PPARβ/δ ACTIVATION PROTECTS FROM MITOCHONDRIAL DEGENERATION, INFLAMMATION AND FIBROSIS IN A GENETIC ANIMAL MODEL OF HEART FAILURE

Dimitra Palioura[1], Kyriakos Mellidis[1], Eleftheria Galatou[1,] Eleni-Taxiarchia Mouchtouri[2], Emmanuel Panteris[3], Manolis Mavroidis[2], Yassemi Capetanaki[2], Antigone Lazou[1]

[1]*Laboratory of Animal Physiology, School of Biology, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece,*
[2]*Center of Basic Research, Biomedical Research Foundation, Academy of Athens, Athens, Greece,*
[3]*Department of Botany, School of Biology, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece*

PPARβ/δ is a primary transcriptional regulator of cardiac energy metabolism with pleiotropic properties, including anti-inflammatory, anti-oxidative and cardioprotective action. The aim of the present study was to investigate whether pharmacological activation of PPARβ/δ could ameliorate cardiac tissue damage in desmin null mice (*Des*$^{-/-}$), a genetic model of heart failure and explore the potential effects on the impaired mitochondrial network. In *Des*$^{-/-}$ mice, ultrastructural abnormalities with severely damaged mitochondria, massive cardiomyocyte death, an early acute inflammatory response and severe cardiac remodeling lead to dilated cardiomyopathy and eventually heart failure. Our findings demonstrate that PPARβ/δ activation protects from extensive cardiac inflammation, fibrosis and cardiac remodeling, all hallmarks of the *Des*$^{-/-}$ heart. Importantly, PPARβ/δ activation stimulates mitochondrial biogenesis, protects mitochondria from exacerbated degeneration and improves the deranged mitochondrial network as observed in transmission electron microscopy images of *Des*$^{-/-}$ hearts. Concomitantly, PPARβ/δ restores the balance in fission/fusion protein markers, attenuates ATP depletion and enhances mitochondrial functionality in *Des*$^{-/-}$ hearts. Furthermore, PPARβ/δ activation alleviates oxidative stress as evidenced by almost 50% decrease in superoxide levels through transcriptional activation of the antioxidant regulator, Nrf2 and major ROS scavengers, in the failing myocardium. In conclusion, pharmacological activation of PPARβ/δ during myocardial degeneration and heart failure in *Des*$^{-/-}$ hearts demonstrates cardioprotective action by preserving the structural and functional quality of the mitochondrial network and alleviating inflammation and fibrosis.

Keywords: heart failure; inflammation; mitochondria; peroxisome proliferator-activated receptor β/δ

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