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Opinion

Role and Therapeutic Perspectives of mTOR in Cardiovascular Diseases

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The mechanistic (previously named 'mammalian') receptor of rapamycin, mTOR, constitutes one of the major nodes for the integration of eukaryotic signalling and environmental conditions, hence controlling metabolism and organism physiology [1]. mTOR is a serine/threonine protein kinase, in the PI3K/AKT axis, which forms the catalytic subunit of two distinct protein complexes: mTORC1 and mTORC2. mTORC1 nucleates signals from growth factors, oxygen levels, amino acids availability, stress responsiveness and energy variations to address proteins, lipids and nucleic acids synthesis, eventually regulating cell growth. On the other hand, mTORC2 responds to a plethora of growth factors for the coordination of actin cytoskeletal organisation and cell cycle, survival and proliferation. Due to these numerous functions, mTOR is crucial in the emergence and development of many different disorders, including cardiovascular diseases (CVD).

In a recent review in *Circulation Research*, Sciarretta., *et al.* [2] give a thorough overview of the main aspects regarding mTOR implication in CVD. They break down both mTORC1 and mTORC2 pathways in the heart, from response to oxidative stress conditions, hypertrophic signals and remodelling factors upon ischemic injury, to ageing process, making emphasis in the most relevant clinical trials driving all these issues, which are being carried on with innovative assessment to mTOR axis regulation. It is worth noting also that they painstakingly detail the current knowledge about mTORC2 control of cardiac haemostasis and its role in the heart adaptation to mechanical stress. Moreover, interesting perspectives are also highlighted in the field of implantation, altogether smoothing the way for future lines of research.

However, a deeper debate is missed out regarding mTOR action on fine-tuning the regulation of developmental genes networks involved in CVD. Albeit the genetic component of cardiomyopathies is discussed, linkage among crucial transcription factors in both early development and adult disorders emergence is scarce, and conclusions are thus superficial. In this regard, arrhythmias and the implementation of genome-wide association studies (GWAS) would serve as a pretty example on how these interactions take place and whether population statistics can shed light on complex regulatory gene networks.

This is the case of atrial fibrillation, the most common cardiac arrhythmia in humans, where GWAS has unravelled strong associations with non-coding regions of the genome, and has made researchers to closely look for enhancers and regulatory elements of neighbourhood genes. Thus, *PITX2* regulation of atrial fibrillation has being unveiled to be a consequence of distant 4q25 located regulatory elements [3]. *PITX2* encodes an evolutionarily conserved homeodomain transcription factor that is involved in the establishment of left-right asymmetry and cardiovascular development in the vertebrate embryo, and its PITX2c isoform is also active in adult heart. Interestingly, mTORC1 promotes *PITX2* expression [4] and this regulation might be mediating the atrial fibrosis attenuation observed after rapamycin inhibition of mTORC1 [5].

Another weakness in Sciarretta's review is the lack of debate regarding the critical role of the immune system on a vast number of mechanisms involved in heart physiology in normal conditions, and in cardiac injury and posterior healing, as well as that most of those mechanisms are closely controlled by the PI3K/AKT/mTOR axis.

Heart failure emergence is strongly associated to maladaptive innate immune system response [6]. Remarkably, new macrophages are immediately recruited to the infarcted region and become M1-polarised, then acquiring pro-inflammatory and antimicrobial activities. Nevertheless, after several days, macrophages shift to an M2-polarised anti-inflammatory stage, thus attenuating inflammation to address

tissue repair [7]. Likewise, evidences are also available on how T cells are crucial for both cardiac injury and healing process. In this line, cardiac fibrosis, which represents one of the first structural changes in heart remodelling previous to heart failure, but also a protective process to heal and repair after injury, is orchestrated by TH1 effector cells [8]. Impairment of this activity during events such as exhaustion or anergy of T cells, drastically reduce macrophages, monocytes and neutrophils mediation for proper cardiac fibrosis process.

It is noteworthy that mTORC1 exerts a tight control in both macrophages polarisation [9] and T-cells exhaustion/anergy [10]. Accordingly, mTORC1 regulates intermediate stages to guarantee the metabolic changes necessary to accomplish the macrophages/monocytes polarisation shifting and T cells activated stages. As a matter of fact, apoptosis, angiogenesis and autophagy, three of the main pathways involved in heart injury and healing development, are strictly controlled in those cells by mTOR axis [11].

Overall, PI3K/AKT/mTOR axis is crucial in the maintenance of heart homeostasis. Taking into consideration all these facts will improve quality of treatments and increase therapeutic options in CVD.

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