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High-Dimensional Single-Cell Imaging Maps Inflammatory Cell Types in Pulmonary Arterial Hypertension

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Abstract : Recent experimental and clinical observations are advancing immunotherapies to clinical trials in pulmonary arterial hypertension (PAH). However, comprehensive mapping of the immune landscape in pulmonary arteries (PAs) is necessary to understand how immune cell subsets interact to induce pulmonary vascular pathology. We used multiplexed ion beam imaging by time-of-flight (MIBI-TOF) to interrogate the immune landscape in PAs from idiopathic (IPAH) and hereditary (HPAH) PAH patients. Massive immune infiltration in I/HPAH was observed with intramural infiltration linked to PA occlusive changes. The spatial context of CD11c+DCs expressing SAMHD1, TIM-3 and IDO-1 within immune-enriched microenvironments and neutrophils were associated with greater immune activation in HPAH. Furthermore, CD11c-DC3s (mo-DC-like cells) within a smooth muscle cell (SMC) enriched microenvironment were linked to vessel score, proliferating SMCs, and inflamed endothelial cells. Experimental data in cultured cells reinforced a causal relationship between neutrophils and mo-DCs in mediating pulmonary arterial SMC proliferation. These findings merit consideration in developing effective immunotherapies for PAH.

Keywords : pulmonary arterial hypertension, vascular remodeling, indoleamine 2-3-dioxygenase 1 (IDO-1), neutrophils, monocyte-derived dendritic cells, BMPR2 mutation, interferon gamma (IFN-γ)
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