# Myeloid-Derived Suppressor Cells in Aged Humans

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**Abstract**

Myeloid-derived suppressor cells (MDSCs) are immature myeloid cells whose immunosuppressive activities contribute to cancer and other diseases. MDSCs appear to increase with age, and this presumably contributes to immunosuppression and the increased incidence of certain diseases. Why MDSCs increase with age is not entirely clear. Herein we present evidence that MDSC expansion is due in part to age-related changes in hematopoiesis, including the acquisition of mutations that favor myelopoiesis, which are compounded by changes in the aging microenvironment that favor the production of MDSCs.

**Keywords**

Immunosenescence • Myeloid-derived suppressor cells • Inflammation • Myelodysplastic disorders • Myelopoiesis

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## Contents



## Introduction

It has been known for over a century that the presence of some cancers caused an increase in extramedullary hematopoiesis and neutrophilia and that these cells had immunosuppressive properties (reviewed in Talmadge and Gabrilovich 2013). Further characterization of these cells indicated that they were of myeloid origin and that their presence was often a negative prognostic indicator for tumor progression or cancer survival (Talmadge and Gabrilovich 2013). We now know that these myeloid-derived suppressor cells (MDSCs) are immature myeloid precursors that are generated due to dysregulated myelopoiesis which may occur as a response to soluble factors secreted from tumors or due to alterations in the hematopoietic niche that occur as a result of myelodysplasia and other myeloid cancers. Interestingly, many of the changes in the bone marrow and circulation that are associated with an increase in myeloid-derived suppressor cells during cancer also appear to occur during aging and likely contribute to age-related immune dysfunction. In this chapter, we describe the phenotype and function of MDSCs in humans and mice and describe how the aging microenvironment increases myelopoiesis at the expense of proper maturation, leading to increased levels of MDSCs and possibly contributing to age-related immune dysfunction.

## Myeloid-Derived Suppressor Cells (MDSC) Phenotype and Function

The difficulty in characterizing MDSCs is in large part due to the heterogeneity within the cells, due to variation in their maturation status, and the fact that they are morphologically indistinguishable from normal monocytes, neutrophils, and more immature cells, such as promyelocytes (Rodriguez et al. 2009; Solito et al. 2011; Youn et al. 2012). This variability of maturation and phenotype has resulted in confusion as to whether MDSCs are actually a distinct cell or are "pathologically activated" monocytes or neutrophils (Nagaraj et al. 2013). Studies in which it was shown that MDSC could form colonies upon stimulation with colony stimulating factors provided further evidence that they included myeloid precursor cells (Youn et al. 2012). The current consensus is that MDSCs are immature myeloid cells that express either granulocytic (G-MDSC or PMN-MDSC) or monocytic (M-MDSCs) markers, including "early-stage" MDSC (eMDSC) although characterization and

nomenclature issues still abound (Bronte et al. 2016). The general, but not universal, consensus is that mouse G-MDSCs are characterized as $Ly6C^{low}$, $Ly6G^{high}$, and $CD11b^{+}$ and mouse M-MDSCs as $Ly6C^{high}$, $Ly6G^{low}$, and $CD11b^{+}$. One important caveat is that the above mentioned markers for M-MDSCs are often identical to inflammatory/$Ly6C^{high}$ monocytes and very similar to that used for tumor-associated macrophages. Consequently, interpretation of the relative abundance, especially in tumors, is challenging and many researchers use a functional assay of suppression of T-cell proliferation to validate the cell type. A further confounding factor is that M-MDSCs can take on the G-MDSC phenotype in some situations (Youn et al. 2013). Despite the challenges of immunophenotyping mouse MDSCs, the ability to genetically or pharmacologically manipulate their abundance in mice has been used to characterize differences between G-MDSCs and M-MDSCs. For example, although both suppress T-cell responses, they may use different cytokines and signaling pathways to do so (Movahedi et al. 2008). In general, tumors contain both M-MDSCs and G-MDSCs but the relative ratio changes with the tumor type (Movahedi et al. 2008). Fortunately, characterizing human MDSCs is slightly more straightforward. Human PMN-MDSC are characterized as $CD11b^{+}CD14^{-}CD15^{+}$ (or $CD66b^{+}$); human M-MDSC are $CD11b^{+}CD14^{+}CD15^{-}HLA\text{-}DR^{low/-}$. Although eMDSCs are poorly characterized in mice, in humans are characterized as being $Lin^{-}HLA\text{-}DR^{-}CD33^{+}$(Bronte et al. 2016). Age-related changes in myelopoiesis and the probable origin of MDSCs with aging are illustrated in Fig. 1.

Normally, immature myeloid cells (e.g., common myeloid precursors or common granulocyte precursors) are more immunosuppressive than their mature counterparts; however, MDSCs are more immunosuppressive than these myeloid progenitors (Pu et al. 2016). MDSCs suppress the function of both CD8+ and CD4+ T cells, and this contributes to their cancer-promoting properties. Tumors secrete a variety of factors such as colony stimulating factors (CSFs), angiogenic factors (e.g., VEGF), and inflammatory mediators (e.g., IL1β, TNF, PGE2) that influence hematopoiesis and increase MDSC production and promote their recruitment to the tumor where they contribute to local immunosuppression (Bronte et al. 1999; Huang et al. 2007; Bunt et al. 2006; Sinha et al. 2007). Once recruited to the tumor, MDSCs present antigen on both MHCI and MHCII but since they do not express the costimulatory receptors CD80/86, and secrete suppressive factors such as arginase and prostaglandins, the result is immunosuppressive rather than immunostimulatory (Nagaraj et al. 2013). In addition, they produce peroxynitrite (PNT) which inhibits binding of processed antigen to MHC and has also been shown to decrease cytotoxic T-cell function (Lu et al. 2011). They also increase Treg responses by promoting the recruitment of Tregs through secretion of chemokines (reviewed in Nagaraj et al. 2013).

In addition to their role in suppressing T-cell function, MDSCs have been shown to have other contact-mediated functions. For example, they have been shown to impair hematopoiesis and contribute to myelodysplasia in the bone marrow by inducing apoptosis of neighboring erythroid and myeloid precursors via granzyme B mediated contact (Chen et al. 2013). Mouse models indicate that they may be involved in suppressing vaccine responses, contributing to chronic diseases such as

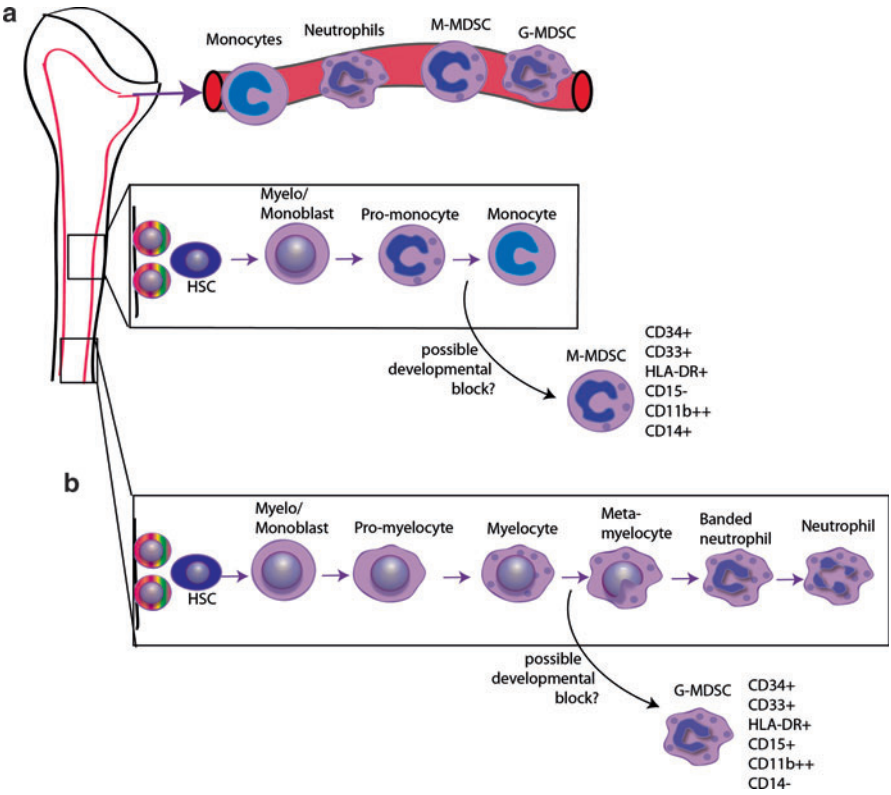


**Fig. 1** Age-related changes in myelopoiesis. (**a**) monocytic-MDSCs (M-MDSCs) express markers that are normally found on pro-monocytes are therefore believed to be produced at greater rates with age due to a developmental block in monopoiesis and (**b**) granulocytic-MDSCs express markers that are normally expressed on myelocytes/meta-myelocytes and are therefore believed to be produced at a greater rate with age due to a developmental block in granulopoiesis

multiple sclerosis and inflammatory bowel disease and chronic infections such as *Trypanasoma cruzi* infection (reviewed in Nagaraj et al. 2013). Although these diseases are diverse in etiology, they all appear to increase expression of Th1 cytokines, especially IFNγ and TNF, and it may be that elevated levels of these cytokines also contribute to age-associated increases in MDSCs. In humans, MDSCs increase in the circulation with age, as do a number of cytokines associated with MDSC production such as TNF, IFNγ, and IL1β (Farha et al. 2013). Whether these cytokines are directly involved in MDSC expansion has yet to be determined; however, based on studies of patients with myeloid cancer, which we discuss below, this seems likely.

## MDSC Ontogeny

MDSCs increase as a result of dysregulated hematopoiesis. Normally, the repertoire of immune cells in the circulation are polyclonal, meaning that they are derived from perhaps a few thousand hematopoietic stem and progenitor cells (HSPC); however, with age, HSPCs' capacity to self-renew (Yahata et al. 2011), to engraft (Kollman et al. 2001), and to differentiate (Pang et al. 2011) decreases. One prominent change in hematopoiesis that occurs with age is the development of "myeloid skewing," which is the increased production of myeloid cells at the expense of lymphoid cells. This phenomenon may explain the increase in MDSCs that occurs in both aging and myeloid cancers.

In the 1980s, it was discovered that the increased representation of myeloid cells during myeloplastic syndrome was a result of the outgrowth of specific progenitor clones. Researchers measured the ratios of expression of X-linked genes in circulating leukocytes (Raskind et al. 1984; Janssen et al. 1989). In females, one of the two X-chromosomes becomes randomly inactivated at the 6–8 cell stage of embryonic development and as a result, each cell that derives from the early progenitors will express only one of the two X-linked alleles. Consequently, one would expect that 50% of the daughter cells would express one version of the gene and 50% the other, but due to the stochastic nature of X-inactivation there is a normal distribution that ranges from 25% to 75%. If the ratio of the alleles is >3:1, this is considered to be a "skewed" ratio, which implies that either the process of X-inactivation was not random or the more likely case in which growth and proliferation of one of the daughter clones is favored. In the 1980s to early 1990s, studies of skewing in leukocytes reported that between 3% and 33% of the female population had clonal skewing, which was challenging to reconcile with contemporary theories of X-inactivation and clonal hematopoiesis. These discrepancies were reconciled when it was discovered that this variability was due to the age of the donors. In fact, not only was there an almost linear increase in leukocyte skewing with age, but the degree of skewing was also more pronounced (i.e., >10:1 ratio) with increasing age (Busque et al. 1996). Subsequent studies have demonstrated that this skewing is not uniform over the entire leukocyte compartment. Lymphoid cells are derived from hematopoietic stem cells that have a normal distribution of X-inactivation but myeloid cells become more skewed with age, implying that fewer clones produce a greater proportion of myeloid cells (Pang et al. 2011; Gale et al. 1997). Subsequent studies have confirmed that there is an age-related increase in expansion of specific clones (Laurie et al. 2012; Genovese et al. 2014) that are generally a result of mutations in genes which provide a growth advantage, such as in the epigenetic modifiers *DNMT3A* and *TET2*, occur more frequently with age, and contribute to expansion of specific myeloid clones (Jaiswal et al. 2014; Busque et al. 2012; Challen et al. 2012). This phenomenon is called "clonal hematopoiesis of indeterminate potential" (CHIP) and is associated with poor health outcomes (Steensma et al. 2015).

There are many theories as to why myeloid skewing occurs. One school of thought suggests that it is a result of intrinsic changes within the HSPCs themselves

(reviewed in Wang et al. 2011; Snoeck 2013). Aged HSPCs appear to have an intrinsic bias toward producing common myeloid progenitors (CMPs) over common lymphoid progenitors (CLPs) with age due to decreased expression of genes associated with lymphoid development and increased expression of genes required for myeloid development (Rossi et al. 2005). Additionally, HSPCs seem to accumulate mutations that either favor production of myeloid cells or provide a growth advantage to specific clones (Shlush et al. 2015). In fact, many mutations that are associated with clonal expansion during myeloid cancers are the same genes that acquire mutations associated with clonal expansion and myeloid skewing with age (e.g., *TET2, DNMT3A, ASXL1,* and *SF3B1*), providing further evidence that these mutations provide a competitive growth advantage (Busque et al. 2012; Steensma et al. 2015; Xie et al. 2014; McKerrell et al. 2015; Shlush et al. 2014; McKerrell and Vassiliou 2015). Whether the increase in MDSCs with age is due to expansion of specific clones that have acquired similar mutations is not yet known.

Although it is generally believed that the majority of MDSCs are released from the bone marrow in the steady state, under certain conditions MDSCs may be formed as part of extramedullary hematopoiesis. For example, in a mouse model of sustained inflammation the presence of TNF increased MDSC numbers in the spleen (Sade-Feldman et al. 2013). Another study found that there was increased replication of myeloid precursors in the spleens of old (18+ month) wildtype but not TNF knockout mice and that resulted in splenomegaly due to the expansion of immature monocytes, but it was not clear whether these included MDSCs (Loukov et al. 2016). The relative importance of extramedullary production versus output from the bone marrow in aging humans is not clear.

As mentioned above, solid tumors secrete factors that result in expansion and recruitment of MDSC, and although the mechanisms are much less well defined, it appears as though this is also a feature of myeloid cancers. MDSC are also expanded in myeloproliferative neoplasms (Giallongo et al. 2014; Wang et al. 2016), myelodysplastic syndrome (Huang et al. 2007; Kittang et al. 2016), and acute myeloid leukemia (Sun et al. 2015). Since MDSCs are also myeloid cells, their expansion may be because they are generated from the same neoplastic clone, although at least one study in MDS suggests this may not always be the case (Chen et al. 2013). Whether the expansion of MDSC that occurs in these myeloid cancers simply reflects a block in differentiation or whether they are bona fide MDSC remains to be fully determined.

## Changes in the Aging Microenvironment Likely Contribute to Expansion of MDSCs

In addition to the intrinsic changes in HSPCs that occur with age, changes within the aging bone marrow likely contribute to increased production of MDSCs. Although the bias toward production of myeloid cells increases with age, even young mice have a few HSPC clones that are intrinsically biased toward producing myeloid cells

(Cho et al. 2008; Beerman et al. 2010; Challen et al. 2010). Changes in the bone marrow microenvironment that occur with age may make these clones more "fit" to survive and proliferate. Many of the soluble mediators associated with increased production of MDSCs (e.g., TNF, IL1β, $PGE_2$) increase in the circulation (Farha et al. 2013) and bone marrow (Brusnahan et al. 2010; Abdelmagid et al. 2015)with age. Whether age-related increases in these cytokines influence MDSC production has not been definitively shown, although age-related abnormalities in monocytes and neutrophils are ablated in old (18mo) TNF knockout mice, implying that reducing the inflammatory milieu may repair myelopoiesis (Loukov et al. 2016; Puchta et al. 2016; Verschoor et al. 2015a). Cytokine production by bone marrow resident or developing leukocytes may also alter the bone marrow microenvironment in a way that is conducive to production of MDSCs. For example, monocyte precursors produce VEGF, which induces production of TNF and IL1β from stromal and myeloid precursors and contributes to defective myelopoiesis (Huang et al. 2007; Bellamy et al. 2001). In addition to cytokines, other soluble factors associated with increased MDSC production also increase with age in the bone marrow. For example, the CD33 ligand, S100A9, is found at higher levels in the bone marrow and plasma of MDS patients compared to healthy controls (Chen et al. 2013) and is transcribed at higher levels in the HSPCs from old mice compared to young (Rossi et al. 2005). Ligation of CD33, which is expressed on myeloid precursors, by S100A9 leads to increased IL-10 and TGF-β production, creating an environment which is conducive to MDSC production (Chen et al. 2013). Lastly, circulating bacterial products such as lipopolysaccharide, muramyl dipeptide, and others increase in the circulation with age (Verschoor et al. 2015a, b). Hematopoietic stem cells express toll-like receptors that sense bacterial products and promote myelopoiesis at the expense of lymphopoiesis (Bellamy et al. 2001; De Luca et al. 2009; Bandow et al. 2010). Although this is an important factor for increased myeloid output during infection, the chronic increase in circulating bacterial products that occurs with age may contribute to pathological defects in myelopoiesis and MDSC expansion.

Myeloid progenitors that have acquired mutations may have a proliferative advantage over normal progenitors in inflammatory environments. This was first demonstrated in a murine model of the congenital bone marrow failure syndrome, Fanconi anemia (FA). Levels of TNF and IFNγ increase in the bone marrow during FA, and HSPC are genetically unstable and sensitive to apoptosis in this inflammatory environment. This creates a selective pressure that favors the outgrowth of HSPCs that have acquired mutations that make them resistant to TNF (Li et al. 2007). Human FA patients have a markedly increased risk of acquiring myelodysplastic syndrome or acute myeloid leukemia, which is likely a result of these selective environmental pressures. Similarly, in myeloproliferative neoplasia, myeloid progenitors produce more TNF and simultaneously acquire mutations that increase resistance to induced apoptosis, which has the end result of promoting expansion of clones with these mutations (Fleischman et al. 2011). Similarly, we have shown that murine *Tet2*- and human *TET2*-mutant HSPC have increased clonogenic potential in vitro, under the stress of environmental TNF or IFNγ

(Abegunde and Rauh unpublished). Since TNF and IFNγ are also increased with age, these may provide a Darwinian advantage to *TET2*- and *DNMT3A*-mutant clones, at least partly explaining the associations between aging, inflammation, and myeloid skewing. We believe this is worthy of further investigation.

Some of the mutations that drive clonal hematopoiesis in older adults may also contribute to the inflammatory environment of the bone marrow, which contributes to the vicious cycle that is inflamm-aging. For example, mutations in the epigenetic regulators *TET2* and *DNMT3A* may produce progeny that also contribute to the environment of inflamm-aging. We and others (Cull et al. 2017; Zhang et al. 2015) have found that macrophages derived from *Tet2*-deficient mice do not resolve LPS-induced inflammation as effectively as those derived from wildtype mice. Specifically, IL1β and IL6 remain elevated for longer than wildtype macrophages, in both in vitro and in vivo challenge models. *Dnmt3a*-deficient murine macrophages also demonstrate innate immune dysregulation (Li et al. 2016), and mining of the published data also reveals a constitutive proinflammatory signature in peritoneal macrophages, with remarkable overlap with *Tet2*-deficient counterparts (Cull et al. 2017). Since at least 10% of elderly demonstrate clonal hematopoiesis of indeterminate potential (CHIP), most commonly associated with *TET2* and *DNMT3A* mutations, it is conceivable that mutant myeloid cells may contribute to the inflammatory environment associated with increased MDSCs.

Although the definitive studies describing how MDSCs increase with age have not been performed, evidence from patients with myeloid cancers, mouse models, and clinical observations imply that there are three likely possibilities that we have outlined in Fig. 2. First, the aging microenvironment may favor the production of

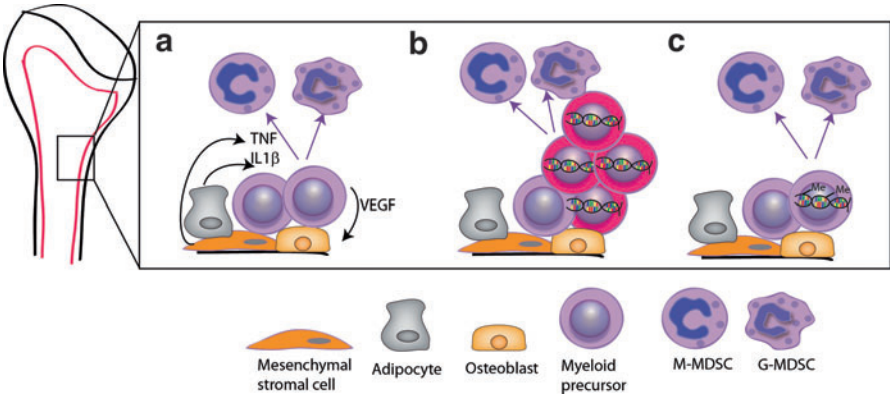


**Fig. 2** Three possible mechanisms by which MDSCs are increased with age are: (**a**) progenitor cells may respond to signals in the aging bone marrow microenvironment such as elevated levels of proinflammatory cytokines and respond by producing more MDSCs; (**b**) mutations in genes such as *TET2* may make specific progenitors more "fit" to expand in the aging bone marrow, and this may result in an expansion of MDSC producing progenitors; and (**c**) differences in methylation patterns (which may result from mutations in epigenetic regulators such as *TET2*) may alter myeloid alteration and promote the production of MDSCs

myeloid progenitors over lymphoid progenitors and promote rapid production of myeloid cells that prematurely leave the bone marrow. Second, mutations in genes such as *TET2* and *DNMT3A* may increase the fitness of progenitors that are myeloid biased, promoting the production of MDSCs and other myeloid cells. Third, differences in epigenetic regulation which result from mutations in epigenetic regulators, but may also be due to other environmental cues, might favor myeloid differentiation. Although we have presented these as three discrete possibilities, in actuality they likely occur simultaneously.

## Conclusions

Although we know that MDSCs increase in aged humans, we do not yet understand why or how or whether these contribute to poor health outcomes. One of the most evocative studies suggesting that age-related changes in myelopoiesis broadly affect the health of older adults found that individuals with evidence of myeloid bias were at increased risk of all-cause mortality (Jaiswal et al. 2014). The authors expected that having these mutations would increase the risk of having myeloid cancers, which they did, but only if additional cancer promoting mutations were also acquired. What they did not expect was that the risk of death by cardiovascular disease, ischemic stroke, and the rate of type 2 diabetes all increased two or more fold. The authors were left to muse that this might because "cells of the monocyte-macrophage lineage are considered to be important mediators" in cardiovascular homeostasis. Although this study did not quantitate MDSCs directly, it provides further importance that dysregulated myelopoiesis in general contributes to poor health in old age. Genome-wide association studies repeatedly demonstrate that genes associated with hematopoietic stem cell (HSC) proliferation and survival are found to be associated with conditions of late-life such as frailty (Melzer et al. 2007; Matheu et al. 2009), type 2 diabetes (Scott et al. 2007; Saxena et al. 2007; Zeggini et al. 2007; Wellcome Trust Case Control Consortium 2007), and cardiovascular disease (Wellcome Trust Case Control Consortium 2007; Helgadottir et al. 2007; McPherson et al. 2007), providing further indirect evidence that a long healthy life depends on robust hematopoiesis. Understanding how MDSCs contribute to diseases such as cancer, myelodysplastic disorders, and even chronic age-associated inflammation may open up novel therapeutic strategies.

Age-associated increases in MDSCs are not irreversible. In a study of patients with renal carcinoma who had high levels of circulating MDSCs, treatment with all-trans retinoic acid, which causes MDSCs to terminally differentiate (Nefedova et al. 2007), reduced levels of circulating MDSCs and improved the myeloid/lymphoid ratios (Mirza et al. 2006). Similarly, treatments for myeloid cancers often involve the hypo-methylating agents which induce terminal differentiation of myeloid cells (Pinto et al. 1989; Pinto et al. 1984) and more directed modulation of the epigenome has been proposed as a method of reversing myelodysplastic disorders and clonal expansion (Garcia-Manero 2007). Whether some variant of these

treatments could improve health outcomes in older adults that result from changes in myelopoiesis is an exciting possibility that requires further investigation.

## References

Abdelmagid SM, Barbe MF, Safadi FF (2015) Role of inflammation in the aging bones. Life Sci 123:25–34

Bandow K et al (2010) Molecular mechanisms of the inhibitory effect of lipopolysaccharide (LPS) on osteoblast differentiation. Biochem Biophys Res Commun 402(4):755–761

Beerman I et al (2010) Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion. Proc Natl Acad Sci U S A 107(12):5465–5470

Bellamy WT et al (2001) Vascular endothelial cell growth factor is an autocrine promoter of abnormal localized immature myeloid precursors and leukemia progenitor formation in myelodysplastic syndromes. Blood 97(5):1427–1434

Bronte V et al (1999) Unopposed production of granulocyte-macrophage colony-stimulating factor by tumors inhibits CD8+ T cell responses by dysregulating antigen-presenting cell maturation. J Immunol 162(10):5728–5737

Bronte V et al (2016) Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun 7:12150

Brusnahan SK et al (2010) Human blood and marrow side population stem cell and Stro-1 positive bone marrow stromal cell numbers decline with age, with an increase in quality of surviving stem cells: correlation with cytokines. Mech Ageing Dev 131(11–12):718–722

Bunt SK et al (2006) Inflammation induces myeloid-derived suppressor cells that facilitate tumor progression. J Immunol 176(1):284–290

Busque L et al (1996) Nonrandom X-inactivation patterns in normal females: lyonization ratios vary with age. Blood 88(1):59–65

Busque L et al (2012) Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. Nat Genet 44(11):1179–1181

Challen GA et al (2010) Distinct hematopoietic stem cell subtypes are differentially regulated by TGF-beta1. Cell Stem Cell 6(3):265–278

Challen GA et al (2012) Dnmt3a is essential for hematopoietic stem cell differentiation. Nat Genet 44(1):23–31

Chen X et al (2013) Induction of myelodysplasia by myeloid-derived suppressor cells. J Clin Invest 123(11):4595–4611

Cho RH, Sieburg HB, Muller-Sieburg CE (2008) A new mechanism for the aging of hematopoietic stem cells: aging changes the clonal composition of the stem cell compartment but not individual stem cells. Blood 111(12):5553–5561

Cull AH et al (2017) Tet2 restrains inflammatory gene expression in macrophages. Exp Hematol. pii:S0301-472X(17)30716-6. doi: 10.1016/j.exphem.2017.08.001

De Luca K et al (2009) The TLR1/2 agonist PAM(3)CSK(4) instructs commitment of human hematopoietic stem cells to a myeloid cell fate. Leukemia 23(11):2063–2074

Farha MA et al (2013) Collapsing the proton motive force to identify synergistic combinations against Staphylococcus Aureus. Chem Biol 20(9):1168–1178

Fleischman AG et al (2011) TNFalpha facilitates clonal expansion of JAK2V617F positive cells in myeloproliferative neoplasms. Blood 118(24):6392–6398

Gale RE et al (1997) Acquired skewing of X-chromosome inactivation patterns in myeloid cells of the elderly suggests stochastic clonal loss with age. Br J Haematol 98(3):512–519

Garcia-Manero G (2007) Modifying the epigenome as a therapeutic strategy in myelodysplasia. Hematology Am Soc Hematol Educ Program 2007:405–411

Genovese G et al (2014) Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 371(26):2477–2487
Giallongo C et al (2014) Myeloid derived suppressor cells (MDSCs) are increased and exert immunosuppressive activity together with polymorphonuclear leukocytes (PMNs) in chronic myeloid leukemia patients. PLoS One 9(7):e101848
Helgadottir A et al (2007) A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science 316(5830):1491–1493
Huang Y et al (2007) Distinct roles of VEGFR-1 and VEGFR-2 in the aberrant hematopoiesis associated with elevated levels of VEGF. Blood 110(2):624–631
Jaiswal S et al (2014) Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 371(26):2488–2498
Janssen JW et al (1989) Clonal analysis of myelodysplastic syndromes: evidence of multipotent stem cell origin. Blood 73(1):248–254
Kittang AO et al (2016) Expansion of myeloid derived suppressor cells correlates with number of T regulatory cells and disease progression in myelodysplastic syndrome. Oncoimmunology 5(2): e1062208
Kollman C et al (2001) Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. Blood 98(7):2043–2051
Laurie CC et al (2012) Detectable clonal mosaicism from birth to old age and its relationship to cancer. Nat Genet 44(6):642–650
Li J et al (2007) TNF-alpha induces leukemic clonal evolution ex vivo in Fanconi anemia group C murine stem cells. J Clin Invest 117(11):3283–3295
Li X et al (2016) Methyltransferase Dnmt3a upregulates HDAC9 to deacetylate the kinase TBK1 for activation of antiviral innate immunity. Nat Immunol 17(7):806–815
Loukov D et al (2016) Tumor necrosis factor drives increased splenic monopoiesis in old mice. J Leukoc Biol 100(1):121–129
Lu T et al (2011) Tumor-infiltrating myeloid cells induce tumor cell resistance to cytotoxic T cells in mice. J Clin Invest 121(10):4015–4029
Matheu A et al (2009) Anti-aging activity of the Ink4/Arf locus. Aging Cell 8(2):152–161
McKerrell T, Vassiliou GS (2015) Aging as a driver of leukemogenesis. Sci Transl Med 7 (306):306fs38
McKerrell T et al (2015) Leukemia-associated somatic mutations drive distinct patterns of age-related clonal hemopoiesis. Cell Rep 10(8):1239–1245
McPherson R et al (2007) A common allele on chromosome 9 associated with coronary heart disease. Science 316(5830):1488–1491
Melzer D et al (2007) A common variant of the p16(INK4a) genetic region is associated with physical function in older people. Mech Ageing Dev 128(5–6):370–377
Mirza N et al (2006) All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. Cancer Res 66(18):9299–9307
Movahedi K et al (2008) Identification of discrete tumor-induced myeloid-derived suppressor cell subpopulations with distinct T cell-suppressive activity. Blood 111(8):4233–4244
Nagaraj S, Youn JI, Gabrilovich DI (2013) Reciprocal relationship between myeloid-derived suppressor cells and T cells. J Immunol 191(1):17–23
Nefedova Y et al (2007) Mechanism of all-trans retinoic acid effect on tumor-associated myeloid-derived suppressor cells. Cancer Res 67(22):11021–11028
Pang WW et al (2011) Human bone marrow hematopoietic stem cells are increased in frequency and myeloid-biased with age. Proc Natl Acad Sci U S A 108(50):20012–20017
Pinto A et al (1984) 5-Aza-2′-deoxycytidine induces terminal differentiation of leukemic blasts from patients with acute myeloid leukemias. Blood 64(4):922–929
Pinto A et al (1989) 5-Aza-2′-deoxycytidine as a differentiation inducer in acute myeloid leukaemias and myelodysplastic syndromes of the elderly. Bone Marrow Transplant 4(Suppl 3):28–32
Pu S et al (2016) Identification of early myeloid progenitors as immunosuppressive cells. Sci Rep 6:23115

Puchta A et al (2016) TNF drives monocyte dysfunction with age and results in impaired anti-pneumococcal immunity. PLoS Pathog 12(1):e1005368
Raskind WH et al (1984) Evidence for a multistep pathogenesis of a myelodysplastic syndrome. Blood 63(6):1318–1323
Rodriguez PC et al (2009) Arginase I-producing myeloid-derived suppressor cells in renal cell carcinoma are a subpopulation of activated granulocytes. Cancer Res 69(4):1553–1560
Rossi DJ et al (2005) Cell intrinsic alterations underlie hematopoietic stem cell aging. Proc Natl Acad Sci U S A 102(26):9194–9199
Sade-Feldman M et al (2013) Tumor necrosis factor-alpha blocks differentiation and enhances suppressive activity of immature myeloid cells during chronic inflammation. Immunity 38(3):541–554
Saxena R et al (2007) Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 316(5829):1331–1336
Scott LJ et al (2007) A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 316(5829):1341–1345
Shlush LI et al (2014) Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia. Nature 506(7488):328–333
Shlush LI et al (2015) Aging, clonal hematopoiesis and preleukemia: not just bad luck? Int J Hematol 102(5):513–522
Sinha P et al (2007) Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells. Cancer Res 67(9):4507–4513
Snoeck HW (2013) Aging of the hematopoietic system. Curr Opin Hematol 20(4):355–361
Solito S et al (2011) A human promyelocytic-like population is responsible for the immune suppression mediated by myeloid-derived suppressor cells. Blood 118(8):2254–2265
Steensma DP et al (2015) Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood 126(1):9–16
Sun H et al (2015) Increase in myeloid-derived suppressor cells (MDSCs) associated with minimal residual disease (MRD) detection in adult acute myeloid leukemia. Int J Hematol 102(5):579–586
Talmadge JE, Gabrilovich DI (2013) History of myeloid-derived suppressor cells. Nat Rev Cancer 13(10):739–752
Verschoor CP et al (2015a) Circulating TNF and mitochondrial DNA are major determinants of neutrophil phenotype in the advanced-age, frail elderly. Mol Immunol 65(1):148–156
Verschoor CP et al (2015b) Circulating muramyl dipeptide is negatively associated with interleukin-10 in the frail elderly. Inflammation 38(1):272–277
Wang J, Geiger H, Rudolph KL (2011) Immunoaging induced by hematopoietic stem cell aging. Curr Opin Immunol 23(4):532–536
Wang JC et al (2016) Myeloid-derived suppressor cells in patients with myeloproliferative neoplasm. Leuk Res 43:39–43
Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447(7145):661–678
Xie M et al (2014) Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med 20(12):1472–1478
Yahata T et al (2011) Accumulation of oxidative DNA damage restricts the self-renewal capacity of human hematopoietic stem cells. Blood 118(11):2941–2950
Youn JI et al (2012) Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. J Leukoc Biol 91(1):167–181
Youn JI et al (2013) Epigenetic silencing of retinoblastoma gene regulates pathologic differentiation of myeloid cells in cancer. Nat Immunol 14(3):211–220
Zeggini E et al (2007) Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. Science 316(5829):1336–1341
Zhang Q et al (2015) Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. Nature 525(7569):389–393