To the Editor:

Recent studies on the development of the hematopoietic system have led to substantial progress in describing the variety of hematopoietic cells within the mammalian embryo, but have resulted in the nonuniform and confusing usage of the term hematopoietic stem cell (HSC). In its conventional and well-accepted usage, the term (definitive) HSC describes those cells at the foundation of the adult hematopoietic hierarchy that, upon transplantation, give rise to long-term, multilineage, high-level hematopoietic engraftment of adult recipients. However, within a developmental framework, unique challenges are presented in naming the hematopoietic cells of the embryo, because lineage relationships between the embryo and adult have not been established. We propose here a terminology that reflects our current but limited understanding of the embryonic and developing definitive hematopoietic hierarchies.

Confusion in the terminology appears to stem from the implicit belief that the embryonic hematopoietic hierarchy is identical to that in the adult. Because the yolk sac is the first hematopoietic site during development, it was assumed for many years that the first HSCs emerge there. Yolk sac-derived HSCs were thought to give rise to the primitive erythroid lineage and then sequentially migrate, expand, and differentiate into the definitive hematopoietic lineages in the fetal liver, spleen, and bone marrow. This convenient dogma suggested that the process of adult HSC differentiation might be applied to embryonic blood development. But how can HSCs differentiate into the first yolk sac erythrocytes (7.5 day postcoitum [dpc]) within 1 day after mesoderm formation (6.5 dpc), when it is assumed that in the adult it takes weeks to months for the HSCs to generate mature red blood cells? The most convincing evidence indicating that the embryonic hematopoietic hierarchy is constructed differently from that of the adult is that a variety of lymphoid and hematopoietic progenitors are detected in the embryo before the first definitive HSCs emerge. The first HSCs capable of giving rise to complete hematopoietic engraftment of adult recipients appear in the embryo only by the end of 10 dpc within the aorta-gonad-mesonephros (AGM) region. These observations in the mouse embryo indicate that such a concept of the yolk sac origins of adult HSCs might not necessarily be correct and indicate that, as with other embryonic tissues, the rudiment of the hematopoietic system is not simply a small model of the adult tissue. Indeed, the molecular genetic program supports this notion; the definitive blood system requires some gene products, eg, β1 integrin or AML1, that are not necessary for normal yolk sac hematopoiesis.

So, how does it happen that embryonic blood cells differentiate in the absence of definitive HSCs? One idea is that, during development,
ALK with the recurrent translocation t(2;5)(p23;q35) that results in activation of the anaplastic lymphoma kinase (ALK) gene at 2p23 by fusion to the ALK, ubiquitously expressed gene encoding the nucleolar phosphoprotein nucleophosmin (NPM) at 5q35. This translocation leads to aberrant nuclear (and cytoplasmic) expression of ALK, which is normally silent in hematopoietic tissues.\(^1,2\)

Approximately 20% of ALK-positive ALCLs do not express ALK in its native context, suggesting it is induced by the translocation. The ALK expression leads to the development of anaplastic large-cell lymphoma (ALCL), a type of lymphoma characterized by large, pleomorphic cells with abundant cytoplasm and a high nucleus/cytoplasm ratio.

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Anaplastic large-cell lymphoma (ALCL) is frequently associated with the recurrent translocation t(1;2) with TPM3-ALK fusion gene due to cryptic ALK gene rearrangement in anaplastic large-cell lymphoma. Complex Variant Translocation t(1;2) With TPM3-ALK Fusion Due to Cryptic ALK Gene Rearrangement in Anaplastic Large-Cell Lymphoma

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Development of the Hematopoietic Stem Cell: Can We Describe It?

Alexander Medvinsky and Elaine Dzierzak