Journal of Cardiovascular Translational Research
https://doi.org/10.1007/s12265-024-10536-4

EDITORIAL

Cirbp: A Key Regulator in Hypothermic Cardioprotection of Aged Donor Hearts During Transplantation

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Received: 27 May 2024 / Accepted: 7 June 2024

Heart transplantation is the most effective strategy for treating end-stage heart failure. However, the shortage of available donor hearts is an increasingly prominent issue. Due to the low survival rates of aged donor hearts, those older than 45 years are generally not recommended for transplantation. It is essential to protect donor hearts from ischemia and hypoxia by using cold storage. Dysfunction of factors that respond to hypothermia may impair the protective mechanisms of aged donor hearts in cold storage, resulting in myocardial damage during transplantation.

Cold inducible RNA-binding protein (CIRBP), a nuclear protein highly homologous across mammals, was initially identified in studies of cold stress response. As one of the cold-shock proteins (CSPs), CIRBP can be rapidly induced under cellular stress conditions, such as hypothermia, hypoxia, and ultraviolet radiation, to stabilize target mRNAs. It regulates their translation by selectively binding to the untranslated region at the 3' end of the transcripts, thereby promoting cellular responses to various extracellular stresses. Studies have demonstrated that CIRBP increases the concentration of ubiquinone (CoQ10) in the heart through the cardiac ubiquinone biosynthesis pathway, thereby resisting the attenuation of hypothermic cardioprotection caused by chronic hypoxia during cardiopulmonary bypass [1]. Another study indicated that while CIRBP is abundant in the brain of infants, its expression level decreases with age [2]. Ferroptosis, a regulatory cell necrosis caused by lipid peroxidation induced by free iron and reactive oxygen species, may also be influenced by CIRBP in relation to the NAD(P)H/FSP1/CoQ10, one of the ferroptosis defense systems. Thus, CIRBP may play a role in myocardial damage induced by ferroptosis, which could contribute to the failure of aged donor hearts in maintaining hypothermia protection during heart transplantation.

A recent study by Zhu et al., published in the Journal of Clinical Investigation, entitled "*Cirbp* suppression compromises DHODH-mediated ferroptosis defense and attenuates hypothermic cardioprotection in an aged donor transplantation model" discovered that inhibiting *Cirbp* in aged hearts reduced the dihydroorotate dehydrogenase (DHODH) mediated ferroptosis defense, thereby weakening hypothermic cardioprotection and exacerbating the ferroptosis in transplantation [3].

To confirm the hypothermic cardioprotection of aged donor hearts, hearts from 10-week-old (young) and 1-year-old (aged) rats were transplanted into young rats after cold storage (6 h). The heart function of aged donor hearts was significantly reduced after transplantation. Moreover, with the treatment of liproxstatin-1 (a ferroptosis inhibitor) during cold storage, it was observed that the primary form of injury in aged donor hearts post-transplantation was ferroptosis, induced by the impairment of hypothermic cardioprotection during cold storage. The study further investigated the

Editor-in-Chief Enrique Lara-Pezzi oversaw the review of this article.

Comment on: Y. Zhu, C. Jiang, J. He, C. He, X. Zhou, X. Huang, Y. Shen, L. Wu, Y. Li, B. Feng, Y. Yan, J. Li, H. Zhang, Y. Liu, *Cirbp* suppression compromises DHODH-mediated ferroptosis defense and attenuates hypothermic cardioprotection in an aged donor transplantation model. J Clin Invest. 2024;134(9):e175645.

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Published online: 15 July 2024

mechanisms linking aging to the impairment of hypothermic cardioprotection. The results demonstrated that the expression of CIRBP is inhibited by the decreasing of its transcriptional factor SP1 and the inhibited translocation of *Cirbp* from nucleus to cytoplasm in aged donor hearts, suggesting that *Cirbp* is a crucial regulator in the impairment of hypothermic cardioprotection in these hearts. Further examinations revealed that *Cirbp* deficiency attenuates hypothermic cardioprotection in young donor hearts during cold storage in vivo and exacerbates ferroptosis in cardiomyocytes induced by a cold ischemia model in vitro. Conversely, *Cirbp* overexpression improves hypothermic cardioprotection in aged donor hearts during cold storage. Mechanistically, CIRBP was proved to bind to *Dhodh* mRNA, promoting its translation and subsequently increasing the concentration of $CoQH_2$ in hearts, which inhibits ferroptosis induced by the impairment of hypothermic cardioprotection during cold storage. Lastly, treatment with a *Cirbp* agonist (Zr17-2) during cold storage was shown to enhance hypothermic cardioprotection in aged donor hearts.

In summary, the suppression of *Cirbp* expression by SP1 in aged donor hearts leads to the inhibition of *Dhodh* mRNA translation and a decline in $CoQH_2$ proportion. Thus, the hypothermic cardioprotection in aged donor hearts during cold storage is attenuated, resulting in increased ferroptosis levels. The use of a ferroptosis inhibitor (liproxstatin-1) and a *Cirbp* agonist (Zr17-2) improves hypothermic cardioprotection in aged donor hearts, offering a promising strategy to protect cardiac function in transplantation and increase the survival rate of patients post-transplantation. This study has significant clinical implications for enhancing the efficacy of aged donor hearts in transplantation and expanding the selection criteria for donor hearts.

Funding This work was supported by grants from the National Natural Science Foundation of China (82020108002 and 82225005 to J.X.), the Science and Technology Commission of Shanghai Municipality (23410750100, 20DZ2255400 and 21XD1421300 to J.X.), as well as the "Dawn" Program of Shanghai Education Commission (19SG34 to J.X.).Research Involving Human Participants and/or Animals This article does not contain any studies with human participants or animals performed by any of the authors.

Declarations

Informed Consent This article does not contain any studies with human participants.

Conflict of Interest Junjie Xiao is an editor of Journal of Cardiovascular Translational Research. The other authors declare no competing interests.

References

1. Liu Y, et al. Chronic hypoxia-induced Cirbp hypermethylation attenuates hypothermic cardioprotection via down-regulation of ubiquinone biosynthesis. Sci Transl Med. 2019;11(489):eaat8406.
2. Jackson TC, Kotermanski SE, Kochanek PM. Infants Uniquely Express High Levels of RBM3 and Other Cold-Adaptive Neuroprotectant Proteins in the Human Brain. Dev Neurosci. 2018;40(4):325–36.
3. Zhu Y, et al. Cirbp suppression compromises DHODH-mediated ferroptosis defense and attenuates hypothermic cardioprotection in an aged donor transplantation model. J Clin Invest. 2024;134(9):e175645.