

Zarpelon AC, Rodrigues FC, Lopes AH, Souza GR, Carvalho TT, Pinto LG, Xu D, Ferreira SH, Alves-Filho JC, McInnes IB, Ryffel B, Quesniaux VF, Reverchon F, Mortaud S, Menuet A, Liew FY, Cunha FQ, Cunha TM, Verri WA Jr. (2015). Spinal cord oligodendrocyte-derived alarmin IL-33 mediates neuropathic pain. *FASEB J.* 30(1):54-65.

Neuropathic pain from injury to the peripheral and CNS represents a major health care issue. We have investigated the role of IL-33/IL-33 receptor (ST2) signaling in experimental models of neuropathic pain in mice. Chronic constriction injury (CCI) of the sciatic nerve induced IL-33 production in the spinal cord. IL-33/citrine reporter mice revealed that oligodendrocytes are the main cells expressing IL-33 within the spinal cord together with a minor expression by neurons, microglia, and astrocytes. CCI-induced mechanical hyperalgesia was reduced in IL-33R (ST2)^{-/-} mice compared with wild-type (WT) mice. Intrathecal treatment of WT mice with soluble IL-33 receptor (IL-33 decoy receptor) markedly reduced CCI-induced hyperalgesia. Consistent with these observations, intrathecal injection of IL-33 enhanced CCI hyperalgesia and induced hyperalgesia in naive mice. IL-33-mediated hyperalgesia during CCI was dependent on a reciprocal relationship with TNF- α and IL-1 β . IL-33-induced hyperalgesia was markedly attenuated by inhibitors of PI3K, mammalian target of rapamycin, MAPKs (p38, ERK, and JNK), NF- κ B, and also by the inhibitors of glial cells (microglia and astrocytes). Furthermore, targeting these signaling pathways and cells inhibited IL-33-induced TNF- α and IL-1 β production in the spinal cord. Our study, therefore, reveals an important role of oligodendrocyte-derived IL-33 in neuropathic pain.-Zarpelon, A. C., Rodrigues, F. C., Lopes, A. H., Souza, G. R., Carvalho, T. T., Pinto, L. G., Xu, D., Ferreira, S. H., Alves-Filho, J. C., McInnes, I. B., Ryffel, B., Quesniaux, V. F. J., Reverchon, F., Mortaud, S., Menuet, A., Liew, F. Y., Cunha, F. Q., Cunha, T. M., Verri, W. A. Spinal cord oligodendrocyte-derived alarmin IL-33 mediates neuropathic pain.