SL Cell Science & Report

SCIENTIFIC LITERATURE

Short Review

Generation of Hemangiogenic Progenitors from Human Embryonic Stem Cells

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ARTICLE INFO

Received Date: January 18, 2019
Accepted Date: February 01, 2019
Published Date: February 06, 2019

KEYWORDS

Pluripotent stem cells (PSC)
Hemangioblast
Hemogenic endothelium
Hematopoiesis
Endothelial cells

Citation for this article: Vargas-Valderrama A, Guenou H and Mitjavila Garcia MT. Generation of Hemangiogenic Progenitors from Human Embryonic Stem Cells. SL Cell Science & Report. 2019; 2(1):113

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ABSTRACT

The close spatio-temporal relation during development between the hematopoietic and endothelial cells suggests the existence of a common progenitor of these two lineages, the hemangioblast. Since the isolation and characterization of this bipotent progenitor from chick embryos in 1920, many efforts had made in identifying the mouse and human equivalents, but they have been hampered by the difficult access to early mammal embryos and the reduce number of these transient progenitors. The derivation of Embryonic Pluripotent Stem Cells (ESC) from mice and human blastocysts opened new possibilities to study the early embryogenesis *in vitro*. Here we review the major contributions of ESC differentiation into endothelial and hematopoietic cells to the field of hematovascular developmental biology.

INTRODUCTION

One of the major breakthroughs of the 20th century in biological sciences was the isolation and culture of embryonic stem cells, first achieved with mice [1], and later with humans [2]. These cells, also called embryonic pluripotent stem cells, are derived from the inner mass of embryo blastocysts (at day 4-6 in mice and day 8 in humans). Pluripotent Stem Cells (PSCs) have the capacity to self-renew indefinitely *in vitro* and to differentiate into the three germ layers: ectoderm, mesoderm and endoderm. In the field of developmental biology, PSCs represented an important *in vitro* model to study early embryogenesis due to the impossibility to access early mammal embryos. Concretely, PSCs have greatly contributed to our understanding of blood cells and vascular development. Here, we discuss the most important contributions of PSCs to the understanding of hemangiogenic development, the current state-of-art of PSC differentiation into these two lineages and the future perspectives.

HEMANGIOBLAST VS HEMOGENIC ENDOTHELIUM

At the beginning of the 20th century, the close spatio- temporal relation during development between the hematopoietic and endothelial cells suggested the existence of a common progenitor of these two lineages. Experiments with living chick blastoderms made by Sabin [3], confirmed the presence of bi- potent progenitors derived from mesoderm and organized in clumps within the embryo and in the yolk sac, the so-called angioblasts. This mass of cells differentiates, at the center, in both blood plasma and red-blood corpuscles (erythrocytes) and, at the exterior, in the endothelium of the vascular plexus, forming all together the blood islands. Sabin used

the termed "angioblast", coming from the Greek word angeîon (vessels) and blastos (origin) to describe these progenitors. Years later, Murray [4] referred to these cells with a more suitable term which included both the hematopoietic and endothelial lineage, "the hemangioblast".

In parallel, studies of chick and mouse embryos suggested a different origin of hematopoietic cells, namely the hemogenic endothelium [5]. Lineage tracing and time-lapse imaging allow to identify a transitory specialized endothelial population located in the dorsal aorta and in the umbilical and vitelline arteries during mouse [6-8] and human embryogenesis with definitive hematopoietic potential [9]. How this HE population is related to the hemangioblast is a question to which developmental biologists have tried to find an answer for years. The lack of a clear answer has led to the misuse of both terms and frequently, they are referred to indistinctly in literature while being, at their origin, two different concepts. The HE could not represent the hemangioblast because its bi-potency has not yet been proven: there is no evidence that hemogenic endothelial cells can proliferate and produce other fully mature endothelial cells. By contrast, the hemangioblast, as an earlier progenitor of both lineages, could theoretically generate both hematopoietic cells and an endothelium with hemogenic properties. Thus, both populations of progenitors may exist during endothelial and hematopoietic development without being exclusive. In addition, while the HE has been proven to exist in zebrafish, xenopus, chick, mice and humans; the existence of hemangioblast remains controversial.

To the purpose of this review, we analyse the contributions of mESC and hESC experiments to the broad field of hematovascular development separately according to the definitions of the hemangioblast and the HE formerly described.

THE HEMANGIOBLAST

First successful experiments in mammals aiming to identify the hemangioblast were carried out with mESCs. Thanks to the spontaneous differentiation of PSCs into Embryoid Bodies (EBs), cell aggregates containing the three-germ layer, Doetschman et al., [10] described for the first time in 1985 the emergence *in vitro* of blood islands within 8 to 10-days mEBs.

Later, the team of Gordon Keller [11,12] identified hemangiogenic progenitors within 3,5-days EBs, the blast-colony forming cells (BL-CFC). Differentiation of transgenic mESC confirmed BL-CFCs were derived from Brachyury+ (Bry+) mesoderm [13] and expressed Flk-1$^+$ (KDR or VEGFR-2) and Scl [14]. Moreover, as their name indicates, those progenitors generated BCs in methyl cellulose upon the addition of VEGF and c-kit ligand in methyl cellulose. Through this population, BL-CFC gave rise to erythroid and myeloid lineages and endothelial-like cells [11,12].

Confirmation of the hemangioblast character of BL-CFC was only achieved later, when Huber et al., [13] isolated and characterized the *in vivo* murine hemangioblast. As observed in mESC experiments, this population, found between mid-strake and early neural plate stage, was derived from Bry$^+$ mesoderm and expressed Flk-1. Interestingly, the BCs generated from the hemangioblast exhibited a similar, almost identical phenotype than those derived from mESC-EBs. They both expressed hematopoietic and endothelial markers such as Flk-1, Scl, Gata1 or VE-cadherin (CD144), among others, and gave rise to hematopoietic and endothelial lineages.

Like in mice, hESC opened the possibility to investigate early human embryogenesis. hESC-derived EBs (hEBs) were shown to recapitulate early events of hematopoietic development. In accordance with previous results found in chick, mouse and human embryos [6], two waves of hematopoiesis were observed in hEBs. The first wave or primitive hematopoiesis occurs from day 7 to 12 of differentiation and yields exclusively primitive-type erythroblasts while the second wave, observed from day 12 to 20, generated definitive erythroid and myeloid lineages [15]. Emergence of hemangiogenic progenitors was evidenced prior the onset of primitive hematopoiesis, between day 3-5 of hEBs, and was characterized by the co-expression of KDR, Glycophorin-a (CD235a) and endothelial markers PECAM-1 (CD31) and Ve-cadherin [15-18]. Those progenitors were able to generate BC and consequently, hematopoietic (Ery-P and myeloid lineages) and endothelial cells, but unlike mice, they did not express c-Kit (CD117) at this stage [17,19]. Further characterization of the endothelial potential of hESC-derived BC revealed their *in vivo* positive angiogenic properties in ischemic retinal diabetic rat models, hind limb ischemic model and myocardial infarction in non-obese diabetic mice [19].

Even though the existence of human hemangioblast has not been confirmed yet, fine-tuning of hESC culture and serum-free differentiation conditions have contributed to elucidate the role of diverse cytokines and signaling pathways in early hemangiogenic development. In fact, besides the crucial role of VEGF, BMP-4 has been described as an important growth factor involved in hemangiogenic mesoderm specification [20,21] while TPO and FGFb have been shown to improve blast colony formation from BL- CFC [22]. The discovery of the angiotensin-converting enzyme (ACE, BB9 or CD143) as a marker of the hemangioblast pointed out the importance of the Renin-Angiotensin (RAS) system in hemangioblast expansion and differentiation. As demonstrated by Zambidis et al., [22], inhibition of the Angiotensin Receptor (AGTR1) increased the number of hematopoietic cells from BC at expenses of the endothelial lineage. In addition, the role of WNT canonical and Activin-nodal signaling pathways have been described as crucial for both human and mice differentiating ESC before the onset of Flk-1$^+$ cells and will be discussed later.

HEMOGENIC ENDOTHELIUM

Adult Hematopoietic Stem Cells (HSCs) are generated in the Aorta-Gonad-Mesonephros (AGM) region. According to studies on avian, murine and human embryos, the endothelium lining the ventral side of the dorsal aorta, yolk sac capillaries, vitelline and umbilical arteries undergoes the so-called Endothelial-Hematopoietic Transition (EHT) giving rise to the second and definitive wave of hematopoiesis. This specialized endothelium corresponds to a Ve-cadherin $^+$Runx1$^+$ transitory endothelial population, the HE, derived from the splanchnopleural mesoderm and detected at 30-36 days of gestation in humans and from 8,25-10 days in mice [6,9].

As for the hemangioblast, murine and human PSCs have been a useful tool to characterize this population. However, the lack of specific markers distinguishing among different endothelial populations has hampered the research on this field over the years. First indices of the existence of an *in vitro* HE were published in 1998 by Nishikawa et al., [23] who derived a FLK1$^+$Ve-cadherin$^+$ bipotent progenitor from mESC. In concordance with those results, Lancrin et al., [24] isolated a hemangioblast-derived intermediate and transitory population Ve-cadherin$^+$CD31$^+$Tie2$^+$CD117$^+$CD41$^-$ prior to the onset of BC. Interestingly, this endothelial population was dependent on Runx1 expression to produce BC and hematopoietic progenitors. Other transcriptions factors involved in HE differentiation have also been identified. ETV2 was suggested to mark the onset of the hemangioblast (ETV2$^+$Flk-1$^+$tie2$^-$), while the transcription factor SOX7 was crucial for the generation of the hemangioblast-derived HE (ETV2$^+$Flk-1$^+$tie2$^+$) [25,26].

It is important to notice that studies focused on PSC differentiation into the hemangioblast have been preferentially carried out through EB formation, while 2D culture conditions using either bone marrow stromal cells (e.g., OP9 or S17) or matrix-coated dishes (e.g., Collagen IV) have been the main choice for HE derivation. These differences have made difficult the comparison of derived hemangiogenic populations and more importantly, the understanding of the link between hemangioblast and HE. Some studies focused on establishing the relation between these two early hematopoietic progenitors have suggested they are derived from different mesoderm populations. Thus, hESC-derived APLNR$^+$PDGFRα$^+$ mesoderm generates hemangioblasts responsible of primitive hematopoiesis while APLNR$^+$PDGFRα$^-$ mesoderm is responsible of definitive hematopoiesis through the HE. Kinetics following hESC-derived APLNR$^+$PDGFRα$^-$ mesoderm commitment into HE revealed an intermediate progenitor APLNR$^+$PDGFRα$^-$Ve-cadherin$^+$KDR^{bright}CD31$^-$CD73$^-$CD43$^-$CD105$^-$CD45$^-$ around day 3 of differentiation. Expression of CD235a, CD31, CD34, CD41 and CD43 increased progressively until day 5 when three different populations were described: Ve-cadherin$^+$CD235a$^+$CD41$^-$CD117$^-$ corresponding to immature hematopoietic cells; Ve-cadherin$^+$CD73$^+$CD117$^+$ or endothelial cells without HE potential; and Ve-cadherin$^+$ CD73$^-$CD235a$^-$ CD117^{intermediate} with HE potential [27].

Hemangioblast and HE seem also to differ in the requirements of Activin-nodal, Wnt and Notch pathways. Inhibition of activin-nodal pathway during the two first days of differentiation reduced the KDR$^+$CD235a$^+$ population and increase the number of definitive progenitors [18,20,28,29]. In contrast, early inhibition of the Wnt pathway increased KDR$^+$CD235a$^+$ hemangioblast population and further primitive hematopoiesis, while Wnt activation, through a small molecule CHIR [30], improved definitive hematopoiesis. This latter has been recently proven to be sufficient to differentiate hESC into HE without the

addition of any cytokine [18,31,32]. Finally, the Notch pathway plays an important role in HE commitment. In fact, the Ve-cadherin^{+}CD43^{-}CD73^{-}DLL4^{+} arterial-type HE formation relies on Notch activation. Activation of Notch signaling at HE stages potentiates EHT initiation since it was evidenced by the Notch dose-dependent increase of Runx1 expression. Notch seems also a key factor downstream in hematopoiesis since hematopoietic progenitors coming from Notch-inhibited HE did not generate T lymphocytes [33].

IN VIVO RECONSTITUTION OF ADULT HEMATOPOIESIS

To date, the contribution of the hemangioblast to adult definitive hematopoiesis remains unclear. *In vivo*, adult definitive Hematopoietic Stem Cells (HSCs) are produced during the second wave of development from HE and are defined for their potential to reconstitute hematopoiesis after transplantation in irradiated NOD/SCID mice models. Experiments aiming to reconstitute adult *in vivo* hematopoiesis in murine models as they have been conducted for bone marrow or Umbilical Cord Blood (UCB) cells could contribute to our understanding of early hematopoietic events. However, no successful long-term (>20 weeks) engraftment from any type of mice or human PSC- derived progenitors has been reported so far. In addition, short-term engraftment has only been achieved from mice [34] and human PSC-derived through more than 15 days EB [35] or hPSC differentiation on stromal cells [28,36,37] and in any case, from direct hemangioblast or HE populations. Remarkably, these studies showed a low chimerism of PSC-derived cells compared to UCB cells suggesting these cells possess a lower potential of hematopoietic reconstitution.

CONCLUSION

Pluripotent stem cells have largely contributed to our understanding of early events in hematovascular development. They represent an excellent *in vitro* model that recapitulates early embryogenesis, yields large number of cells and allows genetic modifications. Thus, the use of PSC has allowed describing two early hematopoietic progenitors: the hemangioblast and the HE.

In the case of the humans hemangioblast, all the experiments confirming its existence have been carried out *in vitro* and its bipotency remains debatable. In addition, the contribution of the hemangioblast to primitive and definitive hematopoiesis remains unclear. Some authors claim that the hemangioblast corresponds to a multilineage progenitor population that, additionally, could also generate pericytes and smooth muscle cells besides endothelial and hematopoietic stem cells [38].

On the other hand, the endothelium has been proven to play an important role both *in vivo* and *in vitro* in the generation of hematopoietic cells even in the case of the hemangioblast. Differentiation of PSCs has been shown to be crucial to identify new markers of populations contributing to hematopoiesis. The large number of precursors cells obtained from PSCs have allowed high throughput transcriptomic analysis such as microarrays, RNA-seq and recently, single-cell analysis [33,36,39,40]. Commonly, these technologies rely on a great number of samples which are difficult to obtain from early embryos, where most of the populations are transient intermediates.

Besides the interest of PSC model in developmental biology, large-scale *in vitro* hematopoietic production is a promising tool for cell therapy where only heterologous BM and UCB transplants are possible. Unfortunately, two main factors limit the advance of this technology: heterogeneity among PSC lines [35] in the case of future autologous engraftments and more importantly, the reduced reconstitution potential of hematopoietic cells derived from PSCs. Therefore, most of the current studies aim to understand the mechanisms underlying survival, quiescence/proliferation balance and migration of PSC- derived cells compared to BM and UCB cells to overcome these limits and translate this technology to clinical applications.

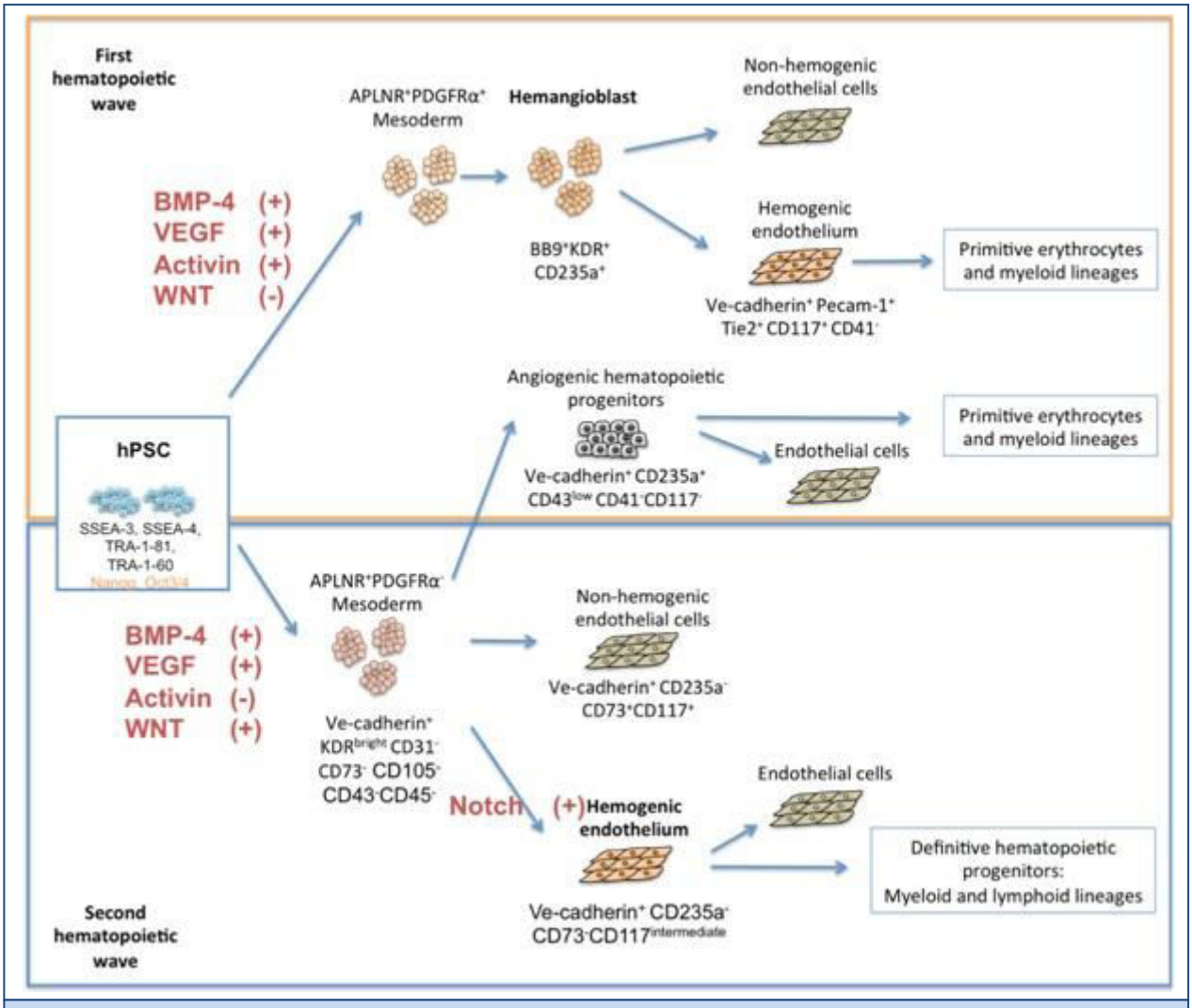

Figure 1: Scheme of hemangionenic differentiation from hPSC. hPSCs generate two types of hemangiogenic mesoderm: APLNR+PDGFRa+ that will further develop the hemangioblast, responsible of the first wave of hematopoiesis containing primitive erythrocytes and myeloid lineages; and APLNR+PDGFRa- generating different intermediate populations, one of them the HE responsible of the definitive hematopoiesis, and therefore, of myeloid and lymphoid lineages plus definitive erythrocytes. Different signaling pathways control mesoderm specification positively (+) or negatively (-) such as Activin/nodal, WNT and Notch signaling.

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