

Prolonged ischaemia caused by coronary artery disease and myocardial infarction leads to aberrant ventricular remodelling and cardiac fibrosis. This is thought to occur through accumulation of gene expression changes in resident fibroblasts, resulting in a fibrotic phenotype. Long term adaption to a hypoxic insult is likely to require significant modification of chromatin structure in order to maintain the fibrotic phenotype. Epigenetic modifications may play an important role in dictating hypoxia-induced fibrosis within the heart. Therefore, the aim of this study was to investigate the pro-fibrotic impact of hypoxia on cardiac fibroblasts, and determine whether alterations in DNA methylation could play a role in this process.

Using human myocardial samples, the degree of tissue hypoxia was associated with increased gene and protein expression of collagen 1, and α -smooth muscle actin (α SMA) mRNA. Human cardiac fibroblast cells exposed to hypoxic conditions resulted in a pro-fibrotic state with increased expression of collagen 1 and α SMA mRNA, and a significantly enhanced response to TGF β 1 stimulation. These hypoxia-induced pro-fibrotic changes were associated with global DNA hypermethylation, and increased expression of DNA methyltransferase (DNMT) enzymes DNMT1 and DNMT3B. DNMT3B significantly correlated with degree of hypoxia in myocardial tissue. Hypoxic regulation of the methylating enzymes was shown to be regulated by HIF-1 α transcription factor.

Epigenetic modifications and changes in the epigenetic machinery occurs in cardiac fibroblasts during prolonged hypoxia which may contribute to the pro-fibrotic nature of an ischaemic event. Targeting aberrant expression of DNMTs in ischaemic heart disease may prove to be a valuable therapeutic approach.

P16

HYPOXIA ALTERS THE DNA METHYLATION PROFILE OF CARDIAC FIBROBLASTS VIA HIF-1 α REGULATION OF DNA METHYLTRANSFERASE

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