EXPERIMENTAL CELL RESEARCH ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/yexcr

Review Article

Cell signaling pathways involved in hematopoietic stem cell specification

*Albert D. Kim, David L. Stachura, David Traver**

Cellular and Molecular Medicine Section of Cell and Developmental Biology, University of California, San Diego 9500 Gilman Drive, Natural Sciences Building 6107, La Jolla, CA 92093-0380, USA

ARTICLE INFORMATION

Article Chronology:
Received 19 June 2014
Received in revised form
4 October 2014
Accepted 6 October 2014

Keywords:
Hematopoietic stem cells
HSCs
Developmental hematopoiesis
Hemogenic endothelium
Somites
Sclerotome
Signaling

Contents

*Corresponding author. Tel.: +1 858 822 4593; fax: +1 858 534 5457.
E-mail address: dtraver@ucsd.edu (D. Traver).

http://dx.doi.org/10.1016/j.yexcr.2014.10.011

Please cite this article as: A.D. Kim, et al., Cell signaling pathways involved in hematopoietic stem cell specification, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.011

Introduction

Generation of HSCs for regenerative medicine

Hematopoietic stem cells (HSCs) are self-renewing, tissue-specific stem cells that give rise to all mature blood cell types. The capacity of HSCs to reconstitute the entire adult hematopoietic system after transplantation makes them invaluable for the treatment of various blood disorders. A significant limitation of this treatment is the need for immune compatibility between donor and host, thus there has always been an acute need for reliable cultivation or generation of HSCs. The recently demonstrated ability to generate induced pluripotent stem (iPS) cells that resemble embryonic stem cells (ESCs) now make generation of HSCs from stem cells a realistic goal. To date, pluripotent stem cells have been instructed by a variety of experimental approaches to recapitulate waves of hematopoiesis such as primitive and transient definitive cells [1], myelomonocytic cells [2], and multilineage progenitors with lymphoid potential [3] (Fig. 1A). Surprisingly, concerted efforts to generate functional HSCs in vitro from pluripotent stem cells have thus far proven unsuccessful, indicating that our understanding of de novo generation of HSCs is insufficient [4] (Fig. 1B). Therefore, it is crucial to precisely characterize the mechanisms of cell signaling events that occur in vivo to form functional HSCs. Importantly, recent studies mapping the process of HSC generation in vertebrate embryos demonstrated that HSCs emerge from hemogenic endothelium present in the floor of the dorsal aorta (DA) [5–9]. For this reason, the generation of hemogenic endothelium likely represents a critical prerequisite for successfully generating HSCs in vitro. While many major cell-signaling pathways conserved throughout the animal kingdom have been demonstrated as requirements for DA and/or HSC formation, the molecular mechanisms that each required effector molecule exerts in this context is unclear. In this paper we summarize the roles of select cell-signaling pathways in HSC generation in the embryo and provide perspective on the in vitro instruction of HSCs fate for use in regenerative medicine.

Hematopoietic stem cell emergence in the vertebrate embryo

The HSCs that maintain homeostasis of the adult hematopoietic system are generated during embryogenesis, but are not the first blood cells to be formed in the embryo. HSC emergence is preceded by primitive and definitive waves that are defined by limited differentiation potentials. Primitive myeloid and erythroid cells are the first hematopoietic cells to emerge, but unlike adult blood progenitors, do not possess multilineage potential or the capacity to self-renew [10,11] (Fig. 1C). Following these primitive waves, the first transient definitive progenitors arise that possess multipotent erythromyeloid potential (EMPs) [10,12,13]. EMPs are similar to HSCs in that they have multilineage potential, but are separated by the fact that they do not possess lymphoid potential or the capacity to appreciably self-renew (Fig. 1D). The anatomical sites of emergence from which these waves arise vary according to species as shown by transplantation, imaging, and lineage tracing studies. The first three hematopoietic waves are found in the yolk sac in mammals and birds, in anterior/posterior ventral blood islands in frogs, and anterior/posterior lateral mesoderm in fish, the details of which are reviewed elsewhere [14,15]. In contrast, HSCs emerge from hemogenic endothelium within the floor of the dorsal aorta in a process termed endothelial to hematopoietic transition (EHT) in all vertebrate species analyzed [6,7,9,16] (Fig. 1E). Nascent HSCs have been defined by their

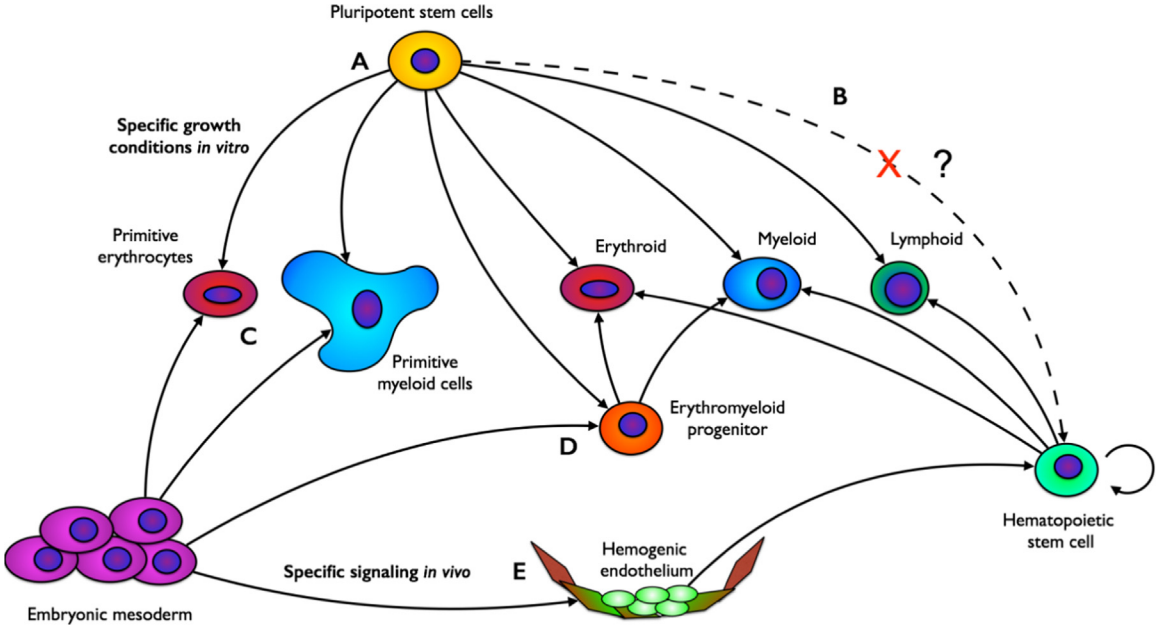

Fig. 1 – Pathways to hematopoietic differentiation in vitro and in vivo. (A) Pluripotent cells from embryonic or induced pluripotent sources have not been successfully instructed to hematopoetic stem cell fate (B), but have been successful in generating primitive (C) and transient definitive blood (D) cell fates. Embryonic hematopoiesis proceeds in four ordered waves with primitive erythroid and myeloid waves preceding a definitive EMP wave, and culminates with the establishment of adult definitive hematopoiesis through specification of hematopoietic stem cells via ventral aortic endothelium (E).

Please cite this article as: A.D. Kim, et al., Cell signaling pathways involved in hematopoietic stem cell specification, Exp Cell Res (2014), http://dx.doi.org/10.1016/j.yexcr.2014.10.011