LETTER

REPLY TO FATTORI ET AL.: Action of SP and IL-33 on mast cells

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We thank Fattori et al. (1) for their positive comments on our report (2). Their letter (1) contains much useful information on possible additional biological effects of IL-33. However, the publications discussed in the text and figure 1 in the Fattori et al. (1) letter do not directly address our findings.

Moreover, the data in our report came only from human cultured mast cells (2), while the studies in the letter (1) discuss mostly experiments in rodents that do not reflect human inflammatory conditions (3, 4).

We are taking this opportunity to highlight the importance of substance P (5) and IL-33 in human diseases (6). New findings presented include the facts that: (*i*) mast cell-derived tryptase can cleave extracellular IL-33 into mature active forms (7); (*ii*) such IL-33 isoforms may have additional abilities to activate mast cells, thus promoting inflammation (8); and (*iii*) human mast cells stimulated by either antigen or IL-33 can also release soluble ST2, which may modulate the biologic effect of IL-33 (9).

The ability of the natural flavonoid tetramethoxyluteolin to inhibit mast cells stimulated by either IL-33, substance P, or their combination (2), which we report in our paper, has now been validated in a pilot clinical trial: a skin lotion containing tetramethoxyluteolin was shown to reduce skin inflammation in patients with atopic dermatitis and psoriasis (10).

1 Fattori V, Borghi SM, Verri WA, Jr (2017) IL-33/ST2 signaling boosts inflammation and pain. *Proc Natl Acad Sci USA* 114:E10034–E10035.
2 Taracanova A, et al. (2017) SP and IL-33 together markedly enhance TNF synthesis and secretion from human mast cells mediated by the interaction of their receptors. *Proc Natl Acad Sci USA* 114:E4002–E4009.
3 Seok J, et al.; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci USA* 110:3507–3512.
4 Masopust D, Sivula CP, Jameson SC (2017) Of mice, dirty mice, and men: Using mice to understand human immunology. *J Immunol* 199:383–388.
5 Suvas S (2017) Role of substance P neuropeptide in inflammation, wound healing, and tissue homeostasis. *J Immunol* 199:1543–1552.
6 Zhan M, et al. (2017) Upregulated expression of substance P (SP) and NK1R in eczema and SP-induced mast cell accumulation. *Cell Biol Toxicol* 33:389–405.
7 Morita H, Nakae S, Saito H, Matsumoto K (2017) IL-33 in clinical practice: Size matters? *J Allergy Clin Immunol* 140:381–383.
8 Gordon ED, et al. (2016) Alternative splicing of interleukin-33 and type 2 inflammation in asthma. *Proc Natl Acad Sci USA* 113:8765–8770.
9 Bandara G, Beaven MA, Olivera A, Gilfillan AM, Metcalfe DD (2015) Activated mast cells synthesize and release soluble ST2-a decoy receptor for IL-33. *Eur J Immunol* 45:3034–3044.
10 Theoharides TC, Stewart JM, Tsilioni I (2017) Tolerability and benefit of a tetramethoxyluteolin-containing skin lotion. *Int J Immunopathol Pharmacol* 30:146–151.

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The authors declare no conflict of interest.

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