Niveta *et al.*
Egyptian Journal of Medical Human Genetics (2022) 23:131
https://doi.org/10.1186/s43042-022-00335-4

Egyptian Journal of Medical Human Genetics

REVIEW

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Telomere attrition and inflammation: the chicken and the egg story

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Abstract

The challenge to improve human life span has progressed with the advent of health care services and technologies. This improvement poses a new challenge of an associated wave of diseases and pathologies that have not been observed or experienced. This has led to rise in geriatric population who are currently facing health challenges that needs to be addressed by the research community. This review focuses primarily on two mechanisms that have contributed to aging and associated pathologies: telomere attrition and inflammatory insults. A strong interplay appears to exist between telomere attrition and inflammation, and this could be the basis of many pathologies associated with increasing age. This creates a scientific dilemma as to what comes first: telomere attrition or inflammation. This review will enthuse the reader to the underlying molecules and mechanisms associated with telomere attrition and inflammation and their contribution to aging.

Keywords: Inflammaging, Telomere, Senescence, Inflammasome, DNA damage response, SASP, cGAS/STING, COPD, Muscular dystrophy, Inflammation

Background

Aging: is it inevitable?

The human race has been in the quest to explore the practices associated with reversal of aging for many centuries. There are two conflicting theories on aging, one which states that aging is a physiological process while the other states that it is a pathological condition where the cells have accumulated stress throughout the lifetime of a person and are no longer able to function normally [1, 2]. When biological aging begins at the appropriate age, it is a physiological phenomenon; however, when this process begins earlier than actual, it requires attention [3]. Aging in the scientific perspective is termed as the accumulation of cellular senescence, a condition where the cells are no longer able to repair, regenerate and maintain a state of homeostasis of functionally healthy cells (principally due to an irreversible cell cycle arrest) [4]. The manifestation of cellular senescence is seen in the form of greying, wrinkles, loss of memory, muscular atrophy, poor immunity and degeneration of bones [5]. Aging is a process regulated both at biochemical and genetic levels, and these could be targets of therapeutic interventions to slow down aging or managing the indications of aging [6, 7]. While we explore to manage or reverse aging, we are employing anti-aging medication that aims to revive the regenerative and repairing property of cells. In this direction, we cannot rule out the risk of the probability of the cells expressing as a neoplasm [8, 9]. Therefore, it is important to understand and develop anti-aging therapies, which adequately maintains cellular homeostasis. This is of concern when the therapy targets a genetic mechanism to manage or reverse aging [10]. Research in anti-aging is gaining thrust as we have observed clinically that humans are aging prematurely and the rate of molecular aging has increased considerably as a consequence of lifestyle choices in terms of diet, sleep cycle, stress management and physical activity [3, 11]. An imbalance has been observed in the process of

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aging which consequently is the reason for a number of pathological conditions that challenge the human race.

Inflammaging

The important hallmarks of aging are misleading cell-to-cell communication and distorted communication in the immunological network, where a pro-inflammatory phenotype is observed and this is termed as inflammaging [12, 13]. Age-associated disorders like obesity, diabetes, atherosclerosis, neurodegenerative disorders and a number of autoimmune conditions have been found to be implicated by cellular senescence of the immune system [14, 15]. Over years, repeated immunological insults and improper clearance of these insults have been major contributing factors to inflammaging [16]. In general, the senescent cells exhibit senescence-associated secretary phenotype (SASP) which is characterized by increased production of pro-inflammatory cytokines [17]. This consequently leads to persistent and aggressive activation of innate and adaptive branches of the immune system. SASP is generally considered to signal immune system for self-elimination [18]. The mutual and continuous activation of the innate and adaptive immunity also leads to senescence of the immune cells [19]. Some of the cellular events strongly associated with senescence are cell cycle arrest, resistance to apoptosis, telomere attrition, endoplasmic reticulum (ER) stress and metabolic reprogramming [20]. The associated molecules include SASP, interleukin-6 (IL-6), interleukin-8 (IL-8), chemokines like monocyte chemoattractant protein 1 (MCP-1) and matrix metalloproteinase 1 and 3 (MMP1 &3) and other protein complexes like inflammasomes composed of caspase-1 and other supporting proteins [21]. Although senescence is considered to have a negative effect on tumorigenesis, senescence in immune cells promotes a microenvironment that is favorable for tumor growth [22, 23]. The master switch for SASP has been found to be nuclear factor kappa B (NF-κB) which is ubiquitous in all cases of inflammaging [24]. The master switch is triggered whenever the integrity of cell's nuclear content is irreversibly compromised or when the nuclear content infiltrates the cytoplasmic zone [16].The inhibition of NF-κB pathway has been found to reverse aging of skin, lung fibroblasts [25] and neuronal cells [26] as well. The cell has its own innate anti-aging mechanisms and systems, such as the AU-rich element RNA-binding protein 1 (AUF1) which has the ability to bind to mRNA of the cytokine genes and inhibit their expression and at the same time induce telomerase activity to aid in maintaining telomere length by binding to the mouse telomerase reverse transcriptase (mTERT) promoter and inducing its transcription, ideally hitting two targets at the same time [27]. Sirtuin-1 (SIRT-1) (depleted under oxidative stress) is a deacetylase involved in the deactivation of NF-κB by acting on its lysine 310 residue, thus inhibiting its transcriptional activity [28, 29].

Telomere attrition

Cellular senescence was first defined by Hayflick and Moorhead in a genetic perspective involving a region of the chromosome called the telomere [30]. They proposed the theory of aging which stated that a human somatic cell can undergo only 50 to 70 divisions, after which the cell cycle ceases and attains a state of senescence [31, 32]. The cessation of the cell cycle upon reaching the determined attrition of telomere is entitled as Hayflick limit or replicative senescence [33]. Telomere guards the ends of the deoxyribonucleic acid (DNA) as a cap to ensure uncompromised transfer of genetic information during every replication cycle [34]. The human telomere is composed of tandem repeats TTAGGG [35], and nearly 50 to 100 base pairs of telomere sequence are lost through each cell division. Telomeres are not fully replicated during cell division due to the end replication problem, which arises since DNA polymerase operates exclusively in the 5′-3′ direction [32]. The telomere is synthesized by the enzyme telomerase encoded by telomerase reverse transcriptase (TERT) gene which also contains a catalytic subunit and ribonucleic acid (RNA) template [32]. The ends of the telomere have a G-rich 3′ overhang. The 3′ overhang of the telomere is folded as a loop and introduced into the double-stranded DNA and termed as T loop [13, 36]. The shortening of telomere symbolizes mitotic clock accountable for aging [37], and this concept is not relevant in the context of stem cells and germ cells. The abnormal attrition of telomere causes telomeric diseases such as aplastic anemia, pulmonary fibrosis and hepatic disease [33]. Some cells break out of senescence and run into crisis, where it undergoes apoptosis, while some cells escape apoptosis and help in the development of cancer [13]. The shortening of telomere affects the expression of the genes located in the sub telomeric regions. This is termed as telomere positioning effect [38, 39]. The telomere includes six proteins telomeric repeat-binding factor 1 (TRF1), telomeric repeat-binding factor 2 (TRF2), telomeric repeat-binding factor 1 interacting nuclear factor 2 (TIN2), repressor activator protein 1 (RAP1), tripeptidyl peptidase 1 (TPP1) and protection of telomere protein 1 (POT1) called as shelterin complex or telosome [40]. The length of the telomere is regulated by telosome, and it protects it from being recognized as double-stranded breaks by DNA repair mechanism and circumvent end-to-end fusion [41].

What comes first: telomere attrition or inflammation?

An unconventional theory: telomere attrition causes inflammation

Telomere attrition is brought about by many factors such as replication, oxidative stress and inflammation [42]. Cells with short telomeres are capable of inducing inflammation through non cell autonomous manner [43]. Telomere shortening is known to be associated with regression in the mitochondrial function and exaggerates age-related pathologies such as cardiovascular disease. The underlying mechanism and association of telomere shortening in pathological conditions is still unclear [44]. In a study conducted 'hitherto,' the telomerase knocked out mice were backcrossed for four generations and the transcriptome of the wild type and G4 mice were compared. The G4 mice exhibited differential expression of genes involved in metabolism, oxidative phosphorylation, mitochondrial biogenesis and redox buffering. This trend was observed in the progression of pathological conditions in the high-energy demanding organs [45]. Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) is one such key regulator of energy metabolism in mitochondria, and its expression and activity are pronounced in the cardiomyocytes. During telomere attrition, p53 is constitutively activated and the transcriptional regulator PGC-1α is repressed by p53 [46]. The repression of PGC-1α results in impaired mitochondrial function and downregulation of adenosine triphosphate (ATP) and the antioxidant enzymes. This causes an upsurge of reactive oxygen species (ROS) which leads to inflammation [47]. Another study validates a similar mechanism in the macrophages with additional involvement of tumor necrosis alpha-induced protein 3 (TNFAIP3), which appears to be downregulated throughout telomere attrition. The PGC-1α also shows a similar expression pattern in the telomere dysfunctional macrophage. This gives a new insight that TNFAIP3 may positively regulate the expression of PGC-1α. TNFAIP3 has also shown to have a negative effect on NF-κB, and hence, NF-κB is activated in macrophages [48–50].

Shorter telomeres are encountered as a double-stranded break by the DNA repair mechanism. It could be hypothesized that DNA damage response (DDR) is activated due to dysfunctional shelterin protein [51] or reduced levels of shelterin proteins are a consequence of telomere attrition. According to the replication fork model, the level of shelterin complex is inversely proportional to the probability of the telomerase binding to it and elongating the telomeric ends [40]. Therefore, more the telomere length, more is the shelterin concentration and better is the protection from DDR. Thus, it could be concluded that the shelterin complex functions to protect the DNA from DDR [41]. Studies state that NF-κB signaling pathway is triggered by DDR and cyclic GMP AMP synthase/stimulator of interferon genes (cGAS/STING) pathway and eventually leads to inflammation [16]. In senescent cells, the nuclear lamin (of the nuclear envelope) disintegrates and the chromatin infiltrates into the cytosolic space with DNA damages to form cytoplasmic chromatin fragments (CCFs). This is recognized by certain DNA sensors in cytoplasm called the cGAS. The cGAS enzyme is activated on binding to CCFs and leads to activation of downstream STING protein that dimerizes via the cyclic GMP AMP cGAMP produced by cGAS and undergoes nuclear translocation where it activates the NF-κB's transcriptional activity [52]. The telomere damage can lead to telomere dysfunction because of alternating non-homologous end joining (NHEJ) which is known for its ability to cause genomic instability [53]. In an attempt to repair the oxidized guanine nucleotides, there is misinterpretation of the telomeric ends as DNA double-stranded breaks by poly [ADP-ribose] polymerase 1 (PARP-1) with the aid of X-ray repair cross-complementing protein 1 (XRCC1) and gamma H2AX variant histone family member 1 (γH2AX1). This makes it impossible to lengthen the telomere again [54]. PARP-1 also acts as a transcriptional coactivator for NF-κB promoting cytokines and adhesion molecules expression for facilitating immune cell interaction and portrays a vicious cycle model [55]

Another research study has revealed that yes-associated protein 1 (YAP1) transcription coactivator is upregulated via ataxia-telangiectasia mutated (ATM)/c-ABL pathway in DNA damage signaling through telomere dysfunction in inflammatory bowel diseases. Activated YAP1 elevates several inflammatory bowel disease (IBD) pertinent genes like the pro-inflammatory cytokines including premature interleukin-18 (IL-18). The premature IL-18 has to be cleaved by the caspase-1 to become matured [56]. Gut microbiome-mediated inflammasome cleaves the premature caspase-1 that results in caspase-1-directed cleavage of premature pro-IL-18. The IL-18 involves in the recruitment of T cells with vigorous secretion of interferon gamma (IFN-γ) and provokes inflammation in IBD [57]. IL-18 is structurally and functionally similar to interleukin 1 beta (IL-1β). *Helicobacter pylori* was found to increase inflammation in gastric mucosa by upregulating Yap1 which in turn upregulates IL-1β. Premature caspase-1 has to be initially cleaved to direct the cleavage of premature IL-1β [58]. Research studies have demonstrated that *Helicobacter pylori* upregulates the Yap1; however, it can also be hypothesized that Yap1 is upregulated due to telomere dysfunction. *Helicobacter hepaticus* can induce cellular senescence via the cytolethal distending toxin (CDT). The CDT is known to

possess a subunit with DNase activity which could trim down the telomeric ends [59]. We understand that *Helicobacter pylori* can also express CDT or a similar toxin which requires more detailed investigation. *Helicobacter pylori* is also able to form the active inflammasome which cleaves premature caspase-1 [60]. Thus, the inflammatory milieu in the gastric mucosa which is tumor promoting is thought to be caused by *Helicobacter pylori* [61].

COPD (chronic obstructive pulmonary disorder) is type of lung disease which mainly includes emphysema and chronic bronchitis that obstructs the airway and causes difficulties in breathing. COPD progresses with heavy load of inflammatory mediators in the pulmonary locale and cellular senescence in the pulmonary endothelial cells [62]. A study in COPD reveals that in spite of cessation of smoking, the release of pro-inflammatory cytokines from the lung cells has been observed. In the cell culture of COPD patient-derived pulmonary endothelial cells, the cells secreted more pro-inflammatory mediators with increase in passage number of cells. The knockout of TERT gene in mice model was able to create an inflammatory atmosphere in them, reiterating that telomeric loss could kick start a cytokine storm [63].

Bacterial and viral DNA have high G-rich sequences which slake the innate immunity by halting the Toll-like receptor 9 (TLR9) receptor and cGAS/STING pathway [64]. These pathways are potent cytoplasmic DNA and cytoplasmic free DNA sensing mechanisms through which the inflammatory responses are quenched by the pathogens (containing DNA and RNA as genetic material) [65]. Apart from cGAS/STING, another DNA sensing molecule called AIM2 is involved in surveillance of exogenous DNA in the cytosolic domain which has gained entry through transfections and infections [60]. Inherently, the telomeres are G-rich sequences (which are capable of suspending innate immune responses) and therefore quench the inflammation during their cytoplasmic release and NF-κB pathway remains inactive [66]. An important reason why the release of telomere depleted DNA elicits pro-inflammatory activity is due to the fact that DNA shed by the young has more G-rich telomere sequence compared to the old [67]. DNA is not only fragmented and released during the replication of cells but also due to the stress caused by 8-oxo-deoxyguanosine triphosphate (8-Oxo-dGTP), which erodes the telomere by displacing the shelterin proteins, especially TRF1 and TRF2, which in turn allows DNA cleavage [68]. The damaged DNA is repaired by substituting the unoxidized through the DDR base excision repair pathway [69]. The continuous erosion of telomere correspondingly causes inflammation via the telomere repeat-containing RNA (TERRA) which is complementary of the telomere in the shortened telomeres, resulting in DNA–RNA hybrids [70]. The DNA–RNA hybrids are potent activators of cGAS and TLR9 via NF-κB [71] (Fig. 1).

The norm: inflammation causes telomere attrition

Inflammation has been proved to cause telomere attrition in multiple pathological conditions. However, the oxidative stress [72] mediated by the phagocytic immune cells, via the Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases [73], is a major contributor of DNA damage especially in the telomeric region, owing to the high levels of G which are susceptible to oxidative damage [74]. Neutrophils are found to accelerate aging of the hepatocytes by inducing oxidative stress by transferring the ROS it produces in a paracrine fashion to the cells in the vicinity and also induce senescence in them by telomere attrition [75]. This phenomenon is analogous to the bystander effect where ROS is released via gap junction and causes clustering of senescent cells [76]. Such bystander effects are mediated by tunneling nanotubes as well [77].

One of the primary causes of inflammation is infection [78] and in that context *Helicobacter pylori* infection of gastric mucosa has been found to cause extensive telomere attrition in gastric mucosa driven by inflammatory oxidative stress by ROS and Reactive Nitrogen species (RNS) [79]. Telomeric loss is not just augmented by bacterial agents but is also observed in protozoan infections such as malaria [80]. When siskins were infected with avian malarial virus, not only telomeric degradation in the blood cells was observed, but a 45–56% telomeric loss was observed in other uninfected organs like liver, kidney, lungs, brain, spleen and heart. This is again attributed to the ROS produced by protective action of phagocytes leading to permanent damage to nuclear content especially in the highly susceptible telomeric region [81]. In a scenario involving any infectious agent, the worst hit population of cells is the immune cells due to their tendency to proliferate rapidly and counteract the antigen [82]. But the consequence of this protective inflammatory function is immunosenescence because of replicative telomere attrition [78].

Oxidative stress can cause telomere attrition in preterm babies in neonatal intensive care as a consequence of constant oxidative stress and inflammation due to operative procedures and exposure to toxins like phthalates in medical equipment [83, 84]. They are found to have accelerated telomere attrition compared to fetus of the same age even in the presence of compensatory increase in telomere length possibly due to the activity of telomerase in fetal developmental stages [85]. Accelerated telomere attrition was observed in chronic kidney disease or end stage renal diseases patients subjecting them to a greater risk for cardiovascular disease (CVD), and was attributed

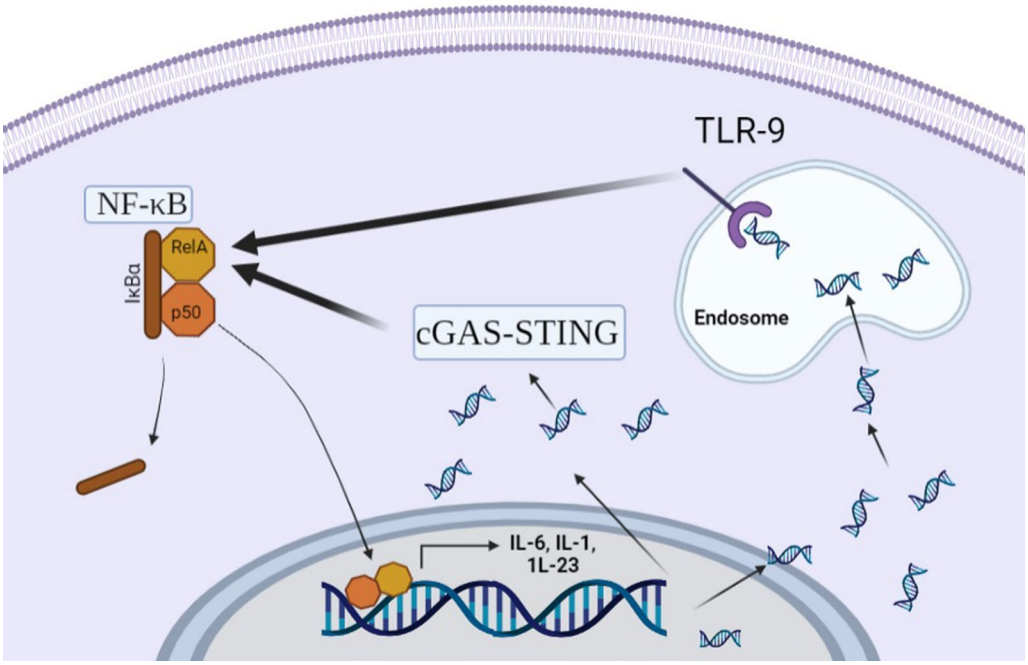

Fig. 1 The DNA fragments obtained after complete telomeric loss, are not G-rich, hence when released into cytoplasm activates cGAS/STING pathway. The fragmented DNA that enter endosomes tend to activate TLR9. Both cGAS/STING and TLR9 activate the NF-κB pathway and induce inflammation

to uremic inflammation and repeated dialysis [86]. Some of the pro-inflammatory cytokines like IL-6 and tumor necrosis factor alpha (TNF-α) tend to subject cells to metabolic stress by upregulating proteasome-mediated catabolism and downregulating anabolic pathways by desensitizing the cells to insulin-like growth factor 1 (IGF-1) [87, 88]. A preliminary study done on the inflammatory marker profile, such as the master controller NF-κB and pro-inflammatory cytokines levels, of peripheral blood mononuclear cells (PBMCs) from primary caregivers of autistic children. It showed increased levels due to the constant psychological stress of the subjects and the rate of telomere attrition in the next 15-month period of time was predictive [89]. Psychological distress is a strong stimulator of inflammation-mediated telomere attrition in depression as well [90].

A similar phenomenon is observed in metabolic diseases like type 1 and 2 diabetes mellitus. The monocytes interacting and extravasating this vasculature exhibit telomere shortening [91] and there is a surge in oxidative product of nucleotides 8-hydroxy-2'-deoxoguanosine in the urine of these patients. This demonstrates that the telomere shortening could be because of oxidative damage caused by the transient exposure of the monocytes to the low-grade chronic inflammation in vasculature [92]. The telomere shortening is not just restricted to monocytes but is observed in the endothelial cells as well denoting accelerated aging in these cells. This categorizes Diabetes mellitus as an aging-related disease [93]. The NF-κB pathway, prime inflammatory pathway, happens to be constitutively active in endothelial cells derived from a diabetic patient and its inhibition was able to increase the life span of these cells [94]. This vascular complication is attributed to the hyperglycemic status of these patients which inadvertently creates a redox imbalance that can potentiate telomere attrition [95]. The excessive glucose uptake by endothelial cells as a consequence of hyperglycemia will increase the oxidative stress through the elevated Oxidative Phosphorylation (OXPHOS) activity in the mitochondria [96]. This oxidative stress is capable of eliciting a hyperglycemia-associated secretary phenotype (HASP) which is an instigator of chronic-low-grade inflammation which in turn elevates oxidative stress and hence causes telomeric erosion [97, 98]. Many studies have reiterated the above phenomenon as the cause of accelerated aging of vascular tissues in atherosclerosis and cardiovascular disorders. It is also considered to be a marker of cardiovascular aging [99].

A number of degenerative disorders like osteoarthritis [100], Alzheimer's disorder and Parkinson's disorder exhibit inflammation-mediated telomere loss [101]. In Alzheimer's disorder, the ROS produced due to hyperactive immune response especially by the microglia and astrocytes is found to be an initiator of the disease

[102, 103], but in the later stages of progression, the oxidative stress shows a decline. This decline is due to the impaired adaptive immune response that is pronounced during the later stages [104]. This reiterates the fact that the inflammation is responsible for the telomeric degradation and not vice versa [105]. A longitudinal study done with a 10-year follow-up bolsters the fact that inflammation is the reason for telomere attrition and aging-associated sarcopenia which was evaluated by measuring the grip strength. When the inflammation was suppressed, the correlation between telomeric erosion and grip strength was lost. In this scenario, inflammation not only accelerates telomeric attrition by ROS imbalance but it also inhibits telomerase, the telomere rescue enzyme [106]. Telomerase is a type of DNA polymerase which incorporates dNTPs during telomere elongation [107]. Telomerase mistakes 8-oxo-dGTP, a product of oxidative DNA damage, for a dNTP and uses it as a substrate in telomere elongation [108]. Once the 8-oxodGTP is added, the elongation terminates, but this inhibition is subjective to the nucleotides preceding the 8-oxodGTP [109].

In genetic disorders with accelerated aging and atrophy of tissues, the inflammatory signaling pathway NF-κB is known to play a crucial role in telomere attrition. Generally, immune signals help the clearance of necrotic cells and are able to activate myogenic stem cells for regeneration in muscle injury by temporal activation of NF-κB [110]. In Duchenne's muscular dystrophy (DMD), there is chronic injury to muscle cells and persistent activation of NF-κB which leads to telomere attrition in a replication-independent manner involving the Ku-80 proteins [111]. Ku-80 protein downregulation is thought to be involved although the exact mechanism is not known. Conventionally, Ku-70/80 heterodimer is involved in non-homologous end joining and its association with telomeres put them at risk of alternate end joining leading to its dysfunction [112], but conversely Ku proteins have been found to have high affinity for the TRF2 shelterin protein and the telomeric sequence as well which is proposed to aid with telomere stability and maintenance [113]. In sickle cell diseases, the telomere shortening is independent of age and indicated that their cellular age was much higher than their chronological age. In this case, the inflammation and increase in ROS are caused by free heme from the lysed RBCs, which interacts with Toll-like receptor 4 (TLR4), a significant receptor of the innate immune response (which activates the NF-κB) [114]. Nitric oxide (NO) has been able to attenuate the vascular inflammation by aiding the clearance of the occlusion through vasodilation [115].

A possible vicious cycle

From what we have read and understood thus far, the lacuna in understanding which comes first in most inflammaging conditions, i.e., telomere attrition or inflammation, still remains a question [116]. It is of concern when both scenarios can coexist and bring in a vicious cycle into action (Fig. 2). Preterm infants are essentially still in the fetal developmental stage and must have considerable telomerase activity in the placental tissues to withstand telomere attrition, but this system fails because preterm infants have a high mortality rate and show high likelihoods of developing aging-related pathologies [117]. A vicious cycle of telomere attrition and inflammation has the potential to trim down the telomeres at a rate that the telomerase is not able to keep up with the damage. In cases of COPD, there is a constant aggravation of pro-inflammatory status even after the cessation of exposure to smoke and pollutants [63]. This scenario is possible only when the vicious cycle model is applicable. In terms of the *Helicobacter pylori* infections, there are evidences supporting both inflammation and telomere attrition as the trigger for gastric mucosal senescence which directs the patient to high risk for gastric cancers [54, 56, 58, 118]. Only a vicious cycle could be involved in inflammatory conditions severe enough to promote neoplastic conditions.

Diagnostic markers and potential drug targets

In most of the inflammaging conditions, diagnosis has been a challenge [119], because it measures the serum cytokine levels and telomere attrition in the associated tissue or cells. But pro-inflammatory cytokines as markers have very poor specificity for any given condition because their upregulation in the system is possible by many other factors such as infections, allergies, exercise, sleep, circadian rhythm and food intake [120]. The understanding of the underlying mechanisms in inflammaging conditions is imperative to find highly specific diagnostic markers and drug targets at the same time [121]. The suppression of inflammation in a condition where telomere attrition instigates inflammatory condition is not going to resolve the disease but provide a temporary relief. Hence, finding the root cause is of utmost importance. One of the most commonly used markers for inflammation-mediated telomeric loss has been found to be the measurements of levels of 8-hydroxy-2′-deoxoguanosine in urine samples of patients [92].

The prediction of a possible preterm birth could be of immense use in bringing down the rates of preterm birth-related mortality and morbidity. An inflammation-mediated aging mechanism could possibly be happening in this scenario. The placental and maternal

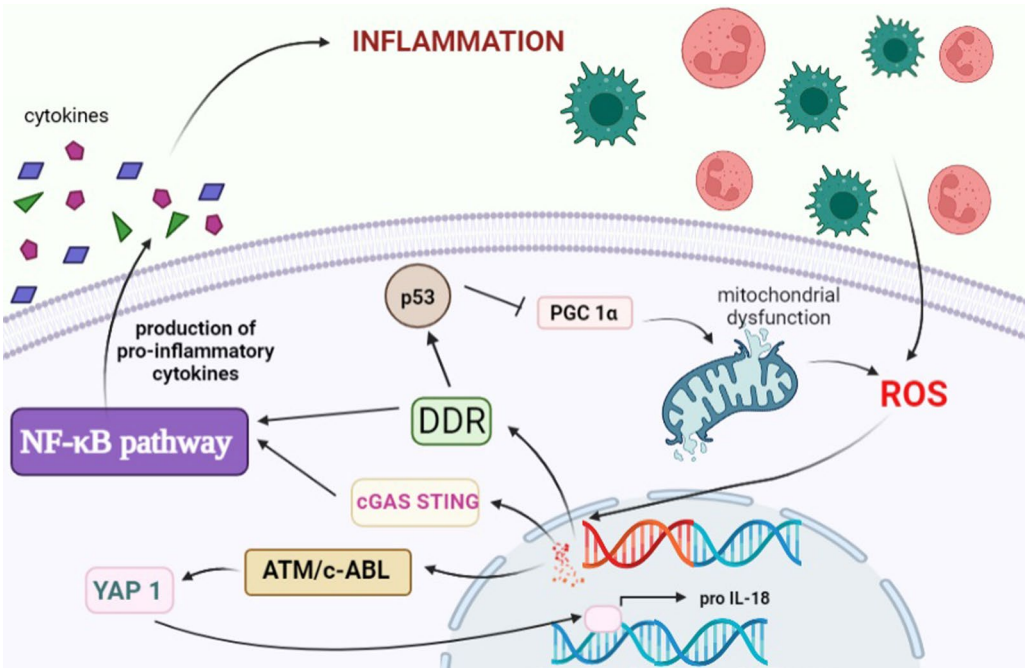

Fig. 2 The vicious cycle: The phagocytic cells produce ROS via oxidative burst mechanism which damages the highly susceptible G-rich telomeric region DNA damage response (DDR) which activates p53 that represses PGC-1α which in turn leads to mitochondrial dysfunction and ultimately leads to ROS imbalance. The cGAS/STING pathway activates NF-κB pathway along with DDR. The ATM/c-ABL DNA damage pathway is also activated which recruits YAP1, a transcriptional coactivator, involved in the expression of pro-IL-18 to the nucleus

serum samples of preterm babies showed elevated galectin-3, an inflammatory molecule produced by senescent cells (belonging to the SASP family), and telomere attrition in the placental tissue [122, 123]. Flow cytometric analysis can be done on placental tissues for the detection of telomere attrition and galectin expression by utilizing fluorescent DNA probes for the hexamer in telomeres and the galectin-3 mRNA.

Understanding the mechanism of these pathological conditions is imperative for determining drug targets as well. To quote an example, muscular dystrophies are diseases with marked senescence of the myocytes [124]. As mentioned earlier, the NF-κB pathway takes the driver seat in the progression of DMD and hence this pathway is a potential candidate for the drug target. But targeting the same in case of limb-girdle muscular dystrophy type 2A (LGMD type 2A) could be detrimental even though they belong to same family of pathological conditions [111]. In LGMD type 2A, the NF-κB pathway-mediated expression of apoptosis inhibiting cellular FLICE (FADD-like IL-1β converting enzyme)-inhibitory protein (c-FLIP) is deregulated. In this context, the inhibition or downregulation of the NF-κB pathway is not an appropriate choice, but mediating this pathway to function the right way could alleviate the condition [125].

Telomere attrition in aging instigates low expression of PGC-1α; this leads to commotion in the metabolism of cardiomyocytes in geriatric population [126]. Myocardial tissues retrieved by endomyocardial biopsy and the transcriptome could be subjected to microarray chip analysis for PGC-1α expression levels [127, 128]. Gastric inflammatory conditions such as IBD are visually confirmed through colonoscopy; however, there are challenges and limitations with these methods [129]. In IBD, the expression of the transcription coactivator YAP1 along with telomere attrition could be used as a molecular diagnostic marker. By tagging fluorescent probes to telomere and antibodies to Yap1, the length of telomere and the expression of YAP1 can be analyzed simultaneously using fluorescence-activated flow cytometry [130]. In IBD, there is an inverse relationship between telomere length and YAP1 levels. To be precise, the shorter the telomere length, the greater is the expression of Yap1.

In COPD, spirometry is used to determine the stage of the disease based on the respiratory capacity of the lungs and there is no molecular level test for staging the disease [131]. In the early stages of COPD, toxins such as smoke and air pollutants cause inflammation in the lungs and instigates telomere attrition in pulmonary endothelial cells. In later stages, even after the withdrawal of the toxins, the inflammatory status persistently worsens as the inflammatory mediators are

Table 1 Classification of diseases based on the inducer with potential diagnostic and therapeutic targets

S.No	Pathological condition	Type	Potential diagnostic markers	Potential therapeutic targets
1	Metabolic disorders	Both possible vicious cycles	8-Oxo-dGTP↑ PGC-1α ↓	PGC-1α ←
2	Irritable bowel syndrome	Both possible vicious cycles	YAP 1 ↑ IL-18↑	YAP 1 ⊥
3	COPD	Telomeric loss-mediated inflammation	Inflammatory status of patient lung tissue culture	–
4	Duchenne's muscular dystrophy	Inflammation-mediated telomeric loss	Ku-70/80 (dysregulated)	NF-κB ⊥
5	Preterm birth	Inflammation-mediated telomeric loss	Galectin-3 ↑	–
6	Aging-associated sarcopenia	Inflammation-mediated telomeric loss	8-Oxo-dGTP ↑	8-Oxo-dGTP ⊥

↑ upregulated; ↓ downregulated; ← activation; and ⊥ inhibition

released by the short telomere pulmonary endothelial cells [63]. To evaluate the stage at molecular level, the pulmonary endothelial cells retrieved from the lungs of the COPD patient can be cultured and the inflammation mediatory profile can be analyzed. There is limited literature available to elucidate the exact mechanisms of inflammaging and that could be a potential reason why we cannot differentiate between telomere attrition-mediated inflammation and inflammation-mediated telomeric loss. Although the literature is limited, we have discussed some promising drug targets and candidates for diagnostic markers in Table 1.

Discussion

This review focuses primarily on two mechanisms that have contributed to aging and associated pathologies, telomere attrition which is a consequence of years of replication and damage caused due to inflammatory insults that have accumulated over the years of their life. This strong and dynamic network and interaction between telomere attrition and inflammation could be attributed to the diseases associated with geriatric patients. The lacuna to understanding whether telomere attrition or inflammation comes first still remains inconclusive. We have discussed certain diseases where inflammation comes first potentiating telomere attrition and vice versa. We also have scientific evidences of both of them coexisting, depicting a vicious cycle. Classifying diseases on this basis can offer to be a great improvement in understanding the underlying mechanisms and thus help us establish standard diagnostic markers, therapeutic targets and therapy regimens for the same. The review also offers a prelude to exploring few promising drug targets and candidates for diagnostic and therapeutic targets.

Abbreviations

SASP: Senescence-associated secretory phenotype; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-18: Interleukin 18; IL-1β: Interleukin 1 beta; IFN-γ: Interferon gamma; CDT: Cytolethal distending toxin; MCP-1: Monocyte chemoattractant protein 1; MMP1: Matrix metalloproteinase 1; NF-κB: Nuclear factor kappa B; mTERT: Mouse telomerase reverse transcriptase; SIRT1: Sirtuin 1; AUF 1: AU-rich element RNA-binding protein 1; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; TERT: Telomerase reverse transcriptase; TRF 1: Telomeric repeat-binding factor 1; TFR 2: Telomeric repeat-binding factor 2; TIN2: Telomeric repeat-binding factor 1—interacting nuclear protein 2; POT 1: Protection of telomeres protein 1; TPP1: Tripeptidyl peptidase 1; RAP1: Repressor activator protein 1; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; TNFAIP3: Tumor necrosis factor alpha-induced protein 3; cGAS/STING: Cyclic GMP-AMP synthase/stimulator of interferon genes; ATP: Adenosine triphosphate; ROS: Reactive oxygen species; DDR: DNA damage response; NHEJ: Non-homologous end joining; CCF: Cytoplasmic chromatin fragments; PARP1: Poly [ADP-ribose] polymerase 1; XRCC1: X-ray repair cross-complementing protein 1; γ-H2AX1: Gamma H2A.X variant histone family member 1; YAP1: Yes-associated protein 1; ATM: Ataxia-telangiectasia mutated; TLR9: Toll-like receptor 9; TERRA: Telomeric repeat-containing RNA; dGTP: Deoxyguanosine triphosphate; NADPH: Nicotinamide adenine dinucleotide phosphate; RNS: Reactive nitrogen species; IGF-1: Insulin-like growth factor-1; PBMC: Peripheral blood mononuclear cells; OXPHOS: Oxidative phosphorylation; NO: Nitric oxide; RBC: Red blood cells; DMD: Duchenne muscular dystrophy; GTP: Guanosine-5′-triphosphate; COPD: Chronic obstructive pulmonary disorder; HASP: Hyperglycemia-associated secretory phenotype; LGMD: Limb-girdle muscular dystrophy; c-FLIP: Cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein; CVD: Cardiovascular diseases; ER: Endoplasmic reticulum.

Acknowledgements

Not applicable

Author contributions

JPSN and AKM contributed to writing original draft and visualization. VDP was involved in conceptualization, writing, review editing, and supervision. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The authors offer their consent for publication.

Competing interests
The authors have no conflict of interest to declare.

Received: 9 March 2022 Accepted: 5 August 2022
Published online: 28 August 2022

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