Linking Wnt Signaling to Mucosal Inflammation

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a complex disease that remains clinically challenging to treat. Adding to the patients' disease burden, which often includes recurrent surgeries for polyp removal, treatments are generally high in costs and ineffective (1). To identify novel potential therapeutics, a better understanding of the underlying molecular mechanisms that cause recurrent inflammation, epithelial cell barrier impairment, and remodeling is urgently needed.

Thus far, the cellular signaling pathways that have been linked to CRSwNP primarily include inflammatory and immunomodulatory pathways. Signaling molecules of the pattern recognition receptor, signal transducer and activator of transcription 3, and Toll-like receptor have been shown to contribute to the ongoing inflammation and subsequent remodeling of nasal tissue (1). In this issue of the *Journal*, Böscke, Vladar, and colleagues (pp. 575–584) present the first evidence of altered Wnt signal activity in the nasal polyps of patients with CRSwNP (2).

Wnt signaling is controlled by several Wnt ligands that can bind to a variety of Frizzled receptors, thereby regulating intracellular signal outcomes. The canonical Wnt signal pathway relies on β-catenin as a signal mediator, translocating to the nucleus and thus driving differential gene expression and cellular function upon Wnt ligand binding (such as WNT3A), while the action of noncanonical Wnt ligands is less defined. The Wnt signal pathway is a classical developmental pathway that is known to be essential for proper lung development (3). More recently, altered Wnt signal activity has been implicated in the pathogenesis of chronic lung diseases such as asthma, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease (COPD) (4). In this context, Wnt signaling has been shown to contribute to epithelial cell injury and repair mechanisms, including inflammatory cytokine induction, which led the authors to elucidate its potential role in CRSwNP. Taking advantage of the availability of human tissue specimens and primary human nasal epithelial cell cultures derived from patient tissues, the authors report the differential expression of Wnt pathway components and nuclear localization of β-catenin, a surrogate marker for active canonical Wnt signaling. Treatment of human nasal epithelial cells in normal and air–liquid interface (ALI) cultures with recombinant WNT3A and pharmacological activation of β-catenin signaling resulted in morphological changes indicative of epithelial cell reprogramming/epithelial-to-mesenchymal transition, a process that has recently been implicated in CRSwNP (5) and more extensively studied in major chronic lung diseases such as asthma, COPD, and pulmonary fibrosis (6).

A defective barrier function of epithelial cells in nasal polyps was previously demonstrated to be a partial consequence of type 2 helper T cell (Th2)-skewed inflammation (5). Here, Böscke and colleagues report that although canonical Wnt signal activation did not induce cytokine transcripts, an increased secretion of IL-6 and granulocyte-macrophage colony-stimulating factor was observed, which might be due to post-translational mechanisms controlling protein turnover and abundance. Similarly, active Wnt β-catenin has been linked to proinflammatory processes in the airway and alveolar epithelium (7, 8). Further exploration of potential immune regulatory mechanisms of Wnt signaling in different immune-cell populations will be critical in the future.

An intriguing novel aspect of the current study is the potential effect of canonical Wnt activation on *de novo* ciliogenesis and the disruption of planar cell polarity (PCP). In early ALI cultures, the authors found that canonical Wnt signaling impaired motile ciliogenesis and led to dislocated expression of the noncanonical Wnt PCP protein VANGL1. Although a more in-depth analysis and validation are needed, recent studies support that noncanonical Wnt signaling impacts ciliogenesis by regulating PCP (9, 10). Feedback loops between canonical and noncanonical Wnt pathways are well described in the literature (11) and should be further explored in this context.

Interestingly, the authors did not observe the above-mentioned alterations after canonical Wnt signaling induction in differentiated cells from longer-term ALI cultures. These results support the idea that a distinct subpopulation of more undifferentiated/progenitor cells is responsive to Wnt signals in adult tissue, and highlight the need for further investigations of this subject. Moreover, it remains unclear whether Wnt β-catenin activation is a critical driver of the onset of CRSwNP, as the data indicate that an initial hit or injury is needed before Wnt signals begin to contribute to an impaired cellular response. Further experiments *in vivo* with inducible overexpression of Wnt ligands will be helpful in addressing these issues.

Notably, these findings may enhance our understanding of other chronic lung diseases, such as pulmonary fibrosis and COPD. Defects in cilia and mucociliary clearance and their potential importance for pathogenesis, as well as therapeutic targets, are emerging topics in chronic lung disease (12–14). Given that the number of studies exploring the role of Wnt signaling pathways in respiratory diseases is constantly increasing and thus novel therapeutic targets and approaches are being developed, we look forward to future studies to validate and extend these findings, and to explore potential therapeutic approaches to tackle epithelial cell injury. ■

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