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Regulation of pain signaling by the innate immune system

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The innate immune system is the body's first response to infections and its activation gives rise to pain. How the innate immune system interacts with the sensory nervous system and contributes to pain is poorly understood. We have shown previously that intraplantar CFA injection leads to an upregulation of the deubiquitinase USP5 in dorsal root ganglia and spinal cord, and this in turn leads to an increase in the numbers of Cav3.2 T-type calcium channels in an activity dependent manner. Blocking USP5 interactions with cell permeant disruptor peptides mediates analgesia. Here we demonstrate that specific Toll-like receptors (TLRs) are up-regulated in response to CFA injection. This leads to macrophage infiltration into the dorsal root ganglia, and the production of interleukin 33 (IL33) which acts on sensory neuron to increase their activity. Block of spinal IL33/ST2 receptor signals attenuates CFA-induced inflammatory pain. The CFA induced upregulation of USP5 is abolished in TLR2 null mice, altogether indicating that the CFA mediated dysregulation of T-type calcium channel activity involves the activation of a TLR2-IL33-ST2 pathway, leading to the development of inflammatory pain.