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Review

HSF1: Guardian of Proteostasis in Cancer

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Proteomic instability is causally related to human diseases. In guarding proteome stability, the heat shock factor 1 (HSF1)-mediated proteotoxic stress response plays a pivotal role. Contrasting with its beneficial role of enhancing cell survival, recent findings have revealed a compelling pro-oncogenic role for HSF1. However, the mechanisms underlying the persistent activation and function of HSF1 within malignancy remain poorly understood. Emerging evidence reveals that oncogenic signaling mobilizes HSF1 and that cancer cells rely on HSF1 to avert proteomic instability and repress tumor-suppressive amyloidogenesis. In aggregate, these new developments suggest that cancer cells endure chronic proteotoxic stress and that proteomic instability is intrinsically associated with the malignant state, a characteristic that could be exploited to combat cancer.

Trends

The heat shock factor 1 (HSF1)-mediated proteotoxic stress response (PSR) is an evolutionarily conserved, powerful transcriptional program that guards the cellular proteome against the dangers of misfolding and aggregation.

Cancerous cells suffer chronic proteotoxic stress from without and within.

The HSF1-mediated PSR is constitutively mobilized within cancerous cells.

HSF1 plays a pivotal role in preserving the proteomic stability of cancer, thereby enabling robust malignant transformation.

Disrupting the fragile proteostasis in cancer provokes proteomic chaos and tumor-suppressive amyloidogenesis, representing a novel antineoplastic therapeutic strategy.

Proteotoxic Stress: An Emerging Characteristic of Cancer

Malignant transformation (see Glossary) brings forth profound alterations in a wide array of biological processes, inevitably disturbing intricate cellular homeostatic states. In cancerous cells, unsurprisingly, various types of **biological stress** accompany their malignant behavior, among which genotoxic [1,2], oxidative [3,4], and metabolic stress [5,6] are well documented and widely recognized. By contrast, little has been known about proteotoxic stress in cancer, despite its prominent manifestation in human neurodegenerative disorders [7]. However, emerging evidence reveals proteotoxic stress as a widespread feature in cancer and is beginning to illuminate its previously unappreciated impact on oncogenesis.

Proteostasis (or **proteome** homeostasis) [8], a process by which cells balance the processes of protein biosynthesis, folding, and degradation, is vital to cellular fitness. However, various environmental cues constantly challenge this homeostatic state, disruption of which elicits proteotoxic stress in cells [8]. Given the necessity of a healthy proteome, the cytoprotective mechanism named the heat-shock, or proteotoxic stress, response (PSR) has evolved to counter such stress [9,10] and is characterized by the induction of heat-shock proteins (HSPs) [9,10]. HSPs are molecular chaperones that maintain cellular proteostasis through facilitation of the folding, transportation, ubiquitination, and proteasomal degradation of proteins [11–13]. A small group of transcription factors named HSFs specialize in activating the PSR in the face of proteotoxic stress (Box 1) [14,15]. Among the many HSFs, HSF1 is the master regulator of this transcriptional program in mammals [9,16]. Genetic ablation of *Hsf1* in mice abrogates HSP induction, rendering cells vulnerable to proteotoxic stress [17–19].

Acute proteotoxic stress translocates HSF1 from the cytosol to the nucleus where it promotes increased transcription of genes involved in protein quality control, thereby allowing cells to survive proteotoxic stress [17–19] (Figure 1). The activation of HSF1 is transient and attenuates in parallel with the alleviation of stress [20]. Moreover, HSF1 is dispensable for cellular and organismal

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Box 1. HSF Paralogs, the Proteotoxic Stress Response, and Development

While yeast and invertebrates express a single HSF, at least nine HSF paralogs – HSF1, 2, 3, 4, 5, X1, X2, Y1, and Y2 – have been identified in vertebrates [15]. All HSF proteins share several structural homologies, including the N-terminal helix-turn-helix DNA-binding domain (DBD), the coiled-coil trimerization domain enriched for hydrophobic heptad repeats (HRs), and the C-terminal transactivation domain (AD) [15,77]. HSFs bind via their DBD to consensus heat shock elements (HSEs) that canonically comprise adjacent inverted arrays of a specific sequence motif (5′-nGAAn-3′) [15,77]. Although mammalian cells deficient for *Hsf2*, *Hsf3*, or *Hsf4* retain stress-induced expression of *Hsp* genes in mice [99–101], *Hsf1* ablation abrogates this response [17–19], indicating its essentiality to the PSR. Nonetheless, accumulating evidence suggests that other HSFs could modify the transcriptional program mediated by HSF1. For example, through heterotrimerization with HSF1, HSF2 either enhances *Hsp72* expression or represses expression of *Hsp40* and *Hsp110* [102]. Moreover, HSF3 is able to induce some non-*Hsp* genes that are also regulated by HSF1 and, importantly, protect *Hsf1*-deficient cells from proteotoxic stress [100]. In addition to their roles in the PSR, HSFs play important roles during development, as revealed in genetically engineered mouse models. Deletion of *Hsf1* in mice causes placental defects, prenatal lethality, and female infertility [17], *Hsf2*-deficient mice display enlarged brain ventricles and defective gametogenesis [103], and mice deficient for *Hsf4* develop cataracts [101]. By contrast, the biological functions of HSF3, HSF5, and sex chromosome-linked HSFX1, HSFX2, HSFY1, and HSFY2 remain largely unclear.

viability under normal non-stressed conditions [17–19,21]. By contrast, HSF1 appears to remain constitutively active in cancer cells [22,23], suggesting the presence of chronic proteotoxic stress. Expression of HSPs is notably elevated in many human cancers [24,25]. Hence, malignancy epitomizes a pathological state inflicted with chronic proteotoxic stress.

Recent evidence is beginning to unravel the molecular mechanisms of HSF1 activation and function in regulating proteostasis in cancer. It is conceivable that the hostile tumor microenvironment, often acidic and hypoxic [26,27], is disruptive to proteostasis in cancer and stress provoking. In addition, proteotoxic stress could arise cell autonomously due to cell-intrinsic alterations. For example, protein biosynthesis is markedly enhanced in cancer cells due to hyperactivation of mTORC1 [28,29], a key regulator of translation [30,31]. Genomic instability of cancer cells also exacerbates proteostasis imbalance. Aneuploidy can increase protein dosage, subsequently exaggerating the proteomic burden [32,33]. Moreover, oxidative damage of proteins is augmented due to elevated levels of reactive oxygen species (ROS) in cancer cells [34,35]. Also, numerous genetic mutations cause protein conformational changes that often lead to decreased protein stability [36].

In this review we summarize the recent exciting findings in proteomic instability and underscore the critical role of HSF1 and its mediated PSR in preserving proteostasis in cancer. Moreover, we highlight cancer's fragile proteostasis as a potential therapeutic target as well as a novel biomarker.

Regulation of HSF1 Activity through Phosphorylation

Activation of HSF1 on challenge by proteotoxic stressors is reliant on its phosphorylation (Figure 1). Several phosphorylation events have been reported to promote HSF1 activation, including Ser230 phosphorylation by calcium/calmodulin-dependent protein kinase II (CaMKII) [37], Ser320 phosphorylation by protein kinase A (PKA) [38], Thr142 phosphorylation by casein kinase 2 (CK2) [39], and Ser419 phosphorylation by polo-like kinase 1 (PLK1) [40]. Furthermore, phosphorylation of Ser326 on HSF1 was identified as a modification that is critical to stress-induced HSF1 activation [41]. Originally this modification was found to be mediated by mTOR [42]; however, a new study indicates that the RAS/MAPK signaling pathway also regulates HSF1 activation through Ser326 phosphorylation [43] (Figure 2). Moreover, some HSF1-phosphorylating events negatively impact its transcriptional activity, such as Ser121 phosphorylation, which has been linked to metabolic sensors, and Ser303, Ser307, and Ser363 phosphorylation [44–46].

Activation of HSF1 by Oncogenic RAS Signaling

The canonical RAS/MAPK signaling pathway governs a plethora of cellular processes including proliferation, differentiation, transcription and translation, and cell survival [47,48] and anomalies

Glossary

Amyloidogenesis: the process of forming amyloids. Amyloids are protein aggregates that are enriched for highly ordered β-sheet structures and are frequently associated with human neurodegenerative diseases.
Biological stress: a state of cells, tissues, or organisms under disrupted homeostasis of a particular biological process or system. There are a wide variety of stresses, including genotoxic, proteotoxic, oxidative, and metabolic, here defined by the primarily affected biological process or system, such as the genome, proteome, oxidants/antioxidants, or metabolism. Of note, many biological stresses are interconnected and one type of stress often triggers other types of stress secondarily. For example, oxidative stress can subsequently cause DNA and protein damage, thereby further provoking genotoxic and proteotoxic stress.
ChIP-seq: a technique that combines conventional chromatin immunoprecipitation with massively parallel sequencing. ChIP-seq enables genome-wide mapping of interactions between protein and DNA.
Genetically engineered mouse model: mice with modified genomes through various genetic engineering techniques, including transgenesis, gene knockout, and gene knock in. These mice are often created to model human diseases *in vivo*.
Malignant transformation: the process during which a normal or precancerous cell undergoes drastic biological changes to become a cancerous cell.
Proteome: the complete collection of proteins expressed by a cell, tissue, or organism.
Proteostasis: first, new polypeptides are produced by ribosomes; subsequently, these nascent polypeptides fold into appropriate 3D conformations with the assistance of HSPs; and last, misfolded or aggregated proteins and proteins reaching the end of their normal lifespan are recognized as waste and promptly removed from cells via the ubiquitin–proteasomal pathway or the autophagy–lysosomal pathway.
Xenograft mouse model: immunocompromised mice that carry transplanted cells or tissues derived from another species, such as humans.