Basement membrane remodeling regulates neointimal hyperplasia and pulmonary arterial thickening in pulmonary hypertension due to left heart disease

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Introduction:
PH-LHD is initiated by passive congestion of blood from the left heart into the pulmonary vasculature, and is further aggravated by vascular remodeling, the pathomechanism of which is little understood. Here, we addressed the role of the endothelial cell (EC)-derived basement membrane (BM) in regulating smooth muscle cell (SMC) behavior in the context of neointimal hyperplasia (NH) in PH-LHD.

Methods and Results: By histological analysis of human PA samples, we identified SMC-formed NH as a hallmark of PH-LHD. NH increases PA wall thickness up to 10% and correlates with mean pulmonary arterial pressure (mPAP) indicating a potential role in PH pathogenesis. Transcriptomic analysis and immunohistological detection of collagen IV and laminin in PAs highlighted an upregulated expression of structural BM constituents and BM thickening in LHD patients without PH prior to NH formation. Furthermore, PH-LHD samples showed increased expression of matrix metalloproteinases capable of digesting BM proteins. This finding is in line with results of PA immunostainings, which identified diminished collagen IV and laminin in PH-LHD. While in immunostainings of control PAs, the EC, BM, and SMC layers appeared distinctly separated, SMCs intercalated with the BM in PAs of LHD without PH and PH-LHD patients. *In vitro*, SMC isolated from PH-LHD PAs showed significantly increased migration (scratch assay) and proliferation (Ki67 staining) by 5- and 2-fold, respectively, as compared to SMC from control PAs. To test whether BM may regulate NH in PH-LHD, we analyzed the effect of a decellularized BM, produced by either control or PH-LHD ECs, on migration and proliferation of control and PH-LHD SMCs. PH-LHD BM increased control SMC proliferation and migration, while control BM inhibited these functions in PH-LHD SMCs. To investigate the influence of the Hippo-signaling pathway as a regulator of (among others) cell proliferation and migration in this scenario, we examined YAP-1 expression and activation (nuclear translocation) in SMC immunostainings. YAP-1 was reduced in LHD w/o PH and increased in PH-LHD SMC immunostainings. While seeding isolated SMCs on control BM reduced YAP-1 expression, PH-LHD BM increased YAP-1 in SMC immunostainings. Additionally, PH-LHD BM increased YAP-1 nuclear translocation in SMCs, while control BM inhibited this process, demonstrating that the BM regulates not only YAP-1 expression but also its activation in SMCs.

Conclusion: Changes in BM structure and/or composition regulate SMC migration and proliferation, YAP-1 expression and activation, and potentially promote NH formation in PH-LHD. As such, the BM may present a promising target to prevent NH formation and – putatively – PH in LHD patients.

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