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A Hairline Crack in the Levee: Focal Secretory IgA Deficiency as a First Step toward Emphysema

Among the many ways smoking annually kills more than 5 million humans (1), arguably none is as cruel as the slow, relentless suffocation inflicted by emphysema. Attaining comprehensive molecular understanding of emphysema pathogenesis has also been agonizingly slow. Emphysema was recognized at autopsy in the early 1800s by Laennec (2), who advanced a now-refuted theory of its origin, but the first conceptual breakthrough came from identification of emphysema subtypes, notably centrilobular emphysema (CLE) (3). With these subtypes now quantifiable in living subjects by radiographic imaging (4), there is hope that research progress will accelerate.

Emphysema might be arrested at many downstream steps, but it would be most efficient to block its initiation. Two major hypotheses on the origin of emphysema have emerged. One could be termed the Canadian hypothesis, as it germinated in Montreal and flowered there and in Vancouver among the groups of Profs. Cosio and Hogg, respectively. It emphasized inflammation in small (<2 mm diameter) airways, leading to their disappearance before CLE develops (5). A second hypothesis, from investigators originally and now largely again in Denver, focused on vascular endothelial apoptosis (6). It was heavily influenced by experimental models (7) and less specifically linked to emphysema subtype. Importantly, neither group claimed that their mechanisms exclusively explain emphysema pathogenesis. Both might pertain in different disease stages, or perhaps specific emphysema subtypes result from the balance between epithelial damage, vascular injury, or other factors.

The goal of this simplified formulation is not to slight the very significant contributions of other investigators worldwide but to contextualize another compelling advance, coincidently supporting the Canadian hypothesis. In this issue of the *Journal*, Polosukhin and colleagues (pp. 1010–1021) demonstrate a molecular mechanism that explains why airway injury develops in small airways precisely where Hogg and colleagues showed it begins (8). This exciting new study builds on decades of work on the key role of secretory immunoglobulin A (SIgA) in respiratory epithelial defense (9). Hence, appreciating three points about SIgA physiology is essential (Figure 1).

First, relative to serum IgA, the SIgA complex is specialized for export into mucosal lumens and subsequent sustained activity (Figure 1A). Second, IgA does not activate complement, permitting "immune exclusion" without inflammation. Third, because epithelial tight junctions, like the levees protecting cities along major rivers from devastating flooding, block bidirectional macromolecule transit, IgA cannot simply diffuse into the airway lumen. Instead, dimeric IgA (and pentameric IgM) must be transcytosed by the polymeric Ig receptor (pIgR) expressed on basolateral epithelial cell membranes (Figure 1B). At the luminal surface, cleavage of pIgR liberates SIgA, still bound to a portion of pIgR called the secretory component. Reduced secretory component (and hence SIgA) was shown in bronchoalveolar lavage fluid of smokers (10) and in small airways of patients with chronic obstructive pulmonary disease (COPD) (11), and then the Vanderbilt group and collaborators linked reduced pIgR expression and localized SIgA deficiency in small airways to cross-sectional COPD severity (12, 13).

The next and crucial step in the logical chain of emphysema pathogenesis comes in this issue of the *Journal*, which meticulously used fluorescence microscopy (for SIgA) and *in situ* hybridization (for intracellular bacteria) to analyze human lung samples (total n = 89, including lifelong nonsmokers, ex-smokers without COPD, and all Global Initiative for Chronic Obstructive Lung Disease stages) (8). Results convincingly show that pathological changes, regardless of subject group, were limited almost exclusively to small airways classified as SIgA deficient. Changes included all those characterizing early COPD, including distorted epithelial morphology, inflammatory cell infiltration, and fibrotic remodeling. Most tellingly, only SIgA-deficient small airway epithelia were invaded by bacteria and showed nuclear factor-κB activation (Figure 1C). Together with complementary results from this group's studies using transgenic mice lacking PIgR (14), these data strongly implicate a specific localized defect in innate immunity in the earliest stages of smoking-induced damage to terminal bronchi.

This significant advance is congruent with findings in the skin and gut, where failure to contain bacteria leads to escalating adaptive immune countermeasures, culminating in frank autoimmunity. As at those other interfaces, subtle innate immune defects, perhaps acquired as in this study (8), but likely also genetic, could explain why only certain ever-smokers transition into greater epithelial damage plus a more aggressive lung microbiome exploiting that damage (15) and why, once initiated, pathology may be sustained despite smoking cessation.

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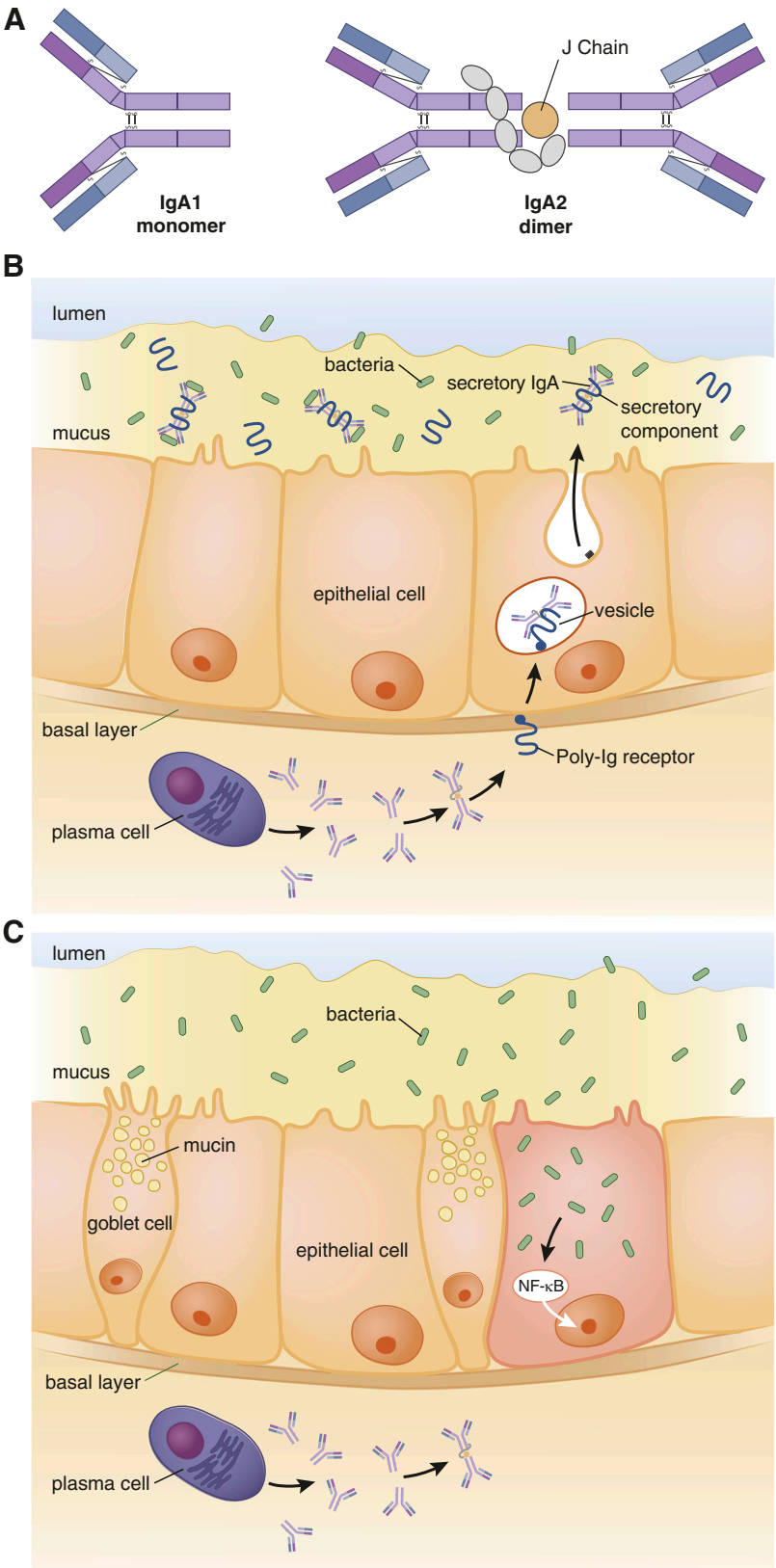

Figure 1. Secretory immunoglobulin A (SIgA) secretion in small airways and its alteration in chronic obstructive pulmonary disease (COPD). (*A*) Structures of monomeric IgA versus SIgA. In serum, IgA principally circulates as IgA1 monomers, whereas SIgA is a dimer of two IgA monomers linked by J ("joining") chain. SIgA is optimized to resist degradation at mucosal surfaces, both because its subunits are primarily IgA2 (which, relative to IgA1, possess a shorter

Whether along river levees or airways, the tiniest cracks can initiate catastrophic breakdown of protective systems. The research community's response should be innovative and flexible, taking inspiration from Emperor Yu of the Xia dynasty, long considered mythical but recently supported by archeology (16). According to Sima Qian, Yu finally controlled flooding of the Huang He, not by simply again rebuilding levees but by dredging the river channel.

Thus, to convert these insights into novel therapies, one next step should be identifying which bacterial species invade SIgA-deficient respiratory epithelium. This point could not be addressed in this study (8), which used "universal" probes recognizing essentially all bacteria (and archaea). Obvious candidates are nontypeable *Haemophilus influenzae* and *Streptococcus pneumoniae*, both comprising rapidly evolving clonal populations uniquely adapted to humans and known to invade respiratory epithelia. However, bacteria reside in temporally and spatially dynamic communities that regulate dominance of any single species. Hence, thoroughly understanding how bacteria exploit focal SIgA deficiency will require unbiased analysis of the lung microbiome in multiple subject groups, especially the many symptomatic ever-smokers who do not meet the current spirometry-based definition of COPD (17, 18).

Also unanswered is how bacterial invasion triggers epithelial cell apoptosis, a characteristic of emphysema. Here, the prime suspects (19, 20) are $CD56^+$ natural killer (NK) cells, which eliminate cells displaying signs of excessive stress. *In vitro*, lung NK cells from patients with COPD induced significantly greater apoptosis in autologous respiratory epithelial cells than lung NK cells from smokers without COPD (21). Importantly, specific lytic activity was limited to $CD3^-CD56^+$ NK cells (which coexpress CD8) and was not mediated by conventional $CD3^+CD8^+$ T cells (21). NK cell recognition is controlled by the balance of highly complex activating and inhibitory receptor families but might still be a therapeutic target to halt emphysema progression, especially if the epithelial ligands triggering cytolysis result from bacterial invasion. Defining the relative contributions of host versus microbial processes in emphysema progression will be crucial to develop precision approaches to this worldwide scourge. ■

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Figure 1. (Continued). hinge region that resists bacterial cleavage) and because the J chain protects portions of its structure. (*B*) In health, dimeric IgA (and pentameric IgM) are transcytosed across epithelial cells, from the basolateral surface into the mucosal lumen, by the polymeric Ig receptor (pIgR). Cleavage of pIgR at the luminal surface liberates SIgA, still bound to a portion of pIgR called the secretory component. SIgA prevents bacterial invasion of respiratory epithelium. (*C*) In COPD, pIgR is reduced, leading to localized SIgA deficiency in small airways (although not in larger airways where SIgA secretion directly via submucosal glands can compensate [13]). In the absence of SIgA, bacteria can invade respiratory epithelial cells. The resulting nuclear factor (NF)-κB activation initiates and sustains airway inflammation, setting the stage for development of centrilobular emphysema due to epithelial cell apoptosis. Artwork by Patricia Beals, adapted by permission from References 9 and 22.

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Choosing Sides in Predicting Fluid Responsiveness

Fluid resuscitation is a cornerstone of therapy in the management of hemodynamically unstable patients. Administering volume incorrectly—either too little and/or too slowly—will result in increased morbidity and mortality. Similarly, giving fluids to a non–volume-responsive patient promotes volume overload and can be equally detrimental (1). Approximately one-half of all patients presenting with cardiovascular insufficiency (i.e., shock) are not volume responsive (2). Thus, using a fluid bolus approach to plumb cardiovascular reserve in these patients is prone to be both inefficient and promoting volume overload in at least one-half of cases. Luckily, numerous dynamic hemodynamic indices of cardiac responsiveness exist that do not require intravascular fluid challenges. In patients receiving mechanical ventilation, the ventilator-induced phasic increases in intrathoracic pressure create right-sided changes in the diameter of the superior and inferior venae cavae (ΔSVC and ΔIVC, respectively) and subsequent left-sided left ventricular stroke volume and arterial pulse pressure variation. Most of these parameters can be measured noninvasively or with minimally invasive echocardiography and arterial pressure monitoring (3–5). Similarly, longer term dynamic volume challenges induced by passive leg raising (PLR) induce transient changes in various estimates of cardiac output (6). However, the validity of these parameters has been questioned in the setting of various shock etiologies, smaller tidal volumes used for protected lung ventilation, and in the presence of increased intraabdominal pressure, all common conditions in critically ill patients. This makes the study reported in this issue of the *Journal* by Vignon and colleagues (pp. 1022–1032) relevant (7). These authors performed a 5-hospital study of 540 patients with acute circulatory failure of any cause accrued over 2 years to assess the ability of various echocardiographic indices and pulse pressure variation to predict a greater than 10% increase in left ventricular outflow tract velocity–time integral ($Vmax_{Ao}$) in response to a PLR maneuver. About one-half (42%) of their patients were volume responsive. Furthermore, they confirmed that ΔSVC equal to or exceeding 21%, $\Delta Vmax_{Ao}$ equal to or exceeding 10%, ΔIVC equal to or exceeding 8%, and pulse pressure variation equal to or exceeding 11% predicted volume responsiveness. $\Delta Vmax_{Ao}$ had the best overall sensitivity and ΔSVC the most specificity; ΔIVC and pulse pressure variation fared worse. Thus we can conclude that in these centers with expert echocardiographers, in sedated, muscle-relaxed ventilated patients with a wide variety of acute circulatory shock etiologies, tidal volumes, and intraabdominal pressures, these echocardiographic indices are robust predictors of volume responsiveness. These data lend strong support to the American Thoracic Society–endorsed position that training in bedside ultrasound is an essential part of critical care physician education (8).

However, the study has some major limitations. First, the authors did not assess whether the patients were volume responsive but rather whether these indices correlated with a PLR $\Delta Vmax_{Ao}$ greater than 10%. Still, in a subset of their patients given a fluid challenge, this "surrogate" rule proved to be robust. Second, all investigators were expert in advanced bedside echocardiography and all patients were not only sedated but receiving muscle relaxants. Thus, the quality of the data in the hands of less well-trained clinicians and in patients without muscle relaxants will probably degrade. Still, the American Board of Echocardiography approved a board certification process for Critical Care Point-of-Care Echocardiography, and therefore the level of expertise and availability of bedside echocardiography in all acute care units should increase.

Interestingly, the authors have created two artificial dichotomies. The first is the comparison of continuous pulse pressure variation with intermittent echocardiographic measures. Both stroke volume and pulse pressure variation can be monitored continuously, using an arterial catheter or noninvasively by finger plethysmography, without an expert clinician at the bedside. Such continuous data can effectively drive personalized resuscitation protocols (9). Repeated transesophageal or transthoracic echocardiography are labor intensive and do not lend themselves to frequent repeated measures. Still, both provide a wide range of valuable diagnostic information not readily available with any other bedside tools. Transthoracic echocardiography measures of $\Delta Vmax_{Ao}$ and ΔIVC are rarely measured every few minutes, whereas pulse pressure variation is always available for clinical decision-making.