Inflammaging, an Imbalanced Immune Response

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Nowadays, new advances in society and health have brought an increased life expectancy. However, at the same time, aging comes with complications that impact the development of autoimmunity, neurodegenerative diseases and cancer. These complications affect the quality of life and impact the public health system. Specifically, with aging, a low-grade chronic sterile systemic inflammation with self-reactivity in the absence of acute infection occurs termed inflammaging. Inflammaging is related to an imbalanced immune response that can be either naturally acquired with aging or accelerated due to external triggers. Different molecules, metabolites and inflammatory forms of cell death are highly involved in these processes. Importantly, adoptive cellular immunotherapy is a modality of treatment for cancer patients that administers ex vivo expanded immune cells in the patient. The manipulation of these cells confers them enhanced proinflammatory properties. A general consequence of proinflammatory events is the development of autoimmune diseases and cancer.

inflammaging immunosenescence SASP immunotherapy T cells NK cells

1. Introduction: Immunosenescence and Inflammation during Aging, and its Consequences in Cancer and Other Age-Related Diseases

Nowadays, the elderly population (>65-year-old) in Europe represents 19.7% of the population. This number is predicted to continue increasing and reach 28.5% in 2050 [1]. With that in mind, those numbers will impact social life and public healthcare. Thus, a new discipline termed “Geroscience” has emerged to decipher the link between mechanisms of aging and susceptibility to age-related diseases [2][3].

Biologically, aging is associated with a physiological process of tissue degeneration related to chronic inflammation [4]. This age-related chronic inflammation is highly associated with inflammaging, which was initially defined as a progressive increase of proinflammation in aged organisms [5], leading to increased morbidity and mortality [6]. Currently, inflammaging is defined as the elevated low-grade chronic sterile systemic inflammation with self-reactivity in the elderly in the absence of acute infection [7].

“Immunosenescence”, a process associated with aging that impairs the immune function, is highly responsible for inflammaging. Different age-associated events cause immunosenescence. Specifically, during aging, occurs a thymic involution that reduces the pool of naïve T cells and amplifies the oligo-clonal expansion of memory T cells. These events will cause a reduced immune repertoire diversity [8], leading to reduced ability to fight infections and

increased cancer incidence [9]. Thymic involution also leads to an amplified release of self-reactive T cells and reduced capacity of T-regulatory (reg) cells to suppress these self-reactive T cells and preserve immune homeostasis. Consequently, these events will enhance tissue damage with autoimmunity and chronic inflammation, being essential contributors to inflammaging [7][10].

Immunosenescence also occurs in the BM, which constitutes the primary site of hematopoiesis [11]. Thus, aging causes both a gradual replacement of the different cellular components of the BM by adipocytes and a skew towards the generation of myeloid cells [12]. These changes negatively impact the repertoire and activity of T and B lymphocytes [13]. Moreover, this cellular degeneration in the BM will increase the production of proinflammatory cytokines [12][14][15], impacting the activity of immune cells.

The innate immune system is also impacted by immunosenescence. Thus, neutrophil and macrophage capacity for phagocytosis and subsequent elimination of dead cells is reduced with aging [16][17]. Macrophages also acquire an increased polarization towards M2 cells [18], and natural killer (NK) cells present a reduced capacity to secrete cytotoxic molecules [19].

Overall, immunosenescent cells will not be able to remove senescent somatic cells that also accumulate with aging [20][21][22][23][24] and are characterized by secretion of proinflammatory molecules known as senescence-associated secretory phenotype (SASP) [25]. The SASP is another crucial contributor to inflammaging [7][25]. This accumulation of senescent cells will enhance the SASP promoting further inflammaging and accelerated aging [22] and will contribute to cancer development [7][25][26]. Furthermore, the SASP transmits cellular senescence to neighboring non-senescent cells [27][28], leading to enhanced senescence and inflammaging.The SASP is also increased with anti-cancer therapies that induce senescence in both immune and tumor cells, leading to enhanced inflammation and treatment resistance [29][30].

Moreover, microbes debris of exogenous origin and cell debris of endogenous origin are recognized through the pathogen-associated molecular pattern (PAMPs) and damage-associated molecular patterns (DAMPs), respectively [31], the latter being part of the SASP [32]. PAMPs and DAMPs become more abundant during aging, and PAMP stimulation induces DAMP secretion by immune cells [33], leading to enhanced inflammaging.

This feedback occurring between immunosenescence and inflammaging explains the involvement of both processes in age-related diseases, including cancer, neurodegenerative diseases, metabolic diseases and cardiovascular diseases [7] (see **Table 1**). For instance, Alzheimer's disease is a chronic neurodegenerative disease with pathological accumulation of amyloid-beta (Aβ) peptides and neurofibrillary tangles containing tau protein. Aβ and tau deposition cause an age-dependent deterioration of the blood-brain barrier that leads to the infiltration of immune cells into the central nervous system exacerbating the neurodegenerative process and promoting inflammatory responses [33]. Type-2 diabetes is a multifactorial metabolic disease with chronic hyperglycemia and dyslipidemia as main pathological features. A chronic low-grade inflammation resembling inflammaging induces insulin resistance and dysfunction of β-cells, emerging as a relevant factor contributing to the development of diabetes [34].

Table 1. Side effects of inflammaging.

Age-Related Diseases	Mediators	References
Atherosclerosis	Secretion of IL1β, IL18 and IL6 among others	[7][35]
Cardiovascular diseases	CRP and IL6 in blood	[7]
Frailty, Sarcopenia	Inflammatory markers in blood, IL6	[36]
Decline of innate and adaptive immune system	Immunosenescence	[8][9]
Type 2 diabetes	Secretion of IL1β among others	[34][37][38]
Cancer	CRP, IL6, immunosenescence	[7][25][26][39][40][41][42]
Osteoporosis, bone remodeling	IL1, IL6, TNFα	[43]
Neurodegenerative disease	Immune cells infiltration	[33]

In cancer, aging and chronic inflammation are highly involved in its development [39][40]. However, the intricate relationship between aging and cancer is not clear. In detail, half of the cancers occur in individuals older than 70. Yet, whereas aging and cancer share disease mechanisms, such as genomic instability, they also present opposite features, such as hypoactive cells in aging vs. hyperactive cells in cancer [40].The role of chronic inflammation in cancer is also controversial. Thus, inflammation is required initially for immune surveillance; however, failure to resolve inflammation will promote tumor growth [44][45]. The relevant impact of chronic inflammation in cancer is suggested by different studies that estimate that 15–20% of cancers are inflammation-related [46].

For instance, autoimmune diseases such asinflammatory bowel disease (IBD) increase the risk of developing colorectal cancer [47]. Moreover, numerous studies have revealed associations of high levels of inflammatory markers, such as C-reactive protein (CRP) [41] and IL6 [42], with an increased risk of developing different types of cancer.

The relevant role of chronic inflammation in cancer and of the immune response in the development of inflammaging should be considered incancer patients treated with adoptive cellular immunotherapy. These treatments administer various immune cells in patients, such as chimeric antigen receptor (CAR)-T cells [48], tumor-infiltrating lymphocyte (TIL) [49] or NK cells [50] which previously have been modified and expanded in vitro. The in vitro expansion changes the phenotype of immune cells and their cytotoxic mechanisms that activate inflammatory forms of cell death [50][51][52][53]. For instance, after encountering tumor cells, CAR-T cells [53] and NK cells [41] initiate pyroptosis, an inflammatory form of cell death. Pyroptosis was initially described as a type of cell death triggered by the innate immune system after recognition of intracellular pathogens by intracellular receptors. Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and among them NLRP3, belong to these receptors. They initiate the assembly of inflammasomes that will activate caspase-1 leading to release of IL1β and

IL18 and the pore-forming protein gasdermin-D (GSDMD) the latter inducing pyroptosis [54]. Of interest, in CAR-T cellimmunotherapy, NLRP3 activates pyroptosis with release of DAMPs, IL1β and IL6 [53]. In addition, immune cells after encountering tumor cells release different types of Granzymes (Gzm). Besides the classic GzmB, other inflammatory Gzm, such as GzmA and GzmK, are involved in the anti-tumor activity of immune cells [55][56].

These relevant associations of inflammaging with an inadequate immune response and the development of inflammatory diseases and cancer, added to the fact that cancer associates with aging suggest their relevance in the field of cellular immunotherapy. Here, we will review the contribution to inflammaging of different subsets of T cells and NK cells, as they are administered in cancer patients, either unmodified or modified with a CAR [51][57][58]. Moreover, the role of NLRP3 and inflammatory granzymes, activated during the innate and adaptive immune response, will be presented, focusing on their impact on inflammation. Other intrinsic and external inflammation triggers related to cancer will be mentioned, and some preclinical models that associate inflammation with cancer development will be cited.

2. Variation of T-reg Cells and Th17 Cells during Aging and Their Impact on the Development of Inflammaging

Human centenarians represent a model with low inflammaging to study healthy aging. Of interest, although those human centenarians present a systemic inflammatory state (e.g., high levels of IL6 and IL8 in plasma), they also count on efficient anti-inflammatory networks termed anti-inflammaging that compensate for inflammaging [59]. Analyses of the immune cell populations in centenarians have concluded that longer survivors present higher leucocytes with a higher number of naïve, activated/memory and effector/memory CD4 and CD8 T cells [60]. Proteomic studies in centenarians also show a pattern with less inflammaging and autoimmunity, increased B cell-mediated immune response, higher expression of proteins involved in angiogenesis and enhanced intercellular junctions [61].On the other side, elderly cancer patients, such as multiple myeloma (MM), present immunosenescent T cells with deficient immune responses [62] that will increase inflammaging.

Among the different subsets of T lymphocytes, we will focus on T-reg and Th17 cells that share a common precursor and present opposing roles in developing inflammaging. Thus, Th17 cells cause autoimmunity and inflammation, and T-reg cells inhibit their activity [63]. Specifically, during aging, there is an increased production of Th17 cells that will contribute to inflammaging [64] and a decrease in the functionality of T-reg cells that will increase chronic inflammation [65]. Even though Th17 cells are very well-known for their role in inflammation and autoimmunity, their role in cancer is less understood. Notably, an intricate balance between T-regs and Th17 cells must be maintained to avoid developing these pathologies [64][66][67].

2.1. Changes in the T-reg Cell Compartment during Aging and Impact in Inflammation and Cancer

The impact of T-reg cells during aging should be analyzed considering the variation in numbers and their functionality. As previously mentioned, thymic involution with aging reduces the capacity of T-reg cells to suppress

self-reactive T cells and preserve immune homeostasis [7][10]. Two different origins have been described for T-reg cells. The first one is the thymus, at the early stages of life, which gives rise to naturally occurring T-reg (nT-reg) cells after escaping from the negative selection in the thymus, followed by appropriate TCR stimulation. The second one is in the peripheral blood (PB) and secondary lymphoid organs, where different triggers induce the expression of Foxp3 in naïve T cells, originating inducible T-reg (iT-reg) cells. iT-reg cells have a similar phenotype and suppressive function to nT-regs [68]. Data suggest that aging induces a decline in iT-regs and an increase in the number of nT-reg cells [69].

Regarding the functionality, it remains controversial whether aging induces a loss of T-reg functionality or just an effect of the variation in the number of T-reg cells [69]. Studies in aged mice have observed an increased proportion of functional CD4 T-regs in PB and lymphoid tissues, decreasing the effector T cell responses against *Leishmania* infection [70]. In humans, there is also an increase in the number of CD4 T-regs in PB with immunosuppressive properties [71]. In addition, the increased number of T-reg cells with aging can be explained by the polarization of CD4 conventional T cells to cells with T-reg cell properties, an event observed in aged mice [72]. Moreover, CD8 T-reg cells are a relevant immunosuppressive cell population [73], increasing with aging in absolute numbers in PB, the spleen and lymph nodes presenting functionality [74][75].

Various studies have associated the functionality of T-regs with the progression of different tumors due to their immunosuppressive activity [76][77]. Thus, in melanoma and colon carcinoma models, intratumoral T-reg cells inhibit the anti-tumor activity of TILs [78]. In these models, T-reg cells can adapt to the lactic acid-enriched TME through CD36 up-regulation that enhances their mitochondrial fitness [78]. In MM, where most patients represent an elderly cancer population, elevated frequencies of functional T-reg cells are present in newly diagnosed and relapsed patients compared to healthy volunteers [79].

On the other side, autoimmunity and chronic low-grade inflammation, both hallmarks of inflammaging [80], are also recognized as drivers of cancer [39][46]. In this scenario, murine models of autoimmunity have shown the beneficial impact of T-reg cells ameliorating inflammation. For instance, in models of multiple sclerosis, T-reg cells produce CCL1 that upregulates its receptor, CCR8, and induces the expression of CD39, granzyme B and IL10, which suppress the disease [81]. In autoimmune colitis, aged T-reg cells present equal suppressive in vitro activity than young T-regs to mitigate the disease. In these models, aged T-reg cells were able to restrain IFN-γ T cell responses. Even though, they controlled Th17 cells only in cases of acute inflammation and not in cases of chronic inflammation, leading to autoimmunity and promoting colitis [82]. T-reg cells also present contradictory roles in inflammation. Thus, IBD is another autoimmune disease that increases the risk of developing colorectal cancer [47]. In this scenario, different murine models have demonstrated the protective role of T-reg cells in IBD development through the suppression of T effector cells. In detail, IL35 secretion by T-reg cells suppresses the proliferation of effector T cells. However, on the other side, IL35 overexpression associates with the induction of gastrointestinal cancer [83][84].

Another relevant model that contradicts the relationship of chronic inflammation mediated by T lymphocytes and cancer and where T-reg cells are involved is the graft versus host disease (GVHD). Chronic GVHD (cGVHD) is a

relevant complication after allogeneic stem cell transplantation (allo-SCT) mediated by donor's T lymphocytes that enhances mortality due to a chronic inflammatory response and at the same time reduces the risk of cancer relapse [85]. T-reg cells associate with reduced development of GVHD [86]. Of interest, pediatric allo-SCT recipients have a lower incidence of cGvHD than adults [87], which might reflect in this context the beneficial impact of lower immunosenescence levels in pediatric patients compared to adult patients. Indeed, it has been observed that cGVHD-derived T-cells present high expression of genes that positively regulate cellular senescence (*CDKN2A*, *SERPINB9*, *LYPLA1* and *CKTM1A/B*) [88].

To summarize, two opposite scenarios,"enhanced immunosuppression and chronic inflammation", associate with cancer, and T-reg cells play either a detrimental or beneficial role in both systems. These findings bring the question of the exact contribution of T-reg cells in the regulation of inflammation and cancer development, specifically in the elderly.

2.2. Th17 Compartment and Its Delicate Balance with T-reg Cells

Th17 cells are critical players in maintaining mucosal immune homeostasis and protection against pathogens. They are also very well-known for their role in inflammation and autoimmunity. An intricate balance between T-regs and Th17 cells is maintained to avoid developing these pathologies [66][67]. A common precursor for T-reg cells and Th17 cells will differentiate into one cell subtype depending on the cytokine environment [67]. In detail, TGFβ is required for differentiation from naïve CD4 T cells to both Th17 and iTreg. Thus, TGFβ upregulates the retinoic acid-related orphan receptors-γt (RORγt) and Foxp3, which give rise to a common precursor of T-regs and Th17 cells. In the presence of TGF-β, both IL6 and IL21 induce differentiation to Th17 cells. Otherwise, T cells will differentiate to T-reg cells. Moreover, Foxp3 inhibits Th17 development through binding to RORγt. Without IL6, TGFβ reinforces this inhibition and favors the formation of T-reg cells. In addition, Th17 and T-reg cells can also polarize to each other [67].

The role of T-reg cells in maintaining the number of Th17 cells has been observed in different contexts. For instance, intestinal T-reg cells constrain microbiota-dependent IL-17-production by Th17 cells. This activity is dependent on the transcription factor c-Maf that controls IL10 production by T-reg cells [89]. In a murine model of neuroinflammation, imaging of T-reg and Th17 cells in the spinal cord demonstrated that T-regs suppress Th17 cells by inhibiting Ca^{2+} signaling and limiting the access of Th17 cells to APCs, avoiding neuroinflammation [90]. On the contrary, in hepatic carcinoma, increased Th17 levels are detected in the PB, correlating positively with metastasis progression and T-reg cells in the TME [91].

Altogether, T-reg and Th17 cells present opposite roles with an intricate regulation between them. Monitoring their changes in elderly cancer patients and patients receiving adoptive cellular immunotherapy will provide relevant information in this field.

2.3. Changes in the Th17 Compartment during Aging and Implications for Autoimmunity and Cancer

Aging causes an increased Th17/T-reg ratio that contributes to inflammaging [92]. Indeed, older subjects present higher Th17 cytokine production than younger subjects. One of the causes described is defective autophagy in CD4 T cells occurring with aging, leading to reduced mitophagy with an accumulation of malfunctioning mitochondria. These events result in the upregulation of Th17 cytokines contributing to inflammaging [64][93]. The detrimental impact of this higher Th17/T-reg ratio in cancer is observed at specific stages of tumors. Thus, oral squamous cell carcinoma patients increase the Th17/T-reg ratio at early stages and decrease it at late stages [94]. In colorectal tumor specimens, patients with increased expression of Th17 genes presented a poor prognosis [95]. Others have found that the increased IL1β and IL2 reduction in aged mice contributed to an elevated Th17 differentiation [96].

In MM, a variety of studies confirm the detrimental role of Th17 cells. Thus, Th17 cells promote MM growth and inhibit immune functions [97]; and in MM patients with lytic bone disease, numbers of Th17 cells were the highest [98]. Of interest, IL6, which is over-expressed in MM, creates a proinflammatory TME, a crucial factor mediating the conversion of T-regs into Th17 cells [99]. Th17 cells also cause osteoclast-dependent bone damage in vitro and in vivo, where miR-21 activates differentiation of naïve T cells in Th17 cells, promoting these detrimental effects in MM [100]. IL17, produced by Th17, cells induces osteoblasts pyroptosis in vitro, through activation of the NLRP3 inflammasome complex with Caspase-1 execution and release of IL1β [101]. In newly diagnosed MM patients, Th17 cell levels fluctuate considerably. Of interest, Th17 increased further when the disease reached partial remission, decreased to normal levels when complete remission was achieved and increased again when the disease recurred [102].

Moreover, in MM, dendritic cells (DCs) infiltrate the BM as efficient inducers of Th17 cells and promote higher levels of Th17 in BM than PB. Of interest, in monoclonal gammopathy of undetermined significance (MGUS) patients, an initial stage of the MM disease, this increase in Th17 cells was not observed. Another study analyzing the microbiota in MM observed that *Prevotella heparinolytica* promotes the differentiation of Th17 cells that colonize the gut and migrate to the BM, to favor the progression of MM. Similarly, in smoldering MM patients, higher BM IL17 levels predicted faster disease progression [103].

Moreover, the imbalance of the Th17/T-reg ratio in MM is reinforced by studies, where MM and MGUS patients show a reduction in the number of T-reg cells compared to healthy donors, being these T-reg cells dysfunctional [104]. Another study observed fewer T-regs in the BM of MM patients compared to healthy individuals, where Th17 cells are responsible for osteoclast activation mediating lytic bone disease [105].

To summarize, Th17 cells are highly involved in this connection between chronic inflammation and cancer development. Moreover, they are related to different types of cancer and to the pathogenic events of MM patients, who represent elderly cancer patients. Novel studies are required to decipher their role in the progression of these diseases.

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