



# IL-33/ST2 signaling boosts inflammation and pain

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We read with interest the work of Taracanova et al. (1) on the synergic effect of substance P (SP) and IL-33 over TNF- $\alpha$  production. Notably, IL-33 potentiates SP-induced TNF- $\alpha$  production by more than 100-fold in mast cells. Both IL-33 and SP increase the expression of each other receptor, and more interestingly, ST2 coimmunoprecipitates with neurokinin-1 (NK-1, SP receptor), demonstrating a formation of an ST2-NK-1 complex. The Taracanova et al. study expands the importance of mast cells in inflammation and the understanding that IL-33 potentiates the effects of other peptides to enhance inflammation. IL-33 also enhances by 50% SP-induced vascular endothelial growth factor release by human mast cells (2). At the single-cell level, IL-33 augments the frequency and magnitude of Fc $\epsilon$ R1 (using suboptimal concentrations) -induced mast cell degranulation and production of chemokines (3). In a model of collagen-induced arthritis, intraperitoneal injection of IL-33 and adoptive transfer of wild-type mast cells to mice lacking ST2 worsens clinical index. Thus, IL-33 exacerbates arthritis (4) and potentiates mast cell activation. IL-33 also potentiates the response of other immune cells and dorsal root ganglion neurons. IL-33 potentiates TNF- $\alpha$  and IL-1 $\beta$  production by LPS-primed and ATP-stimulated macrophages (5). Targeting IL-33/ST2 signaling reduces hyperalgesia in antigen-induced arthritis and IL-33 induces hyperalgesia in immunized mice (6). IL-33 synergizes with carrageenan (using suboptimal doses of both compounds) to induce

mechanical hyperalgesia and the production of TNF- $\alpha$  and IL-1 $\beta$  (7). IL-33 also enhances formalin-induced overt pain-like behavior (8). Furthermore, spinal cord oligodendrocyte-derived IL-33 mediates mechanical hyperalgesia in a chronic constrict injury model of neuropathic pain by activating other glial cells (9). The intrathecal injection of IL-33 into chronic constrict injury mice augments the mechanical hyperalgesia (9). Regarding itch, IL-33 increases the calcium influx in dorsal root ganglion neurons of urushiol-challenged mice (10). Taken together, these data demonstrate that IL-33 worsens diseases by potentiating inflammatory and nociceptive stimuli even at low concentrations (Fig. 1). Conversely, the inflammatory mediators triggered by these noxious stimuli induce IL-33 production. For example, cocubation of TNF- $\alpha$  and IL-1 $\beta$  increases IL-33 production in human fibroblast from patients with rheumatoid arthritis (4). Therefore, preclinical data demonstrate that targeting IL-33/ST2 signaling ameliorates varied diseases and thereby may represent a potential target for new drugs. Given that IL-33 potentiates the production of several mediators in a wide range of conditions (Fig. 1), a better clinical profile would be achieved using IL-33/ST2-targeting drugs alongside with current treatments.

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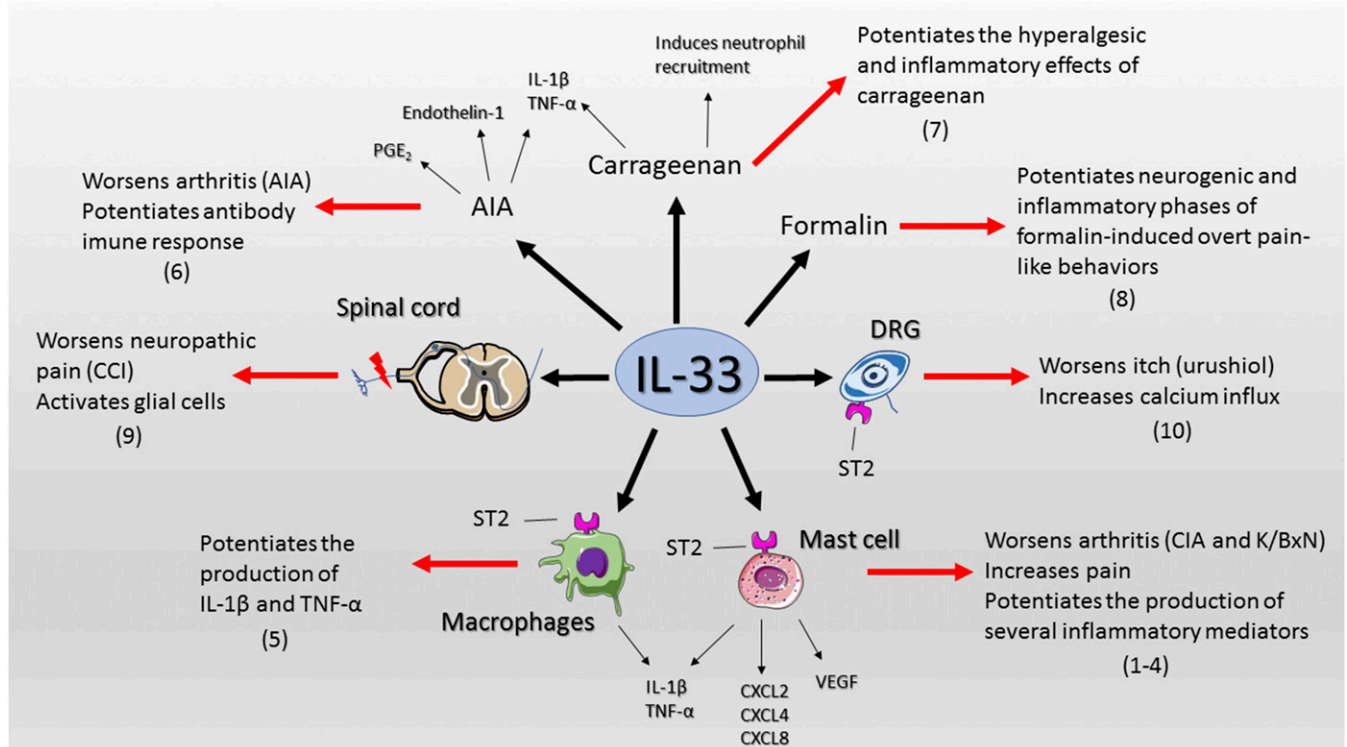
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**Fig. 1. IL-33 boosts inflammation and pain in diseases.** References in parenthesis are placed next to the observed outcome. AIA, antigen-induced arthritis; CIA, collagen-induced arthritis; CCI, chronic constrict injury; DRG, dorsal root ganglion; VEGF, vascular endothelial growth factor.

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