Potential Contribution of Phenotypically Modulated Smooth Muscle Cells and Related Inflammation in the Development of Experimental Obstructive Pulmonary Vasculopathy in Rats

We tested the hypothesis that phenotypically modulated smooth muscle cells (SMCs) and related inflammation are associated with the progression of experimental occlusive pulmonary vascular disease (PVD). Occlusive PVD was induced by combined exposure to a vascular endothelial growth factor receptor inhibitor Sugen5416 and hypobaric hypoxia for 3 weeks in rats, which were then returned to ambient air. Hemodynamic, morphometric, and immunohistochemical studies, as well as gene expression analyses, were performed at 3-13 weeks after the initial treatment. Experimental animals developed pulmonary hypertension and exhibited a progressive increase in indices of PVD. Cellular intimal lesions comprised SM1+, SM2+/- immature SMCs that were covered by endothelial monolayers, while fibrous intimal lesions typically included SM1+, SM2+ mature SMCs. Plexiform lesions comprised a smooth muscle actin+, vimentin+, SM1-, SM2- myofibroblasts covered by endothelial monolayers. Immature SMC-rich intimal and plexiform lesions were proliferative and were infiltrated by macrophages. Compared with controls, the number of perivascular macrophages was already higher at 3 weeks and progressively increased during the experimental period; gene expression of IL6, MCP1, MMP9, cathepsin-S, and RANTES, was persistently or progressively up-regulated in lungs. We concluded that phenotypically modulated SMCs and related inflammation are potentially associated with the progression of experimental obstructive PVD.