Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Atrial Fibrillation-Mediated Upregulation of miR-30d Regulates Myocardial Electrical Remodeling of the G-Protein-Gated K^+ Channel, $I_{K.ACh}$

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Background: Atrial fibrillation (AF) begets AF in part due to atrial remodeling, the molecular mechanisms of which have not been completely elucidated. This study was conducted to identify microRNA(s) responsible for electrical remodeling in AF.

Methods and Results: The expression profiles of 1205 microRNAs, in cardiomyocytes from patients with persistent AF and from age-, gender-, and cardiac function-matched control patients with normal sinus rhythm, were examined by use of a microRNA microarray platform. Thirty-nine microRNAs differentially expressed in AF patients' atria were identified, including miR-30d, as a candidate responsible for ion channel remodeling by in silico analysis. MiR-30d was significantly upregulated in cardiomyocytes from AF patients, whereas the mRNA and protein levels of *CACNA1C*/Cav1.2 and *KCNJ3*/Kir3.1, postulated targets of miR-30d, were markedly reduced. *KCNJ3*/Kir3.1 expression was downregulated by transfection of the miR-30 precursor, concomitant with a reduction of the acetylcholine-sensitive inward-rectifier K^+ current ($I_{K.ACh}$). *KCNJ3*/Kir3.1 (but not *CACNA1C*/Cav1.2) expression was enhanced by the knockdown of miR-30d. The Ca^{2+} ionophore, A23187, induced a dose-dependent upregulation of miR-30d, followed by the suppression of *KCNJ3* mRNA expression. Blockade of protein kinase C signaling blunted the $[Ca^{2+}]$-dependent downregulation of Kir3.1 via miR-30d.

Conclusions: The downward remodeling of $I_{K.ACh}$ is attributed, at least in part, to deranged Ca^{2+} handling, leading to the upregulation of miR-30d in human AF, revealing a novel post-transcriptional regulation of $I_{K.ACh}$. (*Circ J* 2016; **80:** 1346–1355)

Key Words: Atrial fibrillation; $I_{K.Ach}$; miRNA microarray; miR-30d; Remodeling

Atrial fibrillation (AF), the most common cardiac rhythm disorder, is a major cause of cardiovascular morbidity and mortality.[1] AF is characterized by the rapid and irregular activation of the atrium[2] with diverse abnormalities, including electrical, structural, metabolic, neurohormonal, or molecular alterations.[3] Although the pathophysiology of AF is complex, it has traditionally been treated with antiarrhythmic drugs that control the rhythm by altering cardiac electrical properties, principally by modulating ion channel function.[3,4] However, treatment for AF with antiarrhythmic drugs have usually failed to control the rhythm or the pharmacological effect is limited, because the electrical characteristics of atrial cardiomyocytes are eventually altered or remodeled during the course of AF.[2,3] Atrial electrical remodeling is characterized by a marked shortening of the action potential duration (APD) and refractoriness.[3,5] In cardiomyocytes from patients with AF (hereafter referred to as AF cardiomyocytes), the amplitude of the L-type Ca^{2+} currents ($I_{Ca.L}$) and the transcription of the gene (*CACNA1C*) encoding Cav1.2 decreased, which might engage a homeostatic defense mechanism against chronic Ca^{2+} overload.[6] In contrast, the inward-rectifier K^+ current (I_{K1}), along with expression of the principal underlying subunit *KCNJ2* mRNA and its encoded Kir2.1 protein, is upregulated in AF.[7] Because I_{K1} is one of the key K^+ currents responsible for setting the resting potential and APD in atrial cardiomyocytes, the augmentation of I_{K1} is an important factor favoring AF

Received December 6, 2015; revised manuscript received April 3, 2016; accepted April 11, 2016; released online May 13, 2016 Time for primary review: 18 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-15-1276