Chapter 6
HSF Modulates Neural Development Under Normal and Stress Conditions

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Abstract Over the last decade, laboratories working with knockout mice have contributed data substantiating that heat shock factors 1 and 2 (HSF1, HSF2) play critical roles in the normal development of the central nervous system. More recent studies have determined that these factors also play critical, but altered, roles during pathological brain development elicited by prenatal exposure to environmental stress. Those researches have, in fact, provided new insights into the roles of heat shock factors at the molecular level in both normal and pathological brain development, strengthening the view that the malresponse of HSFs to environmental stress is predisposed or highly influenced by genetic mutations associated with the incidence of neuropsychiatric disorders. In this chapter, we summarize the roles of HSFs in both normal and pathological brain development with a primary focus on the cerebral cortex and discuss potential mechanisms governing the multifaceted roles of HSFs under both normal and pathological conditions.

Keywords HSF1 • HSF2 • Neurogenesis • Cortical development • Prenatal stress

6.1 Introduction

Throughout life, humans are inevitably exposed to many types of stress, principally psychological and environmental. The earliest stress we encounter in life occurs in the womb where prenatal exposure to diverse agents such as alcohol or illegal drugs may cause anatomical and functional anomalies in the developing brain. Even

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subtle disturbances in the cerebral cortex may impair cognitive and memory functions, thereby increasing susceptibility to neuropsychiatric disorders such as autism, attention deficit/hyperactivity disorder (ADHD), and schizophrenia. Accordingly, increased attention is being paid to understanding the underlying epigenetic programs governing neuropsychiatric deficits or disorders. Here, we focus on recent papers that illuminate the roles of HSFs in prenatal environmental stress-induced pathological cortical development and identify the risks posed for the genesis of neuropsychiatric disorders.

6.1.1 Normal Cortical Development and Its Disturbance by Environmental Stress

The initial step of corticogenesis is proliferation of the neural progenitor cells in the germinal zone, known as the ventricular zone (VZ) (Fig. 6.1a). The neural progenitor cells in the cerebral cortex consist of several different cell types defined by their morphological, physiological, and molecular properties (Gleeson and Walsh 2000; Kriegstein and Noctor 2004; Kriegstein et al. 2006; Ayala et al. 2007; Barnes and Polleux 2009; Rakic 2009; Rakic et al. 2009). Among them, radial glial cells have unique characteristics that enable them to produce the layered structure or early scaffold of the cerebral cortex. The radial glial cell extends an elongated shaft that spans the entire thickness of the fetal cerebral wall (Rakic 1988), and neurons differentiated from neural progenitor cells appose to this transient scaffolding and migrate toward the cortical plate (CP) during the neurogenic phase (Fig. 6.1a). In the following gliogenic phase, radial glial cells give rise to oligodendrocytes that are required for myelination of neuronal axons and astrocytes that support neurons physically and metabolically. The radial glial cells are then transformed into adult neural stem cells in the ependymal layer (EL in Fig. 6.1a) (Kriegstein and Alvarez-Buylla 2009).

A number of independent histological analyses using postmortem tissues with a history of exposure to prenatal environmental insult, such as alcohol, have documented various anomalies in the cerebral cortex, including heterotopias, microcephaly, hydrocephaly, and agenesis of the corpus callosum (Clarren and Smith 1978; Roebuck et al. 1998; Muralidharan et al. 2013). In addition, animal exposure models have reproduced many of the morphological and behavioral phenotypes that are seen in human subjects (Thompson et al. 2009). Disturbances in the multiple events involved in corticogenesis, including proliferation, differentiation, apoptosis, and cortical cell migration (Fig. 6.1b), are considered the principle causes underlying these anomalies.

Collectively, corticogenesis consists of numerous extremely intricate multifaceted steps that must be controlled precisely and are therefore vulnerable to impairment by exposure to even minimal levels of environmental stress.

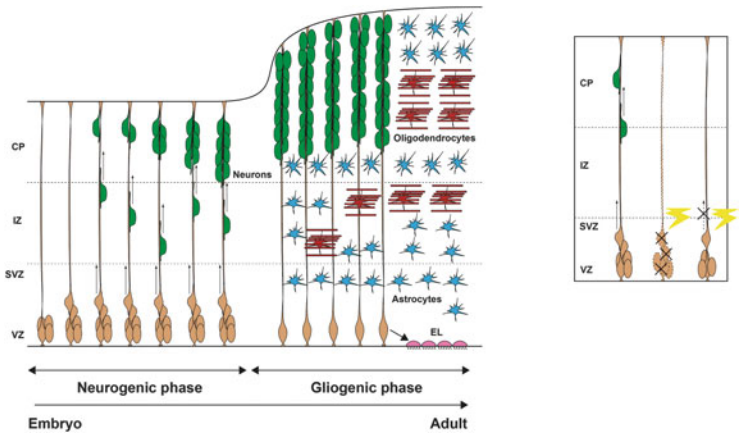

Fig. 6.1 Prenatal exposure to environmental stress increases the cell death and cell cycling arrest and delays neuronal migration in the developing cerebral cortex. (**a**) Cortical neurons are generated from the neural progenitor cells located in the ventricular zone (*VZ*)/subventricular zone (*SVZ*) of the cortex. Then, the produced neurons migrate through the intermediate zone (*IZ*) to the cortical plate (*CP*). Following the neurogenic phase, the oligodendrocytes and astrocytes are produced from the same progenitor cells. (**b**) The cortical malformations caused by prenatal environmental stress are as follows: cells are at increased risk of cell death or cell cycling arrest (*left*), and other cells show impaired migration (*right*)

6.2 Roles of HSFs in Normal Cortical Development

In the course of neural development, both HSF1 and HSF2 are ubiquitously expressed in the developing brain until birth (El Fatimy et al. 2014), and phenotypes of the loss of functions are also prominent in the brains. In the following subsections, we review the data and discuss the potential mechanisms governing how these two genes regulate normal brain development.

6.2.1 HSF1 Controls Normal Neurogenesis, Gliogenesis, and Behavior

Xiao et al. (1999) found that the brains of *Hsf1* knockout mice were generally smaller than their wild-type littermates, becoming discernible only after the first postnatal week. Adding to the list of neuropathological consequences arising from deletion of *Hsf1*, Santos and Saraiva found that brains of *Hsf1* knockout mice were hydrocephalic upon the onset of birth (Santos and Saraiva 2004). The knockout mice showed reduced anxiety and sociability, but increased depressive behavior and aggression (Uchida et al. 2011). By restoring *Hsf1* specifically into the hippocampus, anxiety and depression-like behaviors were partially reversed along with mitigation of impaired synaptic connections. Further, histological analyses of the

brains showed a reduction of spine density in the granule cells (a type of neurons) of the hippocampus. Furthermore, chromatin immunoprecipitation assays demonstrated that the expression of genes encoding polysialytransferases is directly controlled by Hsf1 in the hippocampus (Uchida et al. 2011). Given that the polysialylated-neural cell adhesion molecule (PSA-NCAM) is required for synapse formation (Dityatev et al. 2004) and that the expression level of PSA-NCAM is lowered in the hippocampus of *Hsf1* knockout mice (Uchida et al. 2011), the transcriptional controls of polysialytransferases by HSF1 might be a mechanism governing the behaviors that are altered in *Hsf1* knockout mice. Uchida et al. provided additional evidence of brain pathology showing reduced proliferation of adult neural stem cells and delayed maturation of de novo neurons in the dentate gyrus, the neurogenic site of the hippocampus in young adult mice (Uchida et al. 2011). Although the data nicely demonstrate evidence for a multifaceted role of HSF1 in adult neurogenesis, the underlying mechanisms remain largely undetermined. However, *Hsf1* knockout mice exhibit impaired cilia (Takaki et al. 2007), and thus together with accumulating evidence that ciliopathy is linked to impaired adult neurogenesis (Breunig et al. 2008; Han et al. 2008; Amador-Arjona et al. 2011; Tong et al. 2014), yet another possible mechanism on how HSF1 regulates the adult neurogenesis and behavior might be through the regulation of the primary ciliary structure and functions (please refer to Chap. 7 for the function of HSF1 in cilia formation).

Impaired gliogenesis observed in *Hsf1* knockout mice also suggests a critical role for HSF1 in glial specification and development (Homma et al. 2007). In these mice, the number of glial fibrillary acidic protein (GFAP)-positive astrocytes was increased in the ependymal layers surrounding the lateral ventricles. In contrast, the number of myelin basic protein (MBP) expressing oligodendrocytes was significantly reduced in the corpus callosum and the hippocampus (Homma et al. 2007). Given that radial glial cells, the neural stem cells in the cerebral cortex, give rise to both oligodendrocytes and astrocytes sequentially during development, HSF1 may control gliogenesis in the mouse brain just as it controls proliferation of adult stem cells and differentiation of de novo neurons.

Taken together, this entire body of work strongly supports the critical roles of HSF1 in the brain by both directly and indirectly influencing multiple facets of brain development and, consequently, behavior.

6.2.2 *HSF2 Is Required for Proper Neuronal Migration in the Cerebral Cortex*

Consistent phenotypes were observed in *Hsf2* knockout mice made in different laboratories, including hydrocephalus and higher rates of fetal lethality (Kallio et al. 2002; Wang et al. 2003), similar to rates observed in *Hsf1* knockout mice. A unique phenotype, however, was observed in the cerebral cortex of the *Hsf2*

knockout mice in which Hsf2 was found to be strongly expressed in the VZ. While the effects on proliferation/differentiation of the neural progenitor cells appeared to be minimal, rather prominent effects were found in the descendent neurons that migrate out from the VZ. As a potential mechanism, Mezger's group (Chang et al. 2006) demonstrated direct transcriptional control of Hsf2 on the *p35* gene that is involved in migration control through the phosphorylation of CDK5 (Chae et al. 1997). Another gene, *p39*, the product of which forms a protein complex with p35 (Ko et al. 2001) that is required for neuronal migration, also shows reduced expression in *Hsf2* knockout mice. However, this appears to occur via an indirect Hsf2 control mechanism as the direct binding of Hsf2 on the promoter region of *p39* was not observed.

Furthermore, disturbances were also found in the morphology of the radial glial cells which form the scaffold for neuronal migration and in the number of Cajal-Retzius cells that secrete signals required for neuronal migration (Rice and Curran 2001; Tissir and Goffinet 2003) in *Hsf2* knockout mice, suggesting indirect effects of *Hsf2* depletion on neuronal migration. Genome-wide expression profiling of *Hsf2* knockout mice performed by Mivechi's group (Wang et al. 2003) reported reduced expression of several genes that are potentially involved in the migration of cortical neurons as well as genes involved in corticogenesis. The list of genes exhibiting reduced expression included the *T-box brain gene 1* (*Tbr1*), proximal promoter regions of which include sequences that both HSF1 and HSF2 can bind to. Since the knockout mice showed impaired neuronal migration in the cerebral cortex and also exhibited reduced numbers of Cajal-Retzius cells (Hevner et al. 2001), it is feasible to consider that *Hsf2* may control neuronal migration via transcriptional control of the *Tbr1* gene in Cajal-Retzius cells.

6.3 Roles of HSFs in Cortical Development Under Conditions of Prenatal Exposure to Adverse Conditions

Recent studies demonstrated that both HSF1 and HSF2 play important roles in pathological cortical development provoked by prenatal environmental stress. In the following subsections, we review and discuss the findings obtained in these studies.

6.3.1 HSF1 Protects the Embryonic Cortex from Various Types of Environmental Stress

Although subjects exposed prenatally to various types of environmental challenge share increased susceptibility to late-onset neurological dysfunction, factors that determine the degree of susceptibility among individuals, however, remain obscure.

Hashimoto-Torii et al. (2014) showed that HSF1 serves as a guardian against damage caused by prenatal exposure to various environmental challenges such as alcohol, methylmercury, and maternal seizure (Fig. 6.1b). By chromatin immunoprecipitation, mice exposed in utero to these three types of challenge exhibited increased Hsf1 binding to heat shock element (HSE) in the *Hsp70* gene of the embryonic cerebral cortex. To examine the role of activated Hsf1 under conditions of exposure to such prenatal challenges, *Hsf1* knockout embryos were exposed to subthreshold levels of exposure at the peak of corticogenesis. While subthreshold exposure alone induced neither structural nor behavioral abnormalities in the cerebral cortex, *Hsf1* deficiency plus subthreshold exposure to these challenges increased the frequency of leptomeningeal heterotopias and reduced the size of the cortex (Fig. 6.2). The offspring also exhibited increased seizure susceptibility after birth (Fig. 6.2). These structural abnormalities were attributed to impaired survival and cell cycling of neural progenitor cells due to autonomous cell defects (Fig. 6.3) and secondary effects produced by compromised meninges. These findings uncovered the role of Hsf1 in conferring tolerance to prenatal environmental perturbation in the mouse cerebral cortex, thereby securing a lower incidence of cortical dysplasia than might have occurred in the absence of functional Hsf1.

With regard to humans, there are a number of reports identifying a number of prenatal environmental risk factors thought to potentially cause or contribute to schizophrenia (SZ) (Sullivan 2005). In addition, there are multiple reports demonstrating abnormalities in HSF1-HSP70 signaling (Schwarz et al. 1999; Kim et al. 2001; Pae et al. 2005). To test the possibility that HSF1 activation is altered in humans exposed to harsh prenatal environmental conditions, induced pluripotent stem cells (iPSCs) derived from patients diagnosed with SZ (Brennand et al. 2011) were employed as a model. The same three types of environmental challenges mentioned above were applied in vitro to these cultured human iPSC-derived neural progenitor cells (NPCs) at subthreshold levels for 3 h (Fig. 6.4). The copy number of *HSP70* and *GAPDH* was measured in individual cells, and the results revealed that all cell lines, including control NPCs, showed a robust increase in *HSP70* expression in response to these challenges (Fig. 6.4). Notably, although the mean of both *HSP70* and *GAPDH* expression levels showed no differences between control and SZ NPCs, cell-to-cell variability among the SZ NPCs was found to be significantly larger in *HSP70* expression, but not in the *GAPDH* (Fig. 6.4). The observation of abnormal levels of HSF1 variability among single cells within a subpopulation of SZ NPCs demonstrated different degrees of cell susceptibility upon exposure to adverse conditions. These results support the suggestion that variable responses of HSF1-HSP signaling among a population of SZ neural progenitor cells exposed to environmental stress is predetermined by genetic predisposition and may increase the risk for the onset of schizophrenia and possibly other neuropsychiatric diseases (Hashimoto-Torii et al. 2014; Brennand et al. 2014).

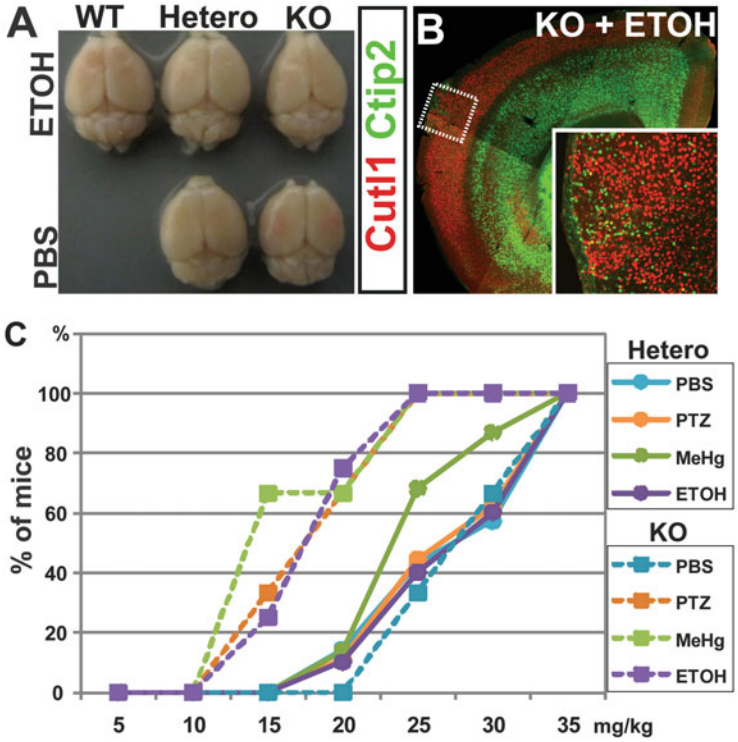

Fig. 6.2 Chances of cortical malformation and risk of epilepsy are increased by combining prenatal challenges and *Hsf1* loss of function. (**a**) An image of whole brains of postnatal day 25 mice with indicated *Hsf1* genotypes and substrate exposure, showing a slightly smaller cerebral cortex in the *Hsf1* KO mouse prenatally exposed to ETOH. (**b**) Immunohistochemistry for Cutl1 (marker for upper layer) and Ctip2 (lower layer) in a cortical section of a P25 *Hsf1* KO mouse prenatally exposed to ETOH, showing the formation of heterotopias (inset). (**c**) *Hsf1* KO mice with a prenatal history of challenge exposure show increased susceptibility to PTZ-induced seizures at the juvenile stage. Dose-response cumulative curves for induction of tonic-clonic seizures demonstrate greater PTZ (convulsant) sensitivity of *Hsf1* KO mice prenatally exposed to challenges (ETOH, MeHg, or PTZ) compared to heterozygous littermates and KO mice exposed to control treatment (This figure is adopted from Hashimoto-Torii et al. (2014))

6.3.2 *HSF1-HSF2 Heterotrimer Participates in the Control of Pathological Cortical Development*

Contrary to fact that heat shock inactivates HSF2 (Mathew et al. 2001), El Fatimy et al. (2014) found that alcohol (ethanol) exposure maintains Hsf2 activity concomitantly with HSF1 de novo activation both in vivo and in vitro brain. Both HSF2 and HSF1 were shown to occupy the promoters of *Hsp70* and *Hsp90*, respectively, in embryonic cortices exposed to alcohol. Furthermore, posttranslational modifications of Hsf1 upon exposure to alcohol were also different from those observed upon heat shock. Reduced acetylation, absence of hyperphosphorylation, and

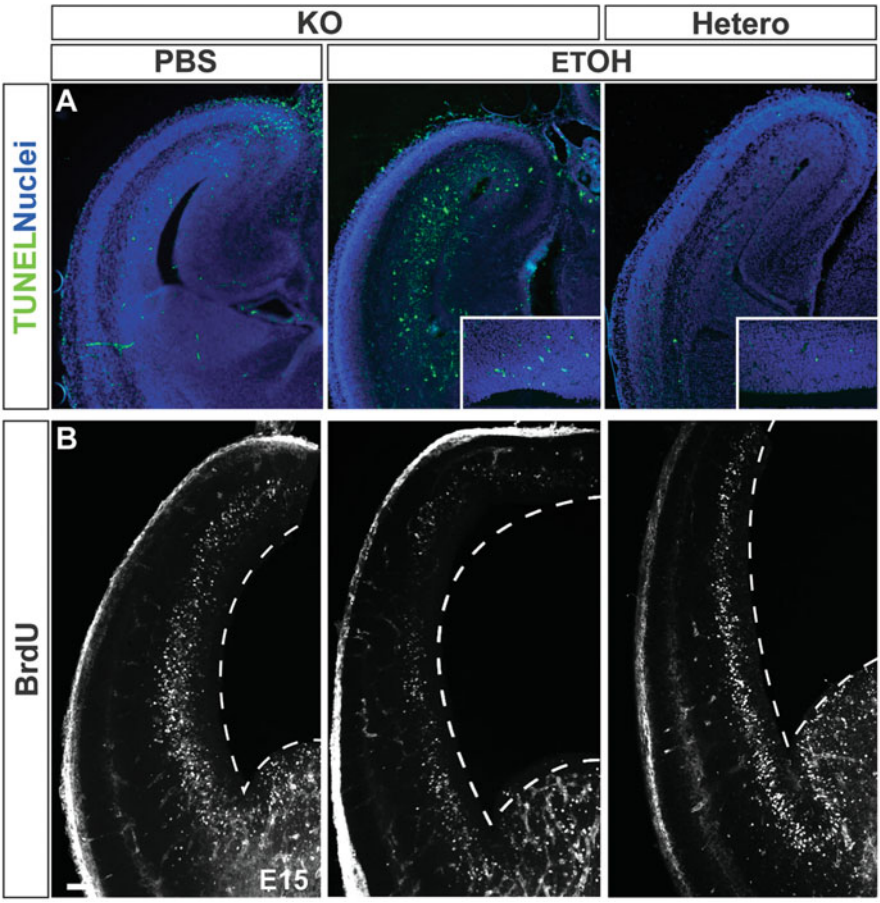

Fig. 6.3 Increase of apoptotic cell death and decrease of cell cycling in the cortex of *Hsf1* KO embryos exposed to challenges. (**a**) TUNEL staining at E16 in cortical slices from embryos with indicated genotypes and prenatal exposure. An increase in apoptosis in the cortex of *Hsf1* KO embryos exposed to ETOH is evident. (**b**) Pulse labeling with BrdU for 30 min at embryonic day 15 in the cortex of PBS- or ETOH-exposed embryos with indicated genotypes. The number of $BrdU^+$ progenitors is decreased in the *Hsf1* KO cortex exposed to ETOH, indicating the decreased cell proliferation/cell cycling (All panels are from Hashimoto-Torii et al. (2014))

delayed sumoylation of Hsf1 occurred in response to alcohol, but not in response to heat shock (El Fatimy et al. 2014).

In addition to such differences between the responses of HSFs to heat shock and alcohol, El Fatimy et al. found similar subcellular distributions of Hsf1 and Hsf2 in response to alcohol exposure, but not to heat shock (El Fatimy et al. 2014). This result suggested that HSF1 and HSF2 may form heterotrimer complexes upon exposure to alcohol in contrast to the predominant formation of HSF1 homotrimer complexes upon exposure to heat shock. Given that depletion of *Hsf2* cannot

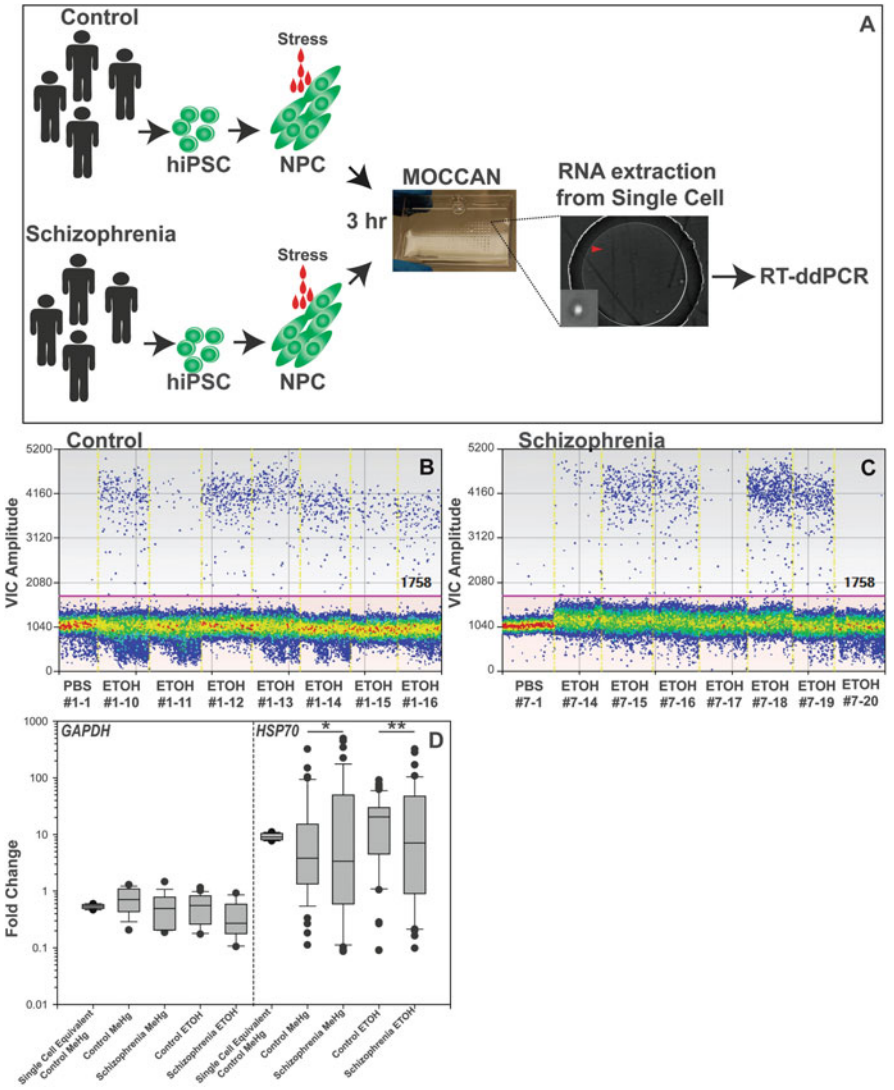

Fig. 6.4 Cell-to-cell variability of *HSP70* mRNA levels in response to environmental challenges is increased in schizophrenia neural progenitor cells. (**a**) Human iPS cells were differentiated to neural progenitor cells (*NPCs*), and the NPCs were exposed to stress for 3 h. Then sorted single cells were subject to single-cell RT-droplet digital PCR of *Hsp70*. (**b**) (**c**) Representative results of single-cell ddPCR of human *HSP70* (VIC label) in control (**b**) and schizophrenia (**c**). The clone number of each cell and substrates applied are shown under the graph. The *red line* shows cutoff of positive and negative droplets. (**d**) Graph shows fold change of *GAPDH* and *HSP70* expression compared with PBS exposure. Significantly increased variability was observed in schizophrenic cells as compared with the control ($^{*}p < 0.0001$, $^{**}p = 0.002$ by Levene's test). Significant differences in the comparison of means were not observed in all sets of comparisons ($p > 0.05$ by Welch's *t*-test). The single-cell equivalents were made by using 1/10 of a pool of ten lysed cells for the template of reverse transcription (All panels are from Hashimoto-Torii et al. (2014))

facilitate Hsf1 binding on the HSE under conditions of exposure to alcohol, Hsf2 is still required for binding of Hsf1 on HSE, thus suggesting the likelihood that HSF1 and HSF2 heterotrimer complexes form to facilitate HSF1 binding to HSE.

In the alcohol-exposed embryonic cortex, El Fatimy et al. (2014) also observed occupancy of HSF1 and HSF2 on the HSEs of genes that control neuronal migration, including *doublecortin (Dcx)*, *doublecortin-like kinase 1 (Dclk1)*, and *p35* (Ayala et al. 2007). Since the binding of Hsf2 homotrimer is required for the expression of these genes during normal neuronal migration in the embryonic cortex (El Fatimy et al. 2014; Chang et al. 2006), the reduction of their transcription upon exposure to alcohol may be caused by the loss of functional HSF2 homotrimer or by dominant occupation of HSF1-HSF2 heterotrimer that does not, by itself, activate transcription of these genes, thereby inhibiting neuronal migration (Fig. 6.5). However, given that the loss of *Hsf2* rescued the impaired radial neuronal migration elicited by alcohol exposure, the HSF1-HSF2 heterotrimer complex seems to play an instructive role in the inhibition of neuronal migration by alcohol exposure (Fig. 6.5). Consistent with the alcohol-reduced expression levels of genes (*Dclk1*, *Dcx*, *p35*, *Chl1*, *Myo10*, *MapT*, and *Mark2*) that pertain to functions required for neuronal migration, it is noteworthy that the impaired migration was reversed in the *Hsf2* knockout embryo (El Fatimy et al. 2014).

6.3.3 *HSF1 May Control Neurogenesis Through the Control of Synaptic Functions and the GABAergic System*

Using microarrays, Harrison and colleagues performed transcriptome analyses on mouse cortical neurons to identify genes that are commonly increased under conditions of exposure to alcohol or heat (Pignataro et al. 2007). Among nine genes identified (*glycoprotein m6a* (*Gpm6a*), *microtubule-associated protein 1B* (*Mtap1b*), *neurogranin* (*Nrgn*), *ELMO domain-containing 1*, *spectrin β2 transcript variant 1* (*Spnb2*), *glypican 5* (*Gpc5*), *SEC23A*, *synaptotagmin 1* (*Syt1*), and *cadherin 13* (*Cdh13*)), *Spnb2*, *Nrgn*, *Cdh13*, *Gpm6a*, and *Syt1* are known to be involved in synaptic functions (Pignataro et al. 2007). By demonstrating that shRNA-mediated *Hsf1* knockdown reduced the expression level of *Syt1n*, Varodayan et al. (2011) proved that the increase of *Syt1* mRNA upon exposure to environmental stress is directly mediated by Hsf1. They also revealed that the expression of another gene encoding the core synaptic vesicle fusion protein, vesicle-associated membrane protein 2 (Vamp2), is increased by exposure to both alcohol and heat shock (Varodayan et al. 2011). Since *Vamp2* is predicted to include HSF binding sites in the second intron (Varodayan et al. 2011), the increase of *Vamp2* mRNA by alcohol may also be mediated by activated HSF1 (Varodayan and Harrison 2013). Altogether these findings suggest that environmental stress-induced disturbance of synaptic functions may be mediated, at least in part, by the transcriptional activity of activated HSF1.

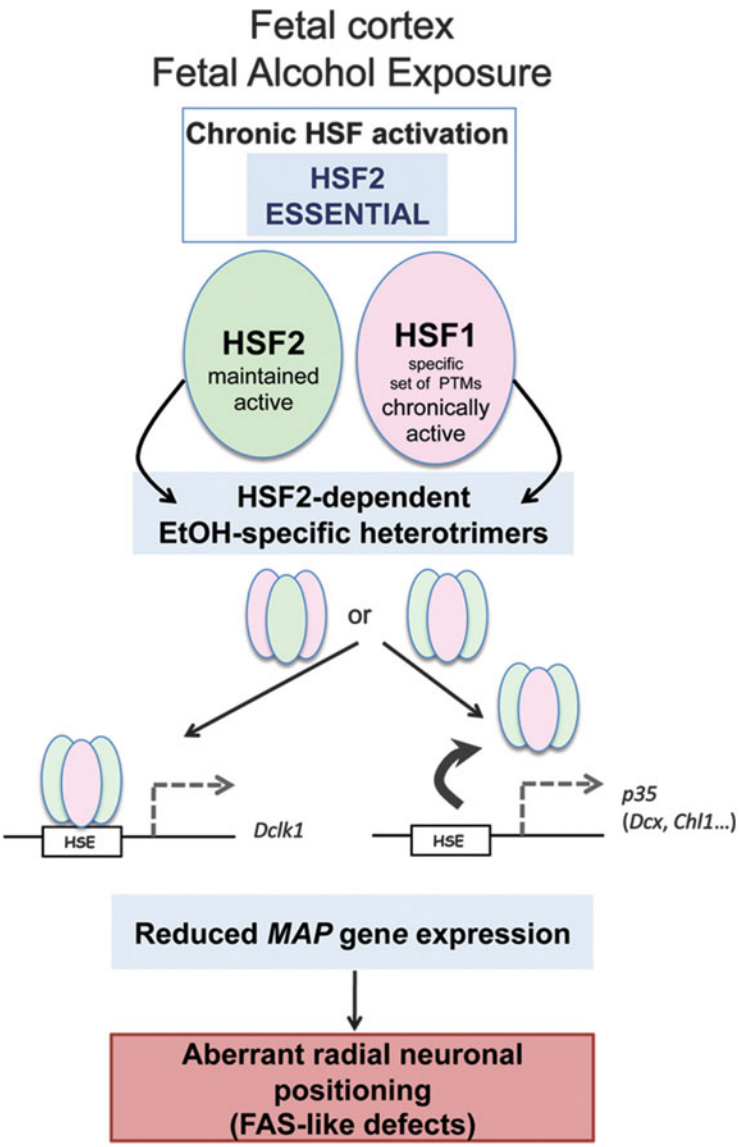

Fig. 6.5 Models for the functions of HSF1-HSF2 heterotrimers in migration defects upon fetal alcohol exposure. Fetal alcohol exposure may lead to persistent HSF1-HSF2 heterotrimers that bind to HSF2 target genes involved in neuronal migration (which are bound by HSF2 homotrimers under normal conditions) and disturb their expressions (*left*). Alternatively, the formation of heterotrimers may simply prevent bindings of HSF2 homotrimers to the HSE (*arrow*) (Figure was modified from El Fatimy et al. (2014))

Environmental insults such as alcohol exposure also increase the release of GABA (*gamma*-aminobutyric acid) and the frequency of inhibitory currents that have the potential to disturb overall brain development and function (Varodayan and Harrison 2013). In addition to all of the previous findings, Harrison's group also obtained evidence that support the possibility that HSF1 is involved in environmental stress-induced dysfunction of the GABAergic system (Pignataro et al. 2007). In the case of both heat shock and alcohol exposure, they observed increased expression of *Gabra4* mRNA that encodes the alpha 4 subunit protein of the GABA receptor in mouse embryonic cortical neurons (Pignataro et al. 2007). Then, using the luciferase assay, they demonstrated that Hsf1 controls *Gabra4* expression by binding to HSE in the promoter, thus proving that the increase of *Gabra4* mRNA by alcohol is mediated by Hsf1 (Pignataro et al. 2007).

These results reported by Harrison et al. add additional support for the critical involvement of HSF1 in environmental stress-elicited brain dysfunction, and they raise the possibility that a reduction in or inhibition of HSF1 functionality might alleviate the pathological consequences emanating from prenatal exposure to harmful agents or conditions.

Interestingly, GABA is also released in the neurogenic domains where neuronal progenitor cells reside, and it plays important roles in the proliferation/differentiation of the neural progenitor cells in both embryonic and adult cortex (LoTurco et al. 1995; Antonopoulos et al. 1997; Haydar et al. 2000; Liu et al. 2005). Therefore, the possibility also exists that the environmental stress-induced disturbance in proliferation/differentiation of neural progenitor cells (Miller and Nowakowski 1991; (Miller 1996) may also be mediated by HSF1-controlled GABAergic signaling.

6.4 Perspective

We are now on the verge of establishing with scientific certainty the importance of HSFs in mediating environmental stress-provoked pathological brain development in animal models. Although both detrimental and beneficial roles of HSFs were documented in the various studies of pathological brain development, it is yet to be determined if excess activation of HSF1 reduces or increases the risk of developing neural pathology and whether observations such as cell-to-cell variability in HSF1 responses to environmental stress in NPCs are random or directly connected to genetic predisposition.

The body of data reviewed in this chapter represents the cornerstone of evidence leading to the formulation of more fundamental questions that need to be addressed. However, further progress for comprehensive understanding of the molecular basis of HSF responses against prenatal environmental stress is inevitably important and may well lead to the discovery of prophylactic and/or therapeutic interventions of the neurodevelopmental diseases.

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