CCI-03

The research for the mechanism of chronically intractable pain based on the functions of microglia as brain immunocompetent cell: The role of microglial cathepsin B

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Abstract

Two signals mediated by Toll-like receptors (TLRs) and Nod-like (NLRs) are generally required for the production and secretion of interleukin (IL)-1β and IL-18. TLRs leads to the transcriptional induction of their proforms though activation of nuclear factor (NF)-κB. On the other hand, the NLRP3 inflammasome contributes to the conversion of procaspase-1 to its mature form, which is responsible for the activation of proforms. We have recently reported that cathepsin B (CatB), a lysosomal cysteine protease, directly contributes to the activation of proIL-1β in the endosomal/lysosomal system of microglia after treatment with chromogranin A (CGA) without activation of NLRP3 (Terada et al., Glia 2010). Furthermore, CGA was found to activate NF-κB through activation of TLRs. These observations prompted us to examine the roles of CatB and CGA in chronic pain hypersensitivity, because IL-1β and IL-18 play critical roles in the induction of chronic pain hypersensitivity. CatB-deficiency or the intrathecal administration of CA074Me, a specific CatB inhibitor, significantly inhibited both complete Freund's adjuvant (CFA)-induced mechanical allodynia and thermal hyperalgesia without affecting peripheral inflammation (Sun et al., J Neurosci 2012). In contrast, CatB-deficiency had no significant effect on spinal nerve injury-induced mechanical allodynia. The IL-1β expression in spinal microglia and the induction of tactile allodynia following the intrathecal administration of CGA depended on CatB, whereas those induced by the intrathecal administration of ATP or lysophospatidic acid were CatB independent. These results strongly suggest that CatB is an essential enzyme for the induction of chronic pain through its activation of procaspase-1. Furthermore, CGA is a candidate activator of microglia, which is responsible for the induction of inflammatory pain, because CGA could mimic the CFA injection-induced inflammatory pain.

Therefore, CatB-specific inhibitors or CGA receptor-specific inhibitors may represent a useful new strategy for treating inflammation-associated pain.