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On the origin of blood cells - Hematopoiesis revisited

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Faiyaz Notta and his colleagues from Dr. John Dick's group in Canada recently published an elegant study of blood cell development in *Science* (Notta et al., 2015) (Notta et al., 2015). Their data suggest that a different model from the prevailing one may explain the origin of diverse cells found in blood. This involves hematopoiesis, a term derived from two Greek words: *haima* (blood) and *poi sis* (to produce something). The process occurs in bone marrow (BM) and other organs: liver and umbilical cord in the fetus, and spleen in species like mice. In BM, hematopoietic stem cells (HSCs) give rise to all blood cell lineages (Al-Drees et al., 2015, Barminko et al., 2015, Ogawa, 1993).

The formation of blood cells from HSCs moves through a series of more and more differentiated (and "committed") progenitor cells--a hematopoietic hierarchy (Ackermann et al., 2015). An excellent review of the history of the discovery of blood stem cells was written by Ramalho-Santos and Willenbring (Ramalho-Santos & Willenbring, 2007). A brief summary follows:

In the early 1960s, Till and McCulloch showed that there is a population of bone marrow cells in animals that can repopulate the BM if one destroys it with lethal irradiation, for example (Till et al., 1964). Subsequently, it was discovered that such stem cells circulate in the blood too, and in the 1990s methods were developed that allowed these cells to be purified so that they could be transplanted into human patients (Bensinger et al., 1996, Shpall et al., 1999). The technique relied on boosting stem cell numbers in the blood of donors by treating them with cytokines that drive the exit of progenitors from BM and their entry into blood. The discovery, characterization, and use of multipotent stem cells that can give rise to a variety of blood cells has allowed previously fatal diseases to be treated.

Characterization of stem- and progenitor-cells in BM has relied on specific surface markers that allow subpopulations of cells to be isolated using Fluorescence Activated Cell Sorting (FACS) (Akashi et al., 2000, Kondo et al., 1997). In vitro assays (Colony Forming Unit or CFU assays) are used to learn what kinds of cells the isolated progenitors produce. Such assays have revealed the lineage potential of progenitors in defined environments. (Cytokines and growth factors affect the outcome of such analyses.) It is thought that subsets of BM cells isolated by FACS using antibodies directed against specific sets of surface markers are functionally homogeneous (Manz et al., 2002), and based on this, a cellular

hierarchy, which is pyramidal in shape, has been suggested to account for the development and expansion of blood cell lineages (Fig.1 A). According to this model, oligopotent HSCs that spawn all blood cell types differentiate into a variety of multipotent progenitors that are capable of giving rise to several, but not all, of these blood cells. Multipotent progenitors, in turn, generate unipotent cells that can only differentiate into a single blood cell lineage. Although several groups have questioned specific details of the model outlined above (Adolfsson et al., 2005, Mansson et al., 2007) no one until now has tried to re-evaluate (and re-imagine) the whole process. This is what Notta and his colleagues set out to do. They obtained samples of fetal liver, umbilical cord blood, and bone marrow aspirates from normal subjects and patients with aplastic anemia, and developed a novel cell sorting method that appears to resolve myeloid, erythroid and megakaryocytic lineages produced from single CD34+ progenitor cells. They went on to create an assay that allowed them to evaluate the lineage potential of single sorted cells, and an expression profiling technique that could be applied to thousands of HSCs and progenitors isolated from cord blood.

Based on the work they did, they concluded that 1) the cellular hierarchy of human blood elements changes during development, and 2) in contrast to the present view, there are no intermediate oligopotent progenitors. Instead, after the megakaryocytic lineage branches off, three unilineage progenitors are left. These give rise to erythroid, myeloid and lymphoid cells, respectively (Fig.1B).

If these findings are confirmed, bone marrow stem cell populations must be much more heterogeneous than we thought they were, and we will have to account for the newly revealed complexity. We will also have to review data in the literature to see if we need to revise our interpretation of them based on this newly discovered hierarchy of blood progenitors.

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Significance of the finding

1. Notta's data should contribute to a better understanding of hematological diseases--genetic and/or epigenetic ones.
2. A more accurate description of blood cell lineages should help scientists isolate cells that can be used in regenerative medicine using iPS (induced pluripotent stem cell) technology (Yamanaka, 2007). We should soon be able to manufacture red blood cells and platelets that can be given to patients who are deficient in these blood elements, and identifying the exact precursors of erythrocytes and megakaryocytes will accelerate this effort.
3. Being able to isolate lineage-specific blood cell progenitors will facilitate repairing genetic defects in patients using CRISPR-based methods (Doudna & Charpentier, 2014). It is likely to be important to target specific cell populations when DNA is edited.

Figure 1.

A. Conventional depiction of human hematopoiesis

The oligopotent HSC (hematopoietic stem cell) is at the top of the pyramid. (This cell can reproduce itself and differentiate into all lineages.) MPP cells are multipotent progenitors with limited self-renewal and multilineage reconstitution capacity. They give rise to the common myeloid progenitor (CMP) and the common lymphoid progenitor (CLP) that generates lymphocytes (Ly). CMPs differentiate into megakaryocyte (Mk)/erythroid (Ery) progenitor cells (MEPs) and granulocyte (Gr)/ monocyte (Mon) progenitors (GMP). According to this hypothesis, multipotent, oligopotent and then lineage-restricted cells are derived gradually, one after another, from HSCs.

B. New hypothesis of human adult hematopoiesis

The oligopotent HSC first gives rise to the Mk lineage and multipotent MPP cells. The latter give rise to three unipotent lineages: the erythroid (Ery), myeloid (My) and the monocytic/ lymphoid (Mono-Ly) lineages.