Infarct size was similar (38.3±2.0% vs 39.9±2.8%). Transgenic mice also exhibited less apoptosis and interstitial cardiac fibrosis (0.52±0.03% vs 0.65±0.05%, p<0.05), and lower increases in the expression of fibronectin and procollagen III mRNA. Both echocardiography and cardiac catheterisation demonstrated less left ventricular cavity dilatation and a preservation of cardiac function in transgenic than wt mice.

**Conclusions** In contrast to Nox2, which contributes to cardiac dilation, contractile dysfunction and fibrosis, cardiomyocyte Nox4 was found to exert protective effects against adverse remodelling post-MI.

**A NEW MOLECULAR MECHANISM FOR FAMILIAL DILATED CARDIOMYOPATHY BASED ON STUDIES WITH INTACT MUTANT TRANSGENIC MOUSE AND HUMAN EXPLANTED HEART MUSCLE**

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We created a transgenic mouse that expressed the dilated cardiomyopathy (DCM) mutation ACTC E361G at 50% of total cardiac actin. We isolated F-actin from transgenic and non-transgenic (NTG) mice and reconstituted thin filaments using native human cardiac troponin and tropomyosin (from donor heart). In vitro motility assays we could observe no differences between E361G and non-transgenic mice at expected. Thus the only functional change induced by the E361G mutation in cardiac actin was a blunted response to troponin I phosphorylation. We also studied troponin extracted from the explanted heart of a DCM patient carrying the cardiac TnC G159D mutation. In vitro motility assay investigation of reconstituted thin filaments showed that the E361G Ca\(^{2+}\) sensitivity was lower than non-transgenic, as previously observed with the recombinant proteins (EC\(_{50}\) E361G/NTG 2.2±0.1). When we compared native phosphorylated and dephosphorylated thin filaments we observed that Ca\(^{2+}\) sensitivity did not change in E361G mouse thin filaments (EC\(_{50}\) P/ unP=1.0±0.1) but the Ca\(^{2+}\) sensitivity increased 3.0±3.0-fold on dephosphorylation of non-transgenic mice as expected. Thus the only functional change induced by the E361G mutation in cardiac actin was a blunted response to troponin I phosphorylation. We also studied troponin extracted from the explanted heart of a DCM patient carrying the cardiac TnC G159D mutation. In vitro motility assay investigation of reconstituted thin filaments showed that the Table

**REGULATION OF GENE TRANSCRIPTION BY HYDROGEN PEROXIDE IN CARDIOMYOCYTES**

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Introduction Reactive oxygen species (ROS) levels rise during ischaemia and reperfusion and may contribute to myocardial injury, remodelling and progression to heart failure. ROS (hydrogen peroxide; H\(_2\)O\(_2\)) activates both apoptotic and pro-survival signalling pathways, although at higher concentrations cardiomyocyte death invariably results. Here, transcriptional responses of cardiomyocytes to varying concentrations and duration of H\(_2\)O\(_2\) were investigated.

**Results** Transcription factors of activating protein 1 (AP-1) and early growth response (ERG) families were upregulated rapidly and transiently by 0.1–1 mM H\(_2\)O\(_2\), which induce cardiomyocyte apoptosis and are IEG. In contrast, upregulation of transcripts for antioxidant proteins (second-phase genes) was slower and more sustained, occurring at a lower concentration of H\(_2\)O\(_2\) (0.05–0.5 mM).

**Conclusions** AP-1, ERG and antioxidant transcripts were regulated by H\(_2\)O\(_2\) in a time and concentration-dependent manner. Induction of antioxidant expression at lower concentrations of H\(_2\)O\(_2\) could represent enhancement of ROS-scavenging capacity to prevent apoptosis. At higher H\(_2\)O\(_2\) concentrations, the AP-1 and ERG transcription factor IEG may mediate apoptosis. These studies increase the understanding of transcriptional responses in cardiomyocytes to ROS.

**IS NITRIC OXIDE SYNTHASE PRESENT IN MITOCHONDRIA?**

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In addition to the three known forms of nitric oxide synthase (NOS) in the heart, it has recently been proposed that NOS is also present in mitochondria. However, studies are controversial due to the possibility of contamination by non-mitochondrial NOS, and because none of the known forms of NOS contain a mitochondrial targeting sequence. We investigated whether NOS was present in isolated mitochondria using antibodies against all three forms of NOS (endothelial NOS (eNOS), inducible NOS (iNOS) and neuronal NOS (nNOS)). Crude fractions of heart and liver mitochondrial NOS may provide an important modulatory mechanism for respiration under either physiological or pathological conditions.

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**THIN FILAMENTS RECONSTITUTED WITH TRO PonIN EXTRACTED FROM PATIENTS WITH HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY ARE FUNCTIONALLY ABNORMAL**

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Tissue obtained from a septal myectomy represented an opportunity to characterise the molecular phenotype of hypertrophic