Identification of Multipotent Progenitors that Emerge Prior to Hematopoietic Stem Cells in Embryonic Development.

Journal: Stem Cell Reports

Publication Year: 2014

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PubMed link: 24749071

Funding Grants: Antibody tools to deplete or isolate teratogenic, cardiac, and blood stem cells from hESCs, Stanford CIRM Training Program

Public Summary:
Hematopoietic stem cells (HSCs), which give rise to all blood and immune cells, are used routinely in the clinic to treat patients with cancer or other blood disorders. Despite their widespread utility, HSC transplantation (HSCT) is rarely performed because of the dangers associated with ablating a patient's own blood system prior to transplantation. As such, there is considerable interest in using stem cell technology to generate therapeutic HSCs from pluripotent stem cell lines. However, this has yet to be robustly and reproducibly achieved. To solve this technological hurdle, a better understanding of the pathway by which HSCs arise naturally in embryonic development is needed. Specifically, the cellular precursors to HSCs need to be identified and characterized. We hypothesized that embryonic HSC precursors would possess the ability to form all blood cell types (red blood cells, platelets, innate immune cells, and adaptive immune cells), and developed an assay to screen candidate mouse embryonic cells for this multilineage potential. We identified a group of cells that can each individually give rise to all major blood lineages both in culture and upon transplantation. We found these multipotent cells in multiple regions in the embryo, but they appear first and are most abundant in the yolk sac, a tissue outside the main body of the embryo, suggesting that many of these multipotent cells originate here. With the identification of a clearly defined population of multipotent cells that appear prior to the emergence of HSCs in embryonic development, we can now begin to dissect the molecular events that may allow these putative HSC precursors to mature into functional adult HSCs. This will get us one step closer to our ultimate goal of generating HSCs from pluripotent stem cells.

Scientific Abstract:
Hematopoiesis in the embryo proceeds in a series of waves, with primitive erythroid-biased waves succeeded by definitive waves, within which the properties of hematopoietic stem cells (multilineage potential, self-renewal, and engraftability) gradually arise. Whereas self-renewal and engraftability have previously been examined in the embryo, multipotency has not been thoroughly addressed, especially at the single-cell level or within well-defined populations. To identify when and where clonal multilineage potential arises during embryogenesis, we developed a single-cell multipotency assay. We find that, during the initiation of definitive hematopoiesis in the embryo, a defined population of multipotent, engraftable progenitors emerges that is much more abundant within the yolk sac (YS) than the aorta-gonad-mesonephros (AGM) or fetal liver. These experiments indicate that multipotent cells appear in concert within both the YS and AGM and strongly implicate YS-derived progenitors as contributors to definitive hematopoiesis.