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Cells in focus

Hemogenic endothelium: A vessel for blood production

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ABSTRACT

Blood cell production, or hematopoiesis, is critical to the survival of the developing mammalian embryo. The origins of hematopoietic stem cells, capable of giving rise to all blood cell types, are being revealed. During embryogenesis, hematopoietic stem and progenitor cells are generated from a unique population of vascular endothelium termed hemogenic endothelial cells. These unusual endothelial cells are found in a restricted number of sites in the conceptus and within a narrow window of embryonic development. Loss of hemogenic endothelial cells through gene ablation leads to a lack of blood production and embryonic lethality. Here, we describe historical and recent observations exploring the biology of these intriguing endothelial cells and their roles in hematopoiesis both in the embryo and, possibly, in the adult.

Cell facts

- Hemogenic endothelial cells are extremely rare.
- Hemogenic endothelial cells are able to differentiate into hematopoietic stem and progenitor cells.
- In the embryo, hemogenic endothelial cells are restricted to a small number of anatomical sites.
- Hemogenic endothelial cells co-express hematopoietic and endothelial genes and proteins.
- Hemogenic endothelial cells are highly conserved among vertebrates and are found in fish, reptiles, birds and mammals.

1. Introduction

Hemogenic endothelial cells (herein termed hemEC) are rare, differentiated vascular endothelial cells that generate hematopoietic (blood) cells during embryogenesis. In mammals, hematopoiesis, or blood cell production, occurs in successive waves that take place in distinct regions of the conceptus. The first transient wave of blood production is primitive hematopoiesis and is generated in the extra-embryonic yolk sac (YS). Definitive hematopoiesis commences later in development and characterised by the life-long generation of all hematopoietic lineages including hematopoietic stem cells (HSC) (extensively reviewed in Medvinsky et al., 2011).

The idea that endothelial cells in the developing embryo can generate blood cells was first postulated in the early 20th century. Pioneering microscopists observed "hematopoietic clusters" arising from the vascular endothelium of the dorsal aorta (DA) in numerous species. The origin and nature of these clusters rapidly became a controversial issue. It was argued that these clusters were not hematopoietic cells, that no evidence existed supporting an endothelial origin or that they were simply dividing cells of the vessel wall. H.E. Jordan, in 1917, feistily summarized the arguments for and against the "hemogenic capacity of endothelial cells in the dorsal aorta". A century later, molecular tools are helping to demonstrate a hemogenic endothelial origin of hematopoiesis in the embryo. While other vertebrate models such as the zebrafish have been very useful in studying hemogenic endothelial cell biology, we will restrict this review to mammals as exemplified by the mouse.

Hemogenic endothelial cells are rare cells found in restricted anatomical locations within a narrow window of development

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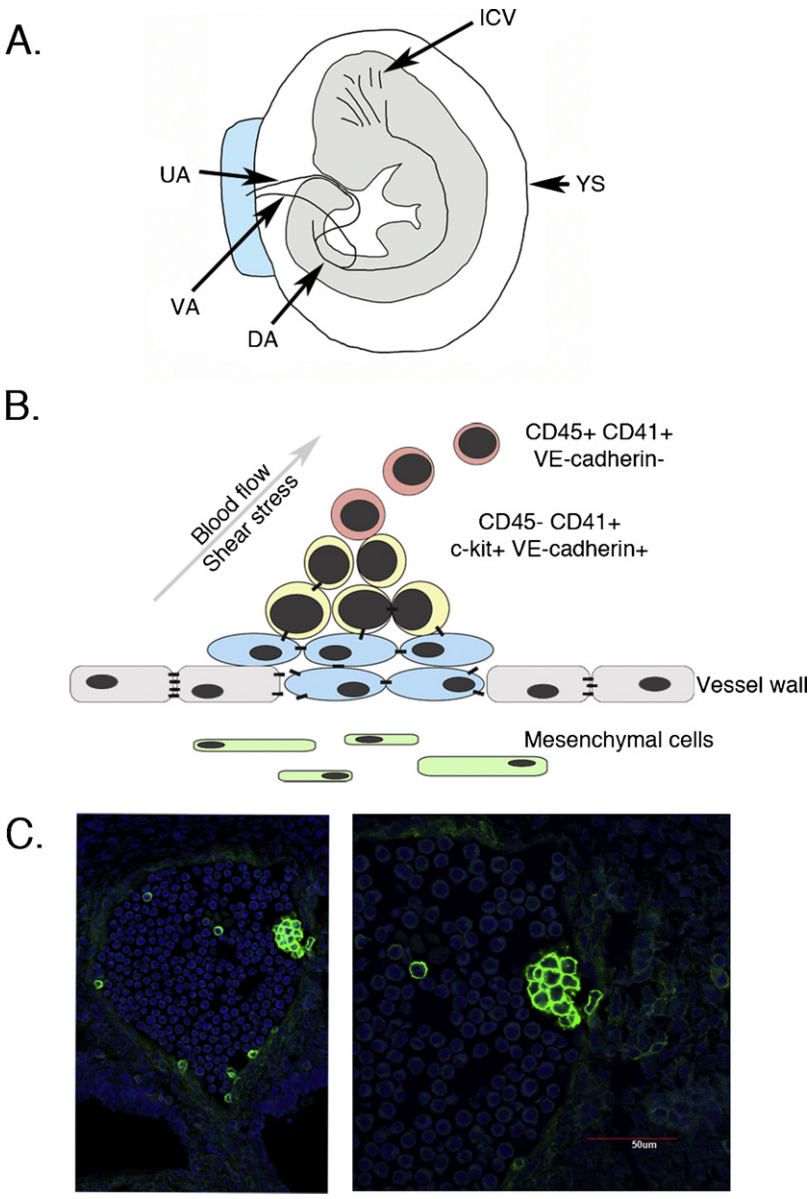

Fig. 1. The anatomy of hemogenic endothelium. (A) Hemogenic endothelial cells are found throughout the developing conceptus. A representation of a mid-gestation mouse embryo shows the major anatomical location of hemogenic endothelial cells including the placenta (blue), vitelline artery (VA), umbilical artery (UA), dorsal aorta (DA), yolk sac (YS) and the intracerebral vessels in the head (ICV). (B) shows a model of the developmental progression of free-floating hematopoietic cells from intra-aortic clusters. Mesenchymal cells (green) underlying the cluster are thought to transmit growth and differentiation signals. The hemogenic endothelial cells (blue) in this region loosen their adherens junctions with neighbouring endothelium (grey), down-regulate endothelial markers (yellow) and up-regulate blood cell surface antigens in response to blood flow and other signals (red). (C) Immunostaining and confocal imaging of the E10.5 AGM reveals c-Kit$^+$ clusters adherent to the vascular wall. c-Kit protein is labeled in green while nuclei are counterstained in blue with ToTo-3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

(Fig. 1A). The embryonic mouse tissues which possess hemogenic endothelial cells are the YS, the DA at the level of the developing gonad/mesonephros (AGM) and the placenta (Zovein et al., 2008). This unusual endothelial cell type is also found in the vitelline artery (VA) connecting the embryo and YS, and the umbilical artery (UA) linking the embryo proper and placenta (Zovein et al., 2008). Very recently and quite controversially, it has been reported that the embryonic head may also contain hemEC activity (Li et al., 2012). In these tissues, groups of hematopoietic cells extend from the vessel wall into the vascular lumen and have been termed hematopoietic, aortic, intra-aortic or intra-arterial clusters (Fig. 1B and C). In the mouse DA, hematopoietic clusters are detected from E9.5 until E14, with the greatest number occurring at E10.5 (Yokomizo and Dzierzak, 2010).

The vast majority of endothelial cells in the embryo are not hemogenic. How can we identify those that can give rise to blood cells? A single marker to segregate hemogenic from non-hemogenic endothelial cells has not yet been identified. Expression of surface antigens such as CD31 (PECAM-1), CD34 and Flk1 (VEGFR2) is shared by both endothelial and hematopoietic cells (Nishikawa et al., 1998b). Markers with greater lineage-specificity for endothelial cells such as Vascular Endothelial (VE)-cadherin have been used in combination with hematopoietic-specific antigens (CD45 and Ter-119), to isolate vascular endothelial cells (Nishikawa et al., 1998b; Fraser et al., 2002) (Fig. 1B). Further dissection of this population to enrich for hemogenic activity has included the use of; integrin α4 (CD49d) expression (Ogawa et al., 1999), Hoechst dye efflux (Nadin et al., 2003) or the