7 The Role of HSF1 and the Chaperone Network in the Tumor Microenvironment

Nil Grunberg, Oshrat Levi-Galibov, and Ruth Scherz-Shouval

Abstract

Tumors are stressful environments. As tumors evolve from single mutated cancer cells into invasive malignancies they must overcome various constraints and barriers imposed by a hostile microenvironment. To achieve this, cancer cells recruit and rewire cells in their microenvironment to become pro-tumorigenic. We propose that chaperones are vital players in this process, and that activation of stress responses helps tumors adapt and evolve into aggressive malignancies, by enabling phenotypic plasticity in the tumor microenvironment (TME). In this chapter we will review evidence supporting non-cancer-cell-autonomous activity of chaperones in human patients and mouse models of cancer, discuss the mechanisms by which this non-cell-autonomous activity is mediated and provide an evolutionary perspective on the basis of this phenomenon.

Keywords

HSF1 · Chaperones · Tumor microenvironment · Cancer-associated fibroblasts · Heat shock · Stress responses · ER-stress · UPR · Cancer

N. Grunberg · O. Levi-Galibov · R. Scherz-Shouval (✉)
Department of Biomolecular Sciences, The Weizmann Institute of Science, Rehovot, Israel
e-mail: Ruth.shouval@weizmann.ac.il

7.1 Introduction

Malignant transformation is initiated by oncogenic mutations and loss of tumor suppressor genes, causing loss of growth control. However, the resulting proliferative imbalance is usually controlled by the normal surrounding tissue, thereby suppressing tumorigenesis (Bissell and Hines 2011). Tumors form when cancer cells succeed to distort local tissue homeostasis and recruit normal cells to support their sustained proliferation and evasion of immune surveillance. These non-transformed cells protect the cancer cells and support them by creating a pro-tumorigenic tumor microenvironment (TME) or tumor stroma (Fig. 7.1a). The TME comprises a variety of cell types, including lymphocytes, macrophages, neutrophils, fibroblasts, and endothelial cells as well as extracellular matrix (ECM) components (Hanahan and Weinberg 2011; Hance et al. 2014; Place et al. 2011). Endothelial cells give rise to the neoangiogenic vasculature, recruit immune cells, and modulate cancer cell dissemination and metastasis. Neutrophils and lymphocytes can mount cancer cell-killing responses or release pro-inflammatory factors that stimulate tumor progression (Hanahan and Coussens 2012; Sagiv et al. 2015). Cancer-associated fibroblasts (CAF), which are perhaps the most abundant cells in the TME of carcinomas (Hanahan and Weinberg 2011) support cancer cells through secretion of ECM, chemokines and

© Springer Nature Switzerland AG 2020

M. L. Mendillo et al. (eds.), *HSF1 and Molecular Chaperones in Biology and Cancer*, Advances in Experimental Medicine and Biology 1243, https://doi.org/10.1007/978-3-030-40204-4_7

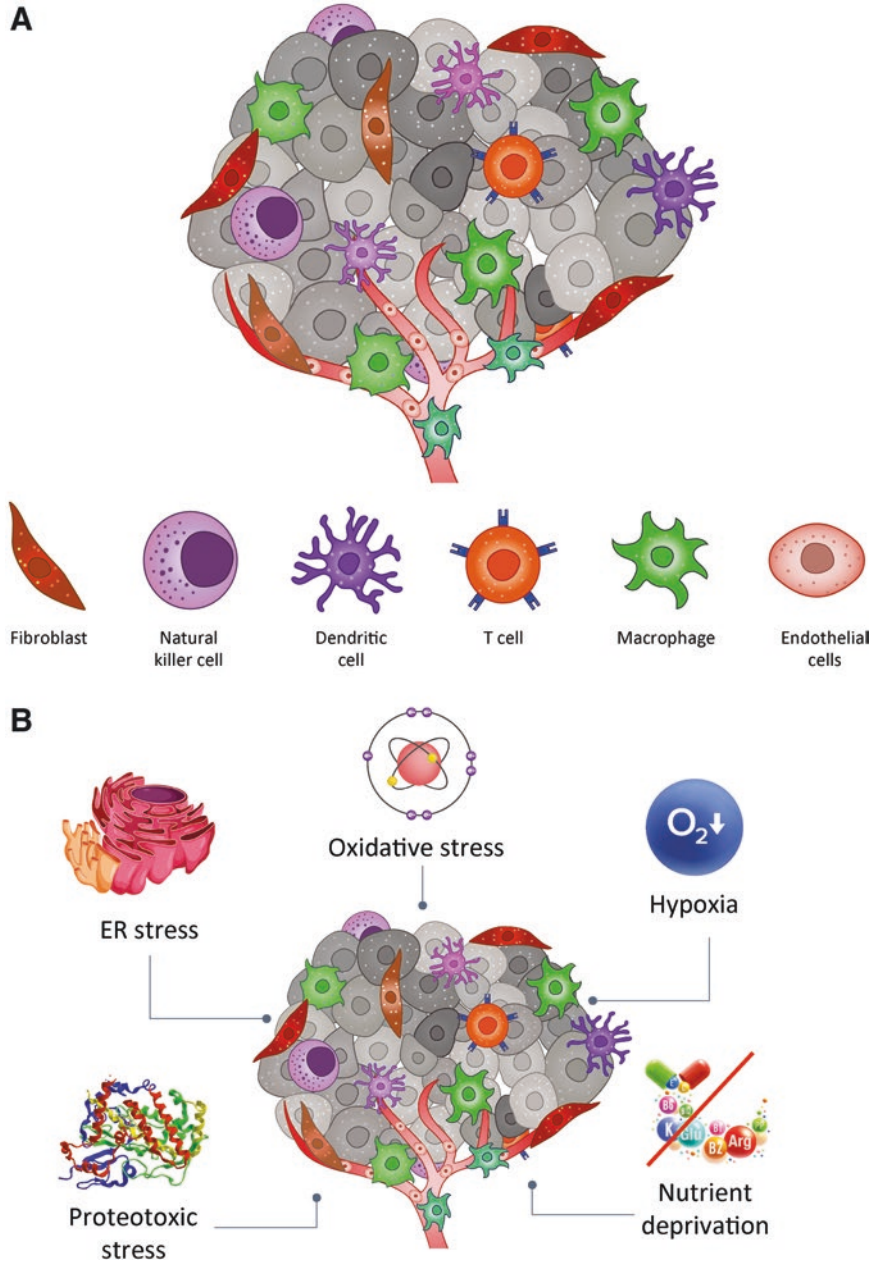

Fig. 7.1 Tumors are stressful microenvironments. (**a**) Cancer cells are depicted in shades of grey, different cell types interacting with cancer cells in the tumor microenvironment are highlighted in colors as detailed. (**b**) Stress conditions inherent to the tumor microenvironment are shown

cytokines (Alspach et al. 2014; Coppe et al. 2008; Erez et al. 2010; Finak et al. 2008). CAFs also promote the recruitment of tumor-associated macrophages (TAMs), with which they engage in a reciprocal relationship that promotes malignancy (Cirri and Chiarugi 2011; Comito et al. 2014; Erez et al. 2010). TAMs further stimulate angiogenesis, enhance cancer cell migration and invasion, and suppress anti-tumor immunity (Qian and Pollard 2010).

Throughout evolution, stress responses have helped cells and organisms survive in harsh conditions and overcome population bottlenecks. Rapidly evolving tumors are exposed to oxidative stress, DNA damage, metabolic stress, hypoxia and low pH (Fig. 7.1b; (Leprivier et al. 2015)). Moreover, they are exposed to population bottlenecks imposed by natural steps of tumor progression such as invasion and metastasis, as well as by external forces such as surgery and drug treatments. Under these extreme conditions cells of the TME and cancer cells constantly communicate with one another via secreted factors such as cytokines, chemokines, growth factors, and proteases (Witz 2008). This ongoing cell-to-cell communication helps cancer cells adapt to the stressful environment by modifying signalling pathways and reprogramming normal neighbouring cells. Cancer cells need a means of adapting their own protein machinery to function under stressful conditions and to signal to the TME to enable survival and metastasis. One way of surviving under extreme conditions is via activation of molecular chaperones.

Molecular chaperones or heat-shock proteins (HSPs) are a large family of highly conserved proteins traditionally known to be involved in protein folding, protein trafficking and assembly/disassembly of oligomeric structures. Under stress conditions they facilitate correct folding and prevent toxic protein aggregation (Hartl et al. 2011). Chaperones can be found in various subcellular and extra-cellular localizations, such as the nucleus, cytosol, endoplasmic reticulum (ER), mitochondria, lysosomes, cell-surface and blood (Henderson 2010). Depending on their localization chaperones can play important roles in inter and intracellular signalling. They interact with transcription factors, hormone receptors and kinases (Whitesell and Lindquist 2005). They integrate a wide range of cellular signalling pathways which help cells adapt to extreme environments (Maguire et al. 2002).

In tumors, chaperones promote the survival of cancer cells in the harsh tumor microenvironment. Master regulators of cytosolic chaperones such as Heat-shock factor 1 (HSF1), and ER chaperones such as XBP1 were shown to be associated with poor patient outcome and to promote cancer in mice (Romero-Ramirez et al. 2004; Santagata et al. 2011). The pro-tumorigenic activity of master regulators of stress responses such as HSF1 and XBP1 is mediated in part by activation of chaperones. Importantly however, these transcription factors activate a large repertoire of cancer-specific targets, and their activity in cancer is distinct from the typical stress-induced activity (Chen et al. 2014; Mendillo et al. 2012; Scherz-Shouval et al. 2014). Cancer cell-autonomous activities are discussed in other chapters of this book. Here we focus on the non-cancer-cell-autonomous activity of stress-activated transcription factors and chaperones and on the various ways by which they modulate the TME (Fig. 7.2; Table 7.1).

7.2 Chaperones in Human Cancer

Increased expression of chaperones is a common feature of various human cancers. Heat-shock protein 70 (Hsp70) is overexpressed in most human cancers, including breast, colon, liver, prostate and acute myeloid leukaemia (AML) (Sherman and Gabai 2015; Steiner et al. 2006). Importantly however, the correlation between its expression and patient outcome is mixed and is cancer type specific: in gastric cancer Hsp70 expression has no prognostic value, and in renal and oesophageal cancer increased levels of Hsp70 are associated with better disease outcome (Maehara et al. 2000; Sherman and Gabai 2015; Shiozaki et al. 2000). Heat-shock protein 90 (Hsp90) is overexpressed in various human cancers as well (Ciocca et al. 2013; Pick et al. 2007), and has been a long sought-after therapeutic target in cancer. To date, 18 Hsp90 inhibitors have entered the clinic, of which 5 are still in active clinical trials. Unfortunately, none of these inhibitors have been FDA approved yet (Yuno et al. 2018). The main hindrance in developing cancer-selective Hsp90 inhibitors is the dependence of normal cells on Hsp90 for sur-

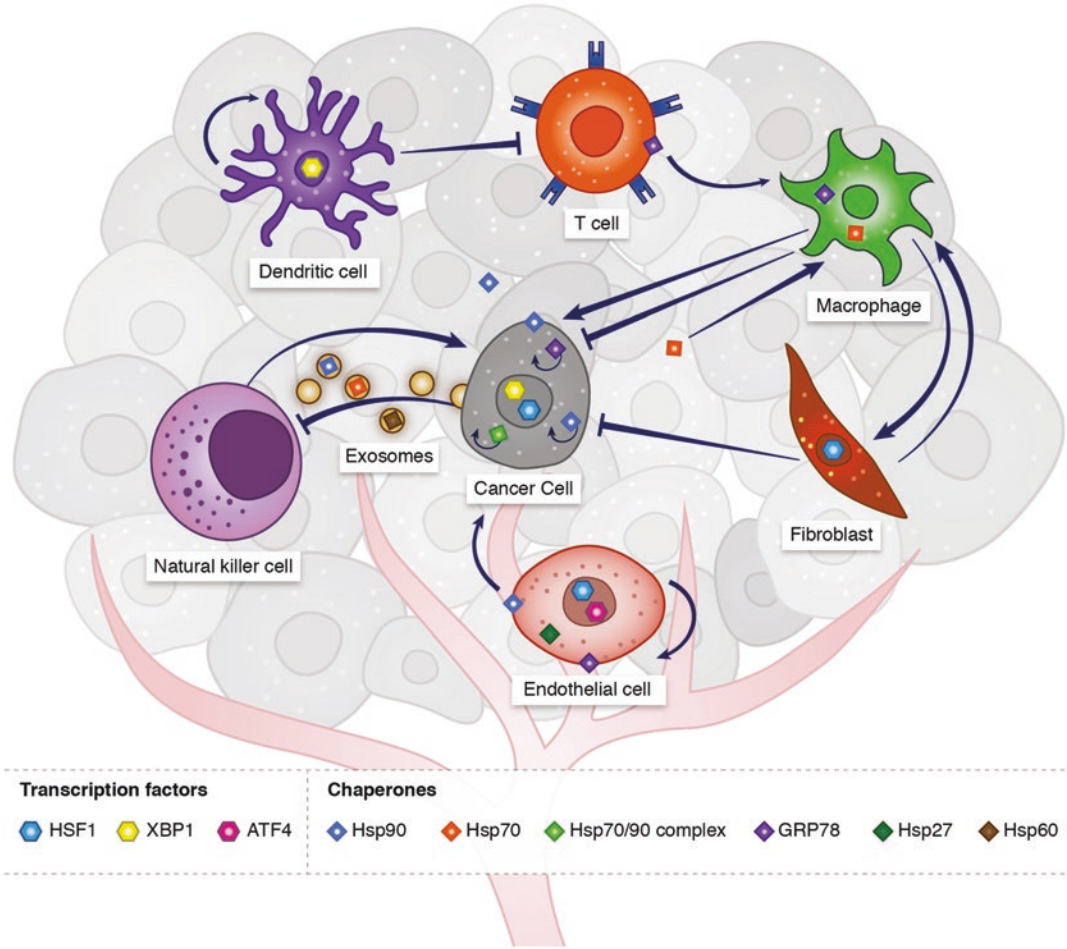

Fig. 7.2 Chaperones mediate cell-cell interactions in the tumor microenvironment. Signaling pathways mediated by stress-activated transcription factors and chaperones are presented. (See Table 7.1 for details and references)

vival, and the fact that inhibition of Hsp90 leads to activation of HSF1 (Whitesell et al. 2014; Yuno et al. 2018). Both could potentially be overcome by applying low-level inhibition of Hsp90 in combination with chemotherapy or hormonal therapy (Whitesell et al. 2014). The ER Hsp70 chaperone glucose regulated protein 78 (GRP78), also known as the immunoglobulin heavy chain binding protein (BiP), is induced under stress conditions such as glucose depletion, anoxia, acidosis and ER stress. In patients GRP78 is thought to be involved in the development of castration-resistant prostate cancer and increased levels of it are associated with disease recurrence in prostate cancer (Daneshmand et al. 2007; Pootrakul et al. 2006). Not only chaperones, but also the factors driving their expression are activated in human cancer. Activation of HSF1 both in cancer cells and in CAFs is associated with poor patient outcome in a variety of human carcinomas (Liao et al. 2015; Mendillo et al. 2012; Scherz-Shouval et al. 2014). Overexpression of activated XBP1 correlates with poor prognosis in glioblastoma (Avril et al. 2017; Obacz et al. 2017; Pluquet et al. 2013; Rubio-Patino et al. 2018), and in luminal/ER+ as well as triple-negative breast cancer (TNBC) (Cancer Genome Atlas Network 2012; Chen et al. 2014). Another arm of the unfolded protein response (UPR), that of PKR-like ER kinase (PERK) is upregulated in human breast ductal carcinomas in situ (DCIS), where PERK phosphorylation is higher in DCIS tissue than normal breast (Avivar-Valderas et al. 2011).

Table 7.1 Non-cell-autonomous signaling mediated by stress-activated transcription factors and chaperones in the tumor microenvironment

Molecule	Cell of origin	Target cell	Effect	References
HSP70/90 complex	Cancer	Cancer	Regulates MMP2 activation-promotes tumor invasion	Eustace et al. (2004) and Sims et al. (2011)
eHSP90	Cancer	Cancer	Interacts with client proteins such as HER2 and regulates signaling	Hance et al. (2014) and Sidera et al. (2008)
HSF1	Cancer	Cancer	Promotes proliferation, invasion and migration	Mendillo et al. (2012)
GRP78	Cancer	Cancer	Activates the UPR	Obacz et al. (2017)
eHSP90	Cancer	Fibroblast	Regulates MMP activation-promotes tumor invasion	Correia et al. (2013)
eHSP70	Cancer	Antigen Presenting Cells (APC)	Triggers an immune response	Theriault et al. (2005) and Zhou and Binder (2014)
HSP60, HSP70, HSP90 in exosomes	Cancer	Natural Killer (NK) Cells	Trigger NK migration and cytosolic activation- anti-tumor effects	Gastpar et al. (2005)
IRE1/XBP1	Cancer	Macrophages	Activate innate immune responses	Martinon et al. (2010)
HSF1	Fibroblasts	Cancer	Activates a wound healing program that promotes tumor growth and survival	Scherz-Shouval et al. (2014)
HSF1	Endothelial cells	Endothelial Cells	Thermotolerance	Bagley et al. (2015)
Hsp70	Macrophages	Cancer	Promotes migration and infiltration into tumors	Gabai et al. (2016)
GRP78	Macrophages and T cells	Cancer	Leads to secretion of cancer associated cytokines	Li and Li (2012)
CHOP	Myeloid derived suppressor cells (MDSCs)	Cancer	Promotes anti-tumor immunity	Thevenot et al. (2014)
GRP78	Endothelial	Endothelial	Angiogenesis	Virrey et al. (2008) and Dong et al. (2011)
XBP1	Dendritic cell (DC)	DC/cancer	Prevents T-cell mediated anti-tumor immunity	Cubillos-Ruiz et al. (2015)
PERK/ATF4	Endothelial	Endothelial	Induce secretion of pro-angiogenic factors	Cubillos-Ruiz et al. (2017) and Wang et al. (2012)
HSP27	Endothelial	Endothelial	Promotes angiogenesis	Lee et al. (2012)
HSP90	Endothelial	Endothelial	Increases angiogenesis by regulating HIF1-alpha and VEGF signaling	Okui et al. (2011)

7.3 Mechanisms of Chaperone Mediated Tumor-Stroma Interactions

Chaperones play an important role in linking stress at the cellular level to stress in the organism. Though classically considered cell autonomous survival pathways, evidence suggesting non-cell autonomous activation of the heat shock response (HSR) and the unfolded protein response (UPR) has been accumulating. This systemic activation of proteostasis mechanisms allows a coordinated response to stress and coordinated ageing of cells in different tissues (Taylor et al. 2014; van Oosten-Hawle et al. 2013). Hijacked by cancer, it also supports the growth of tumors at the expense of

the host. Chaperones and stress-activated transcription factors in tumors exert their non-cell autonomous effects via two main routes: (1) Activated in cancer cells, they mediate intercellular communication with cells of the TME through direct secretion from cancer cells or by chaperoning of cell-surface proteins, ECM components, and secreted molecules (2) Activated in cells of the TME, they facilitate cancer-promoting activities such as immune modulation, ECM remodeling and angiogenesis.

7.4 Chaperones Are Secreted to the Extracellular Space

In addition to their canonical cytosolic activity, both Hsp70 and Hsp90 can act as cell surface and extracellular chaperones, and this activity could be tumor promoting but also anti-tumorigenic. The term 'chaperokine' was coined to describe extracellular Hsp70's dual role as a chaperone and a cytokine (Asea 2005). Extracellular Hsp70 (eHsp70) can bind to cell surface receptors such as CD91 and LOX-1 on antigen presenting cells (APC) and elicit immune responses through presentation of peptides from its chaperoned clients (Theriault et al. 2005; Zhou and Binder 2014). This antigen presenting activity is shared with other Hsps including Hsp60 and Hsp90 (Asea et al. 2000; Quintana and Cohen 2005). Such immune modulating activities could explain why, in some cancers, Hsp70 expression is correlated with better prognosis.

Extracellular Hsp90 (eHsp90) can play a tumor-repressive role through similar antigen presentation activities to those of Hsp70. However, it has many tumor-promoting effects, since it supports wound healing, tissue regeneration and cell migration (Hance et al. 2014). Selective inhibition of eHsp90 activity by cell impermeant molecules results in reduced cancer cell motility and invasion (Tsutsumi et al. 2008). But how is it secreted and what is the mechanism by which it promotes migration and invasion? eHsp90 release is triggered by necrosis, disruption of membrane integrity, growth factors and a variety of stress factors including DNA damage, oxidative stress, heat stress, hypoxia and exposure to chemotherapy (Hance et al. 2014). In the extracellular space eHsp90 serves as a major regulator of metalloprotease (MMP) activity (Correia et al. 2013; Eustace et al. 2004). MMP-2 is a client of the Hsp70/Hsp90 organizing protein (HOP) complex and the stabilizing interaction of these chaperones with MMP-2 promotes tumor invasion (Eustace et al. 2004; Sims et al. 2011). In advanced stage gastric cancer patients Hsp90 expression is significantly correlated with MMP-9 expression, and associated with poor prognosis (Wang et al. 2013). Secreted eHsp90 also promotes mammary epithelial invasion through its activation of MMP-3 (Correia et al. 2013). By controlling the activity of MMPs, eHsp90 indirectly controls the structure and composition of the ECM. eHsp90 also regulates signalling through its interaction with cell surface receptors such as low-density lipoprotein receptor-related protein 1 (LRP1) and HER2 (Hance et al. 2014; Sidera et al. 2008).

7.5 Chaperones Mediate Cell-Cell Communication via Exosomes

Chaperones were spotted on the surface of cancer cells and in extracellular domains more than a decade ago (Shin et al. 2003; Tsutsumi et al. 2008), but the mechanism by which they are exported from cells was not clear. A growing body of evidence suggests that at least part of the extracellular activity of chaperones is mediated through exosomes. Exosomes are nano-extracellular vesicles released by different types of mammalian cells. They contain protein, RNA and DNA. In cancer, exosomes are critical mediators of the communication between cancer cells and cells of the TME (Becker et al. 2016). Under stress conditions and in response to drug treatment, the secretion of Hsp60, Hsp70 and Hsp90 from cancer cells via exosomes is increased (Lv et al. 2012), stimulating migratory and cytolytic activity of natural killer (NK) cells and thereby serving as anti-tumor agents (Gastpar et al. 2005). Beneficial effects were also reported for small

Hsps (Hsp27 and Hsp20) secreted through exosomes in various pathological conditions (Reddy et al. 2018), and Hsp20 has been implicated in exosome biogenesis (Wang et al. 2016). Notably, intercellular transmission of chaperones mediated by exosomes was shown to maintain and improve proteostasis in recipient cells (Takeuchi et al. 2015). Though this hasn't been reported in cancer, one could envision how such non-cell-autonomous maintenance of organismal proteostasis is subverted to promote the survival of tumors.

7.6 Chaperones Are Activated in Cells of the TME

With the growing understanding that cells of the TME play important roles in cancer, an increasing number of studies have recently shown activation of stress-induced transcription factors such as HSF1 and XBP1 and chaperones including Hsp70, Hsp90 and GRP78 in cells of the TME. HSF1 is activated in cancer cells as well as in fibroblasts and endothelial cells, and in each cell type it drives a distinct transcriptional program. In cancer cells HSF1 promotes proliferation, invasion and migration (Mendillo et al. 2012). In fibroblasts HSF1 drives a wound-healing CAF signature, promoting the growth and malignant properties of adjacent cancer cells (Ferrari et al. 2019; Scherz-Shouval et al. 2014). In tumor-associated endothelial cells exposed to thermal treatment, HSF1 drives classic thermotolerance, leading to decreased transport of therapeutic agents in mouse tumors (Bagley et al. 2015). How does the same transcription factor drive different transcriptional programs in different cell types and different contexts? Possibly epigenetic alterations alter promoter accessibility. Alternatively the combination of stresses in the tumor – hypoxia, nutrient deprivation, genotoxic and proteotoxic stress all together leads to activation of multiple stress responses, resulting in different transcriptional outputs in different cell types in the TME.

Nevertheless, evidence for activation of canonical chaperones in the TME is accumulating as well. In particular, Hsp70 activation in macrophages promotes their migration and infiltration into tumors, and inhibition of this activity by a pharmacological inhibitor (JG-98) or by knockout of Hsp70 in the stroma profoundly affects tumor growth in mice (Gabai et al. 2016). The ER Hsp70 GRP78 is also activated in macrophages, as well as on the surface of T-cells, in response to stress, and regulates the activity of several cancer-associated cytokines, such as interleukin-6 (IL-6), macrophage migration inhibitory factor (MIF), transformed growth factor β (TGF-β) and interleukin-10 (IL-10) (Mendillo et al. 2012). IL-6 independent proinflammatory conditioning of macrophages by cancer cells was shown in a pathway termed transmissible ER-stress (TERS), where macrophages cultured in conditioned medium from ER-stressed cancer cells become activated, and themselves undergo ER stress with the up-regulation of *Grp78*, *Gadd34*, *Chop,* and *Xbp-1*splicing (Mahadevan et al. 2011). GRP78 is also expressed on the surface of endothelial cells, where it promotes tumor vascularization and angiogenesis (Virrey et al. 2008). Its overexpression drives resistance to anti-angiogenic therapy in models of glioblastoma (Virrey et al. 2008), whereas loss of GRP78 in endothelial cells supresses tumor growth and angiogenesis in a mouse model of melanoma (Dong et al. 2011).

GRP78 controls all 3 arms of the UPR through its binding to activating transcription factor 6 (ATF6), PERK, and inositol-requiring enzyme 1 (IRE1) (Obacz et al. 2017). Upon ER-stress GRP78 releases these proteins, and the UPR is activated. All three arms of the UPR have been linked to cancer, mostly through activation in cancer cells. The IRE1/XBP1 arm has been known to regulate innate immune responses in macrophages in response to pathogen-induced TLR activation (Martinon et al. 2010) and was suspected to do so in tumors as well. Recently an immunomodulatory role was shown for IRE1/XBP1 in dendritic cells (DC) in ovarian cancer (Cubillos-Ruiz et al. 2015). Activation of XBP1 in tumor-associated DCs disrupts their homeostasis and prevents T cell mediated anti-tumor immunity. Silencing of XBP1 in DCs reversed this process and prolonged survival of

ovarian cancer-bearing mice (Cubillos-Ruiz et al. 2015). The cellular stress sensor CHOP is also activated in the TME, where it modulates anti-tumor immunity. Deletion of CHOP in Myeloid-derived suppressor cells (MDSCs) leads to induction of IL-6, resulting in T cell proliferation and anti-tumor responses in tumor-bearing mice (Thevenot et al. 2014). Thus, activation of chaperones in cells of the TME does not merely promote survival of the cells in which they are activated, but actually drives specific cancer phenotypes, thereby supporting survival of the tumor in a non-cell-autonomous manner.

7.7 Chaperones Play a Role in Angiogenesis

Starvation for oxygen leading to hypoxia triggers angiogenesis. Cancer cells sense hypoxia through HIF1-alpha, and trigger angiogenesis by upregulation of vascular endothelial growth factor (VEGF). The UPR plays a critical role in this process, triggered by exposure of endothelial cells to different types of stress such as hypoxia, low pH and glucose deprivation. The PERK/ATF4 axis promotes pro-angiogenic factors including VEGF, FGF-2 and IL-6 while decreasing angiogenic inhibitors including THBS1, CXCL14 and CXCL10 mRNA (Cubillos-Ruiz et al. 2017; Wang et al. 2012). XBP1 and ATF4 can directly bind and transactivate the promoter of VEGFA (Pereira et al. 2010), and all three arms of the UPR (IRE1, ATF6 and PERK) can induce endothelial cells to secrete VEGF (Karali et al. 2014). Several reports imply that HSPs may also play a role in angiogenesis (Calderwood and Gong 2016). Hsp27 secreted from endothelial cells regulates angiogenesis via direct binding to VEGF (Lee et al. 2012). Hsp90 can also increase angiogenesis by regulating HIF1-alpha/VEGF signalling, and inhibition of Hsp90 induces HIF1-alpha and VEGF degradation (Okui et al. 2011). To continue positively regulating angiogenesis endothelial cells secrete Hsp90 to the TME where it acts through chaperoning of MMP2 (Song et al. 2010).

7.8 Concluding Remarks

Cancer cells co-evolve with cells of the TME. The balance between tumor promoting and tumor repressive activities of the TME dictates whether tumors will progress, invade, and metastasize, or whether they remain dormant. Normal cells will naturally repress cancer-promoting phenotypes, and must be massively rewired to do otherwise. How do chaperones play into this rewiring? As mechanisms of stromal rewiring are being discovered, the paradoxical role of chaperones in cancer unravels. Chaperones are activated in cancer-associated fibroblasts, macrophages, dendritic cells, NK cells, MDSCs, and endothelial cells. As crucial mediators of cell survival they are potentially ideal targets for anti-cancer therapy – they promote invasion, angiogenesis, ECM remodeling, immune evasion, and drug resistance. Yet they also activate anti-cancer immunity. Moreover, inhibition of chaperone activity could lead to protein aggregation and related pathological conditions. Deeper mechanistic study of the pathways activating chaperones in different types of cancer – the regulators, the clients, the targets and the balance between cytosolic and extracellular activities are crucial for our understanding of the interplay between cancer, stress and evolution, and for successful translation of this knowledge into useful therapies.

Acknowledgements N.G. is supported by the Israel cancer research foundation. O.L.G. is supported by the Minerva foundation and the Thompson family foundation. R.S.S is supported by the Israel Science Foundation (grants No. 401/17 and 1384/1), the European Research Council (ERC grant agreement 754320), the Laura Gurwin Flug Family Fund, the Peter and Patricia Gruber Awards, the Comisaroff Family Trust, the Estate of Annice Anzelewitz, and the Estate of Mordecai M. Roshwal. R.S.S is the incumbent of the Ernst and Kaethe Ascher Career Development Chair in Life Sciences.

References

Alspach E, Flanagan KC, Luo X, Ruhland MK, Huang H, Pazolli E, Donlin MJ, Marsh T, Piwnica-Worms D, Monahan J et al (2014) p38MAPK plays a crucial role in stromal-mediated tumorigenesis. Cancer Discov 4:716–729

Asea A (2005) Stress proteins and initiation of immune response: chaperokine activity of hsp72. Exerc Immunol Rev 11:34–45

Asea A, Kraeft SK, Kurt-Jones EA, Stevenson MA, Chen LB, Finberg RW, Koo GC, Calderwood SK (2000) HSP70 stimulates cytokine production through a CD14-dependant pathway, demonstrating its dual role as a chaperone and cytokine. Nat Med 6:435–442

Avivar-Valderas A, Salas E, Bobrovnikova-Marjon E, Diehl JA, Nagi C, Debnath J, Aguirre-Ghiso JA (2011) PERK integrates autophagy and oxidative stress responses to promote survival during extracellular matrix detachment. Mol Cell Biol 31:3616–3629

Avril T, Vauleon E, Chevet E (2017) Endoplasmic reticulum stress signaling and chemotherapy resistance in solid cancers. Oncogene 6:e373

Bagley AF, Scherz-Shouval R, Galie PA, Zhang AQ, Wyckoff J, Whitesell L, Chen CS, Lindquist S, Bhatia SN (2015) Endothelial thermotolerance impairs nanoparticle transport in tumors. Cancer Res 75:3255–3267

Becker A, Thakur BK, Weiss JM, Kim HS, Peinado H, Lyden D (2016) Extracellular vesicles in cancer: cell-to-cell mediators of metastasis. Cancer Cell 30:836–848

Bissell MJ, Hines WC (2011) Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med 17:320–329

Calderwood SK, Gong J (2016) Heat shock proteins promote cancer: It's a protection racket. Trends Biochem Sci 41:311–323

Cancer Genome Atlas Network (2012) Comprehensive molecular portraits of human breast tumours. Nature 490:61–70

Chen X, Iliopoulos D, Zhang Q, Tang Q, Greenblatt MB, Hatziapostolou M, Lim E, Tam WL, Ni M, Chen Y et al (2014) XBP1 promotes triple-negative breast cancer by controlling the HIF1alpha pathway. Nature 508:103–107

Ciocca DR, Arrigo AP, Calderwood SK (2013) Heat shock proteins and heat shock factor 1 in carcinogenesis and tumor development: an update. Arch Toxicol 87:19–48

Cirri P, Chiarugi P (2011) Cancer associated fibroblasts: the dark side of the coin. Am J Cancer Res 1:482–497

Comito G, Giannoni E, Segura CP, Barcellos-de-Souza P, Raspollini MR, Baroni G, Lanciotti M, Serni S, Chiarugi P (2014) Cancer-associated fibroblasts and M2-polarized macrophages synergize during prostate carcinoma progression. Oncogene 33:2423–2431

Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J (2008) Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol 6:2853–2868

Correia AL, Mori H, Chen EI, Schmitt FC, Bissell MJ (2013) The hemopexin domain of MMP3 is responsible for mammary epithelial invasion and morphogenesis through extracellular interaction with HSP90beta. Genes Dev 27:805–817

Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, Chopra S, Perales-Puchalt A, Song M, Zhang S, Bettigole SE, Gupta D, Holcomb K et al (2015) ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. Cell 161:1527–1538

Cubillos-Ruiz JR, Bettigole SE, Glimcher LH (2017) Tumorigenic and immunosuppressive effects of endoplasmic reticulum stress in cancer. Cell 168:692–706

Daneshmand S, Quek ML, Lin E, Lee C, Cote RJ, Hawes D, Cai J, Groshen S, Lieskovsky G, Skinner DG et al (2007) Glucose-regulated protein GRP78 is upregulated in prostate cancer and correlates with recurrence and survival. Hum Pathol 38:1547–1552

Dong D, Stapleton C, Luo B, Xiong S, Ye W, Zhang Y, Jhaveri N, Zhu G, Ye R, Liu Z et al (2011) A critical role for GRP78/BiP in the tumor microenvironment for neovascularization during tumor growth and metastasis. Cancer Res 71:2848–2857

Erez N, Truitt M, Olson P, Arron ST, Hanahan D (2010) Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-kappaB-dependent manner. Cancer Cell 17:135–147

Eustace BK, Sakurai T, Stewart JK, Yimlamai D, Unger C, Zehetmeier C, Lain B, Torella C, Henning SW, Beste G et al (2004) Functional proteomic screens reveal an essential extracellular role for hsp90 alpha in cancer cell invasiveness. Nat Cell Biol 6:507–514

Ferrari N, Ranftl R, Chicherova I, Slaven ND, Moeendarbary E, Farrugia AJ, Lam M, Semiannikova M, Westergaard MCW, Tchou J et al (2019) Dickkopf-3 links HSF1 and YAP/TAZ signalling to control aggressive behaviours in cancer-associated fibroblasts. Nat Commun 10:130

Finak G, Bertos N, Pepin F, Sadekova S, Souleimanova M, Zhao H, Chen H, Omeroglu G, Meterissian S, Omeroglu A et al (2008) Stromal gene expression predicts clinical outcome in breast cancer. Nat Med 14:518–527

Gabai VL, Yaglom JA, Wang Y, Meng L, Shao H, Kim G, Colvin T, Gestwicki J, Sherman MY (2016) Anticancer effects of targeting Hsp70 in tumor stromal cells. Cancer Res 76:5926–5932

Gastpar R, Gehrmann M, Bausero MA, Asea A, Gross C, Schroeder JA, Multhoff G (2005) Heat shock protein 70 surface-positive tumor exosomes stimulate migratory and cytolytic activity of natural killer cells. Cancer Res 65:5238–5247

Hanahan D, Coussens LM (2012) Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell 21:309–322

Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674

Hance MW, Nolan KD, Isaacs JS (2014) The double-edged sword: conserved functions of extracellular hsp90 in wound healing and cancer. Cancers (Basel) 6:1065–1097

Hartl FU, Bracher A, Hayer-Hartl M (2011) Molecular chaperones in protein folding and proteostasis. Nature 475:324–332

Henderson B (2010) Integrating the cell stress response: a new view of molecular chaperones as immunological and physiological homeostatic regulators. Cell Biochem Funct 28:1–14

Karali E, Bellou S, Stellas D, Klinakis A, Murphy C, Fotsis T (2014) VEGF signals through ATF6 and PERK to promote endothelial cell survival and angiogenesis in the absence of ER stress. Mol Cell 54:559–572

Lee YJ, Lee HJ, Choi SH, Jin YB, An HJ, Kang JH, Yoon SS, Lee YS (2012) Soluble HSPB1 regulates VEGF-mediated angiogenesis through their direct interaction. Angiogenesis 15:229–242

Leprivier G, Rotblat B, Khan D, Jan E, Sorensen PH (2015) Stress-mediated translational control in cancer cells. Biochim Biophys Acta 1849:845–860

Li Z, Li Z (2012) Glucose regulated protein 78: a critical link between tumor microenvironment and cancer hallmarks. Biochim Biophys Acta 1826:13–22

Liao Y, Xue Y, Zhang L, Feng X, Liu W, Zhang G (2015) Higher heat shock factor 1 expression in tumor stroma predicts poor prognosis in esophageal squamous cell carcinoma patients. J Transl Med 13:338

Lv LH, Wan YL, Lin Y, Zhang W, Yang M, Li GL, Lin HM, Shang CZ, Chen YJ, Min J (2012) Anticancer drugs cause release of exosomes with heat shock proteins from human hepatocellular carcinoma cells that elicit effective natural killer cell antitumor responses in vitro. J Biol Chem 287:15874–15885

Maehara Y, Oki E, Abe T, Tokunaga E, Shibahara K, Kakeji Y, Sugimachi K (2000) Overexpression of the heat shock protein HSP70 family and p53 protein and prognosis for patients with gastric cancer. Oncology 58:144–151

Maguire M, Coates AR, Henderson B (2002) Chaperonin 60 unfolds its secrets of cellular communication. Cell Stress Chaperones 7:317–329

Mahadevan NR, Rodvold J, Sepulveda H, Rossi S, Drew AF, Zanetti M (2011) Transmission of endoplasmic reticulum stress and pro-inflammation from tumor cells to myeloid cells. Proc Natl Acad Sci U S A 108:6561–6566

Martinon F, Chen X, Lee AH, Glimcher LH (2010) TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages. Nat Immunol 11:411–418

Mendillo ML, Santagata S, Koeva M, Bell GW, Hu R, Tamimi RM, Fraenkel E, Ince TA, Whitesell L, Lindquist S (2012) HSF1 drives a transcriptional program distinct from heat shock to support highly malignant human cancers. Cell 150:549–562

Obacz J, Avril T, Rubio-Patino C, Bossowski JP, Igbaria A, Ricci JE, Chevet E (2017) Regulation of tumor-stroma interactions by the unfolded protein response. FEBS J 286(2):279–296

Okui T, Shimo T, Hassan NM, Fukazawa T, Kurio N, Takaoka M, Naomoto Y, Sasaki A (2011) Antitumor effect of novel HSP90 inhibitor NVP-AUY922 against oral squamous cell carcinoma. Anticancer Res 31:1197–1204

Pereira ER, Liao N, Neale GA, Hendershot LM (2010) Transcriptional and post-transcriptional regulation of proangiogenic factors by the unfolded protein response. PLoS One 5(9):pii: e12521

Pick E, Kluger Y, Giltnane JM, Moeder C, Camp RL, Rimm DL, Kluger HM (2007) High HSP90 expression is associated with decreased survival in breast cancer. Cancer Res 67:2932–2937

Place AE, Jin Huh S, Polyak K (2011) The microenvironment in breast cancer progression: biology and implications for treatment. Breast Cancer Res 13:227

Pluquet O, Dejeans N, Bouchecareilh M, Lhomond S, Pineau R, Higa A, Delugin M, Combe C, Loriot S, Cubel G et al (2013) Posttranscriptional regulation of PER1 underlies the oncogenic function of IREalpha. Cancer Res 73:4732–4743

Pootrakul L, Datar RH, Shi SR, Cai J, Hawes D, Groshen SG, Lee AS, Cote RJ (2006) Expression of stress response protein Grp78 is associated with the development of castration-resistant prostate cancer. Clin Cancer Res 12:5987–5993

Qian BZ, Pollard JW (2010) Macrophage diversity enhances tumor progression and metastasis. Cell 141:39–51

Quintana FJ, Cohen IR (2005) Heat shock proteins as endogenous adjuvants in sterile and septic inflammation. J Immunol 175:2777–2782

Reddy VS, Madala SK, Trinath J, Reddy GB (2018) Extracellular small heat shock proteins: exosomal biogenesis and function. Cell Stress Chaperones 23:441–454

Romero-Ramirez L, Cao H, Nelson D, Hammond E, Lee AH, Yoshida H, Mori K, Glimcher LH, Denko NC, Giaccia AJ et al (2004) XBP1 is essential for survival under hypoxic conditions and is required for tumor growth. Cancer Res 64:5943–5947

Rubio-Patino C, Bossowski JP, De Donatis GM, Mondragon L, Villa E, Aira LE, Chiche J, Mhaidly R, Lebeaupin C, Marchetti S et al (2018) Low-protein diet induces IRE1alpha-dependent anticancer immunosurveillance. Cell Metab 27:828–842.e7

Sagiv JY, Michaeli J, Assi S, Mishalian I, Kisos H, Levy L, Damti P, Lumbroso D, Polyansky L, Sionov RV et al (2015) Phenotypic diversity and plasticity in circulating neutrophil subpopulations in cancer. Cell Rep 10:562–573

Santagata S, Hu R, Lin NU, Mendillo ML, Collins LC, Hankinson SE, Schnitt SJ, Whitesell L, Tamimi RM, Lindquist S et al (2011) High levels of nuclear heat-shock factor 1 (HSF1) are associated with poor

prognosis in breast cancer. Proc Natl Acad Sci U S A 108:18378–18383

Scherz-Shouval R, Santagata S, Mendillo ML, Sholl LM, Ben-Aharon I, Beck AH, Dias-Santagata D, Koeva M, Stemmer SM, Whitesell L et al (2014) The reprogramming of tumor stroma by HSF1 is a potent enabler of malignancy. Cell 158:564–578

Sherman MY, Gabai VL (2015) Hsp70 in cancer: back to the future. Oncogene 34:4153–4161

Shin BK, Wang H, Yim AM, Le Naour F, Brichory F, Jang JH, Zhao R, Puravs E, Tra J, Michael CW et al (2003) Global profiling of the cell surface proteome of cancer cells uncovers an abundance of proteins with chaperone function. J Biol Chem 278:7607–7616

Shiozaki H, Doki Y, Kawanishi K, Shamma A, Yano M, Inoue M, Monden M (2000) Clinical application of malignancy potential grading as a prognostic factor of human esophageal cancers. Surgery 127:552–561

Sidera K, Gaitanou M, Stellas D, Matsas R, Patsavoudi E (2008) A critical role for HSP90 in cancer cell invasion involves interaction with the extracellular domain of HER-2. J Biol Chem 283:2031–2041

Sims JD, McCready J, Jay DG (2011) Extracellular heat shock protein (Hsp)70 and Hsp90alpha assist in matrix metalloproteinase-2 activation and breast cancer cell migration and invasion. PLoS One 6:e18848

Song X, Wang X, Zhuo W, Shi H, Feng D, Sun Y, Liang Y, Fu Y, Zhou D, Luo Y (2010) The regulatory mechanism of extracellular Hsp90{alpha} on matrix metalloproteinase-2 processing and tumor angiogenesis. J Biol Chem 285:40039–40049

Steiner K, Graf M, Hecht K, Reif S, Rossbacher L, Pfister K, Kolb HJ, Schmetzer HM, Multhoff G (2006) High HSP70-membrane expression on leukemic cells from patients with acute myeloid leukemia is associated with a worse prognosis. Leukemia 20:2076–2079

Takeuchi T, Suzuki M, Fujikake N, Popiel HA, Kikuchi H, Futaki S, Wada K, Nagai Y (2015) Intercellular chaperone transmission via exosomes contributes to maintenance of protein homeostasis at the organismal level. Proc Natl Acad Sci U S A 112:E2497–E2506

Taylor RC, Berendzen KM, Dillin A (2014) Systemic stress signalling: understanding the cell non-autonomous control of proteostasis. Nat Rev Mol Cell Biol 15:211–217

Theriault JR, Mambula SS, Sawamura T, Stevenson MA, Calderwood SK (2005) Extracellular HSP70 binding to surface receptors present on antigen presenting cells and endothelial/epithelial cells. FEBS Lett 579:1951–1960

Thevenot PT, Sierra RA, Raber PL, Al-Khami AA, Trillo-Tinoco J, Zarreii P, Ochoa AC, Cui Y, Del Valle L, Rodriguez PC (2014) The stress-response sensor chop regulates the function and accumulation of myeloid-derived suppressor cells in tumors. Immunity 41:389–401

Tsutsumi S, Scroggins B, Koga F, Lee MJ, Trepel J, Felts S, Carreras C, Neckers L (2008) A small molecule cell-impermeant Hsp90 antagonist inhibits tumor cell motility and invasion. Oncogene 27:2478–2487

van Oosten-Hawle P, Porter RS, Morimoto RI (2013) Regulation of organismal proteostasis by transcellular chaperone signaling. Cell 153:1366–1378

Virrey JJ, Dong D, Stiles C, Patterson JB, Pen L, Ni M, Schonthal AH, Chen TC, Hofman FM, Lee AS (2008) Stress chaperone GRP78/BiP confers chemoresistance to tumor-associated endothelial cells. Mol Cancer Res 6:1268–1275

Wang Y, Alam GN, Ning Y, Visioli F, Dong Z, Nor JE, Polverini PJ (2012) The unfolded protein response induces the angiogenic switch in human tumor cells through the PERK/ATF4 pathway. Cancer Res 72:5396–5406

Wang J, Cui S, Zhang X, Wu Y, Tang H (2013) High expression of heat shock protein 90 is associated with tumor aggressiveness and poor prognosis in patients with advanced gastric cancer. PLoS One 8:e62876

Wang Z, Chen JQ, Liu JL, Tian L (2016) Exosomes in tumor microenvironment: novel transporters and biomarkers. J Transl Med 14:297

Whitesell L, Lindquist SL (2005) HSP90 and the chaperoning of cancer. Nat Rev Cancer 5:761–772

Whitesell L, Santagata S, Mendillo ML, Lin NU, Proia DA, Lindquist S (2014) HSP90 empowers evolution of resistance to hormonal therapy in human breast cancer models. Proc Natl Acad Sci U S A 111:18297–18302

Witz IP (2008) Tumor-microenvironment interactions: dangerous liaisons. Adv Cancer Res 100:203–229

Yuno A, Lee MJ, Lee S, Tomita Y, Rekhtman D, Moore B, Trepel JB (2018) Clinical evaluation and biomarker profiling of Hsp90 inhibitors. Methods Mol Biol 1709:423–441

Zhou YJ, Binder RJ (2014) The heat shock protein-CD91 pathway mediates tumor immunosurveillance. Oncoimmunology 3:e28222