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Development of the hyaloid, choroidal and retinal vasculatures in the fetal human eye

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ABSTRACT

The development of the ocular vasculatures is perfectly synchronized to provide the nutritional and oxygen requirements of the forming human eye. The fetal vasculature of vitreous, which includes the hyaloid vasculature, vasa hyaloidea propria, and tunica vasculosa lentis, initially develops around 4–6 weeks gestation (WG) by hemo-vasculogenesis (development of blood and blood vessels from a common progenitor, the hemangioblast). This transient fetal vasculature expands around 12 WG by angiogenesis (budding from primordial vessels) and remains until a retinal vasculature begins to form. The fetal vasculature then regresses by apoptosis with the assistance of macrophages/hyalocytes. The human choroidal vasculature also forms by a similar process and will supply nutrients and oxygen to outer retina. This lobular vasculature develops in a dense collagenous tissue juxtaposed with a cell constitutively producing vascular endothelial growth factor (VEGF), the retinal pigment epithelium. This epithelial/endothelial relationship is critical in maintaining the function of this vasculature throughout life and maintaining it's fenestrated state. The lobular capillary system (choriocapillaris) develops first by hemo-vasculogenesis and then the intermediate choroidal blood vessels form by angiogenesis, budding from the choriocapillaris. The human retinal vasculature is the last to develop. It develops by vasculogenesis, assembly of $CXCR4^+/CD39^+$ angioblasts or vascular progenitors perhaps using Muller cell Notch1 or axonal neuropilinin-1 for guidance of semaphorin 3A-expressing angioblasts. The fovea never develops a retinal vasculature, which is probably due to the foveal avascular zone area of retina expressing high levels of anti-angiogenic factors. From these studies, it is apparent that development of the mouse ocular vasculatures is not representative of the development of the human fetal, choroidal and retinal vasculatures.

1. Introduction

Development of the vasculatures in the embryonic and fetal human eye is an orchestrated, synchronous process that is dependent on the oxygen demand of the developing tissue. The elegant work of Ida Mann suggested that the choroidal vasculature develops first and then the fetal vasculature of vitreous and finally the retinal vasculature (Mann, 1928). A thorough investigation of the development of the ocular vasculatures in the human has not been done since the work of Mann. The goal of this manuscript was to review recent studies of these events, which used modern immunohistochemical, biochemical, and molecular techniques. Our approach was to examine the chronological development of the three vascular systems starting at 5 weeks gestation. The development of the vasculature in each compartment or niche is described separately due the complexity and uniqueness of the developmental events in each niche.

2. Fetal vasculature of vitreous: hyaloid vasculature, tunica vasculosa lentis and vasa hyaloidea propria

2.1. Five and one half through six weeks gestation (WG)

The eyecup forms and the fissure closes at 5.5 WG (Mann, 1928). Undifferentiated mesenchymal cells invade the future vitreous space through the annular opening between the optic cup and lens primordium and through the closing fissure (Balazs et al., 1980). Using Giemsa staining of glycol methacrylate sections (JB4), it was clear that some cells in the mesenchymal anlage entering through the pupillary margin were mesenchyme (blue, basophilic), while others appear to be erythroblasts, nucleated cells with acidophilic (pink) cytoplasm (Fig. 1). In serial Giemsa stained sections, these streams of cells were often composed entirely of “erythroblast” islands but, in subsequent sections, the erythroblasts were surrounded by mesenchymal cells (Fig. 2) (McLeod et al., 2012). Additional evidence for these nucleated

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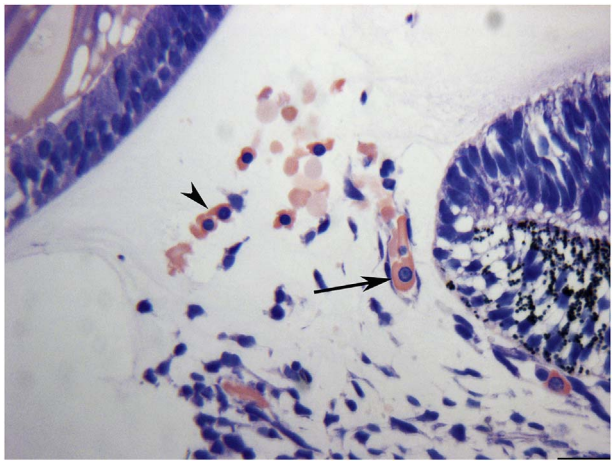

Fig. 1. Anlage of mesenchymal cells in the annular opening at the pupillary margin in a 5.5-week gestation (WG) human eye. Note the free erythroblasts (arrowhead, acidophilic cytoplasm with a prominent nucleus) and an erythroblast in a developing blood vessel (arrow). (Wright's Giemsa) Scale Bar = 20 μm.

acidophilic cells being “erythroblasts” was that some of these cells in these islands expressed epsilon hemoglobin (Hbε), embryonic globin made between 2 and 9 WGs (weeks gestation) in erythroblasts, notably in yolk sac from 2 to 6 WGs. Hbε was expressed in cells co-expressing endothelial cell markers like VEGFR2 (vascular endothelial cell receptor-2), CD31 (PECAM), and CD34 (Fig. 3). This population of cells co-expressing erythroblast and endothelial cell markers suggested that these formations were like blood islands in yolk sac (Eichmann et al., 1997). Furthermore, most of the cells in the anlage also expressed endoglin, a TGFβ receptor produced during hemangioblast specification and commitment (Fig. 4) (Perlingeiro, 2007). At 5.5 WG, serial JB4 sections demonstrated that the hyaloid artery had not entered the vitreous cavity, while islands of blood vessels were forming in vitreous, most prominently near lens capsule (Fig. 5A–B). Even at 6.5 WG,

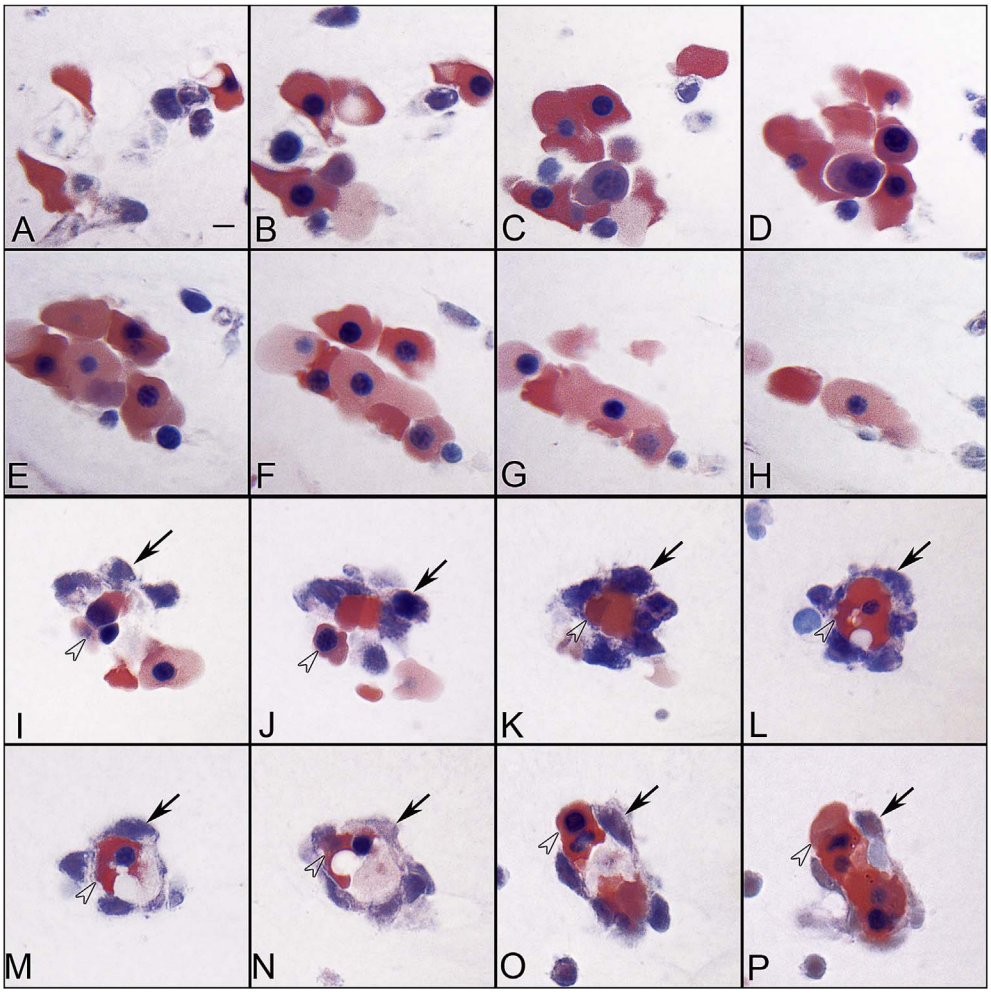

Fig. 2. Blood island-like structures in serial sections of the vitreous at 5.5 WG. Some island-like structures are aggregates of erythroblasts (A–H), while others were composed of basophilic mesenchyme (arrows) (I–P) around a core of acidophilic erythroblasts (arrowheads). (Wrights-Giemsa stain, Scale bar in A = 10 μm for all) (Fig. 2 from McLeod et al., *Invest. Ophthalmol. Vis. Sci.* 53:7915, 2012, with permission).