Up-Stream Treatment Strategies for Patients with Atrial Fibrillation

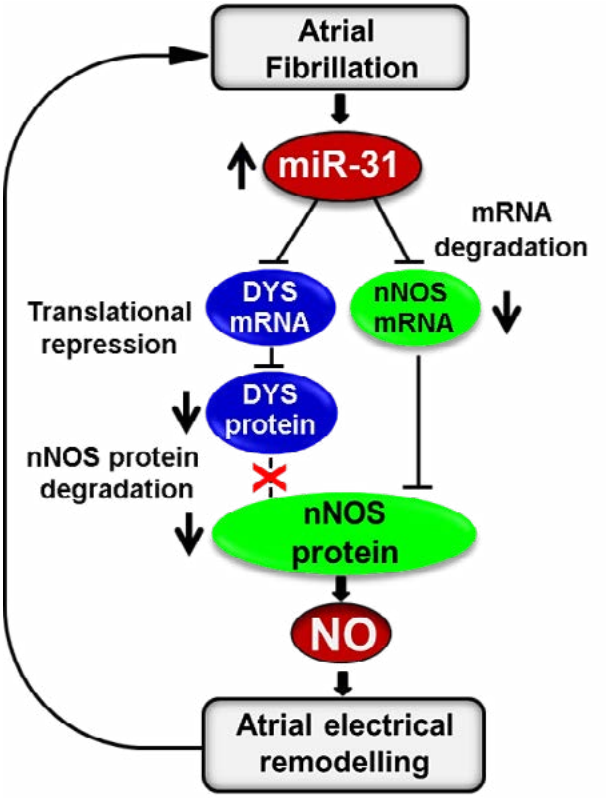
Atrial fibrillation (AF) is the most common heart rhythm disorder worldwide and a major public health burden due to its impact on the risk of stroke and heart failure. To date, therapeutic strategies to restore sinus rhythm in patients with AF have been marred by poor efficacy, lack of benefit on patient outcomes, and safety concerns.

AF leads to electrical remodelling of the atria, which in turn promotes AF maintenance and resistance to treatment. Although remodelling has long been a therapeutic target in AF, its causes remain poorly understood.

We show that atrial-specific up-regulation of microRNA-31 (miR-31) in goat and human AF depletes neuronal nitric oxide synthase (nNOS) by accelerating mRNA decay and alters nNOS subcellular localization by repressing dystrophin translation. By shortening action potential duration and abolishing rate-dependent adaptation of the action potential duration, miR-31 overexpression and/or disruption of nNOS signalling recapitulates features of AF-induced remodelling and significantly increases AF induction in vivo.

By contrast, silencing miR-31 in atrial myocytes from patients with AF restores dystrophin and nNOS and normalizes action potential duration and its rate dependency. These findings identify atrial-specific up-regulation of miR-31 in human AF as a key mechanism causing atrial dystrophin and nNOS depletion, which in turn contributes to the atrial phenotype begetting this arrhythmia.

These data have uncovered similarities between AF-induced molecular and electrical remodelling of the atrial myocardium and the cardiomyopathy of Duchenne Muscular Dystrophy, and identified miR-31 as a potential therapeutic target for both conditions.



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