blood® commentary

MYELOID NEOPLASIA

Comment on Inaba et al, page 2891

Puzzling pieces of chromosome 7 loss or deletion

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In this issue of *Blood*, Inaba et al review the challenges and questions to be answered in the molecular and functional dissection of loss of chromosome 7 (monosomy 7 [−7]) and deletion of a segment of the long arm (del(7q)) found in patients with various syndromes involving the myeloid blood cell lineage.[1]

Large hemizygous deletions that may be drivers of cancer are found in various types of tumors. −7 and del(7q) are recurrent cytogenetic abnormalities that are strongly associated with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) with adverse outcome (eg, in AML with chromosome 3q26 abnormalities and aberrant *EVI1* expression).[2] They also occur in cases of MDS and AML that arise in a number of other contexts, including occupational exposure to mutagens, following aplastic anemia, or in certain germ line predisposition syndromes.

The similar biological and clinical features of patients with different antecedent risk factors raises the question whether the alteration of 1 common gene on 7q is particularly responsible for the pathogenesis of all of these myeloid disorders. Cytogenetic and fluorescent in situ hybridization analyses identified 2 commonly deleted regions (CDRs) in patients with myeloid disorders with chromosome 7 loss or del(7q), 1 located in band q22 accounting for most cases and a second segment in bands q32-33. These data are consistent with the hypothesis that recessive mutations, which inactivate tumor suppressor genes within these CDRs, contribute to leukemogenesis in patients with −7 or del(7q). Targeted sequencing of candidate myeloid tumor suppressor genes located within a 2.5-Mb 7q22 CDR delineated by Le Beau et al and recent comprehensive genomic analyses of clinical specimens implicate a haploinsufficient role of 7q22 deletions in leukemogenesis.[1,3] Consistent with the proposed mechanism, biallelic inactivation of any 7q gene is rare in MDS patients with −7/del(7q), and haploinsufficiency seems to be the pathogenic mechanism. Given the number of genes involved and also various biallelic or monoallelic mutations, as also reviewed in Inaba et al, the question remains if the pathophysiology is more complex than just haploinsufficiency for 1 or multiple genes. Moreover, it is possible that not just a single mechanism can explain the effects caused by either −7 or 7q− aberrations in the different types of myeloid disorders.

CDRs provide a starting place for the search for critical genes in the clinical phenotype and disease pathogenesis. In del(5q) MDS, a functional RNA interference screen identified *RPS14* as a critical gene responsible for pathognomonic anemia and the erythroid differentiation defect.[4] Additionally, murine models of heterozygous inactivation of candidate genes provided a critical demonstration of the effects of haploinsufficiency for a gene in vivo in del(5q) MDS.[5,6]

Inaba et al describe in their review the various efforts made in −7/del(7q) over the decades, which ultimately led researchers to accept that the identification of CDRs as the first approach to determine classical-type recessive tumor suppressors, was not effective. This most likely reflects the multitude of potential myeloid tumor suppressor genes that may act in a haploinsufficient manner, driving the development of myeloid disorders. In contrast to del(5q), where the focus has been on identifying the central pathogenic genes for the distinct clinical phenotype, studies in −7/del(7q) have focused on directly analyzing the biological effects of large segmental loss of the chromosome.[7,8] These studies make investigators wonder whether combinatorial haploinsufficiency of many genes on chromosome 7 is responsible for the aberrant behavior of hematopoietic stem and progenitor cells (HSPCs).

Inaba et al describe in detail genes located at chromosome 7 that may play a critical role in the disease phenotype and pathogenesis and discuss their role in myeloid malignancies: *SAMD9* and *SAMD9L*, *EZH2*, *MLL3*, and *CUX1*. A recent study demonstrated that heterozygous *SAMD9L* missense mutations are found in patients of familial MDS (reviewed in Inaba et al). Inherited cancer syndromes have greatly contributed to basic concepts of tumor biology (eg, leading to the "2-hit" hypothesis by Knudson and providing the concept of "multistep" carcinogenesis by Vogelstein and Kinzler). Importantly, a recent study on childhood MDS demonstrated that mutated *SAMD9L* alleles were lost in MDS cells. Thus, instead of representing malignancy-predisposing mutations of tumor suppressor genes in the classical sense, gain-of-function mutations in *SAMD9* or *SAMD9L* together provide the first human examples of "adaptation by aneuploidy." This means that HSPCs that eliminate *SAMD9* or *SAMD9L* gain-of-function mutations through aneuploidy gain a competitive advantage, simultaneously predisposing to MDS (see Figure 2

in Inaba et al). This represents an intriguing new paradigm in malignant transformation and also adds additional complexity to dissecting the disease pathogenesis in −7/del(7q).

Based on their literature review, Inaba et al hypothesize that −7/del(7q) can be an early event in HSPCs. They picture 2 scenarios: (1) an unperturbed environment and (2) a perturbed environment. They reason that in scenario 1 (in a normal HSPC and normal bone marrow), the −7/del(7q) clone has a relative growth advantage over normal HSPCs in the bone marrow and sequentially acquires secondary genetic or epigenetic events. In scenario 2, during bone marrow failure, hematopoietic stem cells are embedded in an inflammatory environment (cytokines). Here, aneuploid stem cells with haploinsufficiency of multiple genes implicated in the regulation of DNA damage checkpoints, the cell cycle, and apoptosis facilitate the accumulation of additional mutations and aberrant expansion, ultimately leading to leukemogenesis.

Notably, data obtained so far are correlative. Dissecting how abnormalities affecting large chromosomal regions mechanistically give rise to distinct cancers is challenging. Future efforts need to focus on validating findings in greater numbers of patients, in addition to identifying more definitive causal relationships between genes and function. Additional single-cell studies and gene editing using CRISPR/Cas9 in HSPCs will be instrumental in delineating how distinct chromosomal abnormalities interact with additional gene mutations to determine the stepwise transformation to leukemia. These studies will also help in dissecting gene targets for targeted therapies.

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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Huang et al, page 2955

Lipid metabolism in terminal erythropoiesis

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In this issue of *Blood*, Huang et al have provided evidence that altered lipid metabolism is critical for terminal erythropoiesis. A key role is proposed for the *PHOSPHO1* gene product, a phosphocholine phosphatase. *PHOSPHO1* knockouts (KOs) showed reduced erythroblast proliferation and enucleation in both mice and human erythroid tissues, apparently through energy depletion mediated via inhibition of oxidative phosphorylation of fatty acids and reduced adenosine triphosphate (ATP) production in late glycolysis. This work emphasizes that altered expression of genes involving lipid metabolism are important during late red cell maturation.[1]

The mature red cell is unique. Although highly specialized for gas transport, it is much more than an inert receptacle for hemoglobin, with many surprisingly sophisticated properties. Among these, the subtle control of glucose metabolism, cytoskeletal integrity, and membrane permeability by oxygen tension has recently been elucidated.[2] During maturation, the developing red cell must both proliferate and undergo considerable modifications to acquire the necessary properties to survive in the circulatory system, where it lacks the ability to synthesize proteins de novo while experiencing profound challenges such as repeated episodes of shear and oxidative stress. Many important changes occur during later erythrogenesis, including loss of the nucleus, shedding of surface markers, establishment of the final surface area/volume ratio, and establishment of a robust but malleable cytoskeleton.[3]

Our understanding of the processes occurring during erythropoiesis remains partial. Much is known about globin gene switching, which is of particular relevance to a number of the common hemoglobinopathies.[4] Some other nonglobin protein changes have also been well studied. These include accumulation of cytoskeletal elements with condensation of spectrin, increased expression of band 3, and acquisition of other requisite membrane transporters.[3] Mutations in these proteins are relatively rare, but are sometimes associated with hemolytic anemia and irregularities in red cell shape or volume (such as stomatocytes and spherocytes).[5] Elucidation of their molecular causes continues to improve our understanding of red cell physiology.

Diseases involving altered lipid metabolism are arguably less well characterized. As for those involving protein transporters, they can be secondary (ie, subsequent to other diseases). An obvious example here is loss of aminophospholipid asymmetry in a number of hemoglobinopathies such as sickle cell disease.

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