Plk1 in Asthma: Ready for Primetime?

Plk1 (polo-like kinase 1) belongs to a family of serine/threonine protein kinases for which there are five members (Plk1–5), with Plk1 being the most well studied (1). Plk1 is an essential regulator in cell cycle progression in meiosis, mitosis, and cytokinesis. Hence, it is not surprising that overexpression of Plk1 mRNA and protein in various human cancers is observed, with its expression levels correlating with poor prognosis. Plk1 is, therefore, a promising target for cancer treatment (2).

A role for Plk1 in asthma pathogenesis is slowly gaining momentum. Asthma is characterized by three main features: chronic airways inflammation, airway wall remodeling, and airways hyperresponsiveness. Airway smooth muscle contributes to all three features of asthma pathophysiology. Hence, its multifunctional properties make it an attractive target for developing antiasthma agents (3, 4). Plk1 appears to influence many aspects of airway smooth muscle function.

For activation of airway smooth muscle cell proliferation, growth factor (i.e., platelet-derived growth factor or epidermal growth factor) stimulation results in phosphorylation of the Thr-210 site of Plk1 and subsequent activation of the MEK–ERK axis (5), which is essential to cell growth. In terms of airway smooth muscle contraction signaling, activation of Plk1 phosphorylation at Thr-210 by acetylcholine stimulation results in vimentin phosphorylation and subsequent airway smooth muscle contraction signaling (6). Importantly, conditional knockout of Plk1 in airway smooth muscle attenuated allergen (house dust mite)-induced airway resistance and contraction of tracheal rings (6).

Reduced cell apoptosis is one of the mechanisms proposed to underlie the increase in airway smooth muscle mass over time in patients with asthma (7). In this issue of the *Journal*, Liao and colleagues (pp. 223–234) report on their explorations of the role of Plk1 in the regulation of airway smooth muscle cell apoptosis (8). They show that activation of Plk1, via either treatment with platelet-derived growth factor or overexpression of Plk1, induced phosphorylation of caspase 9 at Ser-196 (but not Thr-125) in a time-dependent manner, resulting in attenuation of apoptosis in airway smooth muscle cells. In support of this, knockdown of Plk1 by RNA interference induced cell apoptosis, which was marked by reduced levels of Caspase 9 phosphorylation at Ser-196. Moreover, the authors show that phosphorylation of caspase 9 at Ser-196 is controlled by Akt and not Plk1 in airway epithelial cells, suggesting that the role of Plk1-induced phosphorylation of caspase 9 is cell type dependent. The authors further show that asthmatic airway smooth muscle cells exhibit elevated Plk1 and caspase 9, supporting the clinical relevance of Plk1 to not only cancer but also asthma.

Questions that remain from these studies include whether the overexpression of Plk1 is the cause of asthma or a consequence of enhanced airway smooth muscle proliferation observed in subjects with asthma. Immunohistochemical analysis of Plk1 expression relative to airway smooth muscle abundance measurements will be required to address this. The airway smooth muscle cells used by the investigators came from patients with severe asthma who were treated with bronchodilators and steroids. Is the overexpression of Plk1 inherent to asthma, or is it induced by asthma medications? Plk1 regulates cell surface expression levels of β1 integrin via phosphorylation of vimentin in epithelial breast cancer cell lines (9). The extracellular matrix protein laminin is required and sufficient to suppress airway smooth muscle cell apoptosis (7). It remains to be determined whether overexpression of Plk1 functions to increase the surface expression of laminin-binding integrins, which could influence caspase 9 phosphorylation and subsequent reduction in airway smooth muscle cell apoptosis.

Because Plk1 plays a key role in cell cycle progression and DNA damage repair, targeting Plk1 as a therapeutic strategy for treating airway wall remodeling in asthma would require careful fine-tuning. The development of Plk1 inhibitors would require modulation of its elevated levels rather than a complete knockdown, as Plk1 is essential for early embryonic development and genetic loss of Plk1 in mice results in embryonic lethality (10). Targeting high expression of Plk1 in cancer has proved to be effective, with many Plk1 inhibitors reaching clinical trials. The majority of Plk1 inhibitors are those that target either the kinase ATP–binding domain site of Plk1 or the polo-box domain C-terminal site (non-ATP–competitive inhibitor) (11). Whether similar effects could be obtained in asthma treatment, at least to target airway wall remodeling features such as airway smooth muscle mass, remains to be investigated. Based on these studies by Liao and colleagues (8), together with earlier findings of its multifunctional role in regulating airway smooth muscle function, it may be time for Plk1 to take center stage! ■

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