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What is the role of the microenvironment in MDS?

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ABSTRACT

Treating myelodysplastic syndromes (MDS) remains challenging. Hematopoiesis occurs within a heterogeneous, complex and dynamic microenvironment, and a multiplicity of mutations in hematopoietic stem and progenitor cells (HSPCs) lead to MDS. But is there a role for the microenvironment? Here we review experimental and conceptual arguments that support a role for the microenvironment, provide evidence for the disruption of the microenvironment in MDS, and explore microenvironmental signals that may provide a targetable and conserved vulnerability in MDS that transcend genetic heterogeneity.

Introduction

Hematopoiesis occurs within a heterogeneous, complex and dynamic microenvironment. In myelodysplastic syndromes (MDS), the driving mutations are critical for many of the known defects of the disease [1]. Among the mutational targets are molecules involved in DNA methylations, chromatin modification, RNA splicing, transcription, signal transduction, cohesin regulation, and DNA repair. Conceptual arguments support a role for the microenvironment in the development of MDS. For example, mutational burden exists in hematopoietic stem and progenitor cells (HSPC) that should be quiescent; clonal expansion happens in the setting of mutations that really don't provide any intrinsic advantage to the clone; and inhibition of normal hematopoiesis occurs in the setting of the coexistence of the clone with normal hematopoietic cells. Experimental arguments also support the importance of the microenvironment. While exploring bone abnormalities in patients with MDS, scientists have discovered abnormalities of plastic adherent stroma [2]. Many laboratories have shown that when stroma is grown from the microenvironment of patients with MDS, there is impaired growth capacity of these cells, accelerated senescence, impaired osteogenic differentiation, and diminished capacity for support of hematopoietic stem cells [2].

Additional evidence supporting the dependence of MDS on the microenvironment is the difficulty growing MDS cells, particularly from patients with low-grade MDS, in xenograft models. Human MDS cells engraft poorly in mouse xenotransplant models. When co-transplanted with MDS-derived mesenchymal stromal cells, however, MDS cell engraftment is improved [3]. One conclusion that can be drawn from this evidence, in the context of the coexistence of healthy hematopoietic stem and progenitor cells (HSPC) and MDS cells, is that the bone marrow microenvironment (BMME) may play a role in inhibiting normal, healthy HSPCs while simultaneously supporting MDS cells.

Recently scientists have found that mesenchymal and osteolineage cells, while a heterogeneous population of cells, are likely

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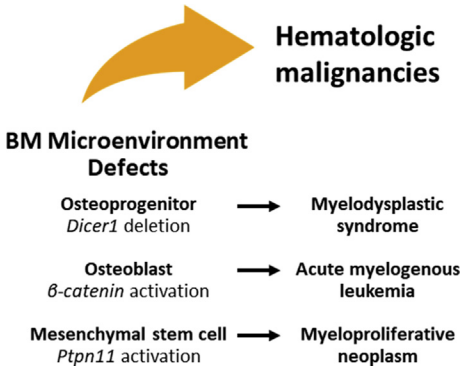

Fig. 1. Microenvironmental cells can initiate MDS/MPN.

critical for the maintenance and support of HSPCs because they secrete maintenance factors, such as CXCL12, KITL, and ANGPT1, in proximity to HSPCs and regulate a number of HSPC effects, including retention, proliferation, and differentiation of mature blood and immune cells [4–9]. This is illustrated by genetic models with altered mesenchymal cells that demonstrate decreased support of HSPCs. A number of studies have shown that the microenvironment may initiate myeloid abnormality. Using genetic models of osteoprogenitors, for example, *Dicer1* deletion can initiate MDS; activation of *β-catenin* and osteoblastic cells can initiate acute myeloid leukemia (AML); and *PTPN11* activation can initiate a myeloproliferative neoplasm (Fig. 1) [10–12].

Reciprocal interactions in the MDS environment

To study these interactions in vivo, investigators in the Calvi lab have used NUP98-HOXD13 (NHD13) transgenic mice to repeat hallmark features of human MDS [13,14]. This model recapitulates MDS in that the mice exhibit peripheral cytopenias, dysplasia, and eventually transform to acute leukemia. The murine model highlights the impact of the microenvironment on disease progression and transformation: non-functional mesenchymal populations expand, and normal hematopoietic stem cells decrease. Transplanting mutant bone marrow to a normal microenvironment improves hematopoietic function and decreases the risk of transformation to leukemia. Normal hematopoietic stem cells, when they are exposed to the microenvironment from this MDS model, can develop myeloid skewing.

Further in vivo studies are currently ongoing, modeling the coexistence of normal hematopoiesis and MDS. By transplanting normal wild-type cells or MDS cells into a normal microenvironment, there is an expansion of the dysfunctional mesenchymal cells. The number of hematopoietic stem cells decreases, despite the presence of normal hematopoietic cells, which leads to the inhibition of blood differentiation from normal hematopoietic cells [15]. These unpublished data show that there is clearly an effect of the microenvironment on healthy hematopoietic stem cells and that MDS cells can modulate the microenvironment.

Scientists are currently studying signals and mechanisms that may regulate how MDS cells impact the microenvironment (Fig. 2). Many studies show that BMME abnormalities are dependent on the presence of MDS; there is an acquisition of an inflammatory program by normal mesenchymal stromal cells (MSCs) when they are exposed to MDS. There is also evidence to suggest that MDS mutations initiate an inflammatory process. For example, in a number of murine models of clonal hematopoiesis or MDS, such as the Tet2 −/− and a 5q- MDS mouse models, there are increases in the alarmins, primarily S100A9, with activation of the inflammasome/NLRP3 and interleukin-1 β [16–19].

There are also signals from the microenvironment that impact MDS cells. Many studies show that activation of Wnt β-catenin can increase *Jagged1* and not only initiates the disease process, but also disrupts the microenvironment and initiates inflammatory signals [11,14,20–27]. Zambetti et al. [23] have shown that by sorting human cells, CD271 positive cells previously found in close proximity to MDS [28]. When sorted, these cells illustrate an increase in the alarmins S100A9 and S100A8, which in turn can increase local

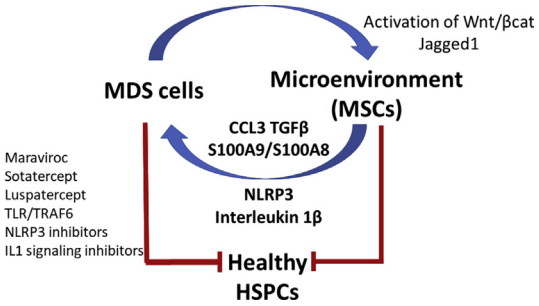

Fig. 2. Therapeutic targeting of reciprocal interactions in the MDS microenvironment.

interleukin-1β. Some of these changes also increase cytokines and TGFβ and can disrupt the normal bone marrow microenvironment, decreasing CXCL12. Other laboratory studies show that myeloid malignancies induce bone marrow neural damage, cellular senescence, remodeling of the blood vessels occurs, and osteoblastic defects. These disruptive MSCs not only may initiate inflammatory processes, but also show that the microenvironment is modified. These signals can be initiated directly by MDS cells; for example, myeloid-derived suppressive cells can also produce these inflammatory signals. Thus, there is an increase in the inflammatory signals found in the setting of MDS, which has prognostic value.

Now we and others are investigating the targetability of reciprocal interactions in the MDS microenvironment. There seem to be multiple ways to interrupt or interfere with these signals. We already know that we can target CCL3 and that TGFβ can be blocked by several strategies. The receptors for the NLRP inflammasome for the alarmins, the TLR, and signaling downstream of the TLRs—TRAF6—can be targeted, too. In fact, there are multiple available NLRP inhibitors and interleukin-1 signaling inhibitors (Fig. 2).

Conclusion

These data support the hypothesis that it is possible to target the microenvironment as a new tool for the treatment of MDS. Disrupting the microenvironment in MDS has led us and others to investigate the most important pathways, including the increased inflammatory signals found in the disease, as well as increased chemokines that recruit immune cells to the bone marrow. MSCs produce signals that increase support for MDS and decrease normal hematopoiesis. The most important takeaway, however, based on the available evidence is that immunity pathways are activated in the disease and can certainly be targeted therapeutically. Whether these pathways are influenced by the genetic heterogeneity of MDS remains an open question.

Disclosure

Laura Calvi has received Intellectual Property Rights/Patent Holder: US Patent No. 7,429,383, US Patent No. 8,309,095 B2, US Patent No. 8,802,104 B2 (for the use of teriparatide or prostaglandin E2 analogues for the expansion of hematopoietic stem cells). Allison J. Li and Michael W Becker have nothing to disclose.

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