Comment on Shaham et al, page 1292, and Wang et al, page 1302

A 2-way miRror of red blood cells and leukemia

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In this issue of Blood, the articles by Shaham et al1 and Wang et al2 are the first to identify microRNA 486 (miR-486) as a requisite oncomiR and credible therapeutic target in myeloid leukemia of Down syndrome (ML-DS) and chronic myeloid leukemia (CML) by showing that these 2 leukemias co-opt miR-486 functions in normal erythroid progenitor progrowth and survival activity.

The figure summarizes these 2 independent reports, which delineate the mechanisms leading to the aberrant overexpression of miR-486 in ML-DS and CML (panel A). Their highlights are described in greater detail below. In sum, the articles clearly demonstrate that miR-486 directs erythroid differentiation of normal hematopoietic cells involving activation of the AKT pathway (panel B), which is mirrored by a similar erythroid phenotype signaled through miR-486/AKT in leukemia cells that also acts to promote cell survival (panel C). The extensive and congruent results using human and mouse in vivo and in vitro models combined with primary human leukemia and normal hematopoietic cells underscore the importance of miR-486 as a conserved mediator of erythropoiesis and leukemogenesis. Moreover, these studies provide the initial proof of principle for miR-486 as a therapeutic target in CML and ML-DS, laying the groundwork for follow-up in vivo preclinical testing.

Infants and children with Down syndrome (DS) have significantly increased risk of developing transient myeloproliferative disorder (TMD), which sometimes transforms to myeloid leukemia (ML-DS), the most common subtype being acute megakaryoblastic leukemia (AMKL).3 Acquired somatic mutations in the megakaryocyte/erythroid-lineage specifying transcription factor GATA1 generate a short isoform (GATA1s) that cooperates with trisomy 21 early on in the evolution of TMD and ML-DS.4 Reported herein, microRNA (miRNA) expression analyses on bone marrow from patients with ML-DS, non-DS AMKL, or remission samples led to the discovery by Shaham et al that miR-486 is uniquely overexpressed in ML-DS patients (panel A). On the other hand, Wang et al independently discovered that miR-486 is the most highly expressed miRNA in their cohort of patients with CML, a molecularly, pathologically, and phenotypically distinct myeloid neoplasm from ML-DS. The Philadelphia chromosome t(9;22) rearrangement generating the BCR-ABL tyrosine kinase fusion protein is the most common and the earliest initiating event in CML pathogenesis.

What is driving miR-486 expression? Because GATA1 mutations are exclusively found in ML-DS, the expression pattern of miR-486 hinted that GATA1s might be its upstream regulator in normal and malignant hematopoiesis. Indeed, Shaham et al uncover that (1) miR-486 is encoded within the GATA1 target gene AKT1; (2) miR-486 positively correlates with GATA1s in primary ML-DS; and (3) miR-486 expression changes concordantly with manipulation of GATA1 or GATA1s in human ML-DS cell lines. Conversely, in CML, Wang et al find that expression of BCR-ABL leads to significant self-glycolipid. *Proc Natl Acad Sci USA.* 2010;107(24):10984-10989.


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A new link between miR-486 and erythroid differentiation is established, suggesting that miR-486 may work best as a combination therapy with the current standard of care. The authors declare no competing financial interests.

REFERENCES

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Comment on Malleret et al, page 1314

Bone marrow reticulocytes: a Plasmodium vivax affair?

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In this issue of Blood, Malleret and colleagues show the importance of the bone marrow in Plasmodium vivax biology by proving the preferential infection of young reticulocytes (generally restricted to the bone marrow), which then experience accelerated maturation postinvasion.

P. vivax mainly invades reticulocytes, a heterogeneous population of red blood cell precursors characterized by a reticular network of residual RNA, whose maturation is indicated by the decreasing expression of the transferrin receptor CD71. This host cell specificity shapes P. vivax pathobiology, and the strict requirement for reticulocytes has hampered the establishment of an in vitro culture system for this parasite. By sorting different developmental stages of cord blood reticulocytes for use in an ex vivo invasion assay, Malleret and colleagues show that P. vivax merozoites prefer the youngest of the young erythrocytes. The immature CD71+ reticulocytes, generally restricted to bone marrow, were more efficiently invaded than older CD71+ reticulocytes principally
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