TRPM2 channels in oxidative stress-induced cell death

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Overproduction of reactive oxygen species (ROS) and ensuing cell damage are often accompanied by a rise in the cytoplasmic free Ca^{2+} concentration ($[Ca^{2+}_{cyt}]$). The relationship between oxidative damage and Ca^{2+} signalling pathways is complex and not well understood, but removal or chelation of extracellular Ca^{2+} spares many cell types from oxidative stress-induced death. This suggests a significant role for Ca^{2+}permeable channels in the process (Guo *et al.*, 2009). Several members of the transient receptor potential (TRP) channel family have been shown to function as redox sensors and to contribute to ROS-induced $[Ca^{2+}_{cyt}]$ rise (Takahashi *et al.*, 2011). TRPM2 (melastatin 2), is expressed in a variety of organs, including the brain, bone marrow, pancreas, heart, spleen, liver and cells of the immune system (Takahashi *et al.*, 2011). It is gated by intracellular ADP-ribose and H_2O_2, and plays an essential role in H_2O_2-induced neuronal death and in alloxan-induced damage of pancreatic beta-cells. In both cases, siRNA-mediated knockdown of TRPM2 protein significantly attenuated or prevented cell death (Takahashi *et al.*, 2011).

The liver performs a multitude of functions, and is a highly aerobic, oxygen-dependent tissue susceptible to hypoxia and toxic insults (Malhi *et al.*, 2010). At the cellular level, many liver disorders are characterized by increased production of ROS, enhanced hepatocellular death and impaired cell regeneration. Research from our group has identified TRPM2 as a major oxidative stress-induced Ca^{2+} entry pathway in primary hepatocytes. Using RT-PCR, western blot analysis, Ca^{2+} imaging and patch clamping, we show that TRPM2 channels are expressed in high levels in rat hepatocytes and are activated by ADP-ribose and H_2O_2. In hepatocytes TRPM2 current is also activated by 6-12 h treatment with high concentrations of paracetamol (5-10 mM). However, knockdown of TRPM2 expression by siRNA attenuates paracetamol activated cation current and pharmacological inhibition of TRPM2 reduces paracetamol-induced hepatocellular death in culture. Furthermore, subjecting TRPM2 KO mice to paracetamol overdose shows that lack of TRPM2 results in a less significant dysregulation of the liver enzymes profile and a significantly lower level of hepatocellular death, compared to WT mice. These results suggest that elevation of $[Ca^{2+}_{cyt}]$ induced in human liver by paracetamol overdose may also be mediated by TRPM2, and further, that blockade of TRPM2 may prove useful in treatment of paracetamol overdose and other liver diseases associated with oxidative damage.

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