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Review

Does proteostasis get lost in translation? Implications for protein aggregation across the lifespan

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ABSTRACT

Protein aggregation is a phenomenon of major relevance in neurodegenerative and neuromuscular disorders, cataracts, diabetes and many other diseases. Research has unveiled that proteins also aggregate in multiple tissues during healthy aging yet, the biological and biomedical relevance of this apparently asymptomatic phenomenon remains to be understood. It is known that proteome homeostasis (proteostasis) is maintained by a balanced protein synthesis rate, high protein synthesis accuracy, efficient protein folding and continual tagging of damaged proteins for degradation, suggesting that protein aggregation during healthy aging may be associated with alterations in both protein synthesis and the proteostasis network (PN) pathways. In particular, dysregulation of protein synthesis and alterations in translation fidelity are hypothesized to lead to the production of misfolded proteins which could explain the occurrence of age-related protein aggregation. Nevertheless, some data on this topic is controversial and the biological mechanisms that lead to widespread protein aggregation remain to be elucidated. We review the recent literature about the age-related decline of proteostasis, highlighting the need to build an integrated view of protein synthesis rate, fidelity and quality control pathways in order to better understand the proteome alterations that occur during aging and in age-related diseases.

1. Introduction

With the number of individuals aged 60 years or older predicted to double by 2050 and aging being the main driver of human chronic diseases, research efforts are intensifying to better understand the complexity of aging biology (Beard et al., 2016). Recent works show a systemic decline of multiple cellular processes and pathways with aging, including proteostasis (López-Otín et al., 2013), however, the causes and effects of such decline remain poorly understood in both aging and chronic diseases.

The proteostasis network (PN) is a collective group of 2000 molecular components and multiple pathways responsible for balancing the synthesis of new proteins and the degradation of damaged and aged proteins in order to prevent both the accumulation of unfolded and/or misfolded protein clusters and proteotoxic stress (Balchin et al., 2016; Klaips et al., 2018; Morimoto and Cuervo, 2014; Sontag et al., 2017). The PN acts at the levels of protein synthesis, assisted protein folding and protein degradation (Klaips et al., 2018) mainly through 4 integrated cellular pathways: the heat shock response (HSR), the ubiquitin proteasome system (UPS), the unfolded protein response (UPR) and autophagy (for reviews on the PN with emphasis on protein folding, see (Balchin et al., 2016; Díaz-Villanueva et al., 2015)). Multiple studies from a variety of laboratories provide evidence that link PN dysfunction, protein aggregation and proteotoxic stress during aging and in age-related diseases (Duran-Aniotz et al., 2017; Luna et al., 2018; Ma et al., 2013; Sacramento et al., 2020; Thibaudeau et al., 2018)). For instance, proteostasis decline driven by protein aggregation has been extensively studied in Alzheimer´s Disease (AD) (Canter et al., 2016) and in Parkinson's Disease (PD) (Mealer et al., 2014; Wakabayashi et al., 2013). Interestingly, postmortem brains of cognitively unimpaired individuals, without dementia, also contain clusters of altered proteins that are usually associated with neurodegenerative diseases namely hyperphosphorylated tau localized exclusively in the locus coeruleus and hippocampus, amyloid-β (Aβ) in the cortex, TAR DNA-binding protein 43 (TDP43) in the amygdala, medulla and hippocampus, and α-synuclein in the amygdala and the medulla (Elobeid et al., 2016). Notably, 41 % of subjects aged 80 − 89 years had a combination of at least three types of protein clusters, indicating that

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protein aggregation occurs during aging even in the absence of disease (Elobeid et al., 2016a). Aging studies in Caenorhabditis elegans (*C. elegans)* have extended our knowledge of protein aggregation across the lifespan. Indeed, hundreds of aggregated proteins of the mitochondrial respiratory chain and proteostasis pathways were also identified in healthy aged worms (David et al., 2010). Among the identified aggregated proteins, casein kinase I (KIN-19) and Ras-like GTP-binding protein rhoA (RHO-1) showed the highest insolubility propensity across the lifespan, in somatic tissues such as the pharynx and body-wall muscle and in oocytes, respectively (David et al., 2010), producing amyloid-like aggregates shortly after synthesis (Huang et al., 2019). Also in *C.elegans,* Par-5 was identified as highly aggregation-prone at late middle age (day 10) and also shown to seed and accelerate Aβ toxicity while its human homolog, the late-aggregating protein 14 − 3-3 has been associated with the initiation of tau fibrillation providing a link between age-related protein aggregation and disease-associated aggregation (Groh et al., 2017; Li and Paudel, 2016; Qureshi et al., 2013). In rats (*Rattus norvegicus*), polyubiquitin aggregates associated with p62 tend to accumulate with age in the kidney and pancreas (Cui et al., 2012; Liu et al., 2013b). Detergent-insoluble protein clusters are also visible in the mouse (*Mus musculus*) heart during normal aging and after sustained angiotensin II-induced hypertension, which is known to mimic many features of cardiac aging (Ayyadevara et al., 2016). Furthermore, in the bone marrow and spleen, the amount of detergent-insoluble proteins was shown to be greater in 22-month-old mice compared to 3- and 12-month-olds (Tanase et al., 2016) while protein clusters associated with neurological diseases are also present in the human retina and other tissues (Leger et al., 2011). More recently, it has been reported that fragments of mRNAs, ribosome-associated 3′ UTRs, accumulate specifically in D1 spiny projection neurons of the mouse striatum and in the cortex in humans during aging (Sudmant et al., 2018). Furthermore, lysosomal aggregates containing the ribosomal protein RPS6 were detected in old killifish (*Nothobranchius furzeri*) brains and RPS6 was significantly enriched in SDS-insoluble aggregates in old mouse brains (Sacramento et al., 2020).

Taken together, these results show differential amounts of insoluble proteins among tissues, indicating that each tissue has a different propensity for insoluble proteins to accumulate with age (Table 1) In other words, while proteostasis loss driven by protein aggregation appears to be involved in aging, the exact mechanism for such aggregation to occur remains to be clarified.

Although the majority of studies indicate an age-associated dysregulation of the PN, the contributing role of the translation machinery to proteostasis imbalances across the lifespan has been less explored (for comprehensive reviews on PN, aging and disease, see (Hipp et al., 2019; Kaushik and Cuervo, 2015; Klaips et al., 2018; Labbadia and Morimoto, 2015; Morimoto and Cuervo, 2014)). Recent research has started to shed a light on this topic, with accumulating evidence suggesting that the translation process is also affected with age.

2. Alterations on translation machinery components contribute to proteostasis imbalances across the lifespan

The accurate translation of messenger RNA (mRNA) into the correct and functional corresponding protein is a complex process that is affected by many factors, including mRNA codon composition and distribution, transfer RNA (tRNA) expression, a balanced mRNA codon demand and aminoacylated-tRNA supply model, aminoacylation fidelity ensured by aminoacyl-tRNA synthetases (aaRS), tRNA and ribosomal RNA (rRNA) modifications by modifying enzymes and translation elongation factors (Chan and Lowe, 2016; Phizicky and Hopper, 2010; Stein and Frydman, 2019). Alterations in any of these components can affect the translation process and ultimately lead to proteostasis imbalances.

2.1. Codon usage and context impact translation elongation rates and co-translational folding

It is now widely accepted that some proteins begin to fold co-translationally, i.e., before synthesis is completed (for reviews, see (Kolb, 2001; Komar, 2018; Stein and Frydman, 2019)), with folding being influenced by the dynamics of translation, and, more specifically, by the speed at which translation elongation occurs (Purvis et al., 1987; Spencer et al., 2012; Wruck et al., 2017; Zhang et al., 2009). Translation elongation takes place at variable rates, with alternating periods of fast and slow decoding (Rodnina, 2016; Thommen et al., 2017). Periods of slow decoding are believed to favor protein folding by providing enough time for each domain to acquire its proper conformation, thus avoiding misfolding and aggregation, while fast decoding periods are probably related to protein synthesis efficiency and yield allowing faster ribosomal turnover (Evans et al., 2008; Frydman et al., 1999; Hess et al., 2015; Klumpp et al., 2012; O'brien et al., 2014a; O'Brien et al., 2014b; Rodnina, 2016; Siller et al., 2010; Thanaraj and Argos, 1996). Therefore, modulators of translation elongation rates, such as mRNA codon composition and tRNA abundance, should have an impact in the final conformation of proteins.

The genetic code is degenerate; a single amino acid can be encoded by different synonymous codons. These codons were thought to be

Table 1
Tissue-specific differences in age-related protein aggregation in the non-disease context.

Type of protein aggregate	Organism	Organ	Age of highest aggregation level	References
Ribosomal protein S6 (RPS6)	Killifish (*N. furzeri*)	Brain	30 wph	Sacramento et al. (2020)
Casein kinase I isoform alpha(KIN-19)	Worm (*C. elegans*)	Pharyx	9 d	David et al. (2010)
Ras-like GTP-binding protein rhoA (RHO-1)		Oocytes	9 d	
Detergent-insoluble		*nr*	10 d	
14 − 3-3-like protein 1 (PAR-5)		*nr*	10 d	Groh et al. (2017)
Polyubiquitin-associated p62	Rat (*R. norvegicus*)	Kidney	24 m	Cui et al. (2012)
		Pancreas	24 m	Liu et al. (2013b)
Detergent-insoluble	Mouse (*M. musculus*)	Heart	30 m	Ayyadevara et al. (2016)
		Bone marrow	22 m	
		Spleen	22 m	Tanase et al. (2016)
Hyperphosphorylated Tau (HPτ)	Human (*H. sapiens*)	Brain – *locus coeruleus*	80 − 89 y	Elobeid et al. (2016b)
		Brain – hippocampus		
Amyloid-β (Aβ)		Brain – cortex		
TAR DNA-binding protein 43 (TDP43)		Brain – *medulla oblongata*	70 − 79 y	
		Brain –amygdala	80 − 89 y	
		Brain – hippocampus		
α-synuclein		Brain – *medulla oblongata*		
		Brain –amygdala		

wph – weeks posthatch; *d* – days; *m* – months; *y* - years; *nr* – not reported.

functionally equivalent, but they display different frequencies of occurrence both within and between genomes (Codon Usage Bias – CUB), suggesting otherwise (Chaney and Clark, 2015; Im and Choi, 2017; Komar, 2016; Plotkin and Kudla, 2011). CUB positively correlates with protein expression levels whereby highly expressed genes are enriched in optimal codons when compared to lowly expressed genes (Brule and Grayhack, 2017; Komar, 2016; Paulet et al., 2017; Quax et al., 2015). Furthermore, these optimal codons are translated at higher rates because they are recognized by the most abundant cognate tRNAs, whereas rare slowly translated codons are decoded by low-abundance tRNAs (Brule and Grayhack, 2017; Dana and Tuller, 2014; Im and Choi, 2017; Novoa and Ribas de Pouplana, 2012; Quax et al., 2015). Indeed, it was found that the relationship between CUB and tRNA pools is highly dynamic, as these factors coevolve to meet a balanced mRNA codon demand-tRNA copy number supply (Du et al., 2017; Gingold et al., 2012; Higgs and Ran, 2008). Likewise, the context in which synonymous codons occur within the mRNAs (codon-context) was also proven to be functionally impactful (McCarthy et al., 2017; Moura et al., 2011) while influencing translation rates (Chevance et al., 2014; Diambra, 2017; Gamble et al., 2016).

The link between translation rates and protein folding has been supported by evidence from several studies. In one study, the authors found an association between optimal codons and aggregation-prone sites within proteins, potentially to avoid prolonged exposure of these sites during the co-translationally folding process (Lee et al., 2010). In another study, a protein firefly luciferase model engineered with predictably fast translating synonymous codons not only exhibited lower specific activity but also displayed an increased aggregation propensity (Spencer et al., 2012). Similarly, synonymous substitutions predicted to increase translation rates in the first nucleotide binding domain (NBD1) of the cystic fibrosis transmembrane conductance regulator (CFTR), despite producing the same amino acid chain, resulted in the misfolding and aggregation of both the isolated domain and the full-length protein (Kim et al., 2015). In a more recent study, the authors proposed to assess the association between synonymous rare variants and neuroimaging biomarkers for AD where they found significant associations in variants that introduced optimal codons in natively non-optimal sites (Miller et al., 2018a). Although causality was not established, these results strongly suggest a role played by CUB in AD-related phenotype by presumably altering the function and/or the expression levels of proteins (Miller et al., 2018b).

Moreover, some of these codon-related variations in translation rates can also be attributed to codon context. As an example, it was previously found that a synonymous substitution to a rare codon in the multidrug resistance 1 gene (MDR1) results in altered conformations of its product, the ATP binding cassette subfamily B member 1 (ABCB1) drug-transport protein (Kimchi-Sarfaty et al., 2007). A recent re-analysis of these results showed that the conformational alteration in the protein is better explained by an alteration in the native bicodon bias of its encoding gene (Diambra, 2017). The ABCB1 protein (commonly known as P-glycoprotein) functions as a blood-brain barrier transporter and has been reported to be downregulated in both aging and AD, compromising Aβ clearence and favoring its accumulation in the brain (recently reviewed in (Erdő & Krajcsi, 2019)). Curiously, the decrease in ABCB1 protein levels and downregulation of its function with age is not necessarily accompanied by a decrease in mRNA levels (Chiu et al., 2015). In the light of these findings, it would be interesting to compare the codon usage and context biases of the MDR1 mRNAs between young and old individuals, as well as in AD conditions.

Other studies focused on the role played by the tRNA molecules for translation efficiency and accuracy. Fedyunin and colleagues showed that overexpressing low-abundance tRNAs led to the aggregation of many cytoplasmic proteins in *Escherichia coli* (*E. coli*) due to faster translation rates (Fedyunin et al., 2012). Similar observations were made in *S. cerevisiae* where increasing the expression of rare tRNAs resulted in high levels of protein misfolding, saturation of the protein quality control machinery and increased expression of markers of proteotoxic stress (Yona et al., 2013). Conversely, in *S. cerevisiae* and *C. elegans*, hypomodification of a subset of tRNAs was shown to induce ribosome pausing at their cognate codons, which resulted in protein aggregation and proteotoxic stress (Nedialkova and Leidel, 2015). Furthermore, overexpression of these hypomodified tRNAs not only ameliorated ribosome pausing, but also restored proteostasis (Nedialkova and Leidel, 2015).

These results strongly suggest the existence of natural codon biases that are optimal for co-translational folding and specific to different subsets of mRNAs that when altered, disrupt proper protein folding leading to protein aggregation (Buhr et al., 2016). The fact that, across the evolution of mice and humans from their common ancestor, there has been a selective preservation of the codon usage of brain-specific genes (Plotkin et al., 2004), a tissue known to be substantially sensitive to protein misfolding (Drummond and Wilke, 2008), and where both nuclear- and mitochondrial-encoded tRNAs are most abundant (Dittmar et al., 2006), strongly supports this hypothesis (Buhr et al., 2016).

In addition to being differentially expressed between tissues, tRNA pools have been shown to be dynamic across the lifespan and in stress conditions. For example, in *C. elegans*, tRNA expression was reported to decline with age, with emphasis on neuronal tissues (Sagi et al., 2016), while in *S. cerevisiae* differential tRNA abundance between normal and different stress conditions is suggested to occur to favour selective translation of stress-response genes (Torrent et al., 2018). Dysregulation of tRNA abundance is also reported in cancer, which is considered an age-related disease, with overexpression of nuclear and mitochondrial tRNAs being observed in breast cancer and multiple myeloma cell lines and tissues compared to non-cancer controls (Pavon-Eternod et al., 2009; Zhou et al., 2009). Moreover, changes in the global tRNA expression profile were also observed following manipulation of individual tRNA levels (Pavon-Eternod et al., 2013). Considering these results, changes in tRNA pools possibly occur to match the codon usage of specific genes of interest (e.g. highly expressed genes in physiological conditions, stress-response genes in stress conditions or even cancer-related genes in cancer), thus favouring their translation. However, one can argue that, at the same time, these alterations in tRNA pools also impact the translation of other mRNAs, most likely impairing the proper folding of the corresponding nascent polypeptides.

Nevertheless, the evidence regarding dynamic changes in tRNA pools is still scarce. The characteristically folded structure of tRNAs and the fact that these are extensively post-transcriptionally modified impairs the accurate quantification of these molecules. It is important, as new techniques are being developed, to confirm these results and quantitatively determine the behaviour of tRNA pools across the lifespan and in age-related diseases in a wider range of organisms.

Altogether, the data suggest that age-related disruption of the mRNA codon demand-tRNA anticodon supply balance alters the natural ribosome pausing patterns, leading to alterations in co-translational folding, and contributing to age-related protein aggregation (Fig. 1).

2.2. Alterations in translation fidelity activate proteotoxic stress responses

Also, during the translation process, translational errors routinely occur. Translational errors, also known as mistranslation, can be defined as the event of an amino acid being misincorporated at a non-cognate codon site, or in other words, misincorporation at a codon that is not decoded by the correct corresponding tRNA (Mohler and Ibba, 2017). A slight increase in translational error rate is sufficient to downregulate the overall protein synthesis rate, activate the stress response, increase protein aggregation, reprogram gene expression and destabilize the genome in yeast, zebrafish, and human cell lines (Paredes et al., 2012; Reverendo et al., 2014; Varanda et al., 2019). Hence, studying translation error rate can be relevant in monitoring proteostasis loss during aging (Fig. 1).

Notably, the basal level of translational error of 10^{-3} to 10^{-4} amino

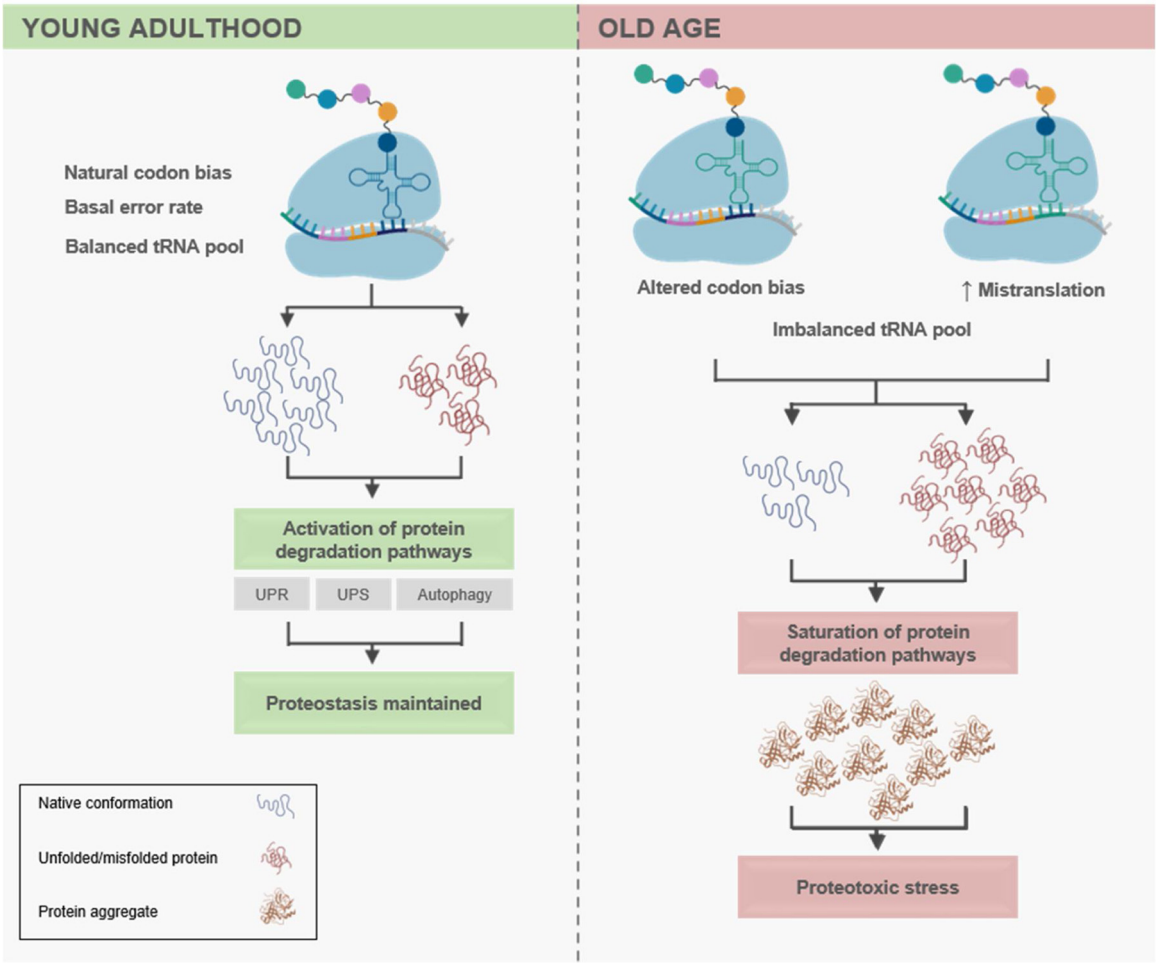

Fig. 1. Age-related alterations in protein synthesis and proteostasis. During young adulthood (left panel), the process of protein synthesis and its components are balanced allowing for the optimal folding of proteins into their native configuration (depicted in blue). In this scenario, any misfolded/unfolded proteins (depicted in red) resultant from occasional errors, are detected and trigger the activation of degradation pathways, thus maintaining the homeostasis of the proteome. During aging (right panel), this equilibrium is disrupted by increased mistranslation, alterations in codon bias and changes in the pools of tRNAs resulting in an over-representation of misfolded/unfolded proteins in the proteome that ultimately leads to the saturation of protein degradation pathways. The misfolded/unfolded proteins then accumulate in the cell as protein aggregates (depicted in dark orange), triggering proteotoxic stress. Figure created with Biorender.com.

acid misincorporations per codon, also known as intrinsic translational error, results in an average of 1 amino acid misincorporation in 15 % of average length eukaryotic protein molecules (Drummond and Wilke, 2009). The majority of these misincorporations result in conserved or semi-conserved mutations with little impact on protein stability. However, the basal level of translational error can be higher in specific conditions that can induce proteotoxic stress and cell death. For instance, in human colon cancer, translational error levels are higher due to deregulation of tRNA expression (Santos et al., 2018).

Until recently, the unavailability of efficient methods that identify misincorporated amino acids has prevented the in-depth analysis of protein synthesis errors and, in particular, the mapping of proteome errors in tissues. New mass spectrometry and bioinformatics methods developed by Mordret and colleagues (Mordret et al., 2019) show that each codon displays a specific error rate threshold in both *E.coli* and yeast, revealing a complex error rate pattern in these species. Considering this, classical methods for measuring the average error rate in organisms by 1) specific gain- of- function reporter systems or 2) direct quantification of radioactive amino acid misincorporation at specific codon sites, provide a simplistic view of the cellular spectra of translational errors.

Attenuation of protein synthesis has been recently shown to be necessary to alleviate proteotoxic stress caused by the accumulation of misfolded proteins in the endoplasmic reticulum (ER) (Shcherbakov et al., 2019; Varanda et al., 2019). The accumulation of misfolded proteins in the ER triggers UPR activation through three branches: i) activating transcription factor 6 (ATF6), ii) inositol-requiring enzyme 1 (IRE1) and iii) protein kinase RNA–like endoplasmic reticulum kinase (PERK) pathway, with PERK activation resulting in the phosphorylation of eukaryotic initiation factor 2α (eIF2α), a master regulator of translation initiation, leading to the downregulation of translation initiation and global protein synthesis rate in mammalian cells (Bertolotti et al., 2000; Harding et al., 2000; Shah et al., 2015; Varanda et al., 2019) (Fig. 2a).Furthermore, there is some evidence pointing to the role of other UPR branches on translation attenuation. Interestingly, experiments in HeLa cells showed that the activation of the IRE1 branch, particularly by the endoribonuclease activity of one of IRE1's paralogues - IRE1β, selectively degraded endogenous ER-localized mRNAs, possibly to limit the influx of newly synthesized proteins into the ER (Iwawaki et al., 2001; Nakamura et al., 2011). Moreover, it was recently shown by our laboratory that human HEK293 cells with mutant tRNAs, specifically $tRNA_{Ser}^{Leu}$ that misincorporate Serine at Leucine sites, present increased protein synthesis errors, leading to the accumulation of ubiquitinated proteins, and subsequent activation of the UPR ATF6 branch, a pathway associated with chronic ER stress tolerance (Varanda et al., 2019). Increased phosphorylation of eIF2α was also observed in these cells, indicating an attenuation of protein synthesis rate in order to cope with proteotoxic stress (Varanda et al.,

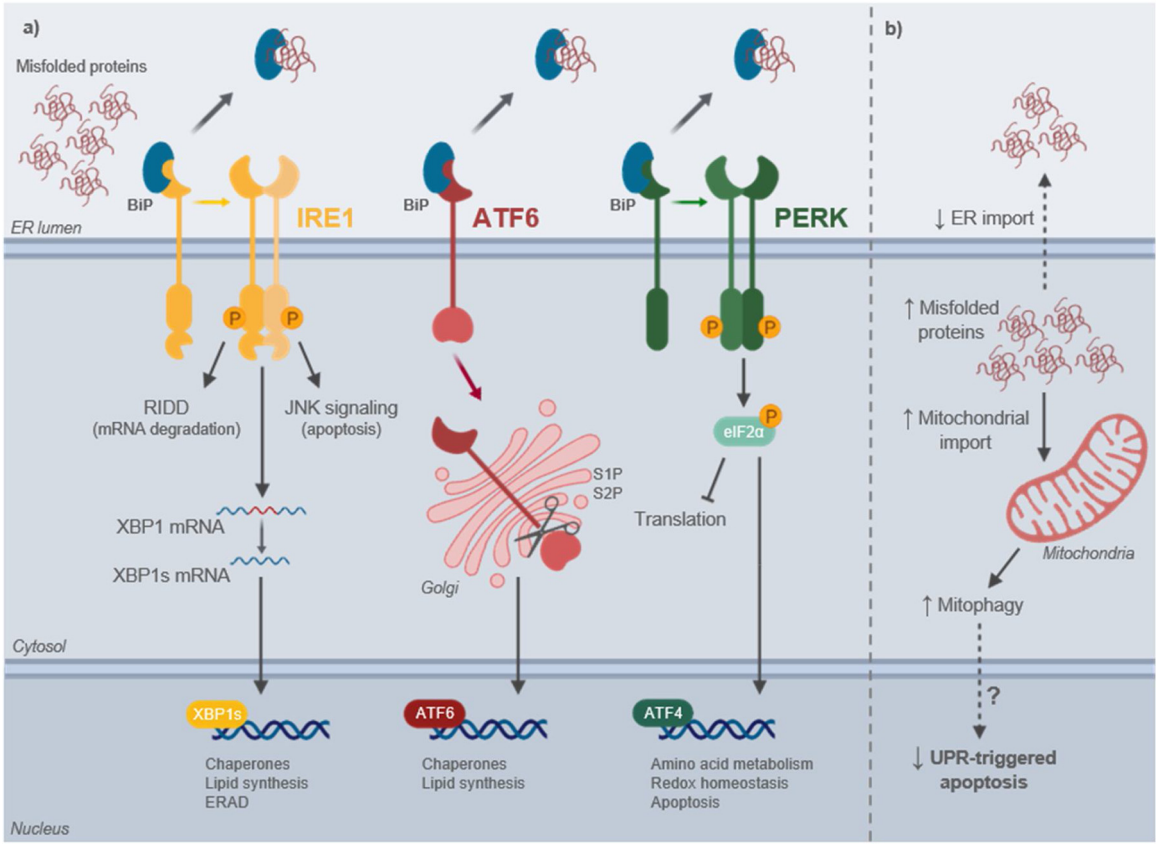

Fig. 2. Schematic representation of the Unfolded Protein Response (UPR) during chronic mistranslation. a) BiP binds to misfolded proteins that are present in the ER lumen activating the IRE1, ATF6, and PERK pathways. This in turn leads to XBP1 splicing, activation of JNK, regulated IRE1-dependent decay (RIDD), ATF6 proteolysis, and eIF2α phosphorylation that attenuate global protein synthesis in order to decrease ER stress caused by accumulation of misfolded proteins. Downstream effects include chaperone production to promote the refolding of misfolded proteins and activation of apoptotic pathways to stimulate cell death. b) An alternative response to chronic mistranslation occurs where misfolded proteins fail to be imported into the ER lumen and accumulate in the cytosol. This leads to increased import of misfolded proteins in the mitochondria ultimately promoting mitophagy. During this process, the UPR is believed to be silenced where reduced ER import of misfolded proteins and UPR activation is observed as a way to circumvent UPR-mediated apoptosis. UPR, Unfolded Protein Response; ER, Endoplasmic Reticulum; BiP, Binding Immunoglobulin Protein; IRE1, Inositol-Requiring Enzyme-1; ATF4, Activating Transcription Factor 4; ATF6, Activating Transcription Factor 6; PERK, Protein Kinase RNA-Like Endoplasmic Reticulum Kinase; eIF2α, eukaryotic Initiation Factor 2 alpha; JNK, c-Jun N-terminal Kinase; XBP1, X-Box-Binding Protein 1; RIDD, Regulated IRE1-Dependent Decay; ERAD, Endoplasmic Reticulum-Associated Degradation. Figure created with Biorender.com.

2019). Accordingly, protein synthesis errors result in UPR activation in mistranslating yeast (Paredes et al., 2012), while in zebrafish embryos engineered with mutant Ser-tRNA$_{CGC}^{Ala}$, Ser-tRNA$_{UCC}^{Gly}$, Ser-tRNA$_{CAC}^{Val}$ and Ser-tRNA$_{CAG}^{Leu}$ that misincorporate Serine (Ser) at Alanine (Ala), Glycine (Gly), Valine (Val), and Leucine (Leu) codon sites, there is UPR activation and upregulation of heat shock proteins (HSPs), namely Hsp90, Hsp70, Hspb1/Hsp27, ER chaperones Hsp90b1/*GRP94* and immunoglobulin binding protein (BiP) (Reverendo et al., 2014). In mice, activation of the PERK branch through phosphorylation of eIF2α has also been shown to increase in 27 and 28-month-old mouse livers compared to younger mice (Kristensen et al., 2017; Pagliassotti et al., 2017), indicating that a similar coping mechanism to proteotoxic stress may occur in mice during aging.

Mitochondria are also highly susceptible to proteotoxic stress and have developed a stress response of their own called the mitochondrial unfolded protein response (UPR^{mt}) (Martinus et al., 1996; Zhao et al., 2002). UPR^{mt} is a stress signaling pathway that is activated by mitochondrial proteostasis imbalances (among other stresses) and elicits a transcriptional response to restore mitochondrial function, with implications in aging and longevity, as well as in health and disease (for interesting reviews on these subjects see (Anderson and Haynes, 2020; Jovaisaite et al., 2014; Qureshi et al., 2017; Shpilka and Haynes, 2018)). In *C.elegans,* the UPR^{mt} is activated by ATFS-1 whereas in mammalian cells this activation is mediated by CHOP, ATF4 and ATF5 (a functional ortholog of ATFS-1), however in both worms and mammals this stress response consists of the upregulation of the expression of mitochondrial chaperones and proteases to, respectively, assist in the correct folding or degradation of proteins (Jovaisaite et al., 2014; Moehle et al., 2019; Qureshi et al., 2017; Shpilka and Haynes, 2018). Despite being organelle-specific stress responses, the ER-associated UPR and the UPR^{mt} are interconnected, as translational attenuation following eIF2α phosphorylation is required for UPR^{mt} activation in mammals and in *C.elegans* was shown to be a protective mechanism of mitochondrial function even though not essential for UPR^{mt} activation (as recently reviewed in (Anderson and Haynes, 2020)).

Notwithstanding the lack of studies linking translation fidelity and the mitochondrial unfolded protein response, there is some evidence regarding age-related protein aggregation. Gene expression analysis of postmortem cortical samples revealed increased levels of mitochondrial chaperones and proteases known to be activated by the UPR^{mt} in the brains of both sporadic (~40–60% increase) and familial AD (~70–90% increase) when compared to cognitively healthy controls, suggesting a greater activation of this signaling pathway (S. Beck et al., 2016). In line with these findings, a *C.elegans* model of α-synuclein proteotoxicity (mimicking PD conditions) not only induced UPR^{mt} but its activation also significantly increased with age (Martinez et al., 2017). Accordingly, experiments with cellular and animal models of amyotrophic lateral sclerosis (ALS)-associated TDP-43 proteinopathy

also revealed activation of the UPR^{mt} as a result of TDP-43 expression (Wang et al., 2019). Nevertheless, in worm and mammalian models of Aβ proteotoxicity, a decrease in the formation and aggregation of these peptides was observed with the genetic and pharmacological activation of UPR^{mt} (Sorrentino et al., 2017). Overall, these results suggest that UPR^{mt} is efficient in dealing with isolated cases of proteotoxic stress, however its prolonged activation seems to further impair proteostasis, highlighting the need for more research on this subject. It would also be important to comprehensively investigate the impact of alterations in translation fidelity on the UPR^{mt}.

A recent study with HEK293 cells transfected with a A226Y mutant ribosomal protein subunit 2 (RPS2) transgene showed that increased mistranslation resulted in an amplified production of protein aggregates (Shcherbakov et al., 2019) (Fig. 2a). In accordance with previous studies, the authors found reduced global translational activity, and increased transcripts for cytosolic chaperones and proteasome components (Shcherbakov et al., 2019). However, the attenuation in protein synthesis that the authors observed was due to alterations in translation elongation rather than initiation (Shcherbakov et al., 2019), a result in line with previous findings linking proteotoxic stress to translation elongation attenuation by ribosome stalling due to chaperone titration to misfolded proteins (Liu et al., 2013a; Shalgi et al., 2013). Moreover, chronic ribosomal mistranslation was found to halt protein import into the ER and the UPR resulting in increased mitochondrial import, biogenesis and mitophagy to cope with the accumulation of misfolded proteins as a potential mechanism to evade UPR-triggered apoptosis (Shcherbakov et al., 2019) (Fig. 2b). Despite the exact mechanisms by which protein synthesis is attenuated in response to proteotoxic stress remaining unclear, there is a consensus regarding the attenuation itself. Accumulation of unfolded/misfolded proteins in toxic aggregates results in a global attenuation of translation. Whether this down-regulation occurs mainly through inhibition of translation initiation or elongation needs to be further addressed by future work while at the same time, the reason for misfolded proteins being re-directed to the mitochondria and subsequent activation of mitophagy have to be studied. Answering these questions is pivotal to understanding the basic biology of aging.

Lastly, aminoacyl-tRNA synthetases (ARSs) are enzymes that ensure translational fidelity by charging tRNAs with the appropriate amino acid, whereas mutations in these enzymes are largely associated with neurological and mitochondrial diseases as well as diabetes (Boczonadi et al., 2018; Cosentino et al., 2019; Suomalainen and Battersby, 2018). Mice with the sticky mutation (*sti*) in the editing domain of the alanyl-tRNA synthetase (AlaRS) synthesize proteins with high levels of Ser misincorporation at Ala sites, due to the mischarging of the tRNA^{Ala} with Ser (Lee et al., 2006). These mutant proteins misfold and aggregate in Purkinje cells, leading to neurodegeneration and UPR activation (Lee et al., 2006). In *D. melanogaster,* mutations in the phenylalanyl tRNA synthetase (PheRS) resulting in increased mischarging of tRNA^{Phe} with tyrosine are also associated with neurodegeneration and increased ER stress (Lu et al., 2014).

Furthermore, mutations in tRNA-modifying enzymes responsible for post-transcriptional tRNA modification (maturation), essential for translation efficiency and fidelity, have been linked to a plethora of human diseases including age-related ALS (Bento-Abreu et al., 2018; Pereira et al., 2018). For example, knockout of elongator protein complex 3 (ELP3) hampers translation fidelity and elongation rate, leading to the production of misfolded proteins and UPR activation in the cortices of mice (Laguesse et al., 2015). And finally, ELP3 silencing in NSC34 cells increases protein aggregation levels and mutant superoxide dismutase 1 (SOD1) accumulation, a hallmark typically associated with ALS (Bento-Abreu et al., 2018). These findings link proteome imbalances, ER stress and UPR activation with mutations in both ARSs and tRNA modifying enzymes, highlighting the role of altered translational fidelity in age-related pathologies.

3. Higher translational fidelity is associated with longevity

Some longevity studies have focused on evaluating translational fidelity in the long-lived naked mole rat *Heterocephalus glaber (H. glaber)*, where proteins are synthesized 4-fold more accurately than in mice (Azpurua et al., 2013). These lower basal rates of amino acid misincorporation are mainly due to high decoding accuracy at the first and second codon positions (Ke et al., 2017). Specific cleavage of the 28S ribosomal RNA (28S rRNA) into two fragments is exclusive to *H. glaber* and may contribute to higher translation accuracy but it is unclear if these fragments are linked with longer lifespan (Azpurua et al., 2013). More importantly, a comparative translational fidelity study in fibroblasts from 16 rodent species (maximum lifespan ranging from 4 to 32 years) showed that fidelity co-evolves with lifespan, with longer lifespan being positively correlated with higher translational fidelity (Ke et al., 2017). Once again, longer-lived species appear to have evolved mechanisms for accurate translation, which may provide evidence that having a lower basal rate of translational errors leads to decreased aberrant protein aggregation and lower levels of proteotoxic stress. In line with this, Perez and colleagues (Pérez et al., 2009) showed that *H.glaber* do not have increased levels of protein ubiquitination with age, as in other species, suggesting that the basal levels of protein misfolding do not increase during aging of *H. glaber*. More recently, it was shown that activation of the eukaryotic elongation factor 2 kinase (eEF2K) slowed down translation elongation, increasing translation fidelity (Xie et al., 2019). Moreover, the authors found that the deletion of the ortholog of this kinase in *C.elegans* lead to a reduced lifespan (Xie et al., 2019), Taken together, these results highlight the role of translation fidelity on the modulation of lifespan.

4. Current views of the dynamics of protein synthesis during aging

Few reports have analyzed the dynamics of protein synthesis in the context of healthy aging, with most limited to studying two age groups, usually comparing older and younger groups, and rarely have observed alterations in several tissues. Inhibition or deletion of protein synthesis components have been shown to increase lifespan extension in *C. elegans* and *S. cerevisiae* (Steffen et al., 2008; Syntichaki et al., 2007). Other works have reported alterations in the abundance of protein synthesis machinery components during aging (Dhondt et al., 2017; Ori et al., 2015; Walther et al., 2015), namely in C. elegans where protein turnover rates decrease in 50 % of ribosomal proteins in older worms with 63 % of these proteins have a tendency to aggregate with age (Dhondt et al., 2017). This decline in ribosomal protein abundance with age is followed by a decrease in protein synthesis rate (Walther et al., 2015), suggesting that protein synthesis may drive proteome imbalances during aging in the worm. In line with these data, mass spectrometry analysis of the *D. melanogaster* proteome showed that 53 % of the 48 ribosomal proteins analyzed decreased in abundance with age, with ribosome biogenesis S24 protein displaying the largest decrease in abundance (Brown et al., 2018). Furthermore, a combination of shotgun mass spectrometry, next generation RNA sequencing and ribosome profiling showed an increased abundance of several ribosomal proteins in 24-month-old rat brains relative to 6-month-olds, however, the level of translation initiation factors declined in older brains (Ori et al., 2015). Interestingly, 15 % of the transcripts were affected by alterations in translation in older rat brains whereas only 2% of transcripts in the liver (Ori et al., 2015), raising the possibility that age-related changes in the translation machinery occur mainly in the rat brain. More recently, RNA sequencing analysis revealed a gradual loss in stoichometry of large protein complexes including ribosomal proteins during aging in the brains of killifish (Sacramento et al., 2020). Among the genes encoding for ribosomal proteins, transcript levels were shown to increase with age while the abundance of ribosomal proteins was either augmented (i.e. RPL8, RPL21, RPS20) or decreased (i.e. RPLP2, RPL22L1, RPS6) in old (39 weeks post-hatching,

wph) killifish compared to the adult group (12 wph), revealing an imbalance in the relative abundance of ribosomal proteins between adulthood and old age (Sacramento et al., 2020). Furthermore, non-radioactive SunSeT assay, a method that quantifies relative puromycin incorporation to measure protein synthesis rates *in vivo*, has been used to show that protein synthesis decreases in the hearts of aged 24-month-old mice compared to 2-month-olds (Ravi et al., 2018). Additional studies using this methodology can elucidate how the dynamics of protein synthesis alter with age in other tissues as well.

4.1. Translation-related alterations in mTOR pathway prolong lifespan

The target of rapamycin (mTOR) pathway plays an important role in lifespan extension (Steffen and Dillin, 2016) and is strongly affected during aging. More specifically, the inhibition of the mTOR pathway via administration of rapamycin, a well-known mTOR inhibitor, has been shown to downregulate protein synthesis and extend lifespan by as much as 60 % of 21-month-old C57BL/6JNia mice (Bitto et al., 2016). It is known that the mTOR complex 1 (mTORC1) is activated to promote cell proliferation and growth by controlling protein synthesis through ribosomal protein S6 kinase 1 (S6K1), involved in translation initiation and translation elongation via eukaryotic elongation factor 2 kinase (eEF2K) (Kennedy and Lamming, 2016). Inhibition of S6K has been shown to reduce the rate of protein synthesis and lead to lifespan extension in several organisms including mice. Weekly administration of rapamycin as early as 9 months in mice results in 100 % survival past 24 months of age, with phosphorylated S6 (p-S6) levels, a marker of mTOR/S6K1 activity, being significantly lower in cardiac muscle and in the liver compared to controls, supporting the hypothesis that inhibition of the mTOR pathway via rapamycin treatments can lengthen lifespan and promote healthy aging (Leontieva et al., 2014). Also, S6K1 knockout mice live longer than wildtype controls and show reduced age-associated motor dysfunction (Selman et al., 2009). Furthermore, treatment with resveratrol, a S6K1 inhibitor, results in decreased oxidative stress and improved endothelial function in the aorta of old rats, providing evidence that S6K1 can be used as therapeutic target for treating vascular aging (Rajapakse et al., 2011).

Activation of eEF2K has been shown to decrease errors during translation elongation, contributing to greater translation accuracy and is also necessary for lifespan extension in *C. elegans* (Haar et al., 2019). This occurs due to increased phosphorylation of eukaryotic elongation factor 2 (eEF2), resulting in a slower elongation process, allowing for ribosomes to correctly distinguish between start codons AUG and their near-cognates, therefore minimizing translational errors (Haar et al., 2019). A prior study showed that rates of mRNA mistranslation are significantly increased in TSC2 null cells, which have constitutive activation of mTORC1-S6K1 signaling, compared to wildtype cells and that these same cells show slower rates of translation elongation as well (Conn and Qian, 2013).

Another mTORC1 target that is involved in protein translation is eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), where mTOR phosphorylates 4E-BP1, which disrupts its interaction with eIF4E leading to cap-dependent protein translation (Demontis and Perrimon, 2010; Le Bacquer et al., 2019). The overexpression of 4E-BP decreases translation initiation rate and limits the accumulation of polyubiquitinated proteins in muscle, fat tissue, eyes, and brain of *D. melanogaster*, prolonging lifespan (Demontis and Perrimon, 2010). During aging, there is a progressive loss of skeletal muscle and decline of muscle function (sarcopenia), which can be ameliorated in BALB/C mice by a double deletion of 4E-BP1 and 4E-BP2 (Le Bacquer et al., 2019).

4.2. Other translation-related alterations with impact on longevity

The role of protein synthesis attenuation on lifespan extension has also been described in other studies. Hofmann and colleagues showed that mice with a heterozygous deletion of Myc (Myc $^{+/-}$) exhibited a 15.1 % increase in lifespan and also an improved healthspan when compared to control animals (Hofmann et al., 2015). They also reported a decrease in the expression of genes encoding ribosomal proteins and mature rRNA levels in these animals, which is in accordance with the observed decrease in translation rates and suggested translation attenuation as a mediator of lifespan extension (Hofmann et al., 2015).

More recently, it was reported that mitochondrial and cytosolic translation are closely connected and that this link has implications on lifespan (Molenaars et al., 2020). The authors describe a retrograde modulation of cytosolic translation based on the levels of mitochondrial ribosomal proteins (Molenaars et al., 2020), adding to previous work in yeast suggesting a unidirectional regulation (Couvillion et al., 2016). In fact, reducing the levels of mitochondrial ribosomes genetically (mrps-5 RNA interference - RNAi) and pharmacologically (doxycycline), impaired mitochondrial translation which lead to decreased levels of cytosolic ribosomes and reduced cytosolic translation, a process mediated by Atf4 in mammals and atf-5 in worms (Molenaars et al., 2020). In addition to slowing down cytosolic translation, Atf4/atf-5-mediated signaling was found to upregulate cyto-protective genes (Molenaars et al., 2020). Considering previous results in *C.elegans* reporting a lifespan increase after mrps-5 RNAi and doxycycline treatment (Houtkooper et al., 2013), it is possible that this “mito-cytosolic translational balance” (Molenaars et al., 2020) has a role in lifespan extension.

Interestingly, protein synthesis decline is a common factor between proteotoxic stress and lifespan extension, which raises the question if protein synthesis is also attenuated during healthy aging and, if so, is this attenuation a cause for longevity or a mere side-effect of cumulative translational defects? Although challenging, measuring protein synthesis rates throughout the mouse lifespan would provide insight to whether putative age-related protein synthesis decline contributes to aging phenotypes.

5. Concluding remarks

Asymptomatic age-related protein aggregation is an intrinsic characteristic of aging, however the molecular mechanisms involved are still unclear. Recent works have provided the first glimpse of a complex network of protein synthesis and quality control pathways whose functional activity declines across the lifespan. It will be important to unravel all the players and functional interactions of this network and determine the molecular pathways responsible for its decline across the lifespan. Considering that protein aggregation triggers the UPR and downregulates protein synthesis, it will also be important to clarify if asymptomatic protein aggregation causes proteotoxic stress, UPR activation and eventual downregulation of protein synthesis rate during aging. The data available to date strongly suggests that the intensity of asymptomatic proteome aggregation is tissue- and cell type-specific and may change in certain metabolic and pathological conditions, opening new research avenues to clarify the molecular mechanisms involved through tissue comparative analysis. Finally, the implications of asymptomatic proteome aggregation on human health andin particular, the relationship with the proteins whose aggregation is characteristic of age-related diseases also need to be clarified. Since proteotoxic stress and downregulation of protein synthesis are both hallmarks of many human diseases, it would be no surprise that age-related protein aggregation could play a crucial role in aging and possibly trigger age-related diseases. Other important issues that need to be fully clarified are the alterations in co-translational folding and the decline of protein synthesis accuracy that occur during aging. It also remains unclear if the gradual decline of protein degradation pathways solely contributes to the formation of aggregates during aging or if the age-related changes in protein synthesis machineries and consequently, the accumulation of translational errors cause asymptomatic age-related protein aggregation. Lack of adequate methodologies have prevented progress

on these topics, however recent works show that the rates of translation can be measured with ribosome profiling, and proteome level analysis of amino acid misincorporations can be performed using mass spectrometry and bioinformatics pipelines. The door is now open to obtain a comprehensive map of age-related protein aggregation in the mouse and human tissues across the lifespan.

CRediT authorship contribution statement

Stephany Francisco: Conceptualization, Investigation, Writing - original draft, Visualization. **Margarida Ferreira:** Investigation, Writing - original draft, Visualization. **Gabriela Moura:** Resources, Writing - review & editing, Supervision, Funding acquisition. **Ana Raquel Soares:** Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition. **Manuel A.S. Santos:** Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors have no interests to declare.

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