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Stabilization of the muscle-specific apoptosis repressor ARC: A new therapeutic modality in management of ischemic disease

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Abstract

Apoptosis is an important mechanism of cardiac myocyte loss during ischemia-reperfusion injury and heart failure. We have identified that the endogenous inhibitor of apoptosis ARC (Apoptosis Repressor with Caspase recruitment domain) is essential for minimizing cardiac damage post-infarction. ARC is degraded quickly, via ubiquitination and proteosomal targeting, upon reperfusion injury which is then permissive for the onset of the apoptosis associated with reperfusion injury. However, the mechanism by which ARC protects the myocardium basally are incompletely understood. We have previously found that ARC prevents activation of both the extrinsic and intrinsic apoptosis pathways. However, what has been unappreciated until now is that ARC directly blocks DNA degradation induced by a variety of apoptotic stimuli. Using antibody arrays, we discovered ARC interacts with the key facilitators of apoptotic nuclear remodeling (ICAD, acinus and helicard) and prevents their activation by executioner caspases. The functional importance of these interactions were demonstrated by the ability of ARC to prevent nuclear remodeling in vivo as the ARC null mice were highly sensitive to the effects of ischemia on processing of ICAD/acinus/helicard. Thus, targeting ARC degradation during reperfusion injury would salvage the myocardium and prevent progression to failure. To this end we have recently identified mineralocorticoid activation as a novel regulator of ARC degradation that is readily antagonized and results in promising reduction of mortality post-infarction. In conclusion, salvage of ARC expression and activity is a novel and readily achievable mechanism by which the after effects of infarction can be targeted therapeutically for patient benefit.

Biography

Anthony Ashton has completed his Ph.D. in 1998 at the University of New South Wales, Australia. His postdoctoral studies at the Albert Einstein College of Medicine focused on novel mechanisms of treatment for the heart post-infarction. He is currently the Director of Basic Research, in the Division of Perinatal Research at the Kolling Institute for Medical Research in Sydney. He has published more than 51 papers in reputed journals (cited over 1,100 times; h index =20), serves on the editorial board and as a reviewer for multiple biomedical journals and for multiple funding bodies.