Placenta (2006), **27**, 535–539
doi:10.1016/j.placenta.2005.05.011

CURRENT OPINION

Sequential Steps During Vasculogenesis and Angiogenesis in the Very Early Human Placenta

R. Demir[a,*], U. A. Kayisli[a], S. Cayli[a] and B. Huppertz[b]

[a] Department of Histology and Embryology, Faculty of Medicine, Akdeniz University, Antalya, Turkey;
[b] Department of Anatomy II, University Hospital RWTH Aachen, Germany

Paper accepted 14 May 2005

Development of blood vessels takes place via two subsequent processes, vasculogenesis and angiogenesis. During vasculogenesis, formation of first blood vessels is achieved by differentiation of hemangiogenic stem cells from pluripotent mesenchymal cells, while during angiogenesis new blood vessels form from already existing vessels. The combination of our data with those from the literature leads us to depict the chronological steps of cell differentiation in the mesenchymal core of placental villi during vasculogenesis and angiogenesis. This current opinion will focus on the temporal and spatial expression of VEGF and its receptors VEGFR-1 and VEGFR-2, and the angiopoietin receptors Tie-1 and Tie-2 in parallel to vascular maturation in human placental villi during very early stages of placental development. There is evidence that the interplay of a variety of growth factors secreted from different cell types during development is needed to trigger as well as maintain placental vasculogenesis and angiogenesis.
Placenta (2006), **27**, 535–539

Keywords: Angiogenesis; Vasculogenesis; Human placenta; Early pregnancy; Hemangiogenic cell

INTRODUCTION

It is generally accepted that blood vessels develop via two subsequent processes. During vasculogenesis, formation of the earliest primitive capillaries is achieved by in situ differentiation of hemangiogenic stem cells that are derived from pluripotent mesenchymal cells. The resulting angioblastic cells give rise to endothelial precursor cells [1] (Figure 1). Only thereafter, during angiogenesis new blood vessels derive from already existing vessels [2].

Physiological as well as pathological processes require vasculogenesis and angiogenesis for the same reason, blood supply. Different inducers and stimulators affect angiogenesis and vasculogenesis by directly or indirectly stimulating proliferation, differentiation and migration of endothelial or respective precursor cells [2,3].

Here, we aim to highlight the chronological steps and consequences of stromal cell differentiation in the placental villous core regarding vasculogenesis and angiogenesis including the action of cytotrophoblast and placental macrophages (Hofbauer cells), known triggers of both processes. Recently, we have analyzed these processes by studying the temporal and spatial expression of VEGF, VEGFR-1 and VEGFR-2, angiopoietin receptors, Tie-1 and Tie-2 in relation to the vascular maturation in the human placenta [4,5]. We have shown that a variety of factors are associated with placental angiogenesis and vasculogenesis. Taking our and other data, this current opinion will describe our view on placental vasculogenesis and angiogenesis early in pregnancy.

VEGF AND ITS RECEPTORS DURING PLACENTAL VASCULOGENESIS

The vascular endothelial growth factors (VEGFs) [6] belong to the main factors of vasculogenesis and angiogenesis [7]. VEGF directly binds to its surface receptors VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR) that have been shown to be type III receptor tyrosine kinases [8]. The recently identified angiopoietin receptors, Tie-1 and Tie-2 are also a class of receptor tyrosine kinases that are related to the formation of blood vessels [9]. VEGFR-1 also binds the placenta growth factor (PlGF) [10] a protein closely related to VEGF and expressed only in a restricted set of tissues such as the placenta [11].

* Corresponding author. Tel./fax: +90 242 227 44 86.
E-mail address: rdemir@akdeniz.edu.tr (R. Demir).

0143–4004/$–see front matter

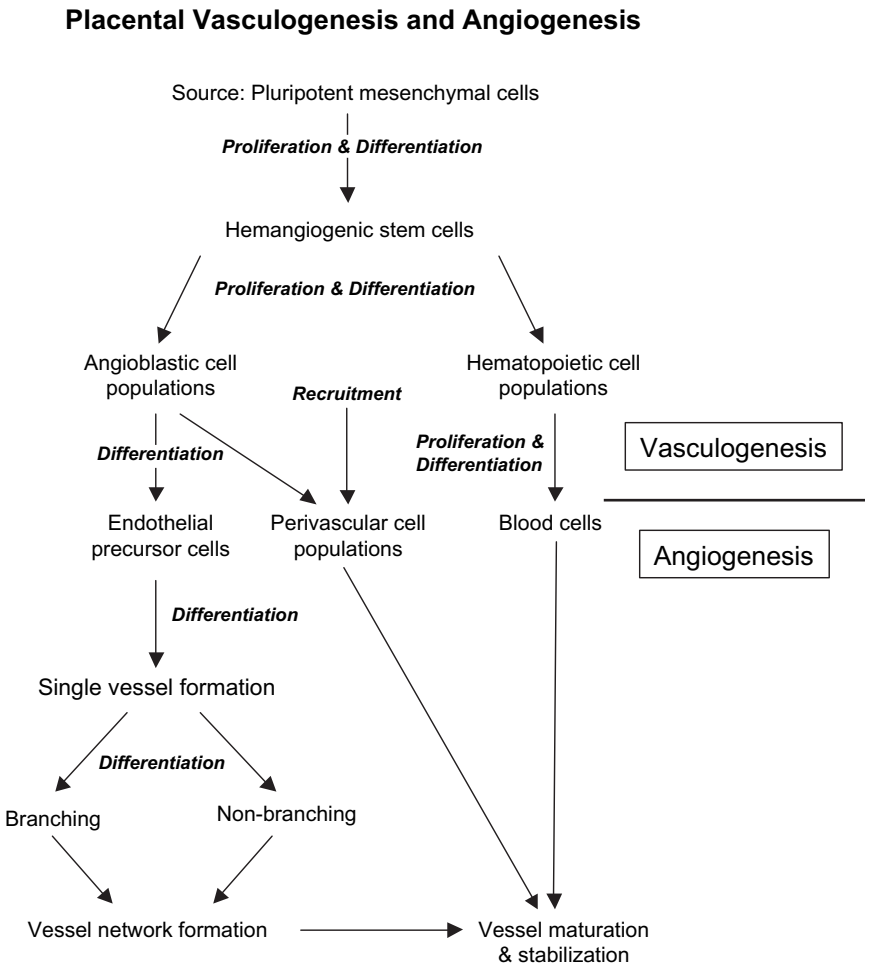

Figure 1. Schematic representation of placental vasculogenesis and angiogenesis. A step-by-step route can be observed from the cellular source to new vessels with proliferation, differentiation and maturation processes.

During very early stages of placentation, the villous trees of the human placenta are composed of two trophoblastic layers and a central extra-embryonic mesoderm. The relation between the mesenchymal core and the trophoblastic layers leads to the suggestion that they may influence each other's functions in a paracrine manner [12,13].

Vascularization of the human placenta is the result of local de novo formation of capillaries from pluripotent mesenchymal cells by several differentiation and transformation steps in the placental villous core, rather than sprouting of vessels from the embryo into the placenta. Placental vasculogenesis starts at day 21 post-conception, during the stage of a 4 somite embryo [14,15]. At this stage, the villous trees are composed of primary (solid trophoblastic) and secondary villi characterized by invasion of a loose extraembryonic mesenchyme into the center of villi. Within this mesenchyme, hemangiogenic stem cells differentiate prior to the formation of first vessels and therefore, these cells are thought to be direct mesenchymal derivatives [14]. Moreover, the early appearance of macrophages (Hofbauer cells) in the villous core, which have been described to regulate distinct trophoblast functions [13] and to express angiogenic growth factors (VEGF) [4], suggests a paracrine role for these cells during the first stages of vasculogenesis [4,16].

The expression patterns of several angiogenic growth factors and their receptors have been analyzed mostly for later stages of placentation, comprising VEGF, PlGF [11], acidic and basic fibroblast growth factor (aFGF, bFGF) and epidermal growth factor (EGF) [17,18]. Moreover, the receptors of VEGF and PlGF have been identified within placental tissues, including VEGFR-1 and VEGFR-2 [19]. Recently, placental vasculogenesis and angiogenesis were reviewed and discussed in detail with different aspects, such as the molecular profile changes of endothelial complexes during normal [15,20] and complicated pregnancies [21].

The findings of our recent study [4] suggest that a possible mechanism could act via an increased expression of VEGF by villous cytotrophoblast and Hofbauer cells together with an increased expression of the VEGF receptors by hemangiogenic stem cells. Both could cordially contribute to the differentiation of the various villous types and to maturation depending on villous vascularization.