Role of Midkine in Pulmonary Vascular Remodeling

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Midkine (MK) is a 13 kDa heparin binding protein expressed during lung morphogenesis. MK is thought to promote vasculogenesis, cell proliferation and migration in various tissues during embryonic development, acting particularly in organs with extensive mesenchymal-epithelial interactions. To study the effects of MK on lung morphogenesis, transgenic mice were developed in which MK was expressed in the respiratory epithelium during embryonic and post-natal development. Using immunohistochemistry, we stained for PECAM in lungs of transgenic mice. Compared to wild-type, there was an increase in the number of peripheral vessels and in their muscularization. Notably, an increase in muscularity was observed in small blood vessels that would normally lack smooth muscle. An increase in α-smooth muscle actin (α-SMA) staining was detected in the abnormal blood vessels. The vascular remodeling and increased muscularization of the vessels may lead to pulmonary hypertension. Right ventricle enlargement was assessed to measure the extent of pulmonary hypertension in the transgenic MK mice under normoxic and hypoxic environments. Right ventricular mass was increased in hypoxic transgenic MK mice. CAST/ei mice, a strain especially susceptible to hypoxia, demonstrated vascular remodeling and an increase in MK staining during hypoxic conditions. Hypoxia-inducible factor-1α (HIF-1α), known to regulate the effects of hypoxemia in many cell types, enhanced expression of MK *in vitro*. We speculate that hypoxemia induces HIF-1α that in turn enhances MK that causes pulmonary arterial vascular hyperplasia. Although the role of MK in pulmonary development and vascular remodeling is only beginning to be elucidated, these studies indicate that MK may play a critical role in the development of pulmonary hypertension during hypoxemia.