The TAB1-p38a complex is a therapeutic target in acute myocardial ischemia: the holy grail of circumstance selective inhibition of p38a.

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p38a 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 all settings and is associated with toxicity in clinical trials. Here we present data that demonstrate it is possible to inhibit p38a under the pathological circumstance of acute myocardial ischemia, without perturbing physiological signalling.

During myocardial ischaemia p38a interacts with TAB1, a scaffold protein, that promotes p38a autoactivation, that drives cardiac damage.

In our previous work we solved the X-ray structure of the p38a-TAB1 complex, identified the TAB1 binding site on p38a 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, p38a. Whereas p38a 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 p38a activation during regional myocardial ischaemia 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<0.01). 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 p38a and TAB1 by solving the X-ray structure of the p38a-TAB1 complex in the active phosphorylated state. The structures show that the phosphorylation state of the two proteins does not modify their binding affinity nor the binding surface involved in the interaction, they suggest that TAB1 does not dissociate from p38a after having induced the kinase auto-activation.

The data reveal that it is possible to selectively inhibit p38a activation without targeting the ATP binding site and that this mode of interaction is relevant to acute myocardial ischaemia and chronic cardiac stress. These indicate that the p38a-TAB1 complex is a therapeutic target that may circumvent the toxicity associated with ATP competitive p38 inhibitors.