models typically train on broad data by using self-supervision and are applicable across a wide range of downstream tasks. Present models primarily emphasize vision and language, neglecting other crucial senses like touch, which restricts their utility in estimating the state of, and predicting the outcome of, physical interactions (*9*). For example, the tactile feedback that one receives when sitting in a chair provides information on the stability of one's posture. But gathering multimodal sensory data on a large scale poses substantial challenges. Acquiring tactile data necessitates actual physical interactions. The i-fiber and intelligent textiles presented by Yang *et al*. offer an unobtrusive method for large-scale tactile data collection during daily human activities. Sensors embedded in clothes, carpets, tables, and beds, for example, could facilitate extensive data gathering. Such datasets could be used to train foundation models, equipping them with new abilities to assess contact, applied forces, and physical interaction patterns. This would open the door to physics-informed models that are characterized by markedly better sample efficiency and generalization capabilities.

The study of Yang *et al*. should inspire the development of functional fibers and application of intelligent textiles across diverse fields. It also highlights applications to ubiquitous computing with sensing, displaying, and communication components weaved into the fabric of everyday life, as envisioned 25 years ago (*10*). The i-fiber system of Yang *et al*. requires further refinement to accommodate more-efficient electromagnetic coupling for energy, a broader bandwidth for wireless information transmission, and robust performance for real-world deployments. Usability challenges also remain in intelligent textiles, particularly regarding washability, resilience, and durability. Addressing these issues requires joint efforts in the development of advanced materials, new textile manufacturing processes, and computation algorithms. But there is great promise for intelligent textiles to transform the way humans live, work, and interact with the world. ■

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MEDICINE

Epithelial cells crowded out in asthma

Bronchoconstriction causes epithelial cell extrusion that promotes airway inflammation

By **Jeffrey M. Drazen** *and* **Jeffrey J. Fredberg**

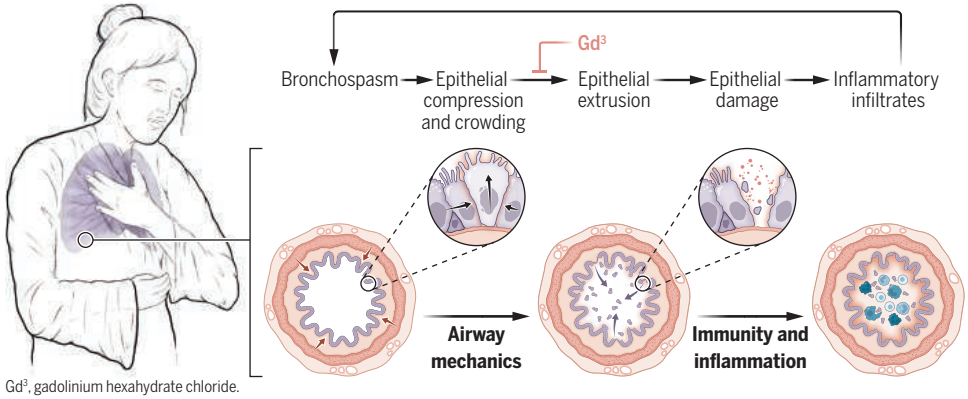
Reports of what were known at that time as "asthmatic fits" can be traced back millennia (*1*, *2*), but a mechanistic understanding of the basis for what are now called asthma exacerbations remains incomplete. Over the past 100 years, multiple mechanisms have been proposed, including constriction of the smooth muscle that encircles the airways (bronchoconstriction), persistent airway inflammation, and disruption of the epithelial layer that lines the airways. Yet how these processes interconnect and contribute to asthma exacerbations has been debated. On page 66 of this issue, Bagley *et al*. (*3*) show that bronchoconstriction results in pathological overcrowding of cells in the airway epithelium, squeezing out (extruding) epithelial cells and thus damaging the epithelial layer enough to trigger inflammation. They also show that drugs that block the extrusion pathway, and thereby prevent mechanical damage to the epithelium during acute airway narrowing, may have the capacity to break the inflammatory cycle and potentially revolutionize how asthma is treated.

Understanding of the pathobiology of asthma has changed substantially over the past 120 years but has shaped current thinking. In the early 1900s, it was discovered that epinephrine treatment could quickly reverse acute shortness of breath, leading to the idea that the primary mechanism underlying asthma must be excessive contraction of the smooth muscle that encircles the airways. As a result, for most of the second half of the 20th century, asthma research focused on identifying the contractile agonists and anatomical factors that predispose for excessive muscle contraction, and on the development of drugs that might ameliorate that contraction. In later decades of the 20th century, everything changed. It became recognized that episodic airway constriction in asthma was associated with persistent airway inflammation. Accordingly, attention shifted to determining the immune and inflammatory pathways that were linked to difficulty in breathing. Immunity was therefore understood to be the upstream mechanism that acts to drive downstream airway mechanics, which, although not ignored, became thought of as a clinically crucial end effect rather than a causal mechanism.

Thinking about asthma as being primarily an inflammatory disease brought progress in identifying key facets of the inflammatory cascade, including but not limited to the

The mechano-inflammatory vicious cycle

Airway immune activation and inflammation were thought to drive bronchoconstriction during asthma exacerbations. However, the demonstration that bronchoconstriction by itself is sufficient to cause epithelial cell extrusion that results in airway damage and inflammation changes the understanding of this causality, revealing a mechano-inflammatory vicious cycle.



Gd^3, gadolinium hexahydrate chloride.

downstream effects of signaling driven by the high-affinity receptor for immunoglobulin E (IgE), interleukin-4 (IL-4), IL-5, IL-13, and thymic stromal lymphopoietin (TSLP). This new understanding led to targeted monoclonal antibody treatments that effectively interrupt specific pathways within these inflammatory cascades (*4*). However, asthma in many patients remained inadequately controlled and poorly understood. It became increasingly clear that the picture of asthma pathobiology and its underlying root causes remained incomplete.

Among the multiple paradigms offered to explain asthma more fully, disruption of the integrity of the airway epithelium was suggested as a potential primary causal event (*5*). This notion is appealing because once it is accepted that the airway epithelium loses its integrity in asthma, a logical chain of events can be envisaged that would explain most of what is recognized as clinical asthma. However, the cause of airway epithelium disruption and resulting exposure of underlying layers to a host of irritants, allergens, and other pro-inflammatory signals has remained the source of much speculation.

In the early 2000s, the idea arose that bronchoconstriction itself might not be only an end effect but also a causal factor in the inflammatory cascade (*6*, *7*). However, the failure of powerful bronchodilator treatments to affect disease outcomes, other than ephemeral relief from symptoms of shortness of breath, caused many to discard this idea. Moreover, there was no clear mechanism by which bronchoconstriction might be imagined to cause epithelial disruption and inflammation.

Bagley *et al.* now identify just such a mechanism. Using mouse models and human lung tissue resection samples, they report compelling evidence that bronchoconstriction squeezes the epithelial layer, causing cellular crowding. In turn, this crowding causes excess extrusion of epithelial cells from the airway epithelial layer, which results in epithelial disruption, breakdown of epithelial barrier function, and then the transport of allergens and irritants to sites that they might not otherwise reach, with the subsequent release of inflammatory mediators.

The stretch-activated channel Piezo-type mechanosensitive ion channel component 1 (PIEZO1) and the transient receptor protein channels TRPA1, TRPV1, and TRPM8 have been implicated in epithelial extrusion but are inhibited by gadolinium hexahydrate chloride (Gd^{3+}). Bagley *et al.* found that inhibition of cell extrusion by Gd^{3+} or the peptide inhibitor GsMTx4 blocks airway inflammation, whereas treatments that act to relax airway smooth muscle do not prevent or reverse extrusion, damage, or inflammation.

These findings not only establish that bronchoconstriction is a pro-inflammatory stimulus but also point toward the potential for new research avenues that seek to inhibit a "mechano-inflammatory" vicious cycle (see the figure). Such a mechanism helps to paint a more complete picture of asthma pathobiology and may be relevant to other conditions, such as irritable bowel syndrome, in which epithelial cells are subject to disruptive mechanical forces.

These findings also point to new questions. For example, it is not currently understood how acute airway constriction causes epithelial layer compression and cell crowding (*8*), or how crowding results in excess cell extrusion and epithelial damage (*9*, *10*). Previous work has shown that mature confluent layers of primary human airway epithelial cells in air-liquid interface respond to mechanical compression by undergoing epithelial unjamming, in which the cell layer transitions from a solid-like nonmigratory collective phase to a fluid-like migratory collective phase while retaining a purely epithelial phenotype (*11*, *12*). Whether this migratory unjammed phase is a beneficial wound repair response, an aberrant wound repair response, or merely an innocent bystander remains to be determined. Similarly, whether the extrusion observed by Bagley *et al.* is a cause or consequence of epithelial unjamming and associated changes in cell shape is unknown (*13*). Furthermore, insight is lacking on the molecular pathways that are key for epithelial crowding, extrusion, and unjamming and whether these are affected by genetic determinants of asthma susceptibility (*14*). Last, it is not yet clear whether overcrowding and extrusion in response to bronchoconstriction occurs in healthy people, or how changes in this process might contribute to disease onset and progression. It may be time for a renewed focus on airway mechanics as an avenue to prevent and treat exacerbations of asthma. ■

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MOLECULAR BIOLOGY

Exceptionally long-lived nuclear RNAs

RNA labeled in young mice is detected 2 years later in adult mouse brains

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RNA has come a long way from a simple "messenger" or "translator" of canonical genic information during the production of proteins. A plethora of new types of noncoding RNAs have been discovered, including thousands of long noncoding RNAs (lncRNAs), many of which have no identified functions (*1*, *2*). Throughout this "RNA revolution," one property of RNA has been thought to be constant: RNAs are short-lived molecules that turn over, unlike DNA, which is much more stable. On page 53 of this issue, Zocher *et al.* (*3*) challenge that paradigm by showing that newly synthesized RNA labeled with 5-ethynyl uridine (EU) in early postnatal mice was still present in many brain cells 2 years later. The complex pattern of when and which cells are labeled suggests that EU that is incorporated into RNA in neural progenitor cells (NPCs) frequently remains in adult neurons. This suggests that a diversity of long and repeat-rich RNAs, collectively called long-lived RNAs (LL-RNAs), can be stable fixtures in postmitotic and quiescent neural cells.

There have been decades of studies that demonstrate that the half-lives of mRNA range from minutes to hours, with relatively "stable" ribosomal RNA persisting for days. So how could LL-RNAs not have been found before? A key difference is that Zocher *et al.* examined RNA in mouse brains filled with postmitotic neurons, whereas most studies have examined proliferative cells. The prior studies show that RNA turnover is dynamically regulated to meet cellular demands (*4*). Thus, because RNAs are not subject to unrestrained ribonucleases (RNases), if they are structurally protected in nuclei, perhaps they can persist indefinitely.

An important point is that the persistent EU label observed by Zocher *et al.* is distinctly nuclear. Why would this be, par-