The primary cilium, a sensory apparatus of cells regulates the profibrotic capacity of fibroblasts in atrial fibrillation

Authors:
M Kawasaki¹, NA Nariswari¹, NWE Van Den Berg², J Neefs², ER Meulendijks², R Wesselink², SWE Baalman², WJP Van Boven², AHG Driessen², JR De Groot², ¹Amsterdam University of Medical Centers, University of Amsterdam, Department of Experimental Cardiology - Amsterdam - Netherlands (The), ²Amsterdam University of Medical Centers, University of Amsterdam, Department of Cardiothoracic Surgery - Amsterdam - Netherlands (The),

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[Background] Atrial fibrosis is a hallmark of atrial fibrillation (AF) and serves as an important arrhythmogenic substrate. It is formed by fibroblasts in response to tissue dyshomeostasis induced by multiple factors such as ageing, hypertension and inflammation. How fibroblasts phenotypically transform into an active form with enhanced profibrotic capacity in AF pathophysiology remains elusive. The primary cilium is an antenna-like small organelle, that function as a sensor to transduce external stimuli to intracellular signaling thereby potentially mediating the fibroblast’s profibrotic capacity. Their involvement in AF pathophysiology is not known.

[Objective] To explore the role of fibroblasts’ primary cilium in the formation of the atrial fibrosis in AF.

[Methods] Left atrial appendages (LAA) were obtained from persistent AF patients (AF: n=10) and patients without AF undergoing cardiac surgery (control: n=10). Primary cilia were immunostained with anti-acetylated α-tubulin in cryosections of the LAA. The loss of cilia in fibroblasts isolated from fresh LAA (AF: n=3, control: n=3) was induced by RNAi targeting IFT88, an essential factor for cilia formation. Gene expression and protein levels in LAA were quantified by qPCR and western blot, respectively (AF: n=20, control: n=20).

[Results] The ratio of fibroblasts with primary cilium was significantly decreased in LAA of AF cohort (AF: 14.7%±4.6 vs control: 25.9%±3.6, p<0.01). Correspondingly, the protein levels of acetylated α-tubulin, an exclusive component of cilia, were significantly decreased both in whole LAA and fibroblast fraction of AF cohort compared to control (p<0.05). The loss of primary cilia induced by RNAi in fibroblasts resulted in increased differentiation of fibroblasts into myofibroblasts and the expression of extracellular matrix genes in response to TGF-β1. Primary cilium is disassembled along with degradation of acetylated α-tubulin by HDAC6. Indeed, a negative correlation between the protein levels of acetylated α-tubulin and HDAC6 were observed in the LAA of AF cohort (p<0.05) but not in control. Furthermore, the gene expression of AURKA and HEF1, upstream activators of HDAC6, was increased by 1.5-fold (p=0.09) and 3-fold (p<0.001), respectively, in the LAA of AF cohort compared to control.

[Conclusion] The formation of primary cilia in fibroblasts is actively suppressed in AF via HEF1/AURKA/HDAC6 cascade, which in turn enhances the profibrotic response of fibroblasts. This study provides an innovative paradigm for fibrosis formation in AF, and implicates that the primary cilium of fibroblasts potentially become a novel therapeutic target to treat the AF substrate.