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Myelodysplastic syndromes - Section 1

The microenvironment in myelodysplastic syndromes: From concept to therapeutic target

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Take Home Messages

- MDS is a disease of the bone marrow tissue, not merely hematopoietic cells.
- Niche alterations in MDS may be primary or induced by mutant HSPC and facilitate disease progression through specific pathways.
- Elucidation of these pathways is paving the way to niche-instructed disease prognostication and therapeutic targeting.

Introduction

Myelodysplastic syndromes (MDS) pathogenesis is driven by (epi)genetic aberrations in hematopoietic stem and/or progenitor cells (HSPC).[1] HSPC in these disorders typically acquire a number of genetic lesions that, in concert, drive malignant transformation. Mounting experimental evidence, however, points at pivotal contribution of non-hematopoietic cells to disease initiation and progression.

In this educational session, we will review recent concepts and mechanisms of microenvironmental contributions to disease initiation and progression, including their diagnostic and therapeutic potential. Focus will be on mesenchymal and endothelial cells in the bone marrow microenvironment (BMME) which constitute a complex, highly interactive environment, encompassing specialized endothelium,[2] nervous system innervation and diverse mesenchymal elements (including mesenchymal stem/progenitor cells and osteoblasts).

Microenvironmental contribution to MDS pathogenesis: Proof of concept

When we think about potential contributions of the HSPC niche to the pathogenesis of MDS, two concepts may be discerned (Figure 1):

a. *Niche-induced malignant transformation*, in which primary alterations in niche cells drive the dysfunction and malignant transformation of supported, but distinct HSPC. Experimental support for the validity of this concept is provided by mouse models of hereditary leukemia predisposition syndromes (Shwachman-Diamond Syndrome[3] and Noonan Syndrome[4]) and by a mouse model of constitutive Wnt pathway activation in osteolineage cells.[5]
b. *Niche-facilitated malignant transformation*, in which primary alterations (e.g. driven by (epi)genetic events in HSPC alter the niche in such a way that the niche starts cooperating with the aberrant HSPC in disease progression.[6,7] More recent examples of mouse modeling supporting this concept have been reported in mouse models of myeloproliferative disorders and acute myeloid leukemia.[8-11]

It is conceivable that the niche-induced alterations play a more important role in the congenital bone marrow failure syndromes where the primary event in niche cells is the germline genetic abnormality defining the disorder. It is less clear if, and how, primary alterations in the niche would occur in the case of acquired bone marrow failure and leukemia predisposition disorders (such as MDS). Age-associated (inflammatory) alterations as well as mutations in mesenchymal cells have been suggested but convincing experimental support that these events are relevant and sufficient to drive disease is currently lacking.

It seems more likely that in the case of acquired disorders such as MDS, primary genetic alterations in the hematopoietic cells induce disruption of niche cells supporting disease progression (as demonstrated in mouse models). Elucidation of the molecular signaling underlying these concepts holds great promise for novel avenues to attenuate bone marrow failure and leukemic evolution in MDS. It must be emphasized in this context that the underlying molecular mechanisms of niche induced/facilitated bone marrow failure and malignant transformation may not be mutually exclusive.

Mechanisms of niche induced/facilitated bone marrow failure and progression of myeloid neoplasm

When reviewing an increasing body of literature, some recurring themes emerge regarding the underlying cellular and molecular mechanisms of niche induced/facilitated disease initiation and progression.

Damage to the architecture and function of the normal HSPC niche

Neoplastic HSPC may damage the HSC niche, undermining the support for (residual) normal HSC and through this mechanism promote a competitive advantage. The relevance of this mechanistic concept is stressed by recent findings in mouse models of myeloid neoplasm. In MPN, sympathetic nerve fibers, support-

ing mesenchymal stem cells are consistently reduced in patients and mice expressing the JAK2(V617F) mutation in HSCs.[8] MSC reduction is caused by bone marrow neural damage and Schwann cell death triggered by interleukin-1 produced by mutant HSCs. In mouse (transgenic/xenograft) models,[9,10] AML leads to remodeling of vasculature caused by the production of pro-inflammatory and anti-angiogenic cytokines by AML cells, that gradually degrade endosteal endothelium, mesenchymal cells and osteoblasts.[9] This damage to the endothelial and mesenchymal niches resulted in reduced support for residual normal hematopoiesis and progression of leukemia. Similarly, in xenograft models of AML disruption of the adipogenic niche resulted in impaired erythropoiesis and myelopoiesis.[10] Finally, in *Flt3*-ITD mice it was shown that *Flt3*-ITD expressing cells induced a reduction of mesenchymal and endothelial cells with increased inflammation-associated gene expression resulting in disease progression at the expense of normal hematopoiesis.[11]

Inflammatory alterations in niche cells driving genotoxic stress in HSPC

Inflammatory cross-talk between mutated HSPCs and niche cells play an important role in the niche damage induced invoked by mutant HSPC. Inflammatory alterations in the niche, however, can promote the initiation and progression through different mechanisms. In the SDS niche model, mesenchymal niche cells induce genotoxic stress in HSPC.[12]. Mechanistically, transcriptional activation of an inflammatory signatures in niche cells, downstream of Tp53 activation, is implicated. In particular, the TP53-S100A8A9-TLR signaling axis was shown to induce genotoxic stress in normal HSPC. Transcriptional activation of the TP53-S100A8A9-TLR signaling axis in the mesenchymal niche was found in a subset of MDS patients to predict leukemic evolution. The findings complement emerging data from other mouse models of niche-facilitated oncogenesis and human disease, pointing at inflammatory signaling in HSPC niches as a biologic commonality in preleukemia and myeloid neoplasm.

Wnt activation in mesenchymal niche cells

Activated Wnt signaling in mesenchymal niche cells has been shown to drive the initiation and progression of MDS/AML in several mouse models.[5,13,14]

Importantly, all these cellular and molecular mechanisms appear relevant for human MDS (and AML) where disruption of the osteoblastic[15] and adipogenic[10] niche and upregulation of inflammatory programs,[12,16] Wnt activation,[4] reduction in expression of supporting cytokines like CXCL12[16] and senescence[16] have been observed in mesenchymal niche cells in subsets of patients.

Niche induced disease evolution: Selection or induction of clones?

The concept of niche induced genotoxic stress in normal HSPC may imply that inflammatory alterations in the mesenchymal niche can induce DNA damage and mutations in HSPC, thus driving bone marrow failure and perhaps contributing to malignant evolution.

Alternatively (or perhaps synergistically), it may be proposed that such an environment may favor the clonal advantage of cells carrying a mutation that confers relative resistance to the environmental inflammation. In this context, it is noteworthy that MDS related mutations may indeed confer such relative resistance, opening the possibility that the aberrant environment drives evolution of MDS clones.[17]

This would provide insight into the central question of how a mutated cell or "preleukemic clone" persists and sometimes gains competitive advantage over non-mutated HSPC, while not always explained by hematopoietic cell-intrinsic capacities caused by the mutated state. Evolution principles predict that a cell's direct environment, or HSPC niche, may play critical roles in the induction and selection of genetic clones within a population.[18]

Future perspectives: Exploiting the MDS niche for prognostication and therapeutic targeting

The emerging notion of MDS as a "disease of a tissue" rather than hematopoietic cells alone, and the pathophysiologic insights emanating from this, may have important consequences for prognostication and treatment of the disease.

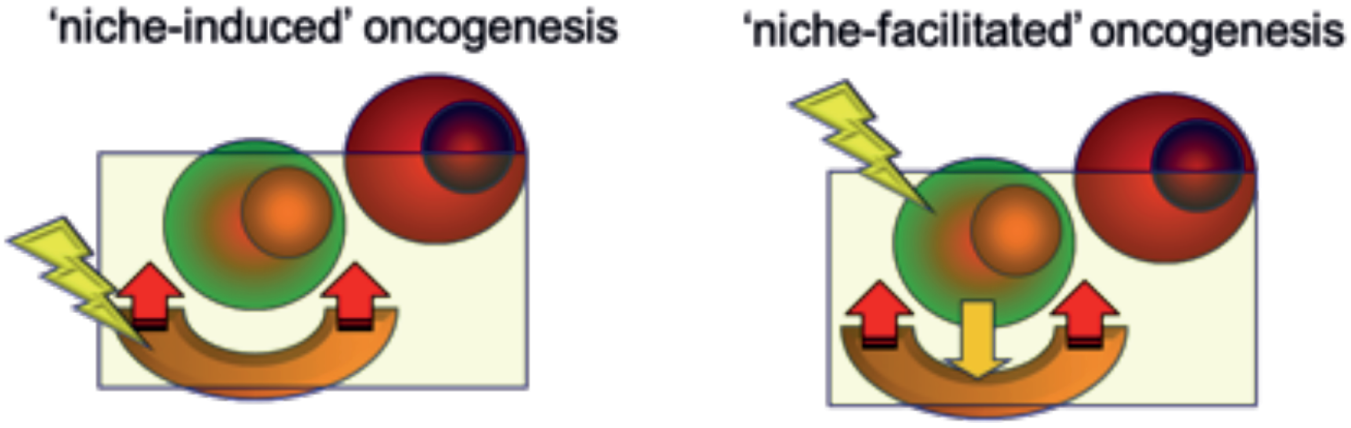

Figure 1. Concepts of niche contributions to disease pathogenesis in MDS. In 'niche-induced' oncogenesis, primary alterations in mesenchymal niche cells drive the malignant transformation of HSPC. This may occur through inflammatory alterations creating a 'mutagenic field' that induces genotoxic stress and DNA damage in HSPC. Alternatively, the mutagenic field may select clones conferring resistance to genotoxic stress and thus facilitate clonal evolution. In 'niche-facilitated' oncogenesis, primary (genetic or epigenetic) alterations in HSPC alter their niche in such a way that the niche starts cooperating in clonal expansion and disease progression. The molecular mechanisms driving these events may be shared by both concepts are addressed in more detail in the manuscript.

Therapeutic targeting of the niche

The preclinical data support the view that therapeutic targeting of the microenvironment has the potential to attenuate disease progression, either by preventing clonal advantage and selection, or by restoring microenvironmental support for the residual normal hematopoiesis. Indeed, part of the success of current therapeutics in MDS, such as demethylating agents and lenolidomide, may be attributed to therapeutic targeting of niche cells. 5-azacytidine, e.g. may revert the widespread aberrant cytosine hypermethylation in stromal cells and thereby enhanced their ability to support hematopoiesis.[14]

Perhaps more exciting, preclinical data from the aforementioned mouse models of niche-induced/facilitated disease progression have identified niche targeting agents attenuating disease progression.

- Administration of deferoxamine rescued the endosteal endothelium in the mouse model of AML which lead to preservation of normal HSCs.[9]
- *In vivo* administration of PPAR agonists induced adipogenesis in the AML marrow, rescuing normal hematopoietic differentiation and repressed leukemic growth.[10]
- Anti-TNF treatment partially rescued the HSC phenotype in Flt3-ITD mice.[11]
- β3-adrenergic agonists restored the sympathetic regulation of MSCs, prevented the loss of normal HSCs and delayed MPN progression.[8]
- Inhibition of WNT signaling (by the FDA-approved drug pyrvinium) prevented the development of MDS in Apcdel/+ mice.[13]
- Blockade of TLR4 partially rescued the DNA damage in HSC.[12]

The niche as a parameter for prognostication

Current prognostication (IPSS-R) is largely based on hematopoietic cell characteristics and remains suboptimal. This is of particular relevance to low-risk MDS (LRMDS), a heterogeneous disease-entity with a subset of patients having a particular dismal prognosis not identified by current risk-stratification strategies and not amenable to targeted therapy because of incomplete understanding of disease pathogenesis. Niche parameters are likely to complement HSPC intrinsic characteristics in future models of prognostication, as suggested by the finding that transcriptional activation of the TP53-S100A8A9-TLR signaling axis in the mesenchymal niche in a subset of MDS patients predicts leukemic evolution.[12]

Collectively, the rapidly emerging insights into niche contributions to disease pathogenesis in MDS will pave the way to niche-instructed prognostication and therapeutic targeting in LRMDS.

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