Title: Impact of Age-, Cancer- and Treatment-Driven Inflammation on T Cell Function and Immunotherapy

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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 ageing, 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.

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 Celsus¹, 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 response². While it is an incredibly effective way to limit infections and initiate tissue remodelling, 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 minimise the impact of chronic inflammation on T cell function in older cancer patients undergoing treatment, we will briefly review the process of inflammation.

The Process of Inflammation

The basic model of acute inflammation involves a number of stages, as reviewed in Newton and Dixit². Firstly, 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 interleukin (IL)-6, tumour necrosis factor (TNF), IL-1 α/β , type I interferons (IFNs), as well as IFN- γ , IL-12, IL-15, IL-18, IL-33 and granulocyte-macrophage colony stimulating factor (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 leads to 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 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 macrophages are activated and neutrophils and monocytes are recruited from circulation by locally generated chemokines. Monocytes differentiate into macrophages that direct local responses and tissue remodelling⁴. Simultaneously, inflammatory cytokines direct haematopoietic stem cells in the bone marrow (BM) to generate more neutrophils and monocytes⁵. Later, once antigen-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 CXCL9/10⁶. 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 haematopoietic 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.

Signalling Pathways and Regulation of Inflammation

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

For initiation of inflammation, signalling from distinct PRRs can trigger a number of downstream pathways². These pathways include Nuclear factor- κ B (NF- κ B), mitogen-activated protein kinase (MAPK), and IFN response factor (IRF) signalling (**Figure 1**). The canonical NF- κ B pathway is essential for inflammation and it is activated downstream of PRRs as well as other stimuli. It is inhibited by the I κ B kinase (IKK) but active NF- κ B triggers production of a number of inflammatory cytokines such as IL-6, TNF, IL-1 α , pro-IL-1 β and pro-IL-18. MAPK pathways are also activated downstream of PRRs, leading to activation of the transcription factor, AP-1. AP-1 can synergise with other transcription factors such as NF- κ B to enforce inflammatory cytokine gene expression. Finally, IRF signalling is induced by select classes of PRRs, generally those that sense nucleic acid such as toll-like receptors (TLR) 3, 7 and 9, RIG-like receptors (RLR) and DNA sensors⁷. This signalling leads to the robust expression of type I IFNs.

For propagation of inflammation, IL-6, TNF, IL-1 α/β and type I IFNs engage receptors on both local and distal cells to elicit a range of effects (**Figure 1**). IL-6 signalling activates signal transducer and activator of transcription 3 (STAT3), phosphoinositide 3-kinases (PI3K)/Akt and MAPK signalling⁸ and it is a pleiotropic cytokine with a range of effects but, notably, it is pro-proliferative for haematopoietic cells. TNF signalling drives NF- κ B and MAPK signalling and, in some cases, caspase-dependent apoptosis⁹. One of its receptors, TNFR1, has broad tissue distribution and is inducible by type I IFNs to further augment inflammatory signalling, while the other receptor, TNFR2, can promote survival of certain T cell subsets, such as memory T cells and T regulatory (T_{REG}) cells. IL-1 α/β signalling leads to MAPK and NF- κ B signalling and this has broad effects to augment inflammatory cytokine production¹⁰. Finally, IFN signalling leads to the formation of the IFN-stimulated gene factor 3 (ISGF3) transcription factor that drives expression of IFN stimulated genes (ISGs)¹¹. ISGs are a diverse group of genes whose expression generates a potent anti-viral 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, signalling pathways can converge. For example, PRRs can induce NF- κ B signalling to generate TNF and pro-IL-1 β , and in turn engagement of TNF receptors and the IL-1 receptor also induce NF- κ B signalling, amplifying production of TNF and pro-IL-1 β . Pathways can also combine to lead to distinct inflammatory outcomes. For example, TLR signalling leads to NF- κ B activation and the production of pro-IL-1 β and -IL-18 but these must be cleaved by active caspase 1 to form active IL-1 β and IL-18¹⁰. In order to activate caspase 1, a cell must engage NOD-like receptor (NLR) signalling to activate the inflammasome complex¹². 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- κ B signalling via TLRs or other PRRs is needed for optimal production of active IL-1 β and IL-18.

Given this potential for amplification and synergy, inflammatory signalling pathways need to be tightly controlled (**Figure 1**). PRRs and cytokine receptors can be internalised or downregulated at later timepoints or decoy receptors, such as IL-1Ra, can be upregulated¹⁰. Suppressor of cytokine signalling (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- κ B to prevent binding at the IL-6 promoter¹⁵. Downstream of the IL-6R, JAK activation is inhibited by SOCS1 and gp130 is inhibited by SOCS^{8,13}. Immunoregulatory cytokines such as IL-10 and transforming growth factor- β (TGF- β) are upregulated at later timepoints to downregulate inflammation and promote tissue repair. Type I IFNs, such as IFN β , can have early anti-viral effects as well as subsequent anti-inflammatory effects, such as inhibiting T cell proliferation¹⁶ and upregulating IL-10 production¹⁷, 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 signalling followed by IL-6, TNF, IL-1 and IFN signalling 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 ageing and cancer, but

we note that there are a number of additional signalling pathways and mediators that we are not able to cover in this review.

Acute, Basal and Chronic Inflammatory States

During an acute infection or tissue damage, inflammatory signalling and cell recruitment progresses 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 signalling pathways with stimuli from our environment, our microbiota and our normal cellular processes. This low-level triggering can be important for maintaining 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 anti-viral state of cells and rendering them highly susceptible to viral infection¹⁸. Some of this signalling 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 infection¹⁹ and basal IFN β in the gut is triggered by TLR3-mediated sensing of commensals²⁰. While basal signalling is important for priming of the type I IFN pathway, IL-6, IL-1 and TNF production are 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, signalling 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 signalling²¹. 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.

Ageing and Chronic Inflammation

As individuals age, they can enter a specific state of chronic inflammation (**Figure 2**), referred to “inflammageing”²². There are a number of potential extrinsic and intrinsic sources for this age-related inflammation. Individuals can acquire chronic infections such as Epstein-Barr virus and cytomegalovirus²³. 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 IFN²⁴. The gut microbiota can become dysbiotic and the gut mucosa can become more permeable, leading to gut leakiness of PAMPs²⁵. Individuals can accumulate adipose tissue with age, which is a major source of IL-6 and TNF²⁶. Cells can accumulate DNA mutations, mislocalised or misfolded proteins or damaged organelles, especially mitochondria, leading to cellular and metabolic stress and production of DAMPs²⁷. Of note, basal inflammation tends to be higher in women than men, leading to increased vaccine responsiveness in women²⁸, but ageing causes a substantial increase in inflammation in both genders, with older men and women exhibiting nearly equivalent inflammatory signatures²⁹. Finally, it is important to note that, compared to acute infection-driven inflammation, chronic age-related inflammation is regarded as low-grade³⁰. It is therefore likely to be the chronicity of the inflammatory signalling, rather than the magnitude of the inflammatory signalling, that drives inflammageing.

Ageing also leads to the emergence of senescent cells in tissues throughout the body, including cells of the immune system²⁷. 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 production of high levels of inflammatory cytokines and chemokines, including IL-6, IL-1, IL-8 and GM-CSF²⁷. 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 development of malignant cells³¹, as will be described below with OC and MM.

Inflammation is not just symptomatic of ageing: it can be a major driver of diseases associated with the ageing process. For example, anti-TNF monoclonal antibodies (mAbs) are a relatively new and highly effective treatment for rheumatoid arthritis (RA). These mAbs block TNF signalling 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 ageing processes. However, ageing 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, ageing 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 antigen-driven proliferation in lymphoid cells and increased proportions of suppressive immune cells such as myeloid-derived suppressor cells (MDSCs)³⁵ and T_{REG} cells³⁶ (**Figure 2**). Immune cells are highly sensitive to chronic inflammation, which can dysregulate key inflammatory signalling pathways. For example, when monocytes from older individuals are stimulated with the influenza virus, IL-6 and IL-1 β production is intact but IFN β production is markedly reduced, suggesting that IRF signalling pathways are selectively inhibited³⁷. This could drive two possible mechanisms- a decrease in early IFN-mediated antiviral mechanisms and/or a decrease in later 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 ageing process due to several factors. First, ageing 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 signalling³⁸ and the resulting lymphoid progenitors are also less able to migrate into thymic tissue³⁹. The thymus itself involutes with age, with deposition of adipose tissue

and loss of thymic stromal tissue⁴⁰. This means that the capacity of the thymus to support *de novo* naïve T (T_N) cell generation is dramatically decreased in older individuals⁴¹. As a result, ageing 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 numbers⁴⁰. 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 antigen 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 perforin⁴⁴, virtual memory (T_{VM}) cells that are partially differentiated due to cytokine signalling^{45,46}, and terminally differentiated T (T_{TD}) and/or senescent T cells that have downregulated both CD28 and CD27 and exhibit markers of DNA damage and cell cycle arrest⁴⁷.

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 signalling^{33,48}. Some dysfunctional subsets have increased basal activation of MAPKs due to inflammatory and metabolic stress signalling^{49–52}, increased basal expression of a number of DUSP transcripts and proteins, which inhibit MAPK signalling^{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 STATs⁵⁵. Cumulatively, this indicates that many inflammatory signalling 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 capacity⁴⁵, which highlights that age-related environment, and likely the inflammatory signalling, has a direct functional impact on T cells.

As will be described below, many mechanisms of ageing can also be triggered by cancer-related inflammation or by treatments for cancer. As a result, the combination of ageing, 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.

Ovarian Cancer: Aetiology, Inflammation and Treatment

OCs are a group of malignancies originating from or involving the ovary. They are one of the most commonly diagnosed cancers amongst 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 disease⁵⁶. 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 are 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 65⁵⁶. 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 stage⁵⁷, 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 increased 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 tumour 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-8⁵⁸⁻⁶⁰. The level of these cytokines in the serum of OC patients is associated with poorer prognosis⁵⁸⁻⁶⁰. 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 OC⁶³. They observed that inflammatory stimulants such as pelvic inflammatory disease from sexually transmitted infections and endometriosis are associated with OC⁶³ 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 development⁶⁴. 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 risk⁶³. Additionally, increased

prostaglandins are often seen in malignant OCs and this is associated with increased invasiveness of the tumour cells⁶⁵. Finally, inflammation alone was shown to be sufficient to promote cancer cell seeding, the starting point of metastasis, in a murine OC model⁶⁶.

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 tumour 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 relapse⁶⁸. 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 ageing, including increased DNA damage and lymphopenia. However, chemotherapy has also been seen to increase the number and activation of tumour-infiltrating lymphocytes (TILs) and can improve outcome in some patients⁶⁹, likely due to killing of malignant cells and release of tumour associated antigens (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 variability in immune ageing.

Ovarian Cancer: T Cell Activation and Dysfunction

Ovarian cancer is immunogenic, as tumour-specific T cells and antibodies can be detected in the circulation, tumours and ascites⁷⁰ (**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 tumour 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 antigen presentation by B cells to T cells⁷⁴.

However, there are several immunosuppressive mechanisms in the ovarian TME that limit the function of T cells, including T_{REG} cells, MDSCs and tumour-associated macrophages (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 cancers⁷⁸. T_{REG} cells are thought to inhibit protective cytotoxic T cell responses in TME. As evidence of this, an increase in the proportion of T_{REG} cells in the TME is associated with poorer prognosis in OC⁷⁹, and a higher ratio of CD8 T cells as compared to T_{REG} cells in the TME correlates with a better prognosis in OC⁷⁰. T_{REG} cells may inhibit tumour-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 the exhaustion of T cells in OC is driven by chronic antigen exposure⁸². The upregulation 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 results⁸³.

Multiple Myeloma: Aetiology, 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 smouldering MM (SMM), which is asymptomatic but plasma cells account for at least 10% of haematological 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 anaemia, bone fractures, hypercalcaemia and/or renal

disease^{84,85}. Treatment strategies for MM have improved over the last 10 years, leading to a significant increase in life expectancy but it remains an incurable disease with 16.8 years of life lost on average⁸⁸. 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 States⁸⁹. 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 agents⁸⁸. 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 progression⁹¹ and higher IL-6 levels at diagnosis correlate with poorer prognosis⁹² (**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 tumour 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-1 β) 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 osteoclasts⁹³. 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 MM⁹⁶. This suggests that the T_{H17}:T_{REG} balance can skew during active MM to favour 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 pre-treating 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 ageing, including increased DNA damage, decreased proteostasis and lymphopenia.

Multiple Myeloma: 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 tumours. 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 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 expression¹⁰³.

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 ageing.

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-ASCT¹⁰⁸ but, in older adults, this ratio takes longer to recover, if at all^{106,107}. There is also evidence that T_{REG} cells expand disproportionately immediately after ASCT and remain high for prolonged periods¹⁰⁹. 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 antigens, during vaccination or infection by limiting TCR repertoire diversity¹⁰⁶. Analysis of p16, which is used as a marker of senescent cells, suggests that ASCT induces molecular ageing of the remaining T cells¹¹¹, further demonstrating the detrimental effect of ASCT.

The combined impact of ageing-, cancer and treatment-derived inflammation

As described above, ageing, 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 tumour¹¹², while age-related inflammation is relatively low level. Inflammation associated with OC and MM would be relatively local to the tumour, especially early on during disease, while ageing 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 PAMPs⁶³, 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 ageing, 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 ageing causes T cell dysfunction but cancer in aged animals further exacerbates this dysfunction¹¹³. If we can define the specific inflammation-driven mechanisms that lead to this dysfunction, we could rationalise approaches for better design of T cell-based immunotherapeutics for older patients.

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 are currently being tested in clinical trials for both OCs and MM. They 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 date⁸². 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 anti-cancer mechanisms¹¹⁴. Cancer vaccines are also in development. They often aim to preferentially expand cancer-specific, antigen-experienced T cells, which can be challenging as these cells can become exhausted or dysfunctional in cancer patients. Moreover, cancer vaccines require well-defined tumour-associated antigens (TAAs). For OC, TAAs such as NY-ESO-1 and CA-125 are currently being explored, and B cell maturation antigen (BCMA) is being assessed for MM. Given that it can be challenging to find a universally expressed, well-defined TAA, personalised 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 lab-generated, tumour-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 antigen receptor (CAR) T cell therapy, where T cells are genetically modified with a tumour-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 tumours with high mutational burden, such as melanoma¹¹⁷. It will be interesting to see if age-related differences in ICB efficacy emerge with tumours 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 age⁴⁵. 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 one recent study did stratify younger (less than 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 towards fewer complete responses after CAR T cell therapy¹²¹. 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.

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 ageing, we should consider how to optimise the efficacy of immunotherapies. In order to optimise 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 antigen presenting cells while reducing responses to *bona fide* stimuli. As an example, aged dendritic cells (DCs) exhibit dysregulation of PI3K signalling, hyperactivation of NF-κB signalling and inhibition of type I IFN signalling, which is collectively symptomatic of broad dysregulation of inflammatory pathways¹²². As a result, aged DCs have a reduced capacity to respond to PRR stimulation, take up antigen, migrate and prime T cells. Chronic, low-dose type I IFN signalling can also drive the development of MDSCs, which suppress T cell responses using a number of mechanisms including L-arginine starvation¹²³. Stromal cells within

tissues also become dysregulated with age, which can both reduce support for T cell survival¹²⁴ and promote tumour development¹²⁵.

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 function¹²⁶. TNF signalling 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 numbers¹²⁷. 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 ageing, with loss of proliferative capacity and enhanced basal activation of MAPK signalling⁴⁵, presumably due to this sensitivity.

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

Firstly, excess inflammation should be avoided wherever possible and cancer treatment regimens should be rationalised based on the biology of ageing and inflammation. A good example is ASCT, which dramatically accelerates immune ageing. 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.

Secondly, 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 prognosis⁶². 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 function³³. 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 antibodies¹³³ 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 tumour-specific CD8 T cells to augment tumour control¹³⁴.

Finally, we can target the signalling pathways themselves by either transiently blocking a signalling 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 ageing^{49–52}. This hyperphosphorylation is thought to be due to cumulative chronic inflammatory signalling and other metabolic/stress signalling and it leads to negative regulation of TCR signalling and T cell dysfunction^{49–52}. Transient inhibition of MAPKs can lead to recovery of T cell function^{52,135}, presumably due to release of negative regulation. Of note, MAPK pathway members are frequently mutated in MM tumour cells and MEK inhibitors are currently being trialled. MEK inhibitors have been seen to prevent acquisition of an exhausted phenotype in T cells and they can promote anti-tumour T cell responses¹³⁶, 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 signalling pathways, and tyrosine kinase inhibitors (TKIs) are used in the clinic for various malignancies, such as chronic myeloid leukaemia. 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 inflammation¹³⁷. Indeed, pre-treatment with a TKI, called ibrutinib, has improved T cell activation and outcomes of CAR T cell therapy in patients with chronic lymphocytic leukaemia¹³⁸. 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 syndrome¹³⁹. This cumulatively suggests that

inhibition of MAPK and/or tyrosine kinases may be sufficient to normalise signalling through inflammatory pathways. Some of this may be mediated by normalisation 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 cells⁵³. Transcription factors that co-ordinate inflammatory signalling 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 signalling and increased their quality during *in vitro* and *in vivo* expansion¹⁴⁰. A similar approach could be taken to increase the quantity and quality of cells that have become dysfunctional due to overactivation of inflammatory signalling.

It is worth noting that many inflammation-associated signalling pathways, such as NF-κB, MAPK, and PI3K, have wide ranging effects on other signalling pathways in many different types of cells. As a result, it will be a challenge to target these signalling 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 signalling 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.

Summary

Collectively, ageing, 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 signalling pathways that contribute to dysfunction during chronic inflammation are complex, modulation of these pathways can lead to recovery of T cell function. In an age where the molecular status of patients is increasingly being used to deliver personalised precision medicine, protocols that are also tailored to age and inflammatory status will lead to improved patient outcomes.

Figures:

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**), signalling from distinct PRRs can trigger NF-κB or MAPK, and IRF signalling. In NF-κB signalling, the IKK subunit is degraded and the active NF-κB transcription factor, comprised

of p50 and p65 subunits, translocates into the nucleus and promotes the transcription of key inflammatory cytokines such as IL-6, TNF, IL-1 α , pro-IL-1 β and pro-IL-18. In MAPK signalling, a kinase cascade leads to activation of p38 and JNK, which dimerise cFos and Jun to generate the transcription factor AP-1. In IRF signalling, 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-1 α/β and type I IFNs engage receptors on both local and distal cells. In IL-6 signalling, IL-6 binds to its receptor, IL-6R, in complex with gp130 to trigger MAPK, PI3K/Akt and STAT3 signalling. In TNF signalling, TNF binds to the TNF receptor 1 (TNF-R1) to recruit TNFR-associated death domain protein (TRADD) and TNFR-associated factors to drive NF- κ B and MAPK signalling. In IL-1 α/β signalling, the cytokine trimerises with IL-R1 and IL-1R3 to trigger MAPK and NF- κ B signalling. In type I IFN signalling, 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 Interferon-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 signalling. For inhibition of inflammatory signalling (**bottom panel**), mediators include SOCS proteins which inhibit STAT signalling and DUSP proteins and inhibit MAPK signalling. STAT3 is also known to inhibit type I IFN signalling. Various stage of inflammation may be targeted to reduce T cell dysfunction, including **1)** reducing initiation, **2)** reducing propagation and **3)** inhibiting chronic signalling or signalling inhibition. Pathways reviewed in more detail in ^{2,7-10}.

Figure 2: The impact of ageing, ovarian cancer and multiple myeloma disease and treatment on T cell function. Ageing, 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 ageing mechanisms and inflammation further. Changes are observed across ageing, OC and MM in a number of key immune or stromal cell subsets. In ageing, 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 T_{REG} 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 T_{REG} cells during active MM. In terms of the characteristics of Dys. T cells, chronic signalling 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- κ B signalling 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.

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