Chapter 11
HSP90: A Key Player in Metal-Induced Carcinogenesis?

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Abstract Three extensively used metals, cadmium, chromium and nickel, are established human carcinogens. The elucidation of the molecular and cellular mechanisms underlying the carcinogenicity of these metals has centered mostly on the signalling pathways that regulate cellular growth, differentiation and death. Unfortunately, our understanding of the involvement of these pathways in metal-induced carcinogenesis is still very incomplete. More recently, research has extended to include the impact of these metals on mechanisms not traditionally associated with cancer, but that are now increasingly viewed as playing a critical role in carcinogenesis. Among them is the stress response, a highly conserved mechanism employed by all cells for protection against protein damage. Indeed, all three metals induce proteotoxic stress, which warrants following this line of research. The present chapter will critically review published studies on the impact

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of carcinogenic metals on the expression of the heat shock protein 90 family (HSP90), one of the protein families that mediate the stress response. HSP90 has been consistently found to be overexpressed in many types of cancer and, significantly, HSP90 overexpression has been correlated with increased tumor growth, metastatic potential and resistance to chemotherapy.

Keywords Cadmium · Carcinogenesis · Hexavalent chromium · HSP90 · Nickel · Stress response

Abbreviations

Grp94	glucose regulated protein 94
HIF-1α	hypoxia-inducible factor 1 alpha
HSE	heat shock elements
HSF	heat shock factor(s)
HSP	heat shock protein family
Hsp	heat shock protein(s)
ROS	reactive oxygen species
TRAP1	tumor necrosis factor receptor-associated protein 1

11.1 Introduction

The stress response is a highly conserved mechanism used by all living organisms to recover from proteotoxic stress, i.e., stress that causes damage to proteins (Schlesinger et al. 1982). Ever since the discovery that several of the proteins that mediate this response, the so-called heat shock proteins (Hsp), are consistently overexpressed in many types of cancer, research on the molecular mechanisms of carcinogenesis expanded to include this response. One of the families of Hsp, HSP90, has received particular attention, as its overexpression has been correlated with increased tumor growth, metastatic potential and resistance to chemotherapy (Ciocca et al. 2013; Nahleh et al. 2012; Whitesell and Lindquist 2005).

The exact mechanisms through which the stress response might promote or facilitate carcinogenesis are not known, but it has been hypothesized that the activation of the stress response by mildly cytotoxic exposure to carcinogens may impart the surviving cells with an increased resistance to subsequent stresses, namely those encountered by incipiently transformed cells as they progress to full malignancy. Alternatively, this type of exposure may select for those cells that already possessed that increased resistance. As promoters of proteotoxic stress, carcinogenic metals are potential activators of the stress response. There is also some indication from in vitro studies that pre-incubation with cadmium or hexavalent chromium confers cells thermotolerance, i.e., tolerance to an otherwise lethal thermal stress (Abreu

et al. 2018; Goering and Fisher 1995). Whether the observed thermotolerance is due to increased Hsp expression and whether a similar protective effect occurs against stresses more relevant in the context of metal-induced carcinogenicity remains to be investigated.

Here, we critically review literature on the impact on HSP90 expression caused by cadmium, chromium (in the hexavalent state) and nickel, three widely used metals that are established occupational carcinogens (IARC 1990, 1993, 2012; NTP 2014). In addition, we highlight, whenever possible, plausible mechanistic links between HSP90 and metal-induced carcinogenesis. The first section of this chapter is devoted to the stress response and its links to carcinogenesis. Next, we provide information concerning the industrial and commercial applications of these metals, as well as the cancer risks to which several million workers employed in the respective industries are exposed. A brief overview of the molecular mechanisms underpinning their carcinogenicity will follow. Next, our current understanding of the impact of carcinogenic metals on HSP90 expression will be addressed, starting by a brief discussion of the promotion of proteotoxic stress by the three metals. Rather than presenting an exhaustive review of the literature, we aim at providing a critical analysis of selected studies, taking into account the context in which the results reported were generated and assessing their relevance in the field of metal-induced carcinogenesis. This analysis focused mostly on mammalian systems. Finally, the potential of HSP90 as a target for cancer therapy will be discussed.

11.2 Carcinogenesis, the Stress Response and Links Between the Two

Carcinogenesis entails the progression from an initial genetic mutation in a single transformed cell to the development of a fully malignant cancer cell, capable of indefinite growth and metastasis. In this process, abnormal growth and proliferation of cells with an increasing number of mutations eventually leads to the formation of a tumor mass, which will expand and colonize distant sites in the body. This journey is accompanied by a plethora of cellular stresses. At the cell intrinsic level, incipient cancer cells experience redox imbalance, endoplasmic reticulum stress (in part due to the accumulation of high levels of oncoproteins), genotoxic stress (arising from chromosome instability and faulty DNA repair) and deranged metabolism (Acharya et al. 2010; Ferreira 2010; Schar 2001; Vandewynckel et al. 2013). The genesis of a solid tumor is accompanied by yet another set of stresses, cell extrinsic in nature, arising in those areas of the solid tumor microenvironment that are characterized by hypoxia, acidosis and nutrient deprivation (Bertout et al. 2008; Herr and Debatin 2001; Neri and Supuran 2011; Pflaum et al. 2014).

There is growing evidence that tumors harbor a subpopulation of self-renewing cells, responsible for tumor growth, metastasis and resistance to conventional anticancer therapies (Reya et al. 2001). Named cancer stem cells, they were first

described in acute leukemia (Lapidot et al. 1994), and later identified in solid tumors (Mani et al. 2008). Cancer stem cells are often found in the most hypoxic and acidic regions of the tumor microenvironment, where they likely experience higher levels of cellular stress (Hjelmeland et al. 2011; Kim et al. 2018).

Several of the above-mentioned stresses are, in turn, strong inducers of proteotoxic stress, i.e., they produce conformational alterations to proteins that may eventually lead to their denaturation and aggregation. To protect themselves against this type of stress, normal cells activate the stress response, a ubiquitous homeostatic system found in all living organisms examined to date (Schlesinger et al. 1982). This response was first observed, in the early 1960s, in the form of a different puffing pattern exhibited by the polytene chromosomes of larval Drosophila tissue submitted to sub-lethal hyperthermia (Ritossa 1962). As chromosome “puffs” are synonymous with intense transcriptional activity, the different puffing pattern revealed that Drosophila cells were responding to heat shock by inducing a set of genes not usually expressed during their stage of larval development.

The products of the small set of genes strongly induced by heat shock belong to a family of highly conserved proteins collectively named heat shock proteins. The designation remains to this day, in spite of the fact that it is now known that these proteins are induced not only by heat shock, but also by any condition capable of inducing proteotoxic stress (Jolly et al. 2000; Morimoto 1993). Hsp mediate the stress response by playing a critical role in protein folding, in the assembly and disassembly of oligomeric protein complexes, in the translocation of proteins to their final subcellular locations and in the regulation of protein degradation (Csermely et al. 1998).

Mammals express many types of Hsp, classified in six families: HSP100, HSP90, HSP70, HSP60, HSP40, and small Hsp (sHSP) (Jolly and Morimoto 2000; Katschinski 2004). Family designations were based on the subunit relative molecular masses of their then known members (or isoforms). New found members are now assigned to a given family based on both subunit relative molecular mass and sequence homology. Of note, initial studies on Hsp did not discriminate between isoforms. For instance, the abbreviations Hsp70 and HSP70 were used to refer to any protein of an approximate molecular mass of 70 kDa strongly induced by heat or other promoters of proteotoxic stress. In an attempt to reduce any confusion that might arise due to this circumstance, the abbreviation HSP will be used throughout this chapter when referring to a family of Hsp (e.g., HSP90, for heat shock protein 90 family), whilst the abbreviation Hsp will be used to discriminate a specific isoform (e.g., Hsp90α, for heat shock protein 90 alpha).

Hsp levels are transcriptionally regulated by transcription factors known as heat shock factors (HSF). HSF are specific to heat shock elements (HSE), regulatory elements within the promoters of Hsp genes (Pirkkala et al. 2001). In mammals, the main regulator of the stress response is heat shock factor 1 (HSF1), one of the several isoforms of HSF present in these organisms (Lindquist 1986; Vihervaara and Sistonen 2014). HSF1 activation under stress conditions involves homotrimerization. In the case of hyperthermia, a “regulatory region” in HSF1 becomes less stable, eventually triggering a separate domain to interact with other HSF1 proteins,

forming homotrimers (Hentze et al. 2016). Yet, homotrimerization does not suffice to confer activity to HSF1. In the basal state, HSP90 inhibits HSF1 activity; only when the intracellular levels of unfolded proteins reach a high value does HSP90 get titrated away, allowing HSF1 activation (Voellmy 2004). Interestingly, HSF1 can also sense the redox state of the cell via two cysteine residues that, when oxidized, form a disulfide bond that prompts HSF1 trimerization and concomitant DNA-binding activity (Ahn and Thiele 2003).

Activation of the stress response is likely the key to understanding how tumor cells manage to thrive under the highly adverse circumstances associated with carcinogenesis. The increased HSF1 activity and elevated levels of most Hsp observed in several types of tumors (Ciocca et al. 2013) are in line with this hypothesis. HSF1 activation might not be the only mechanism responsible for the marked upregulation of Hsp in cancer; well-studied oncogenes and tumor suppressor genes have also been implicated. For instance, the activation of the promoters of some Hsp genes by the oncogenic transcription factor c-MYC, or their derepression when the tumor suppressor proteins p53 and p63 lose function, have been put forward as contributors to Hsp upregulation in cancer (Whitesell and Lindquist 2009). HSF1 has been shown to carry out several other functions in cancer cells and is, along with HSP90 and HSP70, one of the most well-studied components of the stress response in the context of carcinogenesis (Vihervaara and Sistonen 2014).

Increased levels of Hsp allow tumor cells to manage the increased burden of damaged and aggregated proteins, which would otherwise trigger programmed cell death. The contribution of the resulting increased pool of Hsp to protein homeostasis is two-fold: it aids the refolding of damaged proteins, preventing their aggregation, and, if the damage is too extensive for refolding to occur, it assists in sequestering and diverting the severely damaged proteins to the proteasome for degradation (Lindquist 1986; Schlesinger 1990; Whitesell and Lindquist 2005). Importantly, several studies have implicated Hsp in various oncogenesis hallmarks, including epithelial cell migration (Piotrowicz et al. 1998), tumor invasiveness and chemotherapy resistance (Oesterreich et al. 1993).

Interestingly, mortalin, a heat shock protein from the Hsp70 family, is overexpressed in embryonic stem cells relative to their differentiated counterparts (Saretzki et al. 2004) and its ectopic expression suffices to induce malignant transformation and inactivation of p53 in cultured cells (Wadhwa et al. 1999). Thus, a provocative view in the field states that the stress response in cancer cells is not merely an adaptive response that enables survival to multiple stresses, but rather an active driver of carcinogenesis (de Billy et al. 2012). In line with this view, the stress response has been implicated in tumor growth, in the acquisition and maintenance of cancer hallmarks and in chemotherapy resistance (Ciocca et al. 2013; Nahleh et al. 2012; Whitesell and Lindquist 2005). In summary, the stress response might be seen as a double-edged sword: developed throughout evolution to protect individual cells and, consequently, the whole organism against stressful conditions, it provides an escape route for incipiently transformed cells, allowing their progression to full malignancy and, ultimately, death of the organism.

11.3 Carcinogenic Metals: General Information

Among the human carcinogens identified by the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and other highly respected regulatory agencies are three metals: cadmium, chromium (in the hexavalent state; Cr(VI)) and nickel (IARC 1990, 1993, 2012; NTP 2014). All three are viewed as occupational carcinogens, as an increased risk of cancer has been unequivocally confirmed only among workers who were exposed, for extended periods of time, to high doses of these carcinogens.

The physical and chemical properties of these three metals make them particularly suitable for a wide variety of commercial and/or industrial applications. Namely, they all are highly resistant to corrosion and, as such, are used to impart this advantage to diverse materials. For instance, both nickel and chromium are components of stainless steel, whose manufacture accounts for ca. 60% and 80% of, respectively, all nickel and chromium produced. Cadmium is mostly used in the manufacture of nickel-cadmium batteries, accounting for ca. 80% of all cadmium produced. All three metals are also used as pigments and in metal finishing, nickel and chromium are used in welding, and each has a wide range of other metal-specific applications. Worldwide, the different cadmium, chromium and nickel industries employ several million workers (IARC 2012).

Although these metals are viewed mostly as occupational carcinogens, there has been, for some time now, concern regarding the general population, as mass production, recycling and disposal of these metals have turned them into widespread environmental pollutants (Jarup 2003). Fossil fuel combustion and tobacco smoke are additional strong contributors to their widespread presence in the environment (IARC 2012). Environmental exposure to cadmium is of particular concern, as this metal has a half-life of approximately 20–30 years in humans, and thus can accumulate to very high levels (Tully et al. 2000). This is in part attributable to the body's poor capacity to metabolically degrade and excrete this metal (Waalkes 2003). In terms of types of cancer, there is now sufficient evidence that cadmium and nickel metal (but not chromium metal), as well as cadmium compounds, hexavalent chromium compounds, and nickel compounds cause lung cancer. Depending on the metal, there is also either sufficient evidence or positive associations between exposure and other respiratory tract cancers, such as cancer of the nasal cavity. In the specific cases of cadmium metal and cadmium compounds, positive associations have been observed between exposure and cancer of the kidney and the prostate (IARC 2012).

11.4 The Generation of Proteotoxic Stress by Cadmium, Hexavalent Chromium and Nickel

Considering that cancer is traditionally viewed as a genetic disease characterized by disorganized growth, research effort in the field of metal carcinogenicity has mostly been devoted to the elucidation of the interactions that carcinogenic metals establish

with the genome, the genetic and genomic damage they produce, the impact that they have on signalling pathways and, ultimately, the changes they produce at the phenotypic level (Feng et al. 2018; Holmes et al. 2008; Wang et al. 2018). Understandably, the focus has been mainly on those genes/gene products directly involved in the regulation of cellular proliferation, differentiation and death and whose disruption is thought to dictate malignant growth (Hanahan and Weinberg 2011). In spite of their undeniable importance, a complete discussion of the results obtained in this type of research studies is beyond the scope of this chapter. Instead, this section will briefly describe how cadmium, hexavalent chromium and nickel can generate proteotoxic stress. Nonetheless, the impact of carcinogenic metals on cancer-associated HSP90 client proteins will be very briefly addressed in Sect. 11.6.

Exposure to cadmium, hexavalent chromium and nickel can generate proteotoxic stress by direct and indirect mechanisms. In the case of cadmium, an electrophile (or a soft acid, according to Pearson's principle (Pearson 1968)), proteotoxic stress has been ascribed, to a large extent, to a competition with zinc. Zinc, the second most abundant trace metal found in eukaryotic organisms, is required for essential catalytic functions in hundreds of enzymes, playing also a critical role in the stabilization and folding of protein subdomains (Coleman 1992). By displacing zinc, cadmium compromises the structure and function of affected proteins (Waisberg et al. 2003). In the case of proteins belonging to the cellular antioxidant system, this replacement results in increased levels of reactive oxygen species (ROS) (Dorta et al. 2003; Liu et al. 2009; Martelli et al. 2006; Noel et al. 2004) and, ultimately, additional proteotoxic stress. Moreover, and as already mentioned in a preceding section, an oxidizing intracellular environment can promote the activation of HSF1, through oxidation of two critical cysteine residues of this master regulator of the stress response in vertebrates (Ahn and Thiele 2003; Dai et al. 2007). A similar outcome can result from the binding of cadmium to vicinal sulfhydryl groups in proteins, namely those belonging to the cellular antioxidant defense systems, altering their conformations and impairing their functions (Shimizu et al. 1997; Waalkes 2003; Waisberg et al. 2003). Curiously, back in 1980, when it was not even known that Hsp induction was a generalised defense mechanism against stressful conditions, Levinson and co-workers exposed cells to cadmium and other soft metals with known sulfhydryl binding capacity to test their hypothesis that Hsp induction was somehow related to binding to sulfhydryl-containing (then unknown) targets (Levinson et al. 1980). Substitution of zinc by cadmium has many other important biological consequences, namely in the context of carcinogenesis, but an extended discussion of this topic is out of the scope of this chapter. Let it just be briefly mentioned that, by replacing zinc in proteins and enzymes implicated in gene regulation, DNA repair, redox regulation and in the regulation of signaling pathways, cadmium may strongly contribute to the high degree of genomic instability observed in cadmium-exposed cells, thus contributing to tumor initiation and development (Bishak et al. 2015; Hartwig 2013; Waalkes 2003).

In stark contrast with cadmium and nickel (see below), hexavalent chromium interacts poorly with most biomolecules, so direct damage to proteins is unlikely to be a major contributor to proteotoxic stress (Urbano et al. 2012; Urbano et al. 2008).

However, the intracellular reduction of hexavalent chromium produces a variety of reactive species, some of them strong oxidizers, namely carbon, oxygen and sulphur free radicals, which can act as secondary stressors through the generation of oxidative damage, either directly or through depletion of intracellular antioxidant pools (Abreu et al. 2014). Studies reporting that the addition of *N*-acetylcysteine, a known antioxidant, reversed the impact of cadmium and hexavalent chromium on the expression of, respectively, HSP70 and/or HSP90 give some support to the hypothesis that oxidative stress mediates, at least in part, Hsp induction by these two carcinogens (Han et al. 2007; Xiao et al. 2012). The reactive species generated during the intracellular reduction of hexavalent chromium also cause damage to the DNA and, quite often, the carcinogenicity of this metal ion has been associated with the formation of DNA single- and double-strand breaks due to an abnormal processing of primary lesions by DNA repair systems. As a result of lesion accumulation, particularly double-strand breaks, the cell can either undergo apoptosis or attempt DNA repair by the non-homologous end joining system. Unfortunately, this system generates chromosome rearrangements and, ultimately, genomic instability (Reynolds and Zhitkovich 2007). Genomic instability can also result from uncoupling of centrosome duplication from the cell cycle, as a consequence of prolonged arrest at either S or G2 phases to repair double-strand breaks (Urbano et al. 2008).

Like cadmium and hexavalent chromium, nickel can also generate oxidative stress (Salnikow and Costa 2000). In addition, proteotoxic stress can be generated through binding of nickel to secondary amines in the histidine residues of proteins (Waisberg et al. 2003). Importantly, nickel binds to the His-His-carboxylate motive, present in all dioxygenases, with more affinity than iron, which might explain nickel's effects on the inactivation of histone demethylases, enzymes dependent on the 2-oxoglutarate activity (Chen et al. 2006).

11.5 Investigations Into the Involvement of the Stress Response in Metal Carcinogenesis: A Contextualization

As promoters of proteotoxic stress, carcinogenic metals are potential activators of the stress response. Before starting our discussion of this topic, it must be mentioned that most of the studies that will be discussed in this and the following sections were not aimed at establishing correlations between Hsp induction and carcinogenesis. Thus, the model systems used were not always especially suited for the study of the mechanisms underlying metal-induced carcinogenesis. Studies dating back to the 1970s and 1980s aimed to understand why cells responded to heat shock by a strong induction of a small set of specific proteins (Tissieres et al. 1974). One of these studies, already briefly mentioned in the preceding section, involved several metals, including cadmium and nickel (Levinson et al. 1980). This seminal study showed that exposure of chick embryo cells to 10 μM Cd(II) strongly induced the synthesis of 100, 75, 35 and 25 kDa Hsp. For the 100, 75 and 35 kDa Hsp,

enhancement became visible after a 1 h exposure, whereas enhancement of the 25 kDa Hsp required a longer (2 h) exposure. Hsp induction was also observed with copper, zinc and mercury. Nickel, on the contrary, failed to induce these proteins, even at a concentration as high as 500 μM Ni(II). Later, however, HSP70 (but not HSP90) induction by nickel was reported, when primary cultures of rat hepatocytes were exposed, for 4 h, to 2000 μM Ni(II) (Bauman et al. 1993). The same study confirmed cadmium's ability to produce a strong induction of HSP70 in the low micromolar range (4–8 μM Cd(II)). With this exposure regimen, an induction of HSP90 by cadmium could also be detected, albeit smaller than that observed for HSP70. It is important to stress that, in the context of carcinogenesis, the most relevant concentrations are those that induce some, but not overt, cytotoxicity. Thus, although the concentrations of the two metals required for Hsp induction differed by almost three orders of magnitude, their biological significance is likely comparable, as both corresponded to the highest possible toxicity for the corresponding metal, without killing all of the cells. The combined results of these two studies suggested that the impact of metals on Hsp expression depends not only on the metal, but also on the system (e.g., cell type and species), the exposure regimen (duration of the exposure and metal concentration), as well as on the specific Hsp.

Later, the realization that insults that were not overtly cytotoxic promoted Hsp induction led to the suggestion that Hsp levels might be used in molecular toxicology as sensitive biomarkers of early exposure, toxicity and environmental stress. In fact, the first study investigating Hsp induction by hexavalent chromium aimed specifically at verifying the feasibility of using Hsp induction for the rapid detection of low levels of pollutants (Delmas et al. 1998). In this study, rather than relying on protein levels, whose quantification, back then, classically involved the time-consuming and not always straightforward autoradiography or fluorography of electrophoretically separated ^{35}S-methionine-labeled proteins, Delmas and collaborators quantified the transcript levels of a specific Hsp, Hsp72, using an RNase protection method that involved a radiolabeled antisense RNA probe. These authors found that, in HepG2 cells, a 6 h exposure to concentrations as low as 1 μM Cr(VI) significantly increased Hsp72 mRNA. In HT29 cells, Hsp72 induction required a higher Cr(VI) concentration (20 μM). Such higher concentration was, nonetheless, not overtly cytotoxic to this cell line. It is important to note that, in some instances, different study outcomes can be ascribed, at least in part, to the different sensitivities of the methods employed, as is well illustrated in a study by Carroll and Wood (Carroll and Wood 2000). Using immunoblotting, these authors were able to detect HSP90 induction in human keratinocytes after a 1 h exposure to 10 μM Ni(II). Using ^{35}S-methionine-labeling, HSP90 induction only became apparent when the concentration was increased to 1000 μM. The study by Carroll and Wood also confirmed the dependence on the model system employed, as HSP90 induction was much stronger in dermal fibroblasts than in keratinocytes. Finally, as many of the studies did not discriminate which member(s) of a given family was being assessed, comparisons between studies become even more complex.

11.6 The Impact of Cadmium, Hexavalent Chromium, and Nickel on HSP90 Expression

Although activation of the stress response by cadmium, hexavalent chromium and nickel may be mediated by several Hsp families, this chapter will focus specifically on HSP90 induction, with only occasional forays into the induction of other HSP by these metals. HSP90, unlike other HSP, is not required for the correct folding of newly synthesized proteins. Instead, its main role appears to be the stabilization of meta-stable proteins. Significantly, many HSP90 client proteins are involved in the acquisition of cancer hallmarks. Chief among these are several receptor tyrosine kinases and steroid hormone receptors, such as the human epidermal growth factor 2 (HER2), associated with uncontrolled cellular proliferation (Whitesell and Lindquist 2005; Ziemiecki et al. 1986), telomerase, an enzyme required for immortalization and acquisition of cancer stem cell properties (Beck et al. 2011; Holt et al. 1999), AKT, involved in apoptosis (Basso et al. 2002), hypoxia-inducible factor 1 alpha (HIF-1α), essential for angiogenesis (Isaacs et al. 2002) and matrix metalloproteinases (MMP), crucial for successful tissue invasion and metastasis (Eustace et al. 2004). A more complete list of HSP90 client proteins involved in initiating or maintaining cancer hallmarks is provided in Table 11.1. It is important to stress that Table 11.1, which is intended to illustrate the involvement of HSP90 in carcinogenesis, does not constitute an exhaustive list of all reported studies in this field of research.

It has been postulated that stabilization of the above-mentioned proteins by members of the HSP90 family potentiates the metabolic shift and invasiveness observed in tumors (Ferreira 2010; Ferreira et al. 2012; Whitesell and Lindquist 2005). In line with this hypothesis, HSP90 has been consistently found to be overexpressed in many types of cancers and this overexpression correlates with tumor growth, metastatic potential and resistance to chemotherapy (Ciocca et al. 2013; Nahleh et al. 2012; Whitesell and Lindquist 2005). Strikingly, many cancer-associated HSP90 client proteins are modulated by cadmium, hexavalent chromium, or nickel (Table 11.2), with 15 of them being targeted by all three metals (Fig. 11.1).

As is the case with the other HSP of high molecular weight, the chaperoning activity of HSP90 is dependent on ATP. Specifically, ATP must bind to a specific site of their amino terminal domain (N-terminal domain) and suffer hydrolysis. It is believed that ATP binding to HSP90 and its subsequent hydrolysis causes conformational alterations that are essential for substrate binding (Pearl and Prodromou 2006; Wandinger et al. 2008). The ATP-binding pocket of this family of proteins is distinct from the one found in many kinases and in HSP70 (Dutta and Inouye 2000). Although the biological relevance of this feature remains unclear (Whitesell and Lindquist 2005), it has already been exploited for the development of drugs specifically targeting HSP90 (Calderwood et al. 2006), as will be discussed in the last section of this chapter.

Two other domains can be found in HSP90 proteins: a highly charged middle domain (M domain), which is the docking site for the client proteins, and the car-

Table 11.1 HSP90 client proteins involved in initiating or maintaining cancer hallmarks

Cancer hallmark	HSP90 client protein	References
Sustained proliferative signaling	RAF1, HER2, BCR-ABL, Annexins, KIT, PI3K, AKT, EGFR	Ahsan et al. (2012), Citri et al. (2006), Floris et al. (2011), Giulino-Roth et al. (2017), Lei et al. (2004), Sato et al. (2000), Schulte et al. (1995), Solit et al. (2002), and Wu et al. (2008)
Evading growth suppressors	PLK, WEE1, CDK4, CDK6, MYT1, cyclin D, PTEN	Blank et al. (2003), Burrows et al. (2004), Fu et al. (2013), Lokeshwar (2012), Mahony et al. (1998)
Avoiding immune destruction	IKKβ	Lee et al. (2010)
Enabling replicative immortality	Telomerase	Holt et al. (1999)
Tumor-promoting inflammation	IKKβ, NOS, TAK1	Harris et al. (2008), Lee et al. (2010), Presley et al. (2010), Shi et al. (2009), and Trepel et al. (2010)
Invasion and metastasis	MMPs, BRMS1, uPAR, V-ATPase, TAK1, FAK	Asuthkar et al. (2012), Correia et al. (2013), Hartson and Matts (2012), Hurst et al. (2006), Shi et al. (2009), Stellas et al. (2010), and Xiong et al. (2014)
Inducing angiogenesis	FAK, HIF-1α, VEGF-R2, FLT3, SRC, JNK	Bruns et al. (2012), Minet et al. (1999), Nieto-Miguel et al. (2008), Whitesell et al. (1994), Xiong et al. (2014), and Yao et al. (2003)
Genome instability and mutation	BRCA1, BRCA2, CHK1, FANCA, DNA-PKcs, p53, MRE11, RAD50, NBS1	Blagosklonny et al. (1995), Dote et al. (2006), Makhnevych and Houry (2012), Noguchi et al. (2006), Oda et al. (2007), Quanz et al. (2012), and Stecklein et al. (2012)
Resisting cell death	RIPK1, IGF-1R, BCL-2, APAF-1, p53, BID, Survivin	Blagosklonny et al. (1995), Breinig et al. (2011), Dias et al. (2002), Fortugno et al. (2003) Lewis et al. (2000), and Zhao and Wang (2004)
Rewired metabolism	SDH, IDH3G, NDUFS3, MDH2, HIF-1α, SCAP/SREBP, V-ATPase, PKM2, MYC, p53	Blagosklonny et al. (1995), Chae et al. (2013), Hartson and Matts (2012), Kuan et al. (2017), Lee et al. (2018), Minet et al. (1999), and Xu et al. (2017)

boxyl terminal domain (C-terminal domain), which possesses another ATP-binding site and is essential for dimerization (Pearl and Prodromou 2006). It is thought that the chaperoning function of HSP90 requires the assembly of an HSP90 chaperone machine, a dynamic complex comprising, in addition to HSP90 homodimers, HSP70 and proteic co-chaperones (Trepel et al. 2010; Wandinger et al. 2008). Docking of the co-chaperones usually occurs on the M domain, but co-chaperones can also interact with the other two domains and mediate the interaction of HSP90 with its client proteins (Pearl and Prodromou 2006). The fact that HSP90 can chaperone so many distinct client proteins can be explained by the existence of different complexes, assembled from diverse associations of different co-chaperones. So far,

Table 11.2 Cancer-associated HSP90 client proteins modulated by cadmium, hexavalent chromium and/or nickel

Protein/gene modulated by cadmium	References	Protein/gene modulated by hexavalent chromium	References	Protein/gene modulated by nickel	References
Annexin-A3	Lubovac-Pilav et al. (2013)	Annexin-A2	Madureira et al. (2012)	Annexin-A1, -A2, -A8	Wezynfeld et al. (2014)
BCL-2	Fernandez et al. (2003)	BCL-2	Medan et al. (2012)	BCL-2	Lee et al. (2001)
BID	Li et al. (2000)	BID	Hill et al. (2013)	BID	Guo et al. (2016)
Cyclin-D1	Topisirovic et al. (2002)	Cyclin-B1, -D2, -D3, -E2	Stanley et al. (2011)	Cyclin-D1, -E	Ding et al. (2009)
EGFR	Wei et al. (2015)	EGFR	Kim et al. (2015)	EGFR	Chiou et al. (2015)
HIF-1α	Jing et al. (2012)	HIF-1α	Kim et al. (2016)	HIF-1α	Salnikow et al. (2002)
IDH	Kil et al. (2006)	IDH	Shil and Pal (2018)	IDH	O'Leary and Limburg (1977)
IKKβ	Liu et al. (2016)	IKKβ	Chen et al. (2002)	IKKβ	Viemann et al. (2007)
JNK	Chuang et al. (2000)	JNK	O'Hara et al. (2003)	JNK	Wu et al. (2011)
MMP-9	Lian et al. (2015)	MMP-1, -2	Kim et al. (2016) and Lu et al. (2018)	MMP-2, -7, -9, -11, -13	Ota et al. (2018) and Wan et al. (2011)
MYC	Tang and Enger (1991)	MYC	Pratheeshkumar et al. (2016)	MYC	Li et al. (2009)
p53	Tokumoto et al. (2011)	p53	Carlisle et al. (2000)	p53	Maehle et al. (1992)
PI3K/Akt	Tsai et al. (2016)	PI3K/Akt	Kim et al. (2015)	PI3K/Akt	Pan et al. (2011)
SDH	Karthikeyan and Bavani (2009)	SDH	Fernandes et al. (2002)	SDH	Repetto et al. (2001)
CDK-1, -2	Wei et al. (2015)	CDK-1, -2, -4, -6	Stanley et al. (2011)		
CHK1/2	Bork et al. (2010)	CHK1	Ganguly et al. (2018)		
DNA-PKcs	Li et al. (2015)	DNA-PKcs	Hill et al. (2011)		
FAK	Choong et al. (2013)	FAK	Lu et al. (2018)		
IGF-1R	Fujiki et al. (2017)	IGF-1R	He et al. (2013)		
PTEN	Huang et al. (2014)	PTEN	Zhong et al. (2017)		
RAF1	Ju et al. (2017)	RAF1	Bae et al. (2009)		

(continued)

Table 11.2 (continued)

Protein/gene modulated by cadmium	References	Protein/gene modulated by hexavalent chromium	References	Protein/gene modulated by nickel	References
uPAR	Pratheeshkumar et al. (2016)	uPAR	Pratheeshkumar et al. (2016)		
		Plk1	Chun et al. (2010)	Plk3	Li et al. (2017)
NOS	Majumder et al. (2008)			NOS	Gupta et al. (2000)
SRC	Martinez Flores et al. (2013)			SRC	Cabail et al. (2016)
Telomerase	Dai et al. (2010)			Telomerase	Lei et al. (2001)
		MDH2	Shil and Pal (2018)		
		MRE11	Xie et al. (2008)		
		NDUFS3	Zhang et al. (2016)		
		RIPK1	Gavin et al. (2007)		
c-Kit	Weng et al. (2014)				
PKM2	Kim et al. (2014)				
V-ATPase	Herak-Kramberger et al. (1998)				
VEGF-R2	Kim et al. (2012)				
WEE1	Lubovac-Pilav et al. (2013)				
				APAF-1	Guo et al. (2016)
				BRMS1	Ota et al. (2018)

four different proteins have been assigned to HSP90: the classic Hsp90 (i.e., the isoforms Hsp90α and Hsp90β), localizing mostly to the cytosol; glucose regulated protein 94 (Grp94), found in the endoplasmic reticulum; and tumor necrosis factor receptor-associated protein 1 (TRAP1), which localizes to mitochondria (Csermely et al. 1998; Felts et al. 2000). The existence of efficient protein stabilization mechanisms in the mitochondria is amply justified, as these electron- and protein-rich organelles are particularly prone to ROS generation as by-products of respiratory metabolism. Significantly, it was reported that TRAP1 levels are significantly higher in tumor cells than in their normal counterparts (Chae et al. 2013; Kang et al. 2007;

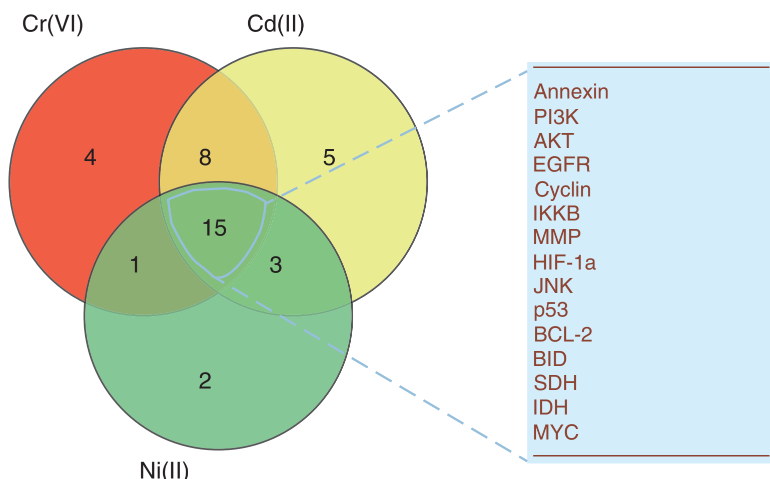

Fig. 11.1 HSP90 clients implicated in cancer are impacted at the protein and/or mRNA level by all three carcinogenic metals: cadmium, hexavalent chromium and nickel. Out of 49 HSP90 client proteins involved in establishing and/or maintaining hallmarks of cancer, 15 are targeted by all three metals. Created using http://genevenn.sourceforge.net/vennresults.php

Leav et al. 2010), likely to ensure mitochondrial genome integrity and safeguard respiratory function and mitochondrial biosynthetic capacity. It must be borne in mind that, although most tumor cells exhibit a higher-than-normal reliance on lactic acid fermentation, they are still dependent on respiration (Abreu and Urbano 2016; Bajzikova et al. 2019; Ferreira 2010; Ferreira et al. 2012; Tan et al. 2015). Interestingly, it has been found that many environmental toxicants, including metals such as cadmium, tend to accumulate in mitochondria (Meyer et al. 2013). As to hexavalent chromium, it was recently reported that, at concentrations in the low micromolar range, it augmented mitochondrial biogenesis in HepG2 cells, suggesting that hexavalent chromium toxicity can be compensated by increasing mitochondrial content (Zhong et al. 2017).

In addition to their different intracellular locations, HSP90 can also be found in the cell surface of many cell types and it can also be secreted to the extracellular environment. Normal cells secrete HSP90 in response to tissue injury, favoring healing by promoting cell motility (Li et al. 2012). HSP90 secretion is mostly regulated by HIF-1α, which is known to be activated by hypoxia and oxidative stress. Considering that many tumors overexpress HIF-1α, which is due, at least in part, to intratumoral hypoxia, this recently identified role of HIF-1α has been proposed as an explanation for the secretion of HSP90 by tumor cells (Li et al. 2012). The consistent observation of HSP90 overexpression in tumors led to the proposal that this feature could be used as a marker of cellular malignancy and to the concept of HSP90 "addiction" (Barrott and Haystead 2013; Trepel et al. 2010). This "addiction" would arise from a constant need of an increased pool of HSP90 to continuously retrieve essential proteins that became misfolded due to extensive proteotoxic

stress, as well as to facilitate the function of oncoproteins and mutated tumor suppressor proteins by protecting them from misfolding and degradation.

Our discussion on the impact of carcinogenic metal exposure on HSP90 levels starts with a study that Andrew and collaborators published in the early 2000s, as this is the only study published thus far that involved all three carcinogenic metals (Andrew et al. 2003). In terms of biological relevance, it is noteworthy that this study employed a cell line (BEAS-2B) established from normal human bronchial epithelium, which is the main target of these metals' carcinogenicity, and none of the concentrations tested caused overt cytotoxicity. Aiming at identifying sensitive and specific biomarkers of exposure, Andrew and collaborators used the then relatively recent cDNA microarray technology to assess the impact of these three metals (as well as arsenic) on the expression of 1200 genes. Cells were exposed for 4 h to 3 μM Cd(II), 10 μM Cr(VI) or 3 $\mu g/cm^2$ Ni. Each metal modified the expression of a relatively small subset of genes, i.e., the changes observed in gene expression were not the characteristic unspecific response to a highly cytotoxic insult. Specifically, cadmium, hexavalent chromium and nickel altered the expression of, respectively, 25, 44 and 31 genes. Each subset was rather unique, as only 7 of the analyzed genes saw their expression altered by all three metals. Interestingly, HSP90 was one of these 7 genes. The same was not observed for either of the two other HSP assessed in this study, HSP40 and HSP60. For these genes, transcript levels were decreased by Cr(VI) exposure, but remained unaltered upon exposure to Cd(II) and Ni. Whenever affected by these metals, Hsp transcript levels were always decreased.

Decreased Hsp mRNA levels do not, *per se*, support activation of the stress response, as would be expected, considering the capacity of all three metals to produce proteotoxic stress, but this does not necessarily imply otherwise. Indeed, it should be borne in mind that a decrease in Hsp transcript levels does not necessarily translate into a decrease in the corresponding protein levels. There are several reports of decoupling of mRNA and protein steady-state levels (Bauernfeind and Babbitt 2017; Greenbaum et al. 2003), which might have resulted, for instance, from the actions of critical post-transcriptional regulators, such as microRNAs and RNA binding proteins (Glisovic et al. 2008; Janga and Vallabhaneni 2011). Moreover, protein stability and turnover may be affected by post-transcriptional protein modifications (Doherty et al. 2009; Sadoul et al. 2008), further contributing to different profiles of mRNA and protein expression.

Decoupling of mRNA and protein steady state levels was observed in the only study to date that assessed the effects of hexavalent chromium on HSP90 expression at both levels (Abreu et al. 2018). After a 48 h incubation with 1 μM Cr(VI), Hsp90α mRNA levels of BEAS-2B cells, assessed by quantitative reverse-transcription polymerase chain reaction (RT-qPCR), remained the same, whereas Hsp90α protein levels, assessed by enzyme-linked immunosorbent assay (ELISA), were decreased by ca. 60%. Apart from the mechanisms just discussed, different kinetics of the transcriptional and translational programs activated by Cr(VI), as well as different rates of mRNA and protein degradation, might also help explain the observed discrepancy. In fact, previous studies on the kinetics of Hsp expression have shown that Hsp overexpression is a transient event (Diller 2006; Wang et al. 2003) and that, at

least under some circumstances, an upregulation observed immediately after shock can be followed by a decline to expression levels lower than the controls during the recovery phase (Liu et al. 2012). In this respect, it is interesting to discuss the results obtained by Rudolf and Cervinka, who investigated the effects, in primary cultures of human skin fibroblasts, of a combined exposure to hexavalent chromium and nickel on, among other parameters, HSP90 expression (Rudolf and Cervinka 2010). First, it was confirmed that cytotoxicity is achieved at much lower concentrations in the case of Cr(VI) (1 μM), than in the case of Ni(II) (250 μM). Secondly, at a non-cytotoxic concentration (25 μM), Ni(II) attenuated significantly the cytotoxicity of Cr(VI). Thirdly, the observed changes in HSP90 expression, which were assessed by immunoblotting, depended on Ni(II) concentration and, for each of the two Ni(II) concentrations tested, were time-dependent. For the non-cytotoxic Ni(II) concentration, a slight induction was observed after 3 h of exposure and this induction became increasingly more pronounced at 6, 12 and 18 h of exposure. For the cytotoxic Ni(II) exposure, a pronounced effect was observed after 3 h of exposure, gradually decreasing afterwards.

In spite of the above considerations concerning decoupling of protein and transcript levels, it might be symptomatic that out of the six studies evaluating the impact of hexavalent chromium on HSP90 protein and/or transcript levels, all employing mammalian cells, four reported a decrease (Abreu et al. 2018; Andrew et al. 2003; Banu et al. 2011; Xiao et al. 2012) and one showed no impact (Izzotti et al. 2002); the only study reporting an increase employed an extremely high concentration of Cr(VI) (600 μM) (Ye and Shi 2001). Altogether, these studies indicate that cells respond to insults that might be viewed as relevant in the context of hexavalent chromium carcinogenicity by decreasing their intracellular HSP90 levels. One hypothesis worth exploring is the promotion of histone deacetylation and/or DNA hypermethylation by hexavalent chromium. Yet, there are other ways through which hexavalent chromium might affect HSP90 activity. Namely, some of the species generated during its intracellular reduction might bind to HSP90, compromising its function. In the case of nickel, binding to HSP90 has been reported in a recent study investigating the inflammatory process caused by nickel eluted from biomedical devices in human monocyte THP-1 cells (nickel is one of the most prevalent contact allergen in the industrialized world (Nielsen et al. 2002)). More specifically, nickel was found to bind to the linker domain on the beta isoform of Hsp90. This binding reduced the interaction of Hsp90β with HIF-1α, and promoted instead the interaction between HIF-1α and HIF-1β, as well as the nuclear localization of HIF-1α (Asakawa et al. 2018).

Nickel has been shown to upregulate HSP90 protein levels in a variety of systems. For instance, using immunoblotting, Hfaiedh and collaborators observed that Gpr94 levels were consistently increased upon exposure of three different mammalian cell lines, A549, COS-7 and HepG2, to 100–400 μM Ni(II) (Hfaiedh et al. 2005). The same study revealed a tissue-specific impact of nickel on Grp94 protein levels: these levels were upregulated in the kidney, yet unaltered in the liver and ovary of Wistar rats. HSP90 induction by nickel in human dermal fibroblasts and keratinocytes was discussed in the previous section (Carroll and Wood 2000). In

terms of studies reporting lack of HSP90 induction by nickel, two of them, already mentioned in preceding sections, employed ^{35}S-methionine labeling, a relatively insensitive technique (Bauman et al. 1993; Levinson et al. 1980). Thus, it cannot be excluded that a different outcome might have been obtained using a more sensitive technique. However, in a recent study employing a sensitive technique (two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) in combination with electrospray ionization tandem mass spectrometry (ESI-MS/MS)), exposure of murine bone marrow-derived dendritic cells to Ni(II) did not elicit any changes in HSP90 protein levels at the two concentrations tested, i.e., 250 and 400 μM (the latter described by the authors as "maximal tolerated dose") (Mussotter et al. 2016). Regarding HSP90 mRNA levels, no changes could be observed in cultured human peripheral lung epithelial HPL1D cells when these were exposed for 24 h to non-cytotoxic Ni(II) concentrations (50, 100 and 200 μM), whereas a decrease was observed when the cells were exposed to cytotoxic concentrations (400, 800 and 1600 μM) (Cheng et al. 2003).

As mentioned before, aiming at testing whether Hsp induction was somehow related to binding to sulfhydryl-containing (then unknown) targets, Levinson and co-workers exposed chick embryo cells to cadmium and other soft metals with known sulfhydryl binding capacity (Levinson et al. 1980). Using ^{35}S-methionine labeling, these authors observed that 10 μM Cd(II) strongly induced the synthesis of 100, 75, 35 and 25 kDa Hsp. It is possible, but not certain, that the 75 kDa Hsp band in the autoradiogram included TRAP1. The interpretation of the results of a comprehensive study by Caltabiano and co-workers is also not straightforward in what concerns HSP90 induction by cadmium in human and murine melanoma cell lines (Caltabiano et al. 1986). The authors did report upregulation of HSP90 protein, but neither the magnitude of this upregulation nor the concentration of cadmium that elicited this response are clearly stated, as this aspect was not the major aim of the study. On the contrary, in the study by Bauman and collaborators, it is clearly stated that the two-fold increase in HSP90 protein levels was observed upon exposure of primary cultures of rat hepatocytes to Cd(II) concentration (4–8 μM) that caused some, but not overt cytotoxicity (Bauman et al. 1993).

In spite of these initial results, several studies reported unchanged HSP90 levels upon cadmium exposure. For instance, using RT-PCR and Western immunoblot analysis, Somji and collaborators could not observe any changes in Hsp90, neither at the transcript, nor at the protein levels, when HPT cells (derived from renal cell carcinoma) were exposed acutely (4 h) or chronically (up to 16 days) to Cd(II) (Somji et al. 2002). The concentration used in the acute exposure (53.4 μM) produced some, but not overt, cytotoxicity. Three different concentrations were used for chronic exposure, ranging from a non-cytotoxic concentration (9 μM) to a concentration that produced cell death early in the 16 day time course (45 μM). Whether this lack of response was related to the constitutively high levels of Hsp90 found in these cells remains to be determined.

In another study, Gottschalg and co-workers reported that, under conditions of "phenotypic anchoring" (i.e., in which the cadmium concentration to which cultures of each cell line were exposed were adjusted as to produce similar levels of cytotox-

icity), Cd(II) was without effect on HSP90 protein levels in FGC4 cells, HepG2 cells and in rat hepatocytes for concentrations of minimal and mild toxicity (5 and 25%, respectively) (Gottschalg et al. 2006). There is also a report of decreased HSP90 protein levels upon cadmium exposure. This downregulation was observed when cultures of HK-2, a cell line established from normal human kidney, were exposed, for 5 h, to an overtly cytotoxic (100 μM) Cd(II) concentration (Madden et al. 2002). Interestingly, the same insult produced an increase in HSP90 protein levels in cultures of NRK-52, a cell line established from normal rat kidney. Recently, in a study designed to investigate the effects of cadmium on the activation of HSP/HSF1 pathway, Shinkai and collaborators observed that Cd(II), in the low micromolar range, promoted, in bovine aortic endothelial cells, a significant upregulation of Hsp90α and Hsp90β mRNA, but this was not accompanied by a similar increase in Hsp90 protein levels (Shinkai et al. 2017). It was also found that, in these cells, HSF1 interacts with Hsp90, as already observed in other systems (Akerfelt et al. 2010), and that Cd(II) facilitated their dissociation. This disruption might explain, at least in part, the observed upregulation of Hsp90 (as well as other Hsp). Using human recombinant Hsp90β, these authors also showed that, under the conditions used, cadmium modified this isoform at Cys412, located in the M domain, and Cy564, located in the C-terminal domain.

11.7 Targeting HSP90 for Cancer Therapy

Cancer cells are infamous for hijacking physiological processes to sustain uncontrolled growth and metastasis, making them exceptionally resilient. In a vicious cycle, exposure to high levels of stressors selects for higher genetic mutation burdens, which in turn cause even higher levels of cellular stress. Yet, this also results in cancer cells with an excessive reliance in these hijacked processes, a liability that may be exploited in the development of a new generation of cancer therapeutics (Galhardo et al. 2007). Mounting evidence that the stress response is activated in cancer cells has led many investigators to propose several elements of the stress response pathway as new therapeutic targets. As such, much effort has been devoted to the development of Hsp inhibitors (Soo et al. 2008). HSP90 inhibitors, in particular, have been the focus of intense activity in the realm of clinical research, kindled by the prospect of achieving simultaneous inhibition of the chaperoning of several oncogenic proteins crucial for the development and maintenance of cancer hallmarks (Donnelly and Blagg 2008; Hanahan and Weinberg 2011; Soo et al. 2008; Trepel et al. 2010) (Table 11.1). The great majority of HSP90 inhibitors developed so far interact with its N-terminal ATP-binding pocket with greater affinity than ATP. Binding of these compounds thus inhibits the ATPase activity of HSP90, disrupting the chaperone cycle and concomitantly promoting client protein degradation (Trepel et al. 2010; Whitesell and Lindquist 2005). Most tested compounds revealed promising anticancer activities both in vitro and in vivo (Sidera and Patsavoudi 2014). To date, 68 clinical trials investigating HSP90 inhibitors have

been registered at clinicaltrials.gov, of which 33 have been completed and 16 are currently ongoing. Yet, no HSP90 inhibitor has been approved for use in the clinic.

Concerns about the safety of this therapeutic strategy have been raised. As HSP90 is ubiquitously expressed and essential for normal cell function, its inhibition may provoke undesirable side effects in normal cells. Interestingly, however, HSP90 has been shown to have ca. 100-fold greater affinity for its inhibitors in cancer cells than in normal cells, leading to an accumulation of the inhibitors within the tumors (Kamal et al. 2003). This differential affinity is likely due to the increased fraction of HSP90 that is involved in multiprotein complexes in cancer cells, possibly as a consequence of the augmented load of misfolded and mutant proteins. In contrast, HSP90 in normal cells is found mostly as free dimers with lower ATPase activity compared with the aforementioned multiprotein complexes (Kamal et al. 2003; Whitesell and Lindquist 2005). These observations indicate the existence of a therapeutic window in which HSP90 inhibitors will efficiently target cancer cells without interfering with neighboring normal cells.

To improve the efficacy of this therapeutic strategy, it will be of utmost importance to choose cancers that are driven by HSP90 client proteins. Indeed, analysis of 15 phase II clinical trials, spanning 10 different types of cancer, using HSP90 inhibitors found several instances of lack of a clinical response due to low expression of HSP90 client proteins in the tumor (Wang et al. 2016). A potential strategy to increase the range of tumors that can be treated with HSP90 inhibitors is to use these molecules synergistically with other therapeutic strategies (Trepel et al. 2010). Currently, there are, for instance, studies investigating the potential of combining HSP90 inhibitors with small molecules targeting co-chaperones essential for HSP90 function, the proteasome machinery or even angiogenesis (Soo et al. 2008; Trepel et al. 2010).

Of note, inhibition of HSP90 by N-terminal domain targeting compounds has been shown to induce the expression of the cytoprotective Hsp70 and Hsp27 proteins (Nahleh et al. 2012). This effect could diminish treatment efficacy, as increased expression of these proteins will protect cancer cells from some of the adverse effects of HSP90 inhibitors. In line with this theory, it was observed that sensitivity of cancer cells to the HSP90 inhibitor geldanamycin can be significantly increased by simultaneous silencing of Hsp70 and/or Hsp27 (Trepel et al. 2010). Mechanistically, HSP90 removes HSF1 trimers from heat shock elements in the genome and sequesters it in unstressed cells, inhibiting HSP70 transcription (Kijima et al. 2018). HSP90 inhibition will thus prolong the duration of gene expression induction by HSF1, in turn promoting the synthesis of Hsp proteins. Moreover, it is known that HSF1 orchestrates a transcriptional program distinct from the heat shock response that promotes carcinogenesis, survival and proliferation of cancer cells (Mendillo et al. 2012), potentially extending the consequences of HSF1 activation well beyond the induction of the stress response.

To overcome the shortcomings inherent to N-terminal domain inhibitors, significant efforts towards the development of HSP90 C-terminal domain inhibitors, which do not seem to have the aforementioned drawbacks, are underway (Ciocca et al. 2013; Donnelly and Blagg 2008; Nahleh et al. 2012). In summary, the devel-

opment of HSP90 inhibitors has the potential to become a milestone in cancer therapy as a rationally designed approach. Unlike conventional radiotherapy and chemotherapy, which target all dividing cells indiscriminately, HSP90 inhibition should disproportionally affect tumor cells as they acquire an increasingly mutated proteome. As we gain further insights into the molecular mechanisms of cancer and the stress response, HSP90 inhibition is likely to become an important part of our armamentarium against cancer.

11.8 Conclusions

The discovery that, at least under some circumstances, heavy metals induce the expression of Hsp triggered a variety of studies aimed at evaluating whether Hsp levels might be used in molecular toxicology. These studies, which were carried out in a variety of experimental systems, clearly showed that the induction of the different Hsp is dependent on the metal, tissue, cell type and species. Importantly, these studies also unveiled significant differences in induction and recovery kinetics for different stressors and different Hsp. As most of the studies on Hsp induction by metals were not aimed at establishing correlations between Hsp induction and carcinogenesis, the model systems used were not always especially suited for the study of the mechanisms underlying metal-induced carcinogenesis. As a consequence, our understanding of the relationship between HSP90 expression and carcinogenesis is still very incomplete. Nonetheless, these studies provided insight regarding the parameters that might influence HSP90 expression and will definitely prove invaluable for the design of future studies addressing this issue. Future studies should be designed taking into account the relevance of the system in the context of metal-induced carcinogenesis, namely in terms of species, target tissue, metal concentration and kinetics of HSP90 induction and recovery.

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