The Immune Landscape in Myelodysplastic Syndromes

Subjects: Hematology

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The Revised International Prognostic Scoring System (IPSS-R) is used to estimate the MDS patients' risk of AML progression and overall survival (OS). In clinical settings, patients with an IPSS-R score of 3.5 or less represent a lower-risk MDS group (median survival; 5.9 years), whereas an IPSS-R score > 3.5 falls into the higher-risk MDS group (median survival; 1.5 years). The lower-risk disease is associated with an inflammatory microenvironment and increased cell death, in contrast to higher-risk disease, which is delineated by immunosuppression and clonal expansion.

myelodysplastic syndromes | acute myeloid leukemia | immune evasion

1. The Inflammatory Microenvironment of Myelodysplastic Syndromes (MDS)

Aberrant innate immune system activation leads to dysfunctional hematopoiesis and induces excessive cellular death; a hallmark of MDS [1]. Several factors, intrinsic and extrinsic of the malignant clone, contribute to the intricate inflammatory network.

1.1. Predisposing Factors Driving Inflammation (Mutations, Aging/Chronic Immune Stimulation)

The genetic lesions of MDS are complex and dynamic and may enable a reciprocal mechanism in which gene mutations upregulate inflammation pathways and the inflammatory milieu contributes to genomic instability and mutagenesis [2]. Recurrent mutations entail spliceosome machinery, epigenetic and transcription regulation, DNA repair, signaling pathways, and the cohesin complex [3]. Spliceosome mutations such as SF3B1, SRSF2, U2AF1, and mutations in epigenetic regulators, e.g., TET2, and ASXL1, which drive clonal dominance and evolution in MDS [2], trigger innate immune signaling pathways and NRP3-inflammasome activation [2][4]. Haploinsufficiency of microRNAs (miR-145, miR-146a), as well as genes, in del (5q) MDS altered signaling intermediates, such as Toll-interleukin-1 receptor domain-containing adaptor protein (TIRAP) and TNF receptor factor-6 (TRAF6), stimulating TLR activation and cytokine (IL-6) production [5][6].

Aging represents a smoldering inflammatory process ("inflammaging") [7] characterized by immunosenescence leading to malfunctioning adaptive immune responses [8][9]. As analyzed, HSCs are capable of directly sensing DAMPs/PAMPs through PRRs, skewing their differentiation program to myeloid lineages [10][11]. Such conditions

create a fertile environment for mutated MDS clones to propagate [2]. Moreover, MDS is associated with a variety of autoimmune diseases, providing another example of chronic immune stimuli [12].

1.2. Significant Signalling Pathways

Innate immune signaling is central in the pathogenesis of MDS. Genes related to immune signaling are overexpressed in more than 50% of MDS patients [13][14]. TLRs and their downstream intermediates (MyD88, IRAK1/4, TRAF6) are hyperactivated, whereas inhibitory regulators are repressed [15]. Sustained TLR activation is damaging to HSCs and their niche [16] and excessive TLR4 signaling results in genotoxicity, possible carcinogenesis [17], and cell death (along with TLR2) [18][19]. Alarmins S100A8 and S100A9 are of particular importance in MDS, because—via autocrine and paracrine actions—they drive TLR4 activation, NLR family pyrin domain-containing protein 3 (NLRP3) inflammasome assembly, and microenvironmental immunosuppression [20]. Pyroptosis—a form of programmed cell death—being driven by NLRP3 inflammasome activation, is responsible for cellular death in MDS, being a point of convergence for cell-intrinsic, (e.g., gene mutations) and cell-extrinsic, (e.g., DAMPs) pathogenesis mechanisms [4]. The NLRP3-pyroptosis axis functioned independently of specific gene class mutations [4]; however, pyroptotic cell death observed in erythroid progenitors was proportional to mutational allelic burden and complexity [20]. The cytopenic phenotype of MDS is further augmented by evidence of increased apoptotic signaling; activation of death receptor Fas–Fas ligand pathway through cytokine induction (like TNFa, IFN-γ), TNF receptor 1 and 2 (TNFR1 and 2) induced apoptosis and p38 mitogen-activated protein kinase (MAPK) apoptotic signalling [12].

1.3. Cytokines

Aberrancy in the cytokine network has been observed in MDS patients by several investigators [1][12][21], with increased levels of inflammatory cytokines, such as TNFa, IFN-γ, TGF-β, IL-6, and IL-8, indicating abnormal inflammatory signaling and myeloid differentiation [12]. Various cell types can secrete cytokines in MDS, such as myeloid-derived suppressor cells (MDSCs) and MDS-derived myeloid cells [15]. Cytokine pressure from chronic immune stimulation has toxic effects on normal HSCs and may provide an evolutionary edge in MDS clones, driving their expansion [1]. In a first-of-its-kind meta-analysis, Xin et al. showed an increased level of inflammatory cytokines implicated in MDS pathogenesis and a cytokine profile changing along with the natural history of the disease [22]. Low-risk disease and its pyroptotic/ inflammatory microenvironment are associated with elevated levels of inflammatory cytokines (TNFa, IL-6, IFN-γ) [23] and type 1 cytokines (IL-1β, IL-7, IL-8), whereas high-risk disease has increased immunosuppressive cytokines (like IL-10), reflecting tumor immune escape [24]. Moreover, a positive correlation can be made between cytokine expression, clinical outcomes [1], and cytogenetic features [21].

2. Defective Cellular Immune Responses Result in MDS Progression

Cellular immune response dysregulation is another important immunological mechanism driving MDS pathogenesis, as it closely interacts with the coexisting inflammatory microenvironment and seems to have distinct

features in different disease states [2].

2.1. T-Lymphocytes in MDS

Low-risk MDS is characterized by increased numbers of cytotoxic (CD8+) T-cells and diminished counts of Tregs [25][26], contradicting the general finding of lymphopenia. The T-cell response of high-risk disease manifests itself with lower levels of CD8+ T-cells and higher numbers of Tregs [24][26].

CD8+ T-cells in low-risk MDS have the potential of suppressing both malignant and normal hematopoiesis in vitro, further augmenting cellular death in this disease state, because of the existence of epitopes on MDS HSCs that can activate cytotoxic T-cells [27]. In younger MDS patients, CD8+ autoreactivity seems to be correlated with reduced numbers of CD4+ helper T-cells [28]. Potential epitopes include Wilms tumor protein 1 (WT1), overexpressed in MDS with trisomy 8, cancer-testis antigen (CTA), proteinase 3, and MHC-I [12]. However, the impact of immunogenic neo-antigens is unexplored territory, with early studies pointing to the presence of a protective effect [2][29]. In high-risk MDS, failing immunosurveillance and anti-MDS function is the major characteristic of the adaptive immune response, possibly through immune checkpoint molecule upregulation [12], mainly cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein 1 (PD-1) [30]. MDS blasts in high-risk diseases overexpress PD-L1 in comparison to normal controls [31] and this can be further augmented by the effects of cytokines, such as TNF-a, and IFN-γ, which induce PD-1 and PD-L1 expression, on T-cells and MDS cells, respectively [32]. Interestingly, Sand et al. reported increased numbers of BM cytotoxic T-cells; however, they were accompanied by dysfunctional T-cell receptor (TCR) cytotoxicity [33].

Regarding helper T cells (Th); Th1/Th2 ratio imbalance might reflect CD4/CD8 imbalance [34]. Shao et al. reported no difference in Th1 in MDS patients and healthy controls, as well as between low versus high-risk diseases. Moreover, Th17 numbers were increased in MDS patients, with greater expansion in low-risk disease, denoting the auto-reactive, possible anti-tumor nature of the process [35][36], whereas Th22 cells were increased in high-risk disease, correlating with increased IL-6 and TNF-a [35].

Tregs are a subset of helper T-cells tasked with immune response modulation and immune tolerance [12]. As a result, reduced Treg functionality is associated with autoimmunity and increased Treg function with cancer cell immune evasion [37]. This is evident in low versus high disease states, where in low-risk disease, patients had diminished Treg numbers and function, in contrast to high-risk disease; increased Treg population and functionality, along with MDS clone expansion [34][38][39].

Apropos of the MDS mutational landscape, the presence of MDS founder mutations on the lymphoid lineage may lead to defective immune responses [2]. Furthermore, the TP53 mutated subset of MDS was associated with increased PD-L1 expression on MDS/secondary AML specimens, as well as ICOS High/PD-1neg Treg expansion, leading to an immunosuppressive microenvironment [40].

2.2. Dendritic Cells in MDS

Dendritic cells are essential for tumor recognition, antigen presentation [41], and T-cell activation [42]. In MDS, dendritic cells have reduced T-cell activation potential and maturation defects—possibly stemming from the malignant clone [43]—along with a different cytokine profile between immature and mature monocytic dendritic cells (high IL-10 and low IL-12) [44]. Moreover, the high-risk disease has been shown to have reduced numbers of myeloid and plasmacytoid precursor dendritic cells [45].

2.3. Natural Killer Cells in MDS

Natural killer cells (NK cells) are a lymphoid subset of innate immunity and their aberration in MDS represents another aspect of defective immune surveillance. Studies have shown low NK cell numbers and impaired NK cell performance [46][47]. Cytotoxic impairment was especially evident in high-risk MDS, which correlated with advanced disease burden (excess blasts, high IPSS score, cytogenetics) [48][49]. Shared genetic lesions with the malignant clone and NK populations might explain an intrinsic defect in the functionality of NK cells [50].

2.4. Myeloid-Derived Suppressor Cells in MDS

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of the myeloid lineage, which expand in pathological conditions such as cancer [51]. They have the ability to suppress non-myeloid immune cell activity, such as T-cell, B-cell, and NK-cells [52][53] and modulate macrophage cytokine production [54]. They can also assist Treg expansion through IL-10 and TGF-β secretion [55]. In MDS, high counts of MDSCs were reported in the BM [56] and peripheral blood of patients [57]. MDSC expansion can be induced by a number of pro-inflammatory cytokines such as IL-6, IL-10, IL-1β, and IFN-γ [55]. Alarmin S100A9 seems to drive MDSC expansion in MDS [56]. Moreover, concomitant age-related myeloid skewing, senescence, and “inflammaging” are involved in age-related MDSC increase [53][58]. In high-risk diseases, Kittang et al. [59] showed MDSC and Treg associated expansion, assisting in immune evasion and cancer progression. MDSCs also play a role in ineffective hematopoiesis [56]. Interestingly, MDSCs in MDS patients seem to evolve from a non-MDS clone, as they did not harbor the same mutations [56].

2.5. Macrophages in MDS

Macrophages come from monocytic differentiation and exhibit a diverse set of biological roles [60]. Defective macrophage function may result from reduced CD206 and signal regulatory protein alpha (SIRPa) expression, as well as increased inducible nitric oxide synthase (iNOS), which aids cancer progression through NO production [61]. INOS+ macrophages were associated with low-risk disease [62]. Macrophages are divided into M1 and M2 subtypes, with M1 having antitumor effects [63]. M2 subtype, but not M1 expansion was observed in MDS, suggesting a further reduced antitumor effect [64].

2.6. Mesenchymal Stem Cells in MDS

MSCs are an essential non-hematopoietic subset for hematopoiesis. Although inconclusive, MSCs might have a role in MDS initiation and maintenance, through pro-inflammatory signaling contributing to immune suppression

and mutagenesis [2][12]. MSCs exhibit an age-related wane in functionality [65]. This is accompanied by the fact that MDS/AML-derived MSCs have functional deficits, as well as chromosomal aberrations different from the malignant clone [2]. Meydouf et al. elegantly showed the influence of MDS HSCs on their microenvironment with their ability to induce gene expression changes in healthy MSCs giving them an MDS-like phenotype [66]. MDS-MSCs produce factors such as S100A8/9 and immunomodulators that enable MDS clone expansion [67][68][69]. Interestingly, MSCs seem to exhibit different characteristics between risk groups [12]. Low-risk disease MSCs showed reduced DC maturation and differentiation efficiency, whereas high-risk disease MSCs demonstrated immunosuppressive properties, higher TGF-β production, apoptosis, and Treg induction [70][71].

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