Roles of TRPM2 expressed in immune/glial cells in inflammatory and neuropathic pain

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Accumulating evidence suggests that neuroimmune interactions contribute to pathological pain. TRP melastatin 2 (TRPM2) is a nonselective Ca^{2+}-permeable cation channel that acts as a sensor for reactive oxygen species. TRPM2 is expressed abundantly in immune cells and is important in inflammatory processes. In this study, we examined the roles of TRPM2 expressed in immune/glial cells in inflammatory and neuropathic pain. WT and TRPM2-KO mice showed no difference in their basal sensitivity to mechanical and thermal stimulation. Nocifensive behaviors in the acetic acid-induced writhing and formalin tests were reduced in TRPM2-KO mice. In carrageenan-induced inflammatory pain and sciatic nerve injury-induced neuropathic pain models, mechanical allodynia and thermal hyperalgesia were attenuated in TRPM2-KO mice. Carrageenan-induced inflammation and sciatic nerve injury increased the expression of TRPM2 mRNA in the inflamed paw and injured nerve, respectively. TRPM2 deficiency diminished the infiltration of neutrophils and the production of CXCL2, a major chemokine that recruits neutrophils, but did not alter the recruitment of F4/80-positive macrophage. Spinal microglial activation after nerve injury was suppressed in TRPM2-KO mice. Furthermore, CXCL2 production and iNOS induction were diminished in cultured macrophages and microglia derived from TRPM2-KO mice. Intraplantar administration of stimulated macrophages derived from WT mice to WT or TRPM2-KO mice produced mechanical allodynia. In contrast, stimulated macrophages derived from TRPM2-KO mice to WT mice produced no mechanical allodynia. Taken together, these results suggest that TRPM2 expressed in macrophages and microglia aggravates peripheral and spinal pronociceptive inflammatory responses and contributes to the pathogenesis of inflammatory and neuropathic pain.