Elucidating the Molecular Mechanisms of Arrhythmogenesis

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Atrial Fibrillation (AF) is the most commonly encountered cardiac arrhythmia in the clinical setting, and is a leading cause of stroke and heart failure. Hyperactivity of the ryanodine receptor type-2 (RyR2) ion channels results in excessive calcium (Ca2+) leaks, contributing to AF pathogenesis. Elevated RyR2 protein levels in the atria of paroxysmal AF (pAF) patients suggest that epigenetic regulation may be an underlying mechanism. Bioinformatic analysis identified miR-106b and miR-93, members of the miR-106b-25 cluster, as candidates for post-transcriptional regulation of RyR2. Quantitative real-time PCR indicated that miR-106b and miR-93 expression decreased in the atria of pAF patients, while luciferase assays confirmed that miR-93 binds to the RyR2-3'UTR to suppress its translation. Western blots revealed that RyR2 protein levels increased by 42% in miR-106b-25-/- mice compared to WT littermates. Ca2+ imaging of the atrial myocytes showed an increase in spark frequency, while telemetry ECG recordings exhibited greater occurrences of atrial ectopy. In vivo electrophysiology studies revealed elevated susceptibility to AF (75%), which was abolished by the RyR2-blocker, K201. The results of this interdisciplinary study demonstrate that miR-106b-25 cluster regulation of the RyR2 channel is a molecular mechanism in the onset of pAF, revealing a novel epigenetic target for therapeutic development.

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