Point: Counterpoint: Airway smooth muscle is/is not useful

**Point: Airway smooth muscle is useful**

Some ideas just sit and stare at you. Here is one that has bothered me for a year or so. It is hard for me to regard smooth muscles as vestigial (3, 4) and they can not be solely mean-spirited, so they probably have useful function. With no library and no computer, I just fell back on Intelligent Design Un-Googled. And off I went job hunting on behalf of airway smooth muscles.

Do they manage the distribution of inspired gas? Apparently not. In normal breathing, the time constants of the pathways are so low that elasticity of the parenchyma does the job.

Do they influence mucus clearance? The airways are unique conduits. They transport gases and quasi-liquids side by side, the first by the distant pumping of the respiratory muscles; the second, by mucosa-based cilia forming a linear pump, not at a distance but right there along the way. The mucus layer is essentially two phases (1): a periciliary liquid layer (PCL) and a gel-like phase, the two forming the airway surface layer (ASL). The PCL, where the cilia beat, lies against the airway wall and is confined by it. Its other side is covered by the gel-like phase and it, in turn, by gas. So this luminal side is not physically confined at all. As a result, its volume within a single branch can occupy little space or fill it entirely. And here lies a hitch: the bronchial tree narrows in the direction of transport. If the density of ciliary forcing were the same at all points, the amount of the ASL leaving a given generation would be greater than the next generation can handle, and the ASL would pile up. This does not happen in healthy lungs so it must be that forcing increases progressively down the bronchial tree. (It should be discernible histologically in terms of ciliary density.) This would be an innate answer to the problem. But there is no place for airway smooth muscle action here, so I moved on.

Next I considered factors that influence ASL thickness; not the ones that produce it or modify its constituents, but short-term mechanical influences, which are more my line. During inspiration, the airways are expanded and lengthened, and the surface area of the mucus layer lining the airways is increased. As it is incompressible it must become thinner. Airway smooth muscle contraction would have an opposite effect: since the muscles wrap the airways geodesically (2), their contraction would have little effect on airway length, and this would be advantageous; smooth muscle would have no effect on lung volume per se. And smooth muscle action would be suited for stabilizing ASL thickness in the face of lung volume change. The fractional changes in ASL thickness are the same as the sum of the fractional changes of airway diameter and length. The PCL is a free-flowing portion of the ASL. It will change thickness along with the rest if it is not displaced in the process. Short-term displacements in health are unlikely.

I wondered how ASL thickness might be controlled. Isotropie volume change could be monitored by a few stretch receptors even down to lobular levels, but how to inform the smooth muscle? Why involve the nervous system at all? Let the airways themselves do the job. The goal is the PCL thickness, which yields maximal ciliary forcing, and there is a local solution to consider. Ciliary forcing must result in equal and opposite forcing of the parent mucosa, and there must be local distortion associated with the forcing. Let this be sensed and activate smooth muscle. The goal is the level of contraction that provides the optimal thickness for maximum ciliary forcing.

Where is the physiology in this? When are there maintained shifts in lung volume that need attention? I see them mainly as a matter of gravity. We humans unwittingly allow it to produce and maintain higher mean lung volume upright than recumbent. Side-to-side shifts while recumbent shift volume from the upper to the lower lung. The weight of the abdominal contents and the flexibility of the diaphragm are the agents in both instances. Astronauts and small animals are excluded.

A striking aspect of all of this, for me, is the notion that airway smooth muscle action in defense of ciliary effectiveness would be complete at the branch level. This bucket brigade would involve myriad buckets, each self-governed. If we are born that way, it is innateness crying for a full. And one instance of this may be asthma, the mean-spirited action of airway smooth muscle revealed! Inspired allergens hit us not in gaseous form but as discrete items that land within airway branches indiscreetly—hit or miss—and, to shift the metaphor more, throw wrenches into the works. And here is what I have in mind. Airway smooth muscle contraction thickens the PCL and narrows the airway. The first effect optimizes ciliary function and is physiological. The second is potentially pathological. So it is good news and bad news, respectively, or negative feedback and positive feedback, or innateness and inanity, if you will. In health, the bad news is kept out of the way; the flow resistance of the airways peripheral to, say, the third generation of dichotomous bronchial branching is so low that a doubling of it would hardly be sensed. In an asthmatic attack, however, positive feedback is on display. Scattered obstruction of small airways hit by the allergen bullets necessitates tidal volume increases in the unobstructed regions if total ventilation is to be maintained. The attendant regional increase in average volume would get smooth muscle contraction underway, and there is no reason to expect that the process would be homogeneous. Regional increases in flow resistance would result in mean volume increases in other unobstructed regions if overall ventilation is maintained, and the process would be self-potentiating. It would slow down only as the tidal volumes of the unobstructed region approach elastic limits. Patient responses fit this story. Bronchodilators bring substantial but transient relief. The severe symptoms reflect abnormal functioning of normal lung. The slower and more lasting improvement with steroids allows the bullet-riddled regions that upset the innate apple cart to heal.

But back to physiology. After all, lungs do have nerves to account for, and in my job hunt, I have not needed them. Now, in a roundabout way, I have found a spot for them. Bronchial mucus clearance has two regimens: a ciliary realm in the periphery and a gas shearing realm centrally. The periphery realm is calm; the gentle breezes are too low to move much of anything. But ciliated surfaces are extensive, and the cilia can do the entire job. Mouthward, the ciliated surface area decreases as does the total cross-section. The first decreases ciliary effectiveness and the second increases the breeze and brings the gas shearing realm into action. During breathing,
there are dynamic swings in airway transmural pressures that are maximal at the thoracic outlet and decrease up the tree. Airways are dynamically expanded during inspiration and dynamically compressed during expiration. Accordingly there are swings in flow velocities and attendant fluctuations in gas shearing: greater mouthward during expiration than in the opposite direction during inspiration, and the net movement would be mouthward. This effect would be greatest near the thoracic outlet and diminish up the tracheobronchial tree. Overall mucus clearance would combine a diminuendo of ciliary action overlapping a gas shearing crescendo, the latter providing percussive sforzandos during coughing. And with coughing, I can put airway smooth muscle back to work. Nerve-activated generation bronchoconstriction could influence mucus clearance during a cough in two major ways, by determining: 1) the location and extent of airway collapse and 2) the lung volume at which collapse occurs. Without smooth muscle action, cough effectiveness would be limited to the central airways at low lung volumes. With bronchoconstriction, a few generations out of the tree, dynamic compression mouthward would be more extensive and easier to produce (flow limitation can be velocity enhancing!).

My overall conclusion is that airway smooth muscle’s utility is at least twofold; in both instances it assists mucus clearance.

REFERENCES


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AIRWAY SMOOTH MUSCLE IS NOT USEFUL

Airway smooth muscle (ASM) is the appendix of the lung. That is the succinct description rendered by Wayne Mitzner (15). Chun Seow and I had argued similarly that airway smooth muscle serves no useful function (22). Certainly there is no known disease entity or appreciable physiological deficit that is associated with loss of airway smooth muscle contractility, and when it contracts excessively, or contracts even moderately within an altered microenvironment, ASM seems only to cause problems. So in those very instances when ASM manifests itself, the consequences seem to be almost uniformly undesirable, and for that reason medical science has focused itself mainly on the question of how to frustrate its actions, as has evolution itself (10). Things have come so far, in fact, that today ASM is literally being burned at the stake under the scholarly moniker “bronchial thermoplasty” (1, 5, 16). As is often the case, frustration coupled with lack of purpose can be a precursor of misbehavior. As such, Seow and I had suggested that among the various muscle cell types that populate the body we could think of airway smooth muscle not so much as an appendix of the lung as much as the Hell’s Angel of cells, sitting on a Harley-Davidson, unshaven, a cigarette in one hand, a can of beer in the other, and a tattoo on its arm reading “Born to Lose.”

Whether a simple loser in the game of evolution or an appendix of the lung, such points of view have clearly rankled my friend, mentor, and teacher, and seemingly to good effect. Unwilling to accept the loser’s fate for ASM, he has tried to rehabilitate its sinister image by searching for heretofore unappreciated redeeming values. And indeed, he may have found one. His idea reduces to this: if the beating airway cilium is the motor that drives the mucociliary escalator, then airway smooth muscle may act as its transmission—one that is automatic and continuously variable at that. As in shifting the gears of a bicycle transmission, the airway smooth muscle by contracting or relaxing tunes the thickness of the airway surface liquid layer and thereby modulates the mechanical advantage exerted by the beating cilium upon mouthward airway surface layer (ASL) transport.

Before addressing this idea, I will briefly reiterate the case against ASM. But to do so begs a question that is even more basic and that I will deal with first: why is there specialized muscle in general, and why is there smooth muscle at all? An elegant answer was suggested by Richard Murphy (17). The design of striated muscle seems to be optimized for the efficient conversion of chemical energy into external mechanical work. The design of smooth muscle, by contrast, seems to be optimized not at all for efficiency but instead for economy, that is, economical conversion of chemical energy into maintenance of the tone and shape of hollow organs. It is these hollow organs, after all, that are the only places in which smooth muscle is found. Since these latter functions in hollow organs involve only trivial amounts of external mechanical work, efficiency becomes virtually irrelevant, whereas economy becomes all important. Indeed, in support of this argument is the observation that in smooth muscle vs. striated muscle the rate of ATP hydrolysis required to maintain a given level of isometric active stress is smaller by ~300-fold.

It had been recognized quite early that lungs are irritable and that stimulation of its contractile machinery in an animal with an open chest can cause air to be expelled from the lungs, a rise in intratracheal pressure, and an increase in airways resistance (4, 7, 13, 20). However, until the second half of the last century, airway smooth muscle was not regarded as being a muscle of any particular significance in respiration mechanics (20). Airway smooth muscle was first described in 1804 by Reisseisen [as related by Otis (20)] and its functional properties first considered by Einthoven (9) and Dixon and Brodie (7). More recent studies have shown that the fraction of the tissue volume that is attributable to contractile machinery is comparable for airways, alveolated ducts, and blood vessels in the lung parenchyma (18); the lung parenchyma, like the airway, is a contractile tissue (3, 11).

Identification of a normal physiological role of airway smooth muscle has remained elusive (20) and in that regard airway smooth muscle stands in contrast with other smooth muscle systems whose primary functional roles are self-evident. In an earlier report, Mead questioned the extent to which changes of smooth muscle tone might play some homeostatic role to stabilize airways and air spaces (13). He speculated that a moderately constricted state of airway smooth muscle may make airways behave more like the lung parenchyma in which they are embedded, thus improving the homogeneity of lung expansion; he reasoned that homogeneous lung expansion might depend on mechanical interdependence among lung
structures, all operating on a background of smooth muscle activity. It has been argued by others that contraction of airway smooth muscle might serve to modulate the tradeoff between dead space vs. airway resistance in a way that minimizes the work of breathing (23), to serve to adjust airway caliber among parallel pathways and parenchymal compliance among peripheral lung regions in a way that optimizes the distribution of ventilation (6, 8, 18), serve to narrow the airway in a way that improves the ability of cough to expel worms or other foreign objects from the airway, serve to stiffen the airway sufficiently to prevent extreme airway collapse during forced expiration (2, 19), or serve to match the mechanical hysteresis of small airways and alveolated ducts to the rather appreciable mechanical hysteresis of the alveolar surface film in a way that allows for synchronous and uniform alveolar expansion (12–14). Schmittny et al. (21) have demonstrated that throughout gestation of the fetal mouse lung there exist peristaltic waves of airway smooth muscle contraction propagating proximal to distal in the airways; they showed that fluid displaced by this milking action maintains an appreciable positive intraluminal pressure in peripheral airways and air space and suggested that this fluctuating distending pressure might provide a crucial stimulus for lung growth in utero.

Each of these arguments is plausible, but evidence in each case remains less than compelling. Still another explanation for the utility of airway smooth muscle, and perhaps a better one, is that there is no explanation; that is to say, both the phylogeny and the ontogeny of the lung shows that airways derive from foregut, so it cannot be ruled out that the presence of smooth muscle within this adapted piece of gut is merely vestigial and represents nothing more than a frozen accident of nature that finds no useful function.

This brings us back to the airway smooth muscle as a variable transmission of the mucociliary escalator, as is now proposed. I see no logical flaw in the argument, so the issues reduce to two. First, how big is the effect? Second, if it can be shown to have an appreciable physiological effect, can a specific mechanism then be found to effect the local regulation that is proposed? Jere’s hypothesis fits the bill of being simple, plausible, and mechanistic, but we cannot expect him to come out of retirement to test it. That being the case, someone else will have to take up the cause of gathering evidence that might reestablish the virtue of the oft-maligned airway smooth muscle cell.

So, is airway smooth muscle an appendix, a transmission, or a loser yet again? The answer to this question places more at stake than mere philosophy, especially if bronchial thermoplasty is to enter the armamentarium of routine tools to treat asthma.

REFERENCES


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REBUTTAL FROM DR. FREDBERG

My antagonist in this debate had the impossible task of proving a negative, but with a pleasant side effect, a put-down for Intelligent Design. As agonist, my impossible task was to prove a positive with a less pleasant side effect: no data. With only five months of my pension left, I can only make a suggestion. Take advantage of the speed differences of striated and smooth muscle, and I’ll leave it at that.

REBUTTAL FROM DR. MEAD

In quite a different context, Michael Walzer has asserted that disagreements do not invalidate a theory; the theory, if it is a
good one, makes the disagreements more coherent and comprehensible. Or put another way, every model is wrong but some are useful. In that context it is quite beside the point as to whether Jere’s theory is right or wrong. Rather, his perspective is valuable because it gives us a new question to investigate.

In his book *Advice to a Young Investigator*, the Nobel Laureate Santiago Ramon y Cajal (1) suggests that scientific writers govern themselves by the following rules: 1) have something to say; 2) say it; 3) stop once it is said; 4) give the article a suitable title and order or presentation. He goes on to remind us that whatever is good, if brief, is twice as good. Jere is no longer a young investigator, nor am I, but we both recognize good advice when we see it.

REFERENCES