Airway narrowing in asthma: does speed kill?

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THERE IS WIDESPREAD AGREEMENT that shortening of airway smooth muscle is the proximal cause of excessive airway narrowing during an asthma attack, with swelling of airway wall compartments and plugging by airway liquid or mucous being important amplifying factors (15, 18, 29). But it remains unclear why in asthma the muscle can shorten excessively.

The oldest and certainly the simplest explanation would be that muscle from the asthmatic airway is stronger than muscle from the healthy airway, but evidence in support of that hypothesis remains equivocal (2, 3, 24). Indeed, studies from the laboratory of Stephens and colleagues (1, 6, 11, 21) have emphasized that the force generation capacity of allergen-sensitized airway smooth muscle is no different from that of control muscle. As a result, the search for an explanation turned to other factors, and several alternative hypotheses have been advanced. These alternative hypotheses fall into three broad classes, each of which is consistent with remodeling events induced by the inflammatory microenvironment. These include changes of muscle mass (12, 26, 27), changes of the static load against which the muscle shortens (15, 28), and changes of the dynamic load that perturbs myosin binding (7, 9). Together, these hypotheses are attractive because they suggest a variety of mechanisms by which airway smooth muscle can shorten excessively even while the muscle itself remains essentially normal. As such, they have drawn attention away from the issue of the muscle and toward the issue of airway remodeling.

The report from Ma et al., one of the current articles in focus (Ref. 14, see p. L1181 in this issue), now draws attention back to the muscle itself. In a remarkable series of experiments, these investigators have characterized the contractility of airway smooth muscle cells obtained from bronchial biopsies of asthmatics and healthy volunteers. These studies show that cells from asthmatic subjects shorten faster and shorten more than do normal cells. Moreover, these investigators were able to associate these functional differences with increased content of message for myosin light chain kinase (MLCK).

What do we learn from these findings? First and most important, we learn that the airway smooth muscle cell from the asthmatic subject is not simply a “good” cell operating in a “bad” mechanical environment (7, 20). Instead, the cell itself is mechanically different. Second, we learn that these cellular changes would seem to have a relatively simple biochemical explanation. For technical reasons, expression of MLCK could not be measured directly, but the finding of increased content of message strongly implicates MLCK. Although regulation of myosin phosphorylation is a complex process with multiple kinase and phosphatase pathways, this finding substantially narrows the search for the culprit that may account for the mechanical changes observed in these cells. Third, these studies seem to rule out changes in the distribution of myosin heavy chain isoforms. Content and isoform distributions of message from asthmatic cells showed the presence of smooth muscle myosin heavy chain A (SM-A) but not SM-B, the latter of which contains a seven-amino acid insert, is typical of phasic rather than tonic smooth muscle, and is by far the faster of the two isoforms (13). Together, these findings confirm in muscle biopsy specimens from the asthmatic airway a number of findings from the allergen-sensitized dog model.

These new findings lead to new questions. First among these is why is the content of message for MLCK higher in muscle cells from asthmatic subjects? Second, how do these findings change our understanding of the mechanics of airway narrowing in asthma?

The authors are careful to point out that these studies pertain only to unloaded muscle and that the dynamics of shortening would be far different in cells loaded as they are in vivo. To account for increased shortening capacity of these unloaded cells, they point to the role of increased shortening velocity. They reason that upon activation virtually all muscle shortening is completed within the first few seconds. As such, the faster the muscle can shorten within this limited time window, the more it will shorten. Perhaps that is all there is to it, but perhaps not; in isotonic loading conditions at physiological levels of load, muscle shortening is indeed most rapid at the very beginning of the
contraction, but appreciable shortening continues for at least 10 min after the onset of the contractile stimulus (9). An alternative idea for why intrinsically faster muscle might shorten more comes from consideration of the temporal fluctuations of the muscle load that are attributable to the action of spontaneous breathing (8, 9). Load fluctuations that are attendant to spontaneous breathing may be the most potent of all known bronchodilating agencies (10, 22). These load fluctuations perturb the binding of myosin to actin, causing myosin to detach from actin much sooner than it would have during an isometric contraction. But the faster the myosin cycling (i.e., the faster the muscle), the more difficult it is for imposed load fluctuations to perturb the actomyosin reaction. This is because the faster the intrinsic rate of cycling, the faster will a bridge, once becoming detached, reattach and contribute once again to active force and stiffness.

In many but not all species, smooth muscle in the developing lung has higher shortening velocity than in the mature lung (4, 19, 23, 25). Similarly, smooth muscle in the allergen-sensitized animal has higher shortening velocity than does muscle from control animals. If it is true that muscle that shortens faster also shortens more (5, 16), then the findings in the report of Ma et al. (14) may shed light on airway hyperresponsiveness and wheezing as they relate to lung maturation and allergen exposure. In that connection, does the atopic child get a double whammy? As regards the natural history of asthma (17), the findings in this report open such interesting possibilities.

REFERENCES