Genetic–Genomic Insights Into the Metabolic Determinants of Spontaneous Atrial Fibrillation

Shamone R. Gore-Panter, PhD; Julie H. Rennison, PhD; David R. Van Wagoner, PhD

Atrial fibrillation (AF) is a complex aging-associated disease with multiple causes and inadequate treatment options. Beyond anticoagulants, the pharmacological treatments for AF have had limited efficacy and a potential for significant side effects. A major challenge in developing new drugs to treat or prevent AF has been the lack of suitable animal models of spontaneous AF.[1] Studies from Müller et al[2] have shown that overexpression of the cAMP response element modulator (CREM) in mice led to atrial enlargement with atrial and ventricular hypertrophy, leading to spontaneous AF and premature death. In additional studies of this model, changes in calcium cycling that promoted hypertrophy of atrial myocytes and chamber dilatation were shown to precede the development of electrical heterogeneity, conduction slowing, and atrial ectopy.[3] Complementary studies in human atrial tissues and in other animal models of AF have led to an improved understanding of the role of abnormal calcium cycling and metabolism in the development of atrial cardiomyopathies as a substrate for AF.[4]

See Article by Seidl et al

In this issue, Seidl et al[5] extend their previous work in the CREM-Ib-ΔC-X mouse model and now assess the changes in gene expression that underlie the atrial structural and electric remodeling that promotes the development of AF. In a recent study, our group used a large collection of left atrial tissues from maze surgery patients with varying persistence of AF (none versus paroxysmal versus persistent AF) to assess differences in gene expression associated with AF susceptibility and persistence.[6] Using a gene-set enrichment analysis approach, we observed that AF susceptibility was associated with decreased expression of the targets of CREB (cAMP response element-binding protein), HSF1 (heat-shock factor 1), ATF6 (activating transcription factor 6), and several other transcription factors. In contrast, AF persistence was associated with decreased expression in genes and gene sets related to ion channel function. CREB and CREM are closely related transcription factors. The CREM isoform (Ib-ΔC-X) that Seidl et al have overexpressed in mice binds to cAMP-responsive elements on gene promoters and prevents transcriptional activation.

Relative to human tissues studies, it is easier to evaluate the transcriptional changes that promote versus result from the presence of AF using well-defined animal models that develop spontaneous AF. There are few such models, and these are mostly in transgenic mice. In this elegant study, Seidl et al[5] used a 2×2 design to compare mRNA abundance in atrial tissues from young versus old and CREM transgenic versus wild-type animals. The mRNA analyses were supplemented with mass spectrometry analysis of atrial peptide abundance, patch clamp studies of isolated atrial myocytes to assess between-group differences in atrial action potential duration, and electron microscopy to assess differences in mitochondrial and sarcomeric structure.

As previously reported in their model, significant atrial dilation, electric heterogeneity, and calcium dysregulation were evident already in young (7 week) CREM-Ib-ΔC-X mice; here, they further document important metabolic changes that were linked to accumulation of glycogen and utilization of carbohydrates as an energy source, representing a switch to a fetal metabolic gene profile. Targets of PPAR-α (peroxisome proliferator–activated receptor α) and PGC1-α (PPAR-γ coactivator-1-α) were downregulated in the young transgenic versus wild-type mice; a similar trend was present in the older animals as well. In addition to CREM/CREB, it is interesting that HSF1 has been identified as an important modulator of PGC1-α activity.[7]

Although changes in the abundance of mitochondrial genes suggestive of changes in electron transport chain activity were noted at the mRNA level, few significant changes in mitochondrial structure were detected. Changes in mitochondrial function were not assessed. The role of obesity as an important modulator of AF risk is increasingly clear,[8–10] and the links between diet, mitochondrial function, and arrhythmogenesis represent a fertile area of inquiry.

Significant changes in ion channel and exchanger mRNA expression were evident in the transgenic mice, but these changes tended to result in action potential prolongation in both the transgenic and in older mice. In contrast, in most human studies, abbreviation of action potential duration is evident in AF.[11] The electrophysiological changes reported here are perhaps closer to those that occur in the canine ventricular tachypacing model, a model in which AF susceptibility occurs in parallel with the development of ventricular dysfunction.[12] In combination, these studies suggest that electrical and metabolic heterogeneity may be more important than changes in atrial refractory period, per se, as a determinant of AF. There is substantial evidence that metabolism and ion channel expression are closely linked in the ventricle[13,14]; a similar relationship in the atria seems likely.

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Seidl et al are commended for pursuing deeper studies of their interesting model. The current study further enhances our understanding both of the murine CREM-Ib-ΔC-X model and of the genes and gene networks that are impacted by overexpression of this important transcription factor. Their study suggests the interesting possibility that modulators of PPAR signaling may have a useful impact on the treatment or prevention of AF.

Disclosures

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