Published in final edited form as:

Nature. 2009 February 12; 457(7231): 801–803. doi:10.1038/457801a.

Developmental Biology: Birth of the blood cell

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Abstract

Could it be that fetal liver cells and adult bone-marrow cells originate from a subset of endothelial cells that line blood vessels in the mouse embryo? Several lines of evidence suggest that this might be the case.

During development, haematopoietic stem cells, which give rise to blood cells, and endothelial cells, which line blood vessels, both form from the mesodermal germ-cell layer; exactly how though is debatable. On one hand, a controversial, century-old theory proposes that both haematopoietic and endothelial cells arise from a mesoderm-derived common precursor called haemangioblast. On the other hand, a competing, relatively younger theory proposes that haematopoietic stem cells form from a subset of early endothelial cells known as haemogenic endothelium. The relationship between the haemangioblasts and haemogenic endothelium has never been resolved. In this issue, however, three papers^{1–3} clarify the potential relatedness and significance of these cell types.

The concept of haemangioblast initially arose from observations that, in the chick yolk sac, haematopoietic stem cells (HSCs) and endothelial cells form aggregates called blood islands. That blood-island formation in the mouse yolk sac is not a random process and requires expression of specific genes such as *Flk-1* provided further support for this concept. But the strongest evidence for the existence of haemangioblasts came following the development of an *in vitro* assay called blast colony-forming cell (BL-CFC) assay for analysis of differentiating mouse embryonic stem (ES) cells⁴.

BL-CFC describes a population of single-celled (clonal) precursors that gives rise to cell colonies with both HSC and endothelial features. When ES-cell-derived Flk-1-expressing (Flk-1⁺) mouse cells are grown in culture, characteristic colonies appear, which consist of an aggregate of non-adherent HSCs overlying an adherent layer of endothelium. This observation, together with insights into the molecular regulation of blast-colony development and differentiation^{4,5} have been enlightening. Nonetheless little has become clear of the cellular events that herald the generation of the HSCs from BL-CFCs.

Lancrin *et al.*¹ used time-lapse photography to analyse the sequence of cellular events required for the formation of mature blast colonies from cultured Flk-1⁺ cells. They find that blast-colonies form in two stages. First — after 36–48 hours of ‘plating’ Flk-1⁺ cells for growth in culture — the cells form tightly adherent clusters. Subsequently, round non-adherent cells appear, which then proliferate into mature blast colonies. Among the adherent-cell clusters at 48 hours, a transient cell population expressing various endothelial (but not mesodermal or BL-CFC) markers appear, displaying the potential to form HSCs. From this cell population eventually forms both primitive and definitive blood-cell colonies (characterized based on their ability to express the protein haemoglobin).

Lancrin and colleagues' observations suggest that HSCs arise from haemangioblasts through a haemogenic endothelial intermediate — the first linear pathway resolving, at least *in vitro*, the relationship between haemangioblasts and haemogenic endothelium. But, do these findings alter the definition of the haemangioblast? To answer this question, more must be learned about the fate of the haemogenic endothelial cells following the birth of the HSCs. Equally, it will be interesting to assess whether haemogenic endothelial cells differ from the cells producing primitive and others definitive blood cells.

In numerous species, HSCs appear as clusters attached to the endothelium lining the ventral wall of the aorta during embryonic development; this observation has long implicated the endothelium to be the source of developing blood cells. Indeed, when endothelial cells obtained from mouse embryos are grown in culture, a subset of them display the potential to develop into mature blood cells such as erythroid, myeloid and/or lymphoid cells⁶. But despite this and other indirect evidence⁷, direct proof of HSCs emerging from individual endothelial cells has been lacking.

Eilken *et al.*² (page YYY) tracked the fates of all cells (over 6500) generated from individually plated mouse ES-cell-derived mesoderm cells using time-lapse microscopy. Their detailed analysis of the resulting colonies indicates that 1.2% of the colonies display properties of adherent endothelial cells, and that one or more endothelial cells in a colony directly give rise to non-adherent HSCs. The authors also directly isolated primary endothelial cells with haemogenic potential from early mouse embryos. They therefore demonstrate that haemogenic endothelial cells are present in mouse embryos and can be generated *in vitro* from ES cells during a narrow window of development. But the question that these authors² and Lancrin *et al.*¹ did not address is whether HSCs emerge directly from haemogenic endothelial cells *in vivo* during mouse development.

In the developing mouse embryo, the transcription factor Runx1 is required for the formation of HSCs and their progenitors. In fact, Runx1 has been considered necessary for the emergence of HSC clusters from the haemogenic endothelium⁸. Chen *et al.*³ (page 000) show that, within the endothelium, Runx1 expression is indeed essential for the formation of HSCs and their progenitors over a period of roughly 3 days during mouse embryonic development (embryonic day 8.25–11.5). Furthermore, in agreement with another recent report⁹, they show that most fetal liver cells and adult bone-marrow cells are born from the endothelium. So embryonic haemogenic endothelial cells seem to be the source of Runx1-dependent HSCs and their progenitors that populate the fetal liver and the adult bone marrow.

Together, these studies^{1–3} provide substantial evidence that HSCs and progenitor cells of the blood lineage are born of the differentiated endothelium forming functional vasculature in the mouse conceptus. The focus therefore can now turn on determining the intriguing molecular mechanisms involved, which might differ between the various embryonic sites of blood-cell production¹⁰. What's more, translation of this knowledge to humans could be of great assistance in generating human HSCs from human ES cells, either by direct cell reprogramming¹¹ or indirectly through induced pluripotent stem cells.

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Figure 1.

Relationship between endothelial cells and blood cells. Endothelial cells line the inside of blood vessels. During mouse embryonic development, a subset of these cells, known as haemogenic endothelial cells, seems to give rise to haematopoietic stem cells (HSCs) and their progenitors, such as those that seed the fetal liver and the adult bone marrow.¹⁻³