frontiers in Immunology

MINI REVIEW
published: 04 September 2017
doi: 10.3389/fimmu.2017.01078

Chronic Inflammation in Immune Aging: Role of Pattern Recognition Receptor Crosstalk with the Telomere Complex?

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Specialty section:
This article was submitted to Inflammation, a section of the journal Frontiers in Immunology

Received: 24 March 2017
Accepted: 18 August 2017
Published: 04 September 2017

Citation:
Jose SS, Bendickova K, Kepak T, Krenova Z and Fric J (2017) Chronic Inflammation in Immune Aging: Role of Pattern Recognition Receptor Crosstalk with the Telomere Complex? Front. Immunol. 8:1078. doi: 10.3389/fimmu.2017.01078

Age-related decline in immunity is characterized by stem cell exhaustion, telomere shortening, and disruption of cell-to-cell communication, leading to increased patient risk of disease. Recent data have demonstrated that chronic inflammation exerts a strong influence on immune aging and is closely correlated with telomere length in a range of major pathologies. The current review discusses the impact of inflammation on immune aging, the likely molecular mediators of this process, and the various disease states that have been linked with immunosenescence. Emerging findings implicate NF-κB, the major driver of inflammatory signaling, in several processes that regulate telomere maintenance and/or telomerase activity. While prolonged triggering of pattern recognition receptors is now known to promote immunosenescence, it remains unclear how this process is linked with the telomere complex or telomerase activity. Indeed, enzymatic control of telomere length has been studied for many decades, but alternative roles of telomerase and potential influences on inflammatory responses are only now beginning to emerge. Crosstalk between these pathways may prove to be a key molecular mechanism of immunosenescence. Understanding how components of immune aging interact and modify host protection against pathogens and tumors will be essential for the design of new vaccines and therapies for a wide range of clinical scenarios.

Keywords: pattern recognition receptor signaling, telomere shortening, inflammaging, myelopoiesis, NF-κB, toll-like receptor signaling

INTRODUCTION

Aging is a complex process that involves a gradual decline in critical cellular processes, signaling pathways, and regulatory mechanisms, leading to eventual disruption of tissue homeostasis (1). Accumulation of cell functional defects over time, commonly termed "senescence," is a driving force of human aging and confers increased risk of cardiovascular and neurodegenerative disorders, as well as autoimmune disease and infection (2). Cellular senescence-associated changes affect numerous processes including proliferation or changes in secretome. Recent studies have shown that chronic inflammation contributes to pathological aging by promoting stem cell exhaustion,

impairment of cellular communication, and somatic cell loss of the repetitive nucleotide sequences known as telomeres that form protective "caps" at the ends of chromosomes (1).

To maintain telomere length and protect chromosomes against damage, cell types with high proliferative capacity such as hematopoietic progenitors (3, 4) and effector leukocytes (5, 6) employ the inducible enzyme telomerase to maintain telomere length. In addition, the multiprotein complex shelterin coordinates the formation of protective "loop" structures that prevent telomere ends from being recognized as DNA breaks (7). While a large number of studies have investigated telomere length and telomerase activity as prognostic biomarkers in human cancer, this review instead focuses on the potential interactions between inflammation and telomere biology in immunological aging. Indeed, telomerase activity is now known to be strongly influenced by leukocyte proliferative activity, ongoing inflammation, and production of reactive oxygen species (ROS), but the molecular basis of these effects is not yet fully understood. In particular, the transcription factor NF-κB, which has long been associated with pattern recognition receptor (PRR) signaling and inflammation, has recently been identified as an important regulator of the telomere complex. Better definition of potential immune crosstalk with telomerase activity may therefore yield a range of novel therapeutic targets for intervening in age-related and inflammatory pathologies.

IMMUNOSENESCENCE

Effective host immunity is essential for the maintenance of tissue homeostasis and health, but both innate and adaptive responses are subject to natural age-related functional decline termed "immunosenescence" (8). Key features of immunosenescence include a progressive loss of naïve T cells and accumulation of memory T cells in body tissues (9–11) as well as gradual deterioration of innate leukocyte defense mechanisms (8, 12). In this review, we focus mainly on senescence-associated changes in the innate immune compartment, which mediates first line of defense against infections. Senescence impacts on several major mechanisms of innate protection against pathogens, including phagocytosis and ROS production by neutrophils, as well as toll-like receptor (TLR) expression and cytokine release by macrophages and dendritic cells. Key defects in innate cell activity associated with senescence have been reviewed elsewhere (8, 12, 13). These include a range of deficits in myeloid cell functions, which are governed primarily *via* PRR signaling and have been identified as displaying significant impairment in various senescence-related disorders.

Myeloid cell-derived biomarkers of immunosenescence reportedly include increased production of the cytokines interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α), which correlate with elevated serum levels of C-reactive protein to predict increased patient frailty and higher overall rates of mortality (14). IL-6 and TNF-α are produced mainly by tissue macrophages and T cells and have already been implicated in multiple age-related disorders including osteoarthritis, cardiovascular disease, autoimmunity, and neurodegeneration (15). Both IL-6 and TNF-α are able to increase telomerase activity through NF-κB, STAT1, and STAT2 activation (16). However, the mechanism by which these mediators of inflammation impact on the aging process remains poorly defined. For example, serum IL-6 levels have previously been identified as a predictive biomarker of mortality risk in the elderly (17, 18), but this cytokine has also been shown to exert anti-inflammatory effects in certain age-related pathologies including rheumatoid arthritis (19). Therefore, additional studies will be required to identify the molecular mediators involved so that these can be targeted by future therapeutic strategies.

Although immunosenescence occurs naturally as the human body ages, early activation of senescence pathways has been observed in a wide range of human disorders (20, 21). Immunosenescence is also associated with hematopoietic dysfunction, leading to a decline in leukocyte numbers and function across both the innate and adaptive arms of the immune system (22–24). These detrimental effects are typically associated with prolonged, low-grade infection or inflammation (25, 26) and/or persistent infection by pathogens including cytomegalovirus (27, 28). Previous studies have indicated that low-grade inflammation induced by genetic deletion of NF-κB subunit can confer telomere dysfunction (29) and that bone marrow-derived macrophages from aged mice exhibit short telomeres and impaired inflammatory signaling (30). It seems likely therefore that mechanisms of telomere maintenance impact on immune function and *vice versa*, in particular, *via* interactions with the enzyme telomerase. Indeed, emerging data indicate that telomerase likely exerts a range of additional functions that could significantly impact on hematopoiesis and mitochondrial ROS production during age-related immune decline.

"INFLAMMAGING"

Immunosenescence is strongly driven by persistent infections and/or tissue inflammation (1, 31), leading some investigators to term this process "inflammaging" to better distinguish pathological events from natural age-related decline (20, 21, 32). In some settings, inflammaging is a consequence of unresolved "sterile" inflammation resulting from organelle/molecule damage, inappropriate immune signaling, and autoantigen (33). Although inflammation is primarily maintained by secreted cytokines, as already reviewed elsewhere (34, 35), another important factor is damaged cell/tissue release of stimulatory molecules that can activate myeloid cells by signaling through PRRs such as TLRs. PRRs recognize specific pathogen-associated molecular patterns (PAMPs) as well as host-derived damage-associated molecular patterns (DAMPs) that are produced by stressed, malfunctioning, and injured cells. Several DAMPs released by damaged mitochondria (36, 37) and nuclei (38, 39) or derived from the cytoplasm (40, 41) have already been linked with inflammaging. Failure to resolve low-grade inflammation can result in both innate and adaptive immune responses to self-antigens, progressive tissue damage, and pathological cellular aging. Accordingly, sustained activation of PRR pathways has already been identified in a number of chronic inflammatory disorders associated with aging (**Table 1**), and changes in PRR expression and signaling are now widely recognized as critical components of immunosenescence (12,

TABLE 1 | Chronic inflammatory diseases with reported telomere shortening, changes in telomerase activity, and a role for PRRs.

Disease category	Pathology/disease type	PRRs associated with disease and cell types affected	Cell-specific telomere shortening	Telomerase activity
Cardiovascular diseases	Atherosclerosis	TLRs (42–45); Mo, MF, DC, MC, aortic tissue	Leukocytes (46)	MF, aortic tissue, ↗ (47, 48)
	Chronic heart failure	TLRs, NLRs (49); MF, heart tissue	Leukocytes (50)	ND
Pulmonary diseases	Chronic obstructive pulmonary disease	TLRs (51); Mo, MF, lung tissue	Leukocytes (52, 53)	ND
	Sarcoidosis	TLR2 (54); BAL	Leukocytes (55, 56)	ND
Hepatic diseases	Non-pathogenic hepatitis	TLRs (57–60); hepatocytes, biliary epithelia, sinusoidal endothelia, MF, Mo	Liver tissue (61)	ND
	Primitive biliary cirrhosis	TLRs (62), Mo	Bile duct (63)	ND
Gastrointestinal diseases	Ulcerative colitis	TLR4, TLR5 (64, 65); mucosa	Leukocytes, mucosa (66–69)	Mucosa, ↗ (70)
	Celiac disease	TLR2, TLR4 (71)	Leukocytes (72)	ND
Joint and muscle diseases	Idiopathic inflammatory myopathies	TLRs, NLRs (73), skeletal muscle, MF, DC	No significant shortening (74)	Skeletal muscle, ↗ (74)
	Rheumatoid arthritis	TLRs (75, 76), synovial tissue	Leukocytes, T cells (77, 78)	Synovial ts., ↗ (79, 80)
	Juvenile idiopathic arthritis	TLRs (81), Mo	Naïve T cells (82, 83)	ND
	Systemic sclerosis	TLRs (84–86), synovial tissue	No significant shortening (87)	PBMCs, ↘ (88)
Other autoimmune conditions	Systemic lupus erythematosus	TLR7, TLR9 (89–91), mesangial cells	Leukocytes (92)	PBMCs, T cells, ↗ (88, 93)
Infectious diseases (chronic infections)	*Helicobacter pylori*	TLR2, TLR4 (94–96), gastric mucosa, gastric epithelial cells	Gastric mucosa (97)	Gastric mucosa, ↗ (98)
	Hepatitis B	TLRs (99, 100), PBMC	Hepatocytes (101)	PBMCs, ↘ (102)
Alcohol, smoking, and obesity-related diseases	Alcohol consumption	TLR4, TLR2 (103, 104), Kupffer cells, lung epithelia	Eosophageal epithelium (105)	ND
	Smoking	TLR4 (103, 106), Lung epithelia	Leukocytes (107, 108)	↗ (109), lung epithelia
	Obesity	TLRs (110, 111), adipose tissue	Leukocytes (108)	ND

Chronic inflammation plays a major role in progression of various disorders and autoimmune pathologies. This table lists diseases in which shortening of telomeres, changes in telomerase activity, and a role for TLR signaling have been reported. Although direct interaction between these processes has yet to be formally demonstrated, these events have been closely correlated in a range of different disorders and putative mechanisms are now beginning to emerge. While short telomeres have frequently been associated with human disease, telomere length is not always correlated with disease severity.

Mo, monocyte; MF, macrophage; DC, dendritic cell; MC, mast cell; BAL, bronchoalveolar lavage; PBMCs, peripheral blood mononuclear cells; PRR, pattern recognition receptor.

24). Inflammation-induced immune aging in host tissues is therefore a consequence of multiple detrimental pathways acting in concert over a prolonged period of time.

HEMATOPOIETIC STEM CELL EXHAUSTION IN CHRONIC INFLAMMATION

Natural age-associated changes in innate immune function have already been described in adults older than 40 years (112), whereas early-onset immunosenescence has been associated with various pathologies. Changes in TLR expression and function likely represent key components of both healthy and pathological immune aging (113). In particular, various types of hematopoietic progenitors have been shown to express TLRs (114, 115), which may play direct roles in senescence of the progenitor pool (113, 115). Steady-state differentiation of hematopoietic stem and progenitor cells (HSPCs) into myeloid lineage cells is controlled by growth factors including G-CSF, M-CSF, GM-CSF, and Flt3-L, but can be modified by pro-inflammatory cytokines such as IFN-γ during an immune response (116, 117). Chronic inflammation can also generate massive quantities of DAMPs including calgranulins (S100A8/9), high mobility group box-1 (HMGB1), and serum amyloid A, which can engage PRRs expressed by multiple cell types. Direct TLR stimulation of HSPCs in the bone marrow and circulation may therefore accelerate the immune aging process (113, 118).

Direct roles for HSPCs in inflammation have only recently been described by Griseri et al. who identified progenitor cell infiltration of the gut mucosa in experimental colitis (119). Most studies of PRR function in HSPCs have focused on the small number of cells that circulate in peripheral blood, where these progenitors can detect PRR ligands and enhance extramedullary hematopoiesis during inflammation (118, 119). HSPC stimulation with TLR ligands can potently modulate differentiation pathways and typically favors myeloid cell development (114, 115, 120), but prolonged TLR triggering eventually leads to progenitor exhaustion and loss of self-renewal capacity (121–123). Bone marrow HSPCs can also mediate "emergency hematopoiesis" in response to PRR ligation of DAMPs and PAMPs (114, 124), particularly in the context of bacterial infection (125, 126) or fungal invasion (127, 128). However, inflammatory modulation of hematopoietic activity is not restricted to the blood and bone marrow, since somatic cells and tissues also appear to influence this process (129, 130). It is also important to note that PRR signaling in HSPCs can play a role in cell reconstitution even under resting conditions, since TLR4/TRIF reportedly mediates

the steady-state renewal of granulocytes (131). Taken together, these data indicate that inflammation can induce PRR signaling in HSPCs and accelerate/modify cellular differentiation to promote progenitor exhaustion and immune system dysfunction, both of which are important hallmarks of immunosenescence. To what extent stem cell telomeres and telomerase are involved in these events remains unclear, although HSPC skewing toward generation of myeloid-lineage cells has previously been linked with telomere dysfunction (132), and experimental mice lacking the telomerase subunits telomerase reverse transcriptase (TERT) or telomerase RNA component (TERC) exhibit increased myeloid progenitor cell numbers in bone marrow (133).

Formal demonstration of a direct influence of PRRs/inflammation on telomere length/telomerase activity in host leukocytes and stem cells is currently lacking, but experimental data consistent with this concept are continuing to accumulate. Indeed, age-related DNA damage and shortened telomeres have been observed in murine HSCs (134), and senescent progenitor cells with shortened telomeres exhibit increased activity of the pro-inflammatory transcription factor NF-κB (135). TERC-deficient mice also exhibit chromosome instability that enhances signaling through TLR4/NF-κB, leading to increased macrophage expression of pro-inflammatory cytokines and high susceptibility to endotoxin shock (136). These and other influences of PRR signaling on accumulation of DNA damage in host cells have been expertly reviewed elsewhere (137). It seems likely therefore that direct crosstalk between PRRs and telomerase activity will also prove critical to the immunosenescence process in humans. This could have major implications for the design of therapies to maintain effective host immunity in elderly patients and treat various inflammatory disorders. Indeed, immune aging has already been identified as a major determinant of bone marrow progenitor quality and functionality during transplantation (138). Inflammatory DAMP generation and PRR triggering of HSPCs have also been reported to increase pathology in disorders including atherosclerosis (42, 43, 139), colitis (119), and chronic dermatitis (140). Further detrimental effects of inflammation on HSPCs have been observed in models of chronic PRR triggering (117, 126, 141) as well as in human sepsis (142), while age-related change in hematopoietic function have also been shown to confer increased risk of anemic and malignant disorders (143). PRR-driven signaling has now been observed to correlate with altered telomere length or telomerase activity in numerous cell types and tissues from patients with chronic inflammatory disorders (**Table 1**), but the mechanistic basis of this link has not yet been defined. Despite their disparate origins and diverse pathological features, these diseases share common features of oxidative stress and inflammation together with telomere shortening, suggesting tight associations between inflammatory disorders and cellular senescence across a range of clinical settings.

MITOCHONDRIAL DAMAGE IN INFLAMMAGING

Mitochondrial ROS production is a key antimicrobial function of specialized immune cells including macrophages, dendritic cells, and neutrophils. Accordingly, age-related impairment of mitochondrial function can significantly impair host immune responses (144). Increasing age is typically accompanied by decreased mitochondrial output of antimicrobial ROS together with a parallel increase in oxidative stress. While a role for mitochondrial dysfunction in immunosenescence is now well established, the basis of this association may be more complex than initially thought. Recent reports have indicated that DNA release from damaged mitochondria is a major driver of ROS production and inflammation (145, 146) and may therefore promote host immunosenescence *via* a range of different mechanisms (147). ROS accumulation also promotes further mitochondrial dysfunction, oxidative stress, and release of DNA into the cytosol where this can activate the NLRP3 inflammasome (146). While neutrophils exhibit only a short half-life in blood and typically lack TERT expression or telomerase activity (148), during inflammation these cells are a major source of ROS and can reportedly acquire telomerase activity on infiltration of unstable coronary plaques (149). Further studies will now be required to resolve the exact role of cytoplasmic TERT expression in neutrophils that lack TERC (150) and to determine the contribution of these cells to immunosenescent pathology.

Reactive oxygen species have also been strongly implicated in pathological changes in blood vessel structure and function that characterize age-related vascular diseases such as atherosclerosis (151). In this context, Jurk et al. used a genetic model of chronic low-grade inflammation to demonstrate that ROS exacerbate telomere dysfunction (29). It now seems that oxidative stress, mitochondrial damage, and cellular aging are intimately linked in multiple species including yeast (152) and trypanosomes (153), although additional data from animal models and validation in human studies will be required to fully understand this.

INFLAMMAGING, TELOMERASE ACTIVITY, AND TELOMERE LENGTH

Telomere shortening during cell division is a critical process in progression to senescence (154), and telomerase may play an important role in immunological aging. Overexpression of telomerase subunit TERT can decrease oxidative stress in cancer cell lines (155), whereas TERT-deficient HSCs are characterized by ROS impairment and functional defects (156). Similarly, chromosome instability arising from TERC deficiency promotes TLR4 stimulation (136), while telomeric repeats (TTAGGG) can inhibit CpG binding to TLR9 to impair innate immune activation (157). Telomerase activity also appears to be subject to modulation by the activity of NF-κB (29) and/or exposure to pro-inflammatory cytokines (16, 158, 159) as summarized in **Figure 1**. However, it is important to note that telomerase expression level and enzymatic activity do not always directly correlate with senescent status or even telomere length; hence, further studies will be needed to better understand these complex interactions in human cells and tissues.

Even in the absence of NF-κB signaling, prolonged low-grade inflammation is sufficient to induce telomere dysfunction, likely involving accumulation of mitochondrial ROS (29). TERT can

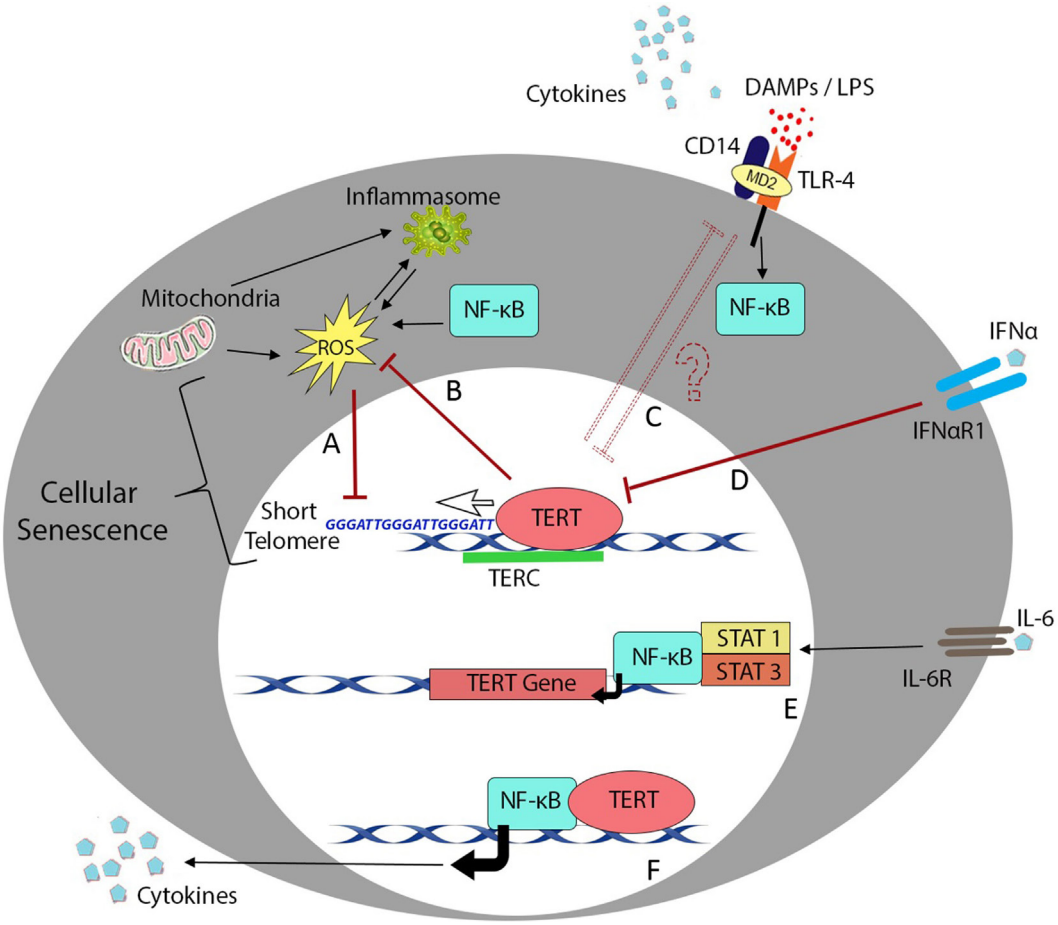

FIGURE 1 | Telomere length and telomerase activity during inflammation. Overview of the major cellular processes linking the telomere complex with inflammatory signaling and immunosenescence. Transcription factor NF-κB plays a crucial role in most inflammatory processes but also interacts with telomere control machinery and putative non-telomeric functions of the telomerase enzyme. **(A)** Low-grade inflammation in nfkb1$^{-/-}$ mice causes increased ROS production and results in telomere dysfunction in mouse hepatocytes and intestinal crypt stem cells (29). **(B)** One of the reported non-telomeric functions of human telomerase enzyme (TERT) is the ability to inhibit endogenous ROS production and regulate oxidative stress in cancer cell lines (155). **(C)** Mice lacking telomerase RNA component (TERC) succumb to LPS administration due to endotoxin shock arising from chromosome instability in splenocytes and macrophages (136). **(D)** Signaling downstream of inflammatory cytokines such as IFN-α plays an important role in downregulation of TERT activity in hematopoietic cells (159). **(E)** In contrast, interleukin (IL)-6 and tumor necrosis factor (TNF)-α reportedly upregulate TERT transcription and telomerase activity through activation and binding of NF-κB in macrophages (47) or NF-κB, STAT1, and STAT3 interactions with the TERT promoter in splenocytes and cancer cells (16, 158). **(F)** Ghosh et al. have also described the ability of TERT to directly regulate NF-κB-dependent gene expression in primary bone marrow blasts from leukemic patients (160).

integrate numerous upstream signals including Wnt/β-catenin developmental cues (161) and can regulate inflammatory signaling through binding to NF-κB promoters and subsequent transcription of NF-κB-regulated genes including IL-6 and TNF-α (160). This crosstalk is exemplified by an alcoholic liver disease model in which NF-κB was observed to regulate protein expression levels of the catalytic subunit TERT (158), which in turn modulated NF-κB signaling to promote macrophage polarization toward an inflammatory M1 phenotype with increased expression of IL-6 and TNF-α (162). Increased peripheral blood expression levels of IL-6 and TNF-α in patients with metabolic disorders have also been shown to correlate with elevated levels of telomerase activity (163).

The central role of NF-κB in regulating chronic, low-grade inflammation has long been established, but only recently have experimental data begun to indicate a possible role for NF-κB in control of telomerase expression or activity in the context of senescence-associated disorders. For example, Gizard et al. showed that inflammation-induced NF-κB activation regulates TERT expression in macrophages and that human atherosclerotic lesions are characterized by high expression of TERT (47). Disease-associated changes in PRR signaling and telomere biology have also been identified within individual cells or host tissues, including the inflamed gut mucosa in ulcerative colitis (64–70), synovial tissues in rheumatoid arthritis (75, 76, 79, 80), and smoke-exposed lung epithelia (103, 106, 109). However, these features have often been described across multiple separate reports; hence, definitive proof of functional links between these processes is still lacking. Indeed, while short telomeres in leukocytes have been identified as a key component

of pathological immune aging (5, 6, 164), direct associations with human senescence have not yet been confirmed, and the majority of relevant mechanistic data have been generated exclusively in mouse models. This is a particular challenge given that mouse telomeres can be up to 10 times longer than their equivalent human sequences despite a much shorter animal lifespan (165). Nonetheless, substantial data have now been obtained using genetically engineered TERC/TERT-knockout mice, which replicate features of human telomere biology as observed in various inflammatory disorders. It will now be critical to perform additional studies of telomere biology/telomerase activity in human leukocytes during natural aging and inflammation before this axis can be exploited for therapeutic benefit in the clinic.

CONCLUSION

Immunosenescence is the culmination of a complex network of molecular processes. Despite intensive study over the last decade and improved understanding of the features of immunological aging, the molecular mediators of these events and the extent to which they interact remain poorly defined. Indeed, while the strong association of telomere length with cellular senescence has been known for decades, the direct/indirect relationship between telomerase activity and PRR signaling is only now coming to light. While the molecular basis of PRR interactions with telomerase activity has not yet been determined, better definition of this crosstalk will be essential to understanding the influence of PRRs and "inflammaging" on human hematopoiesis and tissue regeneration. The recently identified ability of stem cells to directly detect DAMPs and PAMPs *via* PRRs should lead to significant progress in developing methods of combating immunosenescence in a range of human pathologies. Together, these data underscore the importance of inflammaging as a major driver of senescence progression and reinforce the concept that an array of different pathways likely interact to determine the rate of this process (graphically represented in **Figure 1**). Recent analyses of complex data sets from large cohorts of elderly subjects and patients with various chronic disorders have already implicated key regulators of immunosenescence in determining clinical outcomes. However, a complete understanding of the molecular mechanisms at play will require more sophisticated animal models and validation in human studies before these can be effectively targeted for therapy in common diseases of aging and inflammation.

AUTHOR CONTRIBUTIONS

SSJ prepared the figure and wrote the manuscript, KB wrote the manuscript and prepared the table, TK and ZK advised clinical research interpretations, and JF conceptualized, wrote, and critically reviewed the manuscript.

ACKNOWLEDGMENTS

We wish to thank Dr. Neil McCarthy of Insight Editing London for critical review of the manuscript. Authors (JF, KB) were supported by European Social Fund and European Regional Development Fund—Project MAGNET (No. CZ.02.1.01/0.0/0.0/15_003/0000492) and TK, ZK by Ministry of Health of the Czech Republic, grant no. 17-31141A. All rights reserved. SSJ is a recipient of Masaryk University Faculty of Medicine Stipend for Doctoral studies.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.