Growth Factors in Pulmonary Hypertension: Guilty Parties or Just Bystanders?

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Pathological changes in the lungs of patients with pulmonary hypertension (PH) suggest an abnormal response to vascular injury. Many of the same growth factors that stimulate the initial formation of the vasculature during development are also involved in vascular repair. Therefore, understanding the growth factor dependent mechanisms controlling vascular development may provide insight into PH pathogenesis.

EARLY VASCULAR DEVELOPMENT

Formation of an intact circulatory system is among the earliest steps in embryogenesis. The first blood vessels form in the loosely packed mesenchymal cell layer immediately adjacent to the embryonic yolk sac. Growth factors secreted by the yolk sac epithelium cause cells in the mesenchyme to differentiate into immature blood islands containing both blood cell precursors and vascular endothelial cells. The newly formed endothelial cells then undergo a rapid expansion, lining the entire yolk sac with a plexus of immature blood vessels. Remodeling of these immature vessels into intact, mechanically stable vascular tubes permits the flow of blood through the developing embryo.[1]

GROWTH FACTORS AND VESSEL DEVELOPMENT

Blood vessels can form by angiogenesis, where new vessels sprout from existing blood vessels, or vasculogenesis, in which cells differentiate into endothelium and then coalesce to form a new vessel. Both angiogenesis and vasculogenesis require specific vascular growth factors. These factors bind receptors on the endothelial cell surface and regulate cell proliferation, endothelial differentiation, and cell-cell contacts. Perhaps the most studied is vascular endothelial growth factor (VEGF).[2] Humans have 4 VEGF genes (VEGF-A, -B, -C, and -D), each with multiple isoforms. The various VEGF genes have different functions, with VEGF-A and VEGF-B regulating vascular endothelial development and VEGF-C and VEGF-D stimulating lymphatic formation. VEGF-A mediates hypoxia-driven angiogenesis. Low levels of oxygen within tissues cause the expression and stabilization of hypoxia-induced factor (HIF). Hypoxic cells with high levels of HIF express and secrete VEGF-A, which then stimulates endothelial proliferation and the formation of new blood vessels for oxygen delivery.[3] Because formation of new vessels by VEGF-mediated angiogenesis first involves destabilization of existing vessels, a subsequent maturational phase that prevents blood vessel leakiness is required to maintain effective circulation.

Other growth factors that regulate blood vessel development include fibroblast growth factor-2 (FGF-2), the Hedgehog family members Ihh and Shh, bone morphogenic proteins (BMPs), and angiopoietins. FGF-2 was among the first growth factors discovered, playing an important role in wound healing and neuronal development in addition to stimulating blood vessel formation. Like VEGF, levels of FGF-2 increase when oxygen tension is low, again promoting formation of new blood vessels to hypoxic tissues.[4] The role of the Hedgehog signaling during vascular development has been studied primarily during early embryogenesis. Hedgehog proteins are produced in the yolk sac epithelium and stimulate the formation of the first endothelial vessels in the adjacent embryonic mesenchyme.[5] The roles of BMPs and related transforming growth factor beta (TGF-β) family members on blood vessel development have been more difficult to fully understand due to the many BMP and TGF-β family members, multiple receptor combinations, and both stimulatory and inhibitory downstream signaling components. Because of differential expression of stimulatory and inhibitory Smad proteins, BMP4 causes proliferation of arterial endothelial cells but cell death in capillary and venous cells.[6] BMP and TGF-β signaling is clearly important for vascular development, as mutations in multiple receptors or signaling components can cause human vascular disease, including familial PH due to mutations in the BMP receptor BMPRII.[7] The angiopoietins Ang-1 and Ang-2 also have opposing effects on blood vessel development. During formation of new vessels, Ang-2 causes endothelial cell detachment, which allows migration into vessel-deficient tissues. Ang-1 then appears to reverse this process, promoting endothelial cell-cell junctions and formation of a more mature vessel.[8] Like many signals that control cell behavior, suppressing endothelial proliferation and blood vessel formation appears to be just as critical as the initial pro-angiogenic response.

FORMATION OF BLOOD VESSELS IN DIFFERENT ORGANS

Studying formation of unique vascular structures throughout the body provides insight into novel mechanisms that can regulate blood vessel development. The aorta begins initially as a pair of large vessels running along the length of the early embryo. Fusion of the double aorta into a single structure requires extensive vascular remodeling. In addition to formation of the aorta proper, the specific branching of vessels between body somites early in embryo formation pro-

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vides a unique model for studying the patterning of new blood vessels. The coronary blood vessels also develop by a unique process. Endothelial cells that originate either from the early proepicardium or the sinus venosus form an immature vascular plexus covering the heart that resembles the early yolk sac. Remodeling, maturation, and eventual connection to the ascending aorta establish the coronary blood supply to the developing heart.[9] Vascular development in the liver requires the formation of the venous filtration system. Early in liver embryogenesis, mesenchymal cells within the septum transversum between the primitive heart and developing endoderm differentiate into endothelial progenitors. Cells within the adjacent endoderm acquire hepatoblast identity, and a surge of proliferation produces a cell mass that will develop into the liver. The liver endothelial cells must establish vascular structures that form the portal filtration system in addition to the vessels that provide the liver with oxygen and nutrients.[10]

The development of the lung vasculature may be the most relevant to PH pathogenesis. From the earliest stages of lung formation, blood vessels form in parallel with newly branched airways. These vessels make up the peribronchial arteries and veins that flank conducting airways. The alveolar capillary bed develops from a combination of angiogenesis and vasculogenesis within the lung mesenchyme. As airway branching progresses into terminal saccule formation, the plexus of endothelial cells in the lung mesenchyme forms an intact capillary system and becomes closely approximated to the terminal airway epithelium. This close proximity of the mature alveolar capillary bed reduces the barrier for gas exchange between the airspace and the blood.[11]

ROLES OF GROWTH FACTORS IN PH

Vascular growth factors may mediate an exaggerated or persistent response to injury in PH pathogenesis. If the pulmonary endothelium becomes damaged, then many of the growth factors described above, including VEGF, FGF-2, and BMP are required for the repopulation of damaged endothelial cells lining the pulmonary vessels. During the normal repair process, growth factor expression and signaling shuts off to allow vessel maturation. Failure to stop the initial repair response could result in leaky new vessels or hyperproliferation of the endothelium. Whether increased endothelial proliferation following repair leads to the plexiform lesions in PH is not completely clear. The mutations identified in familial PH may affect the ability of smooth muscle cells to properly regulate the endothelial healing response. Injury to the pulmonary vasculature could also lead to differentiation of progenitor cells within the lung mesenchyme or smooth muscle into abnormal endothelial cell structures. In addition to a possible exaggerated response following injury in PH, hypoxia could stimulate pathological endothelial proliferation and angiogenesis. As hypoxia is a potent stimulus for VEGF and FGF-2 expression, even small drops in local oxygen tension in the pulmonary vasculature during PH disease progression could lead to increased endothelial proliferation. So while endothelial repair and angiogenesis are crucial for normal development and wound healing, excessive or persistent response to injury could lead to vascular disease. Further research will hopefully determine if excessive growth factor expression or signaling in the lung vasculature truly contributes to PH pathogenesis.

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