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The role of the T cell in age-related inflammation

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Abstract Ageing is accompanied by alterations to T-cell immunity and also by a low-grade chronic inflammatory state termed inflammaging. The significance of these phenomena is highlighted by their being predictors of earlier mortality. We have recently published that the proinflammatory cytokine TNFα is a strong inducer of $CD4^+$ T-cell senescence and T-cell differentiation, adding to the growing body of literature implicating proinflammatory molecules in mediating these critical age-related T-cell alterations. Moreover, the inflammatory process is also being increasingly implicated in the pathogenesis of many common and severe age-related diseases, including cancer, cardiovascular diseases and type 2 diabetes. Furthermore, major age-related risk factors for poor health, such as obesity, stress and smoking, are also associated with an upregulation in systemic inflammatory markers. We propose the idea that the ensuing inflammatory response to influenza infection propagates cardiovascular diseases and constitutes a major cause of influenza-related mortality. While inflammation is not a negative phenomenon *per se*, this age-related dysregulation of inflammatory responses may play crucial roles driving age-related pathologies, T-cell immunosenescence and CMV reactivation, thereby underpinning key features of the ageing process.

Keywords Immunosenescence · Inflammaging · Influenza · Inflammation · TNFα · p38

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Introduction

Ageing is accompanied by a progressive, multidimensional, physiological degeneration with immune system alterations thought to play a key role in regulating these declines (suggested by Gorczynski and Terzioglu 2008). This decrease in immune cell activity is in part mediated by the accumulation of factors in the serum of old animals and humans (Gomez et al. 2006; Bagnara et al. 2000). In particular, the in vitro addition of exogenous interleukin (IL)-2 can rejuvenate many lymphocyte functions of the aged (Haynes et al. 2000; Haynes and Eaton 2005). The complex immune system remodelling observed during ageing includes a well-characterised profound modification of the cytokine network. A key feature of this phenomenon is a decrease in IL-2 plasma levels alongside an increase in proinflammatory molecules, particularly tumour necrosis factor α (TNFα) (Bruunsgaard et al. 2003a), IL-6 (Cohen et al. 1997) and C-reactive protein (CRP) (Ballou et al. 1996). These circulating inflammatory parameters can be positively correlated with each other, suggesting a

generalised activation of the entire inflammatory network (Bruunsgaard et al. 2003a). However, this increase in proinflammatory agents is much smaller than that attained during an acute phase response, and ageing is thus said to be associated with a low-grade chronic proinflammatory condition that has been termed 'inflammaging' (Franceschi et al. 2000). Although inflammation is critical for dealing with infections and tissue damage, inflammaging appears to be physiologically deleterious and is predictive of all-cause mortality in multiple elderly cohorts (Bruunsgaard et al. 2003a, b). This age-related inflammatory activity is composed of local events and systemic activation of both the innate and adaptive immune system. The role of the innate immune system has been reviewed elsewhere (see Licastro et al. 2005), and as T-cell functional alterations are recognised as the most significant and best-characterised feature of immunosenescence (Pawelec et al. 2009), this article will concentrate on the role of T cells in age-related inflammation.

Age-related remodelling of the T-cell compartment

Although peripheral T-cell numbers do not diminish with age, the T-cell pool undergoes a striking age-associated remodelling, exhibiting an inverted CD4/CD8 T-cell ratio alongside a diminution in naïve T cells and accumulation of more differentiated memory cells, most profoundly observed within the $CD8^+$ T-cell compartment (Pawelec et al. 2009). Ageing is associated with an accumulation of $CD8^+$ T cells lacking expression of the lymphoid homing receptor CCR7 and the costimulatory molecules CD27 and CD28 alongside re-expressing CD45RA, termed T effector memory cells re-expressing CD45RA (T_{EMRA}). These T_{EMRA} produce large amounts of proinflammatory cytokines allowing them to potentially participate in immune pathology (Zhang et al. 2002). The significance of these age-related phenotypic changes is highlighted by their inclusion in the immune risk phenotype (IRP), a cluster of immune parameters associated with poor immune function and predictive of earlier mortality (Wikby et al. 2002), characterised by an inverted CD4/CD8 ratio, increased levels of $CD28^-CD8^+$ T cells, poor T-cell mitogen responses, low B-cell counts and cytomegalovirus (CMV) seropositivity.

CMV is associated with global changes to the host's immune profile, which are particularly well documented in the peripheral T lymphoid pool (van de Berg et al. 2008), being associated with lymphocyte phenotype alterations very similar to those published as age-associated (Weinberger et al. 2007). Proinflammatory cytokines have been substantially implicated in these age- and CMV-related alterations to T-cell immunity. Indeed, accelerated immune ageing is observed in many inflammatory conditions including rheumatoid arthritis (RA), whereby patients have prematurely aged immune systems by over 20 years (Goronzy et al. 2010). Moreover, TNFα, which is augmented by ageing and CMV infection (Geist et al. 1997), induce CD28 expression loss and T-cell differentiation, in RA and ankylosing spondylitis, where these immune alterations are reversible following anti-TNFα therapy (Parish et al. 2009; Bruns et al. 2009; Bryl et al. 2005). Interferon-alpha (IFNα), secreted at high levels in response to CMV (Fletcher et al. 2005), is a component of inflammaging (Giunta 2008) and induces T-cell differentiation (Fletcher et al. 2005). Indeed, IFNα induces production of IL-15 (Zhang et al. 1998), which induces CD45RA re-expression on $CD45RO^+$ EBV- and CMV-specific and bulk $CD8^+$ T cells (Dunne et al. 2005).

Ageing is also associated with impairment of lymphocyte telomerase upregulation and progressive telomere attrition (van de Berg et al. 2010), the significance of which being a strong correlation between shortened lymphocyte telomeres and a variety of age-associated pathologies (reviewed in Calado and Young 2009) and predictive of earlier mortality (Cawthon et al. 2003). TNFα and IFNα are also implicated in this age-related telomere shortening, as they inhibit lymphocyte telomerase activity (Reed et al. 2004; Parish et al. 2009). When telomeres reach a critically short length, they initiate a DNA damage response that can induce apoptosis or growth arrest termed replicative senescence, an increasingly recognised important factor in T-cell immunosenescence (reviewed in Akbar and Henson 2011). It has been shown that p38 MAP kinase is one of the key molecules that regulate both telomere dependent and independent senescence (Li et al. 2011a), with roles in cellular activation, proliferation, and cell cycle progression (Rincon and Pedraza-Alva 2003). Signalling through the p38 MAP kinase pathway can be reversed, inducing functional augmentation of $CD4^+$ T_{EMRA} (Di Mitri et al. 2011) and virus-specific $CD8^+$ T cells (Henson et al., author communication). TNFα is further implicated in lymphocyte senescence by its ability to activate p38 (Di Mitri et al. 2011). p38 signalling is implicated in the

production of IFNγ by $CD4^+$ and $CD8^+$ T cells (Merritt et al. 2000; Dodeller et al. 2005), a potent inducer of macrophage TNFα production (Williams et al. 1992), and p38 may also be directly involved in T-cell TNFα production (Schafer et al. 1999). Therefore, a vicious circle is set up, whereby ageing and CMV upregulate proinflammatory markers, driving T-cell differentiation and activating p38, pushing T cells towards senescence and inducing further inflammatory cytokine production (Fig. 1).

Molecular mediators of age-related inflammation

Well-defined molecular inflammatory processes underpin inflammaging and age-related diseases (Chung et al. 2006; Franceschi et al. 2000). The transcription factor NF-κB, thought to be the master regulator of the inflammatory process, controls the transcription of proinflammatory molecules such as cytokines, chemokines, matrix metalloproteinases, adhesion molecules, COX2 and iNOS (Chung et al. 2009; Franceschi et al. 2007). The NF-κB pathway is activated by the PI3K/AKT, MAPK pathways and cytokines. Its activity can also be modulated by IκB kinase (IKK; reviewed in Li and Verma 2002). Activation of NF-κB is greatest amongst the T_{EMRA} subset of $CD8^+$ T cells (Gupta et al. 2006). However, unlike other organs where both MAPK and NF-κB activity increase with age (Kim et al. 2002), in lymphocytes, the activation of NF-κB is diminished amongst old subjects (Gupta et al. 2005). This is due to age-related alterations in T-cell signalling and CD28 loss, decreasing AKT phosphorylation and DNA-binding activity of the NF-κB complex (reviewed in Larbi et al. 2011).

The FoxO family of transcription factors link the AKT, MAPK and NF-κB signalling pathways to regulate the oxidative stress response (Kops et al. 2002). Phosphorylation of AKT directly interferes with FoxO binding to target DNA sequences causing the nuclear export and exclusion of FoxO (Birkenkamp and Coffer 2003). In the absence of AKT signalling, FoxO proteins promote transcription of catalase and MnSOD. The accumulation of ROS during ageing activates NF-κB through the phosphorylation of FoxO leading to the downregulation of MnSOD and catalase, further increasing intracellular ROS (Fig. 2). Once again while aged kidneys exhibit upregulated levels of phosphorylated FoxO (Kim et al. 2008), highly differentiated $CD4^+$ T cells display low levels of phosphorylated FoxO, but rather than being protective, these cells are more prone to apoptosis (Riou et al. 2007).

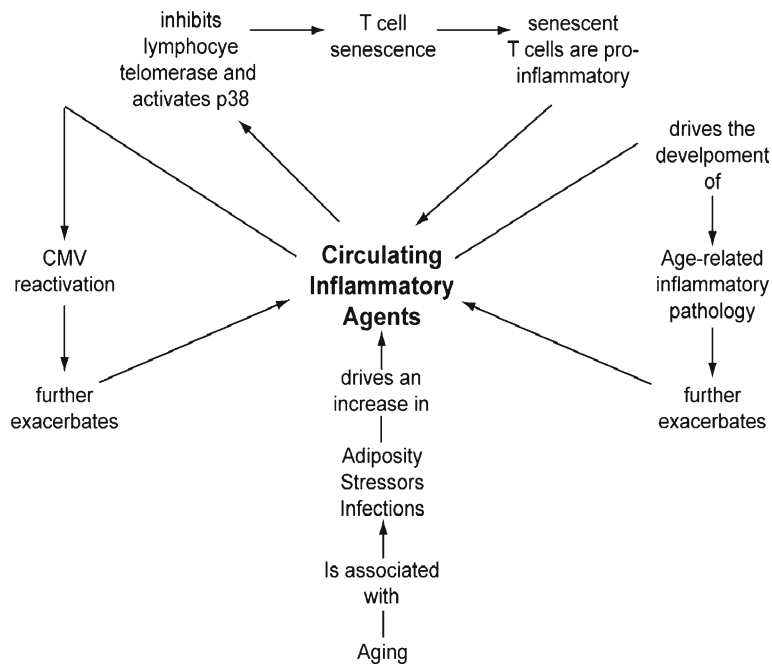

Fig. 1 The vicious cycle of inflammaging. Ageing is associated with augmented ROS and antigenic stress that drives systemic macrophage activation. This, alongside increased adiposity and infection incidence, results in an upregulation in circulating inflammatory mediators that promotes the development of age associated inflammatory diseases, CMV reactivation and T-cell senescence. These in turn further exacerbate inflammaging in a positive feedback loop

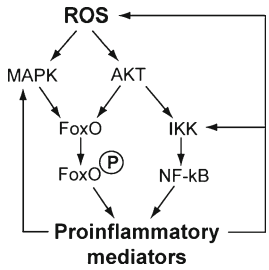

Fig. 2 The mechanism of age-associated inflammation. ROS activates MAPK and AKT signalling pathways leading to the phosphorylation of FoxO proteins and the subsequent down-regulation of MnSOD. Elevated signalling causes an increase in NF-κB activity leading to the generation of more ROS

Age-related pathologies

Inflammation is being increasingly implicated as a characteristic part of the pathological process of many age-related diseases, including RA (Feldmann and Maini 2003), cardiovascular diseases (Libby et al. 2010), cancer (Grivennikov and Karin 2011), osteoporosis (Lencel and Magne 2011), metabolic syndrome (Monteiro and Azevedo 2010), frailty syndrome (Ershler 2007) and Alzheimer's disease (Morales et al. 2010). Suffering from an inflammatory disease acts as a risk factor for other pathologies of old age, setting up a positive feedback loop whereby the systemic inflammatory response associated with diseases of old age initiates and propagates further pathologies (Fig. 1). Indeed, RA patients exhibit a reduced life expectancy of up to 18 years that has been attributed to an increased risk of cardiovascular events (Van Doornum et al. 2002). Metabolic syndrome is frequently observed in diverse inflammatory conditions, including psoriasis (Cohen et al. 2008), RA (Chung et al. 2008) and HIV (Sobieszczyk et al. 2008). Furthermore, muscle wasting (Morley et al. 2001) is substantially over-represented amongst RA (Beenakker et al. 2010), HIV (Wanke et al. 2000), cancer (Dewys et al. 1980) and COPD (Debigare et al. 2001) patients. The efficacy of therapies that target TNFα, IL-6 and IL-1β in treatment of a wide variety of inflammatory conditions (reviewed in Dinarello 2011) heavily implicates these cytokines as causative pathological agents. This is best characterised in the context of RA, in which anti-TNFα treatments are used not only for rapidly controlling joint damage but also reducing RA-associated insulin resistance (Gonzalez-Gay et al. 2010), osteoporosis (Seriolo et al. 2006) and CVD disease risks (Westlake et al. 2011). Additionally, NSAID use is associated with reduced cancer incidence and mortality (Rothwell et al. 2011; Ruder et al. 2011) and anti-IL-6 therapy may be an effective anti-cancer agent (Rossi et al. 2010). Nevertheless, though efficacious in acute myocardial infarction models, clinical trials of TNFα blockade in cardiac heart failure patients were either ineffective (Mann et al. 2004) or mediated deleterious effects (Chung et al. 2003). This may reflect cardioprotective effects of TNFα and IL-6 at low concentrations and durations of exposure (El Ani et al. 2007; Wang et al. 2007b). This highlights that although augmented levels of proinflammatory cytokines may be implicated in age-related immunopathology, any therapeutic approach must take into account their critical physiological roles.

Interventional approaches for reducing inflammation

A reduction in calorie intake (CR) appears to consistently decrease the biological rate of ageing in a variety of organisms, as well as protect against age-associated diseases. The anti-inflammatory effects of CR, rather than being simply a passive mechanism linked to the reduction in inflammatory stimuli, may also effect metabolic, hormonal and gene expression products that repress pathways of inflammation (Fontana 2009; Gonzalez et al. 2011). CR has been shown to enhance anti-inflammatory molecules (Swindell 2009) and inhibit proinflammatory mediators (Kim et al. 2002). However, CR has been shown to impact on immunity (Jolly 2004), improving IL-2 production and T-cell proliferation but impairing innate responses (Nayak et al. 2009). Furthermore, it has been suggested that there is an optimal window during adulthood where CR can delay T-cell senescence and improve immunity. Indeed, inappropriate initiation of CR may be harmful to the maintenance of T-cell function (Messaoudi et al. 2008).

Although CR has beneficial effects in humans (Heilbronn et al. 2006), such a diet is unlikely to be widely adopted and would pose a significant risk to the frail, critically ill or the elderly. This has led to the development of CR mimetic (CRM) compounds that provide some of the benefits of CR without a reduction in caloric intake (Ingram et al. 2004). The best studied CRM is resveratrol, a polyphenolic compound found in grapes, red wine, peanuts and some berries owing to its ability to activate SIRT1 and extend lifespan in cell cultures and animal models (reviewed in

Baur and Sinclair 2006). SIRT1, a negative regulator of NF-κB, is a target of resveratrol and its supplementation has been shown to suppress the release of proinflammatory cytokines (Li et al. 2011b; Pearson et al. 2008). When given to healthy adults, their mononuclear cells showed a significant reduction in the generation of ROS and proinflammatory cytokines (Ghanim et al. 2010).

Major age-related health factors

Major risk factors for poor health in old age are also associated with alterations to systemic inflammatory markers, which underlie many of their health altering effects. Indeed, obesity, smoking and psychological stress are accompanied by an upregulation in circulating inflammatory parameters (reviewed by Gouin et al. 2008), also observed following the menopause (Abu-Taha et al. 2009) and may be associated with declining testosterone levels in ageing men (Maggio et al. 2006). Conversely, key behaviours associated with health benefit such as exercise (Carrel et al. 2009), weight loss amongst obese individuals (Forsythe et al. 2008) and smoking cessation (Bakhru and Erlinger 2005) are also coupled with reductions in systemic inflammatory indices. These circulating inflammatory molecules may propagate and exacerbate age-related inflammatory pathologies. Moreover, proinflammatory agents can induce insulin resistance (Wen et al. 2011), contributing towards a hyper-triglycaemic state, lipid accumulation in tissues with lipotoxic effects (reviewed in Sethi and Vidal-Puig 2007).

Seasonal influenza

An influenza epidemic occurs each winter, infecting up to one fifth of individuals and causing substantial levels of morbidity and mortality amongst aged populations (Centres for Disease Control and Prevention 2010). Current UK health policy targets over 65-year-olds for influenza vaccination and cohort studies demonstrate a 47% reduction in all-cause mortality amongst old vaccinated individuals compared with their non-vaccinated counterparts (Wang et al. 2007a). However, this figure provokes controversy, as amongst aged individuals this vaccine has a low efficacy (Goodwin et al. 2006) and influenza is estimated to account for only 5% of excess deaths during winter (Simonsen et al. 2005). It is recognised that these cohort studies reporting large decreases in all-cause mortality following influenza vaccination are subject to a number of biases (reviewed in Baxter et al. 2010) and the finding of reduced mortality amongst vaccinated individuals outside of the influenza season is considered evidence of the strength of these biases (Campitelli et al. 2010). Nevertheless, we propose the systematic inflammatory response induced by influenza infection be considered and its role in propagating many age-related inflammatory pathologies, particularly CVDs. Vaccinating against influenza is associated with decreased incidence of myocardial infarction (Siscovick et al. 2000) and stroke (Lavallee et al. 2002). Moreover, in mice, influenza propagates the inflammatory response, the progression and thrombosis of atherosclerotic plaques (Naghavi et al. 2003). Influenza vaccination has been shown to be beneficial in reducing major cardiovascular events amongst acute coronary syndrome patients (Phrommintikul et al. 2011). Furthermore, many other disparate acute and chronic pathogens, such as *Clostridium pneumoniae* (Vainas et al. 2009), HIV (Ho and Hsue 2009), CMV (Simanek et al. 2011) and gum disease-causing bacteria (Kebschull et al. 2010), carry an elevated risk of CVD, suggesting that, rather than the nature of the infectious agent, it is the ensuing host-derived inflammatory response that drives this increased CVD risk. Thus, influenza infection may accelerate atherogenesis, resulting in death months after infection.

CMV

CMV is being increasingly implicated in age-related immune decline. Recent epidemiological data reveal that CMV infection is independently associated with premature mortality (Simanek et al. 2011) and is a component of the IRP (Wikby et al. 2002). CMV induces production of a variety of proinflammatory agents (Qiu et al. 2008), which although seemingly counterintuitive, is advantageous to the virus; inflammatory molecules induce CMV reactivation enabling spreading to other hosts through secretions associated with the inflammatory response (Freeman 2009). Thus, it is tempting to speculate that at least part of the deleterious effects of CMV may be related to its upregulation of proinflammatory agents. CMV seropositive subjects who had high baseline CRP levels were at a substantially increased risk of all-cause mortality compared to individuals that exhibited low CRP levels (Simanek et al. 2011). Moreover, individuals genetically enriched for longevity were more resistant to characteristic CMV-

related immune alterations and exhibited significantly lower CRP levels (Derhovanessian et al. 2010). Thus, proinflammatory molecules and CMV may be engaged in a deleterious cycle with inflammation inducing CMV reactivation which in turn exacerbates the inflammatory response. Epidemiological studies associate CMV infection with multiple chronic inflammatory disorders, whereby active CMV replication is specifically detected at sites of inflammation (reviewed in Freeman 2009). Therefore, the age-related upregulation of proinflammatory molecules may mediate some of its effects through exacerbation of the frequency and consequences of CMV reactivation.

Concluding remarks

This article describes how ageing is accompanied by an upregulation of proinflammatory molecules that is heavily implicated in deleterious age-related alterations to T-cell immunity and in the pathophysiology of many common and severe diseases of old age. Major age-related risk factors for poor health, including infections with influenza and CMV, are also associated with increased levels of circulating inflammatory parameters, which may mediate some of their substantial deleterious health effects. These augmented systemic inflammatory molecules initiate and aggravate further age-related pathologies, drive CMV reactivation and induce T-cell senescence, which in turn further exacerbate inflammaging in multiple positive feedback loops. We propose that this may constitute a major force driving the ageing process.

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Authorship

R.M. surveyed the literature and wrote the paper. S.M.H. and A. A. reviewed the manuscript.