Chapter 6

Villous Growth

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  Mature intermediate villi
  Stem villi
  Terminal villi

Molecular biology of placental vascular development
Objectives

The objectives of this Chapter are to review:

1) The general definitions in vascular development.
2) Special aspects of the human placental vascular formation.
3) The process of placental vasculogenesis and angiogenesis.
4) The interaction between the villous vessel formation and villous growth.
5) Formation of different types of chorionic villi and various stages of vessel formation.

Overview of vasculogenesis and angiogenesis

Blood vessel development is classically divided into two stages. These are:

1) Vasculogenesis
2) Angiogenesis

Vasculogenesis refers to the *de novo* differentiation of endothelial cells to form blood vessels, with or without associated angioblast migration. In contrast, angiogenesis refers to the formation of new blood vessels via extension or remodeling of existing blood vessels. Angiogenesis occurs throughout development and in adulthood, whereas vasculogenesis is generally thought to occur during a limited period early in embryonic development (Fig. 6-1).

Vasculogenesis is further divided based on whether it occurs within the extraembryonic or intraembryonic compartments. These waves of vasculogenesis are temporally and spatially distinct (*CARMELIET, ET AL., 2000; AUGUSTIN, ET AL., 2001; DYER, ET AL., 2001*).

VASCULOGENESIS

Extraembryonic vasculogenesis

Extraembryonic vasculogenesis precedes intraembryonic vascular development, and in mammals is first apparent as *blood islands* assembling within the mesodermal layer of the *yolk sac* (Fig. 6-2) (*BRIER, ET AL., 2000; YOUNG, ET AL., 2007*). Blood islands are foci of *hemangioblasts* that differentiate *in situ*, forming a loose inner mass of embryonic hematopoietic precursors and an outer luminal layer of angioblasts. Blood islands eventually coalesce into a functional vascular network.
FIGURE 6-1. Vasculogenesis and angiogenesis.
Diagram summarizing vasculogenesis and different types of angiogenesis. 1) The first precursors of fetal endothelium starting to differentiate de novo. At this stage single cells undergo differentiation. 2) In the next stage these individual precursor cells start to cluster in the villous stroma. 3) These cell clusters then start to form string-like structures called hemangioblastic cell cords. These cell cords can be demonstrated as early as 15–21 days postconception. 4) At this stage sprouting angiogenesis starts and this is responsible for rapid vascular growth and remodeling. 5) When a primitive capillary plexus is generated feeding vessels are subsequently segregated from the capillary plexus by intussusceptive angiogenesis. 6) Intussusceptive branching remodeling and arborization optimizes branching geometry and is responsible for vascular pruning (DJONOV, ET AL., 2003).
FIGURE 6-2. Extraembryonic vasculogenesis.
This diagram illustrates the different stages of a human embryo to demonstrate various aspects of placental (extraembryonic) vasculogenesis and angiogenesis.
A) This area of the illustration shows the early stages of villous development. Primary chorionic villi are comprised of STB and CTB, secondary villi have a mesenchymal core and tertiary villi have de novo vasculogenesis.
B) These new vessels connect with the vitelline vessels formed in the yolk sac and extend to the chorionic plate through the primitive umbilical cord. This establishes the embryonic-maternal circulation. Hematopoietic precursors that initially form outside the vascular structures later become circulating stem cells and seed different parts of the embryo.
C) The blood islands are located in the yolk sac and differentiate into arterial and venous vessels and hematopoietic stem cells.
that constitutes the vitelline circulation, which is adapted to transfer nutrients from the yolk sac to the embryo proper. Recent evidence indicates that extraembryonic blood vessels may also arise independently of blood islands via direct differentiation of angioblasts from mesoderm (NODEN, ET AL., 1990; PARDANAUD, ET AL., 1993; DRAKE, ET AL., 2000; DAVIDSON, ET AL., 2000). Vessels arising in the yolk sac communicate with the fetal circulation via the vitelline vein, but otherwise do not contribute to intraembryonic vasculature (DE BRUIN, ET AL., 2002).

*De novo* extraembryonic vasculogenesis also occurs in the allantois; a structure responsible for the induction of placental development and for the formation of the umbilical vessels but it is not essential for this process (Fig. 6-2) (DOWN, ET AL., 1998). Primitive vessels are already in place in the allantois as it makes contact with the chorion to facilitate the formation of the maternal–fetal circulation. (DOWN, ET AL., 1998; CAPRIOLI, ET AL., 1998, 2001; DEMIR, ET AL., 2006).

**ANGIOGENESIS**

*Angiogenesis* is the growth and remodeling of a primitive vascular network into a complex structure. In normal placental development, capillary growth shows a biphasic pattern and involves an initial phase of *branching angiogenesis*, which is followed by an increase in *non-branching angiogenesis* (KUBIS, ET AL., 2004). The mechanism of angiogenesis in the developing embryo/fetus and placenta is different from the adult. There are different types of angiogenesis.

**Branching angiogenesis**

**Sprouting angiogenesis**

Sprouting angiogenesis is localized at the abluminal aspect of vessels and is characterized mainly by local vasodilation, increased vascular permeability, and cell proliferation (Fig. 6-3). It is initiated by proteolytic degradation of the basement membrane, after which endothelial cells migrate into the extracellular matrix and proliferate or vice versa. The sprouts reorganize internally to form a vascular lumen and are finally connected to other. It is the main form of proliferation in vasculogenesis (RISAU, ET AL., 1988; EICHMANN, ET AL., 02; FEHLING, ET AL., 2003; KAUFMANN, ET AL., 2004; COGLE, ET AL., 2004).

**Bridging (pillar formation) – intussusception angiogenesis**

Intussusception has different morphological and functional outcomes in vascular remodeling. First, the sporadic occurrence of pillars within the capillary bed leads to
Formation of blood vessels by sprouting angiogenesis is a multistep process. 1) Reception all of angiogenic signals (yellow circles) from the surrounding by endothelial cells (EC). 2) Retraction of pericytes from the abluminal surface of the capillaries and secretion of protease from activated endothelial cells (AEC) and proteolytic degradation of extracellular membrane (green dotted-line). 3) Chemotactic migration of EC under the induction of angiogenic stimulators. 4) Proliferation of EC and formation of lumen/ canalization by fusion of formed vessels with formation of tight junctions. 5) Recruitment of pericytes and deposition of new basement membrane and initiation of blood flow (YOU, ET AL., 2007).