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REVIEW

A consonant construction of the hyaloid and retinal vascular systems by the angiogenic process

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Abstract: There has been much debate as to whether the retinal vasculature forms by angiogenesis or vasculogenesis, thus angiogenesis is now accepted.
We suppose that signals necessary for proper localization and development of the hyaloid and retinal vascular systems are already in place prior to the time at which these systems are developed. The remarkable conservation of vascular patterning suggests that specific genetic programs coordinate its formation. Evidence for a genetic program comes particularly from the characterization of gene-targeted mice and mutational analysis in zebrafish, but the exact genetic pathways remain poorly defined.
Considering all the things from the aspect of angiogenesis significant differences exist between the mentioned vascular systems only in their lifetime (a) and location (b):
(a) The hyaloid vasculature is a complex of transient intraocular vessels, while the retinal vessels are adapted for the whole life.
(b) The hyaloid system fills the interior of the optic cup and this way "occupies" three-dimensional space while the distribution of the retinal vessels is relatively planar (two – dimensional) in the retina.
We assume that retinal vessels are "built" in the same manner as the hyaloid vasculature and the outcomes at the embryological, histological, cellular and molecular levels confirm it. We show a consonant construction of both systems. The human organism does not have any rational reason to build up one system (i.e. the hyaloid vasculature) by angiogenesis and practically the same system (i.e. the retinal vessels) by another, de novo process, in the eye. It would be a waste of energy and various essential molecules. Thus, it seems that the retinal vascular system is an advanced copy of the hyaloid vessels *(Tab. 1, Ref. 143).* Full Text in free PDF *www.bmj.sk.*
Key words: hyaloid vessels, retinal vessels, angiogenesis.

Abbreviations: GFP – green fluorescent protein, HVS – hyaloid vascular system, MHC – major histocompatibility complex, PDGF-alfa – platelet-derived growth factor-alfa, RNA – ribonucleic acid, RVS – retinal vascular system, VEGF – vascular endothelial growth factor, VEGFR-2 – vascular endothelial growth factor receptor-2.

The vascular system develops shortly after gastrulation (1). Vascular development requires the integration of signals contributed by mechanical stresses, cytokines, cell-cell contacts, survival controls, glucose uptake, cell movement, and production of intercellular messengers (2). Blood vessel formation during embryonic development is achieved by two successive processes, called vasculogenesis and angiogenesis (3).

During embryonal life, blood vessels first appear as the result of vasculogenesis, i.e. the formation of capillaries from endothelial cells differentiating *in situ* from groups of mesodermal cells (1, 4, 5). Thus vasculogenesis, the de novo formation of vessels by the differentiation of endothelial precursor cells that give rise to primitive vessels, is responsible for formation of the major vessels and the vessels of endoderm-derived organs (1, 6).

A second phase then begins which is referred to as angiogenesis. Angiogenesis include sprouting morphogenesis, intussusceptive growth, splitting, remodelling, stabilization and differentiation into arterioles, venules and capillaries (1, 4, 7, 8). Thus tissues of ectodermal and mesodermal derivation such as the kidney, brain and retina are thought to be vascularised primarily via angiogenesis (1, 9, 10).

The development of the eye, as other organs, depends on the concomitant formation of a complex vascular system to provide nutrients and oxygen. Thus, ocular development is associated with the formation of a vascular network that provides blood flow adapted to the physiologic needs of the mature retina (11).

In this review we report the homology between the hyaloid and retinal circulations at various levels and we demonstrate that the human retina is vascularised by the angiogenic process as an advanced copy of the hyaloid vessels. To the best of our knowledge no study has reported this phenomenon.

History

The hyaloid vascular system

Kofoid CA and Kofoid PW (12) showed that from the optic

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disk to the lens there is a small canal about 1 mm wide in front and spreading out behind; it is lined with very transparent cells, and filled with a substance more fluid than the rest of the vitreous; it marks the position of the arteria hyaloidea. In the foetus the central artery gives off the arteria hyaloidea, which runs forwards from the papilla, through a canal in the vitreous, to the posterior surface of the lens which it covers with vessels (13). Symonowicz as well as Strjcker described that the arteria hyaloidea is "really a branch of the central retinal artery" (13, 14).

The retinal vascular system

Nineteenth Century investigators e.g. Kessler (15), Schultze (16), Voll (17) limited to routine histological techniques recognized that the retinal vessel precursors do not come from the interior or lumenized portion of the hyaloid artery, but rather from the tissue surrounding this vessel (18).

Embryology

The hyaloid vascular system

Once the formation of the lens placode has begun, the expanding optic vesicle begins to invaginate to form a cup-shaped structure, and also to fold along its centreline, enclosing a small amount of angiogenic mesenchyme as it does so (this mesenchyme later forms the hyaloid artery) (19, 20). From a plexus of embryonic capillaries lying beneath the vesicle, one especially plump vessel is taken up into the groove of the optic stalk so that when the lips of this groove finally close, the little vessel lies along the axis of the future optic nerve and forms the hyaloid artery (21). Thus the first signs of the hyaloid network development are seen while the optic cup is just being formed.

The main hyaloid artery, a branch of the primitive dorsal ophthalmic artery enters the optic stalk at the beginning of the 4th week of gestation (22), but it gives no branches to it, and merely runs through it via the open embryonic fissure to reach the cavity of the optic cup (23, 24). It enters the optic cup at the course of the 4th week of gestation, at approximately the 5-mm stage (Carnegie stage 12) (23, 25). Hyaloid artery is near ventral margin of the optic cup at Carnegie stage 13/14, enters the space between the lens and retina at Carnegie stage 15, reaches the posterior pole of the forming lens at the 7 mm stage and gives origin to the branches that increase in complexity, forming the tunica vasculosa lentis as well as a network within the primary vitreous. These vessels, in turn, course around the equator of the lens to anastomose with vessels of the pupillary membrane (10, 25, 26).

During the transformation of the optic stalk into the optic nerve at the 6th week to the 7th week (9 mm – 15 mm stage) the hyaloid artery runs inside the stalk. At the 8th week the hyaloid artery becomes surrounded by the increasing number of axons and is isolated in the centre of the optic nerve (27, 28). Seen at the height of development (40-mm to 60-mm stage), the hyaloid artery emerges from the vascular bulb in the optic nerve in man (23) and the hyaloid system almost completely fills the interior of the optic cup. The retina and the optic nerve are during the first period of their mammalian development completely avascular and oxygenation of the retina is provided by choroidal and hyaloid vessels (23, 24, 29, 30).

The whole vascular net around the lens, the other branches of the hyaloid artery which run along the inner surface of the retina, and the hyaloid artery itself atrophy back to the head of the optic nerve during perinatal period in human.

The retinal vascular system

Michaelson investigated that the retinal vessels do not develop from any in situ cellular component of the retina, but are derived from an outside source and grow into the retina (31). Cogan studied retinal vessel development in human foetus, and he also states that solid endothelial cords sprout from the nerve head, apparently from the same vessels that serve the hyaloid system or from the optic disc at the base of the hyaloid artery (32).

At the 9th week the central artery of the retina is detectable in the optic nerve (27, 28) – the hyaloid vessels within the optic nerve do not degenerate, but remain as the central artery and vein (33). At this time a small bulbous swelling appears on the trunk of the arteria just where it is passing through the disc. This enlarges and from it two small buds grow out, one from its upper aspect, the other from its lower. These are the beginnings of the upper and lower main branches of the arteria centralis retinae (21, 24, 26). Thus, in human of 15 weeks of gestation retinal blood vessels are just beginning to emanate from the optic disc (34). Kohbara et al (35) also acknowledge that angiogenesis commences with initial vessel entry from the optic nerve head, with formation of a primitive vascular plexus in carp.

The normal adult vascular pattern forms over a 3-week period as endothelial cells emerge from the central retinal artery and vascularise the retina through the process of angiogenesis in mouse, analogous to human retinal vascular development in the third trimester (36).

Histology

The hyaloid vascular system

The hyaloid artery has the fine structure of a typical arteriole in rodents (37). The wall of the hyaloid artery is composed of three layers:

1) The intima consists of flattened non-fenestrated endothelial cells connected by tight junctions (38). Underlying these cells is a basement membrane.

2) The media reveals concentric layers of smooth muscle with basement membranes around each fibre. Rhodin states that the dense "bars" are assumed to contain contractile proteins (39).

3) The adventitia contains scattered fibroblasts and collagen (23).

The walls of the vasa hyaloidea propria and the tunica vasculosa lentis are small capillaries of the A-1-alpha structure. They consist of a complete layer of non-fenestrated endothelium in toad (40) with intervening tight junctions (zonulae adherens, macula adherens and possible zonulae occludens) between adja-

cent endothelial cells (38) encircled by a continuous basement membrane and an incomplete layer of pericytes in primates (41). This same structural appearance has been noted in hyaloid capillaries in rodents (37).

The retinal vascular system

The central retinal artery wall consists of three layers:

1) The tunica intima is the inner layer of arteries and veins. In arteries this layer is composed of an elastic membrane lining and smooth endothelium that is covered by elastic tissues.

2) The tunica media is the middle layer of the walls of arteries and veins. It is composed of smooth muscle and elastic fibres. This layer is thicker in arteries than in veins.

3) The tunica adventitia is the strong outer covering of arteries and veins. It is composed of connective tissue as well as collagen and elastic fibres. These fibres allow the arteries and veins to stretch to prevent overexpansion due to the pressure that is exerted on the walls by blood flow (42).

Retinal arterioles, supported by circumferential collagen fibres, elastic tissue, and a thin layer of smooth muscle, branch to form smaller vessels, which branch to form the retinal capillaries. Adjacent retinal capillary endothelial cells are sealed by short tight junctions, making them impermeable to proteins and other large molecules (43).

Retinal vessels in mammals are not fenestrated (44). In addition to the basal lamina of the endothelium, retinal capillaries are partially surrounded by pericytes (45).

Cellular Level

All blood vessels are lined by endothelial cells as a common keystone of them. The retinal vascular complex comprises a number of cell types, in addition to vascular endothelial cells, including pericytes, astrocytes and microglia (46).

The hyaloid vascular system

The endothelium of the hyaloid vessels belongs to the type without pores or fenestrations in toad (40), in zebrafish (29) or in primates (23). The spaces between endothelial cells are spanned by quintuple-layered junctions (47) and they are likely to represent continuous belts around the endothelial cells. Endothelial cells throughout the hyaloid system are immune-reactive to von Willebrand Factor and MHC class-I antibodies (38).

Gerhardt et al (48) observed induction of new tip cells and excessive filopodia formation on hyaloid vessels exposed to high VEGF levels in transgenic animals over-expressing individual VEGF isoforms from the lens crystallin promoter. The key parameter for tip cell migration, tip cell polarization and directional filopodia extension is the precisely controlled extracellular localization of VEGF (7). These filopodia indicate dynamic patterning by angiogenesis (48). Club-like prolongations originate from both surfaces of the endothelial cells and extend towards the lumen and into recesses of the pericytes (41).

Pericytes are almost invariably found on the vitreal surface of the capillaries, but thin processes of these cells are also sometimes present on the capillary surface facing the retina (41). A layer of cytoplasmic filaments then differentiates along the inner aspect of the pericytes, and a basement membrane is formed between the pericytes and endothelial cells, enveloping the pericytes between leaflets of basement membrane. This gradual envelopment of pericytes in basement membrane is similar to that seen in the development of retinal vessels (49). They are immune-reactive to alpha-smooth muscle actin antibody; labelled cells were distributed along large branches of the hyaloid artery, vasa hyaloidea propria and tunica vasculosa lentis (38).

The retinal vascular system

The hypothesis that the primary retinal vessels are formed via vasculogenesis is based on the observations of "angioblasts" invading the retina before the appearance of differentiated endothelial cells (50). These vascular precursors have been described as "spindle-shaped" cells migrating from the optic disc to the retinal periphery. The alignment of these "angioblasts" in vascular cords is followed by lumen formation and differentiation into a primitive vascular network. Finally, via the poorly understood process of remodelling the vessels become mature veins, arteries and capillaries (10). These "spindle-shaped" cells identified by earlier workers in the retina are not vascular precursor cells, but are astrocyte precursor cells and angiogenesis takes place in animal and human retina (50, 51, 52). Evidence in support of this conclusion comes from this source: in situ hybridization with an RNA probe against VEGFR-2 labelled the vascular network but failed to label the "spindle-shaped" cells in front of it. A probe against VEGFR-1, a marker for endothelial cells only, revealed the same staining pattern. However, in situ hybridization with a probe against PDGF-alfa (a marker for retinal astrocytes) labelled "spindle-shaped" cells preceding the vessel network. These observations imply that in the mouse retina the "spindle-shaped" cells preceding the forming vasculature are immature retinal astrocytes and not vascular precursor cells (50).

The endothelial cells of the retinal capillaries form a single layer around the capillary lumen. They are non-fenestrated and possess tight junction intercellular complexes between them (53). The endothelial cells integrate and generate lots of information (from being in the tube, from touching other cells, from the extracellular matrix, from being stretched out as opposed to balled up) (54).

Specialized endothelial cells, termed tip cells, are located at the ends of the vascular sprouts and guide blood vessel growth through the tissue, whereas stalk endothelial cells proliferate to form the vascular lumen (4, 7, 48). Thus tip cells are followed by stalk cells which in turn are followed by phalanx cells. The stalk cell is the first cell located behind the tip cell whereas the phalanx cell is the first cell in the sprout which is covered with perivascular cells (55).

The endothelial cells at the leading edge of the vascular plexus possess long filopodia that closely follow the underlying astrocyte scaffold (36). The directed extension of these filopodia is mediated via VEGFR-2, and is dependent on the correct spatial distribution of VEGF within the retina (48). These three-dimensional filopodia-like processes are observed at the developing

Tab. 1. The main group of signalling pathways that is essential to the both hyaloid and retinal angiogenesis events.

Events	HVS	RVS
Angiopoietin-2 (80, 81, 82)	+	+
Basic fibroblast growth factor (83, 84)	+	+
Coagulation factors (38, 85, 86)	+	+
Crystallins (29, 87)	+	+
Ephrins (88, 89, 90, 91, 92)	+	+
Extracellular matrix proteins (29, 93)	+	+
Integrins (29, 68)	+	+
Laminin (29, 94, 95)	+	+
Netrins (96, 97, 98, 99)	+	+
Notch (100, 101, 102, 103)	+	+
Platelet-endothelial cell adhesion molecule-1 (88, 91, 104, 105)	+	+
Placenta growth factor (106, 107)	+	+
Platelet-derived growth factor beta (108, 109, 110, 111, 112)	+	+
Plexin (29, 113)	+	+
Semaphorins (29, 114, 91)	+	+
Sonic hedgehog (115, 116, 89, 117, 118, 119, 120, 121, 122, 123)	+	+
Sprouty * (124, 125)	+	+
Syndecan 2 (29, 126)	+	+
Transforming growth factor beta-1 (55, 59, 127, 128, 129)	+	+
Vascular endothelial cadherin (48, 130)	+	+
Vascular endothelial growth factor (7, 36, 48, 131, 132, 133, 134, 135, 136, 137)	+	+

* Human sprouty 3 has been reported to be expressed in eye (125). We suppose that sprouty participates in hyaloid and retinal angiogenesis but explicit study discussing this problem is not available yet.

vascular front and within regions behind the vascular front where the complex vascular interconnections are forming. In fact it also exists intracellular signalling mechanism which controlling in vitro vascular tube formation (36). Im and Kazlauskas (54) have demonstrated control switchboard within the endothelial cell for angiogenesis.

The endothelial cells are associated with underlying astrocytes which may be involved in directing endothelial cell migration (36) and can induce endothelial cell differentiation thus demonstrating signalling from astrocytes to endothelial cells (56). Colocalization of endothelial cells and astrocytes may be an indirect result of a third set of factors involved in guidance of both (36).

Pericytes are recruited during blood vessel maturation. The interaction between vascular endothelial cells and pericytes is essential for the formation of mature vascular structures. They appear to lag slightly behind the leading edge of the spreading vascular network, surround the capillary endothelial cells, provide structural support to the microvasculature, contain alfa-smooth muscle actin, have contractile properties and are required for the establishment of the blood-retina barrier (46, 50, 57, 58, 59, 60).

Retinal astrocytes are spreading as a proliferating cell population from the optic nerve head across the retina (52, 61). They play a role in angiogenesis, inducing endothelial cell and pericyte differentiation (62), stimulating blood vessel growth by secreting VEGF (63) and controlling development of the retinal vasculature in mammals (64) – the resulting network of astrocytes acts as a template for the developing retinal vasculature (50). Astrocytes in maintaining vascular integrity may serve to prevent migration of retinal vasculature into the vitreous (65).

They are observed only in regions in which vascularisation occurs (66) and may guide endothelial cell growth and migration through specific cell adhesion molecules including R-cadherin (36, 67) and the selective expression of VEGF isoforms. Growth factor receptors are coordinated with specific integrin receptors (68), the function of which is critical for normal retinal angiogenesis. Cross talk between integrins and cadherins has also been demonstrated (69).

Retinal microglia originate from hemopoietic cells and invade the retina from the retinal margin and the optic disc, most likely via the blood vessels of the ciliary body and iris, and the retinal vasculature, respectively (70, 71, 72).

The microglial precursors that appear in the retina prior to vascularisation are MHC class I- and II-positive and express the CD45 marker, but lack specific macrophage markers. They are present by 10 weeks of gestation, before astrocyte invasion (70, 72, 73). Microglia is considered channel of communication between retinal blood vessels and neurons owing to their special spatial arrangement and regulatory functions (74**).** GFP-positive microglia revealed, with unprecedented precision, the apposition of their processes with the endothelial tip cell filopodia and endothelial stalk cells (34).

A second category of microglial precursors, which do express specific macrophage markers, migrate into the retina along with vascular precursors at approximately 14 weeks of gestation (46, 70, 73). In humans of 15 weeks of gestation microglia already occupy the entire retinal surface (at postnatal day 6 in transgenic mice the microglial cells were present beyond the vascular front) (34). They have been recognized as the key angiogenic effector cells (75). These cells induce angiogenesis by

secreting factors that are pro-angiogenic, break down basement membrane, and stimulate other cells to produce greater amounts of pro-angiogenic substances (76). These macrophage-like MHC class II-positive cells coinciding with the development of the retinal vasculature (these cells are thought to become established as vessel-associated para- and peri- vascular microglia, active in phagocytising the remnants of eliminated endothelial cells during vascular remodelling) (63, 77). Thus appearance, location and mode of spreading of these cells are closely related with developing retinal blood vessels (78)**.** Depletion of resident retinal microglia reduces developmental vessel growth and density, which are restoring by intravitreal microglial injection (34).

Molecular level

Blood vessel formation is a complex morphological process that is only beginning to be understood at the molecular level (2). It can be divided in an activation phase and a resolution phase (79). Both phases are rate-limited by transcription factors, different growth factors, chemokines and adhesion molecules (55). Various signalling cascades and genetic programs are activated during the angiogenesis (see examples in Table 1):

It is very important that all above mentioned mechanisms are involved in the development of the hyaloid vascular system and the retinal vasculature. The actions of these mechanisms are orchestrated in a complex sequence of steps that lead to the development of vascular retinal network.

Conclusion

In this review we report that the construction of the hyaloid and retinal vessel systems is de facto the same at several levels concerning the vascular development (see the text "History", "Embryology", "Histology", "Cellular level") and their developments share practically the all of regulatory features (see the text "Molecular level"). All arguments at the mentioned levels acknowledge that the retinal vascular system is formed by angiogenesis as the advanced copy of the hyaloid vessels.

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