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Editorial

Deciphering the Intricate Molecular Bases of Atrial Fibrillation

Diego Franco

Cardiovascular Development Group, Department of Experimental Biology, Faculty of Experimental Sciences, University of Jaen, 23071 Jaen, Spain; dfranco@ujaen.es

Atrial fibrillation (AF) is the most prevalent electrophysiological disorder in humans [1–3]. With an estimated incidence of 2% in the general population, rising to almost 10% in the elderly, AF is characterized by an irregular beating of the atrial chambers that frequently originates at the entrance of the pulmonary veins into the left atrium [4–6]. Depending on the duration and the course of the irregular beats, atrial fibrillation is categorized into paroxysmal, permanent, or chronic AF [7]. AF can course alone, i.e. lone AF, but in many cases is associated with concomitant and/or even triggering additional cardiovascular diseases, such as hypertension, hyperthyroidism, valvular heart diseases, among others [1–3]. Mechanistically, both structural and electrophysiological alterations can contribute to the onset of AF; however, it is not always easy to tell which occurs first [4–6]. Atrial dilation, inflammation, and fibrosis are among the most common structural defects that can promote AF initiation. On the other hand, the impaired functioning of a large array of electrophysiological determinants has been extensively associated with the onset of AF [7,8]. In recent years, significant genetic analyses of the plausible molecular determinants of atrial fibrillation have emerged. While there are a large number of studies linking single-point mutations in distinct cardiac ion channels in patients with AF [7,8], the incidence and prevalence of such mutations only explains a very small subset of AF patients [9]. The emergence of novel genetic approaches, such as genome-wide association studies (GWASs), has greatly advanced our understanding of the genetic and molecular bases of atrial fibrillation. Pioneering work by Gudbjartsson et al. [10] identified risk variants on the 4q25 locus that are significantly associated with lone AF. PITX2, the closest transcription factor with cardiac involvement on this locus [11–13], has since been widely documented as a key triggering determinant of AF onset and/or susceptibility [14–17]. In addition, PITX2 expression is modulated by AF-triggering cardiovascular conditions, such as hypertension and hyperthyroidism [18]. Importantly, the plausible regulatory role of several of these risk variants in Pitx2 function and expression has also been reported in experimental models [19–21], yet their implications in humans remain elusive. In addition, novel GWAS and meta-GWAS analyses in AF patients have unraveled almost a hundred AF-associated risk variants, most of them located in intergenic regions [22,23], yet 4q25/PITX2 remains the most strongly associated locus. In this context, it is also important to highlight that several of these new AF-associated genes are found downstream of Pitx2 in different AF experimental models [18].

In *Hearts*, Beneke & Molina [24] recently reviewed the molecular basis of atrial fibrillation initiation and maintenance. The authors explored the literature around the electrophysiological mechanisms linked to AF, and they detail the onset of ectopic activity in the atrial chambers, conduction abnormalities, and enhanced automaticity. Subsequently, they investigated the distinct molecular regulatory networks that can initiate AF, to provide an update on the state of the art of genetic contributions, the role of sympathetic signaling, oxidative stress, and inflammation. Finally, all the concepts and mechanisms were placed into a clinical context, including their plausible therapeutic implications.

In addition, within *Hearts*, new evidence on the functional role of PITX2 in the regulation of calcium homeostasis is reported by Herraiz-Martinez et al. [25]. The authors

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identified novel PITX2 mutations in an AF patient. Furthermore, they experimentally demonstrated that such mutations, located in the PITX2 homeodomain region, are required for the proper transactivation of Pitx2-downstream genes, such as *Nppa* and *Shox2*, and that they are critical to controlling the sarcoplasmic reticulum calcium content in atrial cardiomyocytes. Mechanistically, these PITX2 point mutations favor irregular and alternating calcium transient amplitudes that correlate with a deterioration in beat-to-beat stability. Thus, the authors propose that such mutations in PITX2 can be causative of AF onset in the patient.

To summarize, these studies published in *Hearts* revisit, and provide fresh insights into, the genetic and molecular mechanisms leading to atrial fibrillation, the most prevalent electrophysiological disorder in the human population.

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