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RESEARCH HIGHLIGHT

Bone's dark side: mutated osteoblasts implicated in leukemia

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Bone-lining osteolineage cells were previously implicated as contributors to hematological disorders and malignancies. A recent report in *Nature* now demonstrates that a specific mutation in mouse collagen-expressing osteoblastic cells leads to MDS and AML with 100% penetrance and is associated with strikingly similar findings in human patients.

Bones are central to mammalian life in part because they are the place where the vast numbers of blood cells needing replacement each day are generated. All blood cells are derived from hematopoietic stem cells (HSC) that reside and are maintained in specific microanatomical domains in the bone marrow, the 'HSC niches'. This HSC local microenvironment is functionally created by mesenchymal stromal cells and endothelial cells some of which are adjacent to the endosteal margins [1]. However, deregulation of the protective bone marrow microenvironment is now implicated in mouse models of hematopoietic neoplasms [2-5]. The role of specific mesenchymal cells in the bone marrow hematopoietic niche was first demonstrated *in vivo* by studying genetically engineered mice with transgenes under the control of the collagen type I α1 promoter (Col1) [6]. These studies pointed toward a regulatory role for osteolineage cells in modulating the number of hematopoietic stem/progenitor cells (HSPC). More recent studies suggest that the role of mature osteolineage cells is in the regulation of lineage-restricted progenitor cells and they only indirectly affect HSC behavior. Mesenchymal cells with osteolineage potential, but no clear evidence of osteoblast specification, residing in perivascular position are more directly involved in the maintenance of HSC.

Perturbations of osteolineage cells are now implicated in disordered function of HSPC [4] and recent work by Kode and colleagues [7] implicates constitutively active β-catenin in osteoblasts as a driver of acute myeloid leukemia (AML). The authors analyzed mice in which a stabilized form of β-catenin is expressed under the control of a restricted portion of the Col1 promoter, active in osteoblastic cells which includes cells that are not fully mature osteoblasts. Strikingly, all mice were born with a severe hematological disorder resembling myelodysplastic syndrome (MDS) that rapidly progressed to AML. Extensive genetic studies of the myeloid blasts revealed recurrent chromosomal alterations and somatic mutations commonly associated with human MDS and AML. In a series of cell context-dependent experiments, the authors elegantly demonstrated that the immuno-phenotypically defined HSC (SLAM-LSK: Lin^-, $Sca1^+$, $c\text{-}Kit^+$, $CD150^+$, $CD48^-$) are the leukemia-initiating cells in this model, being the only cell population able to transfer the disease in a transplant study. Gene-expression analysis of the mutated osteoblastic cells identified the membrane-anchored Notch ligand, Jagged1, as a potential mediator of the transformation. Active Notch signaling was observed in, and restricted to, the SLAM-LSK leukemia-initiating cells, and not detected in any other hematopoietic population. Additionally, monoallelic deletion of Jagged1 from the mutated osteoblastic cells rescued the malignant phenotype and the animals were free from hematological disorders. Most importantly, the authors linked their finding to the clinic and report that 38% of bone marrow biopsy samples obtained from MDS/AML patients were positive for nuclear β-catenin staining in osteoblasts, with a perfect correlation to Notch activation in their hematopoietic cells. Based on these findings, the authors propose nuclear β-catenin staining in osteoblasts as a new prognostic marker.

These studies raise important issues about the leukemogenic process and provide avenues for therapy extending beyond current approaches. In terms of basic biology, the idea that a microenvironment comprised of mesenchymal, endothelial and neural cells may alter cell fate has many precedents in both normal development and in disease models. Mesenchymal, endothelial and neural cells are known as central drivers of organ formation, patterning and size, and specific morphogens produced by such 'stromal' cells influence the differentiation of parenchymal cell types. Disturbing 'stromal' (or at least non-hematopoietic) cells has been shown to either cooperate with genetic lesions in hematopoietic cells [2] or be sufficient [3] to drive myeloproliferative neoplasia. Gaining greater resolution of what specific cell types in the microenvironment might engender neoplasia, it was

shown that disrupting miRNA processing or ribosomal components in osteolineage progenitors expressing osterix, but not mature osteoblasts (expressing osteocalcin), induced myelodysplasia and the rare emergence of AML [4].

The Kode study points to very specific alteration in the expression of a ligand for the Notch morphogen by osteoblastic cells as a driver of leukemia. While the link between osteoblastic cell dysfunction and HSC leukemia seems in conflict with the emerging sense of osteoblastic cells as more related to progenitor regulation, the dissonance may not be substantial. Firstly, the association of increased Jagged1 expression in osteoblastic cells and Notch activation in SLAM-LSK cells does not mean the interaction was direct. Altered osteoblastic cells may well alter Notch ligand expression in a host of other bone marrow cell types including those more directly implicated in HSC regulation such as Nestin-, LepR- or Prx1-expressing cells [1]. Also, the HSC markers on leukemia-initiating cells does not necessarily mean that the originally transformed cell was a HSC. Altered gene expression is common in cancer cells and progenitors could well have acquired or re-activated expression of the HSC-associated SLAM-LSK signature. Perhaps more perplexing is the role of Notch in the emergence of the AML in this model. The Notch signaling pathway plays a pivotal role in the regulation of many fundamental cellular processes and in hematopoiesis is a key mediator of lineage specifying events. These are most prominent in lymphoid cell generation, but are also implicated in myeloid differentiation, specifically in megakaryocytes and in myeloid progenitor proliferation [8]. In leukemia, Notch activation is well known to drive T-cell acute lymphoid leukemia [9]. Its role in myeloid leukemias, however, is less clear. The canonical Notch response element RBPJ has been implicated in the transformation of megakaryocytes, leading to acute megakaryoblastic leukemia, with a Notch pathway signature [10]. In contrast, elegant studies by the group of Aifantis and others identified somatic inactivation mutations of the Notch pathway in chronic myelomonocytic leukemia and in AML and demonstrated that Notch reactivation induces differentiation and apoptosis of leukemic cells [11, 12]. Whether these differences with the Kode study are related to different subgroups of patients is not clear and requires further clarification with future work.

Overall, the work of Kode and colleagues is an intriguing demonstration of how microenvironment perturbations can be at the center of malignant processes in the tissue where this can be most readily studied, the bone marrow. It offers new insight into molecular mechanisms by which cross-talk between heterotypic cells can result in malignancy and thereby offers the possibility of targeting such interactions as a means to disrupt cancer formation or maintenance. Further validation of the findings by Kode *et al*. and testing the ability to extend them to therapeutics will surely follow shortly. They may give credence to the longstanding notion of niche-directed therapies.

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