Published in final edited form as:

Circulation. 2022 September 20; 146(12): e171–e172. doi:10.1161/CIRCULATIONAHA.122.061220.

Response to Letters Regarding Article, "MicroRNA-210 Controls Mitochondrial Metabolism and Protects Heart Function in Myocardial Infarction"

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Keywords

10112; 10114; 10133

We thank Drs Ding, Zhao, and their colleagues for their interest in our recently published article, "MicroRNA-210 Controls Mitochondrial Metabolism and Protects Heart Function in Myocardial Infarction."1 We appreciate their comments and discussion of the paper.

Increased mitochondrial ROS generation during reperfusion of ischemic myocardium is a crucial driver of IR-induced acute myocardial infarction (AMI), and inhibition of mitochondrial respiratory chain and reduction of mitochondrial oxygen consumption during IR afford protection of ischemic heart disease.2,3 In addition to increased ROS production at complex I and succinate dehydrogenase through reverse electron transport during IR, our study revealed a new mechanism of miR-210 inhibiting GPD2 in controlling ROS flux during IR and protecting the heart from injury. Whereas increasing glycolysis and maintaining higher free energy from ATP hydrolysis are likely to contribute to a beneficial effect of miR-210 in preserving cardiomyocyte energy and fine-tuning heart response to IR, it is not clear whether enhanced mitochondrial OXPHOS contributes to protecting the heart from injury in the setting of IR-induced AMI. The recent finding that mitochondrial telomerase reverse transcriptase (mitoTERT) is responsible for cardioprotection is of interest.4 Whereas mitoTERT mice increased the baseline O2 consumption in the heart, the mitochondrial respiration was not examined in the heart with IR. The findings that enhanced endothelial migratory capacity, activation of endothelial nitric oxide synthase, increased vascularization and myofibroblast differentiation contribute to mitoTERT-mediated cardioprotection highlight the multiplicity of mitochondrial functions in cardiovascular disease, many of which remain unclear.

The observation of sex differences in miR-210-mediated cardioprotection is of great interest. Nonetheless, the mechanisms remain elusive. Given an intricate interplay of sex-

Disclosures

None.

biased miRNA networks and the intrinsic sex differences in mitochondrial genotype and phenotype, the complexity of sex differences in mitochondrial functions are characterized by mitochondrial efficiency, ROS production, antioxidant capacity, substrate preference, Ca2+ handling, mitochondrial fusion, and mitophagy in the heart. The questions needed to be addressed in the future investigation include the role of GPD2 in the regulation of ROS production during IR and the functional consequences of sex differences in mitochondrial phenotype contributing to cardioprotection in the female heart.

The finding of miR-210 targeting GPD2 in controlling ROS flux and protecting the heart from IR-induced AMI reveals a translational potential of preclinical study of miR-210 in animal models. In addition to miR-210 being highly homologous across species and being identical between the human and rodent, human GPD2 gene 3'UTR has near perfect miR-210 complementary binding seed sequences and thus predicts a strong target of miR-210. Indeed, many miR-210 targeting genes share across species homology including ISCU, TET2, etc. Nonetheless, the authentic target of human GPD2 gene by miR-210 needs to be validated in the future study.

Sources of Funding

This work was supported in part by National Institutes of Health Grants P01 HD083132 (L. Zhang).

References

1. Song R, Dasgupta C, Mulder C, Zhang L. MicroRNA-210 Controls Mitochondrial Metabolism and Protects Heart Function in Myocardial Infarction. Circulation. 2022;145:1140–1153. doi: 10.1161/CIRCULATIONAHA.121.056929 [PubMed: 35296158]
2. Pell VR, Chouchani ET, Murphy MP, Brookes PS, Krieg T. Moving Forwards by Blocking Back-Flow: The Yin and Yang of MI Therapy. Circulation Research. 2016;118:898–906. doi: 10.1161/CIRCRESAHA.115.306569 [PubMed: 26941425]
3. Chouchani ET, Pell VR, Gaude E, Aksentijevic D, Sundier SY, Robb EL, Logan A, Nadtochiy SM, Ord ENJ, Smith AC, et al. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. Nature. 2014;515:431–435. doi: 10.1038/nature13909 [PubMed: 25383517]
4. Ale-Agha N, Jakobs P, Goy C, Zurek M, Rosen J, Dyballa-Rukes N, Metzger S, Greulich J, von Ameln F, Eckermann O, et al. Mitochondrial Telomerase Reverse Transcriptase Protects From Myocardial Ischemia/Reperfusion Injury by Improving Complex I Composition and Function. Circulation. 2021;144:1876–1890. doi: 10.1161/CIRCULATIONAHA.120.051923 [PubMed: 34672678]