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An Outline of the Outset of Thrombopoiesisin Human Embryos At Last

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By single-cell transcriptome profiling of human yolk sacs and fetal livers, Wang et al. (2021) (in this issue of Cell Stem Cell) track two alternative routes for differentiation of megakaryocytes. The authors have shown that these megakaryocytes have hemostatic- and HSC-supporting functions, and that hESC-derived thrombospondin1-positive endothelial cells are capable of generating megakaryocytes *in vitro*.

Due to ethical and practical limitations, studies on the outset of hematopoiesis in human embryos have been limited. Prior anatomical studies of human embryos identified the sequential recruitment of the yolk sac and liver as hematopoietic sites during embryogenesis. Subsequently, thanks to hemoglobin being recognized as a user-friendly marker for histological investigations, red cell development was shown to occur in two waves: primitive erythropoiesis, occurring in yolk sac, and definitive erythropoiesis, in the liver (Migliaccio et al., 1986). These early morphological studies also identified the presence in the yolk sac and liver of significant numbers of neutrophils, monocytes, and macrophages, and occasional eosinophils, megakaryocytes, and B cells with the great majority (50%) of the hematopoietic cells present in these organs being blast cells whose lineage was not definable due to the limited technology available at that time. During the 1990s, umbilical cord was shown to contain hematopoietic stem cells (HSCs) in numbers sufficient to serve as grafts for human allogeneic stem cell transplantation (Ballen et al., 2013). These observations prompted studies aimed to identify the embryonic origin of definitive HSCs. Lineage-tracing markers in mice identified that definitive HSCs arose in the aorta-gonad-mesonephric region of embryos from hemogenic endothelium, which gives rise, by asymmetric division, to resident endothelial cells (ECs) and HSCs, which are released into the blood and subsequently colonize the liver (Dzierzak and Bigas, 2018). The Peault laboratory then described the presence of definitive HSCs in the aorta-gonad-mesonephric region of human embryos that were capable of colonizing adult xenografts and reported that definitive HSCs were derived from hemogenic endothelium and resembled those observed in mouse embryos (Zambidis et al., 2005). By using advanced cytofluorimetry, Wang et al. (2021) (in this issue of Cell Stem Cell) have confirmed prior reports of erythroid differentiation in human embryos

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and identify that as many as 10% of cells present in the yolk sac and liver from these early embryos are megakaryocytes. More importantly, thanks to the power of single-cell transcriptomic profiling, they identify a subset of megakaryocytes unique to the yolk sac, which suggests that they are derived from primitive HSCs and, therefore, represent the equivalent of primitive erythroid cells. They also provide profiling data indicating that the definitive megakaryocytes from the liver form six clusters, two immature and four mature subpopulations. Lineage tracking analyses identified that the four more mature population clusters belong to two branches, one containing cells with high expression of GATA1 and genes involved in pro-platelet formation, and the other containing cells expressing low levels of GATA1 and high levels of genes involved in extracellular matrix formation and the TGF-b response. The authors hypothesize that the two branches track two alternative differentiation routes, one generating platelet-forming megakaryocytes, and the other generating megakaryocytes that contribute to the formation of rudimentary HSCs niches. The authors also identify a subpopulation of thrombospondin1- positive ECs derived from human embryonic stem cells (hESCs) that, following induction, differentiate into megakaryocytes and propose that these cells might represent a source for producing in vitro platelets that might ultimately serve as a transfusion product. seminal observations that have important implications. First, two differentiation tracks for megakaryocytes exist, which lead to the formation of cells that exert either pro-hemostatic or HSC-supportive functions.

These findings are consistent with the emerging hypothesis that megakaryocytes exert organ-specific functions (Pariser et al., 2021) and mandate a re-classification of mature megakaryocytes, a process that will require future studies to detail the functions of the different populations and events that regulate their differentiation.

Second, the description of hESCderived ECs that are capable of generating megakaryocytes in vitro provides clues on how the outset of hematopoiesis in the liver is orchestrated. In fact, the timing at which thrombospondin1-positive ECs are detected in hESC culture (day 5) is similar to when hESCs generate the hemogenic endothelium (Zambidis et al., 2005), suggesting that the hemogenic endothelium gives rise at the same time to HSCs and to ECs posed to generate niche-forming megakaryocytes, motile cells that may reach the liver. Unfortunately, Wang et al. (2021) provide little information on whether thrombospondin1-positive ECs are present in human embryos (ideally they should be found in the aorta-gonad-mesonephric region), and they do not further define the relationship between their hESC-precursors and the hemogenic endothelium that generates definitive HSCs (Zambidis et al., 2005). It is also unclear whether thrombospondin1- positive ECs have the potential to generate, in addition to platelet-forming megakaryocytes, niche-forming megakaryocytes. It is however tempting to speculate that the hemogenic endothelium of the aorta-gonad-mesonephric region is responsible for generating both definitive HSCs and the precursors (thrombospondin1-positive ECs) of a supportive megakaryocytic HSC niche.

Finally, although the manuscript contains few data on adult megakaryocytopoiesis, the hypothesis that thrombospondin1-ECs are capable of generating HSC-supportive megakaryocytes that persist in adults would clarify the current puzzling data dealing with the origin of the Philadelphia-negative myeloproliferative neoplasms (MPNs). The MPNs are a group of blood cancers characterized by the hyperproliferation of hematopoietic cells of

one or more lineages in extramedullary organs and are driven by spontaneous mutations in genes involving the thrombopoietin/JAK2 axis at the level of a single HSC clone (Zahr et al., 2016). It has been recently hypothesized that the mutations that underlay these neoplasms induce abnormalities in both hematopoietic cells and microenvironmental cells (Malara et al., 2018). Two cell populations are thought to be responsible for driving MPN development: JAK2V617F-positive megakaryocytes, which remain immature and represent a pro-fibrotic phenotype very similar to that expressed by the niche-forming megakaryocytes described by Wang et al. (2021) (Malara et al., 2018), and JAK2V617F-ECs found in the blood vessels, liver, and spleen of MPN patients (Sozer et al., 2009). The data by Wang et al. (2021) provide a platform for a more complete understanding of the origins of hematological malignancies, suggesting that, as recently demonstrated by Williams et al. (2020), the JAK2V617F mutation may be first acquired during fetal development while the actual MPN phenotype only becomes apparent during adulthood. The confluence of these observations suggests that some hematological malignancies may actually arise during fetal development due to events that generate both malignant HSCs and malignant-thrombospondin1-ECs. Such a working hypothesis would account for the niche-forming megakaryocytes that prompt malignant HSC expansion in extramedullary sites as well as the prothrombotic tendencies that characterize the adult MPNs.

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