Asthma and sarcoplasmic reticulum Ca$^{2+}$ reuptake in airway smooth muscle

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TO THE EDITOR: We were delighted to note the concurrent publication of two studies linking decreased expression and function of sarcoplasmic reticulum Ca$^{2+}$ ATPase (SERCA) in human airway (bronchial) smooth muscle (ASM) to asthma. The first study, published in the July 2009 issue of American Journal of Physiology Lung Molecular Cellular Physiology, was actually from our group (3), whereas the second study by Mahn and colleagues (2) from the United Kingdom appears in the June 30, 2009, issue of the Proceedings of the National Academy of Sciences of the United States of America.

Exaggerated airway narrowing in asthma involves both enhanced ASM contractility and airway remodeling (1). Intracellular Ca$^{2+}$ ([Ca$^{2+}$]i) regulation is key to ASM contractility, with sarcoplasmic reticulum Ca$^{2+}$ release and reuptake being important components. SERCA is the major mechanism for replenishing sarcoplasmic reticulum (SR) Ca$^{2+}$ stores. Our recent study, based on healthy ASM cells exposed to proinflammatory cytokines, suggests that the increase in ASM [Ca$^{2+}$]i observed in asthma may be mediated by suppressed SERCA expression and function. The study by Mahn et al. (2) shows that ASM derived from asthmatics express lower amounts of SERCA but greater proliferation and secretion (features of airway remodeling) compared with ASM from healthy subjects. Furthermore, suppression of SERCA expression [using small interfering RNAs (siRNAs)] in ASM from the latter group mimics the greater proliferation and secretion of asthmatic ASM. Whereas our study found that even short-term (overnight) exposure to cytokines suppresses SERCA and slows [Ca$^{2+}$]i responses to agonist, the study by Mahn et al. (2) found similar [Ca$^{2+}$]i responses in asthmatic ASM (where SERCA expression was decreased). Thus the two studies link SERCA to both components of altered ASM in asthma: contractility and remodeling. However, our results (3) suggest that the decreased SERCA expression observed in asthmatic ASM (2) may occur fairly early following airway inflammation (i.e., even before remodeling occurs), and this status may be maintained with disease progression. Here, cytokines (potentially derived from the remodeling ASM) may have changing roles over time, with altered expression of [Ca$^{2+}$]i and force regulatory proteins at the outset, progressing to airway remodeling. Both studies raise an intriguing question for future research: is it elevated [Ca$^{2+}$]i resulting from decreased SERCA (induced by cytokines) that contributes to airway hyperreactivity and remodeling, or is decreased SERCA expression a marker of more proximal signaling changes induced by inflammation?

REFERENCES

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