S57-5 Physiological role of the oxidative stress-sensitive TRPM2 Ca^{2+} channel in immunocytes

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It is known that a large amount of reactive oxygen species (ROS) exist at inflamed sites. ROS induce chemokines responsible for the recruitment of inflammatory cells at inflamed sites. Here, we demonstrate that the plasma membrane Ca^{2+}-permeable channel TRPM2 controls ROS-induced chemokine production in monocytes/macrophages. In monocytes from *Trpm2*-defecient mice, H_2O_2-induced Ca^{2+} influx and production of the macrophage inflammatory protein-2 (CXCL2), which exhibit potent neutrophil chemotactic activity, were impaired. In the inflammation model dextran sulfate sodium-induced colitis, CXCL2 expression was attenuated by *Trpm2* disruption. Interestingly, the number of recruited neutrophils was significantly reduced in DSS-treated *TRPM2* KO mice, whereas that of DSS-induced macrophages after infiltration into inflamed sites, was indistinguishable in WT and *TRPM2* KO mice. Importantly, TRPM2 deficiency failed to impair important aspects of CXCL2-evoked neutrophil chemotaxis, including Ca^{2+} response, *in vitro* migration, and *in vivo* infiltration after DSS administration. Thus, TRPM2-mediated Ca^{2+} influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration. We propose functional inhibition of TRPM2 channels as a new therapeutic strategy for treating inflammatory diseases.