Ageing and myeloid-derived suppressor cells: possible involvement in immunosenescence and age-related disease

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Abstract Infections, cancer and autoimmune diseases occur more frequently in the elderly, and although many factors contribute to this, the age-related remodelling of the immune system, termed immunosenescence, plays a major role. Over the last two decades, studies have evaluated the effect of ageing on both the adaptive and innate arms of the immune system and demonstrated compromised function in several cells including lymphocytes (naïve, effector and memory), regulatory T and B cells, monocytes, neutrophils and NK cells. In addition, a well-documented feature of ageing is the increase in systemic inflammatory status (inflammageing), with raised serum levels of IL6, TNF α and CRP as well as reduced IL10. Recently, myeloid-derived suppressor cells have been the focus of many reports as these cells show immunosuppressive properties and are present in higher frequency during infections, cancer and autoimmunity. Importantly, there have been publications showing increased numbers of myeloid-derived suppressor cells in aged mice and humans. In this review, we

discuss the current literature on myeloid-derived suppressor cells, their possible role in altered immune function in the elderly, and whether it may be possible to manipulate these cells to alleviate age-related immune dysfunction.

Keywords Ageing · Immunity · Myeloid-derived suppressor cells · Infections · Cancer · Autoimmune diseases

Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of myeloid cells (granulocytes, macrophages, dendritic cells) that are at an early stage of development and have immune suppressive capability. In bone marrow, they are 20–30 % of nucleated cells, whereas in the spleen, they represent 4 % under normal physiological conditions (Youn et al. 2008). However, under pathological conditions instead of maturation to effector granulocytes, macrophages and dendritic cell, MDSCs maintain their immature status and accumulate in lymphoid organs and the circulation. An increase in MDSCs has been associated with conditions such as infections, cancer and autoimmunity (Sunderkötter et al. 2004; Diaz-Montero et al. 2009; Zhu et al. 2007).

In mice under tumour conditions, Youn et al. (2008) found that MDSC surface markers were CD11b⁺Ly6G⁺Ly6C^{low} (granulocytes g-MDSCs) and CD11b⁺Ly6G^{neg}Ly6C^{high} (monocytes m-MDSCs). The absence of specific markers for MDSCs in humans

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makes their characterisation more difficult. It has been proposed that human MDSCs are lineage (CD3, CD19, CD56) negative and express CD33⁺HLADR^{low/neg}CD15⁺ (g-MDSCs) (Zea et al. 2005) and CD33⁺HLADR^{low/neg}CD14⁺ (m-MDSCs) (Poschke et al. 2010). In addition, other authors have identified different cell phenotypes with MDSC-like suppressive capability in conditions such as non-small-cell lung cancer (CD11b⁺CD14⁺S100A9⁺), metastatic melanoma (CD14^{neg}CD66b⁺Arginase1⁺), renal cell carcinoma (CD14⁺CD124⁺, CD15⁺CD124⁺, Lin⁻HLA-DR⁻CD33⁺SSC^{high}, SSC^{im}CD14⁺HLA-DR⁻, CD14⁻CD15⁺CD11b⁺), tuberculosis (CD3^{neg}CD244^{high}:CD3^{neg}CD19^{neg}CD56^{neg}CD15^{neg}CD66b^{neg}CD33⁺CD11b⁺CD14^{neg}HLA-DR^{neg/low}) and multiple myeloma (CD14⁺ myeloid cells co-expressing CD15) (Feng et al. 2013; Schilling et al. 2013; Pohla et al. 2013; Yang et al. 2014; Busch et al. 2014).

Regulation of MDSC expansion

Macrophage colony stimulating factor (M-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF) and granulocyte-colony stimulating factor (G-CSF) are associated with MDSC generation. High expression of M-CSF messenger RNA (mRNA) in mice correlates with expansion of MDSCs (Irvine et al. 2006), and high levels of GM-CSF are associated with immune suppression and the increased generation of MDSCs (Dranoff et al. 1993; Serafini et al. 2004). In human donors, G-CSF administration to mobilise stem cells is accompanied by expansion of g-MDSCs (Luyx et al. 2012). In addition, a broad range of cytokines and chemokines including transforming growth factor- β (TGF- β), IL-1 β , IL-6, IL-10, IL-12, IL-13, CC-chemokine ligand 2 (CCL-2), CXC-chemokine ligand 5 (CXCL-5) and CXC-chemokine ligand 12 (CXCL-12) have been shown to affect MDSC expansion and recruitment (reviewed in Ugel et al. (2009)).

It has also been shown that during cancer development, myeloid cell differentiation can be skewed towards MDSCs instead of maturation to dendritic cells and macrophages. Haematopoietic progenitor cells (HPCs) cultured with GM-CSF and IL-4 in CT-26 tumour cell-conditioned medium did not show downregulation of S100A9 mRNA expression compared to HPCs cultured with conditioned medium from NIH 3T3 fibroblasts. S100A9 (myeloid-related protein 14)

is expressed in circulating neutrophils and monocytes but not in resting tissue macrophages. The authors suggested that upregulation of S100A9 protein in HPCs is primarily responsible for defective myeloid cell differentiation in cancer. They also found that the overexpression of S100A9 protein in myeloid cells of transgenic mice was associated with a potent suppressive effect on T cell activity similar to that seen in tumour-associated MDSCs. Moreover, mice lacking this protein mounted an effective anti-tumour immune response and rejected implanted tumours (Cheng et al. 2008).

MDSC immune suppressive function

MDSCs cause suppression of immune cells via several mechanisms (Fig. 1), notably reactive oxygen species (ROS) generated by g-MDSCs, nitric oxide (NO) generated by m-MDSCs, production of arginase, and also by secretion of cytokines such as IL-10 and TGF- β (Youn et al. 2008; Mandruzzato et al. 2009; Gabrilovich and Nagaraj 2009; Vuk-Pavlović et al. 2010).

ROS can induce the loss of the CD3 ζ chain in naïve T cells leading to decreased production of cytokines by these cells (Schmielau and Finn 2001). The suppression of T cell function by NO occurs by mechanisms such as the inhibition of MHC II expression, the induction of T cell apoptosis and the inhibition of JAK3 and STAT5 signalling in T cells (Harari and Liao 2004; Rivoltini et al. 2002; Bingisser et al. 1998). T cells depend on L-arginine for proliferation (Ochoa et al. 2001), and the increased activity of arginase in MDSCs causes enhanced L-arginine catabolism leading to depletion of this non-essential amino acid and inhibition of T cell proliferation (Rodriguez et al. 2007).

NK cells are also suppressed by MDSCs as shown in an experimental model of cancer developed by Li et al. (2009). Here it was reported that the increase in MDSCs in the liver and spleen was associated with downregulation of NK cell function. Using in vivo and in vitro models, the authors found that MDSCs inhibited NK cytotoxicity, NKG2D expression and IFN- γ production.

MDSCs, immunosenescence and ageing

It is now well established that the immune system is profoundly remodelled with age, contributing to the increased risk of infections, cancer and autoimmune

Fig. 1 Major factors secreted by MDSCs and their role in the suppression of immune cells

disease in older adults. The changes to the immune system affect both the innate (Panda et al. 2009) and adaptive arms of the immune system (Su et al. 2013).

For the innate system, there is a skewing of haematopoiesis towards the myeloid lineage (Beerman et al. 2010), reduced functioning of neutrophils (Wenish et al. 2000; Butcher et al. 2001), NK cells (Hazeldine et al. 2012) and monocytes upon challenge, although monocytes from old donors show increased cytokine secretion in the basal state (Hearps et al. 2012). The latter contributes to another key feature of the aged systemic environment with increased levels of serum pro-inflammatory cytokines (IL6, TNF α , hsCRP) and lower levels of anti-inflammatory IL10, termed *inflammageing* (Franceschi and Bonafé 2003; Franceschi 2007). The adaptive immune system also shows profound changes with age, driven largely by the atrophy of the thymus which begins in childhood

in humans (Mitchell et al. 2010). The resulting reduction in production of naïve T cells leads to proliferation of T cells in the periphery (homeostatic proliferation) and an increase in the memory/naïve T cell ratio (Moro-Garcia et al. 2013), which compromises the ability to respond to new pathogens and vaccines. In addition, repeated antigenic challenge through life leads to telomere shortening in lymphocytes (Akbar et al. 2004), thus compromising immune memory. T cells from aged donors are also prone to autoimmune reactions as they lose expression of the co-stimulatory molecules CD28 and express markers normally associated with NK cells, such as NKG2D (Alonso-Arias et al. 2011) and KLRG1 (Onyema et al. 2012), which allow activation by self-antigens.

Increased systemic inflammation and autoimmunity with age are also indicative of reduced immune regulatory function. The literature is sparse on this topic and

there are differences between model species and between reports on the same species. In humans, most authors agree that numbers of naturally occurring T cells with regulatory function increase with age and that the frequency of inducible regulatory T cells declines (reviewed in Jagger et al. (2014)), although others have reported either no change or increased function. There is only a single report on regulatory B cells which has shown that IL10 production declines with age as do the numbers of these cells (Duggal et al. 2013).

To date, there are very few studies concerning the impact of ageing on MDSCs and consequences for immunity in old age (Fig. 2). It has been shown that MDSCs accumulate in the spleen, peripheral lymph nodes, bone marrow and blood of normal aged mice and are significantly increased in the circulation of individuals aged over 60 years (Enioutina et al. 2011; Verschoor et al. 2013). The skewing towards myelopoiesis with age in the bone marrow haematopoietic stem cells (HSCs) may contribute to the increase of MDSCs in older individuals (Chinn et al. 2012).

In addition, aged MDSCs could have a higher suppressive capability and thus contribute to the altered immune response seen in older adults, discussed in more detail below. For example, Enioutina et al. (2011) showed that Gr1⁺CD11b⁺ cells increased in aged mice and were similar to MDSCs isolated from the lymphoid tissues of septic mice. Moreover, stimulation of spleen cells from aged mice caused increases in the percentage of Gr1⁺CD11b⁺ which were pro-inflammatory expressing TNF α , IL6 and IL12(p40). These cells also showed high iNOS and arginase-1 activity and through this route were able to suppress CD4⁺ T cell proliferation and IL2 production. These

authors found defective signalling through the PI3kinase-AKT pathway in Gr1⁺CD11b⁺ cells leading to increased GSK3 β activity and suggested that in vivo depletion of Gr1⁺CD11b⁺ cells or inhibition of GSK3 β could normalise the immune response in aged mice.

Thus, with regard to the effect of ageing on MDSCs, it is reasonable to conclude that the accumulation of MDSCs with age may contribute to some of the immune dysfunction and pathology observed in older adults (Fig. 2). We now consider how MDSCs may play a role in some of the major morbidities associated with older age and in which the immune system is involved.

Infections, MDSCs and ageing

It is now well accepted that susceptibility to both viral and bacterial infections increases with age. For example, data from the World Health Organisation (WHO) show that influenza infections cause per year three to five million severe cases resulting in 250,000 to 350,000 deaths worldwide (WHO 2011). Moreover, 90 % of all influenza-related deaths occur in older individuals mostly those suffering from chronic diseases or immunological disorders (WHO 2005; Beigel 2008; Monto 2010). Although there are vaccination programs for older adults to combat common life-threatening infections, including influenza, the majority of studies have shown that influenza vaccination does not reduce the risk of acquiring respiratory infections (Jackson et al. 2008; Yao et al. 2011; Chan et al. 2013). In addition, as humans age, they lose immunity to infections that they had previously controlled, allowing them to re-emerge. Examples include *Varicella Zoster* which can become active to produce shingles in older people (Levin 2012)

Fig. 2 Events occurring during the ageing process, their contribution to the increase in MDSCs, and the consequences for immunity in older individuals

and tuberculosis (TB) (Guerra-Laso et al. 2013) which can occur in older adults who had previously had immunity to this infection.

In a mouse model of TB, Tsiganov et al. (2014) showed that at the pre-lethal stage, MDSCs accumulate in the lungs, bone marrow, spleen and blood. These findings suggest that MDSCs play a role in TB pathogenesis and the increased numbers of these cells in old age may contribute to the reduced immunity to TB in some older adults. Similarly, Heithoff et al. (2008) showed that young BALB/c mice immunised with a *Salmonella* bivalent vaccine developed cross-protective immunity against clinical isolates of *salmonella* (from humans and farm animals) whereas non-vaccinated mice died 21 days post-infection. In aged C57BL/6 mice, there was a 10-fold increase in the number of bacteria in the spleen compared to young mice and early death of infected aged animals. The authors found a higher percentage of Gr1⁺CD11b⁺ cells in aged mice and concluded that this contributed to the reduced immunity observed in these animals. In humans, du Plessis et al. (2013) observed increased percentages of MDSCs in patients with recent *Mycobacterium tuberculosis* infection and TB. In vitro, these cells caused reduced CD4⁺ T cell production of cytokines and inhibited cell proliferation. Yang et al. (2014) reported in patients with active TB higher percentages of CD3⁺CD244^{high} cells comparable to previously described MDSCs (CD3⁺HLA-DR⁺CD11b^{int}CD33⁺). These cells expressed high levels of NOS and were negatively correlated with CD4⁺ and CD8⁺ T cell activation.

Other groups (Tam et al. 2014) showed that MDSCs (CD11b⁺Ly6C^{hi}Ly6G^{neg}) accumulate in the spleen and liver of mice infected with *Salmonella typhimurium* (*S. typhimurium*). Although in vitro these cells differentiated into macrophage-like cells and were able to present antigen to T cells, MDSCs from infected mice inhibited T cell proliferation ex vivo by producing NO which has been shown previously to cause immunosuppression in salmonellosis. The authors concluded that MDSCs provide a balance of protective and immunosuppressive functions in response to *Salmonella* infection and the tipping of this balance could affect the outcome of infection. Thus, the reduced macrophage and T cell function seen in old age could tip the balance towards immune suppression.

In the case of viral infections, MDSCs have been reported to be increased in patients with chronic hepatitis C infection and correlated with increased hepatitis C

virus (HCV) RNA load. Also, liver-infiltrating CD8⁺ T cells from these patients had a lower TCR ζ expression than cells from peripheral blood. Crucially, treatment with pegylated interferon- α /ribavirin and improved response against infection was associated with a decreased frequency of MDSCs, suggesting that these cells could contribute to HCV persistence (Zeng et al. 2014).

These studies show that in young adults (animals and humans), the increase in MDSCs is associated overall with a lower immune response against bacterial and viral infections. The question is whether the increased MDSCs seen with age result in increased susceptibility to infection. Further research is now needed to determine a causal link between increased MDSCs and infection in aged mice and ultimately in humans too.

Cancer, MDSCs and ageing

Cancer incidence shows a profound relationship with older age. Data from Switzerland show that both older (>70 years) women and men have a higher cancer incidence than young adults (20–49 years), respectively 13.11 and 7.35 % (colon), 12.7 and 6.69 % (lung/bronchus/trachea), and 31.24 and 3.44 % (prostate) (NICER 2014). Data on the incidence of cancer in the UK (1975–2007) showed a higher incidence for all cancers (excluding non-melanoma skin cancer) in males and females aged from 65 to 74 and 75+ years old than in individuals from 10 to 14, 25–49, or 50–64 years old (Mistry et al. 2011). Reports are now emerging suggesting that increased frequency of MDSCs may play a role in the reduced immune surveillance of cancer.

Grizzle et al. (2007) showed that Gr1⁺CD11b⁺ MDSCs increased in the spleen from young (2-month-old) to mature (12-month-old) BXD12 mice. In the older mice, injected mammary adenocarcinoma (TS/A) cells became established, whereas in young animals, the tumour regressed 4 weeks after implantation. Splenic T cells from mice implanted with tumour were co-cultured with TS/A cells, and it was observed that T cell cytotoxicity and IFN- γ production were higher in young mice. Adoptive transfer of MDSCs from older mice to young mice injected with TS/A led to a delay in tumour rejection, and depletion of MDSCs in older mice slowed tumour growth. Moreover, arginase-1 production and activity were higher in splenic MDSCs from older mice, and its inhibition partially restored T cell cytotoxicity to

TS/A tumour cells. Taken together, these data suggest that the immunosuppressive effect of MDSCs can subvert the immune system of adult healthy mice and their raised numbers in old mice may add to cancer susceptibility. Furthermore, in a model of murine melanoma, the depletion of MDSCs in aged mice (using an anti-Gr-1 antibody) improved anti-tumour immunity (Hurez et al. 2012).

In humans, Verschoor et al. (2013) enumerated MDSCs in peripheral blood mononuclear cells (PBMC) from adults (19–59 years), community-dwelling seniors (61–76 years) and frail elderly (67–99 years). They found a significant increase in numbers of MDSCs in seniors and frail elderly in comparison with healthy young adults. Moreover, 23 donors from community-dwelling and frail elderly which had a history of cancer (breast, lung, prostate, skin, colon) had significantly higher numbers of MDSCs even though they were in partial or complete remission. In seven patients with advanced stage melanoma (<60 years old, $n=2$; 63–81 years old, $n=5$) treated with ipilimumab (a CTLA-4 antagonist), there was a decrease in the granulocytic MDSC population after the first dose which remained low at week 9 in comparison with baseline levels (Pico de Coaña et al. 2013). Importantly, MDSC granulocytic function was also reduced based on the production of arginase-1. Iclozan et al. (2013) evaluated patients (48–74 years old) with small-cell lung cancer who received a standard platinum/etoposide regimen and 4–6 weeks later were vaccinated with dendritic cells (DCs) or DC and all-trans retinoic acid (ATRA) therapy which has been shown to reduce MDSCs (Nefedova et al. 2007). Vaccine + ATRA decreased MDSC numbers, led to a higher number of patients with detectable p53 responses and increased the frequency of granzyme B⁺ CD8⁺ T cells (Iclozan et al. 2013).

Patients with metastatic renal cell carcinoma (mRCC) have been shown to have a higher circulating number of MDSCs compared to healthy controls (Kusmartsev et al. 2008). A study of mRCC patients treated with the frontline therapy sunitinib determined the effect on MDSCs (Ko et al. 2009). Sunitinib blocks cell signalling by vascular endothelial growth factor receptors (VEGFRs), and increased VEGF levels have been implicated in the generation of MDSCs (Gabrilovich et al. 1998). After two cycles of treatment, the frequency of circulating MDSCs declined significantly, and in vitro, the median production of IFN- γ

after T cell stimulation was similar to controls. However, there was no correlation between changes in tumour burden, response to treatment, or survival and changes in MDSCs or T cell modulation suggesting that other mechanisms could be involved. Thus, there are now several reports of an increase in MDSCs in a broad range of cancers, but further proof of causality is required.

Autoimmune disease, MDSCs and ageing

The increased risk of autoimmune disease with ageing has been associated with several factors including changes in immune regulatory mechanisms. For example, patients with myasthenia gravis (MG) and aged <40 years have been reported to have a lower risk of autoimmune antibody (anti-acetylcholine receptor) titre elevation compared to patients aged >60 years (Iwasa et al. 2014). Also, patients with early-onset MG (<40) had lower antibody elevation than patients with late-onset disease (>60). The authors concluded that patients with late-onset MG could have an immunological susceptibility to extrinsic triggers and loss of tolerance. Alterations in the immune system during ageing could contribute to loss of tolerance as discussed above.

Changes in frequency and function of regulatory T (CD4⁺CD25⁺Foxp3⁺; Tregs) and B (CD19⁺CD24^{hi}CD38^{hi}; Bregs) cells have been reported in autoimmune conditions (Knippenberg et al. 2011; Ryba-Stanislawowska et al. 2013). These cells exert suppressive functions, and thus, alterations in Tregs and Bregs occurring in ageing could disrupt both immunologic homeostasis and prevention of autoimmunity. Patients with active systemic lupus erythematosus (SLE) show a significant reduction in the suppressive function of Tregs (after phytohaemagglutinin (PHA) stimulation) compared to healthy donors and SLE patients in remission. However, Tregs from SLE patients stimulated in vitro with plate-bound anti-CD3 and IL-2 (high doses) recovered their suppressive function, suggesting the possibility of therapeutic intervention (Valencia et al. 2007).

As stated above, studies of Tregs in healthy older individuals are contradictory with reports of cell frequency showing increases (Lages et al. 2008; Schimtt et al. 2013) or no difference (Hwang et al. 2009) in CD4⁺Foxp3⁺ cells with ageing. Lages et al. (2008) have shown in functional studies of CD4⁺CD25⁺ T cells

(Tregs) in seven old subjects (≥ 70 years) that their ability to inhibit proliferation of PHA-stimulated monocytes was seen in some ($n=4$) but not all ($n=3$) donors. Hwang et al. (2009) compared old (≥ 65 years old) and young (≤ 40 years old) individuals and observed that in culture $CD4^+ CD25^{bright}$, Tregs from both ages caused similar levels of suppression of cytokine production and proliferation of $CD4^+ CD25^{neg}$ T cells. However, they also found that IL10 levels from the co-culture of $CD4^+ CD25^{bright}$ and $CD4^+ CD25^{neg}$ T cells were lower with cells from old donors suggesting that the control of inflammation at the tissue level could be impaired with age. Schimtt et al. (2013) evaluated four age groups of healthy individuals (20–34, 35–49, 50–65, >65 years old) and found that frequency of $CD4^+ Foxp3^+$ T cells was reduced and the $T_H17/Treg$ ratio was significantly increased in individuals older than 65 years compared to the 20–34 years old group. However, after stimulation of PBMCs, there was a decline in the $T_H17/Treg$ ratio. The authors suggested that a disturbed balance between these T cell populations during the ageing process could contribute to the increased inflammation and poor response to infections seen in older adults.

In healthy individuals, it has been shown *ex vivo* that $CD19^+ CD24^{hi} CD38^{hi}$ Bregs can maintain the equilibrium between Tregs and T_H1/T_H17 (T effector cells) populations. However, Bregs from rheumatoid arthritis patients did not convert $CD4^+ CD25^{neg}$ cells into Tregs or prevent the differentiation of naïve T cells into T_H1 and T_H17 (Flores-Borja et al. 2013). In addition, Duggal et al. (2013) showed that young adults (20–36 years) had higher Breg frequency, number and function compared to older (60–84 years) healthy individuals. Older individuals also showed impaired Breg IL10 expression, and there was a negative correlation between Breg IL10 production and autoantibody (rheumatoid factor) levels. Thus, age-related changes in Tregs and Bregs could contribute to the increased autoimmunity and reduced immune tolerance seen in older adults. But, what of a potential role for MDSCs?

Kurkó et al. (2014) also evaluated patients with RA (33–61 years old) and observed that $CD11b^+ CD33^+ HLA-DR^{low/neg} CD14^{neg} CD15^+$ (g-MDSCs) cells were the most frequent MDSCs in synovial fluid (RASf) whereas a very low $CD11b^+ CD33^+ HLA-DR^{low/neg} CD14^+ CD15^{neg}$ (m-MDSCs) cell population was present. Stimulated T cells (anti-CD3/CD28) from PBMCs showed lower proliferative capability in the presence of autologous RASf than in its absence, suggesting that MDSCs present in RASf may

be essential to negatively regulate local T cell expansion and inflammation/autoimmunity even though these cells may contribute to collateral damage to joint tissues.

Iannou et al. (2012) evaluated MDSCs from subjects with multiple sclerosis (MS) in the active phase of disease and during remission. Patients with active MS had a significantly higher frequency and number of MDSCs in the peripheral blood compared with patients in remission and healthy controls. Moreover, the presence of MDSCs from active MS patients in culture suppressed the proliferative response of autologous responder T cells and reduced the secretion of IL-2. Patients with active ulcerative colitis and Crohn's disease showed a significant increase in circulating MDSCs compared with healthy controls. IFN- γ secretion by peripheral blood mononuclear cells after *in vitro* stimuli was more suppressed by MDSCs derived from IBD patients than from healthy controls (Haile et al. 2008). In this case, one could argue that active colitis induced the increase in MDSCs that in turn inhibited the development of a more severe inflammation. In addition, in rheumatoid arthritis (RA) patients, there was an increase in circulating MDSCs and plasma arginase-1 compared to healthy controls and a negative correlation between increased circulating MDSCs and Th17 inflammatory cells in RA patients (Jiao et al. 2013).

MDSCs and the development of T regulatory cells (Tregs)

Hoechst et al. (2011) isolated myeloid-derived suppressor cells ($CD14^+ HLA-DR^{low/neg}$ MDSCs) and monocytes ($CD14^+ HLA-DR^+$) from human PBMCs and found *ex vivo* that these cells were capable of inducing respectively the generation of regulatory T cells ($Foxp3^+$, iTreg) and IL-17-secreting $RORc^+$ Th17 (effector) cells when co-cultured with autologous $CD4^+$ T cells. In addition, MDSCs also converted Th17 cells into $CD4^+ Foxp3^+$ Treg cells (Hoechst et al. 2011).

An increase in MDSCs and the induction of Tregs could present advantages and disadvantages depending on the context. Considering pathologic conditions, such as autoimmune diseases, the increased frequency of MDSCs and Tregs could inhibit tissue damage and disease progression. In a mouse model of MS treated with the calpain inhibitor SNJ-1945, a reduced disease score was reported with an increase in MDSC

frequency, a relative increase in Tregs, and a decrease in Th17 cells. The treatment prevented the infiltration of immune cells in to the central nervous system (CNS), decreased myelin basic protein degradation and caused increased myelin protection (Trager et al. 2014).

On the other hand, cancer development has been associated with an increased percentage of MDSCs and Tregs (Jordan et al. 2013; Kalathil et al. 2013; Yu et al. 2013). Chronic lymphocytic leukaemia (CLL) patients (69.4±8.5 years old) have been reported to have a significantly higher number of MDSCs (CD14⁺HLA-DR^{low}) compared to healthy donors. MDSCs and T cells from CLL patients were co-cultured, and T cell proliferation upon activation was inhibited. Moreover, CLL patients also showed an increased frequency of circulating Tregs (Jitschin et al. 2014; Krause et al. 2014).

MDSCs as a target for diseases of ageing

The increased number and frequency of MDSCs in older adults and the poor immune response observed in these individuals have led several authors to suggest that the depletion of MDSCs or the inhibition of their function could improve immunity in the aged, including the response to vaccines, infections and cancer.

Studies evaluating the depletion of MDSCs and their immune suppressive products (arginase-1, ROS, iNOS) have been performed in animal models, but the results whilst promising are inconsistent. In these studies, some results have shown increased anti-tumour effects and improved bacterial clearance (Morales et al. 2009; Heim et al. 2014), whilst others found no benefit in preventing tumour progression (Ma et al. 2012; Thaci et al. 2014).

In patients, there are few studies of the effect of MDSC depletion or inhibition, and those carried out to date have not had MDSCs as their primary target, although several have measured their frequency pre- and post-therapy. The data can be summarised as follows:

Cancer Ipilimumab (CTLA4 antagonist) was used by Pico de Coaña et al. (2014) and Tarhini et al. (2014) in patients with melanoma and was shown to reduce MDSCs in both studies, but for Tregs, a decrease and increase were reported respectively. Tarhini et al. (2014) observed a potent CD4⁺ and CD8⁺ antigen-specific T cell immunity against testicular cancer (NY-ESO-1) and melanocytic lineage (MART-1, gp100) antigens. Tumour-infiltrating CD3⁺CD4⁺ and CD3⁺CD8⁺ T cells

were activated with evidence of induction/potentialiation of memory T cells. Other studies (Kaufman et al. 2010; Finke et al. 2011) have shown that favourable patient outcome is associated with low levels of intratumour/lesion MDSCs and levels of T cells responsiveness similar to healthy donors. However, it has also been observed that the treatment for prostate cancer (LHRH-agonist leuprolide in combination with either an anti-androgen or dexamethasone) in patients older than 60 years is associated with higher percentages of MDSCs (Vuk-Pavlović et al. 2010).

Infections There are few studies in this area. Vollbrecht et al. (2012) showed that chronically HIV-infected HAART-naïve individuals had significantly higher MDSC levels than healthy controls which was positively correlated with the viral load and negatively correlated with CD4⁺ T cell count. Qin et al. (2013) found a significant increase of MDSCs in HIV-1-seropositive patients in comparison with healthy controls even in the presence of efficient anti-retroviral therapy. A high MDSC frequency again correlated with HIV-1 disease markers and CD4⁺ T cell loss. MDSCs suppressed T cell responses in antigen-specific and non-specific ways which was dependent on arginase-1 induction and direct cell-cell contact. Cai et al. (2013) evaluated patients with chronic hepatitis C infection (CHC) pre- and post-antiviral therapy (Peg-IFN- α and Ribavirin) for 48 weeks. They found a high level of MDSCs in the circulation which correlated with HCV RNA and activated CD4⁺ and CD8⁺ CD38⁺ T cells. Treatment reduced MDSC levels by 4 weeks while it rebounded at week 12 post-therapy. MDSCs from CHC suppressed T cell function in an arginase-1-dependent manner.

Conclusions

Ageing is a complex process affecting several systems, and the organism's plasticity is essential to maintain homeostasis. The immune system is composed of an intricate network of cells and soluble effectors which interact to ensure that the body provides a defence against pathogens, foreign antigens and cancers while not harming the host. The ageing of the immune system results in compromise to each of these aspects of immunity, represented by increased susceptibility to infection, cancer and autoimmune disease. Myeloid-derived

suppressor cells are a newly described regulatory component of the immune system, and in healthy ageing, the frequency of these cells increases. MDSCs also accumulate in several age-related diseases, but further research is now needed to determine causality and if reducing MDSC frequency may help or hinder the treatment of such diseases.

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