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Genetic - Genomic Insights into the Metabolic Determinants of Spontaneous AF

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Atrial fibrillation (AF) is a complex aging-associated disease with multiple etiologies and inadequate treatment options. Beyond anticoagulants, the pharmacologic 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 and colleagues have shown that overexpression of the cyclic AMP response element modulator (CREM) in mice led to atrial enlargement with atrial and ventricular hypertrophy, leading to spontaneous AF and premature death[2]. 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].

In this issue, Seidl and colleagues 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 electrical remodeling that promotes the development of AF [5]. In a recent study, our group used a large collection of left atrial tissues from Maze surgery patients with varying persistence of AF (none vs. paroxysmal vs. 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, heat-shock factor 1 (HSF1), ATF6, and several other

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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 and colleagues 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 very few such models, and these are mostly in transgenic mice. In this elegant study, Seidl and colleagues used a 2×2 design to compare mRNA abundance in atrial tissues from young versus old and CREM transgenic versus wildtype animals [5]. 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, electrical 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 peroxisome proliferator activated receptor alpha (PPAR-α) and PPAR-gamma coactivator-1A (PGC1A) were downregulated in the young transgenic vs. WT 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 PGC1A activity [7].

While 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 electrophysiologic 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 quite likely.

Seidl and colleagues 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 in the treatment or prevention of AF.

References

1. Van Wagoner DR, Piccini JP, Albert CM, Anderson ME, Benjamin EJ, Brundel B, Califf RM, Calkins H, Chen PS, Chiamvimonvat N, Darbar D, Eckhardt LL, Ellinor PT, Exner DV, Fogel RI, Gillis AM, Healey J, Hohnloser SH, Kamel H, Lathrop DA, Lip GY, Mehra R, Narayan SM, Olgin J, Packer D, Peters NS, Roden DM, Ross HM, Sheldon R, Wehrens XH. Progress toward the prevention and treatment of atrial fibrillation: A summary of the Heart Rhythm Society Research Forum on the Treatment and Prevention of Atrial Fibrillation, Washington, DC, December 9–10, 2013. Heart Rhythm. 2015; 12:e5–e29. [PubMed: 25460864]
2. Müller FU, Lewin G, Baba HA, Boknik P, Fabritz L, Kirchhefer U, Kirchhof P, Loser K, Matus M, Neumann J, Riemann B, Schmitz W. Heart-directed expression of a human cardiac isoform of cAMP-response element modulator in transgenic mice. The Journal of biological chemistry. 2005; 280:6906–14. [PubMed: 15569686]
3. Kirchhof P, Marijon E, Fabritz L, Li N, Wang W, Wang T, Schulte K, Hanstein J, Schulte JS, Vogel M, Mougenot N, Laakmann S, Fortmueller L, Eckstein J, Verheule S, Kaese S, Staab A, Grote-Wessels S, Schotten U, Moubarak G, Wehrens XH, Schmitz W, Hatem S, Müller FU. Overexpression of cAMP-response element modulator causes abnormal growth and development of the atrial myocardium resulting in a substrate for sustained atrial fibrillation in mice. Int J Cardiol. 2013; 166:366–74. [PubMed: 22093963]
4. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim YH, Lip GY, Ma CS, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR, Nattel S. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. Heart Rhythm. 2017; 14:e3–e40. [PubMed: 27320515]
5. Seidl MD, Stein J, Hamer S, Pluteanu F, Scholz B, Wardelmann E, Huge A, Witten A, Stoll M, Hammer E, Völker U, Müller FU. Characterization of the genetic program linked to the development of atrial fibrillation in CREM-Ib-ΔC-X mice. Circulation Arrhythmia and electrophysiology. 2017:10.
6. Deshmukh A, Barnard J, Sun H, Newton D, Castel L, Pettersson G, Johnston D, Roselli E, Gillinov AM, McCurry K, Moravec C, Smith JD, Van Wagoner DR, Chung MK. Left atrial transcriptional changes associated with atrial fibrillation susceptibility and persistence. Circulation Arrhythmia and electrophysiology. 2015; 8:32–41. [PubMed: 25523945]
7. Ma X, Xu L, Alberobello AT, Gavrilova O, Bagattin A, Skarulis M, Liu J, Finkel T, Mueller E. Celastrol Protects against Obesity and Metabolic Dysfunction through Activation of a HSF1-PGC1alpha Transcriptional Axis. Cell Metab. 2015; 22:695–708. [PubMed: 26344102]
8. Gorenek B, Pelliccia A, Benjamin EJ, Boriani G, Crijns HJ, Fogel RI, Van Gelder IC, Halle M, Kudaiberdieva G, Lane DA, Bjerregaard Larsen T, Lip GY, Lochen ML, Marin F, Niebauer J, Sanders P, Tokgozoglu L, Vos MA, Van Wagoner DR, Document r, Fauchier L, Savelieva I, Goette A, Agewall S, Chiang CE, Figueiredo M, Stiles M, Dickfeld T, Patton K, Piepoli M, Corra U, Manuel Marques-Vidal P, Faggiano P, Schmid JP, Abreu A. European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS). European journal of preventive cardiology. 2017; 24:4–40.
9. Nalliah CJ, Sanders P, Kottkamp H, Kalman JM. The role of obesity in atrial fibrillation. Eur Heart J. 2016; 37:1565–72. [PubMed: 26371114]
10. Abed HS, Samuel CS, Lau DH, Kelly DJ, Royce SG, Alasady M, Mahajan R, Kuklik P, Zhang Y, Brooks AG, Nelson AJ, Worthley SG, Abhayaratna WP, Kalman JM, Wittert GA, Sanders P. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. Heart Rhythm. 2013; 10:90–100. [PubMed: 23063864]

11. Van Wagoner DR, Pond AL, Lamorgese M, Rossie SS, McCarthy PM, Nerbonne JM. Atrial L-type Ca2+ currents and human atrial fibrillation. Circ Res. 1999; 85:428–36. [PubMed: 10473672]
12. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs : atrial remodeling of a different sort. Circulation. 1999; 100:87–95. [PubMed: 10393686]
13. Barth AS, Kumordzie A, Tomaselli GF. Orchestrated regulation of energy supply and energy expenditure: Transcriptional coexpression of metabolism, ion homeostasis, and sarcomeric genes in mammalian myocardium. Heart Rhythm. 2016; 13:1131–9. [PubMed: 26776558]
14. Barth AS, Tomaselli GF. Cardiac metabolism and arrhythmias. Circ Arrhythm Electrophysiol. 2009; 2:327–335. [PubMed: 19808483]