

Playing “telephone”: bioactive lipids as mediators of intercompartmental communication in the alveolus

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Commentary

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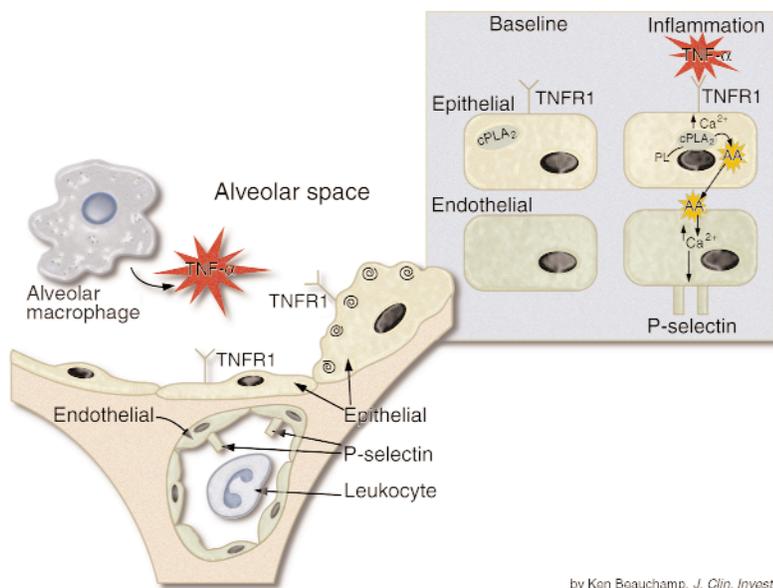
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This need for communication between airspaces and vascular compartments requires epithelial and endothelial cells in the alveolar wall to sense and respond to changes in their local milieu. Indeed, research over the last 30 years has begun to elucidate the vast repertoire of receptors and intracellular signaling systems used by these 2 cell types to carry out this mission (1, 2). However, these cells must also be able to transmit information to each other. The nature of the currency exchanged in such intercellular trans-

actions has been more difficult to pinpoint. Although in vitro experiments using cocultures of alveolar cells provide useful information about cell-cell communication (3), studies are needed in the intact lung, where boundaries between compartments are preserved.

In a series of elegant experiments published in this issue of the *JCI*, Kuebler and coworkers have delineated the molecular events that account for propagation of inflammatory signals from alveolar epithelial cells to endothelial cells (4). The requirement for fidelity of signal transmission at each of the many steps along this sequence is reminiscent of that required in the childhood game of “telephone.” The authors have modeled alveolar inflammation by microinjecting the proinflammatory cytokine TNF- α into the airspace of the isolated, ventilated, and perfused rat lung. Using in situ fluorescence microscopy to quantitate intracellular Ca²⁺, they demonstrated that TNF- α elicits an increase in epithelial cell Ca²⁺ in a manner that depends on ligation of its surface receptor, TNFR1. The authors also observed parallel increases in endothelial Ca²⁺, and showed that expression of the adhesion molecule P-selectin increases on the surface of endothelial cells, a response that would be expected to initiate leukocyte recruitment. The most crucial experiments, however, were those that elucidated the nature of the signal that was released from the basolateral surface of the epithelium, causing endothelial Ca²⁺ to increase.

That signal, as Kuebler et al. showed conclusively, is arachidonic acid (AA). AA is a 20-carbon unsaturated fatty acid that is esterified in cell membrane phospholipids. It is enzymatically cleaved from the parent phospholipid by the action of 1 or more of a family of enzymes termed phospholipases A₂ (PLA₂) (5). Once liberated, AA is available to be metabolized through several dis-



by Ken Beauchamp, *J. Clin. Invest.*

Figure 1

Scheme for alveolar epithelial to endothelial cell signal propagation initiated by TNF- α . The spatial interrelationships of participating cells and receptors are shown on the left. The molecular events are summarized on the right. The crucial molecule mediating intercellular communication is free AA, which is hydrolyzed from epithelial cell nuclear membrane phospholipids (PL) by cPLA₂, and which induces endothelial cell Ca²⁺ flux.

crete pathways to an array of bioactive substances known as eicosanoids. Among these products, the prostanoids and leukotrienes have been the most extensively investigated (6). Studies with isolated and cultured alveolar epithelial cells have demonstrated that these cells can liberate AA in response to agonists that increase intracellular Ca^{2+} , and can metabolize this lipid, primarily to prostanoids (7). The predominant PLA₂ isoform in these cells appears to be an 85-kDa species known as cytosolic PLA₂ (cPLA₂) (8). Interestingly, cPLA₂ is active only after it has been translocated, in a Ca^{2+} -dependent step, from cytosol to the nuclear envelope, where phospholipid hydrolysis takes place (9). In their in situ immunofluorescence microscopy studies, Kuebler et al. took advantage of this fact and inferred cPLA₂ activation from its perinuclear locale. They further confirmed the importance of this enzyme in propagating the epithelial to endothelial signal by showing that endothelial Ca^{2+} entry could be prevented by alveolar infusion of either Ca^{2+} chelators or specific inhibitors of cPLA₂.

Many readers will be surprised by the finding that AA, rather than one of its better-known eicosanoid metabolites, proved to be the mediator of cell-cell communication in this model. However, the ability of exogenous FFAs to mimic the actions of TNF- α and the failure of inhibitors of AA metabolism to abrogate the endothelial response to the cytokine both indicate that AA itself represents the transmitted signal. Moreover, a growing body of literature has demonstrated that free AA, and often other unsaturated fatty acids as well, are indeed pluripotent effectors of signal transduction. Thus, AA has been shown not only to increase Ca^{2+} flux (10), as it did in alveolar capillary endothelial cells in the study by Kuebler et al., but also to promote superoxide generation (11), to activate kinases including protein kinase C (12) and mitogen-activated protein kinase (13), to induce expression of heat-shock genes (14), to act as a ligand for the peroxisome proliferator-activated receptor family of transcription factors (15), and to participate in the activation of

nuclear factor- κ B (16).

Is AA a logical choice to mediate intercellular communication in vivo? Ideally, such a mediator would (a) be produced rapidly but transiently; (b) diffuse readily out of the source cell and into the recipient cell; (c) rapidly elicit an effector signal in the recipient cell; and (d) have a relatively short half-life. These features would facilitate propagation of a message that is quick, short-lived, and local. A small amphipathic molecule that can be generated within seconds to minutes by virtually all cell types, AA readily meets these criteria. The modulation of cPLA₂ expression and enzymatic activity (17) provides further opportunities for fine-tuning this signal. By contrast, many proteins, such as cytokines, are ill suited to act as rapid-response signals by virtue of their size and the temporal requirement for transcriptional or translational induction.

A number of key issues remain to be addressed. First, it must be acknowledged that the experimental system under investigation in the article by Kuebler and colleagues is only a model for pulmonary inflammation. It will be important to test the participation of this molecular "telephone chain," or variants thereof, in studies using physiologically relevant inflammatory agents, such as microbes. Second, the cellular sensors for FFAs are, in many instances, not known. The identity of such sensors and the mechanisms by which they couple to signaling cascades will be an important subject for future research. Third, the potential of other candidate lipid mediators of intercompartmental communication must be explored; these include other fatty acids, other products of PLA₂ action (lysophospholipids and platelet activating factor), and eicosanoids.

There is 1 final implication of this work for those willing to indulge in symbolism. An important feature of the experimental model dissected by Kuebler and colleagues is the cooperation between a cytokine and a lipid. I am often struck by the manner in which scientists studying either cytokines or lipids themselves appear to be segregated into 2 parallel uni-

verses. Scientific inquiry would surely be advanced if communication between investigators inhabiting these 2 worlds occurred as readily as it certainly does between these 2 classes of mediators in biological systems.

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