SUPPLEMENTARY DATA

Inflammaging: From Mechanisms to Clinical Implications and Targeted Interventions

Rola S. Zeidan, Aditya S. Shirali, Simon Reinhard, Anna Picca, Patricia Vial, Lisiane Pruinelli, Joe G.N. Garcia, Christian Leeuwenburgh, Stephen Anton

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Appendix 1 – Evidence of the role of inflammaging in cancer, metabolic disorders and liver diseases.

A- Cancer:

Impaired immune surveillance is associated with a tumor-promoting microenvironment that supports cancer initiation and progression [218]. A key driver of this process is the accumulation of senescent stromal cells that secrete pro-inflammatory components of SASP, which recruit immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T-cells, which inhibit effector T cell infiltration and proliferation, weakening anti-tumor immunity [219]. Elevated levels of SASP-associated cytokines like IL-6 and DAMPs, such as eNAMPT, have been linked to poor prognosis in several cancers [220]. In breast cancer, high circulating IL-6 levels and specific IL-6 gene polymorphisms are associated with increased risk and worse outcomes [221]. Similarly, in non-small cell lung adenocarcinoma, high expression of the SASP-related chemokine receptor CXCR2 correlates with poor prognosis and increased metastatic potential [222]. SASP also promotes tumor progression by facilitating epithelial-to-mesenchymal transition (EMT), a process that enhances local invasion and metastasis [223]. In melanoma and pancreatic cancer mouse models, Wnt-related SASP factors and IL-8, respectively, have been shown to drive these malignant transitions [224]. Single-cell RNA sequencing in human papillary thyroid carcinoma further supports these findings, revealing that SASP-related CXCL12-CXCR4 signaling enhances tumor cell survival and lymphatic invasion [225]. Elevated eNAMPT levels are observed and correlate with disease severity in breast and prostate cancer, suggesting eNAMPT is a potential biomarker, as well as a possible therapeutic target, for these cancers [226]. MicroRNAs also play a role in regulating tumor-promoting inflammation by enhancing pro-inflammatory cytokine release and suppressing anti-inflammatory signaling [227, 228]. Taken together, the accumulation of SASP stromal elements creates a tumor-permissive environment in older adults, allowing enhanced local invasion and metastasis. Emerging therapies targeting DAMPs, such as eNAMPT [229], or senescent cells, such as senolytic therapies including navitoclax, D+Q, piperlongumine, and fisetin, have shown promise in preclinical cancer models by selectively eliminating senescent malignant cells [230]. However, their clinical application remains limited by challenges in selectively targeting harmful versus beneficial senescent cells, potential toxicities, and the emergence of resistance.

B- Metabolic Disorders: Obesity and Diabetes:

It has also become increasingly evident that age-associated systemic low-grade inflammation in adipose tissue elevates the risk of obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) [231]. Age-induced adipose tissue dysfunction is characterized by a proinflammatory state of enhanced expression of cytokines and chemotactic compounds, such as IL-6, IL-1, TNF-α and CCL2, as well as high immune cell infiltration [232, 233]. This pro-inflammatory environment contributes to systemic metabolic dysregulation and impaired insulin sensitivity. Studies in mouse models of diet-induced obesity revealed that adipose-derived senescent cells can directly promote insulin resistance through the release of SASP factors including activin A, IL-6, and TNF [234, 235]. Critically though, it is important to distinguish diet-induced obesity from age-related changes in body composition, as aging is characterized by visceral fat redistribution and muscle loss even in the absence of excess caloric intake. Both aging and obesity are associated with an increased burden of senescent adipocytes (and adipocyte progenitors), which further perpetuate metabolic dysfunction through inflammatory signaling. These age-driven alterations in adipose tissue biology are mechanistically distinct from overnutrition-induced obesity and contribute differently to systemic inflammation.

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Clinical studies have demonstrated elevated circulating levels of inflammatory markers in individuals with T2DM. As such, patients with T2DM have increased circulating levels of several key proinflammatory cytokines, such as CRP, ICAM-1 and E-selectin, compared with non-diabetic individuals [236]. In a prospective cohort of over 1,300 patients with T2DM, elevated high-sensitivity CRP was strongly associated with increased risk of microvascular complications including neuropathy, retinopathy, and nephropathy [237]. These findings support a central role for SASP-producing senescent adipocytes in the pathogenesis of both obesity and T2DM across the lifespan. Notably, while type 2 diabetes becomes more prevalent with advancing age, it is not exclusively age-related, as most cases begin in midlife and progress into older adulthood. Thus, inflammaging may exacerbate metabolic dysfunction in T2DM, but it does not account for the initial onset of disease.

C- Liver Disease:

The accumulation of senescent hepatocytes has been implicated in the development and progression of non-alcoholic fatty liver disease (NAFLD), advancing to non-alcoholic steatohepatitis (NASH) and ultimately hepatocellular carcinoma (HCC) [238]. In early-stage NAFLD, it has been shown that steatosis promotes telomere shortening and DNA damage, inducing hepatocyte senescence [239]. As liver disease progresses, senescent hepatocytes begin secreting proinflammatory SASP factors that exacerbate tissue injury and fibrosis. In a p53-deficient mouse model of steatohepatitis, senescent hepatocytes activated hepatic stellate cells, which in turn induced progressive liver fibrosis [240]. Supporting this mechanism, human studies have shown that patients with NAFLD who progressed to NASH exhibited elevated hepatic expression of senescence markers p53 and p21 [241, 242]. The role of inflammaging becomes more pronounced in advanced liver disease, particularly in NASH-associated HCC. Patients with NASH-related HCC display increased expression of cyclooxygenase-2 (COX2), a key upstream regulator of IL-6 and IL-8, both SASP-associated cytokines linked to tumor-promoting inflammation [243]. Additionally, senescent cholangiocytes (biliary tract cells) can propagate hepatocyte senescence through the paracrine action of TGF-β, a cytokine known to mediate liver fibrosis and carcinogenesis [244]. Several studies have examined the potential role of cellular senescence in NAFLD, and the SASP component eNAMPT was shown to be elevated in individuals with NASH and a major target for ameliorating hepatic fibrosis [245]. Nevertheless, there is a paucity of data on the contribution of inflammaging and SASP-associated elements to the development and progression of liver disease and the use of senolytic therapies in the treatment of NAFLD, NASH, or HCC, highlighting a notable gap in clinical research assessing their therapeutic potential.

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Supplementary Table 1. Organ-specific features of inflammaging across age-related diseases.

Organ System / Disease	Dominant Inflammaging Drivers	Key Immune / Cellular Players	Representative Biomarkers	Disease-Specific Pathophysiologic Consequences
Skeletal Muscle (Sarcopenia)[58,132,135-141]	Chronic low-grade cytokine signaling; senescent myocytes; mitochondrial dysfunction	Senescent myofibers, macrophages, satellite cells	IL-6, TNF-α, CRP, activin A, ICAM-1, VEGFA	Muscle protein catabolism, impaired regeneration, mitochondrial and proteostatic dysfunction
Central Nervous System (Neurodegeneration)[142-148]	Sterile neuroinflammation; cellular senescence; Blood-brain barrier disruption	Senescent microglia, astrocytes, pericytes	IL-6, IL-1β, TNF-α, GFAP, Tau, SASP proteins	Impaired Aβ clearance, synaptic loss, neuronal death, cognitive decline
Cardiovascular System[26,132,153-158]	Vascular senescence; plaque-associated inflammation; endothelial dysfunction	Senescent endothelial cells, smooth muscle cells, macrophages	IL-6, TNF-α, IL-1β, eNAMPT, MMPs	Plaque instability, vascular remodeling, myocardial dysfunction, heart failure
Cancer (Tumor Microenvironment)[208-221]	SASP-driven immune suppression; chronic inflammatory niche	Senescent stromal cells, MDSCs, Tregs	IL-6, IL-8, CXCL12, CXCR2, eNAMPT	EMT, immune evasion, tumor invasion and metastasis
Metabolic Disorders[222-228]	Adipose inflammaging; senescent adipocytes; immune infiltration	Senescent adipocytes/ progenitors, macrophages, T cells	IL-6, TNF-α, CRP, ICAM-1, E-selectin	Insulin resistance, metabolic inflexibility, progression of type-2 diabetes.
Liver (NAFLD/NASH/HCC)[229-236]	Hepatocyte senescence; stellate cell activation; fibrosis-associated inflammation	Senescent hepatocytes, stellate cells, cholangiocytes	IL-6, IL-8, COX-2, p53, p21, eNAMPT	Fibrosis progression, cirrhosis, tumor-promoting inflammatory milieu