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MicroRNAs emerging as mediators of remodeling with atrial fibrillation

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and is now established as an independent risk factor for stroke.[1] Moreover, a concomitant diagnosis of AF greatly complicates treatment for a number of disease processes such as diabetes and congestive heart failure. Given the recognized additional burden that AF places on the health-care system, significant research has been performed in an attempt to delineate mechanisms that contribute to AF initiation as well as progression. Understandably, there is an extensive body of research that has identified abnormalities in ionic channels/electrogenic processes that occur with AF (reviewed in References 2 and 3). For example, abnormalities in the abundance of sodium, potassium, and calcium channels have been reported with AF.[2,3] Therefore, the determination of cellular mechanisms that regulate protein abundance may shed new light on the pathogenesis of AF.

Recent interest in the field of regulation of protein abundance has focused on microRNAs, which are small, single-stranded, noncoding regulatory RNAs approximately 19–23 nucleotides in length. First described in nematodes and plants, microRNAs have been shown to modulate major regulatory mechanisms in eukaryotic cells involved in a broad array of cellular functions. MicroRNAs are transcribed in the nucleus and then undergo a multistepped “maturation” process involving truncation, exportation from the nucleus, and incorporation into a complex (termed the RNA-induced silencing complex [RISC]) that includes endonuclease activity from the Argonaute family of proteins.[4–6] Once incorporated into a RISC, the microRNAs regulate the targeted mRNA by degradation either through direct cleavage or by inhibiting protein synthesis.[7] Therefore, there is—almost always—a negative relationship between the levels of a particular microRNA and the abundance of the protein(s) targeted by that microRNA.[8]

The impact of microRNA-mediated regulation of cellular/extracellular processes is only just being realized. Presently, over 2000 human microRNA sequences have been identified (miRBase, Release 19),[9] and these numbers are steadily growing. It is estimated that microRNAs regulate over 60% of all protein-coding genes. A especially powerful feature of microRNA-mediated regulation is the ability of a single microRNA to regulate multiple mRNAs. Conversely, the mRNA for a given protein may be a target of multiple

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microRNAs.[6] Consequently, the pathways for microRNA-mediated regulation of protein abundance appear to be pervasively complicated.

In this issue of Heart*Rhythm*, Ling et al[10] have identified that the reduced expression of a potassium channel (SK3) was associated with permanent AF in some patients—sought to identify microRNA(s) that may regulate abundance of SK3. Ling et al have addressed this goal by carefully executing a confluence of methodologies. First, a microarray matrix was used to perform principal component analysis and to identify a list of microRNAs that were differentially expressed in these subjects with AF. Next, putative target site efficacy was assessed by using bioinformatics-based algorithms that scored potential interactions between the identified mRNA with a particular microRNA. As computational tools are being continually refined, it is becoming apparent that consensus results from multiple target prediction software programs—as used by the authors—optimize the in silico selection of mRNA targets for a particular microRNA. On the basis of these computational results, the authors have focused on microRNA-499, expression of which was increased in the atrial myocardium of subjects with AF, as a potential regulator of SK3 abundance. Further in vitro validation—as appropriate—was performed by 2 independent methodologies: (1) using a reporter system and (2) an assay designed to demonstrate that binding of the microRNA and the target mRNA occurred within a RISC complex, thus providing specificity that the mRNA for SK3 was a target of microRNA-499. Moreover, the authors clearly demonstrate the existence of an inverse correlation between the expression levels of microRNA-499 and SK3 protein levels, which increases the likelihood that this interaction is real and functional. Specifically, increasing levels of microRNA499 reduced abundance of SK3; conversely, interfering with microRNA-499 production increased SK3 levels in cell culture studies. Nevertheless, there are certain limitations of this study that must be recognized. First, the functional effects of altering SK3 abundance on potassium flux either in vitro or in vivo remains unknown. Specifically, whether and to what degree changes in SK3 levels contribute to AF initiation and progression remains to be determined. Second, as previously mentioned, microRNAs have the ability to target multiple mRNAs. Other validated targets of microRNA-499 include protein phosphatase 3 (Ppp3ca/Ppp3cb), calcium-dependent, calmodulin-stimulated phosphatases, and, importantly, the transcription factor SOX-6.[9] This demonstrates that miR-499 is not only involved with regulating abundance of ionic channels but may also target other mediators of cell function and phenotype. Furthermore, putative targets of microRNA-499 (using TargetScan, a widely used predictor of biological targets of microRNAs), include the mRNA for a number of ionic/electrogenic processes, such as KCNQ5, KCNH8, SCN2B, SCN4A, SCN7A, and TRPA1. Interestingly, the modulation of microRNA-499, as performed by Ling et al, did not affect abundance for a majority of these proteins. Intriguingly, however, there was a counterintuitive relationship between microRNA-499 levels and abundance of the voltage-gated potassium channel KCNQ5. As speculated in the article, this finding suggests the possibility of microRNA-499-mediated regulation of a transcription factor or other regulatory mechanism. Moreover, this finding underscores the importance of the in vitro/ex vivo validation of mRNA targets that were originally identified in silico. Finally, as the authors identified, the sample cohort was limited to 4 individuals with permanent AF. Therefore, whether findings from this study would apply to a broader cohort of patients with AF remains to be established.

The role that microRNAs play in the pathogenesis of various disease states has become an area of intense investigation.[4,6,11] Although the study by Ling et al[10] focused on microRNA-499, other investigations have identified changes in other microRNAs in the setting of AF. Targets for some of these other microRNAs have been identified as mRNAs for the L-type calcium channel, the inward rectifier potassium channel, the slow delayed rectifier current, and some related to remodeling of the extracellular matrix (reviewed in Reference 2). In this light, the study by Ling et al builds on the existing knowledge of microRNA-mediated regulation of ion channel abnormalities in the setting of AF. Future work in this field will likely determine not only additional microRNAs that are altered with AF but also those that may be used as biomarkers for diagnosis/prognosis of AF. Recent studies in cancer and heart disease have provided preliminary evidence that the circulating levels of certain microRNAs reflect the presence of the disease being examined.[5,12,13] Interestingly, Corsten et al[11] reported that circulating microRNA-499 levels were elevated following myocardial infarction and correlated with increased levels of troponin T. Thus, it is evident that we are only beginning to understand the complex field of microRNA-mediated regulation of biological systems, and studies such as those by Ling et al may reveal mechanistic underpinnings of AF progression.

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