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A hierarchical model for the development of cerebral arteriovenous malformations

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ABSTRACT

Objective: Cerebral arteriovenous malformations (AVMs) are vascular lesions whose pathogenesis, although not fully elucidated, is likely multifactorial. Recent research investigating vessel development suggests a potential hierarchical model in which capillary sprouts from higher-flow arteries give rise to lower-flow veins. It is possible that an embryologic structural vascular dysgenesis in this hierarchical development heavily contributes to the formation of AVMs. Subsequent genetic "second hits" may then allow development of a clinically significant cerebral AVM. We review this vascular developmental process and describe a novel proposal for the embryogenesis of AVMs and its implications in relation to recent research on polymorphisms and AVMs.
Methods: A comprehensive literature search was performed using PubMed for recent research relative to cerebral AVMs, embryologic vascular development, and polymorphisms involved in AVM pathology.
Results: It has recently been shown that both centrally, in the axial embryo, and peripherally, in the embryonic yolk sac, veins form via capillary sprouting from parent arteries. In developing intracranial vessels, a derangement in this embryonic process may lead to a primitive arteriovenous shunt. After this structural "first hit," we suggest that single nucleotide polymorphisms (SNPs) are a major component in allowing AVM growth into symptomatic clinical lesions.
Conclusions: This is a novel theory for the embryologic formation of cerebral AVMs. Hierarchical vessel development, where higher-flow parent arteries give rise to lower-flow veins, provides a potential mechanism for the formation of primitive arteriovenous shunts that, with the influence of polymorphisms, allows AVMs to develop.

1. Introduction

Maturation of the human circulatory system is a complex and fragile process that has its beginnings early in embryogenesis. Soon after fertilization, the rapidly proliferating embryo develops the need for an intrinsic oxygen delivery system. This is why vasculogenesis occurs so early in the development process, and it explains why the cardiovascular system is the first fully functioning organ system [1]. Starting with hematopoiesis and vasculogenesis, the primitive circulatory system coalesces to form the major blood vessels, which subsequently undergo angiogenesis and differentiation into arteries and veins to form more intricate smaller vessels.

Embedded in this process is the potential for numerous pathologies to develop, including intracranial arteriovenous malformations (AVMs), whose molecular biology and physiology is reviewed elsewhere [2,3]. AVMs are dynamic abnormalities—they exhibit increased vascular remodeling and aberrant hemodynamics, which contribute to several pathologic characteristics, such as mass effect, pathologic inflammation, unstable vessel walls, and intracranial hemorrhage. Multiple theories exist regarding the congenital nature of these lesions, including the existence of a developmental proliferative capillaropathy [4], a dysfunction in vascular remodeling at the junction between veins and capillaries [5], and aberrations during a stage of absorption of numerous dural-pial subarachnoid veins [6].

Although the exact pathogenesis of AVMs is yet to be elucidated, it is clear there is a strong genetic component. This genetic

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link is especially strong in AVM patients with known comorbid congenital vascular defects, such as hereditary hemorrhagic telangiectasia and Sturge–Weber syndrome. Newer studies are beginning to identify single nucleotide polymorphisms (SNPs) associated with sporadic AVM formation, which are located in genes responsible for angiogenesis [7–11]. However, there is a surprising lack of modern literature focusing on possible structural embryologic explanations of AVM formation during arterial and venous development.

AVMs are likely lesions with multifactorial origins, consisting of physiological, genetic, mechanical, and embryological mechanisms. In normal arteriovenous differentiation, ephrin B2 (EphB2) is an early arterial marker, whereas ephrin B4 (EphB4) denotes venous identity even before the onset of circulation. There is also a varying degree of endothelial plasticity that is largely a result of hemodynamic forces that influence genetic expression of these markers involved in arteriovenous differentiation [12]. While it is proven that these expression patterns regulate vessel differentiation before the onset of circulation in the developing axial trunk, it has recently been shown that the cranial vasculature may not in fact undergo arteriovenous differentiation until after the presence of blood flow and development might instead occur similarly to other areas where arteries hierarchically give rise to veins [13,14]. Thus, it is possible that aberrant embryological cranial blood flow in undeveloped endothelial tubes may give rise to defects in arteriovenous differentiation, potentially causing vascular pathologies such as AVMs. Considering this and other recent studies examining normal vascular development, we discuss a hierarchical embryological mechanism for the pathogenesis of AVMs.

2. Hierarchical vessel development

While most researchers concede that genetic factors predominantly affect the formation and differentiation of blood vessels in the axial embryo, many propose that hemodynamic forces provide a great degree of plasticity in the development of arteries versus veins. In fact, in some anatomic regions like the developing axial embryo and yolk sac, it has been demonstrated that higher-flow arteries give rise to lower-flow veins [14,15]. Beginning with the onset of perfusion, the basic vascular framework becomes remodeled as morphologically distinct arteries and veins develop beyond immature primary plexuses. While investigating this process of flow-regulating vascular differentiation, Le Noble et al. proposed a novel mechanism in the differentiation of arteries and veins [14]. Using the vitelline artery and vein from a chick embryo as a model, small capillary-like vessels, which are part of the vascular plexus, are seen branching from the developing artery and eventually disconnect. These small blind-ending vessels then specifically project to the venular plexus, fuse, and contribute to the newly formed secondary venous vessel, thus restoring their flow. A very similar process occurs early on more centrally in the axial embryo, where the cardinal vein develops from ventral migration of angioblasts derived from the primitive dorsal aorta [15]. Many different factors contribute to the migration of these angioblasts and eventual formation of the cardinal vein, but Herbert et al. elegantly demonstrated that vascular endothelial growth factor (VEGF) limits ventral sprouting whereas reduced EphB2 expression promotes excessive ventral migration and formation of a single fused vessel [15]. In this hierarchical series of events, primitive arterial vessels donate smaller caliber vessels to the immature venous plexus, which consequently remodel to form early veins; this process is seen as arteries giving rise to veins. Much previous work has been devoted to identifying factors necessary for arteriovenous differentiation, but this study by Herbert et al. [15] is the first to depict exactly how these signaling molecules act to form vein from artery. The process depicted in this model has now been observed both centrally, before the onset of circulation with formation of the cardinal vein, and peripherally, after circulation in the embryonic yolk sac.

In early stages of embryonic tissue development, arterial growth is favored in the proximal to distal direction, as the distal high-density capillary beds initially provide a path of least resistance [16]. Thus, a loop-like structure where the artery and vein run in series with one another is initially favored when the width of the developing tissue is greater than its length. As the tissue elongates, the resistance of this route increases, and capillary sprouts from the growing artery disconnect, as described previously, exhibiting positive feedback for a new vessel configuration in which veins form parallel to existing arteries and provide a new path of least resistance. This is a newly described process in which arterial flow exerts morphological control over venous patterning and development.

Although flow-driven studies are specifically examining the developing vasculature of the embryonic yolk sac, it is thought that the cranial vasculature may also develop subsequent to the onset of circulation and, therefore, could be governed by similar mechanisms. Classically, EphB2 and EphB4 are two markers for arterial and venous identity, but *kdrl* and *etsrp* expression are other ways of designating arteries and veins, respectively [17]. Proulx et al. are the first to point out that within endothelial cells of the developing cranial vasculature, just before the onset of circulation, there is relatively equal expression of these two genes; this indicates that differentiation likely occurs after blood flow [13]. As a result, blood flow may be a key factor in the distinction of intracranial arteries and veins, where high-flow proximal vessels (arteries) give rise to low-flow distal vessels (veins). This is separate from the rest of the body where it has been clearly shown that EphB2 and EphB4, downstream of *shh/vegf* expression, delineate an arterial or venous fate well before the commencement of circulation [18]. With these two different processes in mind, it is possible that the cranial vasculature represents a discrete entity of vasculogenesis and angiogenesis within the embryo. Circulation likely has a greater influence on the differentiation of arteries and veins intracranially, which could potentially be a source of pathology in cases of failed differentiation and may explain the commonality of AVMs in the central nervous system relative to other locations.

3. Failed hierarchical arteriovenous differentiation as an embryologic source of AVM formation

In a hierarchical series of events where relatively high-flow arteries give rise to veins, it is conceivable that several vascular pathologies may arise from mechanical defects, genetic defects, or some combination of the two. Just as in the early stages of embryonic yolk sac vasculogenesis and angiogenesis, we propose that in normal development, endothelial angioblasts coalesce to form an initial primary capillary plexus, which subsequently undergoes remodeling upon perfusion to produce early arteries [14]. As these arteries are perfused, their capillary sprouts disconnect, resulting in dangling capillary sprouts that lack circulation. These blind-ending "blood-filled spots" then undergo remodeling and fuse to produce a newly formed venous vessel. Because of the arteriovenous shunt observed in AVMs, it is possible that a defect in this capillary sprout detachment may result in lingering connections to the parent artery and an abnormal fistula between the developing artery and vein, leading to development of an AVM. Due to the lack of an adequate capillary bed and aberrant hemodynamics between the arterial and venous channels, genetic markers that normally delineate artery versus vein persist within the AV shunt but the channels lack the ability to undergo appropriate remodeling. This initial structural developmental defect may be essential in the formation of cerebral AVMs, and genetic predispositions, discussed in detail in the