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Ageing – Oxidative stress, PTMs and disease

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ABSTRACT

Post-translational modifications (PTMs) have been proposed as a link between the oxidative stress-inflammation-ageing trinity, thereby affecting several hallmarks of ageing.

Phosphorylation, acetylation, and ubiquitination cover >90% of all the reported PTMs. Several of the main PTMs are involved in normal "healthy" ageing and in different age-related diseases, for instance neurodegenerative, metabolic, cardiovascular, and bone diseases, as well as cancer and chronic kidney disease. Ultimately, data from human rare progeroid syndromes, but also from long-living animal species, imply that PTMs are critical regulators of the ageing process. Mechanistically, PTMs target epigenetic and non-epigenetic pathways during ageing. In particular, epigenetic histone modification has critical implications for the ageing process and can modulate lifespan. Therefore, PTM-based therapeutics appear to be attractive pharmaceutical candidates to reduce the burden of ageing-related diseases. Several phosphorylation and acetylation inhibitors have already been FDA-approved for the treatment of other diseases and offer a unique potential to investigate both beneficial effects and possible side-effects. As an example, the most well-studied senolytic compounds dasatinib and quercetin, which have already been tested in Phase 1 pilot studies, also act as kinase inhibitors, targeting cellular senescence and increasing lifespan. Future studies need to carefully determine the best PTM-based candidates for the treatment of the "diseasome of ageing".

1. Introduction – Ageing, oxidative stress, and PTMs

The term *ageing* is not universally defined. While some authors define *ageing* as "the set of all processes in an individual that reduce its well-being" (Fuellen et al., 2019) using a universal approach, other groups have described *ageing* patho-physiologically as a natural process of structural and functional decline of tissues and organs (López-Otín et al., 2013). López-Otín and co-workers proposed distinct "hallmarks of health" (López-Otín and Kroemer, 2021), but also introduced nine "hallmarks of ageing" ranging from genomic and epigenomic alterations, dysfunction of different cell compartments (i.e. mitochondria, intracellular signaling cascades, proteostasis), altered intercellular communication, stem cell exhaustion, as well as cellular senescence (López-Otín et al., 2013). Ageing occurs at different rates in different animal species, and data from long-lived animals may provide important clues for ageing processes in humans (Stenvinkel and Shiels, 2019). Conversely, within the human species, there are also different ageing rates, ranging from physiological ageing to premature ageing in certain diseases and ultimately to very rare, mostly monogenetic, progeroid syndromes, which show distinct and pronounced signs of premature ageing (Eriksson et al., 2003; Kubben and Misteli, 2017; Strandgren et al., 2017).

Oxidative stress and ageing have been linked from as early as in the 1950s when free radicals were proposed as the main driver of the ageing process (Harman, 1956). Indeed, oxidative stress is involved in several of the nine hallmarks of ageing, for instance mitochondrial dysfunction and loss of proteostasis (López-Otín et al., 2013). In general, oxidative stress develops when there is an imbalance between generation of oxidant compounds and antioxidant defense mechanisms (Ebert et al., 2021). Mitochondria are the primary site of redox biochemistry and also a natural target for oxidative damage, possibly impairing the cell's energetic metabolism or leading to cell death (Shiels and Davies, 2004; Tang and Dong, 2016). Dysfunctional mitochondria are also major drivers of the intermediate inflammatory phenotype linking oxidative

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stress with inflammation and ageing, consequently named "inflammageing" (Ferrucci and Fabbri, 2018). Importantly, the immune system undergoes several changes during ageing, and inflammageing), therefore, is an important risk factor for mortality (Santoro et al., 2021), thereby framing an oxidative stress-inflammation-ageing trinity (Fig. 1).

Post-translational modifications (PTMs) have been proposed as a link between the components of this trinity (Liu et al., 2016; Mowen and David, 2014; Stadtman, 1988; Victorino et al., 2015). From more than 700 currently listed PTMs (Jennings et al., 2021), the three main PTMs are phosphorylation, acetylation, and ubiquitination, covering the vast majority of all reported PTMs in the dbPTM database (Ramazi and Zahiri, 2021). Ramazi and Zahiri have further identified the amino acids Lys, Cys, and Ser as the most susceptible for PTMs (Ramazi and Zahiri, 2021). Translationally, PTMs have been proposed as a treatment target, especially for cancer (Qian et al., 2020). However, targeting PTMs is also an attractive treatment option for the oxidative stress-inflammation-ageing trinity (Fig. 1), and will be discussed below.

2. PTM in healthy ageing vs. premature ageing

As discussed above, ageing occurs at different rates both in different animal species but also in humans (Stenvinkel and Shiels, 2019). For instance, an accelerated ageing rate compared to 'healthy' or 'normative' ageing has been described in certain human disease states, such as chronic kidney disease (CKD) (Ebert and Stenvinkel, 2022). Furthermore, rare progeroid diseases show distinct and very accelerated signs of premature organ-specific, but also whole-body, ageing (Eriksson et al., 2003; Kubben and Misteli, 2017; Rieckher et al., 2021; Strandgren et al., 2017) (Fig. 2).

Evidence for a link between PTMs and ageing can be derived from published data investigating PTMs in different age-related diseases, for instance neurodegenerative (e.g. Alzheimer's disease (AD)), metabolic (type 2 diabetes, obesity), cardiovascular (coronary artery disease, heart failure), bone (osteoporosis) diseases, as well as cancer and CKD (Stenvinkel et al., 2020a), with most data available for brain disorders (Fig. 2). Thus, several PTMs accumulate in distinct regions of the tau protein at different stages of AD, with phosphorylation and ubiquitination as the most discriminative PTMs for AD compared to controls (Wesseling et al., 2020). In accordance with these data, Dujardin et al. confirm that distinct phosphorylation sites in tau protein are associated with pathological seeding of tau and clinical progression of AD (Dujardin et al., 2020). S-nitrosylation (SNO) is a further PTM being demonstrated in cortical and striatal brain regions of aged mice compared to young mice (Kartawy et al., 2020), and SNO was related to AD, but also other ageing-associated neurodegenerative disorders (Kartawy et al., 2020). Furthermore, SUMOylation is also related to ageing and neurodegeneration, and the SUMO pathway is a potential therapeutic target against neurodegenerative disorders (Vijayakumaran and Pountney, 2018). It is interesting to note in this context, that pathophysiologic mechanisms for increased SUMOylation in ageing and pro-oxidant status are not fully understood. Thus, oxidative stress could either increase or decrease SUMOylation (Vijayakumaran and Pountney, 2018). Furthermore, the natural senotherapeutic compound quercetin (Mafra et al., 2020) was found to increase both total SUMOylation and the expression of the anti-inflammatory and anti-oxidant transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) (Lee et al., 2016).

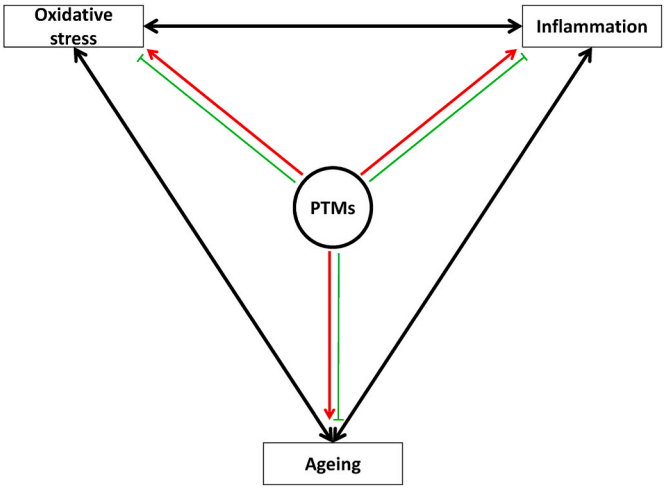

Fig. 1. Post-translational modifications (PTMs) and the oxidative stress-inflammation-ageing trinity.
Oxidative stress, increased inflammation, and ageing are linked and contribute to each other though several mechanisms, including PTMs. Thus, increased oxidative stress induces a pro-inflammatory status, which in turn is associated with ageing, consequently named "inflammageing". Ageing is also directly linked through oxidative stress, for instance through nuclear factor erythroid 2-related factor 2 (NRF2) pathway. PTMs can affect all components of the oxidative stress-inflammation-ageing trinity. Importantly, PTMs can either have beneficial (green lines) or adverse (red arrows) effects on the single components. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The eye lens is a unique structure for the study of PTMs in ageing, as the main group of lens proteins, i.e. crystallins, are lifelong proteins with no turnover (Fan and Monnier, 2021). Therefore, one of the major risk factors for incident cataracts are PTMs, especially oxidative stress-related modifications (Wishart et al., 2021). Thus, oxidation, deamidation, racemization, cross-linking, glycation, methylation, carbamylation, and truncation are established enzymatic and non-enzymatic PTMs of lens proteins in ageing (Fan and Monnier, 2021; Wishart et al., 2021). As a historical proof of concept, drug-induced cataracts occurred through increased carbamylation in patients with sickle cell disease after treatment with sodium cyanate in the 1970's (Nicholson et al., 1976).

A link between bone diseases and PTM has been established for different bone disorder, such as osteogenesis imperfecta (Forlino and Marini, 2016) and Runt-related transcription factor 2-dependent diseases (Kim et al., 2020). With regards to ageing, it is interesting to note that increased non-enzymatic deamidation at asparagine and glutamine residues in bone collagen type I was evident in a BALB/c mouse model of ageing (Creecy et al., 2021). Furthermore, levels of collagen I deamidation were inversely associated with bone toughness in these animal experiments (Creecy et al., 2021).

Carbamylation and other PTMs are also relevant in CKD, i.e. a multisystem disorder frequently accompanied by increased oxidative stress, accumulation of uremic toxins, impaired mitochondrial biogenesis, and low-grade inflammation (Ebert et al., 2020a, 2021). Indeed, ubiquitylation, SUMOylation, phosphorylation, glycosylation, and acetylation interfere with key signaling pathways in CKD, i.e. proinflammatory nuclear factor kappa-B (NF-κB), NRF2, and transforming growth factor-β (TGF-β) (Cao et al., 2021). Distinct PTMs, such as carbamylation, are not only linked to increased renal damage but also to cardiovascular complications of CKD (Jankowski et al., 2021). Importantly, different PTMs can be both protective or adverse for CKD progression, depending on type of PTM and their target (Cao et al., 2021).

While the above-mentioned PTMs are clearly linked to disease- and organ-specific ageing (Fig. 2), it is difficult to identify general mechanisms by which PTMs include whole-body ageing, thereby reducing life span.

3. Learning from extreme human phenotypes – HGPS and PTMs

One possibility to clarify the effect of PTMs for human ageing is to study rare progeroid syndromes which are characterized by a highly accelerated ageing process and premature onset of age-associated pathologies in affected individuals (Rieckher et al., 2021). While most of the progeroid syndromes can be attributed to specific mutations that

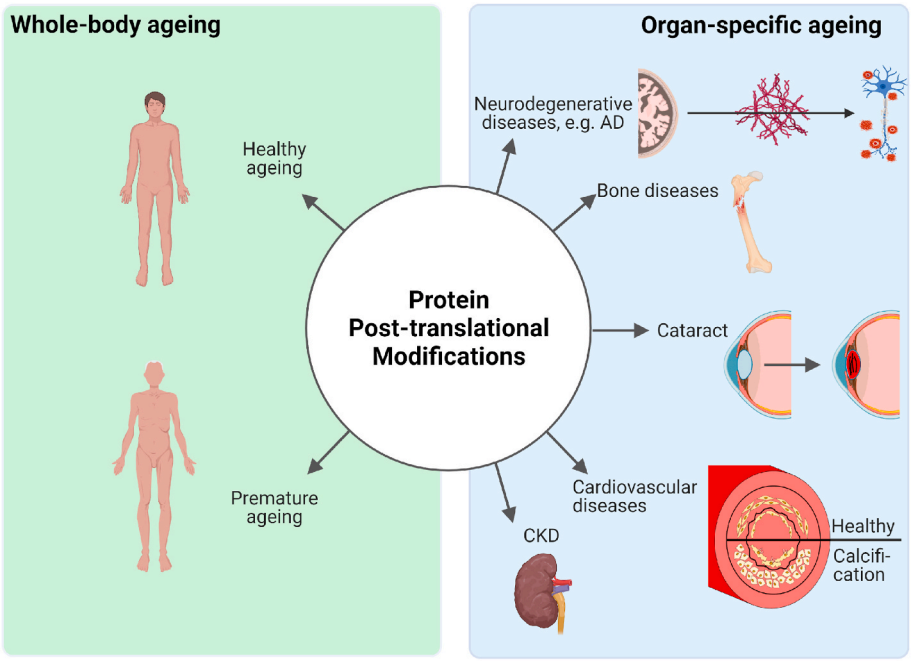

Fig. 2. Post-translational modifications (PTMs) contribute to disease-/organ-specific ageing but also whole-body ageing.
Direct effects of distinct PTMs on disease- or organ-specific ageing have been demonstrated for several age-related disorders, including neurodegenerative diseases (for instance Alzheimer's disease [AD]), bone diseases, eye lens degeneration (i.e. cataract), cardiovascular diseases (including vascular calcification), and chronic kidney disease (CKD). Importantly, PTMs can either accelerate or attenuate ageing rate in a PTM-site-specific and tissue-specific manner. In contrast, distinct PTMs are also associated with a highly accelerated, premature ageing in subjects with rare progeroid syndromes, for instance Hutchinson-Gilford progeria syndrome. Created with BioRender.com.

interfere with genomic stability, molecular patho-mechanistics and potential treatment options focus on PTM's and oxidative stress (Rieckher et al., 2021).

Among the progeroid syndromes, HGPS stands out because affected individuals show a wide range of accelerated ageing features and in particular an extreme phenotype of early vascular ageing (EVA), with cardiovascular diseases frequently observed in the 2nd decade of life (Ebert and Stenvinkel, 2022; Gonzalo et al., 2017; Stenvinkel et al., 2020a). HGPS is caused by a *de novo* single-base substitution within *LMNA* (c.1824C > T) (De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003). The full length (646 amino acids) lamin A is translated as a prelamin A (664 amino acids) that is further processed via distinct PTMs (Gonzalo et al., 2017; Young et al., 2013) (Fig. 3). Thus, the c terminus of prelamin A is farnesylated by farnesyl protein transferase (FTPase) and three amino are cleaved enzymatically by either RCE1 or ZMPSTE24. The next PTM is a methylation of the farnesylcysteine through isoprenylcysteine carboxylmethyltransferase (ICMT). Finally, the last 15 amino acids at the c terminus are cleaved by ZMPSTE24, yielding the full length, mature lamin A protein. In HGPS, the *LMNA* (c.1824C > T) mutation generates a deletion of about 50 amino acids spanning over the final ZMPSTE24 cleavage site, resulting in increased levels of a premature lamin A, called progerin (Gonzalo et al., 2017; Young et al., 2013) (Fig. 3). Mechanistically, increased progerin, the mutant premature form of lamin A, directly impairs cellular function by a plethora of mechanisms, including a disturbed nuclear organization, reduced molecular DNA repair machinery, epigenetic modifications, an altered transcriptional profile, as well as mitochondrial dysfunction and increased ROS levels (Gonzalo et al., 2017; Rivera-Torres et al., 2013).

Importantly, while an ideal treatment of HGPS would interfere with the abnormal splicing of *LMNA* (Erdos et al., 2021; Young et al., 2013), a PTM-based treatment has recently received FDA-approval for treatment of HGPS. Thus, the farnesyltransferase inhibitor lonafarnib attenuates prenylation (i.e. the addition of a farnesyl group) of prelamin A (Misteli, 2021) and has shown beneficial *in vitro* and *in vivo* effects (Gordon et al., 2018; Strandgren et al., 2017).

With regards to the oxidative stress-inflammation-ageing interaction (Fig. 1), it is interesting to note that increased oxidative stress due to mitochondrial dysfunction has been shown to be crucially involved in HGPS (Kubben et al., 2016; Kubben and Misteli, 2017). Thus, progerin binds NRF2 and induces a nuclear mislocalization, thereby impairing the transcriptional activation of NRF2 (Kubben et al., 2016). Conversely, NRF2 activators improved ageing defects in HGPS cells (Kubben et al., 2016) suggesting NRF2 agonists as a further attractive further treatment option for HGPS (Stenvinkel et al., 2020a).

Whereas progeroid syndromes like HGPS are extremely rare, it is important to note that progerin expression can also be detected in normative 'healthy' ageing, albeit at a significantly lower level (Fig. 3). Thus, pioneering work from Scaffidi and Misteli demonstrated HGPS-like nuclear defects in non-HGPS skin fibroblasts from elderly individuals compared to children. Using an oligonucleotide-based approach to inhibit progerin production, the observed nuclear defects, as well as increased cellular senescence markers, could be reversed indicating that lamin A is also relevant for healthy (i.e. non-HGPS) ageing (Scaffidi and Misteli, 2006). Subsequent studies in non-HGPS individuals and/or cells have demonstrated progerin-positive cells in adipose tissue (Revêchon et al., 2017), skin fibroblasts (Rodriguez et al., 2009; Xiang et al., 2021), intervertebral disc degeneration (Xu et al., 2019), during closure of the neonate ductus arteriosus (Bökenkamp et al., 2011), coronary arteries (Olive et al., 2010), hepatocytes (Luo et al., 2019) and other tissues. Future studies, therefore, need to investigate by which pathomechanisms progerin expression in normal ageing occurs and whether PTM-based therapies could be a translational approach also for common ageing processes.

4. Learning from animal models

In recent years, the concepts of "zoobiquity" and "biomimetics" have been introduced with the aim of utilizing findings from the natural world to gain biological insights to better understand human diseases (Stenvinkel et al., 2020b). With regards to (premature) ageing, different animal models stand out as prototype examples for an accelerated (e.g. the turquoise killifish) or decelerated (e.g. naked mole rats and rougheye rockfish) ageing and associated disease (Kolora et al., 2021; Stenvinkel et al., 2020b; 2018).

The long-living naked mole rat does not only show reduced ageing and cellular senescence, but also seems to be resistant to age-related diseases, including neurodegenerative and cardiovascular diseases, as well as cancer (Stenvinkel et al., 2018; Stenvinkel and Shiels, 2019).

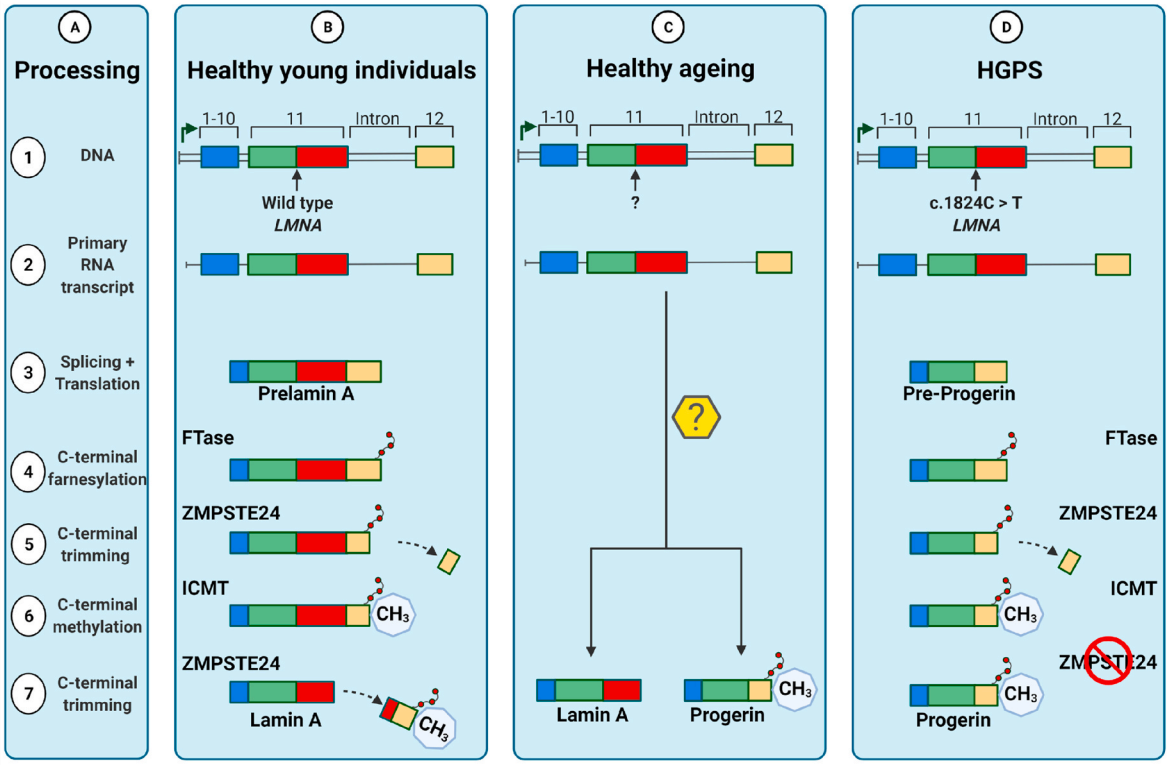

Fig. 3. Lamin A processing in healthy young individuals, common "healthy" ageing, and patients with Hutchinson-Gilford progeria syndrome (HGPS). About seven consecutive steps (panel A) of lamin A processing are depicted from gene level (step 1–3) to protein level (step 3–7) in healthy young individuals (panel B), healthy ageing (panel C) or HGPS (panel D).

The *LMNA* gene comprises 12 exons. The most common mutation in HGPS is a *de novo* single-base substitution within exon 11, i.e. c.1824C > T. The primary RNA transcript is then further spliced. Here, the c.1824C > T mutation activates a cryptic splice site resulting in 150 missing nucleotides in affected transcripts or a deletion of 50 amino acids in the affected protein, respectively (red segment). The premature proteins prelamin A (panel B) or pre-progerin (panel D) then undergo several post-translational modifications (PTMs) at the C-terminus. Thus, farnesyltransferase (FTase) farnesylates the premature protein (step 4), after which three c-terminal amino acids are cleaved by the metallopeptidase ZMPSTE24 (step 5). The isoprenylcysteine carboxyl methyltransferase (ICMT) catalyzes the methylation of the c-terminal end (step 6). Finally, ZMPSTE24 cleaves the c-terminal, farnesylated end releasing the mature lamin A protein (step 7). The final (step 7) ZMPSTE24 cleavage site requires an amino acids sequence (red segment) from the HGPS-mutated deletion of 50 amino acids (panel B). In HGPS (panel D), ZMPSTE24 cannot clip of the c-terminal farnesylcysteine methyl ester resulting in an accumulation of a farnesylated protein, i.e. progerin. In common "healthy" ageing (panel C), both mature proteins, i.e. lamin A and progerin, can be detected in several tissues. Mechanisms by which both lamin A variants occur in non-HGPS ageing, need to be investigated. Created with BioRender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Proteomic analyses in naked mole rats has demonstrated that this species shows less protein ubiquitination and age-related cysteine oxidation compared to mice (Pérez et al., 2009) despite lower anti-oxidant capacity and increased lipid peroxidation (Andziak et al., 2006). Interestingly, signaling activity of NRF2, i.e. a multi-organ protector, was increased in naked mole rats compared to mice, and NRF2 activity correlated positively with maximum lifespan potential in 10 different rodent species (Lewis et al., 2015). This further indicates that NRF2 is a major signaling hub involved in rodent and human ageing syndromes. Data from the same group suggest that fibroblasts from naked mole rats are refractory to reprogramming to induced pluripotent stem cells (Tan et al., 2017). Mechanistically, naked mole rats cells had a more stable epigenome as assessed by histone methylation and acetylation compared to mice (Tan et al., 2017), suggesting that epigenetic PTMs are involved in the decelerated ageing rate of this species.

Hibernating species may also provide insights in the pathogenesis of ageing-related diseases, as they are largely protected from diabetes, cardiovascular diseases, muscle wasting, osteoporosis, CKD, and organ dysfunction during their phases of torpor and arousal during hibernation (Dai et al., 2021; Ebert et al., 2020b). It was recently reported that hibernation slows down epigenetic ageing in marmots (Pinho et al., 2022). Reviewing proteomic studies in hibernating animal species, Grabek et al. have summarized that an unexpectedly low number of proteins are differentially regulated in heterothermic periods when hibernating animals are in torpor compared to their regularly experienced arousal reactions during winter (Grabek et al., 2015). This suggests that there is a high stability of the proteome during hibernation (Grabek et al., 2015). Interestingly, protein changes observed between torpor and arousal periods were frequently associated with PTMs, consistent with the hypothesis that PTMs are the critical proteome regulators during hibernation (Grabek et al., 2015). Hypothetically, PTMs could be reversible and energy-efficient ways to control protein activity during torpor and arousal periods, and acetylation and phosphorylation appear to be the key PTMs in different tissues (Grabek et al., 2015). As hibernating animals during torpor and arousal are subjected to increased reactive oxygen species, maintaining the antioxidant defense is critical (Tessier et al., 2021). Interestingly, NRF2 as a central hub of antioxidant pathways is highly modified through PTMs during torpor and arousal reaction providing an economically effective way to counteracting increased oxidative stress during the winter period (Tessier et al., 2021).

4.1. *Epigenetics and ageing*

Among the nine hallmarks of ageing, epigenetic dysregulation has been proposed as a major determinant for initiating age-related pathologies (Shiels et al., 2017). This is a consequence of disruption of

transcriptional homeostasis leading to dysregulation of cellular physiology. Epigenetics can be defined as "the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence" (Wu Ct and Morris, 2001). Regulation of gene function by the epi-genome is highly responsive to environmental perturbations. Such perturbations within an organism's exposome (i.e. total life course exposure to biotic and abiotic environmental factors-e.g. nutrition, toxins) can be transmitted both inter and intra-generationally. The degree of epigenetic change shows a large degree of inter-individual variation (Shiels et al., 2017). For example, even mono-zygotic twins display substantive age-related epigenetic variation and higher phenotypic disparity with increasing chronological age (Castillo-Fernandez et al., 2014; Greenwood et al., 2011). Phenotypically, changes in the epigenetic landscape (i.e. the combination of both canonical and non-canonical features of the epigenome) dramatically affect cytoprotection and repair capacity. This epigenetic landscape mediates changes in cellular biochemistry in response to a changing environment, by regulating the expression of reciprocal networks of non-coding RNAs (ncRNAs), DNA methylation, and histone modifications, inclusive of PTMs (Pal and Tyler, 2016). For example, introducing methyl groups (—CH_3) to Cytosine-phospho-Guanine (CpG) sites on genomic DNA, allows proteins to bind and change DNA's 3D structure. By measuring the genomic DNA methylation (gDNAm) level, epigenetic clocks have been significantly correlated with chronological age and the probability of all-cause mortality (Marioni et al., 2015; Perna et al., 2016). A range of such DNAm clocks have been developed. Examples include used Horvath's clock, Hannum's clock, PhenoAge and GrimAge. Loss of gDNAm level results in a range of age-related pathologies. Global hypomethylation is a typical feature of ageing in mammals. Several diseases associated with global hypomethylation include CKD, cardiovascular diseases, osteoporosis and diabetes mellitus (Mutirangura, 2019). Notably, methylation loss with age has been reported to result in the derepression and instability of retroviral elements (e.g. LINEs, ALUs) leading to dysregulated age-related gene function. This hypomethylation correlates with chromatin relaxation and unscheduled transcription (Pappalardo and Barra, 2021).

Interestingly, a role for histone PTMs in modulating lifespan has been identified by high-throughput screening of histone mutations (Sen et al., 2015). Among 437 histone mutant sites, 38 unique mutants were selected within histones H3 and H4 with the ability to regulate yeast lifespan by >20%. Sen and colleagues were able to classify two classes of short-lived mutants based on their effects on the expression of genes. The first group, consisting of H3E73, K79, T80, and L82, shortened lifespan by disrupting rDNA silencing. Meanwhile, mutants located near the histone H4 tail, such as K16 and R36, reduced longevity by interfering with chromatin structure. Even though the majority of histone mutations reduce yeast lifespan, six of them (H3K14Q, H3K64A, H3K115A, H3K122A, H3R128A and H4K77A) were found to increase lifespan in yeast by >25%.

In addition, abnormal PTMs in histone acetylation patterns are frequently observed in aged tissues and age-related chronic diseases (Benayoun et al., 2015; Gräff and Tsai, 2013). These changes are not restricted to a single gene mutation, but instead may cause large-scale alterations in chromatin remodeling. As the acetylation process initiates transcription by loosening chromatin structure, histone acetyltransferases (HATs) and histone deacetylases (HDACs) are regarded as key drivers in longevity (Yi and Kim, 2020). Specifically, deletion of HATs gene GCN5 has been reported to decrease yeast replicative lifespan (Kim et al., 2004). Regulation of the process of ageing has been proposed to occur via two main mechanisms, which have a strong link to promoting lifespan, including acetyl-CoA metabolism and the NAD+-dependent deacetylase pathway (Peleg et al., 2016; Yi and Kim, 2020). In yeast, depletion of nucleocytosolic acetyl-CoA has been indicated to stimulate autophagy and improve lifespan by reducing histone H3 acetylation level (Eisenberg et al., 2014). Another study suggested that SIRT6, an NAD+-dependent stress-responsive protein, can extend lifespan by deacetylating H3K9ac and inhibiting NF-κB pathway (Kawahara et al., 2009).

In response to environmental change, epigenetic plasticity is enabled by regulation of cellular biochemistry through ncRNA regulation of a range of distinct pathways. These unique classes of RNA do not encode proteins, yet have putative roles in coordinating gene expression by interacting with DNAm enzymes, histone and chromatin (Wei et al., 2017). Regulatory ncRNAs are classified based on size: short-chain (ranging from 19 to 31 bp, i.e. microRNAs) and long-chain (>200 bp, i.e. lncRNA) (Wei et al., 2017). In human genome, around 2600 functional microRNAs (miRNAs) and >200,000 transcripts have been confirmed (Plotnikova et al., 2019). miRNAs influence a variety of biological pathways related to stem cell renewal, proliferation, apoptosis and metabolism. A specific miRNA can target and modulate the activities of thousands of genes (Lewis et al., 2005). Many of these genes are critical modulators of PTM process, such as histone methyltransferases, methyl CpG binding proteins, chromatin domain proteins, and histone deacetylases. In the context of ageing, miRNAs can affect an organism's lifespan, tissue and cellular senescence (Smith-Vikos and Slack, 2012). Their regulatory roles are vital to maintaining mitochondrial function, telomeric nucleo-protein structure and ribosome structure and function. One class of ncRNAs, the lncRNAs, have a distinct impact on cellular ageing processes due to their interactions with key cell cycle proteins such as p53/p21, p16, cyclin-dependent kinase, and pRb (Degirmenci and Lei, 2016).

Studies using the kidney as a model of ageing (i.e. using renal allografts as a model of normative ageing and CKD as a model of accelerated ageing) has identified a direct link between renal function and the epigenetics of ageing (reviewed in (Shiels et al., 2017):).

Notably, exposome factors, such as diet and the microbiome, have even been implicated in regulation of renal function in the general population. An imbalanced diet and a loss of salutogenic bacteria able to supplement betaine levels and thus contribute to the maintenance of the methylome, is associated with accelerated ageing and diminution of renal function (Craven et al., 2021). These observations have indicated that targeting the cellular epigenome by modulating exposome factors holds promise for enhancing human health and fits well with the developing concept of 'Food as Medicine' (Mafra et al., 2020).

5. Translational potential of PTMs and ageing

Due to the relevance of PTMs in accelerating biological ageing processes, PTM-based therapeutics appear to be attractive candidates for reducing the burden of ageing-related diseases. Furthermore, PTMs themselves are frequently translationally used to modify proteins or peptides to improve their stability, bioavailability, and pharmacokinetics for clinical use.

Similar to the main PTMs reported in the dbPTM database, i.e. phosphorylation and acetylation (Ramazi and Zahiri, 2021), pharmaceutical approaches especially target theses PTMs. With regards to the above-discussed age-related diseases, where PTMs are relevant for the pathogenesis (e.g. neurodegenerative, metabolic, cardiovascular, bone diseases, as well as cancer and chronic kidney disease), most evidence for PTM-based therapeutics has been demonstrated in cancer. Thus, there are several FDA-approved kinase inhibitors interfering with phosphorylation-dependent pathways in different cancer types (Cohen et al., 2021). Recently, kinase inhibitors have also been evaluated in other ageing-associated disease states, such as AD (Cohen et al., 2021; Fagiani et al., 2020), diabetes (Fountas et al., 2015; Lin and Jin, 2017), distinct bone diseases (Metcalf et al., 2002), and CKD (Jamadar et al., 2021; Tesar et al., 2017). Interestingly, the most well-studied senolytic compounds dasatinib and quercetin, which have already been tested in Phase 1 pilot studies in ageing (Hickson et al., 2019), also act as kinase inhibitors targeting cellular senescence (i.e. a hallmark of ageing (López-Otín et al., 2013)) and increasing lifespan (Xu et al., 2018). It should be noted, however, that different FDA-approved kinase inhibitors

targeting phosphorylation also show adverse side effects, for instance on the cardiovascular system (Manouchehri et al., 2020). Thus, despite the term "targeted therapy", several caveats remain in the treatment with kinase inhibitors and careful patient selection and monitoring is necessary.

Histone acetylation is one of the most well-studied and important PTM, and acetylation (through HATs), as well as deacetylation (through HDACs), are an attractive treatment options for the "diseasome of ageing". HDAC inhibitors (HDACi) are the most well-characterized epigenetic targets, as some HDACi are already FDA-approved for the treatment of distinct cancer types (Jones et al., 2016). For a variety of inhibitors of the different HDAC groups, an extension of lifespan has been demonstrated in worms and flies (McIntyre et al., 2019) supporting the hypothesis that HDACi could reverse an ageing phenotype also in human diseases. McIntyre et al. (2019) have summarized potential mechanisms for targeting this specific PTM and suggest that a) HDACi could either directly increase acetylation of entire histones, or in distinct histones close to longevity-associated genes; b) induce mild stress which can delay ageing (i.e. hormesis (Kooman et al., 2014)); c) and/or exert pleiotropic effects through other proteins. Interestingly, distinct HDACi have proven efficacy in inhibiting several age-related disease states.

As HDAC2 and HDAC6 mediate murine and human tau pathology in AD (Gräff et al., 2012; Tseng et al., 2017), several HDACi have shown some efficacy in cognitive function and Tau protein pathology in animal models of AD (Gupta et al., 2020). With regards to age-related metabolic diseases, especially HDAC3 inhibition is an attractive PTM-based treatment target, as HDAC3 induces gluconeogenesis and liver-specific inhibition of HDAC3 ameliorates insulin resistance in a mouse model of non-alcoholic fatty liver disease (Sun et al., 2012). Importantly, inhibition of other HDAC classes also translated into an improved metabolic profile in animal experiments (Lv et al., 2021; Mihaylova et al., 2011). Regarding cardiovascular diseases, the HDACi givinostat was also able to reverse diastolic dysfunction and cardiac fibrosis in a mouse model of early heart failure (Travers et al., 2021). Furthermore, the HDACi TMP195 attenuates atherosclerotic plaque lesion formation, most likely through downregulating pro-inflammatory pathways in macrophages (Asare et al., 2020). Beneficial, anti-inflammatory effects of the HDACi RGFP966 have also been reported for endothelial dysfunction and endothelial-to-mesenchymal transition (Chen et al., 2021). In CKD mouse models, treatment with the HDACi valproic acid and suberanilohydroxamic acid improved proteinuria and glomerulosclerosis in mice, thereby improving animal survival (Inoue et al., 2019). Importantly, valproic acid-treated patients with CKD also showed a smaller decline in renal function compared to non-valproic acid users (Inoue et al., 2019). Further data indicate that the pan-HDACi trichostatin A improved renal function in an adenine CKD mouse model through increasing klotho expression (Lin et al., 2017), i.e. a marker of renal health (Ebert et al., 2020a).

Collectively, these data indicate that PTMs show a therapeutic potential in a wide range of ageing-associated disease states, but also to whole-body ageing itself. As phosphorylation and acetylation inhibitors are already partly used in distinct human disease states, future experiments need to determine the best candidates for the treatment of the "diseasome of ageing". A lack of specificity (for instance pan-HDACi vs. selective HDACi) and potentially adverse systemic effects in distinct organ systems (for instance cardiovascular side effects of different FDA-approved kinase inhibitors) might limit the clinical usage and need to be carefully investigated.

6. Conclusions

PTMs link oxidative stress, inflammation to a "diseasome of ageing". Data from progeroid syndromes and long-living animals implicate PTMs in the ageing process. PTMs affect whole-body, but also organ-/tissue-specific, ageing and contribute to the pathogenesis of age-related diseases, such as neurodegenerative, metabolic, cardiovascular, and bone diseases, as well as cancer and CKD. Mechanistically, PTMs target epigenetic and non-epigenetic pathways during the ageing process. Especially epigenetic histone modification has critical implications for the ageing process and can modulate the lifespan. Therefore, PTMs are potential treatment targets to reduce the burden of age-related diseases. To this date, phosphorylation and acetylation inhibitors are the most promising therapeutic drug classes and distinct candidates are already in clinical evaluation.

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Declaration of interest

The authors have nothing to declare.

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