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Expanding the functional role of miRNAs in the establishment of permanent atrial fibrillation

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and is characterized by the loss of coordinated electrical activity in the atria. The pathophysiology of AF involves initial depolarization trigger events that subsequently evolve to the establishment of a chronic condition [1]. At the cellular level, persistent AF showed a specific gene expression fingerprint characterized by a decreased expression of genes related to ion channel function and transcription factors involved in inflammation and cellular stress responses [2,3]. The role of other genetic and epigenetic factors such as miRNA and mRNA expression levels from a cohort of 14 patients: 3 showing permanent AF, 5 with paroxysmal AF and 6 controls in sinus rhythm. Enrichment analysis of down-regulated mRNAs in permanent AF is considerably higher than the observed in paroxysmal AF, with an overlap of 10 transcripts between both groups. Enrichment analysis of down-regulated miRNAs and their putative down-regulated mRNA transcripts (Fig. 1) using a similar strategy already described only for paroxysmal AF patients [5]. Target prediction of miRNAs was performed by the Mirwalk 2.0 algorithm (http://zmf.umm.uni-heidelberg.de/apps/zmf/miwalk2). The number of down-regulated protein-coding mRNAs in permanent AF is considerably higher than the observed in paroxysmal AF, with an overlap of 10 transcripts between both groups. Enrichment analysis of down-regulated miRNAs in permanent AF allowed to define specific functional groups of genes related with voltage-gated ion channels, growth factors and extracellular matrix, transcription factors and acetylcholine-mediated activity (Fig. 1). Among these functional groups, the dysfunction in some of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels has been related with the onset and establishment of heart arrhythmias [6]. Some down-regulated transcription factors such as ATF3 have been associated with an angiotensin II-responsive specific spatial expression pattern in the atria, being part of the signaling pathway involved in cardiac response to neurohormonal stimulation [7]. In permanent AF, 80% of the down-regulated miRNAs and their putative targets of at least one the observed up-regulated miRNAs, and 74% of them are targeted simultaneously by 2 or more up-regulated miRNAs. Among the up-regulated miRNAs, miR-122-5p, miR-375 and miR-606 together were determined to be...
potential regulators of >65% of the down-regulated mRNAs. In contrast, in paroxysmal AF samples we only observed one up-regulated miRNAs with predicted down-regulated mRNAs showing a clear difference between initial and chronic disease stages. The presence of redundant regulatory activity mediated by miRNAs concomitant to the transcript down-regulation in permanent AF suggests that the contribution of miRNA-mediated regulatory networks is an important factor that collaborates to the establishment and stabilization of the chronic stage of the disease.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References


