell proliferation and tumorigenesis (Jiang et al. 2015; Vydra et al. 2014). In melanoma cancer cells, the ubiquitin E3 ligase complex (Skp1-Cul1-F box) formed by the substrate-targeting subunit F-box and WD repeat domain containing 7 (FBXW7) interacts with and ubiquitylates HSF1. This interaction depends on Ser303/307 phosphorylation mediated by glycogen synthase kinase 3β (GSK3β) and extracellular signal-regulated kinase 1 (ERK1), respectively (Kourtis et al. 2015). Kourtis et al. suggested that reduced levels of FBXW7 or loss of function mutations present in many tumors may lead to increased levels of HSF1. However, a recent study in breast cancer cells showed that FBXW7 knockdown does not enhance HSF1 levels in those cells (Yang et al. 2019). Instead, elevated proviral integrations of Moloney virus 2 (PIM2) kinase phosphorylates HSF1 at Thr120, disrupting HSF1, and FBXW7 and promoting HSF1 accumulation (Yang et al. 2019). On the other hand, a very recent study by Gomez-Pastor et al. found that protein kinase CK2 α prime (CK2α') also phosphorylates Ser303/307 in HD (Gomez-Pastor et al. 2017).

CK2α' is upregulated in HD, leading to increased FBXW7-dependent HSF1 degradation. Recently Jin et al. generated a knock-in mouse model where Ser303/307 were mutated to Ala and showed that HSF1 levels were stabilized and increased compared to wild-type mice (Jin et al. 2018). However, these mice presented age-dependent obesity, fatty liver disease, and insulin resistance, suggesting that phosphorylation of Ser303/307 may exert a positive effect in specific situations.

In general, phosphorylation of residues with inactivation functions is reduced in tumor cells, contributing to the hyperactivation of HSF1 previously reported in cancer. Mitogen-activated protein kinase kinase (MEK)-mediated Ser326 phosphorylation causes the stabilization of HSF1 by preventing it from poly-ubiquitination and subsequent proteasomal degradation (Tang et al. 2015). Repressive Thr367 phosphorylation is also reduced in cancer, although the specific kinase involved in this modification has not been identified yet (Asano et al. 2016). Other phosphorylation with repressive functions reduced in cancer is Ser121 involved in Hsp90 binding, mediated by MAPK-activated protein kinase 2 (MK2) and the 5′-AMP-activated protein kinase (AMPK). By contrast, during metabolic stress, AMPK-mediated phosphorylation of Ser121 increases and dictates HSF1 nuclear localization and stability (Asano et al. 2016; Dai et al. 2015; Guettouche et al. 2005). While several studies have revealed essential PTMs that contribute to HSF1 activity and stability in cancer, our knowledge about the different PTMs that regulate the role of HSF1 in other different diseases is very limited. These studies are necessary to fully understand the mechanisms that regulate HSF1 function under pathological conditions and may identify novel therapeutic targets.

Intriguingly, phosphorylation also serves as a platform for additional PTMs like sumoylation. GSK3β-induced phosphorylation at Ser303 is a prerequisite for Lys298 sumoylation, conjugation of SUMO-2/3, which results in inhibition of the transactivating capacity of HSF1 (Hietakangas et al. 2003). This sumoylation is mediated by the E1 SUMO-activating enzymes SAE1/2 and E2 SUMO-conjugating enzyme UBC9. The authors demonstrated the existence of a phosphorylation-dependent sumoylation motif within HSF1 (ΨKxExxSP, where Ψ is a branched hydrophobic amino acid and x is any amino acid), which resembles a consensus SUMO site (ΨKxE), that is utilized to prime proteins as a SUMO substrate. In general, sumoylation is facilitated by the aid of an E3 ligase, which increases sumoylation efficiency either by accelerating SUMO transfer from UBC9 to the substrate or merely by providing scaffolding support (Brunet Simioni et al. 2009). Site-specific mapping of the human SUMO proteome has revealed co-modifications with phosphorylation and the presence of several sumoylated-Lys on HSF1 (Hendriks et al. 2017). However, their roles in HSF1 regulation under physiological conditions are still unknown.

Another modification influencing HSF1's function is Lys acetylation. Considering the studies reported, acetylation within the DBD has adverse effects on HSF1-DNA interaction. Acetylation at Lys80 in the DBD by p300 shortens the time of HSF1 on DNA, reducing HSF1 activation (Westerheide et al. 2009). In agreement with this, deacetylation at Lys80 by NAD + -dependent sirtuin 1 (SIRT1) accelerates HSF1 activity by increasing HSF1 DNA occupancy. Interestingly, the recognition of SIRT1 is as a nutrient sensor and longevity factor. The gradual loss of SIRT1 during aging correlates with the dissipation of HSF1 and reduced HSR and protein homeostasis in aging (Akerfelt et al. 2010). Zelin et al. demonstrated that general control non-repressed protein 5 (GCN5) histone acetyltransferases target HSF1 Lys80 in the presence of p23 chaperone, which disrupts HSF1 DNA binding (Zelin et al. 2012). An additional study identified that overexpression of histone deacetylases HDAC 7, HDAC9, and SIRT1 stimulated heat-triggered HSF1 DNA binding (Zelin and Freeman 2015). On the other hand, acetylation of Lys residues within the RD contributes to preventing HSF1 degradation. A study conducted in HeLa cells showed that acetylation at Lys208 and Lys298 by p300 prevents HSF1 from proteasomal degradation, maintaining HSF1 stability (Raychaudhuri et al. 2014). Also, HDAC6 has been implicated in the activation of HSF1 by

repressing the Hsp90-HSF1 complex and promoting HSP gene expression (Boyault et al. 2007; Pernet et al. 2014). Future studies are warranted to demonstrate the relevance of these modifications in pathological stages in which there is a dysregulation in HSF1. A summary of the most relevant regulatory proteins based on the HSF1-PTMs they are responsible for, and their role in the regulation of HSF1, is shown in Fig. 4.

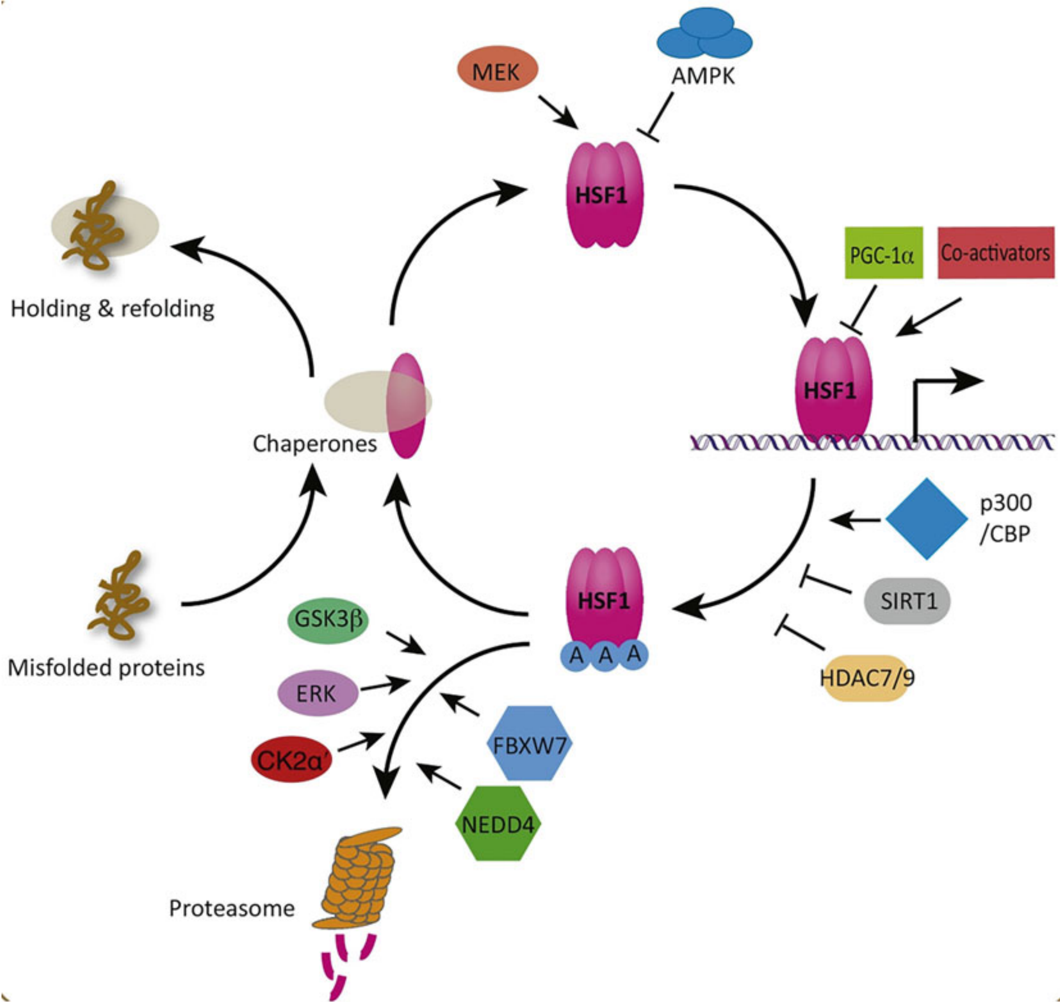


Fig. 4 HSF1-regulatory enzymes and their contribution in HSF1 activation cycle. Upon proteotoxic stress, misfolded proteins titrate away the Hsp repressive complex, allowing HSF1 trimerization and nuclear accumulation. The HSF1 trimer binds to HSE in the promoter region of HSF1 target genes (old model of HSF-DNA binding: see Fig. 2). HSF1 activation is modified by several PTMs (see Fig. 1). Enzymes responsible for controlling nuclear translocation and activation include MEK and AMPK (with opposite functions). PGC-1α and different co-activators modulate HSF1 transcriptional capacity. Enzymes like HDAC7, HDAC9, and SIRT1 prolong HSF1 binding to the DNA, while acetylation by p300/CBP has an opposite effect and mediate DNA dissociation. Ubiquitin proteasome-dependent HSF1 degradation occurs by E3 ligases FBXW7 and NEDD4. FBXW7 is recruited by phosphorylation of HSF1 mediated by GSK3β, ERK, and CK2α', whereas NEDD4 is accessed by p300/CBP-mediated acetylation (Figure reprinted from "Rethinking HSF1 in Stress, Development, and Organismal Health" by Li et al. 2017, with copyright permission from Elsevier. Figure legend has been modified accordingly for this publication)

4 Regulation of HSF1 and the HSR by Non-coding RNAs

Emerging evidence have shown that non-coding RNAs (ncRNAs) are actively involved in the regulation of HSF1 and the HSR (Place and Noonan 2014). A large class of small ncRNAs known as microRNAs (miRNAs) can regulate many biological processes by acting as post-transcriptional regulators of gene expression. Different miRNAs can bind in the 3'UTR of HSF1 altering its expression. miR-378 directly targets and represses the expression of HSF1 in cardiomyocytes (Jie Yuan et al. 2010) therefore affecting the induction of downstream HSPs in the heart while miR-608 operates as an HSF1 positive regulator in human breast cancer (Huang et al. 2012). Levels of HSF2 are also influenced by miRNAs (Björk et al. 2010; Cai et al. 2015). Other key determinant in the regulation of HSFs in human cells is the long non-coding RNAs (lncRNA). The lncRNA HSR1 (heat shock RNA-1), is upregulated during the HSR and plays an essential role in HSF1 trimerization and subsequent DNA binding activity forming a complex with the eukaryotic elongation factor 1A (eEF1A) (Shamovsky et al. 2006; Shamovsky and Nudler 2009). HSR1 is a foreign lncRNA derived from a bacterial genome, functioning as an exogenous auxiliary factor required for mammalian HSF1 activation upon stress conditions (Choi et al. 2015; Kim et al. 2010a, b).

HSF1 also regulates the expression of different non-coding RNAs (ncRNAs) involved in global suppression of transcription, translational processes, and protein aggregation (Lindquist 1986). Upon heat shock, HSF1 induces the expression of a class of lncRNAs known as Satellite III transcripts (Sat3) that accumulate at the site of transcription to form nuclear stress bodies (nSBs) (Jolly et al. 2004; Rizzi et al. 2004; Sengupta et al. 2009) and are known to co-localize with several RNA binding proteins and transcription factors such as HSF1 (Cotto et al. 1997; Jolly et al. 2004; Metz et al. 2004). Although knockdown of Sat3 transcripts does not affect HSF1 recruitment to the nSB-like structures, it has been recently demonstrated that Sat3 transcripts are essential for the recruitment of additional transcription regulators to the nSBs contributing to the heat-induced transcriptional silencing (Goenka et al. 2016). Transcription of the lncRNA satellite 2 (Sat2) is also strongly upregulated in the presence of heat shock in a HSF1-dependent manner (Tilman et al. 2012), and it has been involved in tumor progression (Tilman et al. 2012). Genome-wide studies revealed that HSF1 has also the ability to bind HSE present upstream of different miRNAs and regulate their expression under thermal stress (Srijit Das 2015). Interestingly, some of those HSF1 regulated miRNAs have shown inhibitory effects on HTT protein, and they are significantly depleted in HD, therefore contributing to increased mHTT expression and aggregation (Das and Bhattacharyya 2015). These studies demonstrate an integrated model of ncRNAs and HSF activity in the regulation of the HSR under physiological conditions and human diseases.

5 Role of HSF1 in Physiology and Disease

HSF1 is well known for its role in regulating the HSR, as discussed above. However, it has implications in many other processes, including aging, immune system maintenance, cancer, metabolic stress, neural development, and neurodegeneration. These functions can be accomplished by combining different protein-protein interactions and post-translational modifications that modulate HSF1 activity and stability and end up activating different transcriptional programs. Some of these functions are discussed below and summarized in Fig. 5.

5.1 HSF1 in Aging and Inflammation

For every single living cell, there is constant exposure to environmental and physiological stresses during its lifespan. Therefore, proper mechanisms are necessary to execute an adequate response to ensure cell survival. However, during

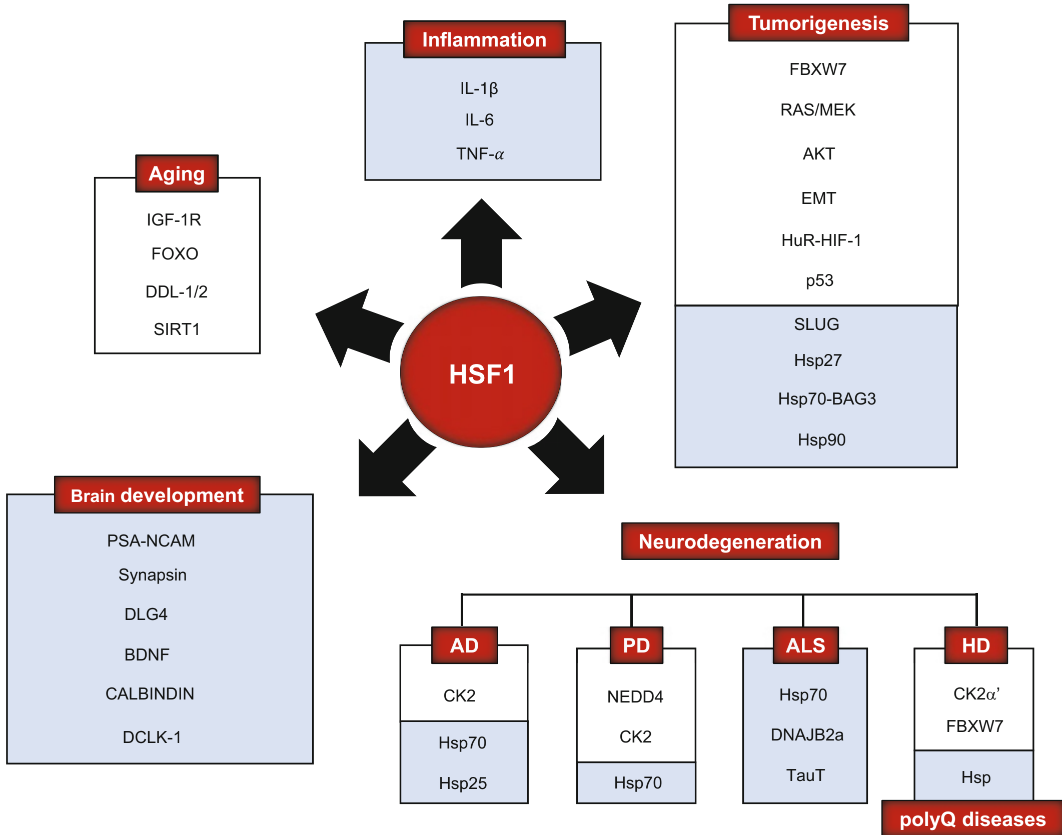


Fig. 5 Relationship between HSF1 and different physiological and pathological processes. Changes in activity and stability of HSF1 are responsible for regulating different cellular processes that are essential for life, including brain development, immune response, metabolism, and cell growth. Dysregulation of HSF1 contributes to different diseases like cancer and neurodegeneration. For each process, we included different proteins related to HSF1 and that contribute to the regulation of such a process. Proteins shown in a white box correspond to proteins that directly or indirectly regulate HSF1 activity or stability. In contrast, proteins shown in a blue box are proteins whose expression is influenced by HSF1

aging, there is a profound decline in the HSR that is accompanied by frail HSF1 activity and downregulation of its downstream target genes that compromise the survival of aged cells exposed to stressful conditions (Kregel 2002). Direct involvement of HSF1 in aging was reported by Garigan et al. showing that HSF1 knockdown speeded up the decline of tissue integrity and shortened lifespan in *C. elegans* (Garigan et al. 2002), while others showed that HSR significantly declines in this organism in early adulthood at reproductive maturity (reviewed in (Labbadia and Morimoto 2015)). These results have been supported by overexpression studies, in which HSF1 expression increased *C. elegans* lifespan by 20–40% (Hsu et al. 2003; Morley and Morimoto 2004). Examples in mammals include diminished HSF1-DNA binding capacity and Hsp accumulation in aged rats (21–26-month-old) upon heat shock and reduced HSF1-DNA binding in human lymphocytes and skin fibroblasts from old individuals (>70 years) when compared with those from a young age (20–40 years) (Fawcett et al. 1994; Gutsmann-Conrad et al. 1998; Jurivich et al. 1997; Locke and Tanguay 1996).

There is a coupling between longevity enhancing capacity of HSF1 with insulin/insulin-like

signaling (ILS) pathway (Barna et al. 2012; Chiang et al. 2012). In *C. elegans*, stimulation of the insulin/insulin-like growth factor 1 receptor DAF-2 (IGF-1R in mammals) inactivates anti-aging and HSP genes via activation of protein kinase B (AKT) and phosphorylation of the longevity-related transcription factor DAF-16 (FOXO in mammals). Increased DAF-2 signaling inhibits HSF1 activity by promoting HSF1 to compete with negative regulators DAF16-dependent longevity-1 (DDL-1) and DDL-2, which accelerates aging (Chiang et al. 2012). Although it is unclear the integration of DAF-2 signaling to HSF1, both HSF1 and DAF-16 are needed for DAF2-mediated extension of lifespan (Cohen et al. 2006; Hsu et al. 2003; Morley and Morimoto 2004). Moreover, both HSF1 and DAF-16 activate the same small hsp genes, hsp-12 and hsp-16, which are essential to promote longevity (Hsu et al. 2003). The ILS-dependent lifespan extension is observed in mammals as well. Heterozygous Igf-1r knockout mice have shown to live approximately 26% longer than their wild-type littermates (Holzenberger et al. 2003). Also, sequence analysis of IGF-1R genes displayed over-representation of heterozygous mutations of the IGF1-R gene in female centenarians (Suh et al. 2008). While these studies did not explore the involvement of HSF1 on long-lived life, given that HSF1 plays a critical role in IGF-1R-dependent lifespan regulation, it is reasonable to speculate that HSF1 might be a controlling factor in the longevity of mammals as it is in invertebrates.

Human aging is also characterized by chronic low-grade inflammation. Several studies indicate that HSF1 modulates normal immune response and inflammation by controlling the expression of different cytokines. For example, HSF1 suppresses tumor necrosis factor-α (TNF-α) by binding to the HSE-like sequences within the TNF-α promoter, while it represses IL-1β through direct interaction with a regulator of IL-1β transcription, a nuclear factor for interleukin-6 (NF-IL6) (Xiao et al. 1999; Xie et al. 2002a). In the case of IL-6, HSF1 represses IL-6 by recruiting an IL-6 repressor activating transcription factor 3 (ATF3) into the open chromatin structure of IL-6 (Inouye et al. 2007). Interestingly, reports have linked HSF1 with the repression of HIV-induced inflammation by impairing the HIV-dependent expression of IL-6 (Inouye et al. 2007; Takii et al. 2010; Xie et al. 2002b), TNF-α (Muralidharan et al. 2014), and IL-1β (Xie et al. 2002a). Additionally, active HSF1 increases the expression of anti-inflammatory cytokine IL-10 (Zhang et al. 2012). Therefore, the decline of HSF1 activity during aging may contribute to increased inflammatory cytokines expression exacerbating aging.

5.2 Tumorigenesis and HSF1

Cancer cells are in a hostile environment enriched with stress, including hypoxia, acidity, ATP depletion, and lack of nutrients (Hanahan and Weinberg 2011). Thus, it can be assumed that under these conditions HSF1 may remain constitutively activated. In 2007, Dai et al. demonstrated that Hsf1−/− mice were far more resistant to skin-induced tumor formation than Hsf1+/+ mice (Dai et al. 2007). The authors showed that HSF1 steers cancer growth by modulating proliferation, signal transduction, protein translation, and glucose metabolism. Since then, there has been growing evidence that shows the increase of HSF1 in many cancer types, including breast cancer, colorectal cancer, gastric cancer, myeloma, non-small-cell lung cancer, oral squamous cell carcinoma, prostate cancer, and many other cancer types (Cui et al. 2015; Fok et al. 2018; Ishiwata et al. 2012; Li et al. 2018; Santagata et al. 2011; Tong et al. 2018). However, it is essential to clarify that increased HSF1 expression is not causative for tumorigenesis. The different roles of HSF1 in cell proliferation and cancer were extensively reviewed recently (Carpenter and Gokmen-Polar 2019; Gomez-Pastor et al. 2018; Jiang et al. 2015). Therefore, we will focus on the most recent and groundbreaking studies that have set up HSF1 as an essential target in cancer biology.

The mechanisms underlying increased HSF1 expression and activity in cancer are complex and vary between different types of tumors and cell

types. Zhao et al. showed that the increased levels of HSF1 in ERBB2-overexpressing cancers are due to an elevation of HSF1 protein translation (Zhao et al. 2009). On the other hand, Kourtis et al. suggested that increased levels of HSF1 in melanoma are due to increased protein stability and decreased proteasomal degradation through decreased or mutated E3 ligase FBXW7 (see HSF1 PTMs section for further details) (Kourtis et al. 2015). As we previously mentioned in the above section, phosphorylation of Ser and Thr with repressive functions within HSF1 is significantly reduced in cancer cells, leading to increased HSF1 activity. In cells from human malignant peripheral nerve sheath tumor (MPNST) lacking neurofibromatosis type 1 (NF1), a tumor suppressor, there is an increase in RAS/MEK-mediated HSF1 Ser326 phosphorylation, which leads to HSF1 trimerization and nuclear translocation. Reports have indicated that this modification significantly contributes to cancer progression (Dai et al. 2012). Also, HSF1 acts in diverse signaling pathways driving cancer initiation, migration, invasion, and metastasis. For example, HSF1 enhances the initiation and progression of breast cancer by upregulating RNA-binding protein Hu-antigen R (HuR) and increasing hypoxia-inducible factor 1 (HIF-1) signaling (Gabai et al. 2012). Knockdown of HSF1 represses epithelial-mesenchymal transition (EMT), a facilitator of metastasis in cancer development, and reduces cell migration in ovarian cancer cells (Powell et al. 2016). Specifically, HSF1 is phosphorylated at Ser326 by AKT and binds to SLUG promoter, an EMT regulator, leading to the upregulation of SLUG in HER2-positive breast cancer cells (Carpenter et al. 2015). These findings suggest that the HSF1-SLUG axis is an essential pathway in cancer progression.

HSF1 exerts its effects on cancer progression, in part through the upregulation of Hsp. In MPNST, loss of NF1 increased HSF1 levels and Hsp90 expression, promoting carcinogenesis (Dai et al. 2012). HSF1 activation and Hsp90 expression are also essential in enhancing tumor growth in HER2-positive breast cancer (Schulz et al. 2014). Hsp70 also enhances tumorigenesis by acting as a survivor factor due to its anti-apoptotic effects. For example, Hsp70 and its co-chaperone BCL-2–associated athanogene 3 (BAG3) mediate apoptosis resistance in glioma cells by supporting cell survival through increasing the levels of pro-survival BCL-2 family members (Antonietti et al. 2017). In addition to the upregulation of Hsp90 and Hsp70, there is also an elevation in the expression of Hsp27 in a variety of different cancers, and it is involved in tumor progression and drug resistance (Fang et al. 2012; Vahid et al. 2016; Xu et al. 2006; Yu et al. 2014; Zhao et al. 2012). Interestingly, a study conducted in hepatocellular carcinoma showed that HSF1-mediated phosphorylation of Hsp27 rather than Hsp27 expression is necessary to promote migration and invasion of carcinoma cells (Fang et al. 2012).

Intriguingly, the upregulation of HSF1 in cancer is associated with the activity of tumor suppressor p53 (Toma-Jonik et al. 2019). Under stress conditions, HSF1 interacts with p53 in the nucleus and form a complex with DNA damage kinases to effect p53 phosphorylation in response to DNA damage (Logan et al. 2009). The presence of mutations in p53 protein is also connected to the activation of HSF1. Specifically, a gain-of-function p53 mutant variant (Arg280Lys) directly interacts with HSF1 phospho-Ser326, enhancing HSF1 transcriptional activity and Hsp90 expression in human breast cancer cells (Li et al. 2014a). Hence, the gain of function of p53 offers not only the drastic acceleration of oncogenic signaling but also the Hsp-induced survival capacity of cells through HSF1. On the other hand, DNA damage induces p53 activation and HSF1 downregulation, resulting in senescence (Kim et al. 2012). Moreover, HSF1 depletion causes growth inhibition of breast cancer cells by promoting p53-induced senescence (Meng et al. 2010), suggesting that lack or loss of p53 combined with HSF1 activation support tumorigenesis by regulating senescence and proliferation. These observations indicate that HSF1 may be a central mediator of the oncogenic function of different mutant variants of p53 observed in cancer cells.

Reports have shown that the transcriptional program triggered by HSF1 in malignant cells is different from those mediated by heat shock. The

genes activated in this program drive oncogenic transformation by accelerating protein folding, translation, mitosis, invasion, metabolism, and metastasis and obstructing immune functions and apoptotic response (Mendillo et al. 2012). Since there is an elevation in the expression levels of HSF1 in many solid tumors and there is an association between its levels with low survival rate and metastasis (Ciocca et al. 2013; Mendillo et al. 2012), HSF1 has been proposed as a prognostic factor in cancer. In addition, there is a link between increased HSF1 and reduced survival in many different tumors like estrogen receptor-positive breast cancer, osteosarcoma, pancreatic cancer, melanoma, and esophageal squamous cell carcinoma (Kourtis et al. 2015; Liang et al. 2017; Liao et al. 2015; Santagata et al. 2011; Santagata et al. 2013; Tsukao et al. 2017; Zhou et al. 2017). In patients with hepatocellular carcinoma (HCC), expression of HSF1 was also found to be correlated with poor overall survival (Fang et al. 2012) and, specifically, the high levels of HSF1 phospho-Ser326 has been reported in HCC progression and invasion (Li et al. 2014b). Notably, the levels of HSF1 phospho-Ser326 have clinical significance in shorter overall survival in ovarian cancer patients (Yasuda et al. 2017). Collectively, the expression and activity of HSF1 can serve as a potential clinical biomarker for patients with cancers. Due to the high levels of HSF1 and its relevance in tumor growth, HSF1 has become a desirable target to treat cancer (Carpenter and Gokmen-Polar 2019; Dong et al. 2019). However, although HSF1 has been validated as a potent target in cancers by genetic knockdown studies, HSF1 inhibitors reported to date have lacked specificity and potency for clinical evaluation (Dong et al. 2019). Hence, it is necessary to make a more systematic design to develop more potent and specific HSF1 inhibitors in the future.

5.3 HSF1 in the Central Nervous System (CNS)

Ubiquitous expression of HSF1 in the developing brain implies a need for HSF1 during neurodevelopment (El Fatimy et al. 2014). It is now known that not only HSF1 but also HSF2 plays essential roles in brain function through modulation of neuronal migration, formation, and maintenance of neuronal synapses. Lack of HSF1 dramatically alters brain structure, neuronal differentiation, and synaptic formation (Chen et al. 2014; Hooper et al. 2016; Uchida et al. 2011). In the hippocampus, a brain area involved in learning and memory, the absence of HSF1 causes a decrease in the dendrite length of the dentate gyrus granule neurons and pyramidal neurons. It reduces dendritic spine density, resulting in reduced synapse formation (Uchida et al. 2011). Additional observations demonstrated that lack of HSF1 in the hippocampus causes low expression of polysialylated-neural cell adhesion molecule (PSA-NCAM), which is fundamental in synapse formation. Other synaptic proteins, such as synapsin and discs large MAGUK scaffold protein 4 (DLG4) involved in synaptogenesis, also depend on HSF1 (Chen et al. 2014). Due to the specific role of HSF1 in regulating synaptic proteins, alteration in the levels of HSF1 during embryogenesis results in alterations in synaptic fidelity and memory consolidation. In this line, HSF1 also regulates the expression of brain-derived neurotrophic factor (BDNF), an essential regulator of synaptogenesis and synaptic plasticity mechanisms underlying learning and memory (Chen et al. 2014; Cunha et al. 2010). Other functions attributed to HSF1 are the regulation of lipid raft formation, the subdomains of plasma essential for postsynaptic consolidation of memory receptors and long-term memory retention (Nagy et al. 2007; Suzuki and Yao 2014), and regulation of Ca2+ homeostasis through the activation of CALBINDIN expression in cerebellar Purkinje cells (Ingenwerth et al. 2016). The deficiency of HSF1 also results in loss of oligodendrocytes and severe demyelination, astrogliosis, increased activated microglia, and neuronal apoptosis across different brain regions (Homma et al. 2007).

HSF1 has critical protective roles in response to stresses during brain development. Research has shown that exposure of Hsf1-/- mice to stressful conditions during prenatal stages increases

neuropsychiatric susceptibility like disorders in the newborns (Hashimoto-Torii et al. 2014). During exposure to stresses like alcohol or a maternal epileptic seizure, HSF1 is retained in the nucleus and activates Hsp70 expression. Intriguingly, under these conditions, HSF1 does not show a characteristic hyperphosphorylation pattern upon activation but rather presents reduced acetylation and sumoylation (El Fatimy et al. 2014). Interestingly, El Fatimy et al. demonstrated that prenatal alcohol exposure (fetal alcohol syndrome) causes brain structural abnormalities dependent on the formation of HSF1-HSF2 heterotrimers (El Fatimy et al. 2014). The group found that fetal alcohol exposure causes HSF1-HSF2 heterotrimers to bind to and downregulate doublecortin-like kinase 1 (Dclk1) expression, a gene that participates in neuronal migration and neurogenesis. The authors also demonstrated that lack of Hsf2 exerts a protective role during prenatal alcohol exposure facilitating HSF1 homotrimerization and regulating neuronal migration genes. These results indicate the complexity of the different HSF1 regulatory mechanisms during physiological conditions and the importance of these transcription factors in every step of an organismal life.

5.4 Neurodegenerative Diseases and HSF1

As we described in the previous section (HSF1 in the CNS), HSF1 participates in the development of the CNS by controlling diverse processes such as neuronal migration, neurogenesis, glycogenesis, synapse formation, and neuronal survival (El Fatimy et al. 2014; Homma et al. 2007; Hooper et al. 2016; Ingenwerth et al. 2016; Uchida et al. 2011). Therefore, maintaining proper levels of HSF1 is essential to ensure the appropriate development and maintenance of the CNS. However, in the adult brain, HSF1 activity significantly declines, contributing to inflammation and neuronal death (Calderwood et al. 2009; Murshid et al. 2013). In line with these observations, there is a significant reduction in HSF1 in many age-related neurodegenerative diseases (NDs), like AD, PD, and amyotrophic lateral sclerosis (ALS), which are characterized by protein aggregation and reduced expression of the protein quality-control machinery (Homma et al. 2007; Santos and Saraiva 2004). Lowered HSF1 has also been reported in other heritable NDs, such as those related to polyglutamine expansions (discussed below and in the section Implication of HSF1 in HD). The causes of HSF1 depletion during neurodegeneration are not well understood and may differ between different NDs. Nevertheless, numerous studies conducted in different animal models of NDs imply that increasing the levels or activity of HSF1 has therapeutic potential (Neef et al. 2011). In this book chapter, we will briefly discuss the role of HSF1 in different NDs with particular emphasis on the advances made in HD.

AD is a common age-associated neurodegenerative disease most often caused by extracellular depositions of amyloid-β, a neurotoxic peptide produced by the amyloid-β precursor protein proteolysis, leading to neuronal death (Mavroudis et al. 2010). Increasing reports show that intracellular levels of HSF1 are essential to maintain neuronal survival in AD. A study conducted in plasma neural-derived exosomes from patients with AD showed a remarkable reduction in the levels of HSF1 compared with unaffected individuals (Goetzl et al. 2015). There was also a reduction in the levels of HSF1 in the cerebellum of an AD rat model (Jiang et al. 2013). Notably, several studies have shown that overexpression of HSF1 results in an increased number of Purkinje cells in the cerebellum, the numbers of which are reduced in patients with AD and mouse models, lowering amyloid-β levels and improving cognitive deficits (Jiang et al. 2013; Khalsa 2015; Kozuki et al. 2011; Lee et al. 2014; Pierce et al. 2013). In line with the beneficial effects of increased HSF1 levels on neuronal survival, boosting HSF1 activity provides synaptic protection in AD. Pharmacological activation of HSF1 by using Hsp90 inhibitors led to the upregulation of Hsp70 and Hsp25 and improved synaptic integrity and memory consolidation in AD mouse models (Chen et al. 2014; Wang et al. 2017). Despite the lack of evidence as to whether the

decrease of HSF1 in AD is due to a pathological degradation, it is essential to note that increased CK2 has been reported in AD mouse models and patients with AD, contributing to the inflammatory phenotype characteristic of AD (Masliah et al. 1992; Perez et al. 2011; Rosenberger et al. 2016). However, the connection between CK2, HSF1, and inflammation in AD has yet to be explored.

PD is characterized by α-synuclein aggregation and an age-dependent loss of dopaminergic neurons in the midbrain (Jellinger 2014). In PD, reports have shown low levels of HSF1 in both mouse models and patients (Kim et al. 2016). Kim et al. showed that α-synuclein accumulation enhanced HSF1 poly-ubiquitination and degradation by elevated ubiquitin E3 ligase neuronal precursor cell-expressed developmentally downregulated 4 (NEDD4) expression. Notably, the authors found that acetylation at Lys80 within the DBD of HSF1 makes it more accessible for NEDD4-mediated ubiquitination (Kim et al. 2016). It is unknown whether phosphorylation contributes to NEDD4-mediated HSF1 degradation in PD. However, several kinases induce HSF1 phosphorylation, such as CK2 in PD (Lee et al. 2004a; Mavroudis et al. 2010). Therefore, it is tentative to speculate that phosphorylation events may control HSF1 degradation in PD, as it happens in HD (Gomez-Pastor et al. 2017; Soncin et al. 2003). While the degradation mechanism of HSF1 in PD is not fully characterized, its therapeutic potential has been demonstrated by studies in which a constitutive active form of HSF1 (caHSF1) is expressed in a human cellular model of PD (Liangliang et al. 2010). In this study, caHSF1 reduced α-synuclein aggregation and toxicity by inducing the expression of Hsp70. As proof of concept, direct overexpression of Hsp70 in a *Drosophila* model of PD inhibited α-synuclein induced neurodegeneration (Auluck et al. 2002). Recently, a new pharmacological activator of HSF1 (echinochrome derivative U-133) administered to a rat model of PD showed increased levels of Hsp70 and neuroprotective effects, including decreased microglia activation, a-synuclein aggregation, and improved motor behavior (Ekimova et al. 2018).

ALS is characterized by progressive dysfunction and death of motor neurons in the brain and spinal cord. Mutations in several genes can cause familial ALS and contribute to the development of sporadic ALS. Mutations in the chromosome 9 open reading frame 72 (C9orf72) gene account for approximately 40% of familial ALS; superoxide dismutase (SOD1) gene mutations cause approximately 20% of familial ALS. TAR DNA binding protein (TARDBP) (also known as TDP-43) and the RNA binding protein fused in sarcoma/translocated in liposarcoma (FUS/TLS) mutations each account for about 5% of cases. Increased microtubule-associated protein Tau has also been linked to ALS (Schreiber et al. 2018). The depletion of HSF1 in ALS significantly contributes to increased oxidative stress and aggregation of TDP-43 (Batulan et al. 2003; Chen et al. 2016). In the cell model of ALS, HSF1-induced TDP-43 clearance is partly mediated by Hsp70 and its co-chaperone DNAJB2a (Jung et al. 2013). HSF1 also regulates taurine transporter (TauT) levels under oxidative stress conditions, acting as an antioxidant to protect motor neurons (Jung et al. 2013). These studies suggest that HSF1 partially protects motor neurons by compensating for constitutive oxidative stress, which is thought to be a key mechanism contributing to ALS's pathogenesis.

Polyglutamine (polyQ) diseases are hereditary degenerative disorders characterized by the aberrant expansion of a CAG repeat in a specific gene, resulting in misfolding and aggregation of the disease-causing protein (La Spada and Taylor 2010). Multiple lines of evidence demonstrated that HSF1 and HSF1-dependent pathways strongly influence the pathogenesis of polyQ diseases. These studies are discussed in detail in the section Implication of HSF1 in HD. Understanding the specific roles of HSF1 in HD and other NDs may help develop new therapeutic strategies to increase the levels of HSF1 and prevent neurodegeneration across multiple NDs.

6 Protein Aggregation in HD

HD is a heritable neurodegenerative disease caused by a CAG trinucleotide (code for glutamine) repeat expansion within exon 1 of the HTT gene (MacDonald et al. 1993). The disease arises when the polyQ tract exceeds approximately 37 CAG repeats (Bates et al. 2015; Novak and Tabrizi 2010). The disease occurs in all populations but is most common in individuals of European ancestry, and it has an overall prevalence estimated to be 1 in every 10,000 individuals (Evans et al. 2013; Fisher and Hayden 2014; McColgan and Tabrizi 2018). Characteristic symptoms include progressive motor dysfunction (chorea, dystonia, bradykinesia, and incoordination), psychiatric disturbances (depression, obsessive-compulsive disorders, and anxiety) and cognitive decline (distractibility, impulsivity, and difficulty in multitasking) (Group 1996; Kieburtz et al. 2001; Novak and Tabrizi 2010). Other symptoms that accompany those mentioned above are weight loss and muscle wasting, metabolic dysfunction, and endocrine disturbance (Novak and Tabrizi 2010; Ross and Tabrizi 2011). Research has shown that such clinical aspects come from progressive and massive loss of neurons, predominantly GABAergic medium-sized spiny neurons (MSNs) located in the striatum. A brain region that controls movement and some forms of cognition (Albin et al. 1992; Deng et al. 2004; Ferrante et al. 1991; Ross and Tabrizi 2011; Rubinsztein 2003; Waldvogel et al. 2015). However, neurodegeneration in other brain regions, including cortex, thalamus, and hippocampus, is also observed as the disease progresses (Cepeda et al. 2007; Puigdellivol et al. 2016; Sieradzan and Mann 2001). The disease's symptoms usually begin in the adult-onset (around age 34–40 years with 15–20 years of progression). However, when the length of the CAG expansion exceeds about >60, it manifests before age 20 years (Juvenile HD) and accounts for 5–10% of all HD cases (Chen et al. 2001; Gusella and MacDonald 2000; Morley et al. 2002; Novak and Tabrizi 2010; Rubinsztein 2003). Despite numerous studies in the past two decades that have been addressing the importance of mutant HTT (mHTT) protein aggregation and MSN degeneration in HD pathology, very little is known about the exact molecular mechanisms by which mHTT induces neuronal death. There are several proposed pathophysiological pathways in this regard, many of which are associated with protein quality control impairment. In this chapter, we will discuss those pathways in which HSF1 may play a key role.

6.1 Structure and Function of HTT

The HTT gene encodes a large ~350 kDa widely expressed protein composed of multiple domains (Fig. 6) that control conformation, protein localization, and function (reviewed in (Jimenez-Sanchez et al. 2017)). PolyQ expansion induces conformational changes in HTT, affecting structural aspects of different regions or the protein proteolytic cleavage, unfolding, and aggregation (Almeida et al. 2013). While HTT is considered a cytoplasmic protein, it can partially accumulate in the nucleus, which is enhanced by the polyQ expansion and is believed to aggravate the disease. The highly conserved domain N17 (17-amino acid-long N-terminus) can modulate nuclear localization and mHTT toxicity (Desmond et al. 2012). N17 interacts with the nuclear pore protein called translocated promoter region (TPR) that is involved in nuclear export, facilitating the shuttling of HTT from the nucleus to the cytoplasm (Cornett et al. 2005). PolyQ expansions decrease this interaction and increase the nuclear accumulation of HTT (Cornett et al. 2005). The N17 is also subject to several PTMs, including sumoylation (Steffan et al. 2004), phosphorylation (Aiken et al. 2009; Thompson et al. 2009), acetylation (Thompson et al. 2009), and ubiquitination that control interactions between N17 and other proteins (Atwal et al. 2007; Graham et al. 2006; Kalchman et al. 1996; Maiuri et al. 2013; Steffan et al. 2004; Thompson et al. 2009; Wellington et al. 2002). The polyQ tract starts right after the N17, and it is composed of a series of CAG repeats interrupted by a CAA codon (also codes for glutamine) as follows (CAG)n-CAA-CAG (where $n \leq 36$ repeats in

Fig. 6 Diagram of human wild-type HTT relative to its known domains and post-translational modifications. HTT is composed of different domains; N17 (containing the first 17 amino acids of the protein), polyQ tract (whose expansion is responsible for HD), polyP repeats, and five helical clusters of HEAT repeats. Several PTMs (e.g., acetylation [Ac, pink], phosphorylation [P, orange], sumoylation [S, green], and ubiquitination [Ub, blue]) alter HTT's cell biology and toxic properties. Within the N17 region, we find (P1) P-Ser13 and P-Ser16, (Ac1) Ac-Lys9, S-Lys6, 9 and 13, and (S1) S-Lys9. Other PTMs can also be detected along with the protein (P2) P-Ser116, (P3) Ser-419, 421, 434, 533, 535, and 536, (P4) P-Ser1181 and 1,201, (P5) P-Ser2076, P(6) P-Ser2653 and 2,657, (Ac2) Ac-Lys178 and 236, (Ac3) Ac-Lys 345, (Ac4) Ac-Lys444, and (S2) S-Lys444. For a detailed list of all the PTMs identified in vivo and in vitro, see (Arbez et al. 2017). The corresponding amino acid sequence from exon 1 is shown in blue for the N17, in purple for the polyQ repeat, and in green for the polyP-rich region. Sequences were obtained from the NCBI protein database (Human: NP_002102.4)

unaffected individuals). There is an inverse correlation between the polyQ tract length and the age of onset (AOO) (Langbehn et al. 2010). However, there is a lot of variability in the AOO that could not be explained by considering the number of polyQ. Two recent studies have shown that the number of the CAG uninterrupted track rather than the number of polyQ determines HD onset timing (Wright et al. 2019). Following the polyQ tract is a polyproline (polyP)-rich region that consists of 10–11 proline and functions in stabilizing polyQ conformation by forming proline-proline helixes (Bhattacharyya et al. 2006; Kim et al. 2009). These domains are followed by tandem arrays of a repeat called HEAT, which is named for the following four functionally characterized proteins: HTT, elongation factor 3 (EF3), the regulatory A subunit (65 kDa) of protein phosphatase 2A (PP2A), and target of rapamycin 1 (TORl). They form rod-like helical structures and serve as a scaffold for many protein interactions (Andrade and Bork 1995; Saudou and Humbert 2016). Recently, a nuclear localization sequence (NLS) has been described between amino acids 174 and 207, preceding the first HEAT domain, allowing the interaction with KARYOPHERIN β2. This protein mediates the nuclear import of proteins (Desmond et al. 2012). The authors showed that polyQ expansion decreased the interaction between the NLS containing region and karyopherin β2, increasing mHTT nuclear accumulation. A nuclear export signal (NES) can also be found in the C-terminus of HTT (Xia et al. 2003). Truant and colleagues have demonstrated that the C-terminus region's proteolytic cleavage occurs during HD and proposes that lack of the C-terminus containing NES facilitates the nuclear accumulation of mHTT and pathogenesis (Xia et al. 2003).

Another factor that contributes to HD pathogenesis is CAG repeat somatic instability. Meaning that the CAG track undergoes progressive length increases over time in somatic tissues, particularly in HD's most affected brain regions. Prior research demonstrated that CAG somatic instability could account for the increased susceptibility of MSNs to mHTT due to cell-type-specific transcriptional programs (Gonitel et al. 2008; Goula et al. 2012; Kennedy et al. 2003;

Lee et al. 2011; Shelbourne et al. 2007). It is known that CAG length variation is tissue-dependent, and it is enhanced in the striatum of HD mouse models and HD patients. A hypothesis for this phenomenon is the tissue-specific positioning of the RNA pol II at the HTT locus, which is enhanced in the striatum (Goula et al. 2012). Pharmacological suppression of CAG instability in the HdhQ150 mouse improved neuropathology and demonstrated the role of somatic instability is pathogenesis (Budworth et al. 2015; Kovtun et al. 2007; Massey and Jones 2018). Also, several mismatch repair genes, including MSH3, influence somatic instability of CAG repeats and are considered critical genetic modifiers for the disease (Flower et al. 2019). Recently, the Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium demonstrated that the uninterrupted CAG repeat is a propensity for length instability leading to its somatic expansion (Lee et al. 2019). Other aspects contributing to the HD pathology include HTT transcriptional dysregulation and HTT mRNA abnormal splicing, two topics recently discussed in (Thomson and Leavitt 2018).

HTT is an essential protein required for normal development since the ablation of Htt in mice resulted in embryonic death (Zeitlin et al. 1995). However, the exact function of HTT is not known yet. There is an expression of HTT throughout the body, but it is highly active in the CNS, suggesting a potential role in brain physiology. Gain-of-function effects of mHTT have been proposed as the primary driver for neurodegeneration in HD. However, recent studies proposed an alternative hypothesis suggesting that loss-of-function may be at the forefront of the pathogenesis (reviewed in (Cattaneo 2003)). Studies using conditional deletion of HTT in mice's forebrain resulted in neurodegeneration, demonstrating that HTT is necessary for neuronal function and survival. A loss-of-function mechanism may contribute to HD pathogenesis (Dragatsis et al. 2000). In support of this study, McKinstry and colleagues demonstrated that silencing HTT in the developing mouse cortex was viable but resulted in alterations in cortical and striatal synaptic connectivity similarly to those deficits observed in mHTT expressing mice (McKinstry et al. 2014). Other studies have also shown that HTT plays a crucial role in neurogenesis by maintaining the lineage potential of primitive neural stem cells during neural induction and synapse formation (Nguyen et al. 2013; Sun et al. 2001). Additionally, HTT has been related to protein scaffolding, vesicular and organelle trafficking, and transcription regulation (Benn et al. 2008; Caviston et al. 2007; Gunawardena et al. 2003; Lee et al. 2004b; Li et al. 2001; Orr et al. 2008; Parker et al. 2001; Rong et al. 2006; Zuccato et al. 2001). While it is still unclear the direct role of HTT in all these processes, it seems evident that alteration in the structure and conformation of HTT can alter many different pathways that complicate the study of HD and difficult the development of effective therapeutic strategies.

Accumulation and aggregation of mHTT are positively associated with mitochondrial dysfunction, which is critical in promoting MSNs degeneration and death in HD. The mHTT disrupts mitochondria by interacting with several mitochondrial proteins and regulators. Consequently, the outcome of mitochondrial perturbation is ATP deficiency and increased reactive oxygen species (ROS) production. Both factors contribute to the exacerbation of mitochondrial damage and mHTT aggregation. Research has shown increased mitochondrial fragmentation in cellular and mouse models of HD and the brain of patients with HD (Cherubini and Gines 2017). Mitochondrial fragmentation is related to the abnormal interaction between mHTT with the central regulator of protein fission and dynamin-related protein 1 (DRP-1), resulting in DRP-1 dysfunction (Cherubini and Gines 2017). The mHTT also disrupts retrograde and anterograde mitochondrial trafficking along axons, resulting in a reduced transport of mitochondria to synapses with high energy demands and contributing to synaptic dysfunction (Orr et al. 2008). Also, mHTT interacts with TIM23, a component of the mitochondrial inner membrane translocase, altering mitochondrial protein import, and leading to respiratory dysfunction and neuronal cell death (Yano et al. 2014). Mitochondria dysfunction is also caused by decreased transcription of

nuclear-coded mitochondrial genes such as peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), a transcription coactivator that stimulates energy metabolism (Costa and Scorrano 2012; Cui et al. 2006; McConoughey et al. 2010; Weydt et al. 2006). One of the main pathways involved in the downregulation of PGC-1α in HD is the CREB/TAF4 signaling pathway, which is altered in the presence of mHTT (Cui et al. 2006). Very recently, Intihar et al. demonstrated that HSF1 also regulates the expression of PGC-1α in striatal like-cells, and deficits in HSF1 contribute to the downregulation of PGC-1α expression observed in HD (Intihar et al. 2019). The contribution of HSF1 to mitochondrial dysfunction in HD is discussed in the section HSF1 as a *Potential Regulator of PolyQ-Dependent Mitochondrial Dysfunction*.

6.2 HSR and Other Protein Quality Control Systems in HD

Full-length mHTT and proteolytic cleaved fragments have the propensity to misfold and aggregate, forming insoluble inclusion bodies, a hallmark of HD (Bates 2003; Davies et al. 1997; DiFiglia et al. 1997). Aggregates arise elsewhere in the cell, including cytoplasm, nucleus, dendrites, and axon terminals (DiFiglia et al. 2007; Vonsattel 2008). The insoluble aggregates have been observed in in vitro cell models of HD, mouse models of HD, and HD patients (Davies et al. 1997; DiFiglia et al. 1997; Gray et al. 2008; Sahl et al. 2012). However, it remains under debate whether the aggregates are a byproduct of a cellular attempt to protect neurons from misfolded mHTT protein or are instead the cause of pathology. Unfortunately, discriminating between these two hypotheses and correlating the presence of aggregates with the onset of a phenotype is technically tricky since in many cases quantifying small polyQ oligomers is challenging. When successful, it does not inform about all the different structural conformers present in the system. Studies conducted by Yang and colleagues demonstrated that preformed polyQ aggregates are highly toxic when directed to the nucleus, establishing proof that aggregates represent species with toxic properties (Yang et al. 2002). The pharmacological intervention aimed at inhibiting aggregate formation has shown beneficial effects in a mouse model of HD (Sánchez et al. 2003; Tanaka et al. 2004). Therefore, studying the regulatory mechanisms that lead to enhanced aggregation in HD may lead to more effective therapeutic strategies that can ameliorate neuronal death.

Neurons are post-mitotic cells in constant need of protein quality control to ensure protein homeostasis and keep cells functional. The HSR is a mechanism to cope with proteotoxic stress by inducing the expression of molecular chaperones and other Hsp, and it constitutes the first line of defense against aggregation. Due to the stress-inducible nature of Hsp, it would be expected to observe increased levels of Hsp in response to the accumulation and aggregation of mHTT. However, several studies demonstrated that Hsp shows a progressive decrease in cellular and mouse models of HD and that depletion of Hsp contributes to disease pathogenesis (Chafekar and Duennwald 2012; Hay et al. 2004). Research has shown decreased Hsp expression in postmortem brain tissue from patients with HD (Gomez-Pastor et al. 2017; Hodges et al. 2006). Multiple proposed hypotheses aim to explain the depletion of Hsp in HD. Hay et al. suggested that changes in the levels of Hsp are due to their sequestration into aggregates, a hypothesis supported by other studies (Park et al. 2013; Seidel et al. 2016; Yamanaka et al. 2008), while Labbadia et al. showed Hsp expression impairment in HD due to altered chromatin structure of the Hsp promoters (Labbadia et al. 2011). Finally, Gomez-Pastor et al. demonstrated that abnormal degradation of HSF1 during HD pathogenesis likely contributes to the downregulation of Hsp (Gomez-Pastor et al. 2017). Recently, a fascinating study conducted by Neueder and colleagues exposing wild-type and HD mice (HdhQ150 and R6/2) to a heat shock treatment demonstrated that HD mice are unable to induce Hsp in affected tissues, revealing a disruption in the HSR in HD mice (Neueder et al. 2017).

Interestingly, recent global chaperone gene expression analysis in the adult mouse brain identified that the striatum shows intrinsically lower levels of Hsp compared to the cortex (Tebbenkamp and Borchelt 2010), which may contribute to the explanation of enhanced abrogation in the HSR in the striatum and the increased susceptibility of MSNs in the presence of mHTT.

The ubiquitin-proteasome system (UPS), an intracellular pathway for degrading unfolded and unnecessary proteins, also constitutes an essential defense mechanism against protein aggregation. The prominent presence of ubiquitin characterizes inclusion bodies in HD. Recent work using the CAG140Q knock-in mice demonstrated that the UPS activity is lower in the striatum than in other brain regions, which correlates with decreased ubiquitin-activating enzyme (UBE1) levels (Wade et al. 2014). Decreased UPS activity, together with the observation that mutations in the UPS components give rise to some neurodegenerative diseases, suggests that UPS impairment may contribute to HD (reviewed in (Ortega and Lucas 2014; Schipper-Krom et al. 2012)). Another route for degradation of dysfunctional or aggregated proteins is via autophagy, a lysosome-mediated degradation pathway, whose role in HD has been widely studied (reviewed in (Croce and Yamamoto 2019)). One example that demonstrates impairment in the autophagy pathway is the decreased expression of high-temperature requirement protein A2 (HTRA2/OMI), a positive regulator of autophagy (Li et al. 2010), in cultured striatal neurons and the striatum of patients with HD (Inagaki et al. 2008). Inagaki et al. proposed that HTRA2/OMI is relevant to the selective vulnerability of striatal neurons in HD. Also, Yamamoto and colleagues identified a new protein, autophagy linked FYVE (ALFY), that mediates selective macroautophagy of aggregated proteins and whose expression is essential for the clearance of HTT aggregates (Yamamoto and Simonsen 2011). Recent studies indicate that the macroautophagic machinery, comprised of a core group of autophagy-related proteins, such as ATG5, ATG7, and LC3, is compromised in HD (Croce and Yamamoto 2019; Filimonenko et al. 2010; Martinez-Vicente et al. 2010). These findings demonstrate that degradative systems responsible for HTT clearance are affected and contribute to the age-dependent accumulation of neuronal aggregates. Very recently, a study led by Li and colleagues implemented the use of a small-molecule-microarray-based screening to identify specific linkers between the autophagy protein LC3 and mHTT that promote cargo recognition and uptake of mHTT into the macroautophagy pathway for degradation (Li et al. 2019). Administration of these linkers to HD mouse models decreased HTT aggregates' load and ameliorated motor deficits associated with HD (Li et al. 2019). This study establishes a start point for developing new therapies that exploit the degradative properties of different protein quality control systems as a strategy to remove mHTT aggregates and alleviate neurodegeneration.

7 Implication of HSF1 in HD

7.1 HSF1 and Hsp Function in HD

As discussed earlier, the HSR facilitates the folding of proteins and maintains protein homeostasis by inducing the expression of a set of molecular chaperones and Hsp (Bjork and Sistonen 2010; Lindquist 1986; Morimoto 1998). Hsp is a family of proteins named by their molecular weight whose functions require ATP (Fink 1999; Wang and Spector 2001). Some of the most critical Hsp players in the HSR include Hsp40, Hsp60, Hsp70, Hsp90, Hsp100, and the small Hsp (De Maio and Vazquez 2013; Kampinga et al. 2009). Among them, Hsp70 and its co-chaperone Hsp40 are central Hsp in the HSR. They are involved in folding proteins correctly and preserving polypeptides in a soluble conformation by binding to misfolded disease proteins, thereby preventing them from generating toxic protein structures (Hartl and Hayer-Hartl 2002). Early studies conducted in yeast expressing polyQ showed that Hsp70 and Hsp40 could alter the formation of detergent-insoluble mHTT

aggregates to detergent-soluble amorphous structures (Muchowski et al. 2000). Additionally, immunolabeling and fluorescence resonance energy transfer (FRET) experiments showed that Hsp70 and Hsp40 directly bind to the N-terminus region of HTT within the inclusion bodies and interfere with the intramolecular rearrangement of HTT by modulating the interaction between HTT and other proteins (Hay et al. 2004; Jana et al. 2000; Schaffar et al. 2004). Atomic force microscopy has also revealed that Hsp70 and Hsp40 reduce the formation of spherical and annular structures of mHTT fragments, resulting in the partition of monomeric conformations of mHTT and acceleration of fibrillization (Wacker et al. 2004). Consequently, deletion of Hsp70 in the R6/2 HD mouse model increased mHTT inclusion bodies' size and exacerbated HD-related physiological and neuropathological features (Wacker et al. 2009). Furthermore, single overexpression of different DNAJ proteins (Hsp40 family members) has shown protective properties in different HD animal models (Bason et al. 2019; Gillis et al. 2013; Kakkar et al. 2016). These studies demonstrated the fundamental role of Hsp70/Hsp40 in preventing polyQ aggregation.

In yeast, Hsp70 also assists Hsp104, a member of the Hsp100 family with disaggregase activity, by binding to protein aggregates and recruiting Hsp104 (Acebron et al. 2009; Okuda et al. 2015; Winkler et al. 2012). After Hsp104 is bound to protein aggregates, Hsp70 stimulates ATP-driven substrate-threading activity of Hsp104, leading to the extraction of single unfolded polypeptides from aggregates (Lum et al. 2004; Schlieker et al. 2004; Tessarz et al. 2008; Weibezahn et al. 2003; Zietkiewicz et al. 2004). Hsp110, the mammalian homolog of Hsp104, also interacts with and disassembles protein aggregates through its ATP-dependent activity (Gao et al. 2015; Garcia et al. 2017; Rampelt et al. 2012; Shorter 2011). In vitro and in vivo assays have recently shown that a trimeric chaperone complex formed by HSC70 (a member of the Hsp70 family), Hsp110, and DNAJB1 (Hsp40) completely suppresses fibrillization of HTT exon1 Q48, demonstrating the effective co-operation between the different Hsp (Scior et al. 2018). Hsp90 also plays a vital role in the triage of HTT. However, contrary to what would be expected, Hsp90 functions in promoting polyQ aggregation. Reports have shown that N-terminal fragments of HTT associate with Hsp90, and inhibition of Hsp90 increases ubiquitination and proteasomal degradation of mHTT by disrupting the Hsp90-mHTT complex (Baldo et al. 2012; He et al. 2017). Hsp90 diminishes the removal of mHTT aggregates by promoting the recruitment of a deubiquitinating enzyme (ubiquitin-specific protease 19 (USP19)) (He et al. 2017).

Several transcriptomic and proteomic studies conducted in different mouse models of HD and patients with HD have demonstrated that several Hsp are in low abundance in HD affected tissues (Ament et al. 2017; Hodges et al. 2006; Kumar et al. 2016; Langfelder et al. 2016). The thought is that this defect contributes to polyQ aggregation and neurodegeneration. The importance of restoring the levels of Hsp has been widely demonstrated in cell cultures, yeast, fly, and mouse models of HD in which overexpression of different Hsp including Hsp70, different members of the Hsp40 family as well as different small Hsp decreased mHTT aggregation and neuropathological features of HD (Bason et al. 2019; Carmichael et al. 2000; Fuchs et al. 2009; Gillis et al. 2013; Gunawardena et al. 2003; Jana et al. 2000; Kuo et al. 2013; Wacker et al. 2004, 1999a). There is an association between the decreased expression of Hsp and impairment in the HSR (Chafekar and Duennwald 2012; Cowan et al. 2003; Duennwald and Lindquist 2008; Maheshwari et al. 2014; Neueder et al. 2017; Riva et al. 2012), and different hypothesis have been proposed in this regard (discussed in HSR and Other Protein Quality Control Systems in HD section). Different studies suggested that Hsp depletion is caused by their sequestration into aggregates (Park et al. 2013; Seidel et al. 2016; Yamanaka et al. 2008), while Labbadia et al. proposed that impaired Hsp expression in HD occurs at the level of transcription due to hypoacetylation of histone H4 at Hsp promoters altering nucleosome landscape and chromatin architecture (Labbadia et al. 2011). However, these studies did not fully explain how Hsp

promoters are preferentially hypoacetylated over other HD gene promoters.

The transcriptional regulation of the HSR is primarily controlled by HSF1 (Parsell and Lindquist 1993; Wu 1995). The importance of HSF1 is demonstrated by the high susceptibility to heat-induced apoptosis in Hsf1-null fibroblasts (McMillan et al. 1998) and the failure to respond to thermal insults in Hsf1-null mice (Neueder et al. 2017; Xiao et al. 1999), whose defects are attributed to the improper induction of HSF1-induced Hsp. The fundamental role of HSF1 in HD was demonstrated by Hayashida and colleagues when they showed increased polyQ aggregation and shortened lifespan in a transgenic mouse model of HD (R6/2) lacking Hsf1 (Hayashida et al. 2010). Additionally, overexpression of a caHSF1 in the same mouse model enhanced Hsp expression, inhibited polyQ aggregation, and ameliorated HD-like symptoms (Fujimoto et al. 2005; Rimoldi et al. 2001). Other authors obtained similar results in *C. elegans*, *Drosophila*, and mammalian cells expressing polyQ (Homma et al. 2007; Hsu et al. 2003; Morley and Morimoto 2004), supporting the importance of HSF1 in HD. acknoHSF2 also plays an important role in polyQ aggregation since lack of HSF2 enhanced mHTT aggregation and shortened the lifespan of R6/2 mice (Shinkawa et al. 2011). Although the exact role of HSF2 in HD has not been fully characterized, it is possible that the defects observed in Hsf2 null mice are associated with an alteration in the ratio of HSF1-HSF2 heterotrimers and the impact on HSF1 activation.

Early studies conducted by Chafekar and Duennwald in immortalized striatal cells derived from wild-type mice expressing full-length HTT-Q7 (STHdhQ7) and knock-in HD mice expressing HTT-Q111 (STHdhQ111; HD cells) demonstrated a significant reduction in HSF1 in HD cells. HSF1 depletion leads to severe impairments when cells are exposed to heat shock conditions (Chafekar and Duennwald 2012). In the study, the authors demonstrated that both nuclear translocation and trimerization of HSF1 were significantly lower in STHdhQ111 cells than STHdhQ7, particularly after heat shock, presumably due to the lowered levels of HSF1 observed in the HD cells. Such deficits correlated with reduced expression of several Hsp upon HS in HD, a phenomenon widely observed in other studies (Chafekar and Duennwald 2012; Duennwald and Lindquist 2008; Maheshwari et al. 2014; Neueder et al. 2017). The authors also demonstrated a significant reduction of HSF1 levels, both mRNA and protein, in the striatum of STHdhQ111 knock-in mice compared to wild-type mice. As with the study above, studies conducted in R6/2 and zQ175 HD mice showed an age-dependent decrease in HSF1 levels in differentially affected brain regions (Gomez-Pastor et al. 2017; Maheshwari et al. 2014). HSF1 ChIP-seq in STHdhQ111 and STHdhQ7 cells under control (33 °C) or HS (42 °C) also showed a marked reduction in HSF1 DNA binding to its target genes in STHdhQ111 cells in both 33 and 42 °C compared to STHdhQ7 cells (Riva et al. 2012). Recently, studies conducted by Neueder et al. in which both R6/2 and CAG-140 HD mice were exposed to HS in vivo showed a significant impairment in the HSR, in which many affected genes were HSF1-dependent (Neueder et al. 2017). Further comparisons between HD and Hsf1 null mice transcriptomes in the absence of HS will be necessary to establish the extent to which HSF1 degradation contributes to large transcriptional changes in HD.

Very recently, Gomez-Pastor et al. demonstrated the existence of a pathological HSF1 degradation pathway in the presence of polyQ and suggested this process as a potential driving force for the HSR impairment in HD (Gomez-Pastor et al. 2017). The authors demonstrated that the presence of polyQ enhanced the expression of two proteins, protein kinase CK2α' and the E3 ligase FBXW7, which sequentially phosphorylated and ubiquitylated HSF1 and signaled the protein for proteasomal degradation. The authors showed that CK2α' mediated phosphorylation of Ser303/ 307 was a prerequisite for FBXW7-dependent ubiquitylation and degradation. Abrogation of HSF1 phosphorylation in vitro by either genetic mutation of the Ser303 into Ala and genetic and pharmacological

inhibition of CK2α' resulted in increased levels of HSF1 and Hsp70 and Hsp25 expression and decreased polyQ aggregation. As proof of concept, the authors generated a zQ175 HD mouse lacking one allele of the CK2α' kinase and demonstrated increased levels of HSF1 and Hsp, decreased polyQ aggregation in the striatum, and improved HD-like phenotypes such as amelioration of synaptic deficits and decreased weight loss (Gomez-Pastor et al. 2017). These studies proposed CK2α' as a potential therapeutic strategy to prevent HSF1 degradation in HD, enhance Hsp expression, and ameliorate protein aggregation. These and other studies have developed different therapeutic strategies aimed at activating HSF1 to enhance the levels of multiple Hsp simultaneously and ameliorate protein aggregation and neurodegeneration (Neef et al. 2011) and discussed in HSF1 as a Therapeutic Target in HD and Other PolyQ Diseases section.

7.2 Crosstalk Between HSF1 and the UPS: Implications in HD

When there is a failure in the correct folding of abnormal proteins, they can be targeted by the UPS for degradation or the lysosome-mediated autophagy pathway. In conjunction with the HSR, these systems ensure protein homeostasis and prevent the accumulation of toxic peptides (Hipp et al. 2012, 2019). However, eukaryotic proteasomes cannot digest polyQ sequences longer than 25Q residues (Venkatraman et al. 2004). Typically, polyQ diseases like HD possess polyQ sequences from 37-300Qs, exceeding standard proteasome products' length and interfering with proteasome function. Inclusion bodies in HD contain ubiquitin and components of the proteasome (20S core proteasome, 19S regulatory complex, and 11S proteasome-activating complex) whose levels increase in an age-dependent manner (Davies et al. 1997; DiFiglia et al. 1997; Waelter et al. 2001). These observations suggest an age-dependent failure of the UPS to degrade polyQ (Sherman and Goldberg 2001). Also, the continued accumulation of these polyQ inclusions may impact the folding of other proteins exceeding the proteasome's capacity and eventually reduce the cell's ability to degrade other proteins (Bence et al. 2001).

Many investigators have connected dysregulation of the UPS and mHTT-induced toxicity in cellular models of HD (Bence et al. 2001; Bennett et al. 2005; Duennwald and Lindquist 2008; Hunter et al. 2007; Maynard et al. 2009), mouse models of HD (Bennett et al. 2007; Wang et al. 2008), and tissues from patients with HD (Bennett et al. 2007; Seo et al. 2004). The HSR and UPS pathways are closely interconnected. When there is a block in proteasome function by inhibitors such as MG132, abnormal proteins accumulate, and the expression of Hsp is enhanced (Bush et al. 1997; Lecomte et al. 2010; Mathew et al. 1998; Pirkkala et al. 2000). Also, damaged UPS is a potent stressor that stimulates HSR (Bush et al. 1997). Various studies indicated that the UPS network's impairment activates HSF1 and HSF2, which in turn elevates Hsp expression (Lecomte et al. 2010; Mathew et al. 1998; Pirkkala et al. 2000). UPS-mediated induction of Hsp70 facilitates the E3 ubiquitin ligase C-terminus of HSC70-interacting protein (CHIP)-dependent ubiquitylation and degradation of protein aggregates (Lackie et al. 2017). The role of CHIP in promoting mHTT ubiquitylation and suppression of mHTT aggregation and toxicity has been extensively studied in cells, flies, zebrafish, and mouse models of HD (Al-Ramahi et al. 2006; Jana et al. 2005; Miller et al. 2005). CHIP is confined to the cytoplasm in unstressed conditions, but it translocates to the nucleus in response to cellular stress (Dai et al. 2003). CHIP promotes HSF1 trimerization and transcriptional activation of HSF1 and is a requirement for protection against stress-induced apoptosis in murine fibroblasts. Lastly, CHIP leads to stable interactions between Hsp70 and activated forms of HSF1. The authors detected CHIP in DNA-bound HSF1-containing complexes that were transcriptionally activated by heat shock (Dai et al. 2003). CHIP exerts a central and unique role in tuning the response to stress at multiple levels by regulating protein quality control and transcriptional activation of stress response signaling via HSF1.

There is a broad acceptance that the UPS function is abrogated in HD, although the causes of such a problem are unclear. It is still under debate whether deficits in the UPS activity cause mHTT accumulation or rather are the consequence of polyQ aggregation. Considering the intricate relationship between HSF1, Hsp70, and the UPS and the fact that HSF1 degradation and Hsp70 expression are impaired during HD, we speculate that the HSR impairment may cause UPS dysfunction in HD. However, further studies are necessary to unravel the role of the UPS in HD since alternative studies have shown no impairment in this system (Bett et al. 2006; Bowman et al. 2005; Diaz-Hernandez et al. 2003; Maynard et al. 2009; Seo et al. 2008).

Recent studies have demonstrated the existence of a mammalian membrane-associated proteasome complex, specifically expressed in the nervous system, that modulates neuronal function by degrading intracellular proteins into extracellular peptides, which can stimulate neuronal signaling (Ramachandran and Margolis 2017). This study challenged the notion that proteasomes function primarily to maintain protein homeostasis. In a follow-up study, the authors indicated that this neuronal-specific 20S membrane proteasome complex (NMP) exclusively degrades a large fraction of ribosome-associated nascent polypeptides that are newly synthesized during neuronal stimulation (Ramachandran et al. 2018). Interestingly, this NMP-mediated degradation is independent of canonical ubiquitylation pathways. However, several aspects of these NMPs remain unknown, including their potential role in the UPS in neurons, whether there is an alteration in their function during HD, and the extent HSF1 influences the regulation of NMPs.

7.3 PolyQ-Induced Oxidative and Metabolic Stress: Convergence into HSF1

Cells possess antioxidant mechanisms responsible for the elimination of harmful byproducts generated during biological processes. However, the failure of these systems often results in oxidative stress and cellular cytotoxicity. Oxidative stress is the imbalance between ROS/reactive nitrogen species (RNS) generation and the biological antioxidant defense system. Accumulation of ROS/RNS leads to damage of proteins, DNA, and lipids and further damages tissues and organs. Many studies in both HD patients and experimental mouse models of HD have documented that oxidative stress is a critical player in HD neuropathology (Johri and Beal 2012; Paul and Snyder 2019). Studies conducted in the striatum of different mouse models of HD (R6/1 and R6/2) revealed the accumulation of ROS, alteration in nitric oxide synthase (NOS) and superoxide dismutase (SOD) activities (Deckel et al. 2002; Perez-Severiano et al. 2002; Santamaria et al. 2001; Tabrizi et al. 2000), and a decline of antioxidant molecules such as ascorbate and antioxidant vitamins (Rebec et al. 2002). Moreover, increased levels of 8-hydroxydeoxyguanosine (8-OHDG), reports have shown that a product of oxidative stress-derived DNA damage is present in the urine, plasma, samples from striatal microdialysis, and brain of R6/2 and BACHD mice (Browne and Beal 2006; Gray et al. 2008; Stack et al. 2008). Studies conducted in plasma and postmortem tissues from patients with HD have also shown increased global oxidative stress manifested by increased lipid peroxidation products (malondialdehyde and lipofuscin), reduction in the antioxidant molecules, and increased DNA damage and fragmentation (Browne et al. 1999; Butterworth et al. 1998; Chen et al. 2007; Hersch et al. 2006; Tunez et al. 2011). The latter correlated with CAG repeat length and instability (Massey and Jones 2018) (see Structure and function of HTT section for details). Biochemical and proteomic studies conducted in the cerebral cortex and the striatum of HD patients also revealed decreased glutathione (GSH), a potent intracellular redox buffer, and a substantial elevation of glutathione peroxidases (GPX1 and 6), peroxiredoxins (PRDX1,2, and 6), and manganese-containing SOD (MnSOD/SOD2) (Beal et al. 1992; Sorolla et al. 2008). Endogenous ROS mainly originates from mitochondria during the synthesis of ATP. There is a large amount of evidence showing that

mitochondrial dysfunction indeed plays a crucial role in polyQ-mediated oxidative stress and the pathogenesis of HD (Carmo et al. 2018b; Costa and Scorrano 2012; Damiano et al. 2010; Guedes-Dias et al. 2016; Lin and Beal 2006; Quintanilla and Johnson 2009). This topic is discussed in detail in the section HSF1 as a Potential Regulator of PolyQ-Dependent Mitochondrial Dysfunction.

HSF1 can sense and respond to oxidative stress by inducing the expression of several Hsp and other anti-apoptotic genes (Ahn and Thiele 2003; Kim et al. 2013; Raitt et al. 2000). Studies conducted by Ahn and Thiele using purified recombinant mammalian HSF1 and H2O2 demonstrated that HSF1 directly senses oxidative stress by forming a disulfide bond between two cysteine residues (C35 and C105) localized within the HSF1 DNA-binding domain (Ahn and Thiele 2003). C35-C105 disulfide bond formation is critical for HSF1 trimerization, nuclear accumulation, DNA binding, and target gene activation in the presence of H2O2 (Ahn and Thiele 2003). This process seems to be reversible since the addition of reducing agents such as DTT to an H2O2 activated-HSF1 trimer decreased binding to an Hsp70 HSE sequence. At the same time, removal of DTT by dialysis and re-exposure to H2O2 recovered HSF1 binding. Additional studies conducted in yeast showed that Hsf1 coordinates the expression of Hsp under oxidative stress conditions by interacting with the yeast oxidative stress response regulator Skn7 (Raitt et al. 2000). Interestingly, Skn7 contains a small polyQ at its C-terminus (Gutiérrez et al. 2017), which implies that polyQ dependent aggregation mechanisms may play a role in regulating the Hsf1-Skn7 mediated response to oxidative stress. While there are no human homologs described for Skn7, it seems to share sequence homology and function with the RHOA effector protein ROCK-I (Alberts et al. 1998), a modulator of dendritic spine morphogenesis upon Ca2+ signaling (Murakoshi et al. 2011). RHOA and ROCK-I mRNA and the induction of protein levels in HD human blood leukocytes and postmortem brain and R6/2 HD mouse brain tissue respond to oxidative stress conditions (Narayanan et al. 2016). Interestingly, studies conducted in cardiomyocytes showed that activation of RHOA negatively regulates the HSR via attenuation of the HSF1-HSE binding and significantly suppressed the proteotoxic stress-induced HSR (Meijering et al. 2015).

Upregulation of Hsp during oxidative stress is key to ensure proper protein folding and prevents further oxidative damage (Janowska et al. 2019). Rubinsztein and colleagues showed that Hsp27, an ATP-independent chaperone, has antioxidant effects on cells expressing mHTT and its overexpression decreased ROS and polyQ-mediated cell death. Surprisingly, the authors also showed that there was not an attribution of benefits exerted by Hsp27 to the suppression of polyQ aggregation but rather the amelioration of polyQ-mediated oxidative stress (Wyttenbach et al. 2002). Reports have shown that Hsp27 protects against oxidative stress through its ability to increase GSH levels and glucose-6-phosphate dehydrogenase activity, preventing the mitochondrial cytochrome-c release and maintaining optimal cellular detoxifying machinery (Paul et al. 2002; Preville et al. 1999). HSF1 plays a crucial role in regulating Hsp27 expression in HD (Gomez-Pastor et al. 2017). Both HSF1 depletion and subsequent downregulation of Hsp27 in HD can contribute to the damages caused by polyQ-induced oxidative stress (Gomez-Pastor et al. 2017). Interestingly, Hsp27 also modulates HSF1 transactivation activity by promoting conjugation of SUMO-2/3 at Lys298 on HSF1 (Brunet Simioni et al. 2009). These studies demonstrate how Hsp27 exerts a feedback inhibition of HSF1 transactivation and enlighten the strictly regulated interplay between HSF1, Hsp, and oxidative stress.

A critical transcription factor that regulates antioxidant proteins' expression and protects against oxidative damage is the nuclear factor E2-related factor 2 (NRF2). NRF2 activation mitigates multiple pathogenic processes involved in HD and other neurodegenerative disorders through upregulation of antioxidant defenses, inhibition of inflammation, improvement of mitochondrial function, and maintenance of protein homeostasis (Dinkova-Kostova et al. 2018). NRF2 has become an attractive therapeutic target

in neurodegeneration, and several small molecules activating NRF2 have shown protective effects in numerous models of neurodegenerative diseases. NRF2 have several common target genes with HSF1, including heme oxygenase 1 (HMOX1, also known as HSP32) (Maines and Ewing 1996; Prestera et al. 1995), HSP70 gene (Almeida et al. 2010), autophagy cargo protein sequestosome 1 (p62/SQSTM1) (Komatsu et al. 2010; Samarasinghe et al. 2014), and ATF3 (Dziunycz et al. 2014; Hoetzenecker et al. 2011). Recent studies conducted in MCF7 breast cancer cells have shown that NRF2 transcriptionally activates HSF1 under oxidative stress conditions, connecting these two critical regulators of cytoprotective mechanisms (Paul et al. 2018). While no studies have yet explored these two transcription factors' dual activities in HD, there is evidence that alteration of their expression levels and activities may affect HD pathogenesis (Dinkova-Kostova et al. 2018; Gomez-Pastor et al. 2017; Quinti et al. 2017).

Oxidative and metabolic stresses and mitochondrial dysfunction are interconnected HD processes (Lou et al. 2016). Proteomic analysis conducted in yeast revealed that cells challenged to menadione, a ROS generator, upregulated antioxidant enzymes, several Hsp, and the expression of metabolic enzymes in a Hsf1-dependent fashion (Kim et al. 2013). Additionally, overexpression of alphaB-crystallin (αB-crys) in astrocytes reversed HD related phenotypes and neuronal cell loss in BACHD mice by restoring antioxidant protection and glucose uptake in astrocytes (Oliveira et al. 2016). On the other hand, AMPK is another important sensor for cell survival by modulating energy homeostasis. Ju and colleagues showed that AMPK is activated in the brains of mice and patients with HD, suggesting that this abnormal activation may contribute to neuronal degeneration in HD (Ju et al. 2014). The authors showed that mHTT-induced ROS contributes to the activation of AMPK-α1 and subsequently facilitates neurotoxicity in STHdhQ109 cells and the striatum of R6/2 mice while AMPK inhibition reduced the level of oxidative stress (Ju et al. 2014). However, conflicting reports have shown the opposite indicating that activation of AMPK in HD protects from neuronal dysfunction and vulnerability (Vazquez-Manrique et al. 2016). Therefore, it is unclear to what extent AMPK activation can be considered a detrimental response. However, the fact that AMPK negatively regulates HSF1 activation via phosphorylation at Ser121 (Dai et al. 2015) points out the possibility that activation of AMPK-α1 could contribute to the impairment of the HSR in HD and therefore negatively contribute to pathology.

7.4 HSF1 as a Potential Regulator of PolyQ-Dependent Mitochondrial Dysfunction

7.4.1 Mitochondrial Dysfunction and Excitotoxicity

Mitochondria are distinct cellular organelles that control vital physiological processes such as energy production, lipid metabolism, and Ca2+ signaling. There is a strong association between mitochondrial function defects with different NDs, including HD (Wang et al. 2019). The overall manifestation of mitochondrial impairment in HD appears in the abnormal mitochondrial morphology (Jin et al. 2013a; Kim et al. 2010a, b; Panov et al. 2002; Squitieri et al. 2006), alteration in the components of the electron transport chain (Browne et al. 1997; Gu et al. 1996; Guidetti et al. 2001; Sawa et al. 1999), reduction in cellular glucose uptake and enzymes in the oxidative metabolism (Antonini et al. 1996; Butterworth et al. 1985; Dubinsky 2017; Feigin et al. 2001; Sorolla et al. 2008; Tabrizi et al. 1999), and increased mitochondrial DNA damage (Acevedo-Torres et al. 2009; Horton et al. 1995; Liu et al. 2008). Reports have shown that all these defects play an important role in promoting MSN degeneration (Carmo et al. 2018a; Costa and Scorrano 2012; Lin and Beal 2006; Quintanilla and Johnson 2009). Indeed, it has been proposed that mHTT-mediated mitochondrial abnormalities underlie the specific vulnerability of MSNs in HD since this type of neurons require a higher-energy demand compared to other cell types in the brain (Ferrante et al. 1991; Mitchell and Griffiths 2003;

Pickrell et al. 2011). This hypothesis is supported by additional studies in which administration of mitochondrial inhibitors in rodents (Beal et al. 1993; Borlongan et al. 1995; Brouillet et al. 1993) and non-human primates (Brouillet et al. 1995) produced selective striatal degeneration and behavioral defects evocative of HD (Brouillet et al. 1999; Brouillet et al. 2005).

The primary function of mitochondria is the generation of energy in the form of ATP. ATP is generated via oxidative phosphorylation through the action of the electron transport chain (ETC) in conjunction with the ATP synthase (Lenaz and Genova 2010). Several components of the ETC present altered levels in postmortem striatum and cortex of patients with HD and cell and mouse models of HD (Browne et al. 1997; Gu et al. 1996; Majumder et al. 2007; Quintanilla and Johnson 2009; Tabrizi et al. 1999; Tabrizi et al. 2000). Interestingly, lymphoblasts from patients with HD, but not from patients with ataxia type-1 (another polyQ disease), treated with toxins targeting different complexes of the ETC, showed increased mitochondrial depolarization and caspase 3-dependent apoptosis (Sawa et al. 1999). This study demonstrated the increased susceptibility of HD cells to mitochondrial dysfunction and mitochondrial-induced cell death. However, analyses conducted in pre-symptomatic patients with HD have not shown ETC abnormalities (Guidetti et al. 2001), suggesting that mitochondrial defects may be secondary to neurodegeneration.

The exact mechanism by which mHTT induces mitochondrial dysfunction is unclear, but several studies have linked these defects to alterations in Ca2+ buffering. The maintenance of mitochondrial Ca2+ levels is by the mitochondrial permeability transition pore (mPTP). When mitochondrial Ca2+ buffering capacity is overloaded, the mPTP opens and causes a decrease in mitochondrial membrane potential (MMP), uncoupling the oxidative phosphorylation and leading to cell death (Choo et al. 2004; Halestrap 2006; Krieger and Duchen 2002; Rasola et al. 2010). Alterations in Ca2+ buffering capacity and decreased threshold for mPTP opening are defects widely reported in HD (Brennan Jr. et al. 1985; Choo et al. 2004; Ciammola et al. 2006; Milakovic and Johnson 2005; Milakovic et al. 2006; Oliveira et al. 2006; Panov et al. 2002; Rockabrand et al. 2007; Squitieri et al. 2006). These defects are more significant in the striatum than in the rest of the brain (Gellerich et al. 2008). They are delayed in cyclosporin A and mPTP inhibitor (Milakovic and Johnson 2005). Additional studies conducted in mitochondria isolated from skeletal muscle from R6/2 mice have shown that reduced Ca2+ accumulation capacity and mPTP opening threshold are also responsible for energetic depression and muscle atrophy (Gizatullina et al. 2006). Further, immunocytochemistry and electron microscopy studies conducted in brain mitochondria obtained from YAC72 HD mice revealed a direct interaction between the N-terminal fragment of mHTT and the outer mitochondrial membrane (Choo et al. 2004; Jin et al. 2013b; Kim et al. 2010a, b; Panov et al. 2002; Rockabrand et al. 2007; Squitieri et al. 2006), suggesting a direct role of mHTT in the alteration of mPTP function.

Yan et al. initially reported that HSF1 plays a significant role in regulating mitochondrial activity (Yan et al. 2002). The authors showed that the heart of Hsf1-/- mice presented increased oxidative damage on a structural component of the mPTP (ANT1 protein), which resulted in decreased ANT1 catalytic activity and increased mPTP opening. Additional studies in oocytes and hepatocytes of Hsf1−/−mice showed mitochondrial functional deficits, ultrastructural abnormalities, and increased caspase-3 activation (Bierkamp et al. 2010; Canto 2017). Recent studies have connected HSF1 with increased mitochondrial membrane depolarization and decreased MMP observed in HD (Intihar et al. 2019). Intihar et al. showed that silencing Hsf1 in the wild-type striatal cell model STHdhQ7 resulted in decreased MMP compared to scramble conditions (Chafekar and Duennwald 2012; Cui et al. 2006; Gomez-Pastor et al. 2017; Intihar et al. 2019). More importantly, these HSF1-induced defects in STHhdQ7 cells recapitulated the MMP decrease observed in untreated STHhdQ111 HD cells (Chafekar and Duennwald 2012; Cui et al. 2006; Gomez-Pastor et al. 2017; Intihar et al. 2019). Due to the fact that HSF1 seems to regulate MMP and dramatically reduce its levels in HD

(Gomez-Pastor et al. 2017), it is reasonable to hypothesize that HSF1 dysfunction in MSNs could be at the forefront of the increased MSN mitochondrial susceptibility to polyQ.

Disrupted intracellular Ca2+ levels in neurons can be provoked by excessive glutamatergic signaling. Glutamate is the primary excitatory neurotransmitter in the CNS and has critical functions in controlling perception, reward circuitry, and cognition. In HD, glutamate release changes, glutamate uptake, and postsynaptic signaling converge into Ca2+ buffering dysregulation and promote mitochondrial energy failure and cell death. This phenomenon is known as excitotoxicity (Dong et al. 2009; Zhou et al. 2013). Different neuronal receptors respond to the extracellular levels of glutamate. However, ionotropic receptors such as N-methyl-D-aspartic acid receptor (NMDAR) and α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor (AMPAR) are the major players (Danysz and Parsons 2003). Reports have shown that mHTT disrupts glutamatergic transmission by reducing the levels of glial glutamate transporter 1 (GLT1) and therefore reducing astrocytic glutamate reuptake (Behrens et al. 2002; Estrada-Sanchez et al. 2009; Li et al. 2000; Lievens et al. 2001; Shin et al. 2005). Decreased GLT1 expression in HD leads to increased extracellular glutamate concentration, and excessive Ca2+ influx through the NMDARs, and increased NMDAR-mediated currents in the striatum from HD mice (Fan et al. 2007; Laforet et al. 2001; Milnerwood et al. 2010; Okamoto et al. 2009; Qiu et al. 2013; Song et al. 2003; Sun et al. 2001; Zeron et al. 2002). Interestingly, in silico analyses have revealed several putative HSE in the promoter region of both human and mouse GLT1 (Liu et al. 2011). Liu et al. showed an increase in GLT1 expression in NG108–15 cells (a hybrid mouse neuroblastoma-rat glioma cell line) exposed to heat shock. The authors also showed that administration of the neuroprotective drug riluzole increased the amount of HSF1 in NG108–15 cells by slowing HSF1 turnover and increasing the levels of GLT1 (Liu et al. 2011). Also, cells exposed to glutamate excitotoxic stress survived better in the presence of riluzole, indicating that increased HSF1 and GLT1 levels protect cells from excitotoxicity. Despite all the evidence discussed, it is still unknown whether depletion of HSF1 in the striatum of HD mice is responsible for GLT1 downregulation and glutamate excitotoxicity in HD (Chafekar and Duennwald 2012; Maheshwari et al. 2014).

7.5 Crosstalk Between HSF1 and Mitochondrial-Mediated Apoptotic Pathways

Mitochondria are a reservoir for pro-apoptotic factors and play a fundamental role in regulating cell death (Dumollard et al. 2009; Suzuki et al. 1999). Dysregulation of two major transcription factors, tumor suppressor p53 and PGC-1α, has been connected to mitochondrial-mediated apoptosis in HD. p53 is responsible for regulating pro-apoptotic genes such as BCL2-associated X (BAX) and p53 upregulated modulator of apoptosis (PUMA), and its activation triggers mitochondrial-dependent intrinsic apoptosis. There is an increase in p53 levels in cell and mouse models of HD and the striatum and cortex of patients with HD (Bae et al. 2005; Reynolds et al. 2018). Also, transcriptomic analysis in the striatum of an allelic series of HD knock-in mice demonstrated CAG length-dependent activation of p53 signaling pathways (Langfelder et al. 2016). Bae et al. also showed that p53 interacts with HTT, and there is an enhancement in such interaction in the presence of polyQ. It is still unknown how mHTT increases p53, although the authors hypothesized a dysregulation in p53 turnover. They also showed that genetic and pharmacological inhibition of p53 provided neuroprotection by altering transcription and improving mitochondrial function (Bae et al. 2005). However, the mechanism by which p53 inhibition mediated such beneficial effects in HD is unknown. Additional studies showed that mHTT increased phosphorylation of p53 on Ser46, a key PTMs involved in decoupling p53 from the apoptosis inhibitor iASPP, thereby inducing the expression of apoptotic target genes (Bae et al. 2005; Grison et al. 2011; Yu

et al. 2001). Alternative studies suggested p53 induces mitochondrial damage and necrosis by directly binding to DRP-1, a primary mitochondrial fission protein (Guo et al. 2013, 2014).

Reciprocal regulation between p53 and HSF1 has been reported in different contexts such as DNA damage and cancer (Jin et al. 2009; Logan et al. 2009; Oda et al. 2018), suggesting that the abnormal degradation of HSF1 may accelerate the harmful effects of p53 on mitochondrial dysfunction in HD. The primary mechanism responsible for keeping p53 levels under control depends on an E3 ligase MDM2, a gene regulated by p53 that promotes p53 ubiquitylation and degradation (Barak et al. 1993; Haupt et al. 1997; Momand et al. 1992). When MDM2 is inefficient or fails, an alternative degradation mechanism involving the small chaperone αB-crys and the E3 ligase FBX4 is activated (Jin et al. 2009). The αB-crys interacts with p53 and facilitates the recruitment of FBX4 (Watanabe et al. 2009). The accumulation of p53 in αB-crys−/− cells is due to the inability of p53 to interact with FBX4 (Jin et al. 2009). The transcriptional regulation of αB-crys expression is made by HSF1 (Gomez-Pastor et al. 2017), and its expression is downregulated in HD (Gomez-Pastor et al. 2017; Hodges et al. 2006). Consistent with this observation, Hsf1 deficient cells express reduced levels of αB-crys and accumulate p53 (Jin et al. 2009). Interestingly, p53 positively regulates the expression of FBXW7 (Kimura et al. 2003; Mao et al. 2004), an E3 ligase involved in the degradation of HSF1 and whose levels are increased in HD (Gomez-Pastor et al. 2017; Kourtis et al. 2015). Therefore, p53 and HSF1 may operate on a unified pathological pathway that controls mitochondrial function and neuronal integrity in HD (Fig. 7).

PGC-1α governs an additional mechanism essential for the regulation of mitochondrial function. PGC-1α is a transcription factor that regulates the expression of nuclear-encoded mitochondrial genes and participates in the regulation of mitochondrial biogenesis, ROS detoxification, and oxidative phosphorylation (Johri et al. 2013; Puigserver and Spiegelman 2003; Wu et al. 1999). Downregulation of PGC-1α has been reported in cell and mouse models of HD as well as in postmortem brain, muscle biopsies, and myoblast cultures from HD patients (Chafekar and Duennwald 2012; Cui et al. 2006; Gomez-Pastor et al. 2017; Intihar et al. 2019; Turner and Schapira 2010; Weydt et al. 2006). Along with a decrease in the expression of PGC-1α, there is also a decrease in the expression of several PGC-1α-dependent targets and MSN markers (Lucas et al. 2012; Weydt et al. 2006). The role of PGC-1α in HD is supported by several studies conducted in different mouse models. Ppargc1a (a gene encoding PGC-1α) null mice displayed similar defects to those observed in HD such as mitochondrial dysfunction, myelination deficits, degeneration of striatal neurons, white matter atrophy, and motor alterations (Cui et al. 2006; Leone et al. 2005; Lin et al. 2004; Lucas et al. 2012; Weydt et al. 2006; Xiang et al. 2011). Recent studies where PGC-1α was knocked out in MSNs showed that PGC-1α is necessary for MSN transcriptional homeostasis and function (McMeekin et al. 2018). Although the loss of PGC-1α in MSNs does not replicate an HD-like phenocopy, its target genes are altered in a CAG-length and age-dependent fashion, suggesting a potential role of PGC-1α in the selective vulnerability of MSNs in HD (McMeekin et al. 2018). In contrast, overexpression of Ppargc1a rescued HD neurological phenotypes and neurodegeneration and decreased mHTT aggregation (La Spada 2012; St-Pierre et al. 2006). Similarly, pharmacological activation of PGC-1α ameliorated both neuropathological features and HD phenotype in different mouse models of HD (Chandra et al. 2016; Chiang et al. 2010; Jin et al. 2013a; Johri et al. 2013).

Despite all the studies showing the importance of PGC-1α in HD, the mechanism responsible for PGC-1α downregulation is still unclear. Different studies have suggested that an impairment in the CREB/TAF4 signaling pathway in HD (Cui et al. 2006; Gines et al. 2003; Weydt et al. 2006) controls the expression of PGC-1α by binding to cAMP-response elements (CRE) present in the PGC-1α promoter (Fig. 7). Other studies indicated that increased extrasynaptic NMDAR

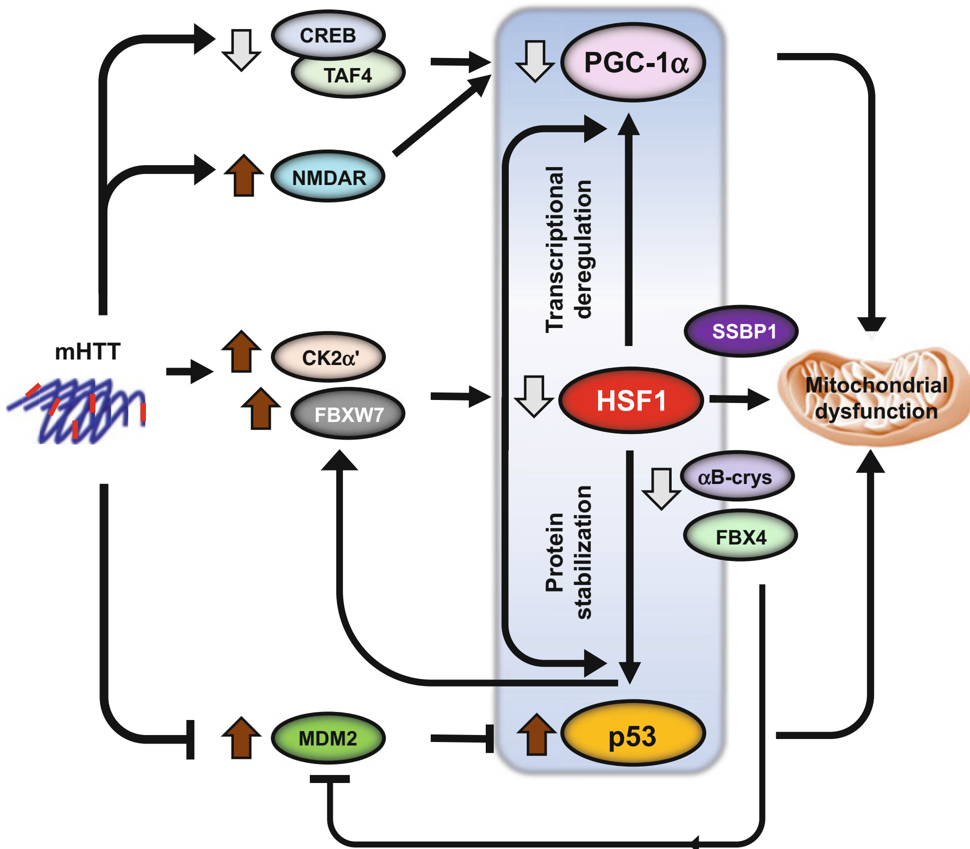


Fig. 7 Model for p53-HSF1-PGC-1α integrated responses in HD. Crosstalk between the transcription factors p53, HSF1, and PGC-1α in regulating transcription, protein homeostasis, mitochondrial function, and apoptosis. There are alterations in different pathways (CREB/TAF4, CK2α'/FBXW7, and MDM2) in the presence of mHTT, which independently leads to the deregulation of the levels and functions of all three transcription factors. However, HSF1 becomes a key player in the subsequent regulation of the levels of p53 and PGC-1α by directly regulating the transcription of PGC-1α and controlling p53 protein stability in HD. The potential role of p53 in regulating the HSF1 degradation pathway in HD would add a positive feedback loop into the p53-HSF1-PGC-1α axis, which triggers mitochondrial dysfunction and neuronal death. Reprinted and modified from "Mitochondrial Dysfunction in Huntington's Disease; Interplay Between HSF1, p53 and PGC-1α Transcription Factors" by Intihar et al. 2019, with permission from the original authors

activity causes PGC-1α depletion (Dickey et al. 2016). More recently, different studies showed that HSF1 directly binds to a non-canonical HSE present in the PGC-1α promoter and regulates its expression (Chafekar and Duennwald 2012; Cui et al. 2006; Gomez-Pastor et al. 2017; Intihar et al. 2019; Ma et al. 2015). Intihar et al. documented a reduction in HSF1 binding to PGC-1α promoter in STHdhQ111 cells compared to STHdhQ7 cells and that overexpression of HSF1 in STHdhQ111 cells restored PGC-1α expression and improved cell viability (Chafekar and Duennwald 2012; Cui et al. 2006; Gomez-Pastor et al. 2017; Intihar et al. 2019). Consistent with this view, increased HSF1 levels in the striatum of zQ175; CK2α' +/− mice enhanced the expression of PGC-1α and its target genes (Gomez-Pastor et al. 2017) and demonstrated an interconnection between HSF1 and PGC-1α in HD. An additional regulatory mechanism that can potentially explain PGC-1α downregulation in HD involves p53, which has

been shown to bind to PGC-1α promoter in neuroblastoma cells and regulates its expression (Aquilano et al. 2013). These studies indicate that HSF1, p53, and PGC-1α conform to an intricate pathway that can operate together in controlling mitochondrial function (Fig. 7). Future efforts should focus on elucidating the molecular mechanisms that directly link the interplay between HSF1, p53, and PGC-1α in HD.

7.6 Excitatory Synapse Regulation in HD; Connection Between HSF1 and Mitochondrial Dysfunction

The striatum receives inputs from both the cortex and thalamus and coordinates these inputs to regulate movement and cognition. Among the different chemical synapses that control striatum function, glutamatergic excitatory synapses play a fundamental role. Several lines of evidence suggested that early clinical manifestations of HD may arise from excitatory synaptic dysfunction, including progressive MSNs axonal degeneration (Albin et al. 1992), alteration of neurite outgrowth and maintenance (Trushina et al. 2004), disruption of synaptic gene expression (Luthi-Carter et al. 2003; Manczak and Reddy 2015; Rozas et al. 2010; Smith et al. 2014), collapse in axonal transport of organelles and neurotrophic factors (Gunawardena et al. 2003; McGuire et al. 2006; Trushina et al. 2004), and an imbalance between excitatory and inhibitory systems (Benn et al. 2007; Twelvetrees et al. 2010). Although the exact function of HTT is not known, McKinstry et al. demonstrated the requirement of HTT for normal excitatory synapse development in both cortical and striatal circuits (McKinstry et al. 2014). Several additional studies have shown the specific deterioration in the cortico-striatal circuitry in HD and proposed that these defects may be responsible for striatum degeneration (Bunner and Rebec 2016; Cepeda et al. 2007; Dogan et al. 2015; Rebec 2018). However, other studies in YAC128 and zQ175 HD mouse models have suggested an early dysfunction in the thalamo-striatal circuit, which occurs before an overt HD phenotype (Gomez-Pastor et al. 2017; Kolodziejczyk and Raymond 2016). Interestingly, Gomez-Pastor et al. showed that manipulation of the HSF1 degradation pathway in the zQ175 mice by removing one allele of CK2α' resulted in increased HSF1 levels and restoration of the thalamo-striatal synapse connectivity (Gomez-Pastor et al. 2017). Unfortunately, the mechanism by which HSF1 regulates this specific circuitry in HD is still unknown.

Previous studies have demonstrated that HSF1 plays a vital role in the regulation of synapse function and formation. Hsf1 deficient mice showed a significant decrease in the number of dendritic spines and dendrite length in the hippocampus, downregulation of polysialylated-neural cell adhesion molecule (PSA-NCAM) required for synapse formation. They decreased expression of the postsynaptic protein PSD-95 needed to anchor NMDARs and AMPARs to the postsynaptic membrane (Uchida et al. 2011). Also, the authors showed that overexpression of a caHSF1 in Hsf1−/−mice rescued PSD-95 expression and improved synapse function (Uchida et al. 2011). Other studies that support the role of HSF1 in the regulation of synaptic genes were conducted in cells and mouse models of AD treated with the Hsp90 inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG) (Chen et al. 2014). In this study, the authors showed that 17-AAG treatment enhanced HSF1 activity and increased the expression of synapsin I and synaptophysin (presynaptic proteins regulating vesicle cycling) and PSD-95, leading to the prevention of amyloid-β-induced memory loss (Chen et al. 2014). Also, the identity of several HSE in different synaptic genes, including DLG4 (encoding PSD-95) and DLG1 (encoding SAP97) (Chen et al. 2014; Ting et al. 2011). These studies suggest that HSF1 plays a direct role in the structural and functional integrity of synaptic connections underpinning learning and memory. However, since the role of HSF1 in synaptic gene expression impairment in HD has not been established yet, other hypotheses may be possible (Fig. 8).

Reports have shown that chaperones exert protective functions at the synapse level, and the sole

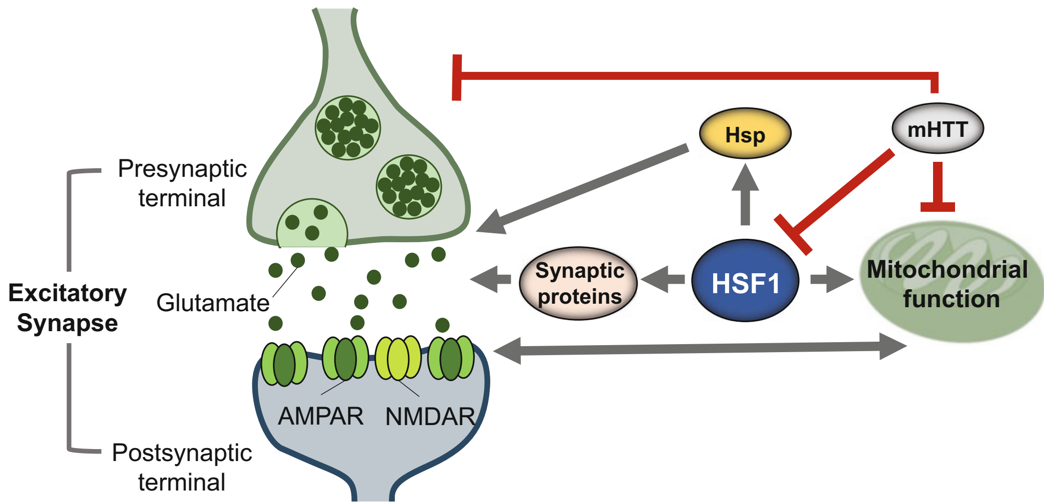


Fig. 8 Working model for the connection between HSF1, mitochondrial impairment, and synapse dysfunction in HD. mHTT alters excitatory synaptic transmission and mitochondrial function by altering Ca2+ buffering capacity and PGC-1α and p53 levels. mHTT is also responsible for promoting HSF1 degradation, which results in downregulation of Hsp and synaptic proteins. The effects caused by HSF1 depletion then further disrupt glutamate release and uptake in neurons, resulting in excitotoxicity. (Reprinted from "Excitatory synapse impairment and mitochondrial dysfunction in Huntington's disease: heat shock factor 1 (HSF1) converging mechanisms" by (Zarate and Gomez-Pastor 2020), with permission from Neural Regeneration Research)

overexpression of Hsp70 in cortical cells provides protection against glutamatergic excitotoxicity and improves glutamatergic synaptic transmission (Mokrushin et al. 2005; Song et al. 2016). Therefore, upregulation of Hsp by HSF1 might impact excitatory synapses in HD by improving protein folding and scaffolding at the synapse zone. An additional mechanism that can explain the restoration of excitatory synapses is an increase in HSF1 levels in the correction of mitochondrial function. Mitochondria are essential in synaptic transmission through ATP production, Ca2+ homeostasis, synthesis of glutamate, synaptic vesicle recycling, and functional maintenance of dendritic spines (Smith et al. 2016; Zeron et al. 2002). As discussed above, HSF1 regulates mitochondrial function and MMP by controlling the expression of PGC-1α in HD cells (Gomez-Pastor et al. 2017; Zarate and Gomez-Pastor 2020). Therefore, HSF1 could modulate excitatory synapses in HD throughout its action on PGC-1α. However, further studies are warranted to ascertain how these mechanisms are selective to thalamo-striatal excitatory synapses, whether HSF1-dependent PGC-1α expression constitutes a causal role in MSNs degeneration in HD, and how HSF1 maintains synapse integrity in the adult brain.

7.7 Role of HSF1 in Other PolyQ-Related Diseases

HD belongs to a family of polyQ-related diseases that include spinal and bulbar muscular atrophy (SBMA), dentatorubral-pallidoluysian atrophy (DRPLA), and several spinocerebellar ataxias (SCAs) (Williams and Paulson 2008). As in HD, the cause of all these diseases is a CAG repeat expansion in the mutated gene. Although it occurs in entirely unrelated genes that affect different cell types and brain regions, all these polyQ diseases share several features. The characterization of PolyQ diseases is nuclear localization of

the toxic protein (Orr 2012; Orr and Zoghbi 2007), the propensity for the mutant proteins to form insoluble aggregates in neurons (Gusella and MacDonald 2000), instability in the CAG repeat number with a tendency for further elongations (Schols et al. 2004), and an inverse correlation between the CAG repeat length and the age of onset (Zoghbi and Orr 2000). Similar to HD, depletion of HSF1 as well as impairment of Hsp expression has been documented in many polyQ diseases and demonstrated that failure in the HSF1-Hsp axis enhances pathogenesis (Evert et al. 2018; Katsuno et al. 2005; Kondo et al. 2013; Tsai et al. 2005). Different studies have also reported the neuroprotective effects of activating HSF1 in many cellular and rodent models of polyQ diseases (Fujimoto et al. 2005; Rimoldi et al. 2001), indicating that failure in the HSR is a common and underlying mechanism in several polyQ-related diseases.

In SBMA, the CAG expansion occurs in the first exon of the androgen receptor (AR) gene (Katsuno et al. 2012; La Spada et al. 1991) and affects males exclusively (Chen et al. 2018; Grunseich et al. 2014). Nuclear accumulation of the polyQ-AR occurs in both neuronal and non-neuronal cells but preferentially affects motor neurons in the brainstem and spinal cord (Adachi et al. 2005; Katsuno et al. 2002). Kondo et al. showed a significant decrease in HSF1 levels in different brain regions of the SBMA mouse model AR-97Q and autopsy specimens from patients with SBMA. The authors also observed that pathogenic polyQ-AR accumulation was greater in tissues where HSF1 levels usually are lower (brain and pancreas). In contrast, tissues with relatively higher HSF1 levels (liver and testis) did not show polyQ-AR accumulation. Interestingly, Hsf1 depletion expanded the distribution of polyQ-AR accumulation to those tissues that are generally not affected, aggravating the SBMA phenotype. On the contrary, lentiviral-mediated overexpression of HSF1 decreased the accumulation of polyQ-AR and neuronal atrophy in the brain of AR-97Q mice (Kondo et al. 2013). Pharmacological activation of HSF1 has also shown beneficial effects on reducing polyQ-AR aggregation and amelioration of SBMA-like phenotypes (Bott et al. 2016; Hargitai et al. 2003). Treatment with arimoclomol, a molecule known to prolong the activation of HSF1, induced chaperones expression and enhanced motor neuron survival, and delayed disease progression in SBMA mice (Bott et al. 2016); (Hargitai et al. 2003).

DRPLA is a rare autosomal dominant polyQ disease and the most HD-like disease among the polyQ disorders. It is clinically characterized by cerebellar ataxia, chorea, myoclonus, epilepsy, dementia, and seizures (Tsuji 2012). The CAG repeat expansion occurs in ATROPHIN-1 (Atro), a transcriptional corepressor (Zhang et al. 2002). Although there are not many studies evaluating the role of HSF1 in this disease, Nisoli and colleagues demonstrated that overexpression of Hsp40 significantly suppressed polyQ-Atro toxicity in a *Drosophila* model of DRPLA (Nisoli et al. 2010). Additional studies in HeLa cells transfected with an expression vector containing 81 CAG repeats of DRPLA cDNA and expressing a dominant active form of HSF1 (Ad-HSF1-ΔRDT) showed decreased polyQ aggregates compared to cells expressing wild-type HSF1 (Fujimoto et al. 2005; Rimoldi et al. 2001). The authors also demonstrated that the effect of Ad-HSF1-ΔRDT on polyQ aggregates suppression was more efficient than overexpression of any of the significant Hsp (Hsp27, Hsp40, Hsp70, and Hsp110). These pieces of evidence suggest a beneficial role of activating HSF1 in DRPLA. However, additional in vivo studies will be necessary to determine the implications of HSF1 in this disease fully.

SCAs are a heterogeneous group of autosomal dominant inherited ataxias that are characterized by degeneration of Purkinje cells in the cerebellum and occasional degeneration in the brainstem, spinal cord, and basal ganglia (Schols et al. 2004; Zoghbi 2000). To date, at least 43 subtypes of SCA have been classified depending on their genetic locus (Klockgether et al. 2019; Sun et al. 2016). Among them, six SCA subtypes, SCA 1, 2, 3, 6, 7, and 17, are the most common ones, and the genes affected are ATAXIN-1 (Banfi et al. 1994), ATAXIN-2 (Satterfield and Pallanck 2006), ATAXIN-3 (Kawaguchi et al. 1994), α1A

subunit of the voltage-dependent calcium channel Cav2.1 (CACNA1A) (Orr 2012), ATAXIN-7 (David et al. 1997), and TATA-box binding protein (TBP) (Koide et al. 1999), respectively. The signs and symptoms may vary between different SCAs, but they also share some phenotypes like an uncoordinated walk (gait), poor hand-eye coordination, and abnormal speech (dysarthria). Interestingly, Ingenwerth and colleagues reported that mice lacking Hsf1 showed gait and other motor symptoms reminiscent of cerebellar ataxia. Also, they showed that CALBINDIN, a calcium-binding protein, was reduced in the cerebellum of Hsf1−/−mice and suggested a role of HSF1 in the regulation of Purkinje cell calcium homeostasis (Ingenwerth et al. 2016). A study conducted in a cell model of SCA6 demonstrated that the levels of HSF1 and Hsp70 were significantly downregulated (Li et al. 2009). Similarly, Tsai et al. showed decreased expression of Hsp27 and Hsp70 in transformed lymphoblastoid cells from patients with SCA7 (Tsai et al. 2005). Conversely, activation of HSF1 by a small molecule HSF1A inhibits the interaction between HSF1 and the chaperonin complex TRiC (Neef et al. 2014), suppressed polyQ aggregation, and ameliorated neurotoxicity in a fly model of SCA3 (Neef et al. 2010). These studies led to pharmacological and genetic manipulations of HSF1 in different SCAs to explore the potential role of HSF1 as a therapeutic target and showed successful induction of Hsp expression and amelioration of polyQ aggregation (Adachi et al. 2003; Chan et al. 2000; Chang et al. 2013; Chen et al. 2010; Cummings et al. 2001; Fujikake et al. 2008; Ghosh and Feany 2004; Gong and Golic 2006; Helmlinger et al. 2004; Katsuno et al. 2005; Kobayashi et al. 2000; Malik et al. 2013; Wang et al. 2013; Warrick et al. 1999b).

Rimoldi et al. utilized a non-neuronal cell system of SCA1 expressing ATAXIN-1 with polyQ tracts of different lengths and determined the effect of de-repressed HSF1 mutant variants on polyQ aggregation (Rimoldi et al. 2001). They showed that HSF1-S303G and S307G, variants unable to be phosphorylated, significantly induced Hsp70 and Hsp40 expression and abolished nuclear polyQ-ATAXIN-1 accumulation. Other pharmacological approaches have used Hsp90 inhibition to activate HSF1. Ding et al. showed that treatment of a neuronal cell model of SCA1 with BIIB021, a synthetic Hsp90 inhibitor, increased the transactivation capacity of HSF1, leading to decreased aggregation and toxicity induced by mutant ATAXIN-1 (Ding et al. 2016). Administration of 17-AAG, another known Hsp90 inhibitor, suppressed inclusion body formation, and eye degeneration in a *Drosophila* model of SCA3 in an HSF1-dependent manner (Fujikake et al. 2008). Alternative treatments with herbal extracts with HSF1 activation properties have also reduced toxic aggregates formation in cells expressing mutant ATAXIN-3 (Chang et al. 2013). The effects of Hsp90 inhibitors in cellular and *Drosophila* SCA models are promising; however further studies are required to determine the effects of these inhibitors in more relevant in vivo models of SCA. This strategy has already been tested in the R6/2 HD mice and showed that pharmacological activation of HSF1 using the Hsp90 inhibitor NVP-Hsp990 failed to maintain long-term benefits in vivo, a problem that may be due to progressive loss of HSF1 protein in HD (Gomez-Pastor et al. 2017). Since previous reports have shown HSF1 depletion in SCAs, further experiments will be necessary to uncover the causes that mediate HSF1-Hsp depletion in the different polyQ diseases and whether this may impact future pharmacological studies.

8 HSF1 as a Therapeutic Target in HD and Other PolyQ Diseases

Over the past decade, there has been a profound advancement in understanding the molecular mechanisms responsible for neuronal death in HD and other polyQ diseases, emphasizing those pathways that lead to protein misfolding and aggregation. This knowledge has resulted in development of several molecules with therapeutic potential (Neef et al. 2011). However, current advances in clinical trials are focused on using antisense oligonucleotides against HTT to lower

HTT expression (Imbert et al. 2019; Lemprière 2019; Tabrizi et al. 2019). This section will discuss the strategies focused on the activation of the HSR as a potential future venue to ameliorate protein aggregation and neurodegeneration in HD and other polyQ diseases.

One of the most exploited strategies to induce the HSR and ameliorate protein aggregation is Hsp90 inhibitors. As discussed earlier, Hsp90 suppresses HSF1 multimerization and transactivation (Bharadwaj et al. 1999; Zou et al. 1998), and therefore pharmacological inhibition of Hsp90 leads to HSF1 activation and Hsp induction. Well-studied Hsp90 inhibitors are geldanamycin, 17-AAG, 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG), celastrol, radicicol, and Hsp990. Geldanamycin is a benzoquinone ansamycin antitumor antibiotic, and Sittler and colleagues reported its first therapeutic effect in a cell culture model of HD (Sittler et al. 2001). The authors showed that geldanamycin induces the expression of Hsp40 and Hsp70 and suppresses aggregation of mHTT. Its anti-aggregation activity was subsequently tested in hippocampal slice cultures derived from HD mice (Hay et al. 2004). However, recent reports have shown that geldanamycin has low solubility, inadequate blood-brain-barrier permeability, and toxicity (Bose and Cho 2017). Less toxic derivatives of geldanamycin are 17-AAG and 17-DMAG. Treatment of 17-AAG strikingly decreased degeneration of photoreceptor neurons in *Drosophila* models of both HD and SCA3 (Fujikake et al. 2008). Importantly, 17-AAG benefits were abolished when HSF1 was knocked down (Fujikake et al. 2008). Research has shown that 17-DMAG inhibits the formation of mHTT aggregates with higher efficiency than geldanamycin and 17-AAG (Herbst and Wanker 2007). Celastrol constitutes a new class of Hsp90 inhibitors that, unlike the classical Hsp90 inhibitors (geldanamycin and 17-AAG), does not block ATP binding to Hsp90. Instead, Celastrol inhibits Hsp90 activity by binding to its C-terminus domain and blocking Hsp90 oligomerization (Zhang et al. 2008, 2009). Celastrol contributes to the activation of HSF1 and Hsp induction (Westerheide et al. 2004) and suppresses polyQ-induced aggregation in vitro (Wang et al. 2005; Zhang and Sarge 2007). However, celastrol has shown activity against numerous targets besides HSF1 (Lee et al. 2006; Sreeramulu et al. 2009; Yang et al. 2006; Zhang and Sarge 2007) and therefore, the HSF1-dependency in the effects mediated by celastrol is unclear.

The use of 17-AAG has been explored in mouse models of SBMA and animal models from other proteinopathies such as AD and frontotemporal dementia and demonstrated its benefits in improving synaptic connectivity and behavior (Chen et al. 2014; Ho et al. 2013; Katsuno et al. 2005; Waza et al. 2005). Unfortunately, the effects of 17-AAG and other Hsp90 inhibitors on HSF1 activation in HD progression in the mammalian brain have remained unknown due to their low efficiency in crossing the blood-brain barrier (Ebrahimi-Fakhari et al. 2013; Egorin et al. 2001; Porter et al. 2010). A new Hsp90 inhibitor developed by Novartis and with brain-penetrant properties is Hsp990 (Jackrel and Shorter 2011; Menezes et al. 2012). Oral administration of Hsp990 increased Hsp, reduced aggregate load in the brain, and improved motor symptoms at early stages in R6/2 HD mice (Labbadia et al. 2011). Unfortunately, the use of Hsp990 failed to provide long-term benefits in the R6/2 mice and resulted in the attenuation of the HSR. The authors attributed this defect to an alteration in the chromatin structure on the Hsp promoters that resulted in chronic Hsp downregulation. However, more recent studies suggested that failure to provide long-term benefits upon Hsp90 inhibition in vivo may be due to the pathological degradation of HSF1 reported in HD (Gomez-Pastor et al. 2017). In support of this study, Chafekar and Duennwald reported that STHdhQ111 cells treated with radicicol, another Hsp90 inhibitor, showed very modest or absent effects on the levels of Hsp70 and Hsp27 as well as increased cell sensitivity (Chafekar and Duennwald 2012). They hypothesized that lack of Hsp induction might be due to the low levels of HSF1 observed in those cells compared with wild-type STHdhQ7 cells (Chafekar and Duennwald 2012). Therefore,

these studies suggest that activation of HSF1 via Hsp90 inhibition in HD may not be a successful therapeutic strategy after all.

Due to the toxicity issues of many Hsp90 inhibitors reported in HD, other strategies have investigated alternative ways of inducing the HSR (Calamini et al. 2011). Calamini and colleagues developed a high-throughput screening using HeLa cells stably transfected with a heat shock-inducible reporter containing the proximal human HSPA2 (a gene encoding Hsp70.1) promoter sequence upstream of a luciferase reporter gene and measured the activation of the HSR in more than 900,000 molecules. The authors identified a series of small molecules (PR, proteostasis regulators) that induced HSF1-dependent chaperone expression, did not inhibit Hsp90 activity, and restored protein folding in PC12 cells expressing HTTQ74-GFP and in *C. elegans* expressing YFP-tagged Q35 protein. Besides the activation of HSF1, the study revealed several molecules provided proteome stability by activating other factors, including DAF-16/FOXO and SKN-1/NRF-2, and suggested an activation in HSR via alternative mechanisms. An additional screening conducted by Neef and colleagues used a humanized yeast-based high-throughput screen insensitive to proteotoxic stress and Hsp90 inhibition and identified a small molecule activator of human HSF1, so-called HSF1A (Neef et al. 2010). The study reported that HSF1A repressed aggregation and cytotoxicity of mHTT in a cell culture model of HD and ameliorated polyQ-induced cytotoxicity in a *Drosophila* model of SCA3. Further studies revealed that HSF1A inhibits the repressive interaction between HSF1 and the chaperonin complex TRiC/CCT, consequently increasing HSF1 activity and Hsp expression (Neef et al. 2014). However, the effects of the PRs or HSF1A in mouse models of HD or other polyQ diseases are still unknown.

Instead of disrupting the interaction between HSF1 and its negative regulators, other strategies have searched for molecules that directly enhance HSF1 activity. Bimoclomol and its derivative arimoclomol are non-toxic hydroxylamine derivatives and are co-inducers of the HSR under stress conditions (Kalmar et al. 2002; Vigh et al. 1997). Reports have suggested that bimoclomol directly binds to HSF1, increasing the time and duration of HSF1 binding to the respective target genes and therefore prolonging the activation of HSF1 (Hargitai et al. 2003). The direct binding was analyzed by measuring binding of radiolabeled [3H]bimoclomol to purified proteins by equilibrium dialysis where [3H]bimoclomol showed binding to both recombinant and native HSF1 but not Hsp70 or Hsp90. However, other studies suggested that bimoclomol enhances HSF1 activity indirectly through altering plasma membrane fluidity (Torok et al. 2003). The mechanism of action for prolonged HSF1 activity by bimoclomol or arimoclomol remains unclear. Despite the controversy in the mechanism of action of these molecules, both bimoclomol and arimoclomol have shown cytoprotective value in mitigating motor neuron degeneration in SBMA (Malik et al. 2013) as well as in an array of different diseases such as ALS (Kalmar et al. 2008; Kieran et al. 2004), diabetes (Biro et al. 1997; Erdo and Erdo 1998), cardiac dysfunction (Jednakovits et al. 2000; Lubbers et al. 2002; Polakowski et al. 2002), and cerebrovascular disorders (Melville et al. 1997). Unfortunately, arimoclomol did not improve motor function or rescue of striatal pathology in YAC128 HD mice (Pouladi et al. 2010). An additional therapeutic strategy pursuing prolonged HSF1 DNA binding is the use of SIRT1 agonists. SIRT1 is a deacetylase responsible for deacetylating HSF1-Lys80 in the DBD domain and promoting DNA binding release (Westerheide et al. 2009). Studies in different animal models provided convincing evidence that SIRT1 and different SIRT1 agonists like resveratrol protect neurons in cell and mouse models of HD and *C. elegans*, although there were controversial results reported in a fly model (Duan 2013; Parker et al. 2005). The therapeutic potential of resveratrol is currently being tested in clinical trials for HD (ClinicalTrials.gov identifier: NCT02336633). The study has revealed a reduction in neurodegeneration among HD patients treated with resveratrol by showing an improvement in brain energy profiles measured by 31P-magnetic resonance spectroscopy.

It is essential to remember that HSF1 undergoes a progressive and pathological degradation in HD, and therefore strategies aimed at stimulating HSF1 activity may not be effective in the long-term. Thus, other strategies are investigating the stabilization of HSF1 protein levels rather than activity stimulation as a more attractive strategy to ameliorate long-term protein aggregation in HD. Riluzole, an FDA approved anti-glutamatergic agent for ALS treatment, has shown the ability to increase HSF1 protein levels by disrupting the association between HSF1 and the chaperone-mediated autophagy pathway (Yang et al. 2008). Moreover, riluzole increased the expression of the glutamate transporter GLT1 and abolished NMDA-induced excitotoxicity in an HSF1-dependent manner (Liu et al. 2011). Experiments using animal models of HD and other proteinopathies have determined the neuroprotective effects of riluzole (Douhou et al. 2002; Scherfler et al. 2005; Schiefer et al. 2002). More importantly, riluzole alleviated clinical symptoms by preserving brain structure and increasing neurotrophin production in patients with HD (Bonelli and Hofmann 2007; Squitieri et al. 2009). Although this molecule failed in phase III HD clinical trials in 2007 (ClinicalTrials.gov Identifier: NCT00277602), its efficacy is currently being tested to treat other polyQ disorders such as SCA2 (ClinicalTrials.gov Identifier: NCT03347344). The use of protein kinase CK2 inhibitors (TID43, Emodin, and CX4945) has also shown the ability to increase HSF1 protein levels by preventing Ser303/307-phosphorylation-dependent degradation. CK2 inhibitors increased Hsp expression and decreased mHTT load and cell death in different cellular models of HD. Inhibition of CK2 has been recently proposed as a potential target to treat different neurological and psychiatric disorders due to its ability to modulate HSF1 levels and inflammation (Castello et al. 2017; Gomez-Pastor et al. 2017). Further studies will be necessary to address these inhibitors' potential benefits in animal models of polyQ-related diseases.

Many of the molecules discussed in this section, whether synthetic or natural, have shown some forms of neuroprotection against HD or other polyQ diseases in different cellular models. However, many of them have failed when tested in more relevant and physiological animal models. Many of the studies have also explored the single use of one molecule or another but never a combination of them. Due to the complexity of the HSR, it may be necessary to combine different strategies to obtain a synergistic effect on the activation and stabilization of HSF1 and Hsp expression and, therefore, a more successful strategy towards preventing long-term aggregation and neurodegeneration.

9 Conclusion

Since the discovery of HSF1 in 1984, hundreds of studies have contributed to improving our understanding of this critical transcription factor's protective roles. While HSF1 was initially ascribed to modulate the Hsp in response to heat shock conditions, we know now that HSF1 controls very diverse physiological processes, including cell growth and differentiation, apoptosis, oxidative stress, aging, immune and inflammatory responses, and neuronal development through the regulation of numerous target genes, mainly in a temperature-independent manner. It is not difficult to predict that defects in HSF1 activation at any stage of an organismal life may lead to devastating consequences. The transcriptional program governed by HSF1 allows cells to survive under adverse conditions induced by proteotoxic stress in diverse diseases. Cumulative evidence presented in this book chapter has demonstrated the critical role of HSF1 in different neurological disorders, specifically in HD. Various groundbreaking studies on HSF1 have helped to elucidate the mechanisms by which neurons fail to fight aggregation and succumb to death, contributing to the design and exploration of potential therapeutic strategies to aid HSF1 in the course of HD and other pathologies. While we have made tremendous advancements in understanding HSF1 role in physiology and disease, many questions remain unanswered. To design effective and successful therapies in the future to ameliorate the

negative effects of aging and neurodegeneration, it will be necessary to fully characterize the differential roles of HSF1 in the young vs. adult brain, assess the spatiotemporal effects of altering HSF1 levels in the adult brain, and characterize all the factors that contribute to the HSR impairment in the aging mammalian brain.

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