

Review

Bone Marrow Immune Microenvironment in Myelodysplastic Syndromes

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Simple Summary: The bone marrow (BM) microenvironment regulates normal hematopoiesis and exerts variable activity in various inflammatory, toxic, autoimmune, or neoplastic diseases and conditions. Most importantly, it has a major role in the pathogenesis of BM failure syndromes and particularly of myelodysplastic syndromes (MDS), in which it is dynamically implicated in the early phase of their pathogenesis, as well as in their course and evolution. This review presents a concise overview of the literature, highlighting the impact of the immune component of the BM microenvironment during normal hematopoiesis, in chronic inflammatory states, and in low- and high-risk MDS, laying the ground for further research on the cellular and biochemical immune parameters that participate in early stages of MDS pathogenesis and in disease evolution.



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Abstract: The BM, the major hematopoietic organ in humans, consists of a pleiomorphic environment of cellular, extracellular, and bioactive compounds with continuous and complex interactions between them, leading to the formation of mature blood cells found in the peripheral circulation. Systemic and local inflammation in the BM elicit stress hematopoiesis and drive hematopoietic stem cells (HSCs) out of their quiescent state, as part of a protective pathophysiological process. However, sustained chronic inflammation impairs HSC function, favors mutagenesis, and predisposes the development of hematologic malignancies, such as myelodysplastic syndromes (MDS). Apart from intrinsic cellular mechanisms, various extrinsic factors of the BM immune microenvironment (IME) emerge as potential determinants of disease initiation and evolution. In MDS, the IME is reprogrammed, initially to prevent the development, but ultimately to support and provide a survival advantage to the dysplastic clone. Specific cellular elements, such as myeloid-derived suppressor cells (MDSCs) are recruited to support and enhance clonal expansion. The immune-mediated inhibition of normal hematopoiesis contributes to peripheral cytopenias of MDS patients, while immunosuppression in late-stage MDS enables immune evasion and disease progression towards acute myeloid leukemia (AML). In this review, we aim to elucidate the role of the mediators of immune response in the initial pathogenesis of MDS and the evolution of the disease.

Keywords: MDS; BM; microenvironment; HSC niche; pathogenesis; inflamm-aging; immune dysregulation; CHIP; immunosuppression; MDSC

1. Introduction

Normal hematopoiesis depends upon a tightly organized hierarchical system within the bone marrow. Pluripotent HSCs reside on the top of the BM hierarchy and have a

self-renewal capacity that is exerted by their symmetrical division, while the asymmetric division of HSCs produces progenitor cells primed for differentiation into mature cells [1,2]. This system, besides ensuring the rapid production of hematopoietic cells, safeguards hematopoiesis from the introduction of mutations. Despite this structure, during HSC division, somatic mutations that provide a relative fitness advantage may occur. These mutations may dominate and give rise to clonal hematopoiesis with the potential of evolution into frank hematological malignancies [3]. MDS derive from such clonal, mutational events, which become more common with advancing age. However, extracellular events occurring also in the BM microenvironment, namely, persistent inflammatory stimulation, immune dysregulation, and increased oxidative stress, have also been associated with MDS development. The inability of MDS cells to engraft in murine models (that would propagate human MDS in experimental animals) has initiated the discussion about the potential pathogenetic or facilitating role of the BM microenvironment, upon which the survival and expansion of MDS stem cells are dependent [4]. In addition, alterations in cellular elements of the BM microenvironment appear involved in MDS pathogenesis, such as Dicer1 gene deletion in BM osteoprogenitor cells, which suffices to induce a myelodysplasia-like phenotype and strongly suggests the carcinogenetic effect of the stromal component of the HSC niche [5]. Herein, we review the involvement of the BM IME in physiologic conditions, in aging, in the generation of clonal hematopoiesis, and in the evolution of established MDS, to unravel its role in disease initiation and progression.

2. BM IME in Physiologic Conditions

2.1. Hematopoietic Cells in the HSC Niche during Homeostasis

The HSC niche constitutes an extrinsic regulator of self-renewal (S), multilineage differentiation (M), apoptosis (A), rest (R), and trafficking (T) of the HSCs, together known as the “SMART” properties of HSCs and consists of the extracellular matrix and various cellular components of the BM microenvironment [6]. Apart from non-hematopoietic cells, namely of osteoid lineage, perivascular, endothelial, fibroblastic, mesenchymal stromal, adipocytic, and neural cells [7], mature hematopoietic cells that normally reside in the bone marrow have a role in regulating hematopoiesis and therefore, they could be considered as constituents of the BM microenvironment [8].

Megakaryocytes (MKs) are localized adjacent to HSCs and restrain their proliferation by producing C-X-C motif ligand 4 (CXCL4), Transforming Growth Factor beta (TGF- β), and thrombopoietin (TPO) [9–11], [Figure 1]. Pinho et al. suggested that MKs selectively influence the proliferative capacity and the fate of platelet and myeloid-biased HSCs, characterized by the surface expression of the von Willebrand factor (vWF) [12].

CD150 expressing T regulatory cells (Tregs) reside in the HSC niche and maintain HSCs' quiescence via the production of adenosine [13], [Figure 1]. In addition, Tregs generate an immune-privileged or immune-tolerant environment in the HSC niche, as becomes evident by their role in preventing the rejection of transplanted allogeneic hematopoietic stem/progenitor cells (HSPCs) [14].

Niche macrophages maintain long-term HSC (LT-HSC) quiescence, as they express Duffy antigen/receptor for chemokines (DARC) which binds to CD82 on LT-HSCs and leads to cell-cycle arrest [15], [Figure 1]. Consistently with the well-described erythroblastic islands with central “nutritional” macrophages, CD139+ macrophages promote normal hematopoiesis [16]. Additionally, they indirectly mediate HSC retention in the BM, by inducing C-X-C motif chemokine ligand 12 (CXCL12) secretion by stromal niche cells [17,18], [Figure 1]. In fact, depletion of the niche macrophages results in HSC mobilization in the periphery [19]. Alpha-smooth muscle actin (α -SMA)+ macrophages safeguard HSCs from exhaustion, by producing prostaglandin E2 (PGE2) and preserving low reactive oxygen species (ROS) levels in HSCs [20]. PGE2 additionally increases CXCL12 expression on the surface of stromal cells, thus preventing HSC to egress through marrow sinusoids into the circulation [21]. Dendritic cells (DCs) reside in the perivascular HSC niche and their

ablation results in HSC mobilization, in part due to increased vascular permeability and CXC chemokine receptor 2 (CXCR2) signaling in the endothelium [22], [Figure 1].

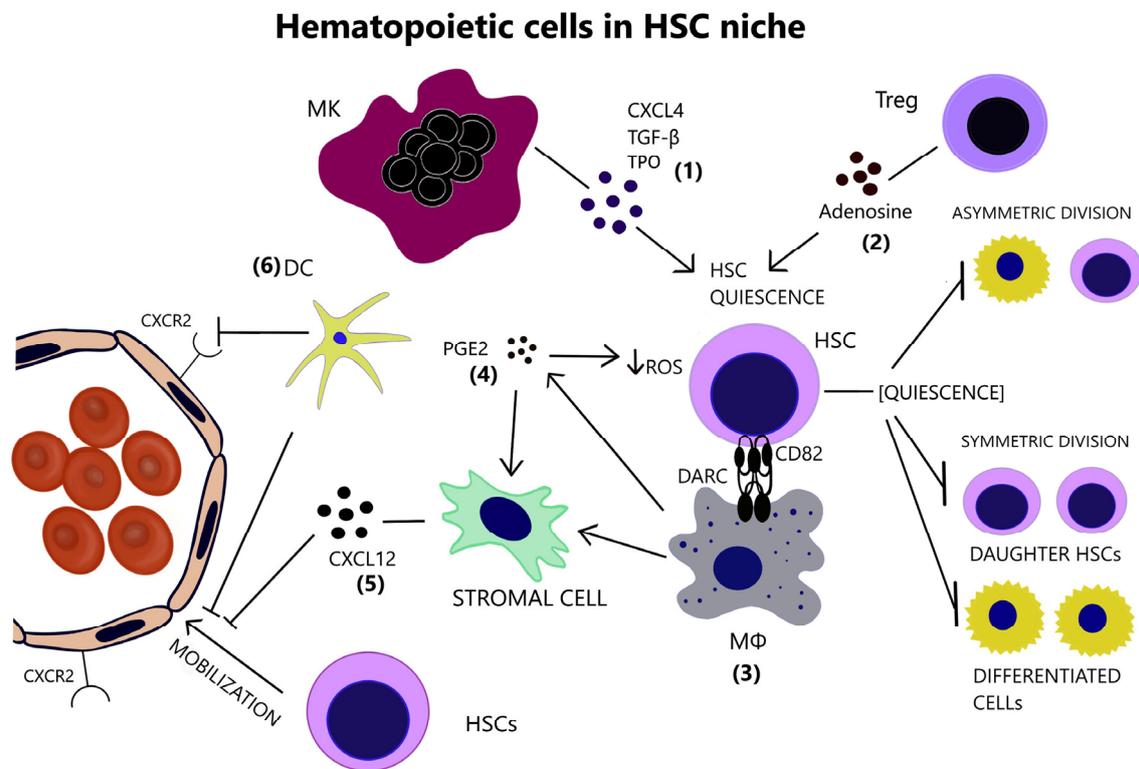


Figure 1. (1) Megakaryocyte support the preservation of HSC quiescence, through the secretion of CXCL4, TGF- β and TPO. (2) Tregs also contribute to HSC quiescence by generating adenosine, which protects HSCs from oxidative stress. (3) Macrophages express DARC, whose interaction with CD82 on the surface of HSCs restrains their proliferative activity. (4) a-SMA(+) macrophages are capable of COX-2-mediated PGE2 production that maintains low ROS levels in HSCs. (5) Macrophages additionally hinder HSC mobilization through the induction of CXCL12 by stromal cells. (6) Dendritic cells further aid HSC retention in the BM via regulation of vascular permeability and endothelial CXCR2 signaling. HSC inactive, quiescent state inhibits self-renewal and differentiation. (CXCL4 = C-X-C motif ligand 4, CXCL12 = C-X-C motif chemokine ligand 12, CXCR2 = CXC chemokine receptor 2, DARC = Duffy antigen/receptor for chemokines, DC = Dendritic cell, HSC = Hematopoietic stem cell, MK = Megakaryocyte, M Φ = Macrophage, PGE2 = Prostaglandin E2, ROS = Reactive oxygen species, TGF- β = Transforming growth factor beta, TPO = Thrombopoietin, Treg = T regulatory cell).

2.2. Inflammatory Response of HSCs during Emergency Granulopoiesis

Emergency granulopoiesis is a compensatory physiological process in cases of systemic infection or inflammation that involves the increased proliferation of myeloid progenitor cells in the bone marrow, to replenish the rapidly consumed granulocytes in the periphery. Pathogen sensing, occurring either in the peripheral tissues or within the bone marrow, is the initiating event, which is mediated either by hematopoietic or by non-hematopoietic cells that express pattern recognition receptors (PRRs) [23]. HSPCs express Toll-like receptors (TLRs), a family of PRRs, which upon activation result in increased survival, proliferation, and myeloid differentiation of HSPCs [24]. TLR agonist stimulation of HSPCs leads to the secretion of hematopoietic growth factors such as Interleukin 6 (IL-6) [25].

Following inflammatory stimulation, HSC proliferative activity is only transiently increased [26] and their quiescence is sustained through the activation of purine-rich box1 (PU.1) transcription factor, that represses genes related to cell-cycle progression and protein synthesis [27].

The maintenance of HSCs' quiescence is crucial for their self-renewal capacity [28]. Under normal conditions, HSCs only infrequently proliferate, and they would rather remain in a quiescent state. HSCs display kinetic heterogeneity with a "dormant" but potent population and a relatively more frequently dividing population, which gradually loses its self-renewal potential and becomes susceptible to DNA damage [29].

3. BM IME in Aging

Impairment of the immune and hematopoietic system in aged individuals has been well-described and can be manifested, for example, by a weak immune response following vaccination, a higher incidence of autoimmunity, the generation of anemia and of non-specific hematopoietic failure and by an increased risk of hematologic malignancies. The impairment is at least partly explained by cell-intrinsic mechanisms, including elevated intracellular oxidative stress and DNA damage, telomere shortening, and various epigenetic changes [30]. However, extrinsic signals of the BM microenvironment, in particular inflammatory signals, may be the initiators of such intrinsic HSC defects [31].

3.1. Myeloid Skewing

Contrary to the former belief that immune memory is an exclusive feature of adaptive immunity, it is now recognized that epigenetic changes in macrophages, monocytes and NK cells are responsible for the "trained immunity" of the innate immune system [32]. Long-lived cells and even HSCs are also susceptible to epigenetic immune memory [33]. HSC exposure to lipopolysaccharide (LPS), besides an acute response, establishes persistent open chromatin regions (OCRs), corresponding to genes of myeloid lineage commitment and primes HSCs for an accelerated myelopoiesis upon secondary exposure [34].

In mice, aging is accompanied by increased platelet and myeloid cell counts and reduced numbers of red blood cells and lymphoid cells, which reflects the myeloid-skewing of HSCs in the BM [35–38]. In fact, while erythropoiesis and lymphopoiesis are compromised in aged individuals, myelopoiesis is maintained [39]. The pattern of the expression of specific markers, namely the overexpression of CD150 and the downregulation of CD68, that characterize the myeloid-biased phenotype of HSCs is noted particularly among aged HSCs [40,41]. The composition of multipotent LT-HSCs shifts with age and myeloid-biased LT-HSCs (mLT-HSCs) prevail and preferentially expand during an inflammatory challenge. The continuous and cumulative exposure to various inflammatory challenges during a lifetime may account for the myeloid bias of aging. CD61 has been identified as a marker of mLT-HSCs and characterizes a population of LT-HSCs primed to respond to inflammatory stimuli. Specific transcription factors, namely Kruppel-like factor 5 (Klf5), Ikaros family zinc finger protein 1 (Ikzf1), and Signal transducer and activator of transcription 3 (Stat3), have been identified as regulators of the inflammatory myeloid bias in aged LT-HSCs [42]. Quantitative analysis of committed hematopoietic progenitors in the human BM reveals a decrease in common lymphoid progenitor (CLP) cells in the elderly, while common myeloid progenitor (CMP) cells are maintained [43].

3.2. Functional Decline of Aged and Overstimulated HSCs

Aged HSCs divide symmetrically, as opposed to asymmetric divisions of young HSCs [44]. Following repeated stimulation by inflammatory challenges, HSCs exhibit a functional decline and inability to regenerate. Transient exposure to polyinosinic:polycytidylic acid (pI:pC) induces Interferon alpha (IFN- α) response and proliferation of HSCs. Conversely, the repeated challenge of pI:pC injection resulted in a compromise of the proliferative potential of LT-HSCs, while no substantial replenishment of functional HSCs was observed after a recovery period [45,46]. Sustained LPS exposure and TLR4 stimulation impinge on HSC competitive repopulation capacity [47].

The HSC niche may contribute to the functional decline of HSCs, as it is implied by transplantation studies, according to which, the myeloid skewing of aged HSCs, transplanted into young recipients was reversed [48]. The stromal compartment in aged BM

acquires inflammatory transcriptional profiles. Interleukin 1 beta (IL1 β) gene is strongly expressed and potentially relevant to age-related HSC defects, given the effect of IL-1 β in driving myeloid skewing and suppressing the self-renewal capacity of HSCs [49]. The complement system, involved in the mobilization of HSPCs in the periphery during stress hematopoiesis, is also activated [50].

3.3. Inflamm-Aging

In the elderly, a chronic, mild inflammatory activity, termed “inflamm-aging” is associated with age-related diseases [51,52]. Increased number of pro-inflammatory cytokines, including Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (Rantes) [48], IL-1 β , Interleukin 6 (IL-6) [36], TGF- β [37], and Tumor Necrosis Factor-alpha (TNF- α) [53], are present in the bone marrow of aged individuals. The pro-inflammatory cytokines in the senescent BM mediate myeloid skewing and HSC impairment [Figure 2]. Even in non-hematologic diseases, such as rheumatoid arthritis, the observed myeloid-biased hematopoiesis is attributed to the elevated numbers of pro-inflammatory cytokines in this disease [54].

Inflamm – aging and myeloid skewing in the BM

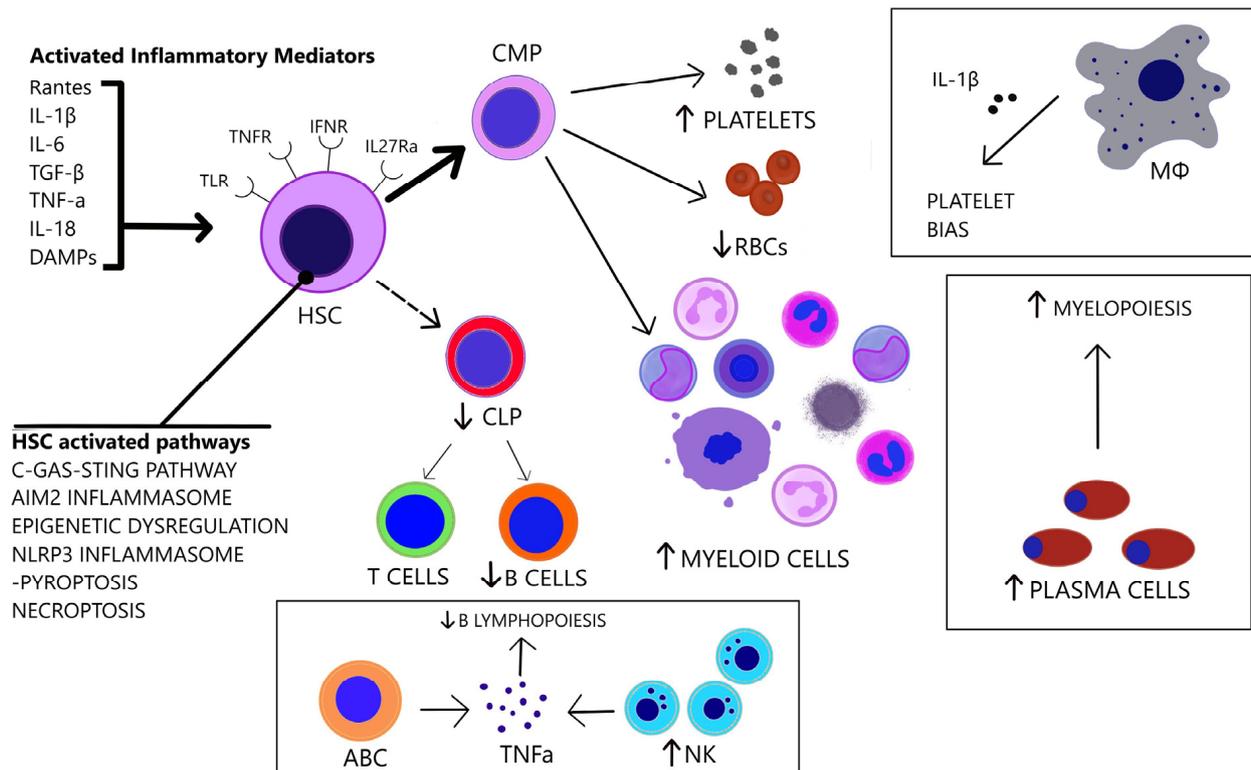


Figure 2. In the aged BM, there is increased number of pro-inflammatory cytokines that act on HSC receptors (TLRs, TNFRs, IFNRs, IL-27R α). Various abnormally activated pathways in HSCs (listed above) link HSC senescence and BM inflammation. The overstimulated HSCs are myeloid-biased. Immune cell alterations in the senescent BM are consistent with myeloid skewing. Aged macrophages drive platelet bias via IL-1 β . Plasma cells are increased and induce myelopoiesis. Increased NK cells and ABCs in the aged BM lead to TNF α -mediated impairment of B lymphopoiesis. (ABC = Age-associated B cell, AIM2 = Absent in melanoma 2, C-GAS-STING = Cyclic guanosine monophosphate-adenosine monophosphate synthase—Stimulating interferon gene, CLP = Common lymphoid progenitor, CMP = Common myeloid progenitor, DAMPs = Damage-associated molecular

patterns, HSC = Hematopoietic stem cell, IFNR = Interferon receptor, IL-1 β = Interleukin-1 beta, IL-6 = Interleukin-6, IL-18 = Interleukin-18, IL-27R α = Interleukin-27 receptor alpha, M Φ = Macrophage, NLRP3 = NOD-, LRR- and pyrin domain-containing protein 3, NK = Natural killer, TGF- β = Transforming growth factor beta, TLR = Toll-like receptor, TNF- α = Tumor necrosis factor-alpha, TNFR = Tumor necrosis factor receptor, Rantes = Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted, RBCs = Red blood cells).

Interleukin 1 (IL-1) promotes myeloid differentiation via Nuclear Factor kappa-light-chain enhancer of activated B cells (NF- κ B) signaling and downstream PU.1-mediated gene expression but chronic IL-1 stimulation impairs the self-renewal capacity of HSCs [49]. Transient exposure to TNF delivers pro-survival messages to HSCs; however, persistent exposure results in NF- κ B inactivation and HSC necroptosis [55]. Aging-related TNF- α overproduction upregulates Interleukin-27 receptor alpha (IL-27R α), a sensor of inflammation on HSCs, and is associated with their functional decline. IL-27R α + HSCs exhibit reduced reconstitution capacity, myeloid bias, and overexpression of inflammatory genes [53]. IFN- α favors HSC exit from quiescence and inflicts proliferation-induced genotoxic stress [46].

While NF- κ B baseline activity is indispensable for the preservation of hematopoietic homeostasis [41], increased NF- κ B signaling during aging predisposes to HSC differentiation, limiting their self-renewal capacity. Chronic inflammatory stimulation of young mice via mechanisms that involve NF- κ B activation also induces myeloid differentiation and recapitulates the effects of aging [56].

3.4. Molecular Association of Aging and Inflammation

Aging and inflammation are variously intertwined on the molecular level [57], [Figure 2]. Cytosolic DNA fragments from incomplete DNA repair activate the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-stimulating interferon gene (STING) aging pathway, that leads to Interferon beta (IFN- β) production [58]. Intracellular double-stranded DNA (dsDNA) from double DNA breaks leads to absent in melanoma 2 (AIM2) inflammasome assembly, which enables the proteolytic activation by Caspase-1 and secretion of IL-1 β and Interleukin 18 (IL-18) [59]. The epigenetic dysregulation of aging results in the upregulation of inflammation-associated genes in HSCs [60]. Moreover, the compromised autophagy of aging and mitochondrial stress activates the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome-Caspase-1 cascade, exacerbating the inflammation via cytokine production and induce pyroptosis of HSCs [61,62]. Pyroptosis and necroptosis are two well-established inflammatory forms of cell death that are activated during aging in addition to traditional apoptotic pathways. Necroptosis is programmed cell death, following activation of tumor necrosis factor receptors (TNFRs), TLRs and interferon receptors (IFNRs), and downstream mediators, such as receptor-interacting protein kinase 1 (RIPK1), receptor-interacting serine/threonine kinase 3 (RIPK3), and mixed lineage kinase domain-like (MLKL) that leads to the release of damage-associated molecular patterns (DAMPs) [63]. Similarly, pyroptosis is activated by inflammatory signals and involves inflammasome assembly and caspase-1 activation, which result in IL-1 β and IL-18 secretion [64].

3.5. Alterations in Immune Cells

The myeloid skewing of advanced age is accompanied by alterations of immune cells in the BM [Figure 2]. Increased natural killer (NK) cells in the senescent BM microenvironment restrain effective B lymphopoiesis by downregulating the transcription factor E47 in B cell precursors in a TNF- α dependent way [65]. Plasma cells accumulate in the bone marrow of aged mice, contribute to myelopoiesis, and acquire a TLR-responsive gene signature [8]. Age-associated B cells (ABCs) are mature B cells that contribute to the inhibition of B lymphopoiesis via TNF- α secretion in the pro-inflammatory BM microenvironment of aged mice [66]. Aged macrophages in the BM induce platelet bias in HSCs via IL-1 β [38].

4. BM IME in Clonal Hematopoiesis

4.1. Clonal Hematopoiesis (CH) in Advanced Age

During chronic immune stimulation, the increased proliferation rate renders HSC statistically more prone to genetic errors [67]. Different studies of DNA-sequencing analysis on many thousands of people, unselected for hematologic malignancies, identified recurrent mutations in leukemia-driver genes, such as DNA-methyltransferase 3A (*DNMT3A*), Tet methyl cytosine dioxygenase 2 (*TET2*), and additional sex combs like 1 (*ASXL1*), whose prevalence increased with age and was associated with an increased risk of hematologic neoplasia and overall mortality [68–70]. Clonal Hematopoiesis of Indeterminate Potential (CHIP) was subsequently defined as the clonal expansion of hematopoietic cells upon acquisition of a somatic mutation in leukemia-associated driver genes at a variant allele fraction of at least 2% and in the absence of diagnostic criteria for another hematologic condition [71]. Intrinsic defects of HSCs and selective pressure mechanisms in aging may explain the generation of clonal hematopoiesis [3]. Replication-associated DNA damage in aged HSCs triggers apoptosis or differentiation and possibly predisposes to further mutagenesis in a fitness landscape where HSCs that retain self-renewal capacity are the ones selected to expand [72]. Sensibly, mutations in epigenetic modifiers *DNMT3A*, *TET2*, and *ASXL1*, that may enhance self-renewal or introduce a differentiation blockage are often present in CH [3]. Recent data, however, suggest that mutations linked to clonal hematological disorders are not newly acquired events at the time of diagnosis, but instead precede the clinical manifestation by many years or even decades. Interestingly, *DNMT3A* mutation has been found to occur already in utero during embryogenesis or during childhood and to slowly grow during a lifetime [73]. Therefore, it is not just the acquisition of mutations but the fitness advantage of the mutated clone in the inflammatory context of these diseases that need to be investigated. To this effect, there is in vitro evidence that *TET2* mutations facilitate clonal expansion in aging, by providing TNF- α resistance [74].

4.2. Dysregulation of Inflammatory Pathways and Competitive Advantage of Mutant HSC

In clonal hematopoiesis and MDS, various dysregulated molecules in mutant HSPCs affect supramolecular organizing centers (SMOCs); thus, major signaling pathways that maintain HSC survival, function and inflammatory response are disrupted. SMOCs are the protein complexes of receptors, adaptors, and effector molecules, following PRR activation and include myddosome and trifosome complex, inflammasome, and necroptosome [75]. *TET2* mutation is linked to the overexpression of myddosome's molecule TRAF6 [76], as well as the activation of NLPR3 inflammasome [77]. According to the suggested model of MDS initiation, a clonal event, for example, the acquisition of *DNMT3A*, *TET2* or *ASXL1* mutation and the subsequent SMOC dysregulation, provide a competitive advantage to HSCs in the context of chronic inflammation and increased exposure to cytokines and alarmins in the bone marrow, derived from aging, chronic infection, or immune dysregulation. The selective advantage of mutant HSCs stems from their altered response to inflammation. MDS HSCs preferentially exhibit noncanonical activation of NF- κ B, over the canonical NF- κ B activation of normal HSCs and inhibition of noncanonical NF- κ B signaling abrogates their competitive advantage [75,76].

4.3. Evidence of Inflammatory Overstimulation in CHIP

The association between CHIP and cardiovascular disease (CVD) is well-established [70,78,79] and inflammation constitutes a plausible link. Inflammation contributes to CVD [80] while CHIP emerges under inflammatory stress and augments inflammation by increasing the release of pro-inflammatory cytokines which, through a feedback loop, aid clonal expansion [81,82]. *TET2* loss of function promotes atherosclerosis due to NLRP3-mediated IL-1 β secretion by macrophages [83]. Patients with *DNMT3A*-CHIP-driver mutation exhibit a pro-inflammatory T-cell distribution as evidenced by a significant increase in the T helper 17 (Th17) cells/Tregs ratio [84].

5. BM IME in MDS

5.1. 5q– Syndrome as a Representative Example of Immune Dysregulation in MDS Initiation

5q– syndrome, a common MDS subtype, provides evidence for the overstimulation of the innate immune system in the development of myelodysplasia. Deletion of miR-145 and miR-146, located on chromosome 5q, phenocopies 5q– syndrome, and activates NF- κ B signaling, since miR-145 and miR-146 target NF- κ B pathway mediators, Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP), and Tumor necrosis factor receptor-associated factor 6 (TRAF6), respectively. The dysplastic phenotype in TRAF6-transduced mice is linked to IL-6 overexpression and paracrine action, while clonal expansion and acute myeloid leukemia (AML) development rely upon TRAF6 activation in a cell-autonomous fashion [85]. Interestingly, lenalinomide, the treatment of choice for 5q– syndrome, has been found to suppress IL-6 expression [86]. Aged mice show decreased miR-146 expression and elimination of miR-146 results in premature HSC aging and development of myeloid malignancy, dependent upon IL-6 and TNF activation. When IL-6 and TNF were targeted, the function of HSCs in miR-146-deficient mice was restored [87].

5.2. Overactivation of Inflammatory Pathways in MDS HSCs

In MDS, emerging data support cell-intrinsic mechanisms in the dysregulated innate immune and inflammatory signaling, involved in disease pathophysiology [75]. MDS HSCs exhibit increased expression of TLR receptors [88]. TLR-4 upregulation correlates with increased apoptosis in MDS [89]. TLR-2 overexpression is linked to low-risk disease while TLR-6 overexpression characterizes high-risk MDS. Chronic stimulation of the TLR-2/TLR-6 complex accelerates progression to AML [90]. The overstimulation of the NLRP3 inflammasome by DAMPs, most notably S100 calcium-binding protein A8 (S100A8) and S100 calcium-binding protein A9 (S100A9), and caspase-1 activation is a central event in MDS, irrespective of the underlying mutational profile [91,92]. In addition, overactivation of the TGF- β signaling, via the upregulation of Mothers against decapentaplegic homolog/SMAD family member 2 (SMAD2) or the inhibition of the negative regulator Mothers against decapentaplegic homolog/SMAD family member 7 (SMAD7), correlates with myelosuppression in MDS [93,94]. Certain driver mutations in MDS, especially in splicing factors, contribute to the dysregulation of immune-related molecules. Mutated U2 small nuclear RNA auxiliary factor 1 (U2AF1) produces a long isoform of Interleukin-1 receptor-associated kinase 4 (IRAK4) (IRAK4-L), that overactivated NF- κ B signaling via myddosome assembly [95]. Splicing factor 3B subunit 1 (*SF3B1*) mutations, one of the most encountered mutations in MDS, also result in IRAK4-L overexpression, but additionally hinder Mitogen-activated protein kinase kinase kinase 7 (MAP3K7) expression, which indirectly restricts NF- κ B signaling, leading to hyperactivated NF- κ B signaling. Serine and arginine rich splicing factor 2 (SRSF2) mutations lead to aberrant splicing of caspase 8, whose inhibition is necessary for the induction of necroptosis instead of apoptosis [96].

5.3. The Immunomodulatory Role of High Mobility Group Box-1 (HMGB1) in MDS BM

HMGB1 is a nuclear, non-histone DNA-binding protein that regulates chromatin remodeling and transcriptional states. HMGB1 belongs to endogenous DAMPs, known as alarmins, and perpetuates inflammation following its passive release from necrotic cells or active secretion by innate immune cells or “stressed” cells. NF- κ B activation is involved in HMGB1 signaling, subsequently to HMGB1 ligation to both advanced glycation end products receptor (RAGE) and TLRs [97]. In the BM, HMGB1 promotes HSC self-renewal and differentiation capacity but is also involved in hematologic malignancies [98]. In MDS, HMGB1 emerges as an important and potentially targetable contributor to the inflammatory BM milieu. Serum HMGB1 levels are significantly increased in MDS patients when compared to healthy controls [99,100] as well as compared to patients with other BM failure syndromes, highlighting its specific role in MDS pathophysiology [100]. Circulating HMGB1 levels are higher in low-risk MDS than in high-risk MDS patients, in consistence with the greater BM inflammatory load of the former group [100]. The defective apoptotic

cell clearance by macrophages in the BM of MDS patients may secondarily initiate cell necrosis and release of HMGB1, which then leads to TLR4 activation and cytokine secretion [99]. Inflammasome activation also results in HMGB1 release [101], which may constitute an additional mechanism of HMGB1 overexpression in MDS. Kam et al. reported a two-to-three-fold higher expression of HMGB1 in MDS CD34+ cells compared to normal hematopoietic cells. Most importantly, they found that HMGB1 inhibition diminishes MDS cell expansion and has an additive effect on azacytidine or decitabine treatment while sparing normal hematopoietic cells. HMGB1 inhibition also correlates with downregulation of TLR receptors and NF- κ B signaling, which suggests the immunomodulatory role of HMGB1 in the BM [102].

5.4. Alterations of Cytokines and Immune Cells in the BM Microenvironment

5.4.1. Cytokines

Increased levels of serum TNF- α , TGF- β , IL-6, and Interleukin 8 (IL-8) have repeatedly been reported in MDS [103–105]. Cytokine levels reflect the distinct immune dysregulation mechanisms that are involved in different disease stages. Low-risk MDS is characterized by an increased apoptotic rate and a pro-inflammatory microenvironment, where type I cytokines (e.g., IL-1 β , Interleukin 7 (IL-7), IL-8, Interleukin 12 (IL-12)) dominate [106], [Figure 3]. On the contrary, high-risk MDS patients exhibit comparatively decreased apoptosis and clonal expansion of malignant cells due to immune evasion that is mediated by inhibitory factors, namely Interleukin 10 (IL-10) and soluble Interleukin-2 Receptor (sIL-2R) [107,108], [Figure 4]. The number of CD8+ T cells and IL-10 levels are inversely related [109].

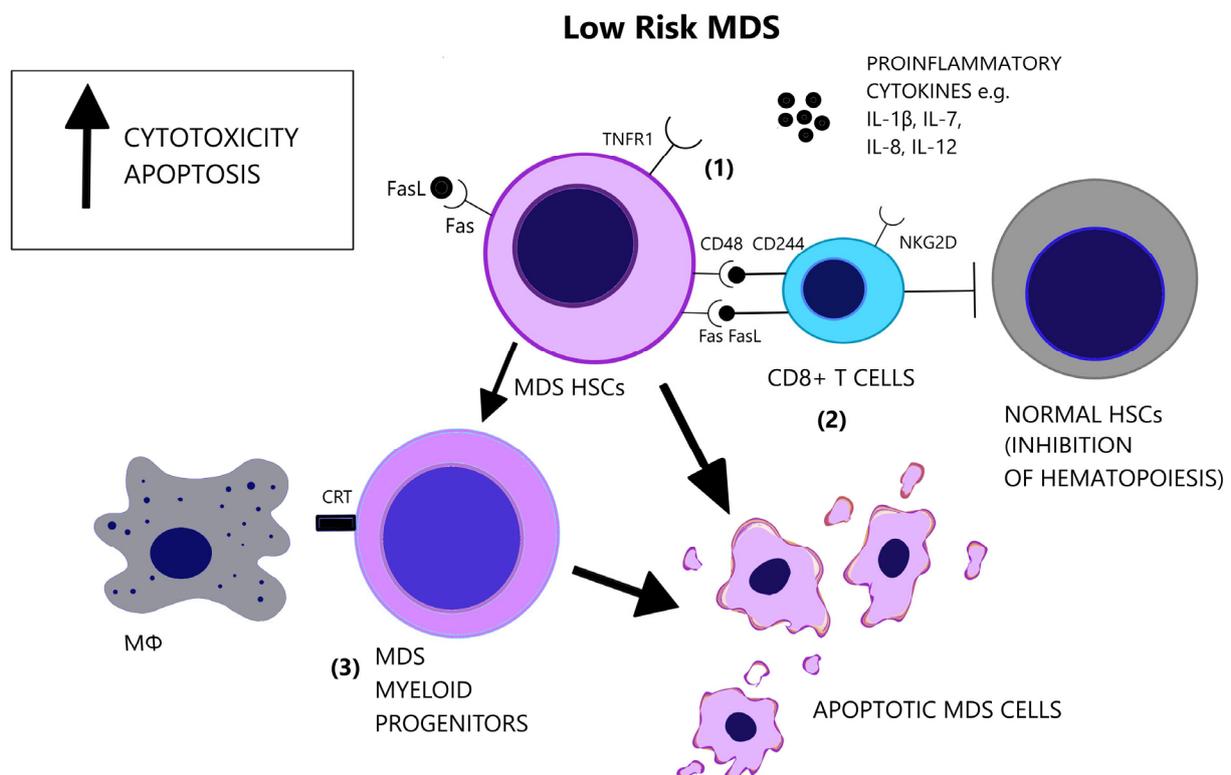


Figure 3. Low-risk MDS is characterized by a pro-apoptotic and cytotoxic microenvironment. (1) Apart from the elevated number of pro-inflammatory cytokines in the BM, there is increased responsiveness of the MDS cells that express the pro-apoptotic receptors, Fas and TNFR1. (2) CD8+ T-cells target MDS cells and exhibit augmented cytotoxicity, partly due to the expression of NKG2D

and CD244 receptors. However, CD8⁺ T-cells suppress also normal hematopoietic cells and inhibit hematopoiesis. (3) MDS myeloid progenitor cells, derived from MDS HSCs, express the prophagocytic molecule CRT, possibly representing the main factor of cellular loss in low-risk MDS. (CRT = Calretinin, Fas = Fas receptor, FasL = Fas ligand, HSCs = Hematopoietic stem cells, IL-1 β = Interleukin-1 beta, IL-7 = Interleukin-7, IL-8 = Interleukin-8, IL-12 = Interleukin-12, M Φ = Macrophage, NK2GD = Natural killer group 2D, TNFR1 = Tumor necrosis factor receptor 1).

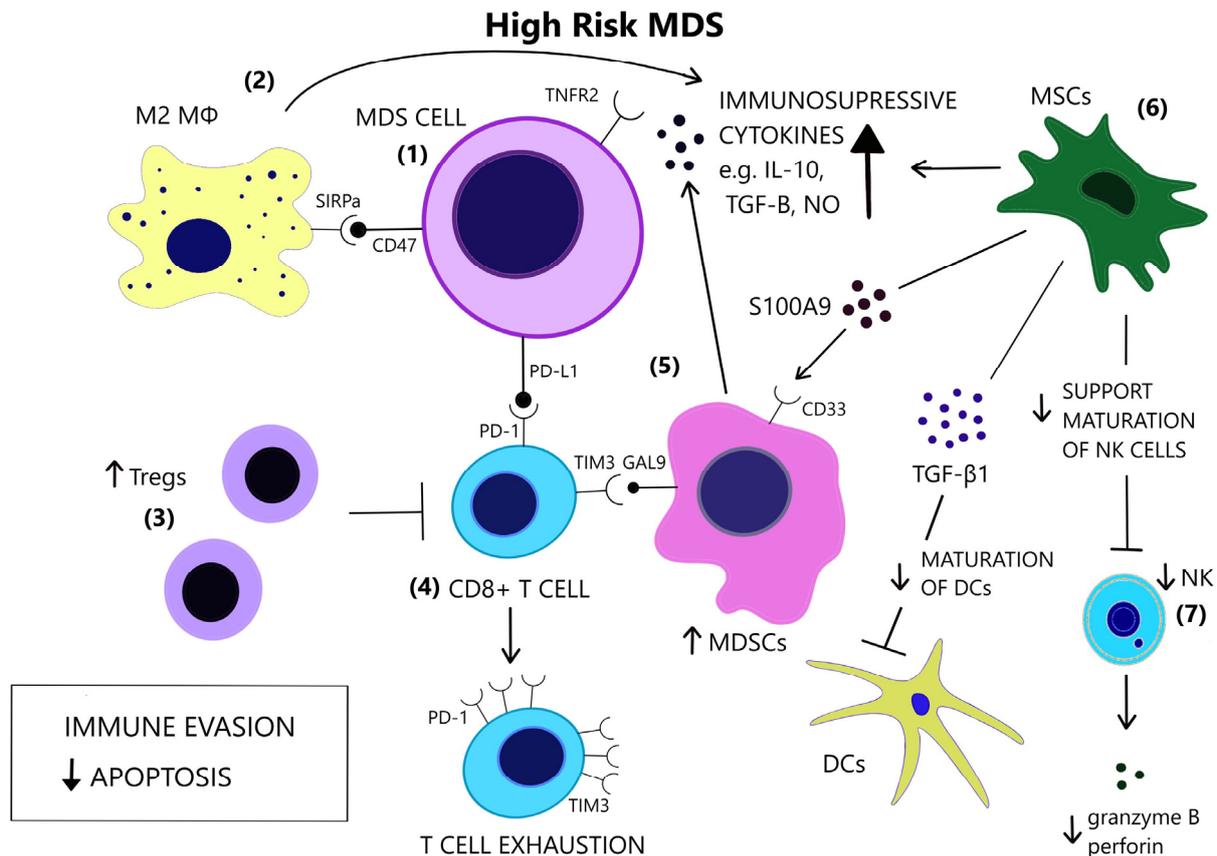


Figure 4. In contrast to low-risk MDS, immune evasion and decreased apoptosis enable clonal expansion in the BM of high-risk MDS. (1) In high risk MDS cells, there is a preferential expression of the anti-apoptotic TNFR2 and the anti-phagocytic CD47. (2) Macrophages acquire a M2 phenotype and produce IL-10. (3) Tregs expand and contribute to immune suppression. (4) CD8⁺ T-cell exhaustion is mediated by the expression of immune checkpoint molecules PD-1, PD-L1 and TIM3. (5) TIM3-ligand, Gal9, is expressed on MDSCs, which are induced upon binding of alarmin S100A9 on their CD33 receptor. MDSCs are increased and provide a large amount of immunosuppressive cytokines in the BM of high risk MDS. (6) MSCs are implicated in the anti-inflammatory microenvironment as they are a source of S100A9 and inhibitory molecules, such as TGF- β 1, which suppresses DC maturation. (7) NK cells receive inadequate support from MSCs and exhibit impaired maturation, numerical and functional deficiency. (GAL9 = Galectin9, DCs = Dendritic cells, IL-10 = Interleukin-10, M2 M Φ = M2 macrophage, MDSCs = Myeloid-derived suppressor cells, MSCs = Mesenchymal stromal cells, NK = Natural killer, NO = Nitric oxide, PD-1 = Programmed cell death protein 1, PD-L1 = Programmed death-ligand 1, S100A9 = S100 calcium-binding protein A9, SIRPa = Signal regulatory protein alpha, TGF- β = Transforming growth factor-beta, TIM3 = T-cell immunoglobulin and mucin-domain containing 3, TNFR2 = Tumor necrosis factor receptor 2, Tregs = T regulatory cells).

Apoptosis is one of the most notably activated pathways in CD34⁺ cells from refractory anemia (RA) patients, when compared to healthy controls or refractory anemia with excess blast (RAEB) patients [110,111], [Figure 3]. The extrinsic apoptotic pathway involves

the activation of the Fas death receptor (Fas) on the cell surface by Fas ligand, which is overexpressed in MDS patients [112]. Whereas normal CD34+ progenitor cells are devoid of Fas, its expression is induced by cytokines such as TNF- α and Interferon gamma (IFN- γ), which are elevated in low-risk MDS patients, when compared to high-risk MDS patients [113,114]. TNF- α selectively stimulates TNF receptor 1 (TNFR1), leading to the activation of proinflammatory signaling pathways and apoptosis, as opposed to TNF receptor 2 (TNFR2), which has an anti-apoptotic function [115]. In line with the proapoptotic microenvironment of low-risk MDS and the anti-apoptotic features of high-risk MDS, BM cells in RA patients overexpress TNFR1 [Figure 3], while TNFR2 expression is notable in RAEB patients [Figure 4], [116]. High serum levels of TNF- α in MDS patients are correlated with poorer performance status, higher leukocyte counts, β 2-microglobulin and creatinine levels and on the contrary, lower TNF- α levels have been associated with favorable prognosis [117]. In advanced MDS, high serum levels of IL-6 and Granulocyte-macrophage colony-stimulating factor (GM-CSF) are observed. IL-6, IL-7, and C-X-C motif chemokine ligand 10 (CXCL10) may serve as independent prognostic factors of survival [118].

5.4.2. Immune Cells

Lymphocytes

A subset of MDS patients exhibit the clonal expansion of T cells, characterized by T cell receptor (TCR) V β -repertoire skewing, probably reflecting an antigen-driven process [119]. Immunosuppressive therapies reverse the TCR-V β phenotype of T cells in hypocellular MDS [120]. A CD8+/CD57+/CD28- T cell phenotype is overrepresented in MDS patients compared to age-matched controls [121–123] and characterizes a population of terminally differentiated, memory/effector T cells that have undergone repeated cell division cycles [124]. Natural killer group 2D (NKG2D) and CD244, which are normally NK receptors, are expressed on MDS T cells and render effector capacity while HSCs express the CD244 ligand, CD48 [121], [Figure 3]. Diminished expression of the lymph node homing receptors C-C chemokine receptor 7 (CCR7) and L-Selectin (CD62L), also found on clonal MDS T cells, coincides with lymphocyte expansion in the bone marrow [121]. CD48 expression on MDS HSCs is further augmented following lenalinomide treatment, which may represent a mechanism of induction of apoptosis by this agent [125]. Deprivation of CD8+CD57+ T cells in vitro triggers colony formation of BM mononuclear cells in a subset of MDS cases. In the cases with abnormal karyotypes (+8, 20q-, 5q-) the proportion of clonal cells increases significantly [126]. These findings support the inhibitory effect of CD8+ cells on the neoplastic cells of MDS.

Potential epitopes on MDS stem cells that activate anti-tumoral CD8+ T cells include Wilms tumor 1 protein (WT1), cancer-testis antigens (CTAs), proteinase 3, and Major Histocompatibility Complex class I (MHC I) [127–129]. Alongside malignant stem cells, CD8+ T cells target non-malignant hematopoietic cells and inhibit hematopoiesis in MDS. CD34+ cells and mononuclear cells of trisomy 8 MDS patients overexpress WT-1, which triggers the clonal expansion of WT1-specific CD8+ cells that contribute to myelosuppression. These findings are consistent with the increased efficacy of immunosuppressive therapy in trisomy 8 MDS patients [128]. Hypomethylating agents (HMAs) significantly upregulate the expression of CTAs on AML leukemic cells, which correlates with the enhanced recognition of tumor cells by T cells [130].

The absolute number of CD4+ T cells is decreased in MDS patients compared to healthy controls and results in a reduction in the CD4/CD8 ratio [131]. The abnormal CD4/CD8 ratio in young MDS patients further correlates with response to immunosuppressive therapy and probably reflects the loss of the regulatory T cell (Treg) compartment of CD4+ cells. A higher proliferative T cell index in these patients may reflect activation of “homeostatic proliferation”, mediated by Interleukin 2 receptor gamma (IL-2R γ), leading to non-specific T cell expansion, including self-reactive T-cells [132]. This model serves as a potential alternative mechanism of CD8+ expansion, besides antigen-specific responses,

and may explain the autoimmunity-associated features of MDS [132,133]. Moreover, in low-risk MDS patients Th17 cells are increased and Tregs are inversely decreased and functionally impaired [101]. In high-risk MDS patients, Tregs are expanded while CD8+ T cells and NK cells are decreased [134–136]. Symeonidis et al. have associated CD3+ and CD8+ cell lymphopenia with increased risk of infections, transformation to AML, as well as decreased overall survival. According to this theory, although in MDS recognition of autologous antigens is impaired favoring autoimmunity, the immune reaction against CD34+ cells is increased, as compared to normal subjects. Thus this *in vitro* finding, together with the increase in suppressive CD8+ cells, might be considered as a defensive mechanism of the host against the expanding MDS clonal cells, which ultimately is abrogated during disease progression to higher-risk disease or AML, generating immune tolerance against the expanding population of blast cells [137].

The conversion to an immune evasive microenvironment in advanced MDS is facilitated by the overexpression of immune checkpoint molecules, including the programmed cell death of protein 1 (PD-1), its ligand PD-L1, and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), leading to T cell exhaustion [138], [Figure 4]. The interaction of PD-1 and PD-L1 suppresses TCR-mediated proliferation and cytokine expression [139]. High-risk MDS patients show increased PD-L1 expression on blast cells, compared to healthy controls [140]. Yang et al. observed at least a two-fold upregulation of PD-L1 on BM CD34+ cells in 36% of studied samples from MDS patients and an enhanced expression of PD-L1, PD-1 and CTLA-4 after HMA treatment [141]. Secreted factors in the microenvironment, such as IFN- γ and TNF- α , upregulate PD-L1 expression [142,143] and recently, the role of S100A9, a central molecule in the MDS pathophysiology, as an inducer of PD-1 and PD-L1, has been detected [144]. Contrary to former knowledge, recently, Ferrari et al. did not observe an inhibition of cytotoxicity after *de novo* PD-L1 expression on MDS cells [145]. Additional inhibitory signals originating from the innate immune system may interfere with anti-tumor immunity.

Macrophages

Macrophage-mediated apoptosis in low-risk MDS affects myeloid progenitor cells expressing the phagocytic receptor calretinin (CRT) rather than HSCs, which lack CRT expression and are rescued from apoptosis [146], [Figure 3]. Myeloid progenitor cells from high-risk MDS patients additionally overexpress CD47, which is a surface anti-phagocytic molecule abnormally expressed on tumor cells that binds to its receptor Signal regulatory protein alpha (SIRPa) on macrophages and inhibits phagocytosis, counteracting CRT [146], [Figure 4]. Despite the increase in monocyte cells in the peripheral blood of MDS patients, decreased differentiation into macrophages and attenuated phagocytic capacity of macrophages are reported [147].

Aside from the impaired recognition and phagocytosis of MDS cells by macrophages [147], Zhang et al. found an abnormal polarization of macrophages with decreased M1:M2 ratio in high-risk MDS patients [148]. M1 macrophages participate in antitumor immune response via secretion of pro-inflammatory factors and recognition of tumor-associated antigens (TAAs) [149]. However, M1 macrophages derived from MDS patients show decreased expression of IL-1 β and TNF- α [148]. Tumor-associated macrophages (TAMs) in late-stage cancer are characterized by an M2-like phenotype (low IL-12 and high IL-10 expression) and potentiate tumor progression through decreased tumoricidal activity, angiogenesis, and matrix remodeling [150]. The increase in the M2 macrophages in high-risk MDS patients may therefore contribute to impaired immunosurveillance and clonal expansion, in line with studies highlighting the role of TAMs in AML progression [151,152] and the promising results of macrophage repolarization [153].

NK Cells

The cytolytic function of NK cells is compromised in MDS patients [154], partly due to the reduced expression of the stimulating receptors DNAX accessory molecule 1 (DNAM-1)

and NKG2D on the surface of NK cells, while their expression is inversely correlated to the BM blast counts [155]. Hejazi et al. observed a significant reduction in NK cell numbers preferentially in high-risk MDS patients and correlated their functional deficiency to low levels of granzyme B and perforin as well as the NK cells' immaturity in MDS [156], [Figure 4]. The inability of NK cells to fully mature may stem from their ineffective support from MDS mesenchymal stromal cells (MSCs) [157], since stromal support is a prerequisite for the development of mature, Killer-cell immunoglobulin-like receptor (KIR)-expressing NK cells [158]. Partial clonal involvement of NK cells [159] and certain congenital mutations that link MDS predisposition and NK cell alterations [160–162] highlight the contribution of potential intrinsic defects to NK cell impairment.

Dendritic Cells

Lower numbers and functional deficiency of DCs in MDS may contribute to immunodeficiency and autoimmunity of MDS. FISH analysis revealed the origin of MDS DCs from the malignant clones [163]. CD34+ progenitor cells from MDS patients exhibit impaired in vitro generation of DCs [164]. Similarly, the differentiation of blood monocytes from MDS patients to DCs is impaired. Immature monocyte-derived DCs (MoDCs) show diminished expression of surface molecules CD80 and CD1a, reduced endocytic capacity and ineffective maturation following TNF- α stimulation [165]. The ineffective induction of T-cells [166] and altered cytokine secretion (less IL-12 and more IL-10 expression) [167] are further aspects of DC impairment in MDS. MDS DCs show downregulation of transcripts involved in pro-inflammatory pathways which may explain their reduced immune responsiveness [168].

MDSCs

MDSCs are immature immune cells increased in the context of immunosuppression, inflammation, and cancer [169] and contribute to cancer progression [170]. The two-stage model of MDSC involvement in cancer requires firstly the expansion of myeloid cells under chronic inflammatory stimulation and secondly their activation in the tumor microenvironment [171]. Rationally, MDS BM inflammatory microenvironment facilitates MDSC development [172]. Elevated numbers of MDSCs are found in the BM of MDS patients, mostly high risk, and correlate with Treg expansion and disease progression [173]. MDSCs serve as a source of inhibitory cytokines, such as IL-10, TGF- β , NO, and arginase [Figure 4] and contribute to the suppression of hematopoiesis in MDS and the induction of T cell tolerance [174]. MDSCs expand also in the bone marrow of aged healthy individuals, parallel to the rise of inflammatory cytokines in the serum, at least in part due to NF- κ B activation [175,176]. However, MDS-derived MDSCs overexpress CD33, and their suppressive function depends upon the binding of pro-inflammatory molecules, such as S100A9, to the CD33 receptor on MDSCs [174,177], [Figure 4]. Forced MDSC expansion in S100A9 transgenic mice suffices to induce human MDS phenotype, while induced terminal differentiation eliminated MDSCs and restored hematopoiesis. A mechanism in which CD33 overexpression overrides maturation signals from Immunoreceptor tyrosine-based activated motifs (ITAM)-associated receptors and retains the expansion of immature MDSCs was proposed [174]. High levels of IL-6 and chemokine (C-C motif) ligand 2 (CCL2) in MDS patients may additionally induce MDSCs, as these molecules activate the STAT3 pathway, which is crucial for MDSC-mediated inhibition of CD8+ T cell function [178]. Tao et al. found that CD8+ T-cell exhaustion in MDS was partially dependent upon activation of the T-cell immunoglobulin and mucin-domain containing 3 (TIM3)/Galectin 9 (Gal 9) pathway [Figure 4] and suggested that Gal 9 upregulation by MDSCs is responsible for this activation [179]. TIM3/Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) pathway activation may also be an alternative mechanism of MDSC involvement in T-cell exhaustion [180]. Irrespective of the specific mechanisms of MDSC-induced inhibition, MDSCs do not harbor the same mutations as the dysplastic clones [174], thus constituting

an independent cellular component of the microenvironment that is actively involved in MDS pathophysiology.

5.5. Role of MSCs in the Inflammatory BM Milieu

MSCs are a stromal component of the MDS microenvironment that may be involved in the pathogenesis and evolution of MDS via inflammatory signaling [181]. MSCs functionally decline with age [182]. In MDS, MSCs acquire distinct genetic alterations from the malignant clone [183] and show activation of inflammatory pathways [184,185]. Importantly, MSCs secrete S100A8/9, which generates genotoxic stress in HSCs [186], [Figure 4]. S100A8/9 expression in MSCs, associated with activation of p53 and TLR pathways, is predictive of leukemic evolution in MDS [186]. MSCs have different immunomodulatory effects depending on the disease stage. They suppress DC maturation and function more potently in high-risk MDS compared to low-risk MDS, and this suppression is mediated through TGF- β 1 secretion by MDS MSCs [187], [Figure 4]. Sarhan et al. attributed the immunosuppressive properties of MDS MSCs, specifically the inhibition of NK cell function and T-cell proliferation, on the induction of suppressive monocytes [188].

6. Therapeutic Implications

The emerging knowledge on MDS IME pathology identifies various potentially targetable molecules for novel therapeutic options that could complement traditional treatment or act as salvage therapy. Agents targeting several of the aforementioned components of the BM IME have been developed and are under clinical trials. Magrolimab, for example, is an anti-CD47 monoclonal antibody that counteracts the inhibition of phagocytosis in MDS [189] and potentially synergizes with azacytidine [190]. The efficacy of novel anti-TIM3 antibodies in combination with azacytidine is tested in phase Ib studies [191,192]. High-risk MDS patients may also benefit from combination therapy of anti-PD-1 inhibitor pembrolizumab with azacytidine [193]. The overexpression of TLRs in MDS provides the rationale for the development and interrogation in clinical trials of the anti-TLR2 antibody OPN-305 [194]. The above represents only a fraction of the factors, that immunotherapy could target to modulate the BM IME in MDS [195].

7. Conclusions

The overstimulation of inflammatory processes in the BM and inflamm-aging lead to functional impairment of HSCs and paves the way for clonal hematopoiesis and MDS initiation. Inflammatory signaling is rewired and confers a selective advantage to HSCs. The IME mediates BM failure and is dynamically involved in MDS pathophysiology, evolving from a pro-inflammatory and pro-apoptotic into a permissive milieu that enables immune evasion, clonal expansion, and disease progression. Our increasing understanding of the intricate mechanisms of the IME's involvement serves to highlight potential targets for immunotherapy in MDS.

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References

1. Orkin, S.H.; Zon, L.I. Hematopoiesis: An evolving paradigm for stem cell biology. *Cell* **2008**, *132*, 631–644. [[CrossRef](#)] [[PubMed](#)]
2. Signer, R.A.; Morrison, S.J. Mechanisms that regulate stem cell aging and life span. *Cell Stem Cell* **2013**, *12*, 152–165. [[CrossRef](#)] [[PubMed](#)]
3. Bowman, R.L.; Busque, L.; Levine, R.L. Clonal Hematopoiesis and Evolution to Hematopoietic Malignancies. *Cell Stem Cell* **2018**, *22*, 157–170. [[CrossRef](#)]

4. Benito, A.I.; Bryant, E.; Loken, M.R.; Sale, G.E.; Nash, R.A.; John Gass, M.; Deeg, H.J. NOD/SCID mice transplanted with marrow from patients with myelodysplastic syndrome (MDS) show long-term propagation of normal but not clonal human precursors. *Leuk. Res.* **2003**, *27*, 425–436. [[CrossRef](#)]
5. Raaijmakers, M.H.; Mukherjee, S.; Guo, S.; Zhang, S.; Kobayashi, T.; Schoonmaker, J.A.; Ebert, B.L.; Al-Shahrour, F.; Hasserjian, R.P.; Scadden, E.O.; et al. Bone progenitor dysfunction induces myelodysplasia and secondary leukaemia. *Nature* **2010**, *464*, 852–857. [[CrossRef](#)]
6. Yuan, S.; Sun, G.; Zhang, Y.; Dong, F.; Cheng, H.; Cheng, T. Understanding the “SMART” features of hematopoietic stem cells and beyond. *Sci. China Life Sci.* **2021**, *64*, 2030–2044. [[CrossRef](#)] [[PubMed](#)]
7. Man, Y.; Yao, X.; Yang, T.; Wang, Y. Hematopoietic Stem Cell Niche During Homeostasis, Malignancy, and Bone Marrow Transplantation. *Front. Cell Dev. Biol.* **2021**, *9*, 621214. [[CrossRef](#)] [[PubMed](#)]
8. Pioli, P.D.; Casero, D.; Montecino-Rodriguez, E.; Morrison, S.L.; Dorshkind, K. Plasma Cells Are Obligate Effectors of Enhanced Myelopoiesis in Aging Bone Marrow. *Immunity* **2019**, *51*, 351–366.e6. [[CrossRef](#)] [[PubMed](#)]
9. Bruns, I.; Lucas, D.; Pinho, S.; Ahmed, J.; Lambert, M.P.; Kunisaki, Y.; Scheiermann, C.; Schiff, L.; Poncz, M.; Bergman, A.; et al. Megakaryocytes regulate hematopoietic stem cell quiescence through CXCL4 secretion. *Nat. Med.* **2014**, *20*, 1315–1320. [[CrossRef](#)]
10. Zhao, M.; Perry, J.M.; Marshall, H.; Venkatraman, A.; Qian, P.; He, X.C.; Ahamed, J.; Li, L. Megakaryocytes maintain homeostatic quiescence and promote post-injury regeneration of hematopoietic stem cells. *Nat. Med.* **2014**, *20*, 1321–1326. [[CrossRef](#)]
11. Nakamura-Ishizu, A.; Takubo, K.; Fujioka, M.; Suda, T. Megakaryocytes are essential for HSC quiescence through the production of thrombopoietin. *Bioch. Biophys. Res. Commun.* **2014**, *454*, 353–357. [[CrossRef](#)] [[PubMed](#)]
12. Pinho, S.; Marchand, T.; Yang, E.; Wei, Q.; Nerlov, C.; Frenette, P.S. Lineage-Biased Hematopoietic Stem Cells Are Regulated by Distinct Niches. *Dev. Cell* **2018**, *44*, 634–641.e4. [[CrossRef](#)] [[PubMed](#)]
13. Hirata, Y.; Furuhashi, K.; Ishii, H.; Li, H.W.; Pinho, S.; Ding, L.; Robson, S.C.; Frenette, P.S.; Fujisaki, J. CD150^{high} Bone Marrow Tregs Maintain Hematopoietic Stem Cell Quiescence and Immune Privilege via Adenosine. *Cell Stem Cell* **2018**, *22*, 445–453.e5. [[CrossRef](#)] [[PubMed](#)]
14. Fujisaki, J.; Wu, J.; Carlson, A.L.; Silberstein, L.; Putheti, P.; Larocca, R.; Gao, W.; Saito, T.I.; Lo Celso, C.; Tsuyuzaki, H.; et al. In vivo imaging of Treg cells providing immune privilege to the haematopoietic stem-cell niche. *Nature* **2011**, *474*, 216–219. [[CrossRef](#)]
15. Hur, J.; Choi, J.I.; Lee, H.; Nham, P.; Kim, T.W.; Chae, C.W.; Yun, J.Y.; Kang, J.A.; Kang, J.; Lee, S.E.; et al. CD82/KAI1 Maintains the Dormancy of Long-Term Hematopoietic Stem Cells through Interaction with DARC-Expressing Macrophages. *Cell Stem Cell* **2016**, *18*, 508–521. [[CrossRef](#)]
16. Chow, A.; Huggins, M.; Ahmed, J.; Hashimoto, D.; Lucas, D.; Kunisaki, Y.; Pinho, S.; Leboeuf, M.; Noizat, C.; van Rooijen, N.; et al. CD169⁺ macrophages provide a niche promoting erythropoiesis under homeostasis and stress. *Nat. Med.* **2013**, *19*, 429–436. [[CrossRef](#)]
17. Christopher, M.J.; Rao, M.; Liu, F.; Woloszynek, J.R.; Link, D.C. Expression of the G-CSF receptor in monocytic cells is sufficient to mediate hematopoietic progenitor mobilization by G-CSF in mice. *J. Exp. Med.* **2011**, *208*, 251–260. [[CrossRef](#)]
18. Chow, A.; Lucas, D.; Hidalgo, A.; Méndez-Ferrer, S.; Hashimoto, D.; Scheiermann, C.; Battista, M.; Leboeuf, M.; Prophete, C.; van Rooijen, N.; et al. Bone marrow CD169⁺ macrophages promote the retention of hematopoietic stem and progenitor cells in the mesenchymal stem cell niche. *J. Exp. Med.* **2011**, *208*, 261–271. [[CrossRef](#)]
19. Winkler, I.G.; Sims, N.A.; Pettit, A.R.; Barbier, V.; Nowlan, B.; Helwani, F.; Poulton, I.J.; van Rooijen, N.; Alexander, K.A.; Raggatt, L.J.; et al. Bone marrow macrophages maintain hematopoietic stem cell (HSC) niches and their depletion mobilizes HSCs. *Blood* **2010**, *116*, 4815–4828. [[CrossRef](#)]
20. Ludin, A.; Itkin, T.; Gur-Cohen, S.; Mildner, A.; Shezen, E.; Golan, K.; Kollet, O.; Kalinkovich, A.; Porat, Z.; D’Uva, G.; et al. Monocytes-macrophages that express α -smooth muscle actin preserve primitive hematopoietic cells in the bone marrow. *Nat. Immunol.* **2012**, *13*, 1072–1082. [[CrossRef](#)]
21. Kumari, A.; Ludin, A.; Golan, K.; Kollet, O.; Niemeyer, E.; Friedlander, N.; Lapidot, T. PGE2 Promotes BM Hematopoietic Stem Cell Retention Via Stromal Lactate Production, cAMP and CXCL12/CXCR4 Regulation. *Blood* **2014**, *124*, 771. [[CrossRef](#)]
22. Zhang, J.; Supakorndej, T.; Krambs, J.R.; Rao, M.; Abou-Ezzi, G.; Ye, R.Y.; Li, S.; Trinkaus, K.; Link, D.C. Bone marrow dendritic cells regulate hematopoietic stem/progenitor cell trafficking. *J. Clin. Investig.* **2019**, *129*, 2920–2931. [[CrossRef](#)] [[PubMed](#)]
23. Manz, M.G.; Boettcher, S.; Boettcher, S. Emergency granulopoiesis. *Nat. Rev. Immunol.* **2014**, *14*, 302–314. [[CrossRef](#)] [[PubMed](#)]
24. Nagai, Y.; Garrett, K.P.; Ohta, S.; Bahrun, U.; Kouro, T.; Akira, S.; Takatsu, K.; Kincade, P.W. Toll-like receptors on hematopoietic progenitor cells stimulate innate immune system replenishment. *Immunity* **2006**, *24*, 801–812. [[CrossRef](#)]
25. Zhao, J.L.; Ma, C.; O’Connell, R.M.; Mehta, A.; DiLoreto, R.; Heath, J.R.; Baltimore, D. Conversion of danger signals into cytokine signals by hematopoietic stem and progenitor cells for regulation of stress-induced hematopoiesis. *Cell Stem Cell* **2014**, *14*, 445–459. [[CrossRef](#)]
26. Pietras, E.M.; Lakshminarasimhan, R.; Techner, J.M.; Fong, S.; Flach, J.; Binnewies, M.; Passegué, E. Re-entry into quiescence protects hematopoietic stem cells from the killing effect of chronic exposure to type I interferons. *J. Exp. Med.* **2014**, *211*, 245–262. [[CrossRef](#)]
27. Chavez, J.S.; Rabe, J.L.; Loeffler, D.; Higa, K.C.; Hernandez, G.; Mills, T.S.; Ahmed, N.; Gessner, R.L.; Ke, Z.; Idler, B.M.; et al. PU.1 enforces quiescence and limits hematopoietic stem cell expansion during inflammatory stress. *J. Exp. Med.* **2021**, *218*, e20201169. [[CrossRef](#)]

28. Wang, Z.; Ema, H. Mechanisms of self-renewal in hematopoietic stem cells. *Int. J. Hematol.* **2016**, *103*, 498–509. [[CrossRef](#)]
29. Bernitz, J.M.; Kim, H.S.; MacArthur, B.; Sieburg, H.; Moore, K. Hematopoietic Stem Cells Count and Remember Self-Renewal Divisions. *Cell* **2016**, *167*, 1296–1309.e10. [[CrossRef](#)]
30. Dorshkind, K.; Montecino-Rodriguez, E.; Signer, R.A. The ageing immune system: Is it ever too old to become young again? *Nat. Rev. Immunol.* **2009**, *9*, 57–62. [[CrossRef](#)]
31. Barreyro, L.; Chlon, T.M.; Starczynowski, D.T. Chronic immune response dysregulation in MDS pathogenesis. *Blood* **2018**, *132*, 1553–1560. [[CrossRef](#)] [[PubMed](#)]
32. Netea, M.G.; Joosten, L.A.; Latz, E.; Mills, K.H.; Natoli, G.; Stunnenberg, H.G.; O'Neill, L.A.; Xavier, R.J. Trained immunity: A program of innate immune memory in health and disease. *Science* **2016**, *352*, aaf1098. [[CrossRef](#)] [[PubMed](#)]
33. Kaufmann, E.; Sanz, J.; Dunn, J.L.; Khan, N.; Mendonça, L.E.; Pacis, A.; Tzelepis, F.; Pernet, E.; Dumaine, A.; Grenier, J.C.; et al. BCG Educates Hematopoietic Stem Cells to Generate Protective Innate Immunity against Tuberculosis. *Cell* **2018**, *172*, 176–190.e19. [[CrossRef](#)] [[PubMed](#)]
34. de Laval, B.; Maurizio, J.; Kandalla, P.K.; Brisou, G.; Simonnet, L.; Huber, C.; Gimenez, G.; Matcovitch-Natan, O.; Reinhardt, S.; David, E.; et al. C/EBP β -Dependent Epigenetic Memory Induces Trained Immunity in Hematopoietic Stem Cells. *Cell Stem Cell* **2020**, *26*, 657–674.e8. [[CrossRef](#)]
35. Yamamoto, R.; Wilkinson, A.C.; Ooehara, J.; Lan, X.; Lai, C.Y.; Nakauchi, Y.; Pritchard, J.K.; Nakauchi, H. Large-Scale Clonal Analysis Resolves Aging of the Mouse Hematopoietic Stem Cell Compartment. *Cell Stem Cell* **2018**, *22*, 600–607.e4. [[CrossRef](#)]
36. Ho, Y.H.; Del Toro, R.; Rivera-Torres, J.; Rak, J.; Korn, C.; García-García, A.; Macías, D.; González-Gómez, C.; Del Monte, A.; Wittner, M.; et al. Remodeling of Bone Marrow Hematopoietic Stem Cell Niches Promotes Myeloid Cell Expansion during Premature or Physiological Aging. *Cell Stem Cell* **2019**, *25*, 407–418.e6. [[CrossRef](#)]
37. Valletta, S.; Thomas, A.; Meng, Y.; Ren, X.; Drissen, R.; Sengül, H.; Di Genua, C.; Nerlov, C. Micro-environmental sensing by bone marrow stroma identifies IL-6 and TGF β 1 as regulators of hematopoietic ageing. *Nat. Commun.* **2020**, *11*, 4075. [[CrossRef](#)]
38. Frisch, B.J.; Hoffman, C.M.; Latchney, S.E.; LaMere, M.W.; Myers, J.; Ashton, J.; Li, A.J.; Saunders, J., 2nd; Palis, J.; Perkins, A.; et al. Aged marrow macrophages expand platelet-biased hematopoietic stem cells via Interleukin1B. *JCI Insight* **2019**, *5*, e124213. [[CrossRef](#)]
39. Geiger, H.; de Haan, G.; Florian, M.C. The ageing haematopoietic stem cell compartment. *Nat. Rev. Immunol.* **2013**, *13*, 376–389. [[CrossRef](#)]
40. Morita, Y.; Ema, H.; Nakauchi, H. Heterogeneity and hierarchy within the most primitive hematopoietic stem cell compartment. *J. Exp. Med.* **2010**, *207*, 1173–1182. [[CrossRef](#)]
41. Shimazu, T.; Iida, R.; Zhang, Q.; Welner, R.S.; Medina, K.L.; Alberola-Lla, J.; Kincade, P.W. CD86 is expressed on murine hematopoietic stem cells and denotes lymphopoietic potential. *Blood* **2012**, *119*, 4889–4897. [[CrossRef](#)] [[PubMed](#)]
42. Mann, M.; Mehta, A.; de Boer, C.G.; Kowalczyk, M.S.; Lee, K.; Haldeman, P.; Rogel, N.; Knecht, A.R.; Farouq, D.; Regev, A.; et al. Heterogeneous Responses of Hematopoietic Stem Cells to Inflammatory Stimuli Are Altered with Age. *Cell Rep.* **2018**, *25*, 2992–3005.e5. [[CrossRef](#)] [[PubMed](#)]
43. Pang, W.W.; Price, E.A.; Sahoo, D.; Beerman, I.; Maloney, W.J.; Rossi, D.J.; Schrier, S.L.; Weissman, I.L. Human bone marrow hematopoietic stem cells are increased in frequency and myeloid-biased with age. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 20012–20017. [[CrossRef](#)]
44. Florian, M.C.; Klose, M.; Sacma, M.; Jablanovic, J.; Knudson, L.; Nattamai, K.J.; Marka, G.; Vollmer, A.; Soller, K.; Sakk, V.; et al. alters the epigenetic asymmetry of HSC division. *PLoS Biol.* **2018**, *16*, e2003389. [[CrossRef](#)] [[PubMed](#)]
45. Bogeska, R.; Kaschutnig, P.; Fawaz, M.; Mikecin, A.-M.; Büchler-Schäff, M.; Paffenholz, S.; Asada, N.; Frauhammer, F.; Buettner, F.; Ball, M.; et al. Hematopoietic stem cells fail to regenerate following inflammatory challenge. *bioRxiv*, 2020; *in press*. [[CrossRef](#)]
46. Essers, M.A.; Offner, S.; Blanco-Bose, W.E.; Waibler, Z.; Kalinke, U.; Duchosal, M.A.; Trumpp, A. IFN α activates dormant haematopoietic stem cells in vivo. *Nature* **2009**, *458*, 904–908. [[CrossRef](#)] [[PubMed](#)]
47. Takizawa, H.; Fritsch, K.; Kovtonyuk, L.V.; Saito, Y.; Yakkala, C.; Jacobs, K.; Ahuja, A.K.; Lopes, M.; Hausmann, A.; Hardt, W.D.; et al. Pathogen-Induced TLR4-TRIF Innate Immune Signaling in Hematopoietic Stem Cells Promotes Proliferation but Reduces Competitive Fitness. *Cell Stem Cell* **2020**, *27*, 177. [[CrossRef](#)] [[PubMed](#)]
48. Ergen, A.V.; Boles, N.C.; Goodell, M.A. Rantes/Ccl5 influences hematopoietic stem cell subtypes and causes myeloid skewing. *Blood* **2012**, *119*, 2500–2509. [[CrossRef](#)]
49. Pietras, E.M.; Mirantes-Barbeito, C.; Fong, S.; Loeffler, D.; Kovtonyuk, L.V.; Zhang, S.; Lakshminarasimhan, R.; Chin, C.P.; Techner, J.M.; Will, B.; et al. Chronic interleukin-1 exposure drives haematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal. *Nat. Cell Biol.* **2016**, *18*, 607–618. [[CrossRef](#)]
50. Helbling, P.M.; Piñero-Yáñez, E.; Gerosa, R.; Boettcher, S.; Al-Shahrour, F.; Manz, M.G.; Nombela-Arrieta, C. Global Transcriptomic Profiling of the Bone Marrow Stromal Microenvironment during Postnatal Development, Aging, and Inflammation. *Cell Rep.* **2019**, *29*, 3313–3330.e4. [[CrossRef](#)]
51. Franceschi, C.; Bonafè, M.; Valensin, S.; Olivieri, F.; De Luca, M.; Ottaviani, E.; De Benedictis, G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci.* **2020**, *908*, 244–254. [[CrossRef](#)] [[PubMed](#)]
52. Fulop, T.; Witkowski, J.M.; Olivieri, F.; Larbi, A. The integration of inflammaging in age-related diseases. *Semin. Immunol.* **2018**, *40*, 17–35. [[CrossRef](#)] [[PubMed](#)]

53. He, H.; Xu, P.; Zhang, X.; Liao, M.; Dong, Q.; Cong, T.; Tang, B.; Yang, X.; Ye, M.; Chang, Y.; et al. Aging-induced IL27Ra signaling impairs hematopoietic stem cells. *Blood* **2020**, *136*, 183–198. [[CrossRef](#)] [[PubMed](#)]
54. Hernandez, G.; Mills, T.S.; Rabe, J.L.; Chavez, J.S.; Kuldane, S.; Kirkpatrick, G.; Noetzli, L.; Jubair, W.K.; Zanche, M.; Myers, J.R.; et al. Pro-inflammatory cytokine blockade attenuates myeloid expansion in a murine model of rheumatoid arthritis. *Haematologica* **2020**, *105*, 585–597. [[CrossRef](#)] [[PubMed](#)]
55. Yamashita, M.; Passegué, E. TNF- α Coordinates Hematopoietic Stem Cell Survival and Myeloid Regeneration. *Cell Stem Cell* **2019**, *25*, 357–372.e7. [[CrossRef](#)]
56. Esplin, B.L.; Shimazu, T.; Welner, R.S.; Garrett, K.P.; Nie, L.; Zhang, Q.; Humphrey, M.B.; Yang, Q.; Borghesi, L.A.; Kincade, P.W. Chronic exposure to a TLR ligand injures hematopoietic stem cells. *J. Immunol.* **2011**, *186*, 5367–5375. [[CrossRef](#)]
57. He, H.; Wang, J. Inflammation and hematopoietic stem cells aging. *Blood Sci.* **2020**, *3*, 1–5. [[CrossRef](#)]
58. Li, T.; Chen, Z.J. The cGAS-cGAMP-STING pathway connects DNA damage to inflammation, senescence, and cancer. *J. Exp. Med.* **2018**, *215*, 1287–1299. [[CrossRef](#)]
59. Rathinam, V.A.; Jiang, Z.; Waggoner, S.N.; Sharma, S.; Cole, L.E.; Waggoner, L.; Vanaja, S.K.; Monks, B.G.; Ganesan, S.; Latz, E.; et al. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. *Nat. Immunol.* **2010**, *11*, 395–402. [[CrossRef](#)]
60. Chambers, S.M.; Shaw, C.A.; Gatz, C.; Fisk, C.J.; Donehower, L.A.; Goodell, M.A. Aging hematopoietic stem cells decline in function and exhibit epigenetic dysregulation. *PLoS Biol.* **2007**, *5*, e201. [[CrossRef](#)]
61. Ho, T.T.; Warr, M.R.; Adelman, E.R.; Lansinger, O.M.; Flach, J.; Verovskaya, E.V.; Figueroa, M.E.; Passegué, E. Autophagy maintains the metabolism and function of young and old stem cells. *Nature* **2017**, *543*, 205–210. [[CrossRef](#)] [[PubMed](#)]
62. Yabal, M.; Calleja, D.J.; Simpson, D.S.; Lawlor, K.E. Stressing out the mitochondria: Mechanistic insights into NLRP3 inflammasome activation. *J. Leukoc. Biol.* **2019**, *105*, 377–399. [[CrossRef](#)] [[PubMed](#)]
63. Royce, G.H.; Brown-Borg, H.M.; Deepa, S.S. The potential role of necroptosis in inflammaging and aging. *GeroScience* **2019**, *41*, 795–811. [[CrossRef](#)] [[PubMed](#)]
64. Sebastian-Valverde, M.; Pasinetti, G.M. The NLRP3 Inflammasome as a Critical Actor in the Inflammaging Process. *Cells* **2020**, *9*, 1552. [[CrossRef](#)]
65. King, A.M.; Keating, P.; Prabhu, A.; Blomberg, B.B.; Riley, R.L. NK cells in the CD19- B220+ bone marrow fraction are increased in senescence and reduce E2A and surrogate light chain proteins in B cell precursors. *Mech. Ageing Dev.* **2019**, *130*, 384–392. [[CrossRef](#)]
66. Ratliff, M.; Alter, S.; Frasca, D.; Blomberg, B.B.; Riley, R.L. In senescence, age-associated B cells secrete TNF α and inhibit survival of B-cell precursors. *Ageing Cell* **2013**, *12*, 303–311. [[CrossRef](#)]
67. Takizawa, H.; Boettcher, S.; Manz, M.G. Demand-adapted regulation of early hematopoiesis in infection and inflammation. *Blood* **2012**, *119*, 2991–3002. [[CrossRef](#)]
68. Xie, M.; Lu, C.; Wang, J.; McLellan, M.D.; Johnson, K.J.; Wendl, M.C.; McMichael, J.F.; Schmidt, H.K.; Yellapantula, V.; Miller, C.A.; et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. *Nat. Med.* **2014**, *20*, 1472–1478. [[CrossRef](#)]
69. Genovese, G.; Kähler, A.K.; Handsaker, R.E.; Lindberg, J.; Rose, S.A.; Bakhoum, S.F.; Chambert, K.; Mick, E.; Neale, B.M.; Fromer, M.; et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N. Eng. J. Med.* **2014**, *371*, 2477–2487. [[CrossRef](#)]
70. Jaiswal, S.; Fontanillas, P.; Flannick, J.; Manning, A.; Grauman, P.V.; Mar, B.G.; Lindsley, R.C.; Mermel, C.H.; Burt, N.; Chavez, A.; et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N. Eng. J. Med.* **2014**, *371*, 2488–2498. [[CrossRef](#)]
71. Steensma, D.P. Clinical consequences of clonal hematopoiesis of indeterminate potential. *Blood Adv.* **2018**, *2*, 3404–3410. [[CrossRef](#)] [[PubMed](#)]
72. Tubbs, A.; Nussenzweig, A. Endogenous DNA Damage as a Source of Genomic Instability in Cancer. *Cell* **2017**, *168*, 644–656. [[CrossRef](#)] [[PubMed](#)]
73. Williams, N.; Lee, J.; Mitchell, E.; Moore, L.; Baxter, E.J.; Hewinson, J.; Dawson, K.J.; Menzies, A.; Godfrey, A.L.; Green, A.R.; et al. Life histories of myeloproliferative neoplasms inferred from phylogenies. *Nature* **2022**, *602*, 162–168. [[CrossRef](#)] [[PubMed](#)]
74. Abegunde, S.O.; Buckstein, R.; Wells, R.A.; Rauh, M.J. An inflammatory environment containing TNF α favors Tet2-mutant clonal hematopoiesis. *Exp. Hematol.* **2018**, *59*, 60–65. [[CrossRef](#)]
75. Trowbridge, J.J.; Starczynowski, D.T. Innate immune pathways and inflammation in hematopoietic aging, clonal hematopoiesis, and MDS. *J. Exp. Med.* **2021**, *218*, e20201544. [[CrossRef](#)]
76. Muto, T.; Walker, C.S.; Choi, K.; Hueneman, K.; Smith, M.A.; Gul, Z.; Garcia-Manero, G.; Ma, A.; Zheng, Y.; Starczynowski, D.T. Adaptive response to inflammation contributes to sustained myelopoiesis and confers a competitive advantage in myelodysplastic syndrome HSCs. *Nat. Immunol.* **2020**, *21*, 535–545. [[CrossRef](#)]
77. Fuster, J.J.; Zuriaga, M.A.; Zorita, V.; MacLauchlan, S.; Polackal, M.N.; Viana-Huete, V.; Ferrer-Pérez, A.; Matesanz, N.; Herrero-Cervera, A.; Sano, S.; et al. TET2-Loss-of-Function-Driven Clonal Hematopoiesis Exacerbates Experimental Insulin Resistance in Aging and Obesity. *Cell Rep.* **2020**, *33*, 108326. [[CrossRef](#)]
78. Jaiswal, S.; Natarajan, P.; Silver, A.J.; Gibson, C.J.; Bick, A.G.; Shvartz, E.; McConkey, M.; Gupta, N.; Gabriel, S.; Ardissino, D.; et al. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. *N. Eng. J. Med.* **2017**, *377*, 111–121. [[CrossRef](#)]

79. Dorsheimer, L.; Assmus, B.; Rasper, T.; Ortmann, C.A.; Ecke, A.; Abou-El-Ardat, K.; Schmid, T.; Brüne, B.; Wagner, S.; Serve, H.; et al. Association of Mutations Contributing to Clonal Hematopoiesis with Prognosis in Chronic Ischemic Heart Failure. *JAMA Cardiol.* **2019**, *4*, 25–33. [[CrossRef](#)]
80. Libby, P.; Kobold, S. Inflammation: A common contributor to cancer, aging, and cardiovascular diseases—expanding the concept of cardio-oncology. *Cardiovasc. Res.* **2019**, *115*, 824–829. [[CrossRef](#)]
81. Cook, E.K.; Izukawa, T.; Young, S.; Rosen, G.; Jamali, M.; Zhang, L.; Johnson, D.; Bain, E.; Hilland, J.; Ferrone, C.K. Comorbid and inflammatory characteristics of genetic subtypes of clonal hematopoiesis. *Blood Adv.* **2019**, *3*, 2482–2486. [[CrossRef](#)] [[PubMed](#)]
82. Papa, V.; Marracino, L.; Fortini, F.; Rizzo, P.; Campo, G.; Vaccarezza, M.; Vieceli Dalla Sega, F. Translating Evidence from Clonal Hematopoiesis to Cardiovascular Disease: A Systematic Review. *J Clin. Med.* **2020**, *9*, 2480. [[CrossRef](#)] [[PubMed](#)]
83. Fuster, J.J.; MacLauchlan, S.; Zuriaga, M.A.; Polackal, M.N.; Ostriker, A.C.; Chakraborty, R.; Wu, C.L.; Sano, S.; Muralidharan, S.; Rius, C.; et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science* **2017**, *355*, 842–847. [[CrossRef](#)]
84. Lin, A.E.; Libby, P.; Ebert, B.L. A new opening on aortic stenosis: Predicting prognosis with clonal haematopoiesis. *Eur. Heart J.* **2020**, *41*, 940–942. [[CrossRef](#)]
85. Starczynowski, D.T.; Kuchenbauer, F.; Argiropoulos, B.; Sung, S.; Morin, R.; Muranyi, A.; Hirst, M.; Hogge, D.; Marra, M.; Wells, R.A.; et al. Identification of miR-145 and miR-146a as mediators of the 5q− syndrome phenotype. *Nat. Med.* **2010**, *16*, 49–58. [[CrossRef](#)]
86. Corral, L.G.; Haslett, P.A.; Muller, G.W.; Chen, R.; Wong, L.M.; Ocampo, C.J.; Patterson, R.T.; Stirling, D.I.; Kaplan, G. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J. Immunol.* **1999**, *163*, 380–386. [[PubMed](#)]
87. Grants, J.M.; Wegrzyn, J.; Hui, T.; O'Neill, K.; Shadbolt, M.; Knapp, D.; Parker, J.; Deng, Y.; Gopal, A.; Docking, T.R.; et al. Altered microRNA expression links IL6 and TNF-induced inflammaging with myeloid malignancy in humans and mice. *Blood* **2020**, *135*, 2235–2251. [[CrossRef](#)] [[PubMed](#)]
88. Wei, Y.; Dimicoli, S.; Bueso-Ramos, C.; Chen, R.; Yang, H.; Neuberger, D.; Pierce, S.; Jia, Y.; Zheng, H.; Wang, H.; et al. Toll-like receptor alterations in myelodysplastic syndrome. *Leukemia* **2013**, *27*, 1832–1840. [[CrossRef](#)]
89. Maratheftis, C.I.; Andreacos, E.; Moutsopoulos, H.M.; Voulgarelis, M. Toll-like receptor-4 is up-regulated in hematopoietic progenitor cells and contributes to increased apoptosis in myelodysplastic syndromes. *Clin. Cancer Res.* **2007**, *13*, 1154–1160. [[CrossRef](#)]
90. Monlish, D.A.; Greenberg, Z.J.; Bhatt, S.T.; Leonard, K.M.; Romine, M.P.; Dong, Q.; Bendesky, L.; Duncavage, E.J.; Magee, J.A.; Schuettpelez, L.G. TLR2/6 signaling promotes the expansion of premalignant hematopoietic stem and progenitor cells in the NUP98-HOXD13 mouse model of MDS. *Exp. Hematol.* **2020**, *88*, 42–55. [[CrossRef](#)]
91. Sallman, D.A.; List, A. The central role of inflammatory signaling in the pathogenesis of myelodysplastic syndromes. *Blood* **2019**, *133*, 1039–1048. [[CrossRef](#)]
92. Basiorka, A.A.; McGraw, K.L.; Eksioğlu, E.A.; Chen, X.; Johnson, J.; Zhang, L.; Zhang, Q.; Irvine, B.A.; Cluzeau, T.; Sallman, D.A.; et al. The NLRP3 inflammasome functions as a driver of the myelodysplastic syndrome phenotype. *Blood* **2016**, *128*, 2960–2975. [[CrossRef](#)] [[PubMed](#)]
93. Bewersdorf, J.P.; Zeidan, A.M. Transforming growth factor (TGF)-β pathway as a therapeutic target in lower risk myelodysplastic syndromes. *Leukemia* **2019**, *33*, 1303–1312. [[CrossRef](#)] [[PubMed](#)]
94. Zhou, L.; McMahon, C.; Bhagat, T.; Alencar, C.; Yu, Y.; Fazzari, M.; Sohal, D.; Heuck, C.; Gundabolu, K.; Ng, C.; et al. Reduced SMAD7 leads to overactivation of TGF-beta signaling in MDS that can be reversed by a specific inhibitor of TGF-beta receptor I kinase. *Cancer Res.* **2011**, *71*, 955–963. [[CrossRef](#)] [[PubMed](#)]
95. Smith, M.A.; Choudhary, G.S.; Pellagatti, A.; Choi, K.; Bolanos, L.C.; Bhagat, T.D.; Gordon-Mitchell, S.; Von Ahrens, D.; Pradhan, K.; Steeples, V.; et al. U2AF1 mutations induce oncogenic IRAK4 isoforms and activate innate immune pathways in myeloid malignancies. *Nat. Cell Biol.* **2019**, *21*, 640–650. [[CrossRef](#)] [[PubMed](#)]
96. Lee, S.C.; North, K.; Kim, E.; Jang, E.; Obeng, E.; Lu, S.X.; Liu, B.; Inoue, D.; Yoshimi, A.; Ki, M.; et al. Synthetic Lethal and Convergent Biological Effects of Cancer-Associated Spliceosomal Gene Mutations. *Cancer Cell* **2018**, *34*, 225–241.e8. [[CrossRef](#)]
97. Klune, J.R.; Dhupar, R.; Cardinal, J.; Billiar, T.R.; Tsung, A. HMGB1: Endogenous danger signaling. *Mol. Med.* **2008**, *14*, 476–484. [[CrossRef](#)]
98. Yuan, S.; Liu, Z.; Xu, Z.; Liu, J.; Zhang, J. High mobility group box 1 (HMGB1): A pivotal regulator of hematopoietic malignancies. *J. Hematol. Oncol.* **2020**, *13*, 91. [[CrossRef](#)]
99. Velegraki, M.; Papakonstanti, E.; Mavroudi, I.; Psyllaki, M.; Tsatsanis, C.; Oulas, A.; Iliopoulos, I.; Katonis, P.; Papadaki, H.A. Impaired clearance of apoptotic cells leads to HMGB1 release in the bone marrow of patients with myelodysplastic syndromes and induces TLR4-mediated cytokine production. *Haematologica* **2013**, *98*, 1206–1215. [[CrossRef](#)]
100. Apodaca-Chávez, E.; Demichelis-Gómez, R.; Rosas-López, A.; Mejía-Domínguez, N.R.; Galvan-López, I.; Addorosisio, M.; Tracey, K.J.; Valdés-Ferrer, S.I. Circulating HMGB1 is increased in myelodysplastic syndrome but not in other bone marrow failure syndromes: Proof-of-concept cross-sectional study. *Ther. Adv. Hematol.* **2022**, *13*, 20406207221125990. [[CrossRef](#)]
101. Willingham, S.B.; Allen, I.C.; Bergstralh, D.T.; Brickey, W.J.; Huang, M.T.; Taxman, D.J.; Duncan, J.A.; Ting, J.P. NLRP3 (NALP3, Cryopyrin) facilitates in vivo caspase-1 activation, necrosis, and HMGB1 release via inflammasome-dependent and -independent pathways. *J. Immunol.* **2009**, *183*, 2008–2015. [[CrossRef](#)] [[PubMed](#)]

102. Kam, A.; Piryani, S.O.; McCall, C.M.; Park, H.S.; Rizzieri, D.A.; Doan, P.L. Targeting High Mobility Group Box-1 (HMGB1) Promotes Cell Death in Myelodysplastic Syndrome. *Clin. Cancer Res.* **2019**, *25*, 4155–4167. [[CrossRef](#)] [[PubMed](#)]
103. Kitagawa, M.; Saito, I.; Kuwata, T.; Yoshida, S.; Yamaguchi, S.; Takahashi, M.; Tanizawa, T.; Kamiyama, R.; Hirokawa, K. Overexpression of tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma by bone marrow cells from patients with myelodysplastic syndromes. *Leukemia* **1997**, *11*, 2049–2054. [[CrossRef](#)] [[PubMed](#)]
104. Gañán-Gómez, I.; Wei, Y.; Starczynowski, D.T.; Colla, S.; Yang, H.; Cabrero-Calvo, M.; Bohannan, Z.S.; Verma, A.; Steidl, U.; Garcia-Manero, G. Deregulation of innate immune and inflammatory signaling in myelodysplastic syndromes. *Leukemia* **2015**, *29*, 1458–1469. [[CrossRef](#)]
105. Shi, X.; Zheng, Y.; Xu, L.; Cao, C.; Dong, B.; Chen, X. The inflammatory cytokine profile of myelodysplastic syndromes: A meta-analysis. *Medicine* **2019**, *98*, e15844. [[CrossRef](#)]
106. D’Silva, S.; Rajadhyaksha, S.B.; Singh, M. Immune Dysregulation in MDS: The Role of Cytokines and Immune Cells. In *Recent Developments in Myelodysplastic Syndromes*; Fuchs, O., Ed.; IntechOpen: London, UK, 2019; Available online: <https://www.intechopen.com/chapters/64447#B13> (accessed on 22 October 2022). [[CrossRef](#)]
107. Kordasti, S.Y.; Afzali, B.; Lim, Z.; Ingram, W.; Hayden, J.; Barber, L.; Matthews, K.; Chelliah, R.; Guinn, B.; Lombardi, G.; et al. IL-17-producing CD4(+) T cells, pro-inflammatory cytokines and apoptosis are increased in low risk myelodysplastic syndrome. *Br. J. Haematol.* **2009**, *145*, 64–72. [[CrossRef](#)]
108. Zombos, N.; Symeonidis, A.; Kourakli, A.; Katevas, P.; Matsoukas, P.; Perraki, M.; Georgoulas, V. Increased levels of soluble interleukin-2 receptors and tumor necrosis factor in serum of patients with myelodysplastic syndromes. *Blood* **1991**, *77*, 413–414. [[CrossRef](#)]
109. Lopes, M.R.; Traina, F.; Campos, P.; Pereira, J.K.; Machado-Neto, J.A.; Machado, H.; Gilli, S.C.; Saad, S.T.; Favaro, P. IL10 inversely correlates with the percentage of CD8⁺ cells in MDS patients. *Leuk. Res.* **2013**, *37*, 541–546. [[CrossRef](#)]
110. Pellagatti, A.; Cazzola, M.; Giagounidis, A.; Perry, J.; Malcovati, L.; Della Porta, M.G.; Jädersten, M.; Killick, S.; Verma, A.; Norbury, C.J.; et al. Deregulated gene expression pathways in myelodysplastic syndrome hematopoietic stem cells. *Leukemia* **2010**, *24*, 756–764. [[CrossRef](#)]
111. Michalopoulou, S.; Micheva, I.; Kouraklis-Symeonidis, A.; Kakagianni, T.; Symeonidis, A.; Zombos, N.C. Impaired clonogenic growth of myelodysplastic bone marrow progenitors in vitro is irrelevant to their apoptotic state. *Leuk. Res.* **2004**, *28*, 805–812. [[CrossRef](#)]
112. Deeg, H.J.; Beckham, C.; Loken, M.R.; Bryant, E.; Lesnikova, M.; Shulman, H.M.; Gooley, T. Negative regulators of hemopoiesis and stroma function in patients with myelodysplastic syndrome. *Leuk. Lymphoma* **2000**, *37*, 405–414. [[CrossRef](#)] [[PubMed](#)]
113. Gersuk, G.M.; Beckham, C.; Loken, M.R.; Kiener, P.; Anderson, J.E.; Farrand, A.; Troutt, A.B.; Ledbetter, J.A.; Deeg, H.J. A role for tumour necrosis factor-alpha, Fas and Fas-Ligand in marrow failure associated with myelodysplastic syndrome. *Br. J. Haematol.* **1998**, *103*, 176–188. [[CrossRef](#)] [[PubMed](#)]
114. Zeng, W.; Miyazato, A.; Chen, G.; Kajigaya, S.; Young, N.S.; Maciejewski, J.P. Interferon-gamma-induced gene expression in CD34 cells: Identification of pathologic cytokine-specific signature profiles. *Blood* **2006**, *107*, 167–175. [[CrossRef](#)]
115. Aggarwal, B.B. Signalling pathways of the TNF superfamily: A double-edged sword. *Nat. Rev. Immunol.* **2003**, *3*, 745–756. [[CrossRef](#)] [[PubMed](#)]
116. Sawanobori, M.; Yamaguchi, S.; Hasegawa, M.; Inoue, M.; Suzuki, K.; Kamiyama, R.; Hirokawa, K.; Kitagawa, M. Expression of TNF receptors and related signaling molecules in the bone marrow from patients with myelodysplastic syndromes. *Leuk. Res.* **2003**, *27*, 583–591. [[CrossRef](#)]
117. Tsimberidou, A.M.; Estey, E.; Wen, S.; Pierce, S.; Kantarjian, H.; Albitar, M.; Kurzrock, R. The prognostic significance of cytokine levels in newly diagnosed acute myeloid leukemia and high-risk myelodysplastic syndromes. *Cancer* **2008**, *113*, 1605–1613. [[CrossRef](#)] [[PubMed](#)]
118. Pardanani, A.; Finke, C.; Lasho, T.L.; Al-Kali, A.; Begna, K.H.; Hanson, C.A.; Tefferi, A. IPSS-independent prognostic value of plasma CXCL10, IL-7 and IL-6 levels in myelodysplastic syndromes. *Leukemia* **2012**, *26*, 693–699. [[CrossRef](#)]
119. Epperson, D.E.; Nakamura, R.; Sauntharajah, Y.; Melenhorst, J.; Barrett, A.J. Oligoclonal T cell expansion in myelodysplastic syndrome: Evidence for an autoimmune process. *Leuk. Res.* **2001**, *25*, 1075–1083. [[CrossRef](#)]
120. Molldrem, J.J.; Jiang, Y.Z.; Stetler-Stevenson, M.; Mavroudis, D.; Hensel, N.; Barrett, A.J. Haematological response of patients with myelodysplastic syndrome to antithymocyte globulin is associated with a loss of lymphocyte-mediated inhibition of CFU-GM and alterations in T-cell receptor Vbeta profiles. *Br. J. Haematol.* **1998**, *102*, 1314–1322. [[CrossRef](#)]
121. Epling-Burnette, P.K.; Painter, J.S.; Rollison, D.E.; Ku, E.; Vendron, D.; Widen, R.; Boulware, D.; Zou, J.X.; Bai, F.; List, A.F. Prevalence and clinical association of clonal T-cell expansions in Myelodysplastic Syndrome. *Leukemia* **2007**, *21*, 659–667. [[CrossRef](#)]
122. Melenhorst, J.J.; Eniafe, R.; Follmann, D.; Nakamura, R.; Kirby, M.; Barrett, A.J. Molecular and flow cytometric characterization of the CD4 and CD8 T-cell repertoire in patients with myelodysplastic syndrome. *Br. J. Haematol.* **2002**, *119*, 97–105. [[CrossRef](#)] [[PubMed](#)]
123. Kook, H.; Zeng, W.; Guibin, C.; Kirby, M.; Young, N.S.; Maciejewski, J.P. Increased cytotoxic T cells with effector phenotype in aplastic anemia and myelodysplasia. *Exp. Hematol.* **2001**, *29*, 1270–1277. [[CrossRef](#)]
124. Strioga, M.; Pasukoniene, V.; Characiejus, D. CD8⁺ CD28⁻ and CD8⁺ CD57⁺ T cells and their role in health and disease. *Immunology* **2011**, *134*, 17–32. [[CrossRef](#)]

125. Ximeri, M.; Galanopoulos, A.; Klaus, M.; Parcharidou, A.; Giannikou, K.; Psyllaki, M.; Symeonidis, A.; Pappa, V.; Kartasis, Z.; Liapi, D.; et al. Effect of lenalidomide therapy on hematopoiesis of patients with myelodysplastic syndrome associated with chromosome 5q deletion. *Haematologica* **2010**, *95*, 406–414. [[CrossRef](#)] [[PubMed](#)]
126. Zheng, Z.; Qianqiao, Z.; Qi, H.; Feng, X.; Chunkang, C.; Xiao, L. In vitro deprivation of CD8(+)/CD57(+)/T cells promotes the malignant growth of bone marrow colony cells in patients with lower-risk myelodysplastic syndrome. *Exp. Hematol.* **2010**, *38*, 677–684. [[CrossRef](#)]
127. Sloand, E.M.; Rezvani, K. The role of the immune system in myelodysplasia: Implications for therapy. *Semin. Hematol.* **2008**, *45*, 39–48. [[CrossRef](#)]
128. Sloand, E.M.; Melenhorst, J.J.; Tucker, Z.C.; Pfannes, L.; Brenchley, J.M.; Yong, A.; Visconte, V.; Wu, C.; Gostick, E.; Scheinberg, P.; et al. T-cell immune responses to Wilms tumor 1 protein in myelodysplasia responsive to immunosuppressive therapy. *Blood* **2011**, *117*, 2691–2699. [[CrossRef](#)]
129. Gang, A.O.; Frøsig, T.M.; Brimnes, M.K.; Lyngaa, R.; Treppendahl, M.B.; Grønbaek, K.; Dufva, I.H.; Straten, P.T.; Hadrup, S.R. 5-Azacytidine treatment sensitizes tumor cells to T-cell mediated cytotoxicity and modulates NK cells in patients with myeloid malignancies. *Blood Cancer J.* **2014**, *4*, e197. [[CrossRef](#)]
130. Wong, K.K.; Hassan, R.; Yaacob, N.S. Hypomethylating Agents and Immunotherapy: Therapeutic Synergism in Acute Myeloid Leukemia and Myelodysplastic Syndromes. *Front. Oncol.* **2021**, *11*, 624742. [[CrossRef](#)]
131. Symeonidis, A.; Kourakli, Katevas, P.; Perraki, M.; Tiniakou, M.; Matsouka, P.; Georgoulas, V.; Zoumbos, N. Immune function parameters at diagnosis in patients with myelodysplastic syndromes: Correlation with the FAB classification and prognosis. *Eur. J. Haematol.* **1991**, *47*, 277–281. [[CrossRef](#)]
132. Zou, J.X.; Rollison, D.E.; Boulware, D.; Chen, D.T.; Sloand, E.M.; Pfannes, L.V.; Goronzy, J.J.; Bai, F.; Painter, J.S.; Wei, S.; et al. Altered naive and memory CD4+ T-cell homeostasis and immunosenescence characterize younger patients with myelodysplastic syndrome. *Leukemia* **2009**, *23*, 1288–1296. [[CrossRef](#)]
133. Sugimori, C.; List, A.F.; Epling-Burnette, P.K. Immune dysregulation in myelodysplastic syndrome. *Hematol. Rep.* **2010**, *2*, e1. [[CrossRef](#)] [[PubMed](#)]
134. Kotsianidis, I.; Bouchliou, I.; Nakou, E.; Spanoudakis, E.; Margaritis, D.; Christophoridou, A.V.; Anastasiades, A.; Tsigalou, C.; Bourikas, G.; Karadimitris, A.; et al. Kinetics, function and bone marrow trafficking of CD4+CD25+FOXP3+ regulatory T cells in myelodysplastic syndromes (MDS). *Leukemia* **2009**, *23*, 510–518. [[CrossRef](#)] [[PubMed](#)]
135. Kordasti, S.Y.; Ingram, W.; Hayden, J.; Darling, D.; Barber, L.; Afzali, B.; Lombardi, G.; Wlodarski, M.W.; Maciejewski, J.P.; Farzaneh, F.; et al. CD4+CD25high Foxp3+ regulatory T cells in myelodysplastic syndrome (MDS). *Blood* **2007**, *110*, 847–850. [[CrossRef](#)] [[PubMed](#)]
136. Epling-Burnette, P.K.; Bai, F.; Painter, J.S.; Rollison, D.E.; Salih, H.R.; Krusch, M.; Zou, J.; Ku, E.; Zhong, B.; Boulware, D.; et al. Reduced natural killer (NK) function associated with high-risk myelodysplastic syndrome (MDS) and reduced expression of activating NK receptors. *Blood* **2007**, *109*, 4816–4824. [[CrossRef](#)]
137. Symeonidis, A.; Zoumbos, N. Defective autologous and allogeneic mixed lymphocyte reaction in patients with primary myelodysplastic syndromes. *Leuk. Res.* **1991**, *15*, 29. [[CrossRef](#)]
138. Jiang, Y.; Li, Y.; Zhu, B. T-cell exhaustion in the tumor microenvironment. *Cell Death Dis.* **2015**, *6*, e1792. [[CrossRef](#)]
139. Hofmeyer, K.A.; Jeon, H.; Zang, X. The PD-1/PD-L1 (B7-H1) pathway in chronic infection-induced cytotoxic T lymphocyte exhaustion. *J. Biomed. Biotechnol.* **2011**, *2011*, 451694. [[CrossRef](#)]
140. Haroun, F.; Solola, S.A.; Nassereddine, S.; Tabbara, I. PD-1 signaling and inhibition in AML and MDS. *Ann. Hematol.* **2017**, *96*, 1441–1448. [[CrossRef](#)]
141. Yang, H.; Bueso-Ramos, C.; DiNardo, C.; Estecio, M.R.; Davanlou, M.; Geng, Q.R.; Fang, Z.; Nguyen, M.; Pierce, S.; Wei, Y.; et al. Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. *Leukemia* **2014**, *28*, 1280–1288. [[CrossRef](#)]
142. Wang, X.; Yang, L.; Huang, F.; Zhang, Q.; Liu, S.; Ma, L.; You, Z. Inflammatory cytokines IL-17 and TNF- α up-regulate PD-L1 expression in human prostate and colon cancer cells. *Immunol. Lett.* **2017**, *184*, 7–14. [[CrossRef](#)] [[PubMed](#)]
143. Garcia-Diaz, A.; Shin, D.S.; Moreno, B.H.; Saco, J.; Escuin-Ordinas, H.; Rodriguez, G.A.; Zaretsky, J.M.; Sun, L.; Hugo, W.; Wang, X.; et al. Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. *Cell Rep.* **2017**, *19*, 1189–1201. [[CrossRef](#)] [[PubMed](#)]
144. Cheng, P.; Eksioğlu, E.A.; Chen, X.; Kandell, W.; Le Trinh, T.; Cen, L.; Qi, J.; Sallman, D.A.; Zhang, Y.; Tu, N.; et al. S100A9-induced overexpression of PD-1/PD-L1 contributes to ineffective hematopoiesis in myelodysplastic syndromes. *Leukemia* **2019**, *33*, 2034–2046. [[CrossRef](#)] [[PubMed](#)]
145. Ferrari, V.; Tarke, A.; Fields, H.; Tanaka, T.N.; Searles, S.; Zanetti, M. Tumor-specific T cell-mediated upregulation of PD-L1 in myelodysplastic syndrome cells does not affect T-cell killing. *Front. Oncol.* **2022**, *12*, 915629. [[CrossRef](#)] [[PubMed](#)]
146. Pang, W.W.; Pluvinaige, J.V.; Price, E.A.; Sridhar, K.; Arber, D.A.; Greenberg, P.L.; Schrier, S.L.; Park, C.Y.; Weissman, I.L. Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 3011–3016. [[CrossRef](#)] [[PubMed](#)]
147. Han, Y.; Wang, H.; Shao, Z. Monocyte-Derived Macrophages Are Impaired in Myelodysplastic Syndrome. *J. Immunol. Res.* **2016**, *2016*, 5479013. [[CrossRef](#)]

148. Zhang, G.; Yang, L.; Han, Y.; Niu, H.; Yan, L.; Shao, Z.; Xing, L.; Wang, H. Abnormal Macrophage Polarization in Patients with Myelodysplastic Syndrome. *Mediators Inflamm.* **2021**, *2021*, 9913382. [[CrossRef](#)]
149. Liu, J.; Geng, X.; Hou, J.; Wu, G. New insights into M1/M2 macrophages: Key modulators in cancer progression. *Cancer Cell Int.* **2021**, *21*, 389. [[CrossRef](#)]
150. Sica, A.; Mantovani, A. Macrophage plasticity and polarization: In vivo veritas. *J. Clin. Investig.* **2012**, *122*, 787–795. [[CrossRef](#)]
151. Al-Matary, Y.S.; Botezatu, L.; Opalka, B.; Hönes, J.M.; Lams, R.F.; Thivakaran, A.; Schütte, J.; Köster, R.; Lennartz, K.; Schroeder, T.; et al. Acute myeloid leukemia cells polarize macrophages towards a leukemia supporting state in a Growth factor independence 1 dependent manner. *Haematologica* **2016**, *101*, 1216–1227. [[CrossRef](#)]
152. Petty, A.J.; Yang, Y. Tumor-Associated Macrophages in Hematologic Malignancies: New Insights and Targeted Therapies. *Cells* **2019**, *8*, 1526. [[CrossRef](#)] [[PubMed](#)]
153. Yang, X.; Feng, W.; Wang, R.; Yang, F.; Wang, L.; Chen, S.; Ru, Y.; Cheng, T.; Zheng, G. Repolarizing heterogeneous leukemia-associated macrophages with more M1 characteristics eliminates their pro-leukemic effects. *Oncoimmunology* **2017**, *7*, e1412910. [[CrossRef](#)] [[PubMed](#)]
154. Kiladjian, J.J.; Bourgeois, E.; Lobe, I.; Braun, T.; Visentin, G.; Bourhis, J.H.; Fenaux, P.; Chouaib, S.; Caignard, A. Cytolytic function and survival of natural killer cells are severely altered in myelodysplastic syndromes. *Leukemia* **2006**, *20*, 463–470. [[CrossRef](#)] [[PubMed](#)]
155. Carlsten, M.; Baumann, B.C.; Simonsson, M.; Jädersten, M.; Forsblom, A.M.; Hammarstedt, C.; Bryceson, Y.T.; Ljunggren, H.G.; Hellström-Lindberg, E.; Malmberg, K.J. Reduced DNAM-1 expression on bone marrow NK cells associated with impaired killing of CD34+ blasts in myelodysplastic syndrome. *Leukemia* **2010**, *24*, 1607–1616. [[CrossRef](#)]
156. Hejazi, M.; Manser, A.R.; Fröbel, J.; Kündgen, A.; Zhao, X.; Schönberg, K.; Germing, U.; Haas, R.; Gattermann, N.; Uhrberg, M. Impaired cytotoxicity associated with defective natural killer cell differentiation in myelodysplastic syndromes. *Haematologica* **2015**, *100*, 643–652. [[CrossRef](#)]
157. Geyh, S.; Oz, S.; Cadeddu, R.P.; Fröbel, J.; Brückner, B.; Kündgen, A.; Fenk, R.; Bruns, I.; Zilkens, C.; Hermsen, D.; et al. Insufficient stromal support in MDS results from molecular and functional deficits of mesenchymal stromal cells. *Leukemia* **2013**, *27*, 1841–1851. [[CrossRef](#)] [[PubMed](#)]
158. Miller, J.S.; McCullar, V. Human natural killer cells with polyclonal lectin and immunoglobulinlike receptors develop from single hematopoietic stem cells with preferential expression of NKG2A and KIR2DL2/L3/S2. *Blood* **2001**, *98*, 705–713. [[CrossRef](#)]
159. Miura, I.; Kobayashi, Y.; Takahashi, N.; Saitoh, K.; Miura, A.B. Involvement of natural killer cells in patients with myelodysplastic syndrome carrying monosomy 7 revealed by the application of fluorescence in situ hybridization to cells collected by means of fluorescence-activated cell sorting. *Br. J. Haematol.* **2000**, *110*, 876–879. [[CrossRef](#)]
160. Carlsten, M.; Järås, M. Natural Killer Cells in Myeloid Malignancies: Immune Surveillance, NK Cell Dysfunction, and Pharmacological Opportunities to Bolster the Endogenous NK Cells. *Front. Immunol.* **2019**, *10*, 2357. [[CrossRef](#)]
161. Dickinson, R.E.; Milne, P.; Jardine, L.; Zandi, S.; Swierczek, S.I.; McGovern, N.; Cookson, S.; Ferozepurwalla, Z.; Langridge, A.; Pagan, S.; et al. The evolution of cellular deficiency in GATA2 mutation. *Blood* **2014**, *123*, 863–874. [[CrossRef](#)]
162. Tesi, B.; Davidsson, J.; Voss, M.; Rahikkala, E.; Holmes, T.D.; Chiang, S.; Komulainen-Ebrahim, J.; Gorcenco, S.; Rundberg Nilsson, A.; Ripperger, T.; et al. Gain-of-function *SAMD9L* mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. *Blood* **2017**, *129*, 2266–2279. [[CrossRef](#)] [[PubMed](#)]
163. Ma, L.; Delforge, M.; van Duppen, V.; Verhoef, G.; Emanuel, B.; Boogaerts, M.; Hagemeijer, A.; Vandenberghe, P. Circulating myeloid and lymphoid precursor dendritic cells are clonally involved in myelodysplastic syndromes. *Leukemia* **2004**, *18*, 1451–1456. [[CrossRef](#)] [[PubMed](#)]
164. Micheva, I.; Thanopoulou, E.; Michalopoulou, S.; Kakagianni, T.; Kouraklis-Symeonidis, A.; Symeonidis, A.; Zoumbos, N. Impaired generation of bone marrow CD34-derived dendritic cells with low peripheral blood subsets in patients with myelodysplastic syndrome. *Br. J. Haematol.* **2004**, *126*, 806–814. [[CrossRef](#)]
165. Micheva, I.; Thanopoulou, E.; Michalopoulou, S.; Karakantza, M.; Kouraklis-Symeonidis, A.; Mouzaki, A.; Zoumbos, N. Defective tumor necrosis factor alpha-induced maturation of monocyte-derived dendritic cells in patients with myelodysplastic syndromes. *Clin. Immunol.* **2004**, *113*, 310–317. [[CrossRef](#)] [[PubMed](#)]
166. Matteo Rigolin, G.; Howard, J.; Buggins, A.; Sneddon, C.; Castoldi, G.; Hirst, W.J.; Mufti, G.J. Phenotypic and functional characteristics of monocyte-derived dendritic cells from patients with myelodysplastic syndromes. *Br. J. Haematol.* **1999**, *107*, 844–850. [[CrossRef](#)] [[PubMed](#)]
167. Ma, L.; Ceuppens, J.; Kasran, A.; Delforge, M.; Boogaerts, M.; Vandenberghe, P. Immature and mature monocyte-derived dendritic cells in myelodysplastic syndromes of subtypes refractory anemia or refractory anemia with ringed sideroblasts display an altered cytokine profile. *Leuk. Res.* **2007**, *31*, 1373–1382. [[CrossRef](#)] [[PubMed](#)]
168. Van Leeuwen-Kerkhoff, N.; Westers, T.M.; Poddighe, P.J.; Povoleri, G.; Timms, J.A.; Kordasti, S.; De Gruijl, T.D.; Van de Loosdrecht, A.A. Reduced frequencies and functional impairment of dendritic cell subsets and non-classical monocytes in myelodysplastic syndromes. *Haematologica* **2022**, *107*, 655–667. [[CrossRef](#)]
169. Gabilovich, D.I.; Nagaraj, S. Myeloid-derived suppressor cells as regulators of the immune system. *Nat. Rev. Immunol.* **2009**, *9*, 162–174. [[CrossRef](#)]
170. Marvel, D.; Gabilovich, D.I. Myeloid-derived suppressor cells in the tumor microenvironment: Expect the unexpected. *J. Clin. Investig.* **2015**, *125*, 3356–3364. [[CrossRef](#)]

171. Gabrilovich, D.I.; Ostrand-Rosenberg, S.; Bronte, V. Coordinated regulation of myeloid cells by tumours. *Nat. Rev. Immunol.* **2012**, *12*, 253–268. [[CrossRef](#)]
172. Velegraki, M.; Stiff, A.; Papadaki, H.A.; Li, Z. Myeloid-Derived Suppressor Cells: New Insights into the Pathogenesis and Therapy of MDS. *J. Clin. Med.* **2022**, *11*, 4908. [[CrossRef](#)] [[PubMed](#)]
173. Kittang, A.O.; Kordasti, S.; Sand, K.E.; Costantini, B.; Kramer, A.M.; Perezabellan, P.; Seidl, T.; Rye, K.P.; Hagen, K.M.; Kulasekararaj, A. Expansion of myeloid derived suppressor cells correlates with number of T regulatory cells and disease progression in myelodysplastic syndrome. *Oncimmunology* **2015**, *5*, e1062208. [[CrossRef](#)] [[PubMed](#)]
174. Chen, X.; Eksioglu, E.A.; Zhou, J.; Zhang, L.; Djeu, J.; Fortenbery, N.; Epling-Burnette, P.; Van Bijnen, S.; Dolstra, H.; Cannon, J.; et al. Induction of myelodysplasia by myeloid-derived suppressor cells. *J. Clin. Investig.* **2013**, *123*, 4595–4611. [[CrossRef](#)]
175. Schroeter, A.; Roesel, M.J.; Matsunaga, T.; Xiao, Y.; Zhou, H.; Tullius, S.G. Aging Affects the Role of Myeloid-Derived Suppressor Cells in Alloimmunity. *Front. Immunol.* **2022**, *13*, 917972. [[CrossRef](#)]
176. Flores, R.R.; Clauson, C.L.; Cho, J.; Lee, B.C.; McGowan, S.J.; Baker, D.J.; Niedernhofer, L.J.; Robbins, P.D. Expansion of myeloid-derived suppressor cells with aging in the bone marrow of mice through a NF- κ B-dependent mechanism. *Aging Cell* **2017**, *16*, 480–487. [[CrossRef](#)] [[PubMed](#)]
177. Sinha, P.; Okoro, C.; Foell, D.; Freeze, H.H.; Ostrand-Rosenberg, S.; Srikrishna, G. Proinflammatory S100 proteins regulate the accumulation of myeloid-derived suppressor cells. *J. Immunol.* **2008**, *181*, 4666–4675. [[CrossRef](#)] [[PubMed](#)]
178. Qi, X.; Jiang, H.; Liu, P.; Xie, N.; Fu, R.; Wang, H.; Liu, C.; Zhang, T.; Wang, H.; Shao, Z. Increased myeloid-derived suppressor cells in patients with myelodysplastic syndromes suppress CD8⁺ T lymphocyte function through the STAT3-ARG1 pathway. *Leuk. Lymphoma* **2021**, *62*, 218–223. [[CrossRef](#)] [[PubMed](#)]
179. Tao, J.; Han, D.; Gao, S.; Zhang, W.; Yu, H.; Liu, P.; Fu, R.; Li, L.; Shao, Z. CD8⁺ T cells exhaustion induced by myeloid-derived suppressor cells in myelodysplastic syndromes patients might be through TIM3/Gal-9 pathway. *J. Cell. Mol. Med.* **2020**, *24*, 1046–1058. [[CrossRef](#)]
180. Yu, S.; Ren, X.; Meng, F.; Guo, X.; Tao, J.; Zhang, W.; Liu, Z.; Fu, R.; Li, L. TIM3/CEACAM1 pathway involves in myeloid-derived suppressor cells induced CD8⁺ T cells exhaustion and bone marrow inflammatory microenvironment in myelodysplastic syndrome. *Immunology*, 2022; ahead of print. [[CrossRef](#)]
181. Winter, S.; Shoaie, S.; Kordasti, S.; Platzbecker, U. Integrating the “Immunome” in the Stratification of Myelodysplastic Syndromes and Future Clinical Trial Design. *J. Clin. Oncol.* **2020**, *38*, 1723–1735. [[CrossRef](#)]
182. Zhou, S.; Greenberger, J.S.; Epperly, M.W.; Goff, J.P.; Adler, C.; Leboff, M.S.; Glowacki, J. Age-related intrinsic changes in human bone-marrow-derived mesenchymal stem cells and their differentiation to osteoblasts. *Aging cell* **2008**, *7*, 335–343. [[CrossRef](#)]
183. Blau, O.; Baldus, C.D.; Hofmann, W.K.; Thiel, G.; Nolte, F.; Burmeister, T.; Türkmen, S.; Benlasfer, O.; Schumann, E.; Sindram, A.; et al. Mesenchymal stromal cells of myelodysplastic syndrome and acute myeloid leukemia patients have distinct genetic abnormalities compared with leukemic blasts. *Blood* **2011**, *118*, 5583–5592. [[CrossRef](#)] [[PubMed](#)]
184. Bhagat, T.D.; Chen, S.; Bartenstein, M.; Barlowe, A.T.; Von Ahrens, D.; Choudhary, G.S.; Tivnan, P.; Amin, E.; Marcondes, A.M.; Sanders, M.A.; et al. Epigenetically Aberrant Stroma in MDS Propagates Disease via Wnt/ β -Catenin Activation. *Cancer Res.* **2017**, *77*, 4846–4857. [[CrossRef](#)] [[PubMed](#)]
185. Ping, Z.; Chen, S.; Hermans, S.; Kenswil, K.; Feyen, J.; van Dijk, C.; Bindels, E.; Mylona, A.M.; Adisty, N.M.; Hoogenboezem, R.M.; et al. Activation of NF- κ B driven inflammatory programs in mesenchymal elements attenuates hematopoiesis in low-risk myelodysplastic syndromes. *Leukemia* **2019**, *33*, 536–541. [[CrossRef](#)] [[PubMed](#)]
186. Zambetti, N.A.; Ping, Z.; Chen, S.; Kenswil, K.; Mylona, M.A.; Sanders, M.A.; Hoogenboezem, R.M.; Bindels, E.; Adisty, M.N.; Van Strien, P.; et al. Mesenchymal Inflammation Drives Genotoxic Stress in Hematopoietic Stem Cells and Predicts Disease Evolution in Human Pre-leukemia. *Cell Stem Cell* **2016**, *19*, 613–627. [[CrossRef](#)]
187. Wang, Z.; Tang, X.; Xu, W.; Cao, Z.; Sun, L.; Li, W.; Li, Q.; Zou, P.; Zhao, Z. The different immunoregulatory functions on dendritic cells between mesenchymal stem cells derived from bone marrow of patients with low-risk or high-risk myelodysplastic syndromes. *PLoS ONE* **2013**, *8*, e57470. [[CrossRef](#)]
188. Sarhan, D.; Wang, J.; Sunil Arvindam, U.; Hallstrom, C.; Verneris, M.R.; Grzywacz, B.; Warlick, E.; Blazar, B.R.; Miller, J.S. Mesenchymal stromal cells shape the MDS microenvironment by inducing suppressive monocytes that dampen NK cell function. *JCI Insight* **2020**, *5*, e130155. [[CrossRef](#)]
189. Chao, M.P.; Takimoto, C.H.; Feng, D.D.; McKenna, K.; Gip, P.; Liu, J.; Volkmer, J.-P.; Weissman, I.L.; Majeti, R. Therapeutic Targeting of the Macrophage Immune Checkpoint CD47 in Myeloid Malignancies. *Front. Oncol.* **2020**, *9*, 1380. [[CrossRef](#)]
190. Sallman, D.A.; Asch, A.S.; Al Malki, M.M.; Lee, D.J.; Donnellan, W.B.; Marcucci, G.; Kambhampati, S.; Daver, N.G.; Garcia-Manero, G.; Komrokji, R.S.; et al. The First-in-Class Anti-CD47 Antibody Magrolimab (5F9) in Combination with Azacitidine Is Effective in MDS and AML Patients: Ongoing Phase 1b Results. *Blood* **2019**, *134*, 569. [[CrossRef](#)]
191. Brunner, A.M.; Esteve, J.; Porkka, K.; Knapper, S.; Traer, E.; Scholl, S.; Garcia-Manero, G.; Vey, N.; Wermke, M.; Janssen, J.; et al. Efficacy and Safety of Sabatolimab (MBG453) in Combination with Hypomethylating Agents (HMAs) in Patients (Pts) with Very High/High-Risk Myelodysplastic Syndrome (vHR/HR-MDS) and Acute Myeloid Leukemia (AML): Final Analysis from a Phase Ib Study. *Blood* **2021**, *138* (Suppl. 1), 244. [[CrossRef](#)]
192. Borate, U.; Esteve, J.; Porkka, K.; Knapper, S.; Vey, N.; Scholl, S.; Garcia-Manero, G.; Wermke, M.; Janssen, J.; Traer, E.; et al. Phase Ib Study of the Anti-TIM-3 Antibody MBG453 in Combination with Decitabine in Patients with High-Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). *Blood* **2019**, *134*, 570. [[CrossRef](#)]

193. Chien, K.S.; Kim, K.; Nogueras-Gonzalez, G.M.; Borthakur, G.; Naqvi, K.; Daver, N.G.; Montalban-Bravo, G.; Cortes, J.E.; DiNardo, C.D.; Jabbour, E.; et al. Phase II study of azacitidine with pembrolizumab in patients with intermediate-1 or higher-risk myelodysplastic syndrome. *Br. J. Haematol.* **2021**, *195*, 378–387. [[CrossRef](#)] [[PubMed](#)]
194. Garcia-Manero, G.; Montalban-Bravo, G.; Yang, H.; Wei, Y.; Alvarado, Y.; DiNardo, C.D.; Naval, G.; Daver, N.G.; Konopleva, M.; Hearn, K.P.; et al. A Clinical Study of OPN-305, a Toll-like Receptor 2 (TLR-2) Antibody, in Patients with Lower Risk Myelodysplastic Syndromes (MDS) That Have Received Prior Hypomethylating Agent (HMA) Therapy. *Blood* **2016**, *128*, 227. [[CrossRef](#)]
195. Lee, P.; Yim, R.; Yung, Y.; Chu, H.T.; Yip, P.K.; Gill, H. Molecular Targeted Therapy and Immunotherapy for Myelodysplastic Syndrome. *Int. J. Mol. Sci.* **2021**, *22*, 10232. [[CrossRef](#)] [[PubMed](#)]