

## Letter to the Editor

**Dexamethasone regulation of thymic stromal lymphopoietin receptor expression on mast cells and their precursors***To the Editor:*

Increasing evidence suggests that thymic stromal lymphopoietin (TSLP) plays important roles in the pathogenesis of allergic diseases such as asthma, atopic dermatitis, and rhinitis. Initially, TSLP was found to enhance potently the maturation of CD11c<sup>+</sup> dendritic cells, and TSLP-primed and activated dendritic cells promoted differentiation of naive CD4<sup>+</sup> T cells into proinflammatory T<sub>H</sub>2 cells.<sup>1</sup> TSLP can also directly act on innate cells, including mast cells (MCs) and hemopoietic CD34<sup>+</sup> progenitors,<sup>2,3</sup> to induce production of proinflammatory T<sub>H</sub>2 cytokines and chemokines, and thus to initiate an innate phase of allergic inflammation in the absence of T cells and IgE antibodies. TSLP exerts its biological activities by binding to a heterodimeric receptor that consists of the IL-7 receptor  $\alpha$  chain and the TSLP receptor (TSLPR)

chain, which is closely related to the common receptor  $\gamma$  chain. TSLPR mRNA has been detected in tissues from heart, skeletal muscle, kidney, and liver on many immune cell types, including dendritic cells, T cells, B cells, MCs, and hemopoietic CD34<sup>+</sup> progenitors.<sup>1</sup> Although the biology of TSLP is well documented, little is known about the regulation of TSLPR, except TSLPR regulation on dendritic cells via Fc receptor ligation.<sup>4</sup> Here we have analyzed the expression profile and the regulation of the TSLPR on MCs and their precursor CD34<sup>+</sup> cells.

We first show that TSLPR expression is enhanced markedly on CD34<sup>+</sup> cells and slightly on MCs with the suboptimal concentrations of proinflammatory cytokines TNF (2.5 ng/mL) and IL-1 (1 ng/mL), both of which are expressed at the sites of allergic inflammation (Fig 1). We next examined the effects of commonly used antiasthma drugs, glucocorticoids and  $\beta$ -adrenergic agonists. Dexamethasone alone induced high levels of TSLPR expression and enhanced the IL-1/TNF-induced TSLPR expression on CD34<sup>+</sup> cells and MCs (Fig 1). Glucocorticoids other

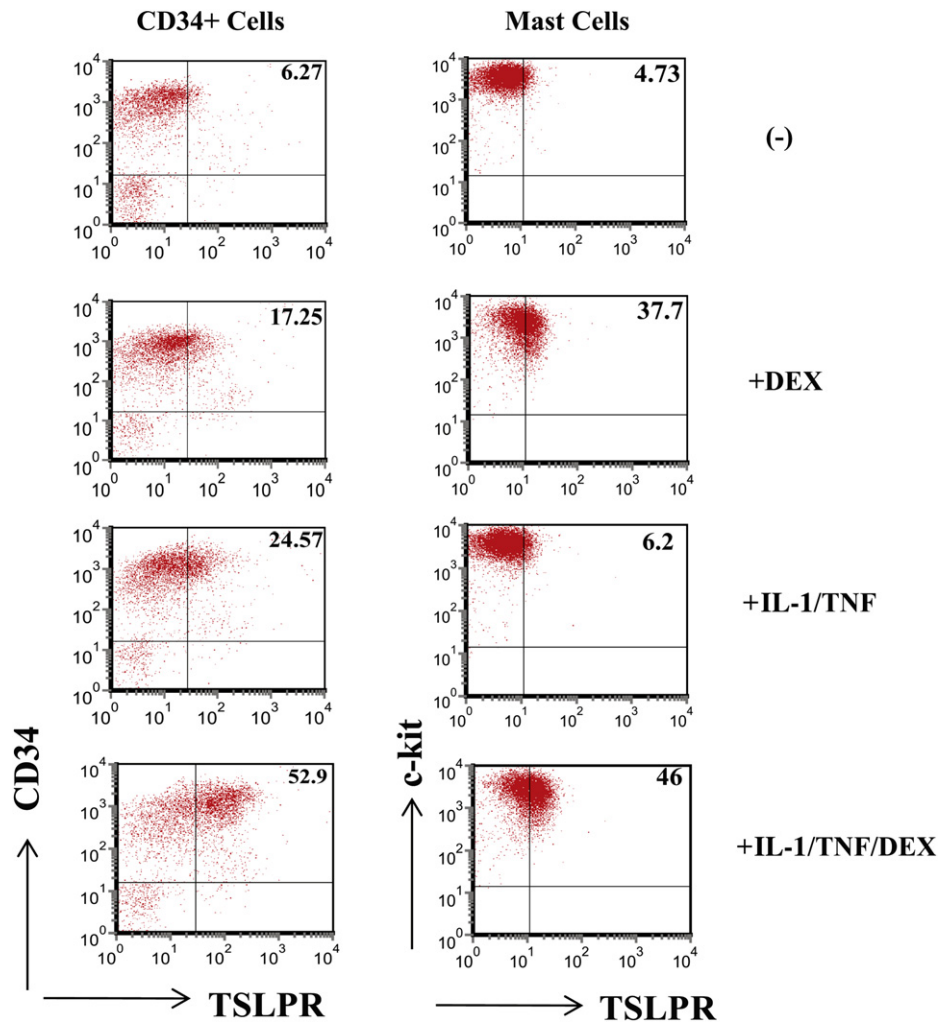


**FIG 1.** TSLP receptor regulation on CD34<sup>+</sup> cells and primary mast cells. CD34<sup>+</sup> cells and MCs were prepared as described<sup>2,3</sup> and stimulated for 48 hours with suboptimal concentrations of TNF (2.5 ng/mL), IL-1 (1 ng/mL), and dexamethasone (DEX; 10<sup>-7</sup> mol/L), as indicated. Representative of 4 experiments.

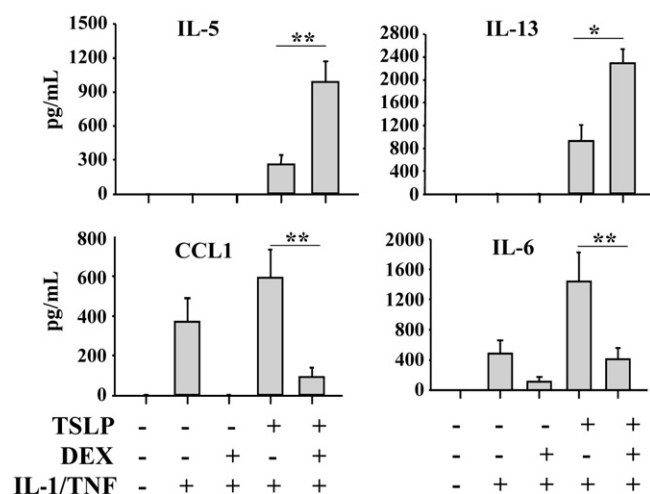


**FIG 2.** Dexamethasone (DEX) modulates the response of MCs to TSLP. Primary peripheral blood-derived MCs were activated with optimal concentrations of TNF (25 ng/mL)/IL-1 (10 ng/mL) and TSLP (10 ng/mL) with or without dexamethasone ( $10^{-7}$  mol/L). The productions of IL-5, IL-13, CCL1, and IL-6 were measured after 16 hours of culture. Means  $\pm$  SEMs of 6 experiments. \* $P < .05$ ; \*\* $P < .01$ .

than dexamethasone (hydrocortisone) showed similar activity. In contrast, isoproterenol had no effect on the regulation of TSLPR on CD34<sup>+</sup> cells and MCs (data not shown). TSLPR was induced on CD34<sup>+</sup> cells but not on MCs by various microbial products *Staphylococcus aureus* Cowan I strain and TLR ligands (peptidoglycan, LPS; see this article's Fig E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Primary MCs used in this study were >98% pure. They were derived from peripheral blood CD34<sup>+</sup> cells after 8 to 10 weeks of culture as in our previous study.<sup>2</sup> All the experiments were conducted in accordance with the ethical committee of our institution.

To explore the biological consequences of glucocorticoid-induced upregulation of TSLPR on CD34<sup>+</sup> cells and MCs, we examined whether the presence of dexamethasone would affect their production of T<sub>H</sub>2 cytokines in response to TSLP. Dexamethasone significantly enhanced the production of IL-5 and IL-13 by MCs (Fig 2), whereas it inhibited T<sub>H</sub>2 cytokine production by CD34<sup>+</sup> cells (see this article's Fig E2 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Importantly, this proinflammatory effect of dexamethasone on MCs was opposed by inhibition of proinflammatory cytokines and chemokines (ie, IL-6 and CCL-1/I-309). Although glucocorticoids are a mainstay of antiasthma treatment, taken together, our data suggest that the enhancing effect of glucocorticoids on T<sub>H</sub>2 production by MCs may be partly responsible for their failure to prevent

long-term progression of the disease—that is, lung function deterioration and remodeling. The paradoxical ability of glucocorticoids to enhance *in vitro* and *in vivo* basic mechanisms leading to allergic inflammation has been well documented: (1) glucocorticoids may favor further differentiation of naive T cells into T<sub>H</sub>2 effector cells,<sup>5</sup> (2) glucocorticoids exert a direct effect on differentiated T<sub>H</sub>2 cells by upregulation of their IL-4, IL-10, and IL-13 production,<sup>6</sup> (3) glucocorticoids potentiate the IgE production *in vitro* and *in vivo*,<sup>7,8</sup> and (4) glucocorticoids do not inhibit the remodeling process associated with chronic inflammation.<sup>9</sup> Because TSLP is only one of several factors involved in allergic diseases, the *in vivo* significance of our *in vitro* findings remains to be established.

Zoufia Allakhverdi, PhD<sup>a</sup>

Michael R. Comeau, BSc<sup>b</sup>

Guy Delespesse, MD, PhD<sup>a</sup>

From <sup>a</sup>the Laboratory on Allergy, CHUM Research Center, Notre-Dame Hospital, Montreal, Quebec, Canada; and <sup>b</sup>Inflammation Research, Amgen Inc, Seattle, Wash. E-mail: z.allakhverdieva@umontreal.ca.

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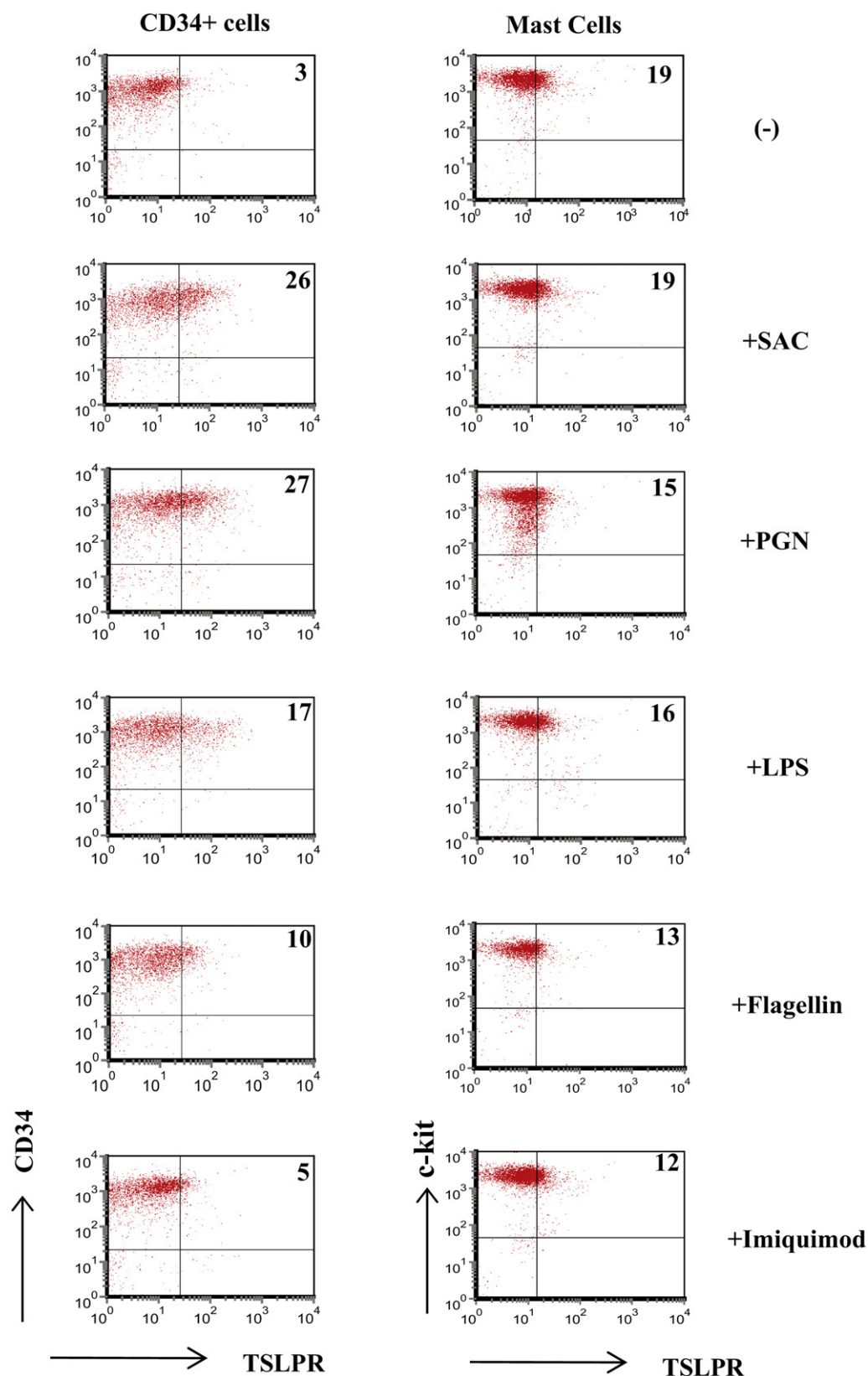


**FIG E1.** TSLP receptor regulation by microbial and TLR ligands on CD34<sup>+</sup> cells and mast cells. *Staphylococcus aureus* Cowan I strain (SAC) (1:5000), peptidoglycan (PGN) (50  $\mu$ g/mL), LPS (1  $\mu$ g/mL), flagellin (1  $\mu$ g/mL), and imiquimod (1  $\mu$ g/mL) were added to cultures of CD34<sup>+</sup> cells and MCs, and 48 hours later, TSLPR expression was detected. Representative of 3 experiments.

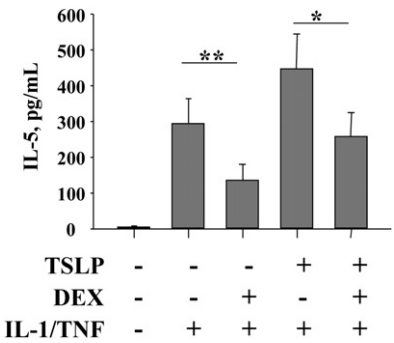


**FIG E2.** Dexamethasone (*DEX*) modulates the response of CD34<sup>+</sup> cells to TSLP. Umbilical cord blood–derived CD34<sup>+</sup> cells were activated with optimal concentrations of TNF (25 ng/mL)/IL-1 (10 ng/mL) and TSLP (10 ng/mL) with or without dexamethasone (10<sup>−7</sup> mol/L). The production of IL-5 was measured after 16 hours of culture. Means + SEMs of 6 experiments. \**P* < .05; \*\* *P* < .01.