Cross-Talk between Epithelial Cells and Type 2 Immune Signaling The Role of IL-25

Type 2 immune responses are evoked strongly by parasitic helminthes at mucosal barriers, but these responses also characterize problematic airway responses to inhaled aeroallergens. Cytokines secreted by epithelial cells, including IL-33, IL-25, and thymic stromal lymphopoietin (TSLP), regulate type 2 immune responses to parasitic infection in the gastrointestinal tract and to aeroallergen exposure in the lungs (1–5). These cytokines, either alone or in combination, activate type 2 responses from group 2 innate lymphoid cells, CD4⁺ T-helper type 2 cells, mast cells, basophils, and IgE-producing B cells. Inhibiting type 2 responses blocks parasite- and allergen-driven type 2 inflammation (6, 7), establishing a potential pathway for therapeutic intervention.

IL-25 (IL-17E), a member of the IL-17 cytokine family, signals through the heterodimeric IL-17RA/IL-17RB receptor to promote expression of downstream mediators of type 2 immunity. Although epithelial cells in the intestine are known sources of IL-25 (8), the details underpinning how IL-25 orchestrates type 2 immunity have only recently been uncovered (9). Studies using mice engineered to express a fluorescent IL-25 reporter revealed that the only apparent source of IL-25 was tuft cells, enigmatic mucosal epithelial cells named for their characteristic tufts of apical microvilli that protrude into the lumen (10). Unexpectedly, these rare tuft cells, including those in the trachea and throughout the bowel, were constitutively positive for IL-25 reporter expression. In response to intestinal helminthes, IL-25 from tuft cells activated lamina propria group 2 innate lymphoid cells to secrete IL-13, which fed back on epithelial crypt precursors to skew differentiation of small bowel epithelia toward mucus-producing goblet cells and additional tuft cells. Thus, as revealed in this model in the small intestine, tuft cells can serve as epithelial sensors that use IL-25, and perhaps additional signals, to activate tissue group 2 innate lymphoid cells to skew epithelial cell fates toward mucus-secreting cells in response to luminal perturbations elicited by parasitic helminthes.

In the reporter mouse, tracheal tuft cells made up the only lung cells that expressed IL-25, but whether additional cells express this cytokine in response to aeroallergens remains unknown. In mouse models, IL-25 can mediate type 2 immunity in the lung (2), both in response to aeroallergens (11) as well as after rhinovirus infection (12). In humans, we have noted low-to-absent IL-25 transcripts in airway epithelial brushings from mild to moderate patients with asthma (13). However, others have reported that airway epithelial cells from subjects with asthma express higher than normal levels of IL-25, which can be induced further by rhinovirus infection

(12). Still others have found increased systemic levels of IL-25 in subgroups of patients with asthma with T helper type 2 high asthma (14). Further work is needed to elucidate more clearly the role of IL-25 in human asthma, as well as any potential participation by tuft cells, particularly in the lung, where the differentiation of epithelial cells from precursors differs markedly from the relatively linear and short-lived (3–5 d) process that occurs in the intestines (15). In addition, the relationships and redundancies between IL-25 and other epithelial cytokines capable of eliciting type 2 immune responses, such as TSLP and IL-33, require further investigation.

The IL-25 receptor is made up by the ubiquitously expressed IL-17RA signaling component and the regulated IL-17RB component; the latter is responsible for specific binding by IL-25 (16). The effects of airway allergen challenge on IL-17RB expression by dendritic cells (DCs) is the subject of the article in this issue of the *Journal* by Tworek and colleagues (pp. 957–964) (17). These authors find that both myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) express IL-17RB and that both DC subsets increase in the airway after allergen challenge, coincident with increases in airway eosinophils and nitric oxide levels and with decrements in lung function. The authors further show that pDCs stimulated *in vitro* with IL-25 increase expression of TLR9 and show heightened activation responses to TLR9 agonists. These findings prompt the authors to suggest that IL-25 may activate mDCs to initiate type 2 immune responses in the airway and also prime pDCs to enhance host defense against airway virus infection.

The emerging data for IL-25 as a regulator of type 2 immunity provides a strong rationale for considering IL-25 as a therapeutic target in asthma. This possibility arises just as the U.S. Food and Drug Administration approved the biologics license applications for mepolizumab and reslizumab, both of which are monoclonal antibodies that inhibit the activity of IL-5. Additional protein therapeutics that target IL-4, IL-5, and IL-13 are in late phases of clinical development. Although blocking these type 2 cytokines improves asthma control, these treatments are not curative and do not fully control the disease, even in patients with the “type 2 high” asthma endotype (18). This raises the possibility that inhibiting IL-25 and/or additional upstream epithelial cytokines that regulate type 2 inflammation might constitute better approaches for asthma therapeutics. Blocking further upstream in this way may abrogate multiple overlapping downstream outputs, including attenuation of IL-4, IL-5, IL-9, IL-13, and so on, and thus more completely sustain lung homeostasis in the presence of mucosal allergens. Indeed, early-phase trials of a TSLP inhibitor revealed the ability to blunt airway responses to inhaled

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aeroallergen in patients with asthma (19) suggesting that such “upstream” epithelial blockers may have great clinical utility.

It is hard to predict from current data whether blocking IL-25, IL-33, TSLP, or all three will prove most effective in treating asthma. Ultimately, it may emerge that tissue differences in expression levels of these three cytokines will dictate therapeutic approaches for cytokine inhibitors in tissue-specific diseases, such as asthma, eosinophilic esophagitis, or nasal polyposis. Alternatively, regulation of cytokine receptors, as revealed in the manuscript by Tworek and colleagues (17), may provide critical insights on the best approaches for intervention. Ultimately, clinical trials will be needed to answer these questions, as well as those related to safety and potential off-target effects. Regardless, recent studies have coalesced much attention on the role of epithelial cytokines in orchestrating type 2 immunity and provided additional information that may ultimately guide further mechanistic insights regarding how this exciting new biology can be best applied to alleviate human disease. ■

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References

- Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, Zurawski G, Moshrefi M, Qin J, Li X, *et al*. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity* 2005; 23:479–490.
- Hurst SD, Muchamuel T, Gorman DM, Gilbert JM, Clifford T, Kwan S, Menon S, Seymour B, Jackson C, Kung TT, *et al*. New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. *J Immunol* 2002;169: 443–453.
- Zhou B, Comeau MR, De Smedt T, Liggitt HD, Dahl ME, Lewis DB, Gyarmati D, Aye T, Campbell DJ, Ziegler SF. Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. *Nat Immunol* 2005;6:1047–1053.
- Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TK, Bucks C, Kane CM, Fallon PG, Pannell R, *et al*. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* 2010;464: 1367–1370.
- Price AE, Liang HE, Sullivan BM, Reinhardt RL, Eisley CJ, Erle DJ, Locksley RM. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci USA* 2010;107: 11489–11494.
- Fallon PG, Richardson EJ, McKenzie GJ, McKenzie AN. Schistosome infection of transgenic mice defines distinct and contrasting pathogenic roles for IL-4 and IL-13: IL-13 is a profibrotic agent. *J Immunol* 2000;164:2585–2591.
- Ramalingam TR, Pesce JT, Sheikh F, Cheever AW, Mentink-Kane MM, Wilson MS, Stevens S, Valenzuela DM, Murphy AJ, Yancopoulos GD, *et al*. Unique functions of the type II interleukin 4 receptor identified in mice lacking the interleukin 13 receptor alpha1 chain. *Nat Immunol* 2008;9:25–33.
- Bezençon C, Fürholz A, Raymond F, Mansourian R, Métairon S, Le Coutre J, Damak S. Murine intestinal cells expressing Trpm5 are mostly brush cells and express markers of neuronal and inflammatory cells. *J Comp Neurol* 2008;509:514–525.
- von Moltke J, Ji M, Liang HE, Locksley RM. Tuft-cell-derived IL-25 regulates an intestinal ILC2-epithelial response circuit. *Nature* 2016; 529:221–225.
- Gerbe F, Legraverend C, Jay P. The intestinal epithelium tuft cells: specification and function. *Cell Mol Life Sci* 2012;69: 2907–2917.
- Tamachi T, Maezawa Y, Ikeda K, Kagami S, Hatano M, Seto Y, Suto A, Suzuki K, Watanabe N, Saito Y, *et al*. IL-25 enhances allergic airway inflammation by amplifying a TH2 cell-dependent pathway in mice. *J Allergy Clin Immunol* 2006;118:606–614.
- Beale J, Jayaraman A, Jackson DJ, Macintyre JD, Edwards MR, Walton RP, Zhu J, Ching YM, Shamji B, Edwards M, *et al*. Rhinovirus-induced IL-25 in asthma exacerbation drives type 2 immunity and allergic pulmonary inflammation. *Sci Transl Med* 2014;6:256ra134.
- Gordon ED, Urbanek C, Woodruff PG, Seibold MA, Fahy JV. Characterization of epithelial cytokines IL33, TSLP, IL25 in human asthma [abstract]. *Am J Respir Crit Care Med* 2015; 191:A2497.
- Cheng D, Xue Z, Yi L, Shi H, Zhang K, Huo X, Bonser LR, Zhao J, Xu Y, Erle DJ, *et al*. Epithelial interleukin-25 is a key mediator in Th2-high, corticosteroid-responsive asthma. *Am J Respir Crit Care Med* 2014; 190:639–648.
- Clevers H. The intestinal crypt, a prototype stem cell compartment. *Cell* 2013;154:274–284.
- Rickel EA, Siegel LA, Yoon BR, Rottman JB, Kugler DG, Swart DA, Anders PM, Tocker JE, Comeau MR, Budelsky AL. Identification of functional roles for both IL-17RB and IL-17RA in mediating IL-25-induced activities. *J Immunol* 2008;181:4299–4310.
- Tworek D, Smith SG, Salter BM, Baatjes AJ, Scime T, Watson R, Obminski C, Gauvreau GM, O'Byrne PM. IL-25 receptor expression on airway dendritic cells after allergen challenge in subjects with asthma. *Am J Respir Crit Care Med* 2016;193:957–964.
- Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol* 2015;15:57–65.
- Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, Fitzgerald JM, Boedigheimer M, Davis BE, Dias C, *et al*. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med* 2014;370:2102–2110.

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