Inflammation Drives Pulmonary Arterial Hypertension

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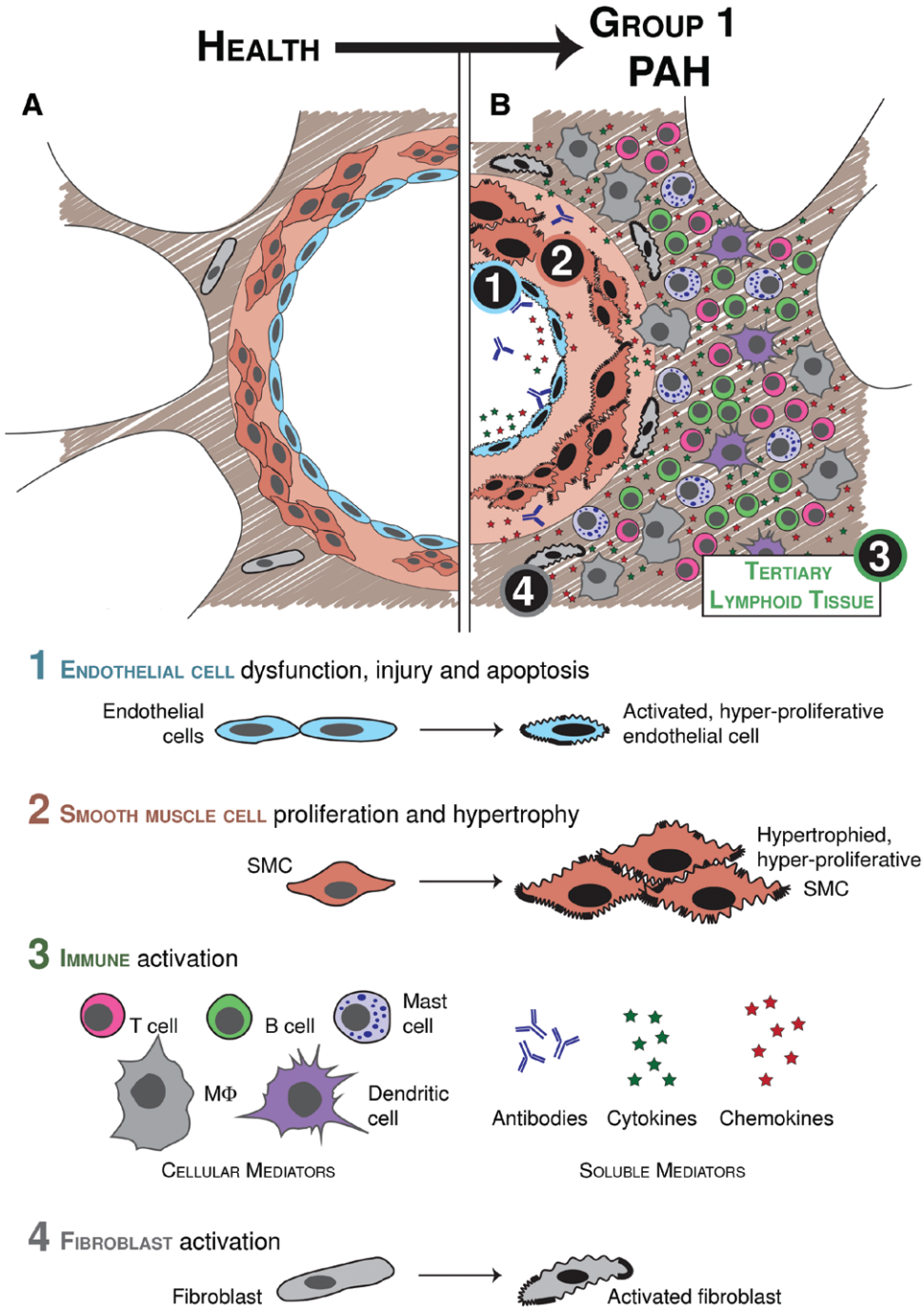

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Patients with pulmonary arterial hypertension (Group 1 pulmonary hypertension, including idiopathic, heritable, connective tissue disease–associated, congenital heart disease–associated pulmonary arterial hypertension, and others) present for noncardiac surgery with an exceptionally high risk of morbidity and mortality even when compared to patients with other forms of pulmonary hypertension.[1] Current pulmonary arterial hypertension–specific therapies are primarily pulmonary vasodilators. Yet pulmonary vasoconstriction only partially explains disease pathology, and the development of better therapies necessitates a deeper understanding of pulmonary arterial hypertension pathogenesis. Indeed, evidence links the immune system to pulmonary arterial hypertension pathogenesis (see fig.) and has fundamentally shifted our understanding of the disease mechanism.[2]

In pulmonary arterial hypertension lungs, endothelial apoptosis and the subsequent proliferation of an abnormal, reprogrammed subset of endothelial cells form a neointimal layer (fig. element 1). Smooth muscle cells hypertrophy and proliferate, leading to medial thickening and loss of vascular compliance (fig. element 2). Together, these phenomena narrow the vessel lumen, impeding blood flow. In the adventitia, lymphocytes, macrophages, dendritic cells, and mast cells form tertiary lymphoid tissue, which produces cytokines, autoantibodies, and other soluble mediators (fig. element 3). Release of these mediators from immune cells and activated fibroblasts further recruits immune cells (fig. element 4). These changes perpetuate vascular damage and drive pulmonary arterial hypertension. Protective elements of the immune system, however, including regulatory T cells,[3] help dampen this response.

Anesthesiologists will welcome agents for perioperative optimization of these high-risk patients.

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Competing Interests

The authors declare no competing interests.

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References

1. Pritts CD, Pearl RG: Anesthesia for patients with pulmonary hypertension. Curr Opin Anaesthesiol 2010; 23:411–6
2. Rabinovitch M, Guignabert C, Humbert M, Nicolls MR: Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension. Circ Res 2014; 115:165–75
3. Tamosiuniene R, Tian W, Dhillon G, Wang L, Sung YK, Gera L, Patterson AJ, Agrawal R, Rabinovitch M, Ambler K, Long CS, Voelkel NF, Nicolls MR: Regulatory T cells limit vascular endothelial injury and prevent pulmonary hypertension. Circ Res 2011; 109:867–79