Drivers of Type 2 Inflammation in Allergic Airway Disease: Wnt You Like to Know?

Allergic asthma is a chronic respiratory disease characterized by profound changes to the structure of the airway wall, resulting in reversible airway obstruction. Although it is currently well understood that these structural and functional changes arise from persistent type 2 inflammation of the airways in response to aeroallergen exposure, the mechanisms responsible for initiating and maintaining eosinophilic inflammation in allergic airway disease remain unclear. In this issue of the *Journal*, Rai and colleagues (pp. 293–301) describe their studies of canonical Wnt signaling pathway and its importance in the regulation of the pulmonary immune response to inhaled allergen, particularly regarding the differentiation and activity of alternatively activated M2 macrophages (1).

The type 2 immune response to inhaled allergen is characterized by the infiltration of T-helper cells type 2 (Th2) cells, eosinophils, and macrophages into the airway wall (2). Macrophages play critical roles in maintaining this immune response and exhibit a considerable degree of plasticity, defined by the M1 versus M2 continuum of polarization. Although macrophages on the M1 end of the spectrum have robust phagocytic and cytotoxic capacity, M2 macrophages are more important in the resolution of inflammation, tissue repair pathways, and the development of tissue fibrosis (3–5). M2 macrophages are functionally diverse (M2a, M2b, M2c, and M2d), with the M2a subtype closely associated with Th2 polarized allergic inflammation in the lung. It is currently understood that M2 macrophages are induced by IL-4 and/or IL-13 and express high amounts of IL-10, TGF-β, and inflammatory chemokines (6). However, the importance of other signaling pathway that participate in the maintenance of M2 polarization remain under investigation. IL-33, expressed as a danger signal following allergen-mediated epithelial cell damage (7), can polarize macrophages toward an M2 phenotype (8). Other cell types, such as eosinophils, innate lymphoid type 2 cells, $CD4^+CD25^+$ T regulatory cells, and mesenchymal stem cells have also been demonstrated to modulate macrophage polarization toward the M2 phenotype (9–12). Rai and colleagues have now added to this panoply of pathways that contribute to alternative macrophage activation through their observations that genetic ablation or pharmacological inhibition of SFRP-1 (secreted frizzled-related protein-1), a key regulator of the canonical Wnt signaling pathway, effectively suppresses M2 macrophage polarization in response to aeroallergen exposure, resulting in a notable reduction in airway eosinophilia and improved lung function.

Using a mouse model of allergic airway disease driven by respiratory house dust mite (HDM) extract exposure (at a relatively high allergen dose of 40 μg/day, 5 days per week for 3 weeks), Rai and colleagues were able to show that genetic ablation of SFRP-1 led to reduced airway resistance at baseline, measured by invasive methacholine challenge using the FlexiVent system. Following chronic HDM exposure, SFRP-1-deficient mice demonstrated reduced airway inflammation, specifically a reduction in IL-5 and eosinophils, with no impact on other inflammatory mediators or a major difference in the intensity of inflammation. As a corollary, further studies using a pharmacological strategy to inhibit SFRP-1 activity using WAY316606 and thereby increase Wnt signaling led to reduced airway resistance and airway inflammation in the chronic HDM model, manifested as reduced total lung inflammatory cell infiltration, reduced numbers of macrophages and eosinophils, and significantly lower amounts of IL-4 and IL-5 in the BAL fluid. Although both strategies to reduce SFRP-1 activity were able to reduce type 2 inflammation and airway dysfunction following aeroallergen exposure, the more profound effect of WAY316606 treatment suggests the presence of some compensatory mechanisms in the SFRP-1 knockout mouse that deserve further study.

Activation of the canonical Wnt pathway results in the accumulation of β-catenin in the cytoplasm and its translocation into the nucleus, where it acts as a transcriptional coactivator of T-cell factor/lymphoid enhancer factor family transcription factors (Figure 1). At the frizzled receptor, interactions with proteins other than Wnt can antagonize signaling; these Wnt antagonists include Dickkopf (Dkk), Wnt inhibitory factor 1, and SFRPs. Of the latter, SFRP-1 has been demonstrated to be a complex modulator of Wnt signaling, as it can suppress Wnt activity at high concentrations and promote it at lower concentrations. Extensive studies have demonstrated that the complex regulatory roles of the Wnt cascade, including Wnt proteins as well as diverse Wnt receptors and effectors, are pivotal in the induction of type 2 immune responses to allergen exposure in the lung specifically and chronic inflammatory diseases in general (13).

Manipulation of Wnt antagonists has been performed in other studies in an attempt to mitigate type 2 inflammation in response to aeroallergen exposure. In agreement with Rai and colleagues, Chae and colleagues have demonstrated that high amounts of Dkk-1 enhance type 2 immune responses by promoting Th2 polarization. Moreover, functional inhibition of Dkk-1 in mice following HDM exposure or *Leishmania major* infection led to reduced Th2 cell cytokine production and leukocyte infiltration (14). Wu and colleagues have more recently demonstrated the importance of Wnt antagonists in driving type 2 responses by showing in *C. albicans*-induced allergic airway disease that robust Th2 and Th17 cell responses are driven by the release of the Wnt antagonist Dkk-1 from platelets, stimulated by the

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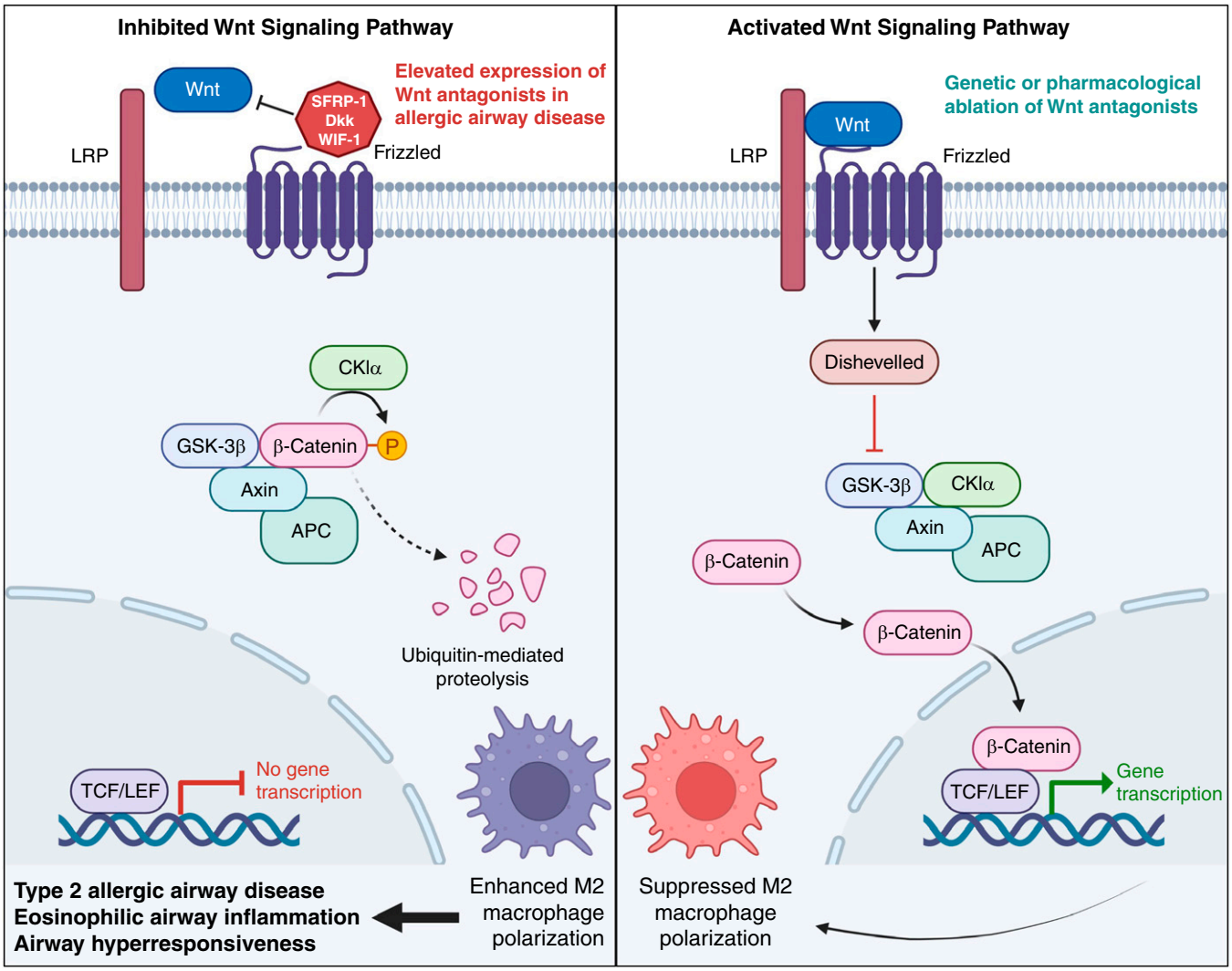

Figure 1. Canonical Wnt signaling, when suppressed by elevated expression of the Wnt antagonists Dkk (Dickkopf), WIF-1 (Wnt inhibitory factor 1) and SFRP (secreted frizzled-related proteins) in allergic airway disease, facilitates the polarization of macrophages to the M2 phenotype, resulting in enhanced T-helper cell type 2 inflammation, eosinophil infiltration of the airways, and airway hyperresponsiveness. Effective ablation of Wnt antagonist activity, by either genetic or pharmacological methods, promotes activation of the Wnt signaling pathway and the suppression of M2 macrophage polarization. Created with BioRender.com. CKIα = casein kinase 1 α 1; GSK-3β = glycogen synthase kinase 3 β; LRP = low-density lipoprotein receptor related protein 1; TCF/LEF = T cell factor/lymphoid enhancer factor.

peptide toxin candidalysin (15). Here, Rai and colleagues further strengthen the notion that the expression of Wnt antagonists enhances type 2 inflammation by showing that the ablation of SFRP-1 facilitates the nuclear translocation of β-catenin in macrophages, thereby impeding M2 macrophage polarization and inhibiting type 2 inflammation after chronic HDM exposure.

In summary, Rai and colleagues elegantly demonstrate that canonical Wnt/β-catenin signaling is critical to the suppression of the M2 macrophage phenotype in allergic inflammation. In response to a 3-week period of respiratory HDM exposure, a time point that has previously been shown to induce a robust Th2-polarized inflammation affecting the large airways (16), mice in which the activity of the Wnt antagonist SFRP-1 had been impaired either genetically or pharmacologically showed marked suppression of airway inflammation and lung dysfunction. Additional studies at later time points are now critical to assess the effects of SFRP-1 inhibition on airway remodeling.

It is anticipated that further studies will be performed to define the role of individual Wnt proteins and modulators of this pathway in eosinophils and macrophages. The authors specifically mention performing experiments on cell-specific SFRP-1 knockout mice, which hopefully will clarify the mechanisms by which SFRP-1 promotes allergic inflammation. Clearly, a better understanding of the molecular mechanisms regulating macrophage polarization and the downstream effects of these pathways on other immune and structural cell types is essential to clarify the relationship between allergen exposure, macrophage activity, and the development of airway remodeling and respiratory symptoms in allergic asthma. ■

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