Scaling Physiologic Function from Cell to Tissue in Asthma, Cancer, and Development

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Abstract

The formation of an integrated tissue from individual cells depends on the properties of the individual cells as well as the interaction of many cells acting as a collective. Three fundamental physiological processes govern the collective scaling from the individual cell to a working tissue: cell sorting, tissue assembly, and collective cellular migration. Mechanistically, cell sorting is governed by differential

adhesion, whereas tissue assembly is controlled by the epithelial-to-mesenchymal transition and its inverse, the mesenchymal-to-epithelial transition. The mechanism driving collective cellular migration, however, is not clear. To fill that gap, here we consider cell jamming and unjamming, and their role in collective cellular migration.

Keywords: jamming; migration; collective; epithelium

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The human bronchial epithelium is a pseudostratified layer that protects the airway from inhaled particles, dust, allergens, viruses, bacteria, and other pathogens. This epithelium is well differentiated, being composed of serous cells, goblet cells, ciliated cells, basal cells, and others. Together, these cells comprise the barrier that separates airway tissue from inspired air. Structurally, these cells completely tile the airway surface like tiles covering a floor. Furthermore, epithelial cells integrate mechanical signals from cell–cell junctions with extracellular biological information to collectively maintain barrier integrity. In response to disease or injury, however, the cell–cell junctions can break down and hinder epithelial barrier functionality. For example, the airway epithelium is deeply implicated in both the pathogenesis of, and exacerbations in, asthma, particularly in the context of viral infections (1, 2).

Cells comprising the mature, healthy epithelial layer tend to be nonmigratory. For

example, airway epithelial cells cultured from the donor without asthma remain immobile. They behave as if they are caged by their immediate neighbors, trapped, and jammed, much as coffee beans can become jammed in a chute (3, 4). Therefore, we were surprised to discover that, in the epithelial layer cultured from donors with asthma, the epithelial cells, although still tiling the surface and remaining confluent, are vigorously scrambling, rearranging, and exchanging places with their neighbors at a rapid rate (3). These asthmatic cells behave as if they are uncaged and unjammed (3).

So what is the cell-jamming phenomenon, and how do cell jamming and unjamming come about? In the confluent epithelium, two major forces, or corresponding energies, are at play. There are energies associated with tensile forces along the cell–cell junctions, and there are energies associated with intercellular adhesive forces between neighboring cells (5–8). Statistical mechanics of cell

collectives predict that, when tensile forces dominate over the adhesive forces, an energy barrier emerges that impedes a cell from changing places with its neighbor. The physical picture becomes analogous to a marble in the bottom of a round bowl, which finds itself stationary and constrained to the bowl bottom. So too for the cell in the nonasthmatic epithelium, which finds itself trapped in an energy well that prevents its motion, and prevents the exchange of places with its immediate neighbors. The cell is caged and jammed (9–11).

On the other hand, when adhesive forces become large compared with tensile forces, that energy barrier vanishes (9–11). It is as if the marble no longer finds itself trapped at the bottom of a bowl, stuck at the bottom of an energy well. Instead, it is more like a marble on a flat surface, unconstrained and able to move about. When energy barriers vanish, the collective as a whole behaves as a fluid—it can flow,

Collective cellular migration

Cell jamming

growth
angiogenesis
embryologic development
wound healing, invasion, metastasis

Tissue assembly/disassembly

EMT & MET

E Hay 1995

Cell Sorting

Differential adhesion

MS Steinberg 1962

Figure 1. The formation of a working tissue from individual cells is governed by three fundamental physiological processes: cell sorting, tissue assembly, and collective cellular migration. The mechanism that controls cell sorting is differential adhesion, whereas tissue assembly is coordinated by the epithelial-to-mesenchymal transition (EMT) and the mesenchymal-to-epithelial transition (MET). The mechanism responsible for collective cellular migration is unknown. To fill this gap, here we consider cellular jamming and unjamming. AJ = adherens junction; DS = desmosome; ECM = extracellular matrix; TJ = tight junction.

and individual cells can readily exchange places with their immediate neighbors. The individual cell is uncaged and the collective is unjammed.

This physical picture of cell jamming and unjamming brings us to the issue of scaling from cell to tissue (Figure 1). In the scaling from cell to tissue, there are three major driving phenomena.

First described by Malcolm Steinberg in 1962 (12–15), cell sorting describes a mixture initially composed of different embryologic cell types, which, in time, manages to sort itself into discrete and homogenous tissue compartments

(Figure 1, bottom right). Steinberg taught us that cell sorting is driven by a specific mechanism, namely, differential adhesion. Low-adhesion cells stick with other low-adhesion cells, whereas high-adhesion cells segregate with other high-adhesion cells. This notion of differential adhesion is equivalent to the statement that the tissue is driven to an overall state of minimum surface energy. Although this idea has subsequently become modified (16), the notion of cell sorting and differential adhesion is thought to be a major factor in the scaling of the individual cell to whole tissues in embryological development.

A second major idea in scaling from cell to tissue is the epithelial-to-mesenchymal transition and the reverse, the mesenchymal-to-epithelial transition, as described originally by Elizabeth Hay in 1995 (Figure 1, bottom left) (17, 18). The epithelial-to-mesenchymal transition is crucial in tissue disassembly, wherein an intact epithelium can disassemble into highly mobile mesenchymal cells, as in the case of the neural crest (19). On the other hand, the mesenchymal-to-epithelial transition is crucial in tissue assembly, wherein multiple mesenchymal cells can assemble into an intact epithelium, as

occurs in the formation of the kidney, heart, liver, and somites (20). Mesenchymal-to-epithelial transition is thought to occur as well in the formation of secondary tumor sites in cancer metastasis (21).

Both cell sorting and tissue assembly impact, and are impacted by, collective cell migration. First described by Holmes in 1914 (22) (Figure 1, top), collective cellular migration is essential in development, wound healing, and cancer wherein cells move in highly cooperative packs and streaks, strands, and sheets (23–25). These

processes of cell sorting, tissue assembly, and disassembly, and collective cellular migration, are all emergent phenomena in the sense that they are inherently collective and cannot be understood from single cells studied in isolation. Moreover, these processes and combinations of them seem to be involved almost everywhere, including growth, angiogenesis, embryological development, wound healing, invasion, and metastasis.

Despite all we have learned about these processes, the governing principles

remain somewhat mysterious. Epithelial cells migrate collectively and in a fashion that demonstrates the disorder and cooperativity that are characteristic of jamming behavior. We propose, therefore, that the physics of jamming may be the central organizing principle of collective cellular migration. However, the jury is still out and the disease-related implications, although potentially quite broad, remain unclear (3, 25–27). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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