Review

Proteostasis and aging of stem cells

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The accumulation of misfolded or damaged proteins is an important determinant of the aging process. Mechanisms that promote the homeostasis of the proteome, or proteostasis, can slow aging and decrease the incidence of age-related diseases. Adult stem cell function declines during the aging process of an organism. This demise of somatic stem cell function could contribute to tissue degeneration and organismal aging. Accumulation of damaged proteins in embryonic stem cells (ESCs) may also have an impact on the aging process, because the passage of these proteins to progenitor cells during asymmetric division could compromise development and aging. Therefore, proteostasis maintenance in stem cells might have an important role in organismal aging. In this review, we discuss exciting new insights into stem cell aging and proteostasis and the questions raised by these findings.

Proteostasis maintenance during aging

The understanding of stem cell biology, differentiation and, cell reprogramming is currently one of the most intense and attractive fields in biology and medicine. Despite the insights gained into stem cell biology, the mechanisms that regulate stem cell identity and differentiation remain largely unknown. Pluripotent ESCs do not undergo replicative senescence and are considered to be immortal in culture [1,2]. Adult organisms have two types of stem cell: (i) adult somatic stem cells, which are found in several tissues and regenerate them; and (ii) germline stem cells (GSCs), which can generate gametes for reproduction [3]. GSCs are designed to maintain an unlimited proliferative capacity to fulfill their biological purpose: to be passed from one generation to the next. Adult somatic stem cells are critical for rejuvenating tissues and persist throughout the lifespan of the organism. However, adult somatic stem cell function declines during the aging process and this failure may contribute to age-related diseases [4,5] (Box 1).

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While genome stability is central for the survival of stem cells, proteome stability may play an equally important role in stem cell identity. Proteostasis is critical for organismal development and cell function [6,7]. The quality of the proteome is regulated by a complex network of cellular mechanisms that monitors the concentration, folding, cellular localization, and interactions of proteins from their synthesis through their degradation (Figure 1) [6–8]. Protein synthesis is controlled by translational rates, which are regulated by ribosome biogenesis, recruitment, and loading [9]. The binding of chaperones to nascent proteins assists their folding into the correct structure. Thermal or oxidative stress, aging, and misfolding-prone mutations challenge the structure of proteins. Chaperones assure the proper cellular localization and folding of proteins throughout their life cycle [10,11]. Misfolded, damaged, aggregated, or unnecessary proteins are degraded by the proteasome or through autophagy [12–15]. The accumulation of misfolded or damaged proteins has a deleterious effect on cell function and viability [6,16]. Damaged proteins can disrupt cellular membranes and form toxic aggregates, overwhelming the cellular machinery required for their degradation [17,18] and causing cell malfunction and death [19]. When the stability of the proteome is challenged, a series of cellular responses is activated to maintain the quality of the proteome [7,16] (Box 2).

Defects in proteostasis lead to many metabolic, oncological, cardiovascular, and neurodegenerative disorders [6,20]. The ability to maintain a functional proteome declines during the aging process [6,11,21,22]. In cells undergoing division, mother cells retain damaged proteins while generating daughter cells with pristine proteomes [23,24]. However, postmitotic cells hold a special distinction for their susceptibility to age-onset protein-aggregation diseases [20]. A decline in the capacity of the cell to protect its proteome has been correlated with multiple age-related diseases such as Alzheimer's [25], Parkinson's [26], and Huntington's [27] disease. Several signaling pathways, such as reduced insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) or dietary restriction (DR), can extend longevity [8]. Furthermore, longevity-promoting pathways modulate the proteostasis network, providing increased stability of the proteome and delaying aging and the onset of age-related diseases [8,28,29].

The immortality and biological purpose of ESCs and GSCs and the ability of adult somatic stem cells to persist throughout life and rejuvenate tissues suggest that these

Box 1. Adult somatic stem cell exhaustion: a hallmark of aging

Adult somatic stem cells are necessary for rejuvenating tissues and persist throughout the lifespan of the organism. However, adult somatic stem cell function declines during the aging process in tissues such as the brain, skin, blood, bone, and skeletal muscle [4,5]. Adult stem cell exhaustion is considered one of the tentative hallmarks of aging in organisms [4]. Stem cell decline with age may contribute to tissue dysfunction and age-associated diseases [4,5,118]. For instance, adult somatic stem cell failure may contribute to diseases such as frailty, atherosclerosis, and type 2 diabetes by reducing the regenerative potential of tissues [118]. Decreased hematopoiesis with age results in diminished generation of adaptive cells and in increased anemia and myeloid malignancies [119]. A decline in the proliferation of NSCs and neurogenesis produced by these cells with age [120–123] has been associated with progressive Parkinsonian disease and impairment of olfactory discrimination in mouse [123]. Besides adult somatic stem cells, specific progenitor and differentiated cells can persist throughout life in regenerative tissues and their decline with age may also contribute to age-related diseases such as type 2 diabetes and reduced immune function [5].

cells could have increased mechanisms to protect their proteome. Recently, new insights into proteostasis in stem cells have supported this hypothesis. Specifically, a role of protein degradation systems and proteotoxic stress responses has been shown. In addition, longevity mechanisms are important determinants of stem cell maintenance and function. Here we review these insights into proteostasis regulation and the role of longevity-promoting pathways in stem cells.

Response to proteostasis stress in stem cells

A series of cellular responses are activated to maintain the integrity of the proteome when damaged proteins accumulate (Box 2). The heat shock response (HSR) is an essential mechanism to assure proper cytosolic protein folding and ameliorate chronic and acute proteotoxic stress [16,22]. The endoplasmic reticulum (ER) also has a critical role in protein folding [30,31]. The ER uses complex surveillance mechanisms to promote proper protein folding and activates the unfolded protein response (UPR^{ER}) to prevent the accumulation of misfolded proteins that are targeted for degradation by ER-associated degradation (ERAD) or autophagy [30–32]. If protein misfolding overwhelms the cellular ability to maintain the quality of the proteome, the ER coordinates with mitochondria to activate apoptosis [32]. Mitochondrial activity is associated with cellular dysfunction and aging [33]. A surveillance mechanism formed by chaperones and proteases, known as the mitochondrial UPR (UPR^{mt}), maintains the quality of the proteome in mitochondria [34]. Activation of these pathways or increased levels of chaperones are associated with enhanced protection against proteotoxic stress [35].

Reactive oxygen species (ROS) generated by the mitochondrial respiration process are frequently responsible for DNA and protein damage. Both mouse ESCs (mESCs)

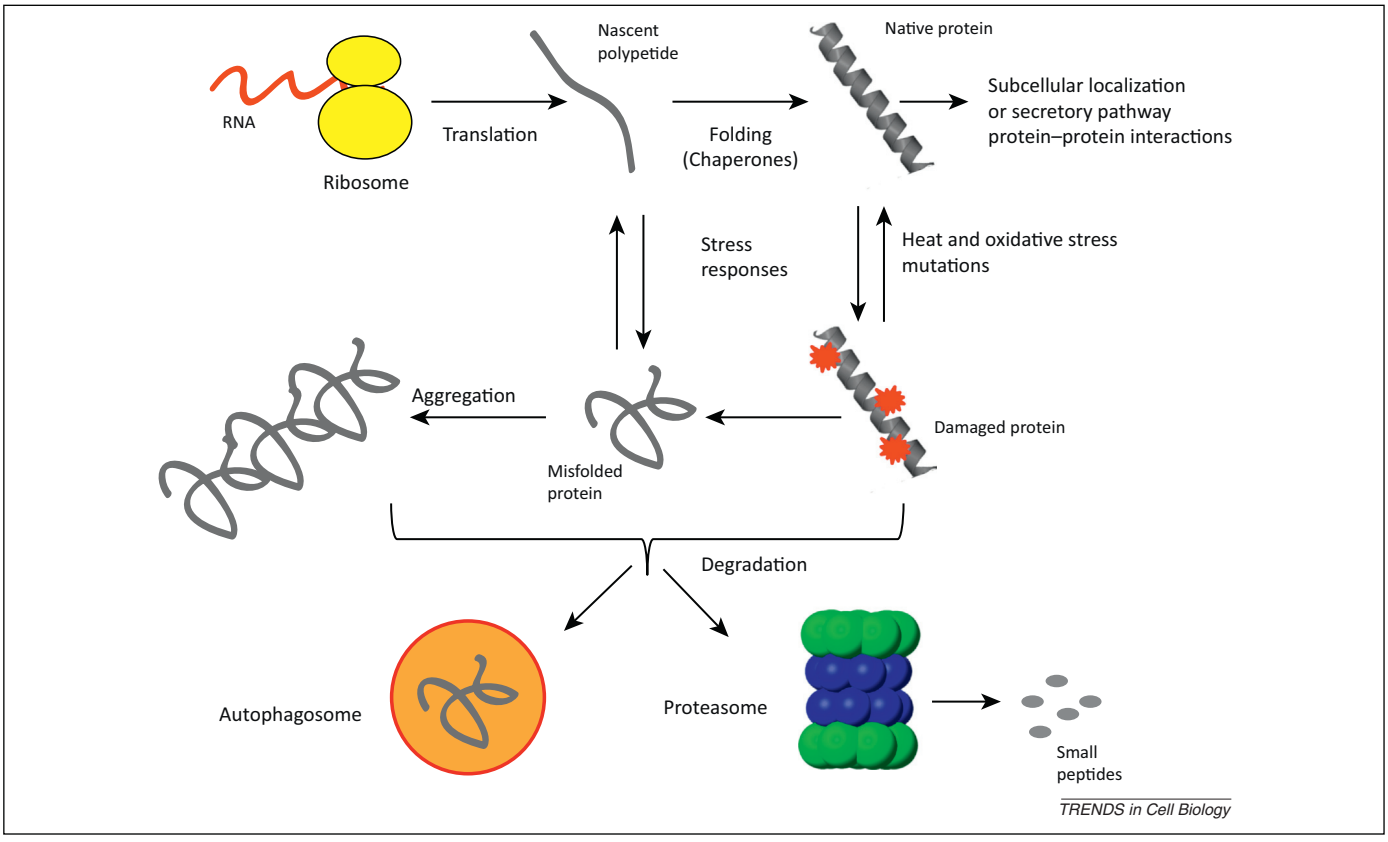

Figure 1. The proteostasis network. Protein synthesis is regulated by translational rates. Translation is controlled by ribosome biogenesis, recruitment, and loading. Chaperones assist the folding of nascent polypeptides into their correct structure. To achieve their function, native proteins are localized to their specific cellular compartment and the correct protein–protein interactions are established. Thermal or oxidative stress and misfolding-prone mutations damage and challenge the structure of proteins. When the stability of the proteome is challenged, a series of cellular stress responses are activated to maintain the quality of the proteome such as the heat-shock response or the unfolded-protein response. Misfolded, damaged, aggregated, or unnecessary proteins are degraded by the proteasome or through autophagy.