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Review Article

Cell interactions and cell signaling during hematopoietic development

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ABSTRACT

Hematopoiesis is a key process that leads to the formation of all blood cell lineages from a specialized, multipotent cell, named the hematopoietic stem cell (HSC). During development, the embryo produces several waves of hematopoiesis that produce specialized subsets of hematopoietic cells. Tissue interactions and cell signaling play an essential role in developmental hematopoiesis by allowing the formation of hematopoietic and endothelial cells (ECs) from the mesoderm particularly in the yolk sac and by instructing the different generations of hematopoietic cells (HCs). The embryonic aorta is another site wherein tissue interaction is essential for the production of the first HSCs that is achieved from a specialized subset of hemogenic endothelial cells. This production is tightly time- and space-controlled with the transcription factor *Runx*1 and the Notch signaling pathway playing a key role in this process and the surrounding tissues controlling the aortic shape and fate. Here we shall briefly review how hemogenic EC differentiates from the mesoderm, how the different aortic components assemble coordinately to establish the dorso-ventral polarity resulting in the initiation of *Runx*1 expression in hemogenic EC and the initiation of the hematopoietic program through modulation of the Notch–*Runx*1 axis. These data should help elucidate the first steps in HSC commitment and bring further insights into the manipulation of adult HSCs.

Contents

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Introduction

Hematopoietic stem cells (HSCs) are specialized multipotent stem cells that emerge during early embryogenesis, whose functions are to maintain hematopoiesis throughout the entire lifespan of the organism. In the adult, HSCs are located in the bone marrow where they self-renew and differentiate to give rise to all blood cell lineages. However, despite at least two decades of intense investigations, their embryological origin remains controversial. It is well accepted that embryonic and fetal hematopoiesis are separated into three waves that occur at different times and locations. The first wave takes place very early during development *i.e.* Embryonic day (E) 7.25 [1] for the mouse embryo and at 19–22 h of incubation for the chick [2,3]. This wave gives rise to primitive erythroid cells, macrophages and megakaryocytes. From E8.9 in the mouse *i.e.* shortly after the onset of primitive hematopoiesis, the first definitive (adult-type) hematopoietic cells emerge from the yolk sac. These cells are definitive erythroid and myeloid progenitors but a recent report indicates that an immune-restricted, lymphoid-primed progenitor also emerges in the yolk sac before colonizing the fetal liver [4]. Similar erythroid and myeloid progenies were shown to take place in the chick yolk sac at a slightly different time between E6 and E12 [5]. The third wave occurs in the embryo and is characterized by the production of HSCs and adult-type erythro-myeloid progenitors from ECs of the aorta and associated arteries through the stereotyped production of intra-aortic hematopoietic cell clusters (IAHC). It was shown however that both cell types originate from distinct types of endothelium [6], suggesting the existence of specialized subsets of EC and/or microenvironments .

In this review, we will focus on some aspects of cell–cell interactions that appear to be the hallmarks of embryonic hematopoietic cell emergence.

Close proximity between endothelial and hematopoietic cells

In vertebrates, the first elements of the blood-forming system differentiate from the mesoderm during gastrulation. The original observation that hematopoietic and endothelial lineages differentiated simultaneously in the yolk sac to form blood islands [7,8] led to the hypothesis that both cell types were generated from a common mesodermal precursor, the hemangioblast [8]. The yolk sac blood islands wherefrom the first HCs emerge are indeed constituted of an outer layer of EC and a core of HC. The possible common origin of both cell types constitutes a biological enigma that is not completely solved after a quarter century of investigations. Studies on embryonic stem cells reveal that hematopoietic and vascular commitment can be completely recapitulated *in vitro* using controlled culture systems. These studies were also instrumental in demonstrating that hematopoietic and endothelial precursors can develop from the same cell [9,10], hence revealing the existence of the hemangioblast postulated half a century ago.

The fact that the AGM region harbors IAHC tightly associated to the aortic endothelium is suggestive of an aorta-borne hematopoietic production by specialized EC, qualified as hemogenic. This idea was reinforced by the observation that EC and HC share common markers *i.e.*, CD34, VE cadherin, and by the fact that Flk-1 and Tie2 knock-out mice showed defects in both hematopoietic and endothelial lineages [11–14]. Using lineage-tracing experiments in chicks [15,16] or in mice [17–19] IAHC were shown to derive from the endothelium through a dynamic process called endothelial-to-hematopoietic transition (EHT). Recently, live imaging technology *in vitro* on ES cells [20,21] and *in vivo* on living embryos or tissues [22–25] allowed visualizing the *de novo* production of phenotypically defined HSC or progenitor cells from the aortic endothelium.

Crucial role of the endoderm

Interactions between neighboring tissue are required for developmental patterning. The endoderm has long been proposed to play an early role during commitment of the blood-forming system. By separating the hypoblast (primitive endoderm) from the yolk sac mesoderm and ectoderm at an early developmental stage, Wilt was among the first to show that endoderm was dispensable, albeit stimulatory, for erythropoietic formation to occur [26,27] but was absolutely required for EC commitment [26]. A key molecule of erythropoietic commitment was shown to be basic Fibroblast Growth Factor (bFGF) produced by the hypoblast [28]. In agreement with these results, M. Baron and co-workers reported that early hematopoiesis in mouse embryo was not mesoderm autonomous but required contact or signals released from the visceral endoderm. They identified Indian Hedgehog as expressed by the visceral endoderm of the gastrulating embryo and showed that the Indian Hedgehog protein was able to activate hematopoiesis in pre or early gastrulating epiblast in the absence of visceral endoderm [29]. Interestingly, in the chick embryo, Indian Hedgehog is regionalized and expressed exclusively in the yolk sac endoblast, the mouse equivalent of the visceral endoderm (TJ personal communication); furthermore the dynamic expression of Gata2 during the onset of yolk sac erythropoiesis showed that this factor is expressed very early during gastrulation in groups of cells, likely to represent the first endothelial precursors, in close association with the endoderm [3]. These first endothelial precursors are formed under the control of a VEGF–VEGF-R2 axis that triggers expression of the SCL-Tal1 transcription factor and the subsequent commitment into the endothelial lineage [30]. In addition to endothelial precursors, SCL-Tal1 was shown to be regulated by a transcription factor complex that consists of Fli-1, Elf-1, two ETS- related transcription factors and Gata-2 [31]. In addition Fli-1 was shown to sit at the top of the hematopoietic hierarchy being able to activate the expression of SCL-Tal-1, Lmo2, Gata-2 and Flk1 [32]. Of note Scl-Tal-1, Fli-1, and Gata2 have been shown to form a