CRACking the Beat of Cilia: Calcium Rocks

Chronic obstructive pulmonary disease (COPD) is associated with airway inflammation, mucus hypersecretion and retention, and increased risk of recurrent airway infection. Enhancing mucociliary clearance reduces the risk of exacerbations and improves quality of life substantially. Hence, strategies that improve airway clearance are desired treatment strategies in COPD (1). Cigarette smoke exposure is a leading cause of COPD (2) and strongly impairs ciliary beating and mucociliary clearance (3). There is evidence that acute cigarette smoke exposure decreases mucociliary clearance by interfering with intracellular Ca^{2+} signaling pathways involved in transepithelial transport, finally causing airway surface dehydration (4). Besides the control of transepithelial ion transport, cytosolic Ca^{2+} is also known as a major modulator of ciliary beat frequency (5). Nevertheless, if and how cigarette smoke or related stimuli interfere with Ca^{2+}-dependent control of ciliary beating is poorly elaborated.

Store-operated calcium entry (SOC entry) is a ubiquitous Ca^{2+} signaling mechanism, especially in nonexcitable cells. SOC entry is activated by ligand binding to its G protein–coupled receptor, activation of phospholipase C, and release of inositol 1,4,5-trisphosphate that induces Ca^{2+} release from intracellular stores (6). Ca^{2+} store depletion results in translocation of the stromal interaction molecules (STIM1 and STIM2) to the plasma membrane, where they interact with the calcium release–activated calcium modulators ORAI1, ORAI2, and ORAI3 (6). This concatemerization finally opens the Ca^{2+}-conducting pore and activates the Ca^{2+} influx that is also referred to as "calcium release–activated calcium current" (I_{CRAC}) (7). Therefore, SOC entry or I_{CRAC} is a Ca^{2+} signaling event that depends on and is subsequent to Ca^{2+} release from intracellular stores. Both components together shape an integrated Ca^{2+} signal.

In this issue of the *Journal* (pp. 501–511), Petit and colleagues report on a study of epithelial cells reconstituted from bronchial biopsies of healthy donors as well as from smokers with and without COPD (8). They demonstrate that central components of SOC entry—the amount of Ca^{2+} released from thapsigargin-sensitive stores and the resulting Ca^{2+} influx—are affected in airway epithelial cells of smokers with and without COPD. Furthermore, they show that the Ca^{2+} pore-forming subunit, ORAI3, is less expressed in smokers and patients with COPD. Because ORAI subunits constitute the I_{CRAC} pore, the observed reduction in ORAI3 transcript and protein expression seems to explain the functional changes of SOC entry in airway epithelia from smokers and patients with COPD. This strongly supports the conclusion that SOC entry–dependent signaling is impaired in the lung epithelia of patients with COPD and smokers. However, overall cellular Ca^{2+} homeostasis appeared to be normal, because cytosolic Ca^{2+} concentrations ($[Ca^{2+}]_c$) were similar in the investigated subgroups of airway epithelia.

Pharmaceutical inhibition of SOC entry did not affect epithelial repair or mucus or IL-8 secretion at all. However, its effect on ciliary beating was quite astonishing. Under basal conditions, the frequency of ciliary beating was similar in the investigated epithelia. When SOC entry was inhibited, the authors noted a reduction in ciliary beat frequency in control epithelia only, whereas ciliary beating in epithelia from smokers with and without COPD remained almost unaffected. It is commonly accepted that $[Ca^{2+}]_c$ is pivotal in modulating ciliary beating (5). However, the mechanisms that mediate the $[Ca^{2+}]_c$-dependent regulation of ciliary beat frequency, especially in airway epithelia, are not completely understood. Early studies identified several physiologically relevant ligands that increase ciliary beat frequency by increasing $[Ca^{2+}]_c$, such as ATP via metabotropic P2Y receptors (9) and acetylcholine via muscarinergic receptors (10). Both ATP (11) and muscarinergic receptor activation (12) were shown to activate SOC entry in nonexcitable cells. In consideration of this background, the authors' observation that SOC entry modulates ciliary beating in airway epithelia is not unexpected. Nonetheless, it makes the authors' observation that SOC entry inhibition did not affect ciliary beating in epithelia of smokers with and without COPD even more important, because it suggests that other mechanisms besides SOC entry take over control of ciliary beating in smokers and patients with COPD. This observation contributes substantially to the novelty and significance of this study. However, because the authors activated SOC entry solely by thapsigargin-induced store depletion, one might miss the effect of more physiologically relevant activators of SOC entry. Experiments that use ligands such as acetylcholine (10, 12), ATP (9, 13), insect allergens (14), or probably receptor-independent activators of SOC entry, such as streptolysin O (15), would give additional mechanistic insights into SOC entry–mediated signaling and its changes in patients with COPD. Such experiments might reveal signaling pathways that replace SOC entry in the control of ciliary beating in epithelia from smokers with and without COPD.

The study of Petit and colleagues links SOC entry with ciliary beating in normal airway epithelia. Their major point that control of airway ciliary beating is substantially different in smokers and patients with COPD than in healthy control individuals is of potential importance for mucolytic treatments. ■

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