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Review

Protein synthesis as an integral quality control mechanism during ageing

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ABSTRACT

Ageing is manifested as functional and structural deterioration that affects cell and tissue physiology. mRNA translation is a central cellular process, supplying cells with newly synthesized proteins. Accumulating evidence suggests that alterations in protein synthesis are not merely a corollary but rather a critical factor for the progression of ageing. Here, we survey protein synthesis regulatory mechanisms and focus on the pre-translational regulation of the process exerted by non-coding RNA species, RNA binding proteins and alterations of intrinsic RNA properties. In addition, we discuss the tight relationship between mRNA translation and two central pathways that modulate ageing, namely the insulin/IGF-1 and TOR signalling cascades. A thorough understanding of the complex interplay between protein synthesis regulation and ageing will provide critical insights into the pathogenesis of age-related disorders, associated with impaired proteostasis and protein quality control.

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1. Introduction

Proteins have been selected as the main executor biomolecules utilized by the cellular arsenal in diverse organisms, ranging from unicellular prokaryotes to complex, multicellular eukaryotes. Approximately half of the total energy output of the cells is consumed for the translation process while specialized systems, for instance the methionine sulfoxide reduction system (Kim, 2013) and the thioredoxin antioxidant system (Lu and Holmgren, 2014), have evolved to remove oxidative damage existing in polypeptides. Additively, autophagy and the proteasome machinery constantly survey for aggregated or dysfunctional proteins, subsequently eliminating them. Hence, a milieu of specialized factors is dedicated to the preservation of proteostasis per se, illustrating once again the importance of maintaining the protein repertoire intact, devoid of any sort of damage. In parallel, the need for maintaining cellular homeostasis dictates that at any given time the protein synthesis rate should be coupled with protein degradation rhythms. When this balance is perturbed, defective or damaged proteins may accumulate in a progressive manner, ultimately leading to a detrimental state and even cell death (Hipp et al., 2014). Considering the importance of the proteome integrity for cellular functions, it is not surprising that the loss of proteostasis is tightly linked with the onset of ageing and neurodegenerative disease and is classified as a typical hallmark of ageing (López-Otín et al., 2013).mRNA translation is a cytoplasmic cellular process which is affected by age. It involves a series of complex reactions, namely the initiation which involves multiple steps followed by the elongation and the termination phase. Elucidating the mechanisms by which translational components function will allow a more profound understanding of their contribution to the ageing process. Here, we review the regulatory mechanisms of the translation initiation phase as well as the role of ribosomal proteins, ribosome biogenesis and structure in whole organism longevity. Dysfunction of mitochondria including altered structure, mitochondrial gene expression and metabolism is a characteristic of ageing (Gomes et al., 2013). However, interestingly enough, the communication between cytoplasmic translation and this organelle is also crucial; thus the interaction between mitochondrial function and cytosolic protein synthesis will also be discussed in the context of the ageing process.

Even at the pre-translation level multiple regulatory mechanisms are utilized so that the process of protein synthesis is tightly controlled both spatially and temporally. Dysregulation of protein synthesis surveillance mechanisms at either the pre-translational or translational level has been related to ageing and the onset of disease (Tavernarakis, 2007; Yoon et al., 2006). From DNA replication to functional protein folding, a pleiad of molecules with distinct functions cooperate in multiple regulatory networks. Studies so far have partially shed light on several of these factors. Specifically, after DNA transcription and before translation initiation, non-coding RNAs and RNA binding proteins (RBPs) function to regulate translation. Intriguingly, recent studies highlight that the endogenous properties of RNA molecules change with age, raising the question of whether artificial intervention on intrinsic RNA properties could either delay ageing or accelerate it.

Genomic studies show that in contrast to the high percentage of the human genome that is being transcribed, fewer than 2% of the produced RNA molecules are finally translated, producing functional proteins (Kapranov et al., 2007). Relative to their coding potential, RNA molecules are divided into two categories: the coding and the non-coding RNAs. Non-coding RNAs are further subdivided into the small and long non-coding RNAs. Both are exponentially attracting the interest of the scientific society as they have been shown to play key roles in fundamental cellular processes such as DNA and mRNA regulation as well as protein synthesis control, thus affecting a variety of complex biological processes such as tissue differentiation, development, senescence, ageing and disease onset (Abdelmohsen et al., 2013; Gong and Maquat, 2011; Kretz et al., 2013; Lovat et al., 2011; Smith-Vikos and Slack, 2012; Wang et al., 2008; Wolfson et al., 2009). Some of their endogenous properties such as 2-D and 3-D folding, modified forms such as methylated or oxidized ones, are implicated in disease onset and cell physiology disruption (Halvorsen et al., 2010; Poulsen et al., 2012; Squires et al., 2012; Wang et al., 2014). The RBPs in concert with non-coding RNAs play a significant role in mRNA homeostasis and more generally, at the regulation of protein synthesis at a post-transcriptional level. This multi-layered regulation of protein synthesis is of high importance for the regulation of the ageing process (Rattan, 2010; Schimanski and Barnes, 2010). RBPs are capable of both repressing and activating protein synthesis by binding to specific mRNAs, with some of them executing both roles. Moreover, it is evident that each one of them can bind to multiple targets (Lebedeva et al., 2011). Besides mRNAs, their targets include transcription factors and other RBPs or proteins that modulate ageing, even if the knowledge concerning this field is still constrained.

Ageing is manifested by the progressive decline in cellular functions, compromising tissue functionality and finally causing fatality. The prevailing theory was that ageing is a stochastic and passive process accelerated by the accumulation of irreversible damage in vital macromolecules. However, it has nowadays become evident that the onset of ageing is tightly regulated by conserved signalling pathways, mainly the TOR and the insulin/IGF-1 (Gems and Partridge, 2013). Protein synthesis, and especially translation initiation, is a rather reasonable node of interaction with ageing-determining pathways, as it essentially enables the replenishment of defective or damaged proteins with fresh, intact ones. Intriguingly, it is the attenuation of protein synthesis, instead of its enhancement, that has beneficial effects on lifespan probably via shifting valuable energy resources from anabolism to repair and the activation of stress-response mechanisms. Concomitantly, depletion of specific amino acids extends chronological lifespan of yeast cells and delays senescence of mammalian cell cultures (Johnson and Johnson, 2014; Kozieł et al., 2014). These findings are consistent with the theory of antagonistic pleiotropy, which postulates that genes which accelerate ageing are maintained in the population because of their requirement in early developmental stages (Parsons, 2007). In this review, we survey the link between protein synthesis quality control mechanisms and the ageing process.

2. Protein synthesis quality control

2.1. mRNA translation initiation

The most tightly controlled step of translation is the initiation phase when the ribosomes initiate translation of the messenger RNA (mRNA) in the 5′ to 3′ direction by pairing of the mRNA initiation codon with the anticodon loop of initiator tRNA. Specifically, the 43S pre-initiation complex, comprised of 40S ribosomal subunit and several initiation factors, is formed to unwind the RNA secondary structure; this is a scanning mechanism invoking several core and auxiliary initiation factors. Alternatively, translation of certain mRNAs can start from the internal ribosome entry sites (Jackson et al., 2010). The pre-initiation complex then attaches to the mRNA and scans the 5′ UTR, followed by recognition of the initiation codon. Initiation is modulated by mechanisms which affect either the eukaryotic initiation factors (eIFs) and the ribosomes or the mRNA itself through ribosome binding proteins (RBPs) and microRNAs (miRs).

Translation initiation control has been directly linked to the ageing process. It has been well established that reduced protein

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