

Correspondence

Effect of IL-33 on *de novo* synthesized mediators from human mast cells

To the Editor:

In their recent interesting review, Olivera et al¹ stress the importance of mast cells as targets not only of allergic stimuli but also of many environmental and cationic molecules. The authors then focus on the role of the cytokine IL-33 in allergen-induced mast cell responses.

We believe it is appropriate to also discuss the effect of IL-33 on mast cell mediators synthesized *de novo*, in addition to augmentation of allergic stimulation and secretion of granule-stored mediators, such as tryptase. Recently, we reported that IL-33 augments allergen-induced secretion of IL-31, which is important in pruritus, as well as stimulates secretion of IL-31 from human mast cells in the absence of an allergic stimulus.²

It is also pertinent to discuss the effect of IL-33 on nonallergic stimuli. We also showed that IL-33 augments the effect of the proinflammatory peptide substance P (SP) in stimulating secretion of impressive amounts of vascular endothelial growth factor (VEGF)³ and TNF,⁴ without concomitant secretion of tryptase, from human mast cells. The 1000-fold increase in secretion of TNF stimulated by IL-33 administered together with SP involves some interaction between their respective receptors. This conclusion is based on the fact that the receptor for IL-33, ST2, was coprecipitated with the receptor for SP, neurokinin-1 (NK-1).⁴ Moreover, preincubation of human mast cells with NK1 antagonists also inhibited the effect of IL-33 used by itself without SP.⁴

ST2 properly known as interleukin 1 receptor-like 1 is a member of the IL-1 receptor family. We had reported that IL-1 stimulates human mast cells to secrete IL-6 without tryptase.⁵ This finding is important given that serum levels of IL-6 are elevated and correlate with disease severity in patients with systemic mastocytosis.^{6,7}

That mast cells can secrete mediators without tryptase (Table I) and that IL-33 augments nonallergic stimuli such as SP is critical for understanding the role of mast cells in diseases such as mastocytosis and mast cell activation syndrome in which most symptoms are neither due to allergic triggers nor due to tryptase.

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TABLE I. Examples of mediators secreted without tryptase from human mast cells

Nonallergic stimuli	<i>De novo</i> synthesized mediators
Growth factors	
CRH	VEGF
SCF	IL-6
Cytokines	
IL-1	IL-6
IL-33	IL-31
IL-33 + SP	VEGF, TNF
Pathogens	
Borrelia b. (Lyme disease)	TNF
Sporothrix (mold)	IL-6, TNF

CRH, Corticotropin-releasing hormone; SCF, stem cell factor.

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