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EDITORIAL COMMENT

Could lncRNA CASC15 be a new target to limit myocardial ischemia/reperfusion injury?

Poderá o lncRNA CASC15 ser um novo alvo para limitar a lesão miocárdica de isquemia/reperfusão?

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Ischemic heart disease is the leading cause of death worldwide. In the event of an acute myocardial infarction (AMI), timely revascularization of the myocardium is imperative to salvage the ischemic region and reduce infarct size.[1] However, in addition to the ischemic injury caused by nutrient and oxygen deprivation, when blood flow is restored (through percutaneous coronary intervention or coronary artery bypass grafting), the myocardium is paradoxically harmed through a myriad of molecular and cellular events, including generation of additional reactive oxygen species, increased calcium cycling, complement activation, acute inflammation, immune system activation, apoptosis and other forms of proinflammatory cell death.[1,2] Therefore, despite advancements in myocardial revascularization, high morbidity and mortality is still observed after AMI, which can be explained by an adverse cardiac remodeling response (a known substrate of heart failure).[3]

With the aim of improving the prognosis of AMI patients, significant efforts have been made in recent decades through numerous pharmacological cardioprotection strategies to reduce post-intervention ischemia/reperfusion (I/R) injury and thereby limit adverse myocardial remodeling. Some have shown potential in the preclinical stage but failed or were inconsistent during clinical testing, such as adenosine, nitrite, cyclosporine A, and protein kinase C-delta inhibitors.[1] Other promising drugs are still in the preclinical stage, such as NAD+ precursors, malonate (a succinate dehydrogenase inhibitor), NLRP3 inflammasome inhibitors, caspase and calpain inhibitors, and angiopoietin-like peptide 4.[2,4] Nonetheless, final translation to clinical practice is yet to be achieved, and no effective therapeutic strategy to limit infarct size is currently established.

Interest in RNA-based therapeutics is growing, enhanced by the success of mRNA-based COVID-19 vaccines. With advances in sequencing technologies, we are now better equipped to dissect the regulatory role of non-coding RNAs, including microRNAs (miRs) and long non-coding RNAs (lncRNAs), in the heart. Consequently, miRs and lncRNAs are increasingly seen as a class of surrogate biomarkers and therapeutic targets for various cardiac diseases. For instance, Santos-Faria et al. found that miR-4268 correlates with left ventricular mass regression following aortic valve replacement.[5] In the context of myocardial I/R injury, it is being reported that many lncRNAs regulate cardiomyocyte death, among other effects. For instance, the lncRNA

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necrosis-related factor (NRF) has been proposed as a target for I/R injury because NRF acts as a sponge for miR-873, precluding its protection against cell death.[6]

During revascularization, targeting cell death pathways is particularly appealing because infarct size, which largely depends on the promptness of the intervention, is strongly associated with all-cause mortality and hospitalization for heart failure within one year.[7] In this regard, the study by Sun and Mei published in this issue of the *Journal*[8] contributes with evidence of a new candidate lncRNA target to mitigate I/R injury by promoting cell survival. The authors focused on cancer susceptibility 15 (CASC15), better known for its pleiotropic role in different types of cancer, from cell proliferation and migration to apoptosis.[9] There is much less knowledge of CASC15s role in the heart, the only study being by Li et al., who reported that CASC15 has a pro-hypertrophic effect by competitively binding to miR-423-5p, favoring TLR4 mRNA translation.[10] Based on the observation that serum CASC15 levels are higher in patients with atherosclerosis and AMI, Sun and Mei sought to investigate the potential mechanistic role of this lncRNA in the context of I/R injury. For this purpose, they used an in vitro model of I/R injury by exposing H9c2 cells to hypoxia/reoxygenation (H/R). They first reported that CASC15 was significantly increased in cells exposed to H/R, which corroborates previous observations in serum. They then found that inhibiting CASC15 conferred protection to H9c2 cells against oxidative stress after a H/R insult and suppressed apoptosis, favoring cell survival. Mechanistically, the protection was shown to be mediated, at least in part, by enhancing miR-542-3p levels. Previously, CASC15 inhibition was found to be protective in an in vitro model of acute ischemic stroke through upregulation of another miRNA (miR-338-3p).[11]

Given the potential of CASC15 inhibition in the context of I/R injury, the multiplicity of mRNA (and potentially protein) targets requires further research to obtain a complete picture of the CASC15-mediated regulation of cell survival/death pathways. Furthermore, considering the sometimes opposing effects of CASC15 in different tumor types, it should be borne in mind that CASC15 may have disparate effects on other cells implicated in I/R injury, including endothelial cells, vascular smooth muscle cells, fibroblasts, neutrophils, and other immune system players. Therefore, clarification of this issue would be of great value before moving on to preclinical models. Regardless, Sun and Mei's findings add value to the field, identifying CACS15 as a new potential lncRNA target to mitigate the dismal effects of I/R on the myocardium.

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Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Heusch G. Myocardial ischaemia–reperfusion injury and cardioprotection in perspective. Nat Rev Cardiol. 2020;17:773–89.
2. Rout A, Tantry US, Novakovic M, et al. Targeted pharmacotherapy for ischemia reperfusion injury in acute myocardial infarction. Expert Opin Pharmacother. 2020;21:1851–65.
3. Jenča D, Melenovský V, Stehlik J, et al. Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail. 2021;8:222–37.
4. Wang Q, Zuurbier CJ, Huhn R, et al. Pharmacological cardioprotection against ischemia reperfusion injury – the search for a clinical effective therapy. Cells. 2023;12:1432.
5. Santos-Faria J, Gavina C, Rodrigues P, et al. MicroRNAs and ventricular remodeling in aortic stenosis. Rev Port Cardiol. 2020;39:377–87.
6. Wang K, Liu F, Liu CY, et al. The long noncoding RNA NRF regulates programmed necrosis and myocardial injury during ischemia and reperfusion by targeting miR-873. Cell Death Differ. 2016;23:1394–405.
7. Stone GW, Selker HP, Thiele H, et al. Relationship between infarct size and outcomes following primary PCI. J Am Coll Cardiol. 2016;67:1674–83.
8. Sun S, Mei X. Effect of CASC15 on apoptosis and oxidative stress of cardiomyocytes after hypoxia/reperfusion injury. Rev Port Cardiol. 2024;43, http://dx.doi.org/10.1016/j.repc.2023.04.017.
9. Gu X, Chu Q, Zheng Q, et al. The dual functions of the long noncoding RNA CASC15 in malignancy. Biomed Pharmacother. 2021;135:111212.
10. Li C, Zhou G, Feng J, et al. Upregulation of lncRNA VDR/CASC15 induced by facilitates cardiac hypertrophy through modulating miR-432-5p/TLR4 axis. Biochem Biophys Res Commun. 2018;503:2407–14.
11. Chen C, Wang L, Wang L, et al. LncRNA CASC15 promotes cerebral ischemia/reperfusion injury via miR-338-3p/ETS1 axis in acute ischemic stroke. Int J Gen Med. 2021;14:6305–13.