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The Potential Role of Myeloid-Derived Suppressor Cells (MDSCs) in Acute Myeloid Leukemia

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Abstract: Acute Myeloid Leukemia (AML) is a highly aggressive hematologic malignancy characterized by the uncontrolled proliferation of myeloid precursor cells and profound disruption of the immune microenvironment. Among the key contributors to immune evasion in AML are Myeloid-Derived Suppressor Cells (MDSCs), a heterogeneous population of immature myeloid cells with potent immunosuppressive properties. MDSCs play a pivotal role in promoting leukemic progression by inhibiting T-cell activity, fostering regulatory T-cell expansion, and producing immunosuppressive factors such as arginase-1 (ARG1), reactive oxygen species (ROS), and nitric oxide (NO). This review examines the expression, phenotype, and functional roles of MDSCs in AML. Elevated levels of MDSCs have been linked to disease progression, resistance to therapy, and poor clinical outcomes in AML patients. Emerging therapeutic strategies targeting MDSCs hold promise for improving immune responses and treatment efficacy in AML. Furthermore, MDSCs are being investigated as potential biomarkers for risk stratification, treatment monitoring, and prognostication in AML. By synthesizing recent advances, this review underscores the critical role of MDSCs in the pathophysiology of AML and highlights novel therapeutic opportunities aimed at overcoming MDSC-mediated immune suppression.

Keywords: *Acute Myeloid Leukemia (AML), Myeloid-Derived Suppressor Cells (MDSCs)*

Introduction.

Acute Myeloid Leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid precursors in the bone marrow, peripheral blood, and other tissues. This leads to the suppression of normal hematopoiesis, causing symptoms such as anemia, neutropenia, and thrombocytopenia. AML is most commonly observed in adults, with an increasing incidence in older populations, reflecting the impact of age-related genetic mutations and environmental exposures [1].

The pathogenesis of AML involves genetic and epigenetic alterations that drive leukemogenesis. Chromosomal translocations, such as t(8;21) and inv(16), are recurrent abnormalities in AML, along with mutations in genes like FLT3, NPM1, DNMT3A, and IDH1/IDH2. These mutations often affect signaling pathways, transcriptional regulation, and epigenetic modifiers, resulting in impaired differentiation, uncontrolled proliferation, and survival of myeloid blasts [2].

AML is classified based on morphologic, immunophenotypic, and genetic features, as outlined by the World Health Organization (WHO) classification. Cytogenetic and molecular profiling are critical for risk stratification and guide therapeutic decisions. Patients are typically categorized into favorable, intermediate, or adverse risk groups, depending on their cytogenetic and molecular abnormalities [3].

The clinical presentation of AML varies widely, from asymptomatic cases detected incidentally to severe manifestations, including fatigue, recurrent infections, and bleeding. Extramedullary involvement, such as myeloid sarcomas, may also occur in some patients. A definitive diagnosis is established through bone marrow biopsy and aspirate, revealing ≥20% myeloblasts in the bone marrow or peripheral blood, along with immunophenotyping and genetic testing [4].

The standard treatment for AML involves a combination of intensive induction chemotherapy, typically cytarabine and anthracycline-based regimens, followed by consolidation therapy or hematopoietic stem cell transplantation (HSCT) in eligible patients. However, elderly or unfit patients often require less intensive therapies, such as hypomethylating agents or targeted therapies, reflecting the high treatment-related toxicity in this group [5].

Targeted therapies have revolutionized AML treatment in recent years. Agents such as midostaurin and gilteritinib target FLT3 mutations, while ivosidenib and enasidenib address IDH1 and IDH2 mutations, respectively. Additionally, venetoclax, a BCL-2 inhibitor, has shown efficacy in combination with hypomethylating agents for elderly patients or those unfit for intensive chemotherapy. These advancements underscore the shift toward personalized medicine in AML [6].

Despite these advances, relapse remains a significant challenge in AML management. Minimal residual disease (MRD) detection using sensitive molecular techniques has become an essential tool for predicting relapse and guiding post-remission therapy. Allogeneic HSCT remains the most effective curative approach for high-risk AML, but its application is limited by donor availability, age, and comorbidities [7].

The tumor microenvironment in AML, particularly the bone marrow niche, plays a crucial role in disease progression and therapy resistance. Leukemic blasts interact with stromal cells, immune cells, and extracellular matrix components to create a supportive niche that protects them from chemotherapy-induced apoptosis. Myeloid-derived suppressor cells (MDSCs) and regulatory T cells contribute to immune evasion, highlighting the need for immunotherapeutic strategies [8].

Emerging therapies targeting the immune system, such as checkpoint inhibitors, bispecific T-cell engagers, and chimeric antigen receptor (CAR) T cells, are being explored in AML. While these approaches have shown promise in preclinical and early clinical trials, challenges such as antigen heterogeneity and immune-related toxicities remain to be addressed [9].

Future research in AML aims to overcome therapeutic resistance, improve MRD detection, and develop combination strategies integrating novel targeted and immunotherapeutic agents. Expanding access to molecular diagnostics and personalized therapies in resource-limited settings is also essential to ensure equitable care for all patients with AML [10].

A critical research gap in the study of Myeloid-Derived Suppressor Cells (MDSCs) in Acute Myeloid Leukemia (AML) lies in the incomplete understanding of the precise mechanisms by which MDSCs contribute to immune evasion and therapy resistance in the leukemic microenvironment. While existing studies highlight the elevated levels and immunosuppressive functions of MDSCs in AML, the specific signaling pathways and molecular mediators involved in their recruitment, expansion, and activation remain poorly characterized. [10].

Furthermore, there is limited data on the heterogeneity of MDSC subsets in AML and how these subsets differentially impact disease progression and therapeutic outcomes. The interaction of MDSCs with other immune cells, such as regulatory T cells (Tregs) and natural killer (NK) cells, as well as their influence on the efficacy of immunotherapies like checkpoint inhibitors, has not been fully explored. [10].

Another significant gap is the lack of standardized biomarkers to quantify and characterize MDSCs in AML patients. This limitation hampers the ability to assess their prognostic value and monitor therapeutic responses

effectively. Additionally, while preclinical studies have shown the potential of targeting MDSCs to enhance antitumor immunity, there is insufficient clinical evidence to validate these strategies in AML. [10].

Addressing these gaps requires a combination of advanced molecular profiling, in vivo modeling, and clinical trials to elucidate the role of MDSCs in AML and develop targeted therapies to overcome their immunosuppressive effects. Understanding these mechanisms could pave the way for novel, immune-based therapeutic strategies to improve outcomes for AML patients. [10].

Myeloid-Derived Suppressor Cells (MDSCs) and Their Expression in Acute Myeloid Leukemia

Myeloid-Derived Suppressor Cells (MDSCs) are a heterogeneous population of immature myeloid cells that play a pivotal role in suppressing immune responses and facilitating tumor progression. In the context of Acute Myeloid Leukemia (AML), MDSCs are increasingly recognized as key contributors to immune evasion, tumor microenvironment modulation, and therapeutic resistance. These cells exert their immunosuppressive effects by inhibiting T-cell activation, impairing natural killer (NK) cell function, and promoting regulatory T cell (Treg) expansion [11].

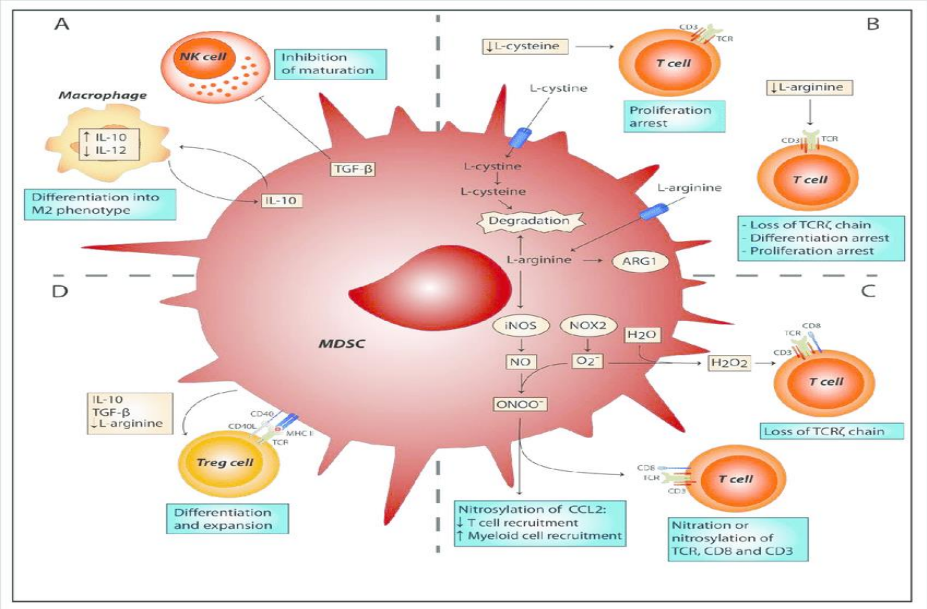

Figure 1: MDSC-suppressive mechanisms target innate and adaptive arms of the immune system. (A) Myeloid-derived suppressor cells (MDSCs) can inhibit the innate immune system by TGF-b-induced inhibition of NK cell function and induction of a M2 macrophage phenotype by secretion of IL-10. (B) MDSCs deprive T cells of amino acids L-cysteine and L-arginine, which are essential for proliferation and differentiation. (C) MDSCs release reactive oxygen species, such as hydrogen peroxide (H 2 O 2) and peroxynitrite (ONOO ¡). H 2 O 2 causes loss of the T cell receptor (TCR)z-chain and peroxynitrite causes nitration and nitrosylation of chemokines like CCL2 and components of the TCR signaling complex, thereby both inhibiting T cell activation and recruitment. (D) MDSCs induce the development of regulatory T cells (Tregs) or expand existing Treg cell populations; these effects are mediated by interaction of the TCR with MHC-II and CD40 with CD40L. Furthermore, secretion of factors like IL-10 and TGF-b, and deprivation of L-arginine by MDSCs induce Treg polarization. ARG1, arginase 1; CCL2, chemokine (C–C motif) ligand 2; iNOS, inducible nitric oxide synthase; NOX2, NADPH oxidase 2; NO, nitric oxide; NK, natural killer; TGF-b, transforming growth factor-b; IL, interleukin. [11].

MDSCs are broadly categorized into two subsets: monocytic (M-MDSCs) and granulocytic or polymorphonuclear (PMN-MDSCs). In AML, both subsets are present, but the relative proportions and roles of

these subsets can vary across patients. M-MDSCs are characterized by high arginase-1 (ARG1) and inducible nitric oxide synthase (iNOS) activity, while PMN-MDSCs produce reactive oxygen species (ROS) and granulocyte-related enzymes, which collectively contribute to immunosuppression [12].

AML blasts actively recruit and expand MDSCs in the bone marrow and peripheral blood by secreting cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-6 (IL-6), and interleukin-10 (IL-10). These cytokines drive the differentiation and expansion of immature myeloid cells into MDSCs while inhibiting their maturation into functional antigen-presenting cells like dendritic cells (DCs) [13].

The bone marrow niche in AML serves as a supportive microenvironment for MDSC development and function. AML cells interact with stromal cells and endothelial cells in the bone marrow to create an immunosuppressive milieu. Hypoxia, a hallmark of the leukemic bone marrow, further enhances MDSC recruitment and activity through hypoxia-inducible factor-1 alpha (HIF-1α)-mediated pathways [14].

MDSCs suppress T-cell activity through several mechanisms. They upregulate ARG1 and iNOS, depleting the amino acid L-arginine, which is essential for T-cell proliferation. Additionally, they produce ROS and nitric oxide (NO), which impair T-cell receptor (TCR) signaling and induce apoptosis in effector T cells. These actions create a profoundly immunosuppressive microenvironment that enables AML cells to evade immune surveillance [15].

In addition to suppressing T cells, MDSCs promote the expansion of Tregs by producing transforming growth factor-beta (TGF-β) and IL-10. Tregs further exacerbate immunosuppression by inhibiting effector T-cell activity and promoting an anti-inflammatory environment. This crosstalk between MDSCs and Tregs amplifies the immune evasion mechanisms of AML cells [16].

Another important function of MDSCs in AML is their ability to modulate NK cell activity. MDSCs inhibit NK cell cytotoxicity by downregulating activating receptors such as NKG2D and impairing their ability to produce interferon-gamma (IFN-γ). This suppression of NK cell function further reduces the immune system's ability to target and eliminate leukemic cells [17].

Elevated levels of MDSCs have been observed in AML patients, correlating with disease severity, relapse risk, and poor prognosis. High MDSC levels are associated with lower numbers of activated cytotoxic T cells and NK cells, highlighting their role in immune dysfunction. Monitoring MDSC levels could serve as a biomarker for disease progression and therapeutic response in AML [18].

The phenotypic characterization of MDSCs in AML has revealed unique markers that distinguish them from normal myeloid cells. Common markers include CD33, CD11b, CD14 (for M-MDSCs), CD15 (for PMN-MDSCs), and the absence of HLA-DR expression. These markers are used in flow cytometry and immunohistochemical analyses to identify and quantify MDSCs in AML samples [19].

Targeting MDSCs in AML is an emerging therapeutic strategy. Several approaches are under investigation, including the use of agents that deplete MDSCs, block their recruitment, or inhibit their immunosuppressive functions. For example, all-trans retinoic acid (ATRA) has been shown to promote the differentiation of MDSCs into mature myeloid cells, reducing their immunosuppressive capacity [20].

Immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways may indirectly affect MDSC activity by enhancing T-cell responses. Additionally, agents that inhibit cytokine pathways, such as IL-6 or GM-CSF inhibitors, could reduce MDSC expansion and activity in the AML microenvironment. These strategies are being explored in preclinical and clinical studies [21].

The interaction between MDSCs and the tumor microenvironment (TME) is complex and dynamic. MDSCs contribute to angiogenesis by producing vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), which promote the remodeling of the bone marrow niche to support leukemic growth and survival. Targeting these angiogenic pathways could disrupt the supportive role of MDSCs in AML [22].

Despite the progress in understanding MDSCs in AML, challenges remain in translating these findings into effective therapies. The heterogeneity of MDSC subsets and their functional plasticity pose significant obstacles.

Furthermore, the lack of standardized assays to measure MDSC activity and their interaction with other immune cells complicates clinical implementation [23].

Preclinical models of AML have provided valuable insights into the role of MDSCs in disease progression and therapeutic resistance. Mouse models with humanized AML xenografts have been particularly useful in studying the interaction between MDSCs and the immune system. These models are critical for evaluating the efficacy of MDSC-targeted therapies [24].

Clinical trials investigating MDSC-targeted therapies in AML are still in their early stages. Recent studies highlight the potential of targeting PMN-MDSCs to improve therapeutic outcomes in AML. Strategies aimed at depleting these cells or reversing their suppressive function include the use of small-molecule inhibitors, immunomodulatory agents, and monoclonal antibodies [25,26]. For instance, inhibitors of the STAT3 and PI3K pathways, which regulate PMN-MDSC expansion and activity, have shown promise in preclinical studies. In addition, drugs like all-trans retinoic acid (ATRA) can induce differentiation of PMN-MDSCs into mature, non-suppressive myeloid cells, thereby restoring immune surveillance and enhancing the effects of existing therapies [27].

Other trials combining ATRA with immune checkpoint inhibitors or hypomethylating agents are underway to evaluate their synergistic effects in reducing MDSC-mediated immunosuppression. The results of these studies will inform the future direction of AML treatment [28].

Future research should focus on elucidating the molecular mechanisms underlying MDSC expansion and activity in AML. Understanding the signaling pathways and transcriptional networks that regulate MDSC differentiation and function could identify new therapeutic targets. Additionally, exploring the interaction of MDSCs with other components of the AML microenvironment, such as mesenchymal stem cells and extracellular vesicles, could provide a more comprehensive understanding of their role [29].

The development of combination therapies that target multiple immune-suppressive pathways is a promising approach to overcoming MDSC-mediated resistance. Combining MDSC-targeted agents with existing therapies, such as FLT3 inhibitors or HSCT, may improve treatment outcomes in AML patients [30].

Biomarker discovery is another critical area of research. Identifying reliable biomarkers for MDSC activity and patient stratification could enable personalized therapeutic strategies. High-throughput technologies, such as single-cell RNA sequencing and proteomics, offer powerful tools for uncovering novel biomarkers and therapeutic targets [31].

The role of MDSCs in AML highlights the importance of the immune system in leukemogenesis and therapeutic response. As our understanding of MDSCs and their interactions with the AML microenvironment deepens, new opportunities for immunotherapeutic interventions will emerge. These advancements hold promise for improving the prognosis and quality of life for AML patients [32].

In conclusion, MDSCs are central players in the immunosuppressive microenvironment of AML. Their roles in immune evasion, disease progression, and therapeutic resistance underscore the need for targeted strategies to modulate their activity. Ongoing research into the biology and therapeutic potential of MDSCs will pave the way for innovative approaches to AML treatment, PMN-MDSCs represent a critical immunosuppressive component of the AML microenvironment. Their ability to inhibit T cell responses and promote tumor progression underscores the need for targeted therapies that can mitigate their effects. By understanding the mechanisms driving PMN-MDSC expansion and function, researchers can develop innovative treatment strategies to improve outcomes for AML patients[33].

References

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. N Engl J Med. 2015;373(12):1136-1152.
2. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016;374(23):2209-2221.

3. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.
4. O'Donnell MR, Abboud CN, Altman J, et al. Acute Myeloid Leukemia, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(7):926-957.
5. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 versus 7+3 cytarabine and daunorubicin induction therapy in older adults with high-risk AML: results of a randomized phase 3 trial. J Clin Oncol. 2018;36(26):2684-2692.
6. DiNardo CD, Stein EM, de Botton S, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. N Engl J Med. 2018;378(25):2386-2398.
7. Short NJ, Ravandi F. Targeted therapies for acute myeloid leukemia: past, present, and future. Clin Adv Hematol Oncol. 2016;14(7):553-565.
8. Isidori A, Salvestrini V, Ciciarello M, et al. The role of the immunosuppressive microenvironment in acute myeloid leukemia development and relapse. Front Oncol. 2014;4:44.
9. Daver N, Boddu P, DiNardo C, et al. Hypomethylating agents in combination with venetoclax for newly diagnosed acute myeloid leukemia: rationale, opportunities, and challenges. Blood Rev. 2018;32(6):499-511.
10. Pollyea DA, Pratz K, Letai A, et al. Venetoclax with azacitidine in untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-629.
11. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009;9(3):162-174.
12. Bronte V, Brandau S, Chen SH, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun. 2016;7:12150.
13. Marigo I, Bosio E, Solito S, et al. Tumor-induced tolerance and immune suppression by myeloid-derived suppressor cells. Immunol Rev. 2020;295(1):72-84.
14. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The nature of myeloid-derived suppressor cells in the tumor microenvironment. Trends Immunol. 2016;37(3):208-220.
15. Gabrilovich DI. Myeloid-derived suppressor cells. Cancer Immunol Res. 2017;5(1):3-8.
16. Veglia F, Perego M, Gabrilovich D. Myeloid-derived suppressor cells coming of age. Nat Immunol. 2018;19(2):108-119.
17. Lindau D, Gielen P, Kroesen M, et al. The immunosuppressive tumor network: Myeloid-derived suppressor cells, regulatory T cells, and natural killer T cells. Immunotherapy. 2013;5(10):1057-1073.
18. Talmadge JE, Gabrilovich DI. History of myeloid-derived suppressor cells. Nat Rev Cancer. 2013;13(10):739-752.
19. Condamine T, Dominguez GA, Youn JI, et al. Lectin-type oxidized LDL receptor-1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients. Sci Transl Med. 2016;8(328):328ra28.
20. Nagaraj S, Youn JI, Weber H, et al. Anti-inflammatory triterpenoid blocks immune suppressive function of MDSCs and improves immune response in cancer. Clin Cancer Res. 2010;16(6):1812-1823.
21. Dohner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. N Engl J Med. 2015;373(12):1136-1152.
22. Chou CK, Fan Y, Chen Y, et al. Targeting myeloid-derived suppressor cells to potentiate cancer immunotherapy. J Hematol Oncol. 2022;15(1):40.
23. Fleming V, Hu X, Weber R, et al. Targeting myeloid-derived suppressor cells to bypass tumor-induced immunosuppression. Front Immunol. 2018;9:398.
24. Zhang Q, Choksi S, Chen K, et al. ROS and immune checkpoints: The interplay between cancer cells and T cells. Immunol Rev. 2021;298(1):58-69.

25. Kim HJ, Cantor H. The role of myeloid-derived suppressor cells in cancer. Cancer Immunol Res. 2014;2(3):189-196.
26. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. Nat Rev Immunol. 2021;21(8):485-498.
27. Bronte V, Brandau S, Chen SH, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. Nat Commun. 2016;7:12150.
28. Cui TX, Kryczek I, Zhao L, et al. Myeloid-derived suppressor cells enhance stemness of cancer cells by inducing microRNA101 and suppressing the corepressor CtBP2. Immunity. 2013;39(3):611-621.
29. Massagué J. TGFβ in Cancer. Cell. 2008;134(2):215-230.
30. Condamine T, Mastio J, Gabrilovich DI. Transcriptional regulation of myeloid-derived suppressor cells. J Leukoc Biol. 2015;98(6):913-922.
31. Molon B, Ugel S, Del Pozzo F, et al. Chemokine nitration prevents intratumoral infiltration of antigen-specific T cells. J Exp Med. 2011;208(10):1949-1962.
32. Marigo I, Zilio S, Desantis G, et al. Tryptophan catabolism generates autoimmune inflammation. J Immunol. 2020;205(7):1571-1580.
33. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-1355.