Uncovering a novel regulatory circuit between miR-182-5p and interleukin-6: new perspectives in human atrial fibrillation

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Background: Atrial Fibrillation (AF) remains the most common arrhythmia among cardiovascular diseases with multiple factors participating in its onset and progression, such as inflammatory mediators. Emerging evidence pointed out the prognostic value of interleukin-6 (IL-6) in AF and recently, the miR-182 was discovered to be causative of cardiac defects and arrhythmias in animal models.

Purpose: We hypothesized that miR-182 could be a molecular factor involved in adverse cardiovascular events linking IL-6 to AF.

Methods: Expression analyses were performed by RT-PCR in human left atrial samples of 49 patients: 11 controls, 18 wilth atrial dilation undergoing valve replacement (AF-prone) and 20 with chronic AF. Human induced pluripotent stem cells (hiPSC) were differentiated into cardiomyocytes (CMs) and cultured for 30/60 days. The spontaneous electrical activity of hiPS-CMs was measured by high-throughput (HT) fluorescence detection and the effects of miR-182-overexpression with/without muscarinic stimulation was studied. hiPS-CMs stably overexpressing miR-182 were treated for 24h with 10ng/mL tocilizumab, an IL-6 receptor antagonist. RT-PCR and Elisa assay were performed.

Results: In human left atrial tissue, miR-182-5p resulted differently expressed in accordance with atrial disease severity. Samples of AF patients showed the highest values of miR-182 expression, whose levels positively correlated with IL-6 expression levels (see Figure). miR-182 overexpression in hiPS-CMs (hiPSC-CM-miR182) significantly incremented IL-6 expression and IL-6 protein secretion. The hiPS-CM-miR182 showed a reduced AP frequency. Accordingly, the expression levels of the gene encoding for the pacemaker current, HCN4, was significantly downregulated, while the expression of CAMKIIgamma and NF-KB were upregulated (see Figure). Treatment of hiPS-CMs-miR182 with tocilizumab resulted in a partial recovery in HCN4 expression levels.

Conclusion: Our results support the hypothesis that miR-182 represents a molecular factor involved in the adverse cardiovascular events leading to AF at different levels of regulation. For the first time, we demonstrated a direct correlation between miR-182 and IL-6, uncovering a novel regulatory circuit that may have important consequences in the prevention or treatment of atrial disorders.