EDITORIAL

The Fly Heart: Genetics, Physiology, Medicine and Beyond

Corazón de mosca: genética, fisiología, medicina y más allá

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The definition of organisms called "models" in biological research has allowed understanding the fundamental laws and processes of living beings. In biomedicine, the study of these species has led to the identification of the molecular mechanisms involved in many diseases and to the development of their treatments. For over a century, the fly *Drosophila melanogaster* has been one of the most emblematic and relevant model organisms in biology. This species has led to the discovery of many fundamental processes in molecular and cellular biology, heredity, population genetics and developmental biology, among others, many of them with important medical applications.

Currently, *Drosophila melanogaster* is an organism with a solid and significant number of genetic and biotechnological resources and tools to study in depth new biological and medical processes, mechanisms and phenomena. The advent of genomic biology enabled the identification of the entire genome sequence of this species in 2000, (1) showing that ~ 70% of human genes are conserved in *Drosophila*. Consequently, the urgent implication of this fly in the understanding of different human pathologies has been relevant and immediate. The study of cardiac physiology and its diseases is one of the fields of research, whose development will have significant medical implications.

The group of Paola V. Ferrero, from the Centro de Investigaciones Cardiovasculares of Universidad Nacional de La Plata and the Department of Basic and Experimental Sciences of Universidad Nacional del Noroeste de Buenos Aires have been pioneers in the use of *Drosophila* and its genetic tools in Argentina to study the molecular biology underlying heart physiology. This group has already demonstrated a strong relationship between aging and cytosolic calcium (Ca^{2+}) transient, a divalent ion essential for cardiac contraction. (2) The proteins responsible for this process are codified by highly conserved genes both in sequence and function between *Drosophila* and humans. One of these proteins is SERCA, a key polypeptide for Ca^{2+} reuptake into the sarcoplasmic reticulum. The studies of Ferrero and of other research groups have shown that Ca^{2+} transient and Ca^{2+} management impairment are among the cellular mechanisms producing cardiac dysfunction. This means that a consequence of abnormal cardiac excitation-contraction coupling is intracellular Ca^{2+} overload, which is one of the main causes of ischemia-reperfusion injury and arrhythmias in humans. (3, 4)

In the work published in this issue of the *Argentine Journal of Cardiology*, Santalla, Portiansky and Ferrero (5) genetically manipulate several *Drosophila* strains to study aging and the effect of alkaloids affecting the central nervous system (in this case, caffeine) on the Ca^{2+} transient, as well as their influence on cardiac contraction frequency. Their results demonstrated that they are correlated, similarly to what occurs in humans. This means that caffeine increases the Ca^{2+} transient throughout the *Drosophila* lifespan. They also observed that aging has also influence on the effect of caffeine on heart rate, and that in this phenomenon SERCA is expressed as in human cardiac tissue, in the cellular intercalated disks.

The results of Santalla et al. (5) indicate that *Drosophila* is a good model to study the genetics of various cardiac physiology phenomena in humans, such as aging and the addiction to substances affecting the nervous system, as caffeine. As stated by the authors, their results demonstrate that the cardiac tissue of this model organism "reproduces de intracellular Ca^{2+} dynamics observed in mammals in different experimental situations, validating the use of the model for future genomic, transcriptomic and proteomic research to study genes and gene products exposed to different noxious agents". This will allow the application of drugs attenuating or exacerbating the activity of distinct proteins and metabolic pathways that regulate the activity of the heart.

One of these proteins it would be serine/threonine kinase TOR (target of rapamycine), crucial in the control of cellular growth in response to different cellular stimuli as growth factors and hormones, as well as to different stresses. (6) TOR integrates these signals to modulate the overall process of protein synthesis by controlling the regulating enzymes eIF4E and 4E-BP. Thus, TOR is essential in the regulation of genetic expression and is highly conserved in eukaryotic organisms. (6) It has recently been shown that TOR is associated with cardiac hypertrophy in humans, (7, 8) but its mechanism of action in this context is not clearly

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known. Thus, the group of Ferrero has also recently started the study of the TOR pathway in the cardiac tissue of *Drosophila*, demonstrating that TOR, eIF4E and 4E-BP are involved in intracellular Ca^{2+} management. These findings emphasize the importance of Drosophila as a model to understand the genetics and physiology of the human heart as well as its validity in the design of different drug treatments.

In the future, the advent of new technologies will broaden the horizon of *Drosophila* as a model for the study of human heart function. For example, gene edition with newly developed and powerful methods (9) promises numerous applications for the study of the fly heart to understand its genetics, physiology, medicine and even beyond.

Conflicts of interest

None declared.
(See authors' conflicts of interest forms in the website/Supplementary material).

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