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Mechanisms Causing Aging, Current Knowledge and the Way Forward

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The rapid advancement in research technologies and bioinformatics over the past few decades has enabled researchers to shed light on the underlying mechanisms behind aging. Whilst the progress in understanding the biochemical processes involved is impressive, a lot more still needs to be uncovered before any potential effective anti-aging treatment can be produced. Unravelling the various root causes of aging is still the most important obstacle to overcome. The data available highlights that the most likely drivers of aging are the proteosome, the ribosome and telomeres. This review focuses largely on these factors and how they contribute to initiating aging and their targeting in potential therapy against the multitude of age-associated disorders. The investigation thus far of these causative factors will be presented. Understanding these root causes and how they cause aging is fundamental to present a way forward, such that the biochemical basis of aging can be discovered, in order to usher in a new wave of therapeutics against complex diseases.

Keywords: Aging; telomeres; proteome; ribosome; proteosome; progeria.

1. INTRODUCTION

Aging can be described as a biological process involving the deterioration of every part of an organism, leading inevitably to death. Aging however, being a general term, can have many distinct definitions. For the purposes of this review aging will be considered as the decline of

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cellular fitness over time in an individual, manifesting itself in the increased death rate of a population with age. As knowledge on cellular and molecular processes improves, a number of general hallmarks of aging have been proposed, namely: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intracellular communication – the latter mainly stemming from increases in inflammatory signalling molecules [1]. As more data is gathered on these hallmarks, other significant alterations in aging organisms have been uncovered such as changes in the gut microbiome [2] alterations in alternative splicing patterns [3] and also aberrant post translational modifications of certain proteins such as collagen [4]. These hallmarks of aging will now be described in more detail to give appropriate context for an in depth analysis of the proteosome, ribosome and telomeres in early aging.

2. GENETIC MECHANISMS

Replacement of worn out or damaged components for new ones is critical to maintaining homeostasis at every level of life. RNA molecules and proteins for instance are continuously degraded ensuring the constant recycling of RNA and proteins [5,6]. Even whole cells are broken down via apoptosis and replaced by new cells via mitosis. The DNA of a cell however cannot be replaced and is therefore very sensitive to damage making it a very likely component of aging. As such, DNA damage has been investigated with regards to aging for over 60 years [7]. In both human and mouse hematopoietic stem cells (HPSC) for instance, an increased amount of DNA damage was detected in aged cells [8]. This triggers the DNA damage response (DDR), which exacerbates the aging process. This is because DDR can lead to a variety of outcomes such as apoptosis and the temporary or permanent cessation of mitosis, the latter of which is known as senescence [9]. In fact mutations that result in hypermorphic p53, one of the core mediators of the DDR results in a shorter lifespan [10].

However it is unlikely that the increase in DNA damage is due to the simple accumulation of random mutations throughout life. This is because a lot of other factors are altered in aging that together likely lead to this increased DNA damage. For instance DNA methylation is one of the most widely studied epigenetic marks involving the addition of a methyl group to a cytosine within the DNA, which then results in gene repression [11]. However in aging, global genomic hypomethylation is observed resulting in decreased DNA repression [12]. Such global activation increases DNA damage by making DNA more accessible to reactive chemicals that alter the DNA and by increasing the expression of transposons that can move to other regions of the genome, potentially interfering with gene function [13]. In fact transposons have been implicated in the aging process and induction of PIWI, a protein that represses transposons, extends the replicative potential of intestinal stem cells (ISCs) [14].

3. PROTEIN MECHANISMS

Despite the fact that unlike the genome the proteome is constantly recycled, it still plays an important role in aging. Chaperones for instance are crucial for maintaining fitness due to refolding undamaged proteins and induction of the Unfolded Protein Response (UPR). The UPR is a pathway mediated by Heat shock factor 1 (HSF1) that results in decreased translation rates and increased proteosome activity in order to mitigate increased protein misfolding caused by stressors [15]. Other proteins however such as the mammalian target of rapamycin (mTOR) tend to increase translation rates and decrease protein degradation, thereby acting antagonistically to the UPR, increasing protein misfolding and aggregation [16]. This is the primary reason why inhibition of mTOR leads to increased lifespan, with drugs that inhibit mTOR such as rapamycin acting as anti-aging drugs [17].

Such changes in the proteome however extend beyond changes in protein production and folding. Post-translational modifications (PTMs) are an important mechanism by which the cell modulates protein function. It is clear that various proteins responsible for adding and removing these modifications are deregulated during aging, resulting in aberrant PTMs that reduce cellular function. Poly-ADP ribosylation for instance is a PTM mediated by Poly ADP-ribose polymerase-1 (PARP1). Its activity is upregulated in aging, resulting in many alterations [18]. PARP1 has been shown to enhance mTOR function, increasing the translation rate, further overwhelming the chaperones [19]. Furthermore, it promotes the expression of inflammatory cytokines such tumour necrosis factor α (TNF-α) [20].

Since adding poly-ADP ribose uses NAD as a substrate, this increased activity quickly depletes the cell of NAD, in turn deactivating the deacylases known as sirtuins (SIRTs) [21]. This also impacts the cell in a number of ways, decreasing both nuclear and mitochondrial DNA integrity and increasing inflammation due to the role various members of the SIRT family play in these processes [22-24]. Additionally SIRT1 is responsible for deacetylating p53, meaning that decreased SIRT1 activity results in a hyperactive p53 and so in a stronger DDR, further contributing to aging [25].

4. CELLULAR MECHANISMS

These alterations throughout both the genome and proteome result in cellular disruption. For instance the increase in cell damage brought about by DNA mutations and proteome alterations leads to increased cellular senescence. Senescent cells contribute to aging by reducing the population of cells capable of replicating, leading to stem cell depletion as shown in satellite cells [26]. Furthermore they also produce increased amounts of inflammatory cytokines due to the senescence associated secretory phenotype (SASP) reviewed here [27]. This increased inflammation then results in further stem cell depletion and an increased growth rate in the cells that are not senescent leading to cancer [28].

It is important to note however that while senescence and inflammation contribute to stem cell depletion they are likely not the only contributors. Mitochondrial dysfunction for instance has been extensively linked to the process of aging via the mitochondria's role in regulating stem cell differentiation through the production of reactive oxygen species (ROS) [29]. Another function which is being increasingly linked with aging is the production of metabolites. However, the role metabolite concentrations play in protein function especially with regards to aging still remains to be determined [30,31]. Whilst this evidence shows a link between mitochondria and aging the extent of their interactions are not fully understood and what is known is considered controversial due to different results being obtained as shown here [32]. As studies begin to characterise and distinguish between different stem cell varieties, it is becoming clear that different populations of stem cells are aging through different mechanisms, with some aging via external factors and others via internal factors as reviewed here [33]. Thus it is highly likely that mitochondrial dysfunction is responsible for stem cell depletion in some but not all stem cell types.

Understanding these processes is crucial to understand aging. However, in order to effectively target age-associated diseases such as cancer or neurodegeneration, most if not all of these factors will need to be addressed at once, which is impractical. Whilst targeting these pathways does have beneficial effects, understanding the core, early causes of aging will be a necessary step in the extension of the human health span [34,35].

Whilst stem cells are essential for replenishing human cell populations, the human organism consists of a lot more than its own cells. In fact the human body is more of an ecosystem in and of itself, hosting more foreign cells than human ones [36]. Such cells play a variety of roles including immune and metabolic functions, with core roles in the progression of aging. For instance *Eubacterium limosum* is capable of stimulating anti-inflammatory pathways and it is preferentially prevalent in centenarians whilst the anti-inflammatory *Faecalibacterium prauznitzii* bacterium levels decline with age [37,38]. Furthermore when bacteria from the intestines of old mice were transferred to younger mice they display marked increases in inflammatory markers as well as increases in Toll-like receptor 2 (TLR2) activation in the blood [39]. TLR2 is a receptor molecular signature typical of bacteria, meaning that the increased inflammation in the intestine likely increased the intestinal permeability and subsequently an increase in bacterial infiltration, resulting in further excess inflammation. In addition, bacteria present in the intestine are essential for the stimulation of intestinal epithelial stem cell (IESC) replication and differentiation, a function that becomes overactive in aging, leading to metabolic impairments that further progress aging [40,41]. A summary of all these general contributors to aging on the genetic, proteomic and cellular level can be found in the table below

5. TELOMERE SHORTENING

Whilst it is reasonable to assume that aging is likely the result of a slow accumulation of biological damage, the existence of organisms such as the Greenland shark and the naked mole rat which have drastically reduced aging rates, points to some other factor being at play. After all the fact that evolutionary distinct organisms

managed to evolve countermeasures to aging points to there being distinct biological mechanisms at play that can be altered by natural selection [50]. Therefore if aging can be effectively delayed or perhaps removed entirely as a response to specific evolutionary pressures it stands to reason that it is possible to develop drugs to alter aging in humans to do the same.

One of the most well-known molecular features of aging is the shortening of telomeres. Telomeres are repeats of DNA found at the ends of chromosomes made up of the repeats TTAGGG, which bind to a group of proteins known as the shelterin complex. This complex among other functions inhibits DNA machinery from interacting with the chromosomal end so that the cell does not mistake the end of the chromosome for double stranded breaks [51]. This crucial function among others is why telomeres were recognised as a primary driver of aging when it was discovered that telomere length decreases with age. This is due to the mechanism of DNA replication, were the ends of the chromosomes get shorter with every replication, with a lot of somatic cells being unable to repair the shortened DNA. It was thus speculated that as organisms age their telomeres shrink before reaching a critical point where they are too short to recruit enough proteins to carry out their function, resulting in aging [52] The role of telomeres in aging was then further solidified with studies showing a link between telomere attrition and the development of several diseases such as pulmonary fibrosis and aplastic anaemia [53,54]. Furthermore aging was shown to be delayed in mice when administered with drugs that extended telomere length [55]. This allows telomeres to serve as accurate markers of biological age with significant clinical value [56].

This mechanism was a very promising model for aging, as unlike other hypotheses it provided a clear pathway by which a group of cells become less fit over time. Despite this however, there is compelling data showing that telomeres are not as crucial to aging as originally suspected. Mice, for instance, despite having a shorter lifespan than humans have longer telomeres. This is in addition to the fact that short-lived rodents such as the mouse express telomerase (an enzyme that can extend telomere length) in a greater variety of tissues when compared to humans [57]. Furthermore blind mole rats (*Spalax ehrenbergi)* have telomeres that shorten with aging to the same extent as rodents of similar sizes despite having a lifespan that is significantly greater [58]. Finally recent reports are suggesting that telomere-mediated cellular senescence is not correlated to telomere length, suggesting other mechanisms are at play that link telomeres to aging [59-61].

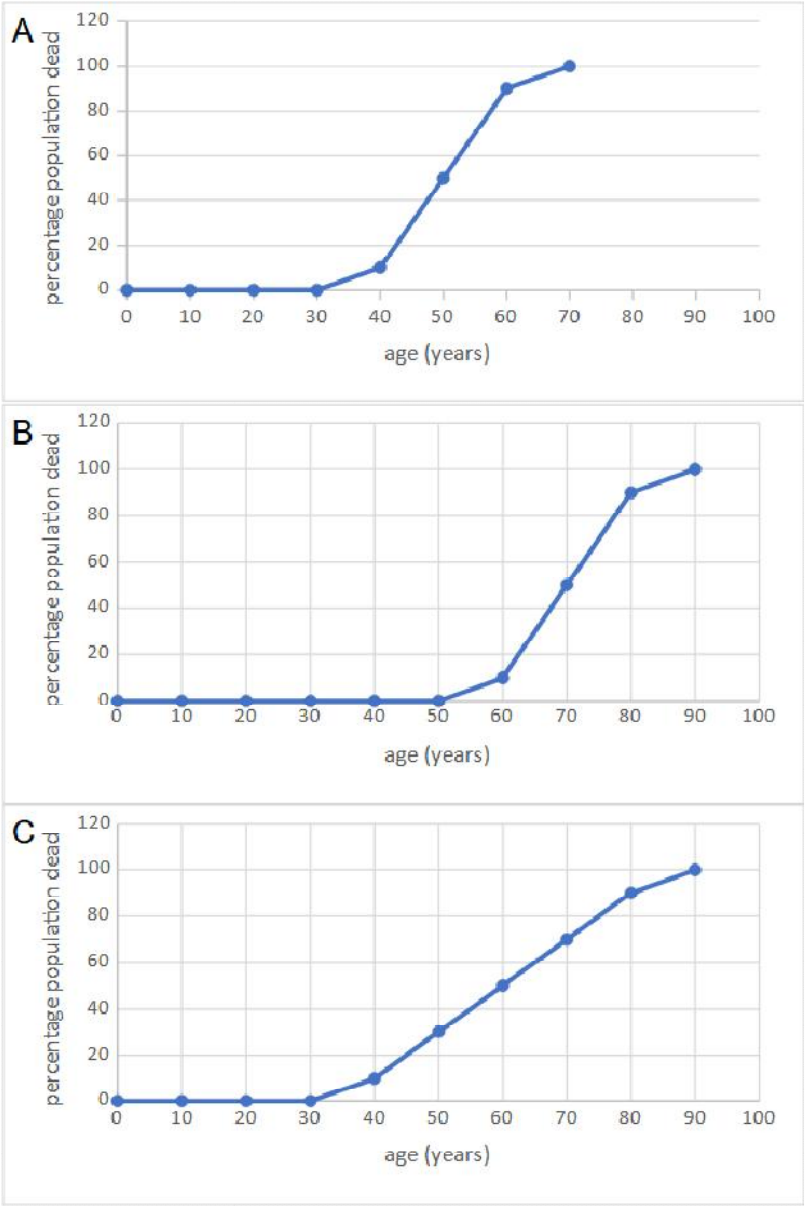
These discrepancies are important to point out as they prove telomeres do have a significant role in the aging process but one which is more complex than simply shortening to induce a DNA damage response. A potential mechanism which could be mediating this telomere aging is the role of telomere gene looping. Long telomeres tend to bind to nuclear lamins A and C through the shelterin complex to be brought near other genomic regions and regulate their expression. As telomere attrition occurs, this function could potentially be hindered, exacerbating aging, although the importance of this mechanism especially with regards to aging still remains to be determined.

6. PROTEOSTASIS AND AGING: RIBOSOME

Another factor which has been shown to play a role in driving aging is dysregulation of the proteome with the ribosome seeming to be a crucial component of this early malfunction. In yeast, proteins involved in ribosome biogenesis and tRNA processing are among the earliest factors to be dysregulated in aging [62]. Furthermore this could explain the decoupling of transcription and translation observed in the primate brain during aging, since ribosomal aberrations would alter the amount of protein produced from mRNA regardless of how much mRNA is present [63,64]. Furthermore an accumulation of 3’ untranslated sequences (UTRs) have been found in aged organisms lacking the remaining 5’ regions, such as the open reading frame. This has been linked to issues in removing ribosomes from mRNA after translation, which is completed in a process known as ribosome recycling [65]. The way this mechanism relates to aging in general and the ribosome’s role in recycling specifically requires further investigation.

Despite this, there seem to be contradictions in the data regarding the role of ribosomal proteins in aging, where they have been found to be up or downregulated as aging progresses [66]. For instance, ribosomal proteins naturally result in decreased protein production, which has been correlated with an increase in lifespan [67]. This is likely due to less protein aggregation and so reduced cytotoxicity to the increasing fragile

cells, as will be discussed shortly. However increased production of ribosomal proteins is essential for growth and replication, to produce the proteins necessary to rebuild damaged structures and produce new cells. This is an important aspect of cancer cells and stem cells, where an increase in ribosomal proteins leads to enhanced growth [68,69]. This is also seen to some extent in aging, where increased ribosomal protein expression in middle-aged mice results in prolonged lifespan [70]. These contrasts are important to point out as they are likely due to the ribosome having multiple roles in the aging process, which will thus have to be taken into account when assessing the role of the ribosome during aging.



Fig, 1A. Graph showing the percentage of dead organisms against age of a fictional population of organisms by the Gompertz model [82] B: A mortality graph of a population with a decreased R_o , note the delay in the increase in the death rate when compared to the top right population. C: graph showing the population with a decreased α. Note the decreased acceleration of the death rate with age when compared to the other populations

Table 1. Various cellular components and their respective effects on lifespan. Multiple factors increase and decrease lifespan through competing mechanisms meaning that further understanding these processes will be crucial to shift these biological processes to increase rather than diminish lifespan

Biological factor associated with aging	Mechanism for increasing lifespan	Mechanism for reducing lifespan	References
DNA repair pathways	Improving genetic stability reducing the likelihood of tumor promoting or detrimental mutations	Activates factors such as p53 stimulating senescence and apoptosis, which deplete cell populations and promote inflammatory signaling	Jackson & Bartek, 2009; Huang et al., 2020 [9,42]
mTOR	Increases anti-inflammatory signaling in immune systems	Increases translation rate resulting in increased proteosome burden and protein degradation	Appenzeller-Herzog & Hall, 2012; Weichhart et al., 2015 [16, 43]
PARlation	Enhances base excision DNA repair and general genomic maintenance	Stimulates NF-κB transcription and inhibits sirtuins and inhibits HSF DNA binding	El-Khamisy et al., 2003; Hassa & Hottiger, 2002; Chung & Joe, 2014. [21,44,45]
Sirtuins	Maintenance of DNA integrity (both nuclear and mitochondrial) as well as resolution of the DDR through p53 acetylation		Wątroba et al., 2017; Vaziri et al., 2001 [46,25]
Oxygen radicles	Damages DNA and various cellular components such as proteins and lipids	Acts as a regulator of stem cell differentiation for replenishing the cellular population	Hameed et al., 2015; Liochev, 2013 [29,47]
Microbiome alterations		Increases inflammatory burden and intestinal permeability	Bana & Cabreiro, 2019; Beek et al., 2017 [36,39]..
Inflammatory signalling	Acts as an immune response without requiring other innate immune responses such as neutrophils, which are more prone to damage cells.	Enhances cancer risk whilst also propagating cellular degeneration.	Fulop et al., 2017; Minciullo et al., 2016 [48,49].

Such multiple roles are likely not restricted to just the ribosome. Ribosomal proteins themselves have multiple other functions when unbound from the ribosome. Ribosome protein L13A (RPL13A) for instance is a ribosomal protein which is phosphorylated in response to interferon-gamma signalling (IFN- γ) signalling resulting in its deplacement from the ribosom to inhibit certain RNAs through their 3'UTR [71]. All this considered, to truly asses the complex relationships between ribosomes and aging it is necessary that multiple points in time of an aging organism are taken as reference rather than only 2, in order to get a clearer picture of exactly when ribosome proteins are up or downregulated and in which tissues since the levels of ribosomal proteins likely fluctuate across different ages and different tissues [64]. Furthermore it is crucial to take into account the full effects of ribosomal proteins from those that extend to those that shorten lifespan.

These early changes could be linked to an increased amount of ribosomal errors occurring in aged cells. The increase in translational errors as aging progresses is highly controversial owing to the fact that various experimental setups have confirmed that ribosome errors remain constant throughout an organism's lifespan [72]. Such experiments are not highly reliable since assaying ribosomal errors is a difficult process, especially when the ribosomes are assayed *in vitro*, without the dynamic context of the cell [73]. In fact, such experimental setups are unable to reliably confirm the translation fidelity of an organism, making it difficult to rely on them for data [74].

Despite this, there is some indirect research supporting this model, namely the fact that translational accuracy and lifespan are correlated across species [75]. Furthermore eukaryotic elongation factor 2 kinase (eEF2K) has been shown to both increase translation fidelity and lifespan [76]. eEF2K has been linked to the mammalian target of rapamycin (mTOR) pathway, which has also been implicated in aging [77]. This link between mTOR and translational accuracy is especially important to investigate, as it could possibly implicate the ribosome in caloric restriction, the most experimentally validated means of increasing lifespan across the tree of life [78,79]. It is important to keep in mind however that despite this evidence, increased ribosomal errors could simply worsen aging, as it would cause more proteins to aggregate and misfold, leading to further damage. This would mean that the ribosome whilst playing a part in aging is not itself a driver.

This hypothesis can be tested by analysing populations of different organisms via the Gompertz model. This model gives the following equation for mortality $R_t = R_o (10)^{\alpha t}$ where R_t is the mortality rate at time t, R_o is the mortality extrapolated to a population at age 0 and α is the exponential mortality rate. Essentially, α can be thought of as the rate at which the chance of death increases after a certain age, whilst R_o is inversely proportional to the time taken to reach this age (Fig. 1) [80]. This is a useful model to consider in this case since if ribosomal errors were one of the factors that initiates aging, then one would expect decreased ribosomal errors to be correlated with a decrease in α as well as R_o. However, if ribosomal errors are simply contributing to the aging process and are not actively aging, it would be correlated with a decrease in R_o but not a decrease in α. This is because if ribosomal errors were not part of the aging mechanism, then the decreased translational fidelity would simply worsen the state of the aging cell so that the organisms express the phenotypes of aging sooner, however the actual mechanism of aging remains unchanged, meaning α remains constant. On the other hand if ribosomal errors were one of the primary drivers of aging, then if it were resolved, the mechanism of aging itself would be affected so that the rate at which organisms die over time, in other words α, would be reduced [81].

Interestingly, some similarities can also be found in bacteria. Whilst there are important differences, bacteria also display forms of aging. One of these is inducible senescence, where bacteria taken from a population that has reached carrying capacity and is thus in its stationary phase tend to grow less in a new medium than bacteria taken from populations in their log phase [83]. This has been shown to be due to ribosomal errors resulting in proteins more sensitive to oxidation [84]. Whilst circumstantial, it is possible that a general aging mechanism is present across all organisms, centred on the increase in ribosomal errors over time in cells.

Knowledge about the complexity of the ribosome is still in its infancy as evidenced by the developing field of ribosome heterogeneity [85]. The fact that the effects of many ribosomal proteins on protein translation are currently unknown means that some underlying

mechanism, which results in decreased ribosomal accuracy over time, is possible. Such investigations could even be carried out in bacteria, serving as a very simplistic model organism for learning how the ribosome leads to replicative senescence. It is also important to note that bacterial aging is important in humans regardless if this mechanism is actually conserved. This is because changes in the bacterial microbiome in the gut modulates aging that could be in part due to inducible senescence [86]. Furthermore, mitochondrial ribosomes are more similar to bacteria than eukaryotic ribosomes and so could age in a similar way [87].

7. PROTEOSOME

However assuming the ribosome is a driver of aging, the next problem to tackle is how exactly does the ribosome lead to the molecular responses associated with aging. The likely explanation for this seems to be through the proteasome. The proteasome is a multi-subunit complex responsible for degrading proteins to facilitate protein turnover and its activity has been shown to decline with age [88] Proteasomal load is dependent on translational fidelity since the proteasome mainly degrades nascent misfolded proteins. Therefore the more ribosomal errors, the quicker the proteasome would be overwhelmed [89] Interestingly, decreased proteasome activity seems to in turn lead to stoichiometric alterations in a variety of other complex multi-subunit protein structures including the ribosome and complex IV and V of the mitochondrial electron transport chain [90]. This points to a positive feedback loop in aging, were decreased proteasome imbalance leads to dysregulation of the ribosome due to stoichiometric imbalances. This in turn produces more damaged proteins overwhelming the proteasome, leading to further imbalance in ribosome stoichiometry and damaged proteins. This process is aided by the stoichiometric imbalances in the mitochondria, resulting in increased production of reactive oxygen species (ROS), which in turn further inhibit the proteasome [91]. Fig. 2 However it is important to note that decreases in the mRNA of proteasome components with age have also been noted This is likely due to the termination of growth of the organism, since cells tend to increase the expression of proteasome subunits upon replication [92]. This could potentially explain the ribosomal alterations with age, were as organisms stop growing, proteasome expression is downregulated leading to ribosomal protein accumulation and aggregation, triggering the positive feedback loop described previously.

This decreased activity of the proteasome observed in aged cells has been linked to the decreased ability of heat shock factor 1 (HSF1) to bind to DNA, which in turn decreases the activity of the UPR, leading to an increase in HSF1 to compensate [93]. However, HSF1 apart from being a transcription factor can also induce activation of the acetyltransferase Tat-interactive protein-60 kD (Tip60), which in turn activates PARP-1 [94]. The effects of PARP-1 have been extensively reviewed elsewhere [95] however it is capable of polyADP-ribosylating HSF1, which in turn decreases its affinity for DNA. In fact a possible reason for the decreased DNA affinity of HSF1 is that the increased half-life of HSF1 due to decreased proteasome activity increases the likelihood of being modified by PARP-1 (as summarized in Fig. 2 below).

This therefore initiates a positive feedback loop resulting in increased PARP-1 stimulation, depleting the NAD+ pool, which decreases the activity of all sirtuins resulting in further decreased DNA integrity, strengthened DDR and telomere attrition as mentioned previously [96,97]. Therefore with all this considered there is a possible mechanism of aging based on established biological interactions that is initiated by the ribosome and proteasome. This could even tie into the telomeres since PARP1 can shorten telomeres as can p53, which as previously mentioned shows increased activity during aging [98,99].

These alterations can lead to the various clinical pathologies associated with aging with extensive therapeutic applications. For instance increasing SIRT 1 expression in the brain resulted in reduced symptoms of various neurodegenerative diseases such as Alzhiemer's and Huntington's [100,101]. and inhibition of PARP1 aids in the resolution of cardiac issues typical of aging [102]. Telomere shortening in particular has been linked to a wide range of age-associated disorders from cardiovascular to respiratory conditions [103,104]. However, more research must be conducted on the role these processes play before therapeutics can be developed to aid a wide variety of patients suffering from age-associated disorders.

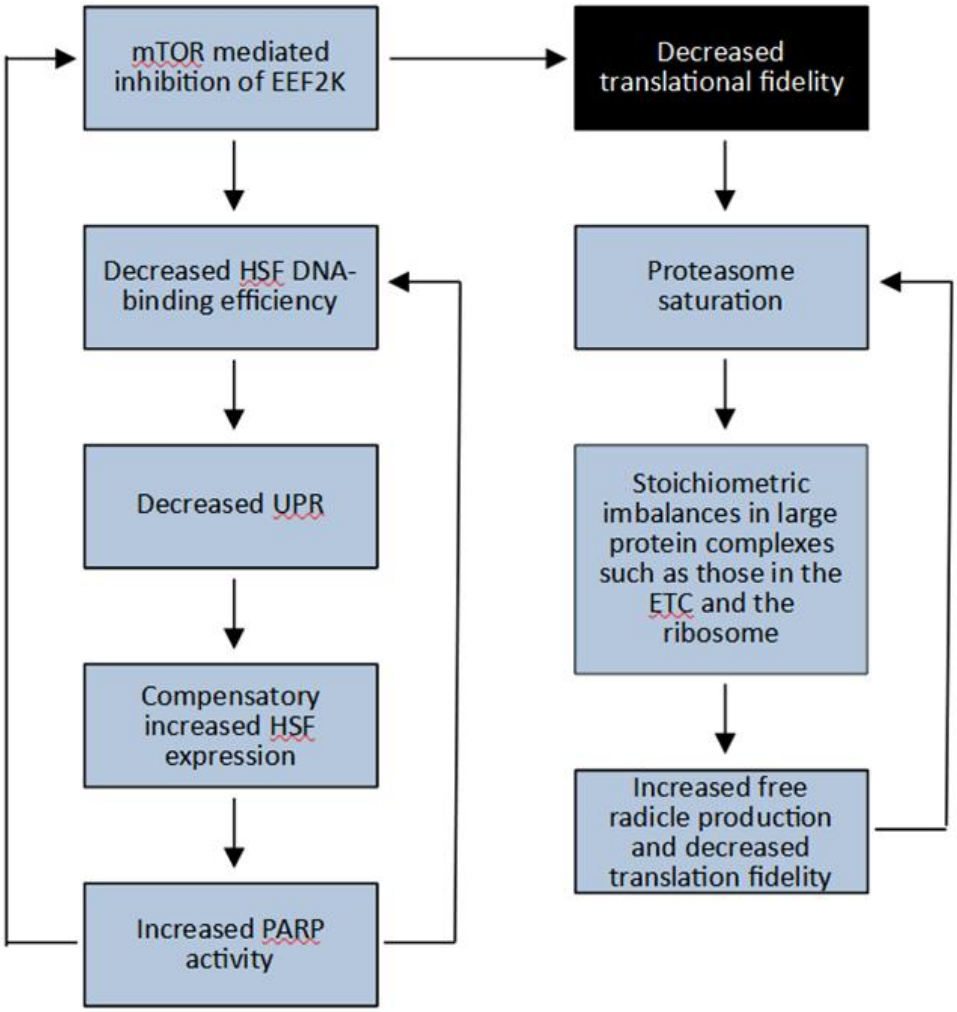


Fig. 2. Diagram displaying a possible mechanism behind aging. Decreased translational fidelity is in black since the fact that it does increase with age has still not been verified and the reason behind it is still completely elusive possibly due to factors of ribosome synthesis and functioning that are still not well understood. That being said other factors such as the decreased production of proteosomes as the organism matures could also potentially trigger aging through this pathway. It is important to note the fact that even though this is only a small part of the mechanism of aging there are 3 positive feedback loops which lends to the difficulty in treating aging. Simply attacking one of the pathways may delay aging until the other pathways counteract the treatment. Therefore to target aging successfully either multiple feedback loops must be targeted in tandem or the factor that is causing this initial destabilisation of the proteome must be discovered and treated

8. PROGERIA SYNDROMES AND THE MECHANISM BEHIND AGING

A lot of information on biological systems can be obtained from studying disorders in such systems. This is also true for aging, were premature aging disorders also known as progerias play a fundamental role in discovering the mechanisms behind aging, in order to assist both the patients suffering from progeria as well as the general aging population.

Werner's syndrome for instance is a progeria caused by a mutation in Werner (WRN) DNA helicase. It results in premature age-related complications such as type II diabetes, cancer

and cardiovascular complications [105]. This DNA helicase is responsible for a diverse array of functions due it recognising and resolving a variety of DNA structures such as G4-quadruplex structures and Holliday junctions, making it a component of multiple DNA repair pathways. The cause of the progeria specifically however is likely due to the role WRN plays in telomere stability. In fact WRN deficient mouse models do not display any of the symptoms associated with Werner's syndrome unless they are also telomerase deficient, supporting the fact that the premature aging seen in Werner's syndrome is dependent on telomere dysfunction [106]. Therefore Werner's syndrome could be a potential model to unravel the exact mechanisms by which telomeres contribute to the aging process.

Another form of progeria is Hutchinson-Gilford progeria syndrome (HGPS), a disease resulting from a mutation in the Lamina (LMNA) gene encoding the components of the nuclear lamina, lamin A and lamin C [107]. This mutation is a deletion of 50 amino acids in the C-terminal end of lamin A. This results in a protein which lacks the C-terminal CAAX motif needed for cleavage to process the protein. This lack of cleavage results in the retention of the farnesyl PTM added onto lamin A as part of the maturation process resulting in the permanently farnesylated immature form of lamin A known as progerin [108,109]. The nuclear lamina is involved in maintaining nuclear architecture, regulating gene expression and interacting with the nucleoporins [110]. Therefore mutations in this structure result in a variety of alterations, making it difficult to pinpoint the link between progerin and aging. That being said, data gathered so far is pointing to telomere stability acting as the link between progerin and progeria. The lamina has been shown to interact with telomeres and promote telomere stability, though progerin does not exhibit this function [111]. Interestingly, the decreased telomere stability leads to changes in the processing of lamin A mRNA so that more progerin is formed, creating a positive feedback loop producing more telomere instability [112].

However, HGPS symptoms have been shown to be abolished upon repression of NAT10, when Transportin-1 (TNPO1) and Nup153, components of the nuclear pore are present. NAT10 has not been shown to be involved with telomeres in any way but has been shown to acetylate tubulin and ribosomal RNA [113]. This activity could mean that the symptoms observed in HGPS could be at least partially mediated by alterations in the ribosome. This is further supported by the fact that HGPS mouse models can be created, which display the symptoms of HGPS without needing to knockout telomerase as was the case with Werner's syndrome [114]. Therefore progerin-expressing cells or organisms could serve as crucial models to understand the ribosome's role in initiating aging or at least the underlying complexity behind the contribution of telomeres to the aging process.

9. CONCLUSIONS AND FUTURE PROGRESSION

When discussing something as complex as aging and the array of diseases that are associated with it, equally diverse approaches are necessary for treatment. Fortunately, there are numerous avenues with potential to further the understanding of the mechanisms behind early aging. Model organisms for instance are key to understanding aging with blind mole rats serving a crucial role in discovering the relationship between telomeres and aging aside from simple DDR initiation. Other than that, analysing general population dynamics of model organisms compared to the rate of ribosomal errors can be used to distinguish whether ribosomal errors are aiding or causing age-related degradation. Even bacteria serve an essential role in future research as understanding reversible senescence can be translated to eukaryotic ribosomes and how they are modified with age. Additionally, reversable senescence could be crucial to understanding mitochondrial ribosomes and intestinal aging. Finally, resolving the role NAT10 plays in HGPS could be core to further understanding aging and how it is accelerated in progeria.

As the omics revolution continues to progress, more and more data is being gathered on the underlying mechanisms causing aging. The ribosome, proteosome and telomere are likely to be the primary candidates for aging and so require further study. Describing the exact mechanisms that link these factors to the aging process itself will be one of the core challenges of the field. The blind mole rat could be an invaluable model for this since it has a rate of telomere shortening equivalent to that of a mouse but a lifespan many times longer, meaning it is delaying aging via other means. This could point to the other ways telomeres result in aging or even potentially the role of the proteosome and ribosome in the process. HGPS

models could also be useful in this context, as progerin production seems to involve both the telomere and the ribosome, and so could be a useful model to understand both. Bacterial cells could also aid in this endeavour, as was previously mentioned, since discovering the exact cause of ribosomal alterations in reversible senescence could shed light on what is occurring to the ribosome as eukaryotes age. Such approaches along with the continuing advances in analytical techniques will be critical to discover the underlying causes of aging and develop treatments in order to save human lives.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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