The Role of Isocitrate Dehydrogenases in Direct Reprogramming to Cardiomyocytes

Tomoaki Ishida,[1] Tomoe Ueyama,[1] Ai Baba,[1] Koji Hasegawa[2] and Teruhisa Kawamura[1]

1. Department of Biomedical Sciences, College of Life Sciences, Ritsumeikan University, Kusatsu, Japan;
2. Division of Translational Research, Kyoto Medical Center, National Hospital Organization, Kyoto, Japan

Citation: *European Cardiology Review* 2021;16:e64. **DOI:** https://doi.org/10.15420/ecr.2021.16.PO8

Objectives: Direct reprogramming with introduction of Gata4, Mef2c and Tbx5 (GMT) genes involved in cardiogenesis can convert fibroblasts to induced cardiomyocyte-like cells (iCMs), whereas only a low percentage of iCMs are obtained due to the low proliferative capacity. Recent studies suggest that oestrogen-related receptors (ERRs) are involved in cardiomyocyte maturation during the differentiation from pluripotent stem cells. In addition, ERRγ regulates the density and morphology of mitochondria in matured cardiomyocytes accounting for prominent aerobic metabolism. ERRγ is also known to induce the transcription of isocitrate dehydrogenases (IDHs), one of the tricarboxylic acid cycle regulators. In the present study, we investigate whether ERRγ-IDH-mediated mitochondria regulation is involved in cellular metabolism during direct reprogramming to iCMs.

Materials and methods: We used retroviral vectors encoding GMT to reprogram mouse embryonic fibroblasts into iCMs with or without pharmacological inhibition of mitochondrial respiration or gene silencing with shRNAs against ERRγ and IDHs. We analysed iCM reprogramming efficiency with quantitative PCR and immunofluorescence labelling with cardiomyocyte marker molecules.

Results: In the course of direct reprogramming, a mitochondrial respiration inhibitor, rotenone, decreased the iCM reprogramming efficiency. In experiments of IDHs knockdown, IDH3α significantly repressed iCM formation. In contrast, overexpression of IDH3α resulted in improvement of iCM programming efficiency, evaluated by QPCR analysis and the incidence of cardiac marker-positive cells. These results suggest the involvement of ERR-IDH-mediated energy metabolism in GMT-mediated iCM production.

Conclusion: We emphasise the significance of aerobic metabolism during direct reprogramming into iCMs that may provide clues to improve the efficiency. ❑