inside blood commentary

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MYELOID NEOPLASIA

Comment on Schinke et al, page 3144

Targets of opportunity for precision medicine

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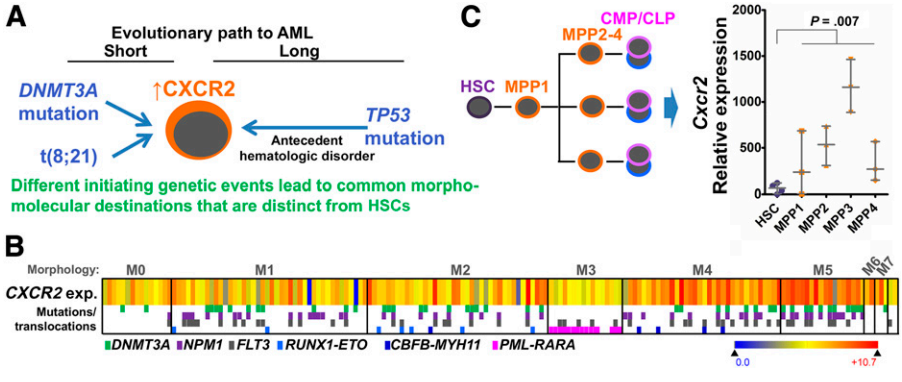
In this issue of *Blood*, Schinke et al have identified a higher expression of CXCR2 in myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) stem cells than in normal hematopoietic stem cells (HSCs) and demonstrated preclinical therapeutic proof of principle.[1]

The intent driving the idea of "precision medicine," or the individualization of oncotherapy based on case-by-case cancer genetics, is selective suppression of malignant clones while sparing the normal stem cells needed for health and life—stated simply, a better therapeutic index. Schinke et al identified higher expression of CXCR2 in MDS/AML stem cells than in normal HSCs and demonstrated preclinical therapeutic proof of principle, affirming that molecular targets offering a good therapeutic index are not restricted to mutated oncoproteins. In fact, CXCR2 and other nononcogene cancer molecular addictions could have advantages as targets for therapy, such as near-term drugability[1] and broad applicability to a histologic diagnosis. Per the latter, it is noteworthy that high *CXCR2* expression is a characteristic of some morphologic subtypes of AML despite different underlying driver mutations (see figure).[2] Stated another way, there is convergent neoplastic evolution, from disparate genetic origins toward expansion of myeloblasts bearing gross molecular and morphologic similarities. Why do multiple roads, cobbled by Darwinian selective pressures working for years, lead to similar molecular-morphologic destinations that are distinct from normal HSCs? Here are some clues: "first hits" in the multihit process of leukemogenesis (eg, *RUNX1* or *DNMT3A* mutations) originate in the germline or HSCs (cells of origin) and, accordingly, can be detected in the germline or HSCs.[3-5] Subsequent evolution into AML-initiating cells (AML stem cells), however, occurs in lineage-committed daughter cells of these cells of origin, most cleanly documented by the detection of secondary mutations needed for transformation into AML (eg, *FLT3* or *NPM1* mutations) only in committed progenitors and not in HSCs.[3-5] In fact, first hits such as RUNX1 loss-of-function have been shown to manifest their most dramatic phenotypic effects not in HSCs but in committed daughter cells (progenitors) by impeding the differentiation (maturation) that is the natural control on the cell growth and division of this intrinsically MYC-enriched, exponentially expanding compartment.[6] In short, transformation into MDS/AML is in a cellular context biologically distinct from that of HSCs,[7,8] and CXCR2 and a number of other molecular targets that have been found to discriminate between MDS/AML stem cells and HSCs[8] are opportunistic targets, reflecting this compartment shift from stem cells to progenitors that occurs in neoplastic evolution (see figure). The wealth of discriminating molecular targets so created is great news, because there could be many reasons, such as lack of drugability without off-target effects or importance to some other normal function,[1]



(A) Neoplastic evolution demonstrates convergence, from disparate genetic origins toward a common destination of myeloblasts bearing gross molecular and morphologic similarities. (B) Heatmap shows *CXCR2* expression (exp.) in primary AML cells categorized by morphology (M0-M7) (TCGA, n = 171, RNA sequencing). The color coding beneath indicates a subset of contained recurrent mutations and chromosome translocations (some of which are known as first hits). Gene expression by RNA sequencing. (C) *Cxcr2* expression is dramatically upregulated in the immediate committed progeny (MPP) of normal HSCs. The implication is that broadly relevant nononcogene therapeutic targets of opportunity such as CXCR2 likely reflect a common theme in neoplastic evolution: transformation in committed progenitors despite origin of the first hit in HSCs or the germline. Box-and-whiskers plot data are expressed as median ± range. $P = .007$, Mann-Whitney test. CLP, common lymphoid progenitor; CMP, common myeloid progenitor; MMP, multipotent myeloid progenitor (public data E-MTAB-2262).

that could undermine the therapeutic index of any one target. This target-rich environment, not restricted to mutated oncoproteins, offers real hope for breakthroughs (or at least improvements in safety and effectiveness) in MDS/AML therapy.

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REFERENCES

1. Schinke C, Giricz O, Li W, et al. IL8-CXCR2 pathway inhibition as a therapeutic strategy against MDS and AML stem cells. *Blood*. 2015;125(20):3144-3152.

2. Cabezas-Wallscheid N, Klimmeck D, Hansson J, et al. Identification of regulatory networks in HSCs and their immediate progeny via integrated proteome, transcriptome, and DNA Methylome analysis. *Cell Stem Cell*. 2014;15(4):507-522.

3. Jan M, Snyder TM, Corces-Zimmerman MR, et al. Clonal evolution of preleukemic hematopoietic stem cells precedes human acute myeloid leukemia. *Sci Transl Med*. 2012;4(149):149ra118.

4. Corces-Zimmerman MR, Hong WJ, Weissman IL, Medeiros BC, Majeti R. Preleukemic mutations in human acute myeloid leukemia affect epigenetic regulators and persist in remission. *Proc Natl Acad Sci USA*. 2014;111(7):2548-2553.

5. Shlush LI, Zandi S, Mitchell A, et al; HALT Pan-Leukemia Gene Panel Consortium. Identification of pre-leukaemic haematopoietic stem cells in acute leukaemia. *Nature*. 2014;506(7488):328-333.

6. Ng KP, Hu Z, Ebrahem Q, Negrotto S, Lausen J, Saunthararajah Y. Runx1 deficiency permits granulocyte lineage commitment but impairs subsequent maturation. *Oncogenesis*. 2013;2:e78.

7. Saunthararajah Y, Maciejewski J. Polycomb segment myeloid malignancies. *Blood*. 2012;119(5):1097-1098.

8. Saunthararajah Y, Sekeres M, Advani A, et al. Evaluation of noncytotoxic DNMT1-depleting therapy in patients with myelodysplastic syndromes. *J Clin Invest*. 2015;125(3):1043-1055.

● ● ● THROMBOSIS AND HEMOSTASIS

Comment on Bauer et al, page 3153

VWF fibers induce thrombosis during cancer

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In this issue of *Blood*, Bauer et al[1] provide an explanation for the formation of luminal von Willebrand factor (VWF) fibers observed in cancer patients, which is initiated through tumor-derived vascular endothelial growth factor-A (VEGF-A). Platelet aggregation on VWF fibers correlated with a prothrombic state associated with decreased a disintegrin-like and metalloproteinase with thrombospondin type I repeats 13 (ADAMTS13) activity in cancer patients.

The association between cancer and thromboembolism was first described by Trousseau more than 100 years ago, when he made the astute observation that patients with unexplained thrombosis sometimes had an occult malignancy.[2] The frequently observed prothrombic state in cancer patients encompasses a broad variety of complications, ranging from thrombotic microangiopathy to deep vein thrombosis. The pathophysiology of cancer-associated thrombosis is rather complex, but can be linked to 3 major features: stasis, vascular injury, and hypercoagulability, according to the criteria of so-called Virchow triad.[3] Vascular alterations are frequently observed both in the primary tumor and at metastatic sites. Increased presence of VWF in the circulation correlates with endothelial damage and is used as an indicator for many pathological situations, including atherosclerosis, cardiovascular disease, and cancer.[4] VWF forms polymer fibers attached to the luminal endothelial cells that contribute to hemostasis-mediating platelet adhesion. This process is normally controlled by the plasma metalloprotease ADAMTS13.[4] However, VWF fibers also promote platelet aggregation, which may result in pathophysiological thrombi formation and vessel occlusion.[5] In the current work, Bauer et al[1] show that VWF fiber formation and the associated platelet aggregation is detected both in primary tumors of melanoma patients and in a mouse melanoma model. Although a clear increase in VWF fiber formation was detected in melanoma patients, there was a small but significant decrease in ADAMTS13 in the tumors. However, enhanced VWF fiber formation in mouse melanoma tumors was associated with a clearly reduced ADAMTS13 activity. Consequently, intravenous infusion of recombinant ADAMTS13 significantly reduced luminal fiber formation in mouse tumors.

What causes endothelial damage during cancer progression that results in enhanced thromboembolism is still heavily debated. It is well known that a variety of procoagulant factors secreted by tumors such as tissue factor, thrombin, VEGF, mucins with selectin binding sites, or tumor necrosis factor has been shown to be abnormally raised during cancer and is linked to a prothrombic state in patients.[2,3,6] In addition, these factors have been shown to trigger thrombosis in a variety of animal cancer models. In particular, VEGF is the primary factor inducing angiogenesis and therefore both physiological and pathophysiological activation of the endothelium. Previously, thrombin release by melanoma cells was shown to induce endothelial activation associated with VWF deposition in the vascular lumen.[7] Bauer et al now provide evidence that tumor-derived VEGF causes endothelial activation, resulting in enhanced VWF fiber deposits in the vasculature and thereby inducing platelet aggregation and thrombosis.

There is abundant literature on the use of heparin and low-molecular-weight derivatives (LMWH) in cancer patients. However, there is accumulating evidence that heparins have cancer inhibitory activity that goes beyond just anticoagulation.[8] Although a rigorous evaluation of heparin or LMWH on inhibition of cancer progression is still missing, virtually all animal models confirmed beneficial effects of heparin or LMWH on cancer progression.[9,10] Because of the complex biological nature of heparins, they can affect several potential mechanisms involved in metastasis, including cell adhesion through selectins, enzymatic activity of heparanase, or the activity of growth factors and cytokines. The study by Bauer et al[1] now provides evidence that LMWH tinzaparin directly binds to VEGF and thereby reduces melanoma-induced endothelial activation associated with VWF fiber formation. These findings show yet another mechanism for how heparins may interfere with endothelial activation and angiogenesis. Long-term tinzaparin treatment of transgenic mice,