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REVIEW

Impact of age-, cancer-, and treatment-driven inflammation on T cell function and immunotherapy

Kylie M. Quinn[1,2] | Apriliana E. R. Kartikasari[1] | Rachel E. Cooke[3,4] | Rachel M. Koldej[3,4] | David S. Ritchie[3,4] | Magdalena Plebanski[1]

[1]School of Health and Biomedical Sciences, RMIT University, Bundoora, Victoria, Australia

[2]Department of Biochemistry, Biomedicine Discovery InstituteMonash University, Clayton, Victoria, Australia

[3]Australian Cancer Research Foundation (ACRF) Translational Laboratory, Royal Melbourne Hospital, Melbourne, Australia

[4]Department of Medicine, University of Melbourne, Melbourne, Australia

Correspondence
Dr Kylie Quinn, RMIT University, Bundoora, VIC, 3073, Australia.
Email: kylie.quinn@rmit.edu.au

Abstract

Many cancers are predominantly diagnosed in older individuals and chronic inflammation has a major impact on the overall health and immune function of older cancer patients. Chronic inflammation is a feature of aging, it can accelerate disease in many cancers and it is often exacerbated during conventional treatments for cancer. This review will provide an overview of the factors that lead to increased inflammation in older individuals and/or individuals with cancer, as well as those that result from conventional treatments for cancer, using ovarian cancer (OC) and multiple myeloma (MM) as key examples. We will also consider the impact of chronic inflammation on immune function, with a particular focus on T cells as they are key targets for novel cancer immunotherapies. Overall, this review aims to highlight specific pathways for potential interventions that may be able to mitigate the impact of chronic inflammation in older cancer patients.

KEYWORDS

IL-1, IL-6, multiple myeloma, ovarian cancer, TNF

1 | INTRODUCTION

Classically, the hallmarks of inflammation were defined as heat (calor), pain (dolor), redness (rubor), and swelling (tumor) in the first century AD by the scholar Celsus,[1] but this definition is evolving. Inflammation can now be defined as a complex process, whereby leukocytes and plasma-derived effector proteins are recruited into specific sites in tissues to drive a local immune response.[2] While it is an incredibly effective way to limit infections and initiate tissue remodeling, it must be tightly controlled to avoid collateral damage to normal tissues. Short periods of acute inflammation enable containment of infection or injury and wound healing, but prolonged periods of chronic inflammation can cause increased tissue damage locally and dysregulated immunity systemically, particularly T cell responses. To understand when to intervene to minimize the impact of chronic inflammation on T cell function in older cancer patients undergoing treatment, we will briefly review the process of inflammation.

Abbreviations: BM, bone marrow; CRP, C-reactive protein; DAMP, damage-associated molecular pattern; DUSP, dual-specificity phosphatase; IKK, IκB kinase; IRF, IFN response factor; ISG, IFN-stimulated gene; ISGF3, IFN-stimulated gene factor 3; MM, multiple myeloma; NLR, NOD-like receptor; OC, ovarian cancer; PAMP, pathogen-associated molecular pattern; PRR, pathogen recognition receptor; RLR, RIG-like receptor; SASP, senescence-associated secretory phenotype; SOCS, suppressor of cytokine signaling; Treg, regulatory T cell.

2 | THE PROCESS OF INFLAMMATION

The basic model of acute inflammation involves a number of stages, as reviewed in Newton and Dixit.[2] First, pathogen- or damage-associated molecular patterns (PAMPs or DAMPs) activate pathogen recognition receptors (PRR) on cells that are local to the site of infection, injury or abnormality. These cells can be stromal, parenchymal, and/or immune cells that reside in the tissue. PRR activation then leads to the release of a number of inflammatory cytokines. These include IL-6, TNF, IL-1α/β, type I IFNs, as well as IFN-γ, IL-12, IL-15, IL-18, IL-33, and GM-CSF. The specific milieu of these cytokines is shaped by the mix of PAMPs and DAMPs present, the cell subsets that are present, and the spectrum of PRRs that these cells express. PRR activation and inflammatory cytokines also lead to the priming of the complement pathway, production of C-reactive protein (CRP) in the liver, and activation of cyclooxygenase isoenzymes, Cox-1 and -2, leading to platelet activation and prostaglandin production

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to support arterial dilation and vascular permeability (reviewed in Ricciotti et al.[3]).

The cells of the immune system respond robustly to acute inflammation. Immediately after infection and/or tissue damage, resident Mϕs are activated and neutrophils and monocytes are recruited from circulation by locally generated chemokines. Monocytes differentiate into Mϕs that direct local responses and tissue remodeling.[4] Simultaneously, inflammatory cytokines direct hematopoietic stem cells in the bone marrow (BM) to generate more neutrophils and monocytes.[5] Later, once Ag-specific CD4 and CD8 T cells have proliferated in secondary lymphoid tissues and entered circulation, they can be recruited to the inflamed site along gradients of inflammation-induced chemokines, such as CXCL9/10.[6] The inflammatory cytokine, IL-6, can promote the proliferation of T cells, as well as the differentiation of CD4 T cells into T helper 17 (T_{H17}) cells and B cells into plasma cells. This illustrates that distal hematopoietic and immune cells are remarkably sensitive to local and systemic inflammatory cytokines and chemokines. However, once the immune response begins to clear the infection or contain the injury, the PAMPs and DAMPs are reduced, the inflammatory response is inhibited, and the repaired tissue can return to a state of homeostasis.

3 | SIGNALING PATHWAYS AND REGULATION OF INFLAMMATION

Many signaling pathways mediate the initiation, propagation, and resolution of inflammation, as well as its dysregulation in aging and cancer. For the purpose of this review, we will focus on IL-6, TNF, IL-1α/β, and type I IFNs (**Figure 1**).

For the initiation of inflammation, signaling from distinct PRRs can trigger a number of downstream pathways.[2] These pathways include NF-κB, MAPK, and IFN response factor (IRF) signaling (**Figure 1**). The canonical NF-κB pathway is essential for inflammation and it is activated downstream of PRRs as well as other stimuli. It is inhibited by the IκB kinase (IKK) but active NF-κB triggers the production of a number of inflammatory cytokines such as IL-6, TNF, IL-1α, pro-IL-1β, and pro-IL-18. MAPK pathways are also activated downstream of PRRs, leading to activation of the transcription factor, AP-1. AP-1 can synergize with other transcription factors such as NF-κB to enforce inflammatory cytokine gene expression. Finally, IRF signaling is induced by select classes of PRRs, generally those that sense nucleic acids such as TLRs 3, 7, and 9, RIG-like receptors (RLR), and DNA sensors.[7] This signaling leads to the robust expression of type I IFNs.

For propagation of inflammation, IL-6, TNF, IL-1α/β, and type I IFNs engage receptors on both local and distal cells to elicit a range of effects (**Figure 1**). IL-6 signaling activates STAT3, PI3K/Akt, and MAPK signaling[8] and it is a pleiotropic cytokine with a range of effects but, notably, it is pro-proliferative for hematopoietic cells. TNF signaling drives NF-κB and MAPK signaling and, in some cases, caspase-dependent apoptosis.[9] One of its receptors, TNFR1, has broad tissue distribution and is inducible by type I IFNs to further augment inflammatory signaling, while the other receptor, TNFR2, can promote survival of certain T cell subsets, such as memory T cells and T regulatory (Treg) cells. IL-1α/β signaling leads to MAPK and NF-κB signaling and this has broad effects to augment inflammatory cytokine production.[10] Finally, IFN signaling leads to the formation of the IFN-stimulated gene factor 3 (ISGF3) transcription factor that drives the expression of IFN stimulated genes (ISGs).[11] ISGs are a diverse group of genes whose expression generates a potent antiviral state in the cell itself and other surrounding cells. Receptors for these inflammatory cytokines are expressed on a wide range of cells, including CD4 and CD8 T cells.

To further amplify inflammation, signaling pathways can converge. For example, PRRs can induce NF-κB signaling to generate TNF and pro-IL-1β, and in turn engagement of TNF receptors and the IL-1 receptor also induce NF-κB signaling, amplifying the production of TNF and pro-IL-1β. Pathways can also combine to lead to distinct inflammatory outcomes. For example, TLR signaling leads to NF-κB activation and the production of pro-IL-1β and -IL-18 but these must be cleaved by active caspase 1 to form active IL-1β and IL-18.[10] In order to activate caspase 1, a cell must engage NOD-like receptor (NLR) signaling to activate the inflammasome complex.[12] NLRs and the inflammasome can be activated by a diverse array of PAMPs, such as muramyl dipeptide from bacteria, and DAMPs, such as ATP release and K^+ efflux from dying cells. Therefore, in this two-signal model, activation of both the caspase 1 via NLRs and NF-κB signaling via TLRs or other PRRs is needed for optimal production of active IL-1β and IL-18.

Given this potential for amplification and synergy, inflammatory signaling pathways need to be tightly controlled (**Figure 1**). PRRs and cytokine receptors can be internalized or downregulated at later time points or decoy receptors, such as IL-1Ra, can be upregulated.[10] Suppressor of cytokine signaling (SOCS) proteins can inhibit STAT activation and certain dual-specificity phosphatases (DUSP) proteins can act to inactivate MAPKs.[13,14] IL-6 is particularly tightly controlled at a number of levels. One key negative regulator is Ahr, which can complex with STAT1 or NF-κB to prevent binding at the IL-6 promoter.[15] Downstream of the IL-6R, JAK activation is inhibited by SOCS1 and gp130 is inhibited by SOCS3.[8,13] Immunoregulatory cytokines such as IL-10 and TGF-β are up-regulated at later timepoints to down-regulate inflammation and promote tissue repair. Type I IFNs, such as IFNβ, can have early antiviral effects as well as subsequent anti-inflammatory effects, such as inhibiting T cell proliferation[16] and up-regulating IL-10 production,[17] to further augment resolution of inflammation. This shift highlights that cytokines may have both pro- and anti-inflammatory effects depending on when they act during the kinetic of an inflammatory response.

PRR signaling followed by IL-6, TNF, IL-1, and IFN signaling are critical pathways involved in the initiation and propagation of acute inflammation, but it should be noted that this basic model is an oversimplification. This review will focus on the impact of these pathways in aging and cancer, but we note that there are a number of additional signaling pathways and mediators that we are not able to cover in this review.

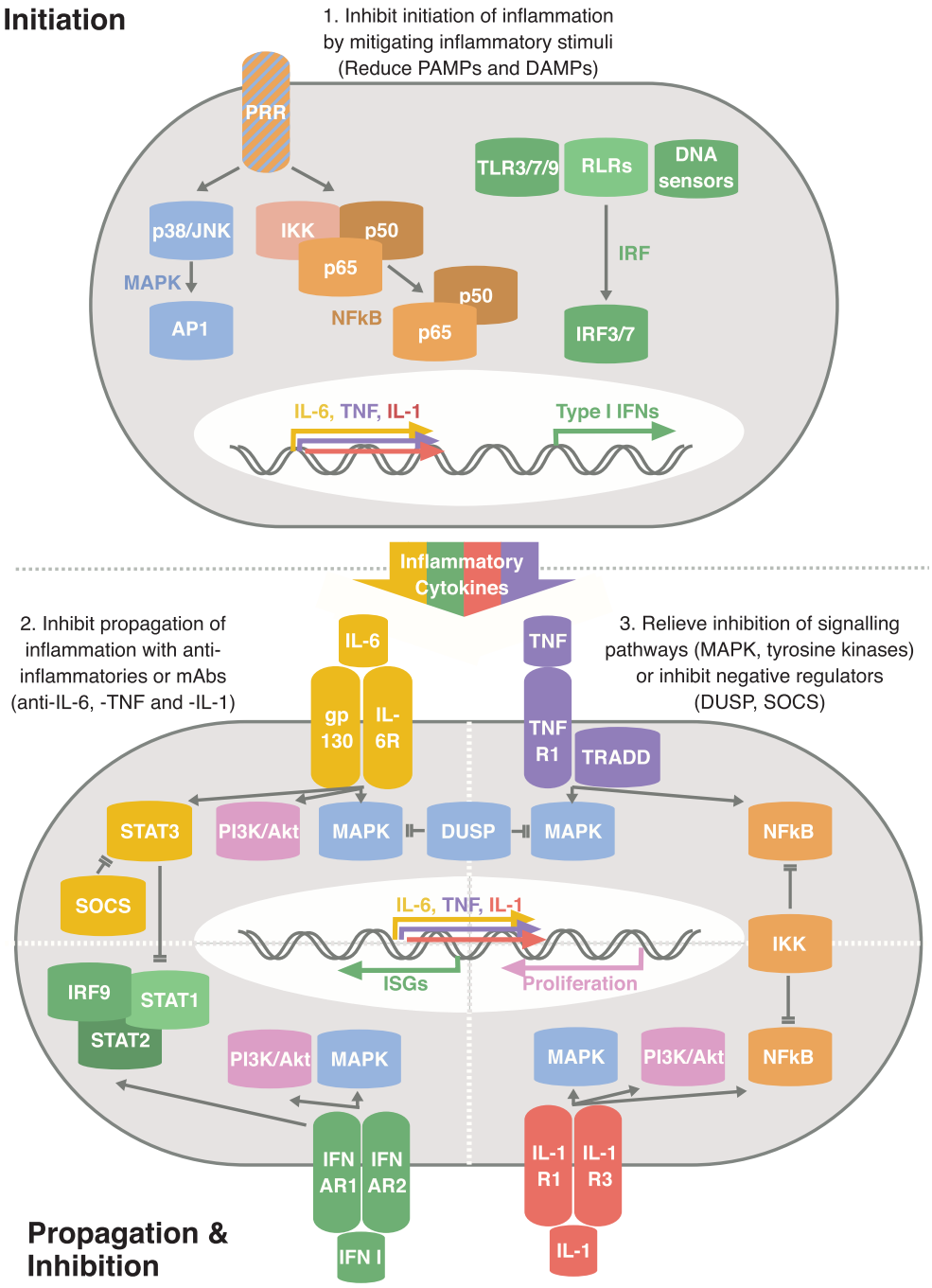

FIGURE 1 Pathways involved in the initiation, propagation, and inhibition of inflammatory signals, and strategies for targeting these pathways to improve T cell activation. For initiation of inflammation (top panel), signaling from distinct PRRs can trigger NF-κB or MAPK, and IRF signaling. In NF-κB signaling, the IKK subunit is degraded and the active NF-κB transcription factor, composed of p50 and p65 subunits, translocates into the nucleus and promotes the transcription of key inflammatory cytokines such as IL-6, TNF, IL-1α, pro-IL-1β, and pro-IL-18. In MAPK signaling, a kinase cascade leads to activation of p38 and JNK, which dimerize cFos and Jun to generate the transcription factor AP-1. In IRF signaling, nucleic acid is sensed by PRRs such as TLR3, 7, and 9, RIG-like receptors (RLR), and DNA sensors, which induces dimerization and activation of IRF3 and/or IRF7 to translocate into the nucleus to induce expression of type I IFNs. For propagation of inflammation (bottom panel), IL-6, TNF, IL-1α/β, and type I IFNs engage receptors on both local and distal cells. In IL-6 signaling, IL-6 binds to its receptor, IL-6R, in complex with gp130 to trigger MAPK, PI3K/Akt and STAT3 signaling. In TNF signaling, TNF binds to the TNF receptor 1 (TNF-R1) to recruit TNFR-associated death domain protein (TRADD) and TNFR-associated factors to drive NF-κB and MAPK signaling. In IL-1α/βsignaling, the cytokine trimerizes with IL-R1 and IL-1R3 to trigger MAPK and NF-κB signaling. In type I IFN signaling, type I IFNs bind to a heterodimer of IFN α receptor 1 and 2 (IFNAR1 and IFNAR2), which leads to trimerization of STAT1, STAT2, and IRF9 to form the IFN-stimulated gene factor 3 (ISGF3) transcription factor that drives expression of IFN stimulated genes (ISGs). The IFNAR1/2 receptor can also lead to MAPK and PI3K/Akt signaling. For inhibition of inflammatory signaling (bottom panel), mediators include SOCS proteins that inhibit STAT signaling and DUSP proteins and inhibit MAPK signaling. STAT3 is also known to inhibit type I IFN signaling. Various stages of inflammation may be targeted to reduce T cell dysfunction, including (1) reducing initiation, (2) reducing propagation, and (3) inhibiting chronic signaling or signaling inhibition. Pathways reviewed in more detail in refs. [2,7–10]

4 | ACUTE, BASAL, AND CHRONIC INFLAMMATORY STATES

During an acute infection or tissue damage, inflammatory signaling and cell recruitment progress as described above. However, some scenarios can induce other inflammatory states, such as basal inflammatory activation or chronic inflammation.

Basal inflammatory activation refers to low-level stimulation of PRRs and signaling pathways with stimuli from our environment, our microbiota, and our normal cellular processes. This low-level triggering can be important for maintaining the expression of genes within inflammatory pathways. For example, IFN-β is normally constitutively produced at low levels. A loss of basal IFN-β undermines basal expression of many ISGs, compromising the basal antiviral state of cells and rendering them highly susceptible to viral infection.[18] Some of this signaling seems to arise from the microbiota interacting with the mucosa. Mice treated with antibiotics have reduced ISG expression in their lung epithelia and are more susceptible to influenza virus infection[19] and basal IFN-β in the gut is triggered by TLR3-mediated sensing of commensals.[20] While basal signaling is important for priming of the type I IFN pathway, IL-6, IL-1, and TNF production is more tightly regulated.

Chronic inflammation, in contrast, refers to sustained heightened levels of inflammatory cytokines. It can be driven by the persistence of the pathogen and associated PAMPs, such as is seen with granuloma formation during latent Tuberculosis, but it can also occur in the absence of a pathogen due to DAMPs derived from ongoing tissue damage, which is called sterile inflammation. During chronic inflammation, signaling pathways become much more complex. There is sustained initiation and propagation of inflammation that leads to concurrent mechanisms of positive and negative regulation, failed resolution of inflammatory processes, and, as a result, substantial dysregulation of inflammatory signaling.[21] Chronic inflammation is thereby a very complex state and its precise mechanisms are very context-dependent, combining an individual's history of disease with their microbiota, age, co-morbidities, adjunct treatments, and stochastic effects.

5 | AGING AND CHRONIC INFLAMMATION

As individuals age, they can enter a specific state of chronic inflammation (**Figure 2**), referred to as "inflammageing."[22] There are a number of potential extrinsic and intrinsic sources for this age-related inflammation. Individuals can acquire chronic infections such as EBV and CMV.[23] A class of retrotransposons, called LINE-1 elements, have been shown to become activated with age, to cause a DNA damage response and production of type I IFN.[24] The gut microbiota can become dysbiotic and the gut mucosa can become more permeable, leading to gut leakiness of PAMPs.[25] Individuals can accumulate adipose tissue with age, which is a major source of IL-6 and TNF.[26] Cells can accumulate DNA mutations, mislocalized or misfolded proteins, or damaged organelles, especially mitochondria, leading to cellular and metabolic stress and production of DAMPs.[27] Of note, basal inflammation tends to be higher in women than men, leading to increased vaccine responsiveness in women,[28] but aging causes a substantial increase in inflammation in both genders, with older men and women exhibiting nearly equivalent inflammatory signatures.[29] Finally, it is important to note that, compared to acute infection-driven inflammation, chronic age-related inflammation is regarded as low-grade.[30] It is therefore likely to be the chronicity of the inflammatory signaling, rather than the magnitude of the inflammatory signaling, that drives inflammageing.

Aging also leads to the emergence of senescent cells in tissues throughout the body, including cells of the immune system.[27] There are a number of different forms of senescence, so senescent cells cannot be defined with a single, universal biomarker. However, they can be functionally defined as having an arrested cell cycle, often due to increased DNA damage response and an increase in cyclin-dependent kinase inhibitors, such as p21 and p16. They can also exhibit a senescence-associated secretory phenotype (SASP), with the production of high levels of inflammatory cytokines and chemokines, including IL-6, IL-1, IL-8, and GM-CSF.[27] SASP may be adaptive during normal physiology, as it is thought to recruit immune cells to a senescent cell and promote its killing and clearance. However, as an individual becomes older and immune cell function declines, this process would become inefficient and senescent cells could accumulate, contributing to systemic chronic inflammation. SASP may even be procarcinogenic, as it could establish inflamed niches that can precipitate the development of malignant cells,[31] as will be described below with ovarian cancer (OC) and multiple myeloma (MM).

Inflammation is not just symptomatic of aging: it can be a major driver of diseases associated with the aging process. For example, anti-TNF mAbs are a relatively new and highly effective treatment for rheumatoid arthritis (RA). These mAbs block TNF signaling and thereby reduce RA-associated symptoms but they can also improve other age-related conditions, such as insulin sensitivity and incidence of Alzheimer's Disease.[32,33] This suggests that reducing inflammation can directly slow aging processes. However, aging is a complex phenotype, with many contributing mechanisms. Key mechanisms include DNA damage, mitochondrial damage, and loss of proteostasis (reviewed in López-Otín et al.[34]). DNA damage can be generated by genotoxic stress through exposure to UV light and genotoxic drugs, and replicative stress through erosion of telomeres. Mitochondrial damage can promote inflammation through the release of mitochondrial DNA or the production of reactive oxygen species that can damage DNA and cellular proteins. Inefficient proteostasis and autophagy can lead to dysregulation of many cellular processes. These mechanisms are interlinked and can augment inflammation.

Ultimately, aging leads to a state of "immunosenescence," which is defined as the immune system becoming dysfunctional to the point that an individual becomes more susceptible to infection, cancer, and autoimmunity. Key characteristics of immunosenescence include increased basal activation of myeloid cells, inhibition of Ag-driven proliferation in lymphoid cells, and increased proportions of suppressive immune cells such as myeloid-derived suppressor cells (MDSCs)[35] and T_{REG} cells[36] (**Figure 2**). Immune cells are highly sensitive to chronic inflammation, which can dysregulate key inflammatory signaling

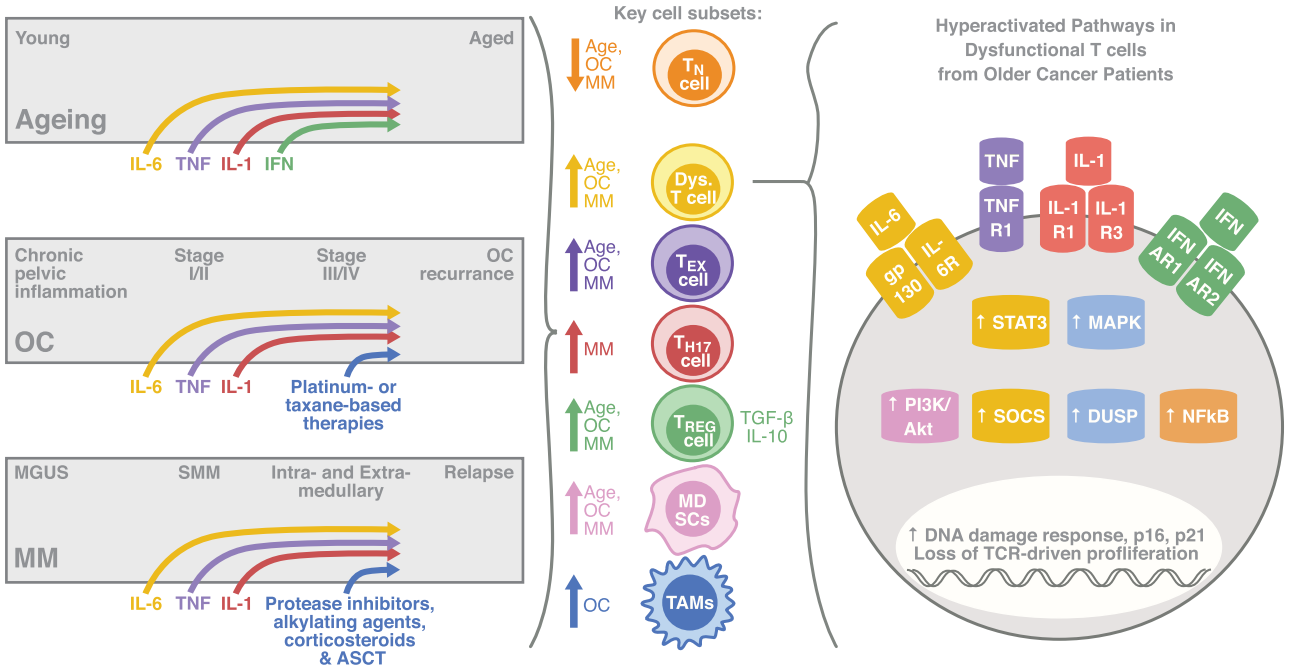

FIGURE 2 The impact of aging, ovarian cancer, and multiple myeloma disease and treatment on T cell function. Aging, OC, and MM are all driven by inflammation, particularly IL-6, TNF, IL-1, and type I IFN, and conventional therapies for OC and MM can exacerbate aging mechanisms and inflammation further. Changes are observed across aging, OC, and MM in a number of key immune or stromal cell subsets. In aging, we see a decrease in T_N cells and an increase in dysfunctional (Dys.) T cells, including T_{EX} cells, and an increase in T_{REG} cells and MDSCs. In OC, TAMs and MDSCs accumulate in the TME and the ratio of Treg cells to cytotoxic CD8 T cells is crucial for OC outcomes, although T_{EX} cells can accumulate with disease progression. In MM, T_N cells decrease, Dys. T cells such as T_{EMRA} and T_{EX} cells accumulate and the balance between T_{H17} and T_{REG} cells shifts during MM progression, with increased T_{H17} cells and high Treg cells during active MM. In terms of the characteristics of Dys. T cells, chronic signaling through IL-6, TNF, IL-1, type I IFN, and other metabolic stress signals can lead to hyperactivation of PI3K/Akt, STAT, MAPK, and NF-κB signaling and increased negative regulation of these pathways. This can lead to an increased DNA damage response, p16 and p21 expression, and a loss of TCR-driven proliferative capacity

pathways. For example, when monocytes from older individuals are stimulated with the influenza virus, IL-6, and IL-1β production is intact but IFN-β production is markedly reduced, suggesting that IRF signaling pathways are selectively inhibited.[37] This could drive 2 possible mechanisms: a decrease in early IFN-mediated antiviral mechanisms and/or a decrease in the latter immunomodulatory mechanism and contribute to increased disease severity observed during viral infections in older individuals.

The T cell population appears to be particularly susceptible to the aging process due to several factors. First, aging leads to a bias in relative output from the BM, with an increase in myeloid progenitors but a decrease in lymphoid progenitors. Mouse models have demonstrated that this shift is due to increased IL-1 signaling[38] and the resulting lymphoid progenitors are also less able to migrate into thymic tissue.[39] The thymus itself involutes with age, with deposition of adipose tissue and loss of thymic stromal tissue.[40] This means that the capacity of the thymus to support de novo naïve T (T_N) cell generation is dramatically decreased in older individuals.[41] As a result, aging can lead to a mild state of lymphopenia and it is thought that the peripheral T_N cell compartment becomes increasingly dependent on homeostatic proliferation to maintain numbers.[40] As a result, older individuals have fewer T_N cells, more differentiated T cells, such as central memory T (T_{CM}) cells and effector memory T (T_{EM}) cells), and more dysfunctional T cells. One key dysfunctional subset is the exhausted T (T_{EX}) cell, which is generated by chronic Ag stimulation, such as might occur during chronic infection.[42,43] Other partially overlapping dysfunctional subsets include effector memory that re-express CD45RA T (T_{EMRA}) cells that lack proliferative capacity but express high levels of perforin,[44] virtual memory (T_{VM}) cells that are partially differentiated due to cytokine signaling,[45,46] and terminally differentiated T (T_{TD}) and/or senescent T cells that have down-regulated both CD28 and CD27 and exhibit markers of DNA damage and cell cycle arrest.[47]

The remaining T cells are chronically exposed to the inflamed, aged environment and this exposure is evident in a number of features of aged T cells. All T cell subsets have decreased expression of the co-stimulatory molecule CD28 due to TNF signaling.[33,48] Some dysfunctional subsets have increased basal activation of MAPKs due to inflammatory and metabolic stress signaling ,[49–52] increased basal expression of a number of DUSP transcripts and proteins, which inhibit MAPK signaling[53,54] and increased expression of markers of the DNA damage response, p16 and p21.[45,49,50] CD4 and CD8 T cells from older individuals also exhibit increased basal phosphorylation and decreased cytokine-induced phosphorylation of STATs.[55] Cumulatively, this indicates that many inflammatory signaling pathways are hyperactivated in T cells from older individuals but these cells respond poorly to further stimulation. Importantly, when young T_N cells are exposed

to the aged environment, it undermines their intrinsic proliferative capacity,[45] which highlights that age-related environment, and likely the inflammatory signaling, has a direct functional impact on T cells.

As will be described below, many mechanisms of aging can also be triggered by cancer-related inflammation or by treatments for cancer. As a result, the combination of aging, cancer-related inflammation, and treatments for cancer can accelerate a number of age-related cellular phenotypes, as is evident in the context of both OC and MM.

6 | OVARIAN CANCER

6.1 | Etiology, Inflammation and Treatment

OCs are a group of malignancies originating from or involving the ovary. They are one of the most commonly diagnosed cancers among women and is the most lethal cancer of the reproductive system. The overall 5-year survival rate is currently only 46%, as 80% of cases are diagnosed at an advanced stage of the disease.[56] Patients with advanced OC may respond to initial treatment but the recurrence rate is high at 70%, which leads to the low survival rate. While the pathophysiology of OCs is still largely unknown, age is the strongest risk factor. Around 90% of cases occur in women older than 40 years old, with the highest risk in those over the age of 65.[56] Indeed, a review of epidemiological studies by Yancik et al. demonstrated that women older than 65 years old were both more likely to be diagnosed and more likely to present at the advanced stage,[57] leading to a substantial decrease in the overall 5-year survival rate with age. The increased diagnosis and the decreased survival rate in older women are most likely due to an increase in cancer aggressiveness, but the molecular drivers of this are still largely unknown.

The presence of OCs leads to increased local and systemic inflammation (**Figure 2**). Within the tumor microenvironment (TME), OC cells, infiltrating immune cells and other cells including fibroblasts, endothelial cells and adipocytes continuously secrete pro-inflammatory cytokines, including IL-6, TNF, IL-1, and IL-8.[58–60] The level of these cytokines in the serum of OC patients is associated with poorer prognosis.[58–60] High levels of IL-6 or TNF in ascites is associated with shorter progression-free survival[58,60] and circulating CRP levels are associated with increased risk of ovarian cancer.[61,62]

However, inflammation is not just a consequence of OC; it may also be a cause of OC. In 1999, Ness and Cottreau first proposed that local low-grade chronic inflammation may cause OC.[63] They observed that inflammatory stimulants such as pelvic inflammatory disease from sexually transmitted infections and endometriosis are associated with OC[63] and they proposed that extrinsic PAMPs and DAMPs could travel from the lower genital tract to the ovaries to induce local low-grade inflammation of the endometrium, tubes, and ovaries. This could cause local immune dysfunction and create conditions that support OC development.[64] This hypothesis was further supported by the observation that hysterectomy and tubal ligation, which presumably block the passage of PAMPs and DAMPs from the lower genital tract to the ovaries, can reduce OC risk.[63] Additionally, increased prostaglandins are often seen in malignant OCs and this is associated with increased invasiveness of the tumor cells.[65] Finally, inflammation alone was shown to be sufficient to promote cancer cell seeding, the starting point of metastasis, in a murine OC model.[66]

The standard treatment for OC is debulking surgery, followed by the first-line platinum-taxane-based chemotherapy, as reviewed in Cortez *et al.*[67] The debulking surgery aims to completely remove the tumor to prevent recurrence in early-stage patients, while chemotherapy is only given after debulking surgery to advanced-stage patients. While the majority of patients initially respond well to chemotherapy, most patients do relapse.[68] Platinum-based chemotherapies, such as carboplatin, work by forming adducts with DNA that lead to DNA damage and inhibit cell division. Taxane-based chemotherapies, such as paclitaxel, inhibit microtubule formation, and again disrupt cell division, with additional cellular stress. Both of these therapeutics can lead to lymphopenia. As a result, the current course of treatment for advanced ovarian cancer is likely to exacerbate a number of mechanisms of immune aging, including increased DNA damage and lymphopenia. However, chemotherapy has also been seen to increase the number and activation of tumor-infiltrating lymphocytes (TILs) and can improve outcome in some patients,[69] likely due to the killing of malignant cells and release of tumor-associated Ags (TAAs) and DAMPs. This highlights that there is a wide spectrum of patient responses to chemotherapy, and some of these differential effects could be associated with variability in immune aging.

6.2 | T cell Activation and Dysfunction

Ovarian cancer is immunogenic, as tumor-specific T cells and antibodies can be detected in the circulation, tumors, and ascites[70] (**Figure 2**). Indeed, the presence of TILs, including CD4 and CD8 T cells, in the ovarian TME strongly correlates with a better clinical outcome and longer overall survival[70,71] (**Figure 2**). There is growing evidence that tissue-resident memory CD8 T cells in the ovaries also play a pivotal role in tumor surveillance, as they make up to 80% of CD8 T cells found in OCs and correlate with a better prognosis.[72,73] In addition, the presence of infiltrating $CD20^+$ B cells that colocalize with CD8 T cells in the ovarian TME may further augment patient survival in comparison to the presence of CD8 T cells alone, possibly due to local Ag presentation by B cells to T cells.[74]

However, there are several immunosuppressive mechanisms in the ovarian TME that limit the function of T cells, including T_{REG} cells, MDSCs, and tumor-associated Mϕs (TAMs) cancer-associated fibroblasts, endothelial cells, adipocytes and the cancer cells themselves[75–77] (**Figure 2**). Local inflammation promotes the secretion of prostaglandins that directly inhibit CD8 T cell function in solid cancers.[78] Treg cells are thought to inhibit protective cytotoxic T cell responses in TME. As evidence of this, an increase in the proportion of Treg cells in the TME is associated with poorer prognosis in OC,[79] and a higher ratio of CD8 T cells as compared to T_{REG} cells in the TME correlates with a better prognosis in OC.[70] Treg cells may inhibit tumor-specific responses in the ovarian TME using a number of mechanisms, including the production of suppressive cytokines, such as IL-10 and TGF-β, that reduce the killing capacity of CD8

T cells. MDSCs and TAMs can also secrete suppressive cytokines and they can suppress T cell activation by engaging the inhibitory molecules.[76,77] Cumulatively, these cells create a local environment of chronic inflammation with high IL-6 and TNF that inhibit T cell function,[80,81] alongside other suppressive mechanisms.

In the ovarian TME, T_{EX} cells are known to accumulate. These cells have a number of features; specifically reduced proliferative capacity, cytokine production and killing capacity, and increased expression of immune checkpoint receptors, such as CTLA-4, PD-1, T cell immunoglobulin domain and mucin domain 3 (TIM3), and lymphocyte activation gene 3 (LAG3) (**Figure 2**). It is thought that the exhaustion of T cells in OC is driven by chronic Ag exposure.[82] The up-regulation of these immune checkpoint receptors are key targets for immune checkpoint blockade (ICB), which aims to block these receptors to reactivate T cell function. Indeed, ICB regimens have entered clinical trials to treat OC and have so far indicated promising results.[83]

7 | MULTIPLE MYELOMA

7.1 | Etiology, inflammation and treatments

MM is a malignancy of plasma B cells that reside within a supportive niche in the BM[84,85] and it progresses through a number of key stages. A preceding, benign phase known as monoclonal gammopathy of undetermined significance (MGUS) is defined as an excess of monoclonal antibody without other disease manifestations of MM.[86,87] This may develop into smoldering MM (SMM), which is asymptomatic but plasma cells account for at least 10% of hematological cells in the BM. Patients are most often diagnosed with MM on progression to intra- and extra-medullary phases due to the emergence of symptoms such as anemia, bone fractures, hypercalcemia, and/or renal disease.[84,85] Treatment strategies for MM have improved over the past 10 years, leading to a significant increase in life expectancy but it remains an incurable disease with 16.8 years of life lost on average.[88] Men are moderately over-represented in terms of incidence at 9.16 cases per 100,000, as compared to 5.88 cases per 100,000 for women in the United States.[89] However, the majority of patients diagnosed with MM are older than 60 years of age and they are not only more likely to have advanced disease at presentation, but they are also more likely to have concomitant medical problems resulting in poor tolerance of chemotherapeutic agents.[88] As a result, there is a higher early mortality rate in older patients.[88,90]

Inflammation is known to be a feature of MM, as it is highly dependent on IL-6 during certain stages of disease progression[91] and higher IL-6 levels at diagnosis correlate with poorer prognosis[92] (**Figure 2**). Plasma cell clones in MGUS and SMM are highly dependent on both the BM stroma and IL-6 for survival. The transition from SMM to intramedullary myeloma requires increased angiogenesis to support tumor growth and can result in osteoclastogenesis leading to bone destruction. The transition from intramedullary to extramedullary myeloma depends on clonal evolution to increase proliferative capacity and decrease dependence on BM stroma and IL-6.

One driver of MM-related inflammation may be the emergence of T_{H17} cells (**Figure 2**). In several studies, patients with MM exhibited increased proportions of T_{H17} cells in peripheral blood mononuclear cells (PBMCs) and the BM microenvironment, and elevated levels of IL-17 and T_{H17}-polarising cytokines (IL-6, TGF-β, IL-23, and IL-1β) in the BM.[93–95] Noonan et al. showed that this was particularly evident in MM patients with lytic bone disease, a pathological manifestation of MM due to the over-activity of osteoclasts.[93] Of note, Bryant et al. observed a decrease in the ratio of T_{H17} cells to T_{REG} cells in peripheral blood from patients with active MM.[96] This suggests that the T_{H17}:Treg balance can skew during active MM to favor a suppressive state and thereby promote a tolerogenic microenvironment (**Figure 2**).

Initial treatment for MM progresses in two phases.[84,85] In the first phase, patients undergo an induction regimen with a proteasome inhibitor, an immunomodulatory drug (IMiD), and/or an alkylating agent plus corticosteroids. Proteasome inhibitors block protein turnover in malignant cells and trigger cell death, while alkylating agents cause DNA damage to inhibit cell division and they, along with corticosteroids, can cause lymphopenia and lymphocyte dysfunction. In the second phase, medically fit patients are offered autologous stem cell transplant (ASCT), after pretreating with BM-ablating dose of an alkylating agent. After ASCT, lenalidomide (an IMiD) is often used as maintenance therapy to prolong a remission or deepen the response. First-line therapy is not curative, but it aims to induce disease remission, the depth of which correlates with progression-free and overall survival.[97,98] The disease follows a relapsing/remitting course requiring sequential therapies and, over time, clonal MM plasma cells evolve increasing resistance (reviewed in Kuehl et al.[99]). Accordingly, the current course of treatment for MM is likely to exacerbate a number of mechanisms of immune aging, including increased DNA damage, decreased proteostasis, and lymphopenia.

7.2 | T cell Activation and Dysfunction

T cells are activated and play a role in the control of MM (**Figure 2**). As evidence of this, a robust biomarker of long-term survival with MM is an increased frequency of proliferating, presumably MM-specific, clonal populations of cytotoxic T cells.[96,100] T cells are therefore regarded as protective in at least a subset of MM patients with sufficiently immunogenic tumors. Interestingly, the MM-specific, clonally expanded cytotoxic T cells express CD57, do not express CD28 and CD27, and do not express high levels of PD-1, which suggests that they are senescent and not exhausted[101,102] (**Figure 2**). It also provides a rationale for why PD-1-directed checkpoint blockade has not been very effective in MM patients, as protective T cell populations are not suppressed via PD-1. The MM-specific, clonally expanded cytotoxic T cells also do not exhibit telomere shortening,[101,102] which might be explained by the high availability of IL-15 in lymphopenic states that has been described to increase telomerase expression.[103]

There are also clear shifts more generally in T cell phenotypes in MM patients, with a decrease in T_N cells and an increase in T_{EM} cells and T_{EMRA} cells[104,105] (**Figure 2**). In CD8 T cells, the decrease in T_N cells is seen at initial diagnosis but, in CD4 T cells, T_N cells are relatively

preserved at initial diagnosis but are noted to be markedly reduced by relapsed/refractory disease. As a result, a decrease in the CD4:8 ratio is a characteristic marker of disease progression in MM.[104,105] An analogous shift, with an early loss of CD8 T_N cells followed by a loss of CD4 T_N cells, is seen during normal immune aging.

One major mechanism that may drive T cell dysfunction in MM patients is the profound lymphopenia induced during ASCT (**Figure 2**). Immediately after ASCT, memory CD8 T cells are seen to expand disproportionately compared to CD4 T cells,[106–108] leading to a low CD4:CD8 ratio. In children and young adults, this ratio recovers to normal levels by 1 year post-ASCT[108] but, in older adults, this ratio takes longer to recover, if at all.[106,107] There is also evidence that Treg cells expand disproportionately immediately after ASCT and remain high for prolonged periods.[109] While memory T cells expand after ASCT, de novo generation of T_N cells is limited in older patients by thymic involution, which leads to phenotypic skewing with fewer T_N cells and more memory T cells.[41,110] This skewing is thought to limit an individual's ability to respond to new Ags, during vaccination or infection by limiting TCR repertoire diversity.[106] Analysis of p16, which is used as a marker of senescent cells, suggests that ASCT induces molecular aging of the remaining T cells,[111] further demonstrating the detrimental effect of ASCT.

8 | THE COMBINED IMPACT OF AGEING-, CANCER-, AND TREATMENT-DERIVED INFLAMMATION

As described above, aging, OC, MM, and conventional treatments can all drive inflammation, but the forms of inflammation are quantitatively and qualitatively distinct. Local inflammation in the TME could be relatively robust, depending on the characteristics of the tumor,[112] while age-related inflammation is relatively low level. Inflammation associated with OC and MM would be relatively local to the tumor, especially early on during disease, while aging results in some sites of local inflammation but more systemic inflammation in tissues throughout the body. Finally, the precise combination of PRRs driving inflammation in each scenario may be distinct. Early OC could be initiated by PAMPs,[63] genotoxic treatments could cause DNA damage and cell death to release a number of DAMPs, and a diverse array of both PAMPs and DAMPs can contribute to age-related inflammation.

Given the range of inflammatory responses generated during aging, cancer, and treatment, the impact of inflammation on immune cells, such as T cells, would be cumulative. This has been demonstrated in mouse models, where aging causes T cell dysfunction but cancer in aged animals further exacerbates this dysfunction.[113] If we can define the specific inflammation-driven mechanisms that lead to this dysfunction, we could rationalize approaches for better design of T cell-based immunotherapeutics for older patients.

8.1 | Implications for immunotherapies with ovarian cancer and multiple myeloma

Given their inherent immunogenicity, immunotherapies appear to be a viable option for some OCs and MM. Immunotherapies cover a wide range of interventions, including ICBs, cancer vaccines, and adoptive cell therapies.

Therapy with ICBs is currently being tested in clinical trials for both OCs and MM. ICBs rely on the presence of cancer-specific T cells that are exhausted but that will respond to blockade of inhibitory pathways. In OC, we observe an increase in exhausted T cells but monotherapies with ICBs have not resulted in marked protection in clinical trials to date.[82] One way to improve this may be to treat selected patients with high expression of immune checkpoint receptors, or to combine several ICBs together and/or with other therapeutics to simultaneously target multiple anticancer mechanisms.[114] Cancer vaccines are also in development. They often aim to preferentially expand cancer-specific, Ag-experienced T cells, which can be challenging as these cells can become exhausted or dysfunctional in cancer patients. Moreover, cancer vaccines require well-defined TAAs. For OC, TAAs such as NY-ESO-1 and CA-125 are currently being explored, and B cell maturation Ag (BCMA) is being assessed for MM. Given that it can be challenging to find a universally expressed, well-defined TAA, personalized cancer vaccine approaches are being developed to target TAAs that are unique to an individual's malignancy.[115,116] Adoptive cell transfer therapies are in development for both OC and MM and they use laboratory-generated, tumor-specific immune cells to induce cancer regression. Two common forms of adoptive cell transfer are TIL therapy, where the patient's TILs are expanded in the lab and then reinfused, and chimeric Ag receptor (CAR) T cell therapy, where T cells are genetically modified with a tumor-specific CAR, expanded and then reinfused. These therapies rely on isolated cells expanding robustly in vitro to generate highly functional T cells that expand robustly again after reinfusion.

One potential limitation on the use of immunotherapies in OC and MM is age- and inflammation-related T cell dysfunction. For ICBs, efficacy appears to be similar across young and aged patients in tumors with high mutational burden, such as melanoma.[117] It will be interesting to see if age-related differences in ICB efficacy emerge with tumors with lower mutational burden, as a more restricted array of neoantigens may reveal age-related holes in TCR repertoire diversity. For cancer vaccines, there is not currently enough evidence of efficacy to stratify age groups. However, we do know with infections and vaccines that T cell responses decrease and become more monofunctional with increasing age.[45,118] This might be predicted to also occur with T cell responses to cancer vaccines. For adoptive T cell therapies, we see clear shifts in T cell phenotype and loss of proliferative capacity with increasing age.[45] When aged PBMCs are used in CAR T cell or TIL protocols, there is a corresponding decrease in the quantity and phenotypic quality of cells generated, as well as reports of reduced CAR transduction, which is likely linked to the poor proliferative capacity of older T cells.[119,120] Currently, there is little data on age-related differences in CAR T cell therapy efficacy but 1 recent study did stratify younger (<30 years old) and older (over 60 years old) patients. The number of older patients was small but older patients were more variable and trended toward fewer complete responses after CAR T cell therapy.[121] This suggests that developing an age-specific CAR T cell therapy protocol could improve outcomes for a subset of older patients. Alternatively, it would be beneficial to develop prognostic

tools to identify immunologically aged patients that would be less likely to respond using the current protocol.

8.2 | Disrupting chronic inflammation to reduce T cell dysfunction

Precision medicine approaches are now aiming to tailor therapies to the individual, and in older individuals or patients that exhibit premature immunological aging, we should consider how to optimize the efficacy of immunotherapies. In order to optimize these therapies, we should use our understanding of molecular changes in T cells driven by age and chronic inflammation (**Figure 1**).

Chronic inflammation has a number of indirect and direct effects on T cell responses. In terms of indirect effects, chronic inflammation alters many immune cells that support T cell activation, inducing basal hyperactivation of innate immune cells and APCs while reducing responses to bona fide stimuli. As an example, aged dendritic cells (DCs) exhibit dysregulation of PI3K signaling, hyperactivation of NF-κB signaling, and inhibition of type I IFN signaling, which is collectively symptomatic of broad dysregulation of inflammatory pathways.[122] As a result, aged DCs have a reduced capacity to respond to PRR stimulation, take up Ag, migrate, and prime T cells. Chronic, low-dose type I IFN signaling can also drive the development of MDSCs, which suppress T cell responses using a number of mechanisms including L-arginine starvation.[123] Stromal cells within tissues also become dysregulated with age, which can both reduce support for T cell survival[124] and promote tumor development.[125]

In terms of direct effects, inflammatory cytokines augment T cell activation during acute infection but chronic exposure in the absence of TCR activation can reprogram T cells and alter their function.[126] TNF signaling can drive reduced expression of CD28 on T cells, which is thought to limit T cell activation in older individuals.[33,48] IL-6 seems to promote T cell survival, as IL-6Ra is highly expressed on naïve T cells and overexpression of IL-6 in mice leads to an increase in T cell numbers.[127] Production of immunosuppressive cytokines such as IL-10 and TGF-β can directly repress T cell activation. These direct effects may be amplified when T cells access the TME, as disease-driven inflammation is concentrated in this environment. In particular, T cells may encounter inhibitory ligands in the TME to drive an exhausted phenotype. These direct effects may also be amplified or manifest differently in specific subsets of T cells that are more sensitive to inflammation. For example, a relatively new subset of antigen naïve T cells, known as T_{VM} cells, are highly sensitive to type I IFN and IL-15 and they undergo accelerated aging, with loss of proliferative capacity and enhanced basal activation of MAPK signaling,[45] presumably due to this sensitivity.

To prevent or reduce the impact of inflammation on T cell populations during aging, cancer, and cancer treatment, there are a number of potential approaches that could be considered (**Figure 1**).

First, excess inflammation should be avoided wherever possible and cancer treatment regimens should be rationalized based on the biology of aging and inflammation. A good example is ASCT, which dramatically accelerates immune aging. Immunotherapeutics are therefore likely to be much more effective prior to ASCT, when the TCR repertoire is more diverse and the T cell population is more functional. In particular, PBMCs should be sampled for adoptive T cell therapies prior to ASCT or lymphopenia-inducing therapies, to capture the most functional T cell populations.

Second, therapeutics could be used to reduce inflammation during the disease course or treatment of cancer to improve outcomes. For example, low dose aspirin, a Cox1/2 inhibitor, is protective against ovarian cancer, leading to both a reduced risk[128,129] and better prognosis.[62] This may in part be due to a decrease in chronic inflammation leading to an increase in protective T cell responses. Similarly, anti-TNF mAbs can reduce several age-related pathologies and leads to increased expression of CD28 expression on T cells, which may improve immune function.[33] Of note, anti-IL-6 mAbs are in clinical use for RA and it would be informative to see whether this similarly reduces age-related pathologies. In any case, there is some evidence that anti-IL-6 mAbs can limit disease progression in individuals with OC or MM,[91,130] which is consistent with the pivotal role of IL-6 in both forms of cancer. These approaches should, however, be used with care. Patients receiving therapies that inhibit inflammation, such as the anti-TNF mAb, can be more susceptible to infections and this risk can be increased in older patients.[131,132] We, therefore, could consider strategies, such as refining the route of delivery or targeting with bispecific Abs[133] to direct anti-IL-6 or -TNF therapies to the OC or MM TME, rather than relying on systemic administration. Another innovative approach may be to administer pegylated IL-10. While IL-10 is generally regarded as anti-inflammatory, high concentrations of IL-10 can promote proliferation and cytotoxicity in tumor-specific CD8 T cells to augment tumor control.[134]

Finally, we can target the signaling pathways themselves by either transiently blocking a signaling pathway that propagates inflammatory signals or blocking inhibitory mechanisms. The MAPK pathway represents a key target for this as MAPKs are hyperphosphorylated in T cells during aging .[49–52] This hyperphosphorylation is thought to be due to cumulative chronic inflammatory signaling and other metabolic/stress signaling and it leads to negative regulation of TCR signaling and T cell dysfunction.[49–52] Transient inhibition of MAPKs can lead to recovery of T cell function,[52,135] presumably due to the release of negative regulation. Of note, MAPK pathway members are frequently mutated in MM tumor cells and MEK inhibitors are currently being trialed. MEK inhibitors have been seen to prevent the acquisition of an exhausted phenotype in T cells and they can promote anti-tumour T cell responses,[136] so part of the activity of MEK inhibitors may be to restore anti-tumour T cell activity. A more general target are tyrosine kinases, which propagate many signaling pathways, and tyrosine kinase inhibitors (TKIs) are used in the clinic for various malignancies, such as chronic myeloid leukemia. Immunological control after the cessation of therapy with TKIs is associated with recovery of function in T_{VM} cells that are exquisitely sensitive to age-related chronic inflammation.[137] Indeed, pretreatment with a TKI, called ibrutinib, has improved T cell activation and outcomes of CAR T cell therapy in patients with chronic lymphocytic leukemia.[138] More recently, concurrent treatment with ibrutinib was shown to improve outcomes

of CAR T cell therapy, in particular by reducing a toxic side-effect known as cytokine release syndrome.[139] This cumulatively suggests that inhibition of MAPK and/or tyrosine kinases may be sufficient to normalize signaling through inflammatory pathways. Some of this may be mediated by normalization of inhibitory mechanisms, involving the SOCS or DUSP family members, and specific inhibitors of SOCS or DUSP proteins may have a similar effect. For example, DUSP6 expression increases markedly in aged T cells, and inhibition of DUSP6 with a microRNA, miR-181a, or a short interfering RNA can improve activation in T cells.[53] Transcription factors that co-ordinate inflammatory signaling could also be targeted. In a recent study, CAR T cells were engineered to overexpress cJun, which is a component of the AP-1 transcription factor. This overexpression protected CAR T cells from exhaustion due to overactivation of TCR signaling and increased their quality during in vitro and in vivo expansion.[140] A similar approach could be taken to increase the quantity and quality of cells that have become dysfunctional due to overactivation of inflammatory signaling.

It is worth noting that many inflammation-associated signaling pathways, such as NF-κB, MAPK, and PI3K, have wide-ranging effects on other signaling pathways in many different types of cells. As a result, it will be a challenge to target these signaling pathways in T cells in isolation in vivo, but cellular therapies offer a chance to target treatments to T cells more specifically. For example, T cells are cultured in vitro for CAR T cell therapy, which would permit specific manipulation of inflammatory signaling pathways in T cells with small molecules or genetic modification, while avoiding systemic effects. This is a significant advantage, but we should also consider that CAR T cells will be transferred back into the patient. Accordingly, it will be important to ensure that CAR T cells generated in vitro for older cancer patients can engraft efficiently into an aged and potentially inflamed environment.

9 | SUMMARY

Collectively, aging, cancer disease processes, and treatments clearly contribute to a state of chronic inflammation in OC and MM patients and T cell dysfunction in OC and MM patients. New immune-based therapies are therefore highly vulnerable to inflammation-driven T cell dysfunction. While the signaling pathways that contribute to dysfunction during chronic inflammation are complex, the modulation of these pathways can lead to the recovery of T cell function. In an age where the molecular status of patients is increasingly being used to deliver personalized precision medicine, protocols that are also tailored to age and inflammatory status will lead to improved patient outcomes.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORSHIP

All authors contributed to the conceptual design of the review, KQ, AERK and REC wrote the initial draft of the review, all authors edited the review, reviewed the final manuscript and contributed to revisions.

ORCID

Kylie M. Quinn https://orcid.org/0000-0002-0417-3625

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