THE ROLE OF IMMUNITY

There is strong circumstantial evidence for an immune pathogenesis of PAH, i.e., PAH is associated with rheumatoid arthritis, systemic lupus erythematosus, collagen diseases (e.g., scleroderma and mixed connective tissue disease), hypothyroidism, hypersensitivity pneumonitis, and infection with HIV (7, 75, 76). Barst and colleagues (77) and Morse and coworkers (78, 79) detected an association of MHC class II alleles with PAH.

Recently, Daley and colleagues demonstrated that activation of the immune system can induce impressive pulmonary arterial remodeling, that is, pulmonary arterial muscularization without intimal EC proliferation. This pulmonary arterial muscularization in the mouse did not cause pulmonary hypertension (80). Novel treatment strategies for PAH should target the apoptosis-resistant phenotypically altered vascular cells and the disruption of the extracellular matrix between the obliterating cells. Drugs that turn the *in situ* local vascular immune response off may be essential to the treatment strategies for PAH because immune responses are likely to regulate signals that control cell proliferation, or the differentiation of smooth muscle actin–positive cells, and the rearrangement of the cellular organization which thus results in a severely remodeled arterial wall (80).

The use of the immunosuppressants methotrexate and prednisone to treat pulmonary hypertension with nonspecific inflammatory signs has shown promising beneficial effects in some patients (81). Ogawa and coworkers reported an immunosuppressant, prednisolone, to have an antiproliferative effect on cultured SMC of pulmonary arteries from patients with idiopathic PAH, thus suggesting that prednisolone may be potentially useful therapeutically in patients with idiopathic PAH (82). Moreover, they have shown that PDGF-induced nuclear translocation of NF-κB may play an important role in stimulating pulmonary arterial SMC proliferation (and/or enhancing pulmonary arterial SMC survival), whereas prednisolone may exert both anti-inflammatory and antiproliferative effects on PASMC by inhibiting NF-κB nuclear translocation (83).

However, it should be acknowledged that, to date, the treatment of PAH with immunosuppressive drugs has been disappointing with the exception of less severe PAH associated with connective tissue disease (84).

CONCLUSIONS

The treatment strategies for PAH should consider that there are at least two types of remodeling: pulmonary vascular disease that develops predominantly because of increased muscularization of vessel walls, and pulmonary vascular disease that develops because of EC proliferation (85). The SMC shift between a proliferative and nonproliferative phenotype may be attributed to cellular plasticity, rather than selective expansion of distinct cell subpopulations (63), thus suggesting that this form of vascular remodeling may be reversible. However, phenotypically altered and hyperproliferative SMC in PAH cannot easily convert back to a normal SMC. A recent study has demonstrated irreversible PAH in congenital heart disease (CHD) to be strongly associated with impaired apoptotic regulation of EC (35), with endothelial damage and with increased circulating EC counts (86), thus suggesting that vascular remodeling that develops because of phenotypically altered EC may be irreversible.

Moreover, after inducing apoptosis of phenotypically altered vascular cells, it may be necessary to allow normal EC to spread out and again form a monolayer. Whether phenotypically altered EC can switch back to a normal monolayer-forming EC therefore remains to be elucidated (Figure 1).

In conclusion, the disobliteration or reopening of occluded small pulmonary vessels is increasingly recognized as a treatment goal in PAH. The reopening of even a fraction of the obliterated arterioles would reduce pulmonary vascular resistance and thus unload the stressed right ventricle. Further studies are necessary to characterize the pulmonary vessel phenotypes to determine the reversibility of vascular remodeling in PAH.

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