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Cardiac-specific overexpression of the transcription factor JunD promotes increased sensitivity to myocardial infarction
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Introduction: Myocardial injury during short-term ischemia (I) and reperfusion (R) has become clinically important with the use of primary PCI as a first-line strategy in patients with acute coronary syndrome (ACS). The Jun family of activator protein 1 (AP-1) transcription factors (c-Jun, JunB, JunD) is involved in fundamental biological processes such as proliferation, apoptosis, tumor angiogenesis, and hypertrophy. Its member JunD is specifically expressed in the developing heart and cardiovascular system. Current evidence suggests a complex role for JunD in the adult heart. However, there is little in vivo evidence about the role of JunD in the infarcted heart. In the present study we analyzed the role of JunD in the heart using cardiac-specific JunD transgenic mouse line (cJunDTG). JunD interacts with TAB1, a scaffold protein, that promotes p38 MAPK activity. We addressed whether cardiac overexpression of JunD could promote increased sensitivity to myocardial injury in a mouse model of cardiac ischemia and reperfusion.

Hypothesis: Cardiac-specific overexpression of transcription factor JunD contributes to myocardial injury in a mouse model of cardiac ischemia and reperfusion.

Methods: 8-12-week-old cJunDTG male and corresponding C57Bl/6 wild-type (WT) controls were subjected to 30 min of ischemia followed by 24h of reperfusion. Infarct size was assessed morphologically.

Results: After ischemia, cJunDTG mice developed markedly larger infarcts as compared to WT (Fig. 1A and 1B). This was further associated with increased post-ischemic levels of serum cardiac troponin I (Fig. 1C). However, the observed effect on infarct size was not due to initial impaired contractility of transgenic hearts as compared to WT as assessed by CD31 and smooth muscle actin staining. This was further associated with impaired VEGF-A levels for both mRNA and protein in infarcted transgenic hearts. In addition, levels of JunD transcription co-factor PGC1α and mitochondrial deacetylase SIRT3 were significantly downregulated in transgenic hearts after ischemia and reperfusion. Finally, there was mitochondrial dysfunction detected in transgenic hearts by performing swelling assay.

Conclusions: Thus, JunD promotes increased sensitivity to ischemia and reperfusion when expressed at unphysiologival levels in the mouse heart. Such JunD-associated cardiac phenotype seems to be driven by the impaired angiogenesis and mitochondrial function. Therefore, JunD might represent a potential therapeutic target to protect human heart from myocardial infarct in future.

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The TAB1-p38α complex is a therapeutic target in acute myocardial ischemia: the holy grail of circumstance selective inhibition of p38α
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p38α is a serine-threonine kinase, it plays a crucial role in several physiological and pathological pathways. Inhibition of the kinase using existing ATP competitive antagonists inhibits catalytic activity of the kinase in in settings and is associated with toxicity in clinical trials. Here we present data that demonstrate it is possible to inhibit p38α under the pathological circumstance of acute myocardial ischemia, without perturbing physiological signalling. Using a mouse model of myocardial ischemia, we identified the TAB1-p38α complex, which we found to be a potential therapeutic target.

In our previous work we have solved the X-ray structure of the p38α-TAB1 complex, identified the TAB1 binding site on p38α and showed the structural rearrangements induced by TAB1 that cause auto-activation.

Based on these data we have now generated a global knock-in mouse encoding four single point mutations within the TAB1 protein that prevent docking onto, and subsequent autoactivation of, p38α. Whereas p38α or TAB1 knock-out mice are embryonal lethal, the knock-in mice we have generated are viable and at baseline have a normal cardiovascular transcriptional and immunological profile. Nonetheless, there is deficient myocardial p38α activation during regional myocardial ischemia and myocardial infarction volume as a percentage of the risk volume is significantly reduced (29.4 ± 2.0 vs 22.2 ± 1.4, n = 8, P < 0.001). Moreover, left ventricular remodelling in response to chronic pressure overload stress is reduced: the percentage of left ventricular shortening ten weeks post banding is 26.7 ± 2.3 vs 39.5 ± 1.8, n = 7, P < 0.001.

We have also further characterized the interaction between p38α and TAB1 by solving the X-ray structure of the p38α-TAB1 complex in the active phosphorylated state. The structures show that the phosphorylation state of the two proteins does not modify their binding affinity but the binding surface involved in the interaction, they suggest that TAB1 does not dissociate from p38α after having induced the kinase auto-activation.

The data reveal that it is possible to selectively inhibit p38α activation without targeting the ATP binding site and that this mode of interaction is relevant to acute myocardial ischemia and chronic cardiac stress. These indicate that the p38α-TAB1 complex is a therapeutic target that may circumvent the toxicity associated with ATP competitive p38 inhibitors.

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