Myeloproliferative neoplasms - Section 1

The microenvironment in myeloproliferative neoplasm

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Introduction

Myeloid malignancies are caused by genetic or epigenetic alterations in hematopoietic stem cells (HSCs) and/or myeloid progenitor cells (MPCs) that can render them leukemic stem cells (LSCs). They comprise myeloproliferative neoplasms (MPNs), myelodysplastic syndromes and acute myeloid leukemia (AML). There is a continuum in the myeloid malignancies that embraces from the clonal expansion of normal HSCs (found in many healthy older subjects) to premalignancy and malignant transformation.1 MPNs can be considered preleukemic disorders because MPN patients have higher risk of developing AML, especially myelofibrosis patients (8-13% transformation rate into AML within 10 yr).2 Streaming from the discovery of driver mutations, MPNs were initially considered purely driven by oncogenic drivers in HSCs/MPCs. However, cumulative evidence indicates that the mutated cells can take over the niche, overcome the control by the normal microenvironment and/or remodel BM niches into permissive microenvironments that support disease progression at the expense of normal hematopoiesis (Figure 1).

Alterations of the microenvironment can promote MPN development

Moreover, research based on experimental mouse models has demonstrated that alterations of the microenvironment have the potential to aggravate or even initiate MPN. The first indications of “oncogenic” niche in MPN arise from reciprocal BM transplantation experiments showing that myeloid malignancies can arise from originally non-mutated hematopoietic cells in an altered microenvironment. For instance, MPN-like disease was observed in mice carrying constitutive Retinoic acid receptor (Rar) non-hematopoietic deletion.3 Likewise, MPN-like developed after combined retinoblastoma protein (Rb) deletion in non-hematopoietic cells and myeloid cells.4,5 Similarly, Notch pathway inhibition by E3-ligase Mind bomb-1 (Mib1) deletion in non-hematopoietic cells caused non-transplantable MPN-like disease, reverted by microenvironmental Notch activation.6 These pioneering studies established the proof of concept of the microenvironment as a potentially oncogenic entity and prompted the search of premalignant niches in MPN.

Regulation of normal hematopoiesis by the bone marrow niche

However, the dissection of pre/malignant niches requires prior understanding of normal HSC niches. Our past work identified bone marrow nestin+ mesenchymal stem cells (BMSCs) with essential HSC niche functions.7 This cell population largely overlaps with BMSCs marked using other methods in subsequent studies that have confirmed this key BMSC role in the HSC niche.8-11 However, the BM microenvironment is complex and involves many different cell types and molecules that dynamically regulate HSCs; therefore, reductionist studies targeting single molecules/cells might be insufficient due to redundancy/compensation. We undertook a holistic approach by studying a master regulator of this complex microenvironment – the autonomnic nervous system.12-14 Our recent data demonstrates that the autonomnic nervous system can use different neurotransmitters to regulate stem cell quiescence (required for self-renewal) and stem cell activation and migration in different BM niches. This physiological regulation of normal niches is damaged in MPN but can be restored or utilized therapeutically. For example, we have shown that pro-inflammatory cytokines produced by JAK2V617F hematopoietic cells, like IL1β, can cause local neuropathy and damage to the microenvironment, which aggravate disease progression. However, neural protection by neurotrophic factors or neural stimulation of the microenvironment by chronic treatment with β2-adrenergic agonists rescued nestin+ cells and improved myelofibrosis in mice.14

Take Home Messages

- Experimental models have shown that genetic alterations of the BM microenvironment can cause MPN-like disease from initially non-mutated hematopoietic cells.
- Mutated hematopoietic cells cause inflammatory damage of the microenvironment, which contributes to MPN progression.
- Current therapies might alter the microenvironment and stage/disease-specific targeting of the microenvironment might be a complementary therapeutic strategy in MPN.
Figure 1. Microenvironmental changes during MPN development. In the BM niche, HSC function is tightly controlled by a specialized microenvironment comprising sympathetic neurons, BM mesenchymal stem/progenitor cells (BMSC), osteoblasts (OB) and endothelial cells (EC). (A) Niche-induced MPN-like disease has been observed in mice with genetically altered microenvironment but initially normal HSC and MPC. During early stages of MPN, HSC/MPC acquire genetic alterations that transform them into leukemia stem/initiating cells (LSC). These mutations also create a pro-inflammatory environment that damages sensitive elements of the microenvironment, such as Schwann cells and their associated nerve terminals. (B) During intermediate stages of the disease the environment (BMSC, OB and EC) remodels into a self-reinforcing niche that interferes with normal hematopoiesis and favors disease progression (C) Late stages of the disease are characterized by a pro-inflammatory environment and myelofibrosis, high blood vessel density and central LSC localization. Figure modified from reference. Modified from Korn et al. Blood 2017;129:811-22; with permission.
Malignant-hematopoiesis derived cytokines render the microenvironment pro-leukemogenic

Whereas the altered niche might be a predisposing factor in MPN, mutated hematopoietic cells can render the microenvironment pro-leukemogenic. Mutated hematopoietic cells cause alterations in BMSCs that contribute to MPN development. Indeed, BMSCs from MPN patients support better in vitro Jak2-V617F mutated CD34+ cells (but not their non-mutated counterparts) than BMSCs from healthy donors. This supportive effect can be abrogated by a histone deacetylase-8 inhibitor. CML cells support BMSC proliferation and abnormal differentiation leading to inflammatory osteoblasts in mice; BMSCs in CML fail to maintain normal HSCs, possibly providing a competitive advantage to LSCs. Another study showed that CML cells also instruct BMSCs to secrete PIGF, which stimulates angiogenesis and promotes CML proliferation and metabolism, in part independently of BCR-ABL1 signaling. We have shown that progression of BCR-ABL MPN disrupts normal BMSC function in mice, promoting disease progression.

Mutations in the microenvironment trigger or aggravate MPN in experimental models

In the case of MPNs driven by germline mutations, the impact of these mutations in BMSCs might have a profound effect on disease development. One example includes germline activating mutations of the protein tyrosine phosphatase SHP2 (encoded in the PTPN11 gene), found in 50% of patients with Noonan syndrome, which have increased risk of developing juvenile myelomonocytic leukemia (JMM). An activating mutation of the PTPN11 gene in nestin+ BMSCs (but not in differentiated osteoblasts or endothelial cells) promotes the development and progression of JMM in mice. Mutations of signal-induced proliferation-associated gene 1 (SIPA1), a RAPI GTPase-activating protein, have been found in some JMML cases. MPN-like disease has been observed in SIPA1 KO mice carrying non-mutated hematopoietic cells. SIPA1 deficiency in the BM microenvironment causes similar BMSC changes previously reported in other MPNs, such as reduced Cxcl12 expression. However, despite reduced Cxcl12 expression, the Cxcl12-CXCR4 axis can be overactive in some MPNs (e.g. primary myelofibrosis) by oncogenic JAK2, which can maintain high PI3K signaling, over the threshold required for CXCR4 activation. Other studies have shown that reduced trabecular bone mass in Rapγ- or Rb-deficient mice correlates with aggravated MPN, suggesting that endosteal niche alterations can promote MPN progression. Osteoblastic cells also expand during the chronic phase of CML, when they negatively regulate HSC and LSC proliferation. In contrast, osteoblastic cells are markedly reduced during the blast crisis, suggesting that osteoblasts are differentially affected in AML and CML. This is further emphasised by another study showing that parathyroid hormone (PTH) receptor activation in osteoblasts increases bone remodelling and attenuates CML progression, but stimulates MLL-AF9 AML progression. These differences suggest the that the same niche cells might play different roles in distinct malignancies and/or disease stages. Besides BMSCs and osteoblasts, the interaction of BM blood vessels with the mutated cells critically affects disease development. A positive feedback loop is established between mutated haematopoietic cells and endothelial cells (ECs): mutated cells secrete pro-angiogenic factors and ECs release factors that promote survival and proliferation of mutated hematopoietic cells. Despite increased angiogenesis, hypoxia still represents a hallmark of these diseases that can influence LSC proliferation, differentiation, metabolism and chemoresistance. Interestingly, the hypoxic microenvironment can suppress the activity of Jak2V617F and inhibit the growth of Jak2V617F+ cells in a SHP2-dependent manner, suggesting a potential mechanism by which the niche might modulate the expansion of MPN. The Jak2-V617F mutation has been detected in endothelial cells and may cause bleeding complications or even contribute to clonal expansion and disease relapse in MPN patients following allogeneic stem cell transplantation (ASCT).

The role of the microenvironment in treatment outcome – finding new therapies

An exciting area under expansion addresses the role of the microenvironment in MPNs and their treatment. It is clear that microenvironment-derived cytokines can either positively or negatively affect the efficacy of inhibitors. The positive effects of JAK inhibitors in MPN might be partially due to their strong anti-inflammatory effects. Pegylated interferon-2α (IFN2α) is a promising therapy in drug-sensitive and tolerant patients who are not likely to undergo ASCT. IFN2α has antiproliferative, immunomodulatory and antiangiogenic properties, some of which might be mediated by the BM microenvironment. Immunomodulation has recently re-emerged as a potential promising avenue in MPN. A recent study demonstrates that constitutive Jak2/STAT3/STAT5 activation causes PD-L1-mediated immune escape by reducing T-cell activation, metabolic activity, and cell cycle progression, and suggests that Jak2V617F-mutant MPN is susceptible to immunomodulatory approaches relying on PD-1 inhibition. Lastly, the identification of monocyte-derived fibrocytes and Gli1+ MSCs as a source of myofibroblasts suggest that pentraxin and Gli inhibitors might have positive effects on myelofibrosis or other types of fibrosis.

Future studies will address the effects of MPN treatment on the microenvironment, how these might influence response to therapy, and whether targeting the microenvironment can improve current therapies.

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This study demonstrates that JAK2-V617F-mutated cells damage BM neuronal cells and nestin+ BMSCs through IL1β production, and that compensation of deficient innervation by chronic administration of β3-adrenergic agonists can rescue nestin+ niches and improve myelofibrosis in mice.

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