

Influenza leaves a TRAIL to pulmonary edema

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Influenza infection can cause acute respiratory distress syndrome (ARDS), leading to poor disease outcome with high mortality. One of the driving features in the pathogenesis of ARDS is the accumulation of fluid in the alveoli, which causes severe pulmonary edema and impaired oxygen uptake. In this issue of the *JCI*, Peteranderl and colleagues define a paracrine communication between macrophages and type II alveolar epithelial cells during influenza infection where IFN α induces macrophage secretion of TRAIL that causes endocytosis of Na,K-ATPase by the alveolar epithelium. This reduction of Na,K-ATPase expression decreases alveolar fluid clearance, which in turn leads to pulmonary edema. Inhibition of the TRAIL signaling pathway has been shown to improve lung injury after influenza infection, and future studies will be needed to determine if blocking this pathway is a viable option in the treatment of ARDS.

Sodium pumps and lung injury

Acute respiratory distress syndrome (ARDS) causes a devastating respiratory failure with significant morbidity and mortality (1). One of the major causes of ARDS is direct lung injury, such as pneumonia or aspiration. ARDS can also occur from indirect injuries — such as sepsis, blood transfusion, or pancreatitis — indicating that factors independent of primary lung damage play a major role in ARDS development. A hallmark of ARDS is flooding of the alveoli with protein-rich fluid, which impairs gas exchange. Destruction of lung epithelial and endothelial cells by pathogens, inflammatory cells, or trauma breaks down natural barriers that prevent pulmonary edema. However, perturbations to intrinsic mechanisms that actively remove fluid from the airspaces also contribute to the development of ARDS.

The primary means by which fluid is cleared from the airspaces is through the creation of an osmotic gradient in the alveolar microenvironment via vectorial transport of sodium and chloride across the epithelium (2, 3). Although chloride channels participate in this process (4), sodium movement out of the alveolus

is the primary driver of fluid removal. Sodium enters into the cell through the apical membrane via epithelial sodium channels (ENaC), whereas Na,K-ATPase pumps sodium through the basolateral surface of the cell. Together, ENaC and Na,K-ATPase effectively transport sodium from the alveolus into the interstitium, and the differential sodium concentrations facilitate passive reabsorption of water to optimize the gas exchange across the alveolar surface (Figure 1).

Influenza causes pulmonary edema

Influenza primarily infects the lungs and can result in ARDS, depending on the pathogenicity of the virus and the host response (5). Classically, respiratory failure from influenza infection was largely understood to result from excessive epithelial cell death due to direct viral toxicity and recruited inflammatory cells (6). However, influenza can also impair alveolar fluid clearance, which up to now has been attributed to disruption of ENaC function (7–9).

In this issue, Peteranderl et al. demonstrate that influenza infection can

reduce alveolar fluid clearance through downregulation of Na,K-ATPase pumps (10). The mechanism of this effect lies within an intimate crosstalk between macrophages and the alveolar epithelium. Through some elegant coculture experiments and in vivo intrapulmonary adoptive transfer studies, the authors show that IFN α induces TRAIL secretion from macrophages, which in turn signals the alveolar epithelium to downregulate Na,K-ATPase expression, resulting in a concomitant decrease in alveolar fluid clearance. Importantly, TRAIL-mediated effects on the alveolar epithelium were not through the induction of apoptosis, but through activation of AMPK and subsequent triggering of Na,K-ATPase endocytosis and degradation (Figure 1).

These findings are an extension of previously published work by this research group and others that have demonstrated the importance of macrophage secretion of TRAIL during influenza infection (11–13). In those studies, a substantial amount of apoptosis occurred from TRAIL signaling on the alveolar epithelium. Barrier integrity likely contributes to the overall development of pulmonary edema, but the current studies by Peteranderl and colleagues clearly demonstrate that TRAIL also impairs alveolar fluid clearance independent of programmed cell death (10). This study also merges nicely with previous publications by several of these coauthors who describe hypoxia and hypercarbia as inducers of AMPK activation, a critical step for Na,K-ATPase endocytosis (14–16). These stimuli increase intracellular ROS and/or calcium and converge on PKC- ζ , which phosphorylates Na,K-ATPase to induce its endocytosis. Peteranderl et al. show that AMPK activation during influenza infection requires intracellular calcium but is independent of transforming growth factor β -activated kinase 1 (TAK1), which has been shown to mediate TRAIL activation of AMPK (17). What remains to be determined is the relative contribution of hypoxia, hypercarbia, and TRAIL in

► Related Article: p. 1566

Conflict of interest: The authors have declared that no conflict of interest exists.

Reference information: *J Clin Invest.* 2016;126(4):1245–1247. doi:10.1172/JCI86802.

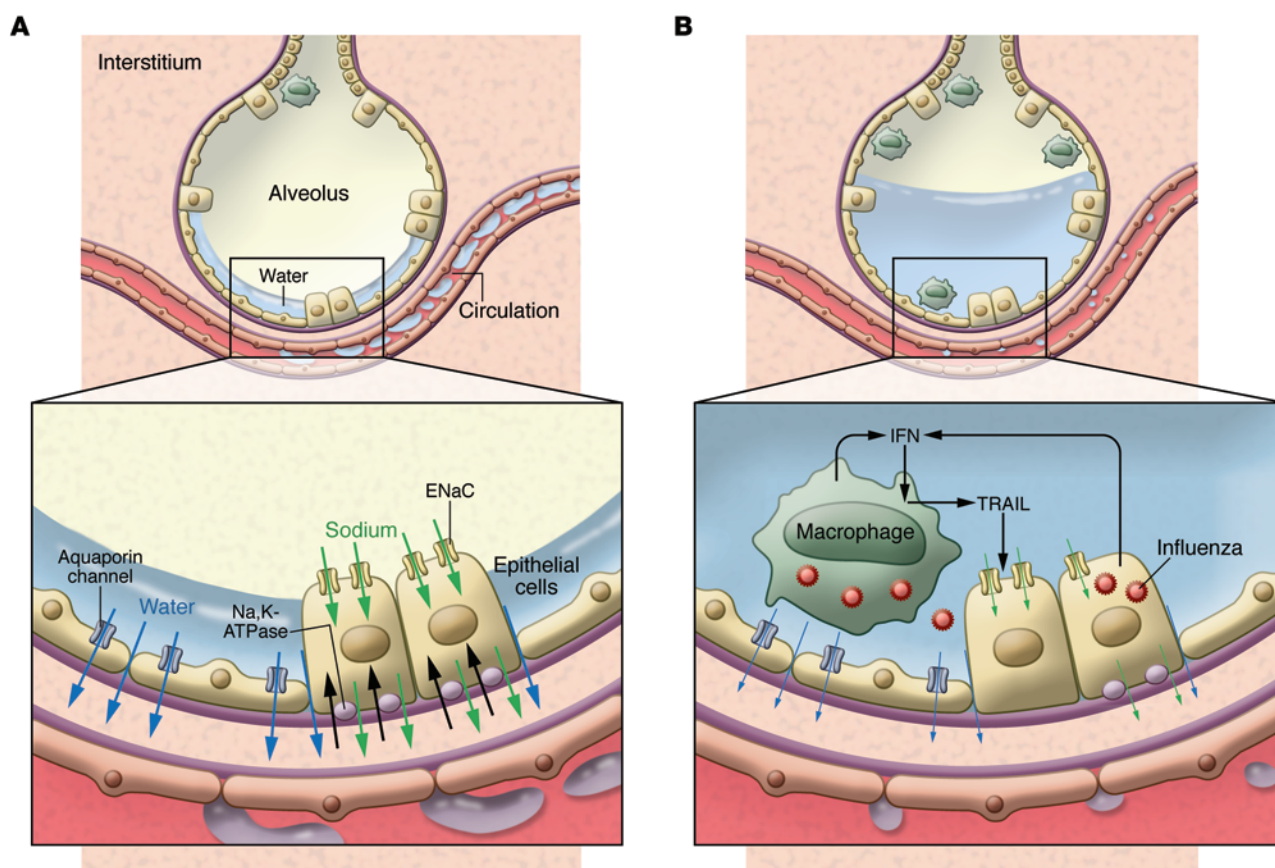


Figure 1. Regulation of alveolar water clearance. (A) Under homeostatic conditions, ENaC and Na,K-ATPase pumps on the alveolar epithelial cells work in conjunction to move sodium out of the alveolus. The osmotic gradient causes water to passively exit the alveolus paracellularly and through aquaporin channels. (B) Influenza infection induces type I IFN expression that stimulates macrophages to secrete TRAIL, which in turn signals endocytosis of Na,K-ATPase in uninfected alveolar epithelial cells. The diminished sodium transport decreases alveolar fluid clearance and contributes to the development of pulmonary edema during influenza infection.

mediating alveolar fluid clearance in vivo after influenza infection.

Together, ENaC and Na,K-ATPase regulate sodium export to maintain a minimal amount of alveolar lining fluid that is necessary for homeostatic functions (3). Therefore, what is the teleological advantage for downregulation of Na,K-ATPase during influenza infection? The cell could be attempting to contain the viral infection through various means that inadvertently result in untoward effects, such as pulmonary edema. It is possible that mechanisms developed to purposefully increase intracellular sodium concentrations, which have been found to inhibit viral replication (18). However, AMPK also attenuates ENaC function and may counterbalance the effects on Na,K-ATPase to minimize the changes to intracellular sodium concentrations (19). Alternatively, TRAIL activation of AMPK can also induce autophagy as a prosurvival mechanism (17). Perhaps

AMPK-mediated autophagy was designed as an immunoregulatory mechanism for pathogen clearance (20). Each of these models fits with the findings of Peteranderl et al. that TRAIL activation of AMPK only occurs in cells not infected with influenza (10). If this model is true, it would also imply that influenza virus has evolved to hijack the cellular machinery and prevent AMPK activation.

Conclusion and future directions

Peteranderl et al. outline a mechanism where TRAIL release by macrophages decreases Na,K-ATPase expression by the alveolar epithelium to attenuate alveolar fluid clearance after influenza infection (10). TRAIL is increased in patients with ARDS secondary to influenza infection (11), and an exuberant host response to infection with augmented TRAIL expression by alveolar macrophages

may be an intrinsic feature that differentiates whether an influenza infection will self-resolve or progresses to ARDS. Indeed, the inherent genetic responses to influenza and other proinflammatory stimuli may be a risk factor that predisposes the host to amplified inflammation after infection (13, 21).

Lower alveolar fluid clearance rates in ARDS patients are associated with higher mortality, highlighting the importance of mechanisms that facilitate fluid transport out of the airspaces in the development of respiratory failure (22). However, previous clinical trials to evaluate inhaled β_2 -adrenergic agonists, which increase sodium transport out of the alveolus, found no mortality benefit, possibly due to issues in the delivery of the inhaled drug to the damaged lungs (23). Intravenous delivery of β_2 -adrenergic agonists does improve lung edema in patients with ARDS. Unfortunately, this treatment also associated with

increased mortality, possibly from toxicity secondary to systemic delivery (24, 25). Therefore, the ability to design and generate more targeted methods to control pulmonary edema may benefit patients with ARDS. In their studies, Peteranderl et al. showed that antibody inhibition of TRAIL and/or IFN α improves alveolar fluid clearance in mice after influenza infection (10). Based on these results, manipulation of this pathway to control lung injury after influenza infection should be further studied. A theoretical concern with this approach would be that blocking vital components of the immune response could result in uncontrolled viral proliferation and a net detrimental effect, regardless of improved pulmonary edema. Despite these concerns, anti-TRAIL therapy does improve outcomes in murine influenza infection models (12, 13). Further, blocking type I IFN signaling improves morbidity and mortality after influenza infection without effects on viral proliferation (13).

In conclusion, this work by Peteranderl et al. extends their previous publications and pushes forward the new concept that TRAIL regulates influenza-mediated lung injury by regulating alveolar fluid clearance independently of effects on apoptosis induction (10). Many questions remain, such as whether this pathway has general effects in ARDS that are not caused by influenza or whether TRAIL levels can be used as biomarkers to delineate those influenza-infected individuals who are at risk of developing ARDS. The results of this study further our understanding of how influenza causes its damaging effects during infection and move us one step closer to finding novel methods to treat this deadly disease.

Acknowledgments

Peter Chen's laboratory is supported by the NIH grants R01 HL103868 and R01 HL120947.

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