EDITORIALS

Selective Inhibition of Extracellular Signal-regulated Kinases 1 and 2: When Less Is More

Asthma is the most common chronic respiratory disease, affecting ~300 million people globally, both children and adults, and its prevalence keeps increasing (1). Asthma exacerbations are often severe, and asthma control has become a major public health issue. Asthma pathophysiology is complex, involving airway inflammation, mucus production, bronchoconstriction, airway hyperresponsiveness, and airway remodeling (2).

The current therapeutic strategies for asthma management are focused mainly on inhibiting bronchoconstriction and airway inflammation. Among pharmacological options, β-agonists are the drug of choice for evoking bronchorelaxation to reverse an acute asthma attack or for providing bronchoprotection when combined with an inhaled corticosteroid as maintenance therapy (2, 3). Other therapeutic approaches include anti–cysteinyl leukotriene receptors, antimuscarinic acetylcholine receptors, and anti–type 2 inflammation immunotherapy (4). However, evidence suggests that the effectiveness of these drugs in preventing or reversing airway remodeling is limited.

The ERK1/2 (extracellular signal-regulated kinase 1/2) signaling pathway plays multiple roles in the pathogenesis of asthma, such as T-helper cell type 2 polarization, smooth muscle cell and immune cell proliferation, epithelial cell chemokine production, and airway remodeling (5). Increased phosphorylated ERK1/2 was detected in epithelial cells and α-smooth muscle cells from patients with asthma, and expression of ERK1/2–inducible proteins JunB, sprout-2, and c-Fos were also significantly increased in airway tissue from patients with asthma (6, 7). Hence, inhibiting ERK1/2 activity seems to be a potential therapeutic method for alleviating cellular hyperplasia, tissue remodeling, and other asthma features.
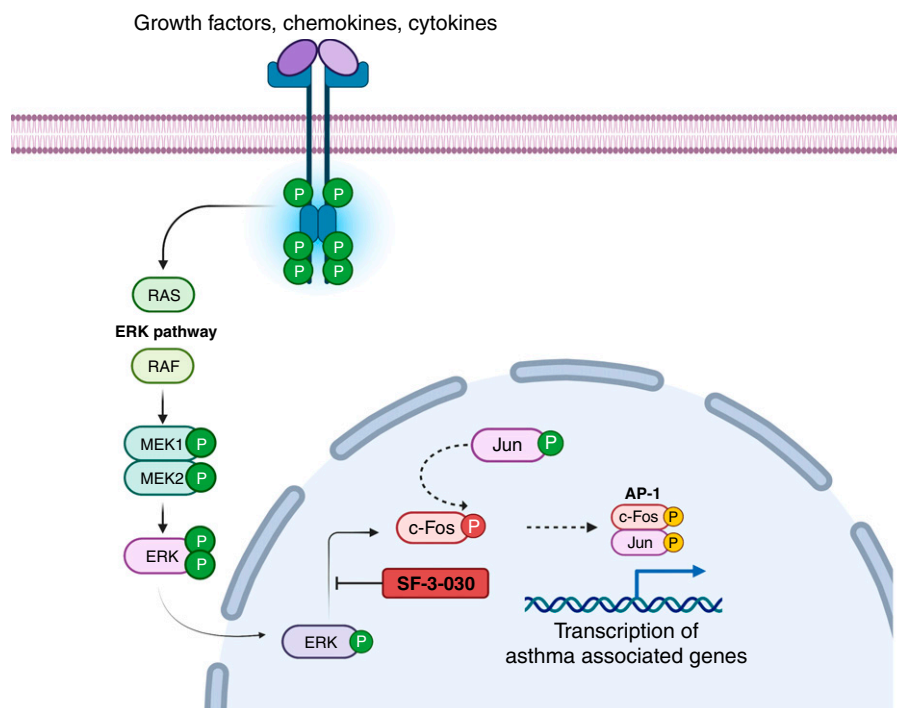

Figure 1. Simplified representation of the ERK1/2 signaling cascade and mechanism of action of S-3-030 in asthma. Tyrosine receptor kinase receptors activated by growth factors, cytokines, and chemokines sequentially activate RAS-RAF-MEK-ERK. Phosphorylated ERK enters the nucleus, activating c-Fos. c-Fos and Jun combine to form the AP-1 (activator protein 1) complex, which acts as a transcription factor for multiple genes associated with asthma features such as inflammation, mucus production, airway hyperresponsiveness, and remodeling. The small molecule SF-3-030, tested by Shah and colleagues (9) in an *in vivo* model, selectively blocks ERK1/2–mediated activation of c-Fos, preventing the formation of the AP-1 complex and the transcription of asthma-associated genes. This figure was created using BioRender.com. ERK = extracellular signal-regulated kinase; RTK = receptor tyrosine kinase.

ERK1/2 also has a critical role in cancer, becoming dysregulated because of mutations in receptor tyrosine kinases and other members of the RAS-RAF-MEK1/2-ERK1/2 signaling pathway in various cancers. A few ERK1/2 inhibitors with different mechanisms of action have been developed in recent years, and some of them are currently used in the treatment of hematologic and solid cancers (8).

In this issue of the *Journal*, Shah and colleagues (pp. 23–38) report that repurposing a substrate-selective ERK1/2 inhibitor may abrogate inflammation and airway remodeling in a mouse model of asthma (9). The group had previously developed the small molecule SF-3-030 and characterized its function in primary airway smooth muscle cells *in vitro* (10). SF-3-030 selectively inhibits c-Fos–ERK2–mediated phosphorylation by interacting near the ERK2 docking site for c-Fos (11) (Figure 1). c-Fos is a member of the AP-1 (activator protein 1) transcription factor complex, which controls various cellular processes, including proliferation, differentiation, and apoptosis, in response to stimulation by growth factors, cytokines, or microbes (12). In addition, previous studies have shown that inhibition of AP-1 significantly attenuated some of the pathological features of the disease in a mouse model of asthma (13, 14), and more recently it was shown that AP-1 also acted as a downstream target of the IL-18 signaling axis in a subgroup of patients with severe asthma (15). In line with these results, Shah and colleagues previously used SF-3-030 *in vitro* and showed that it was effective at inhibiting PDGF (platelet-derived growth factor)–mediated proliferation, collagen production, and IL-6 secretion in primary airway smooth muscle cells (10). Here, they use a house dust mite–induced asthma model to further evaluate the role of SF-3-030 *in vivo*. Using immunohistochemistry and western blotting, as well as transcriptomic and proteomic analysis, they show that pretreatment with inhaled SF-3-030 attenuates house dust mite–induced airway and lung inflammation as well as features of airway hyperresponsiveness and airway remodeling in mice. The bulk RNA sequencing data show downregulation of genes involved in cell proliferation and tissue remodeling. A striking effect of prophylactic treatment with SF-3-030 was observed in the marked decrease in recruitment of immune cells, which could be the key to explaining the overall effect the investigators report on inflammation (9).

ERK1/2 regulates a variety of cell functions across all cell types, so further characterization of the effect of SF-3-030 in other cell types would help us understand what cellular and molecular processes are affected in each cell compartment. Other questions include but are not limited to the effect of SF-3-030 on different asthma types and stages; the dose required for efficacy, safety, and tolerability assessment; and an improved solvent for intranasal drug delivery.

In summary, although further work is required, this study suggests that selectively targeting the ERK1/2 pathway using compounds such as SF-3-030 can be an effective therapeutic approach for asthma control while offering advantages over kinase inhibitors that block all enzyme functions and thereby potentially cause deleterious effects. ■

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