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Title: Lung and circulating immune cell repertoires in PAH

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Body: Background: In PAH, tertiary lymphoid tissues (tLTs) connected to remodeled vessels, Ig deposits in the lung, and circulating autoantibodies directed to vascular wall components, argue for a role of adaptive immune response and autoimmunity, beyond inflammation. Aims and objectives: The presence of tLTs in the target organ is a hallmark of autoimmunity and suggests that lymphoid neogenesis could represent a critical step in maintaining humoral autoimmunity against persisting antigens, particularly autoantigens. Thus we searched for an immune signature in the lung and peripheral blood of PAH patients. Methods: 27 patients with PAH among which 9 were transplanted and 24 controls were included. T and B cell repertoires were analyzed after laser-microdissection of perivascular tLTs and in peripheral purified CD4+ T and CD19+ B cells. A strategy based on genomic detection of TCR (ImmunTraCkeR®) and BCR (Immun'Ig®) rearrangements by multiplex PCR on the whole TCR and BCR loci (http://www.immunid.com) was used to perform an exhaustive quantitative analysis of the combinatorial diversity of immune repertoires. Results: The repertoires in tLTs and in the periphery were compared assuming that stigmata of immune signatures in vascular lesions might be found in the periphery. Preliminary data revealed characteristic features in the immune repertoires in PAH patients. Changes in expression of specific rearrangements in CD4+ cells in the context of HLA type and presence of autoantibodies, together with restricted repertoires in tLTs, may suggest a local immune response. Conclusions: Immune signature may represent a non-invasive early diagnostic and/or prognostic marker of PAH condition, which could then be translated in daily clinical practice.