Respiratory chain signalling is essential for adaptive remodelling following cardiac ischaemia

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Cardiac ischaemia-reperfusion (I/R) injury has been attributed to stress signals arising from an impaired mitochondrial electron transport chain (ETC), which include redox imbalance, metabolic stalling and excessive production of reactive oxygen species (ROS). The alternative oxidase (AOX) is a respiratory enzyme, absent in mammals, that accepts electrons from a reduced quinone pool to reduce oxygen to water, thereby restoring electron flux when impaired and, in the process, blunting ROS production. Hence, AOX represents a natural rescue mechanism from respiratory stress.

This study aimed to determine how respiratory restoration through xenotopically expressed AOX affects the re-perfused post-ischaemic mouse heart. As expected, AOX supports ETC function and attenuates the ROS load in post-anoxic heart mitochondria. However, post-ischaemic cardiac remodelling over 3 and 9 weeks was not improved. AOX blunted transcript levels of factors known to be up-regulated upon I/R such as the atrial natriuretic peptide (Anp) whilst expression of pro-fibrotic and pro-apoptotic transcripts were increased. Ex vivo analysis revealed contractile failure at nine but not 3 weeks after ischaemia whilst label-free quantitative proteomics identified an increase in proteins promoting adverse extracellular matrix remodelling.

Together, this indicates an essential role for ETC-derived signals during cardiac adaptive remodelling and identified ROS as a possible effector.

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