suppression. However, suppression of normal erythropoiesis also occurs in cases with low extent of malignant infiltration.

Bruno et al show that HSPCs, megakaryocyte-erythrocyte progenitors (MEPs) in particular, are significantly diminished in the BM of MM patients not because of the impaction of the BM with tumor cells alone but as a result of functional impairment. Specifically, using genomic profiling of distinct HSPC sub-sets derived from MM patients the authors indicate deregulation of TGFβ/Smad2, p38MAPK, and NFKB signaling pathways. Moreover, inhibition of TGFβ receptor (TβR)–I using SD-208 restores proliferation, cell cycling, and enhanced long-term self-renewal and clonogenic capacity of MM patient-derived HSPCs. Finally, transplantation of HSPCs derived from patients with MM into the BM of MM-free NOG mice shows enhanced engraftment and normal differentiation capacities. Similar to data presented here, previous studies have shown that TGFβ is associated with the induction of anemia in MDS and leukemia.4,5

This article will likely stimulate many additional studies. One could certainly postulate a therapeutic role of TGFβ inhibition in MM-associated anemia. Moreover, given that TGFβ also plays a key role in lytic bone lesions of MM, future clinical studies evaluating the potential therapeutic role of TβRI inhibitors are indeed of high interest. However, TGFβ has diverse and often conflicting roles. While TGFβ levels are increased in the MM BM milieu, surface expression of TβRI, TβRII, and TβRIII on MM cells is reduced.1,8 Functionally, decreased levels of TGFβ receptors counteract the antiproliferative role of TGFβ on MM cells. Taken together, the development and clinical use of TGFβ inhibitors requires further investigation dependent on the context in which they act.

Another intriguing finding of this study is that MM-induced changes within the BM milieu can reversibly affect benign cells, HSPCs in particular. Specifically, transplantation of HSPCs derived from MM patients into the BM of MM-free NOG mice shows enhanced engraftment and normal differentiation capacities. These data are consistent with our clinical experience demonstrating rapid and sustained engraftment in the majority of MM patients after elimination of MM cells by high-dose therapy.9 Bruno et al hypothesize that increased engraftment might be due to a compensatory rebound of HSPCs after discontinuation of TGFβ-mediated inhibitory effects. Moreover, they speculate that increases of TGFβ secreted by stromal cells and tumor cells create a competitive advantage for clonal plasma cells over benign HSPCs. Future studies should explore whether the microenvironment can also reversibly affect stromal cells and thereby induce a malignant phenotype. Already ongoing efforts aim to identify differences of stromal cells derived from the MM tumor microenvironment versus stromal cells derived from the BM microenvironment of healthy individuals. The existence of MM-specific endothelial cells, BM stromal cells, and mesenchymal stem cells (MSCs) has already been proposed.2 Indeed, one might speculate that the maintenance and expansion of the malignant plasma cell clone and thereby the transition of MGUS to MM depends on progressive supportive changes within the tumor microenvironment.

An unprecedented enhancement of our knowledge of MM cell biology and its interrelation with the BM microenvironment has led to the identification of novel targets. The development of derived therapies targeting both the tumor cell as well as the microenvironment that have fundamentally changed MM treatment strategies. The present study further extends our understanding of the impact of changes within the BM microenvironment in MM pathogenesis and provides new avenues for future investigations.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

LYMPHOID NEOPLASIA

Comment on Tili et al, page 2631

MiRly regulating metabolism

Deepa Sampath MD Anderson Cancer Center

In this issue of Blood, Tili et al identify an important link between microRNAs and the metabolic adaptation characteristic of cancer cells.1 In chronic lymphocytic leukemia (CLL), the microRNA, miR–125b becomes down-regulated resulting in an increase in the expression and activity of a myriad of metabolic enzymes that promote metabolic reprogramming in a way that favors malignant transformation.

Cells normally generate the bulk of their energy (ATP) via mitochondrial oxidative phosphorylation and switch to glycolysis under anaerobic stress. Cancer cells, on the other hand, alter their metabolism to preferentially generate ATP via glycolysis, even in the presence of abundant oxygen, a phenomenon termed the “Warburg effect.”2 This adaptation, although inefficient, generates sufficient energy and, more importantly, ensures a steady supply of anabolic carbon and nitrogen that can be used to synthesize the nucleotides, amino acids, and lipids essential for tumor proliferation.2 MicroRNAs are master gene regulators whose expression is widely altered in cancers. They bind to multiple mRNAs in cells by sequence complementarity to negatively impact the expression of their target genes.

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Consequently, deregulation in the expression of even a single microRNA has widespread consequences on downstream gene and signaling cascades. Given their central role in biology, it is not at all surprising that alterations in microRNA expression would be pivotal in the metabolic reprogramming of tumor cells.

CLL is a disease that takes an indolent course in some and aggressive in others. Here, Tili and colleagues demonstrate that miR-125b is expressed at low levels in both indolent and aggressive CLL. Loss of this microRNA was functionally linked to the increased expression of a large number of transcripts that encoded proteins within the lipid, phospholipid, carbohydrate, amino acid, or nucleotide metabolic pathways. This, in turn, led to a preference for aerobic glycolysis as manifested by the enhanced production of glycolytic intermediates, lactates, and other metabolites that could support anabolic growth. Conversely, overexpression of this microRNA reversed metabolic dependence on aerobic glycolysis. Thus, miR-125b may act as a gate keeper that prevents the establishment of the Warburg effect (see figure).

However, several key questions remain unanswered. First, miR-125b is located on chromosome 11, at the genomic location 11q24.1, which is close to that of the ATM gene (11q22-23). This locus is frequently deleted in CLL. However, the actual frequency with which deletions in 11q extend into the miR-125b gene has not been evaluated. Under these circumstances, could there be alternative mechanisms that account for the low levels of expression of miR-125b in CLL? Second, CLL is a quiescent disease with a very low proliferative index; the majority of neoplastic B lymphocytes accumulate due to enhanced survival caused by defects in apoptotic pathways. If this is the case, why do CLL cells undergo metabolic adaptation toward proliferation? Third, is the loss of miR-125b and establishment of the Warburg effect alone sufficient for malignant transformation? Finally, does loss of miR-125b enable the proliferative fraction in CLL?

In addition to miR-125b, other microRNAs as well as protein coding genes are also known to be critical for the establishment of metabolic adaptations and tumorigenesis. In fact, recent evidence indicates that the fundamental objective of alterations in proto-oncogene and tumor-suppressor genes is the reprogramming of cellular metabolism. Multiple microRNAs directly or indirectly regulate key proteins responsible for metabolic reprogramming. Similarly, master regulators such as PI3K, Akt, c-myc, and HIF1 along with their downstream signaling pathways are all well known to facilitate metabolic adaptations to support tumor growth. It would be important to understand the consequences of miR-125b dysregulation on metabolic adaptation within the context of the other regulators of the Warburg adaptation.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

Comment on Mali et al, page 2669

KIT’s ship comes in

Benjamin S. Braun UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Mali et al demonstrate in this issue of Blood that oncogenic KIT alleles can be attacked through their reliance on signaling through the phosphatase SHP2. The importance of aberrant signal transduction in leukemia has long been appreciated. This insight is finally having impact in the clinic, when appropriate tyrosine kinase inhibitors (TKIs) are available.

Activating mutations in KIT are found in systemic mastocytosis and in rare acute myeloid leukemia (AML) cases. KIT mutations in AML are associated with poor prognosis, and inhibition of KIT activity seems warranted. Unfortunately, most oncogenic mutations affect the activation loop of KIT in a way that not only activates its kinase activity...
MiRly regulating metabolism

Deepa Sampath