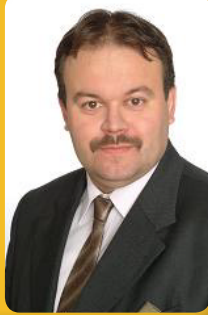


Role of TNF in pulmonary edema reabsorption with

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How does pulmonary edema arise and which treatments exist?

Rudolf Lucas: Fluid reabsorption from the alveolus into the vessels is an inherently required biological phenomenon already at birth. Alveolar fluid clearance is primarily mediated by active transepithelial transport of sodium from the airspaces into the lung interstitium, a process mainly accounted for by the amiloride-sensitive epithelial sodium channel (ENaC) and the chloride channels, which are expressed on the apical membrane of alveolar type II epithelial cells. The basolaterally expressed Na⁺-K⁺-ATPase is implicated in the extrusion of sodium and liquid (1). A dysregulation in the expression or function of the ion channels implicated in lung liquid clearance, an increased capillary pressure in the lungs (cardiogenic/hydrostatic edema), as well as a destruction or an increased permeability of the alveolar epithelial-endothelial barrier (permeability edema), may therefore lead to the formation of pulmonary edema. Interestingly, in the case of ARDS patients, a clear correlation was shown between the inability to clear pulmonary edema and patient mortality (2). Pharmacological treatment with β₂-adrenergic agonists, such as terbutaline, was shown to induce a more sustained stimulation of alveolar fluid reabsorption, thus facilitating recovery from experimental pulmonary edema (3). However, these agents can induce tolerance and can have important side-effects, such as arrhythmia, thus questioning their usefulness in patients with heart disease, which often suffer from cardiogenic edema. Moreover, in some models of acute lung injury, these agents were shown not to work at all (4). Therefore, the search for alterna-

tive candidates, that are able to augment transepithelial sodium transport in both healthy and

injured lungs may lead to more effective treatments of pulmonary edema.

Is there any role for cytokines in the regulation of edema reabsorption?

Rudolf Lucas: Apart from β₂ adrenergic agonists, epithelial growth factors and leukotrienes (5), also cytokines, such as Tumor Necrosis Factor (TNF), have been recently shown to influence epithelial sodium uptake (6). On the one hand, TNF, by means of its TNF receptor-dependent effects, leading to the expression or upregulation of adhesion molecules, the generation of reactive oxygen inter-

mediates and the decrease of transendothelial resistance, contributes to edema formation. Moreover, the cytokine was reported to decrease the expression of the epithelial sodium channel, as such inhibiting edema reabsorption (7). On the other hand, TNF neutralization was shown to inhibit edema reabsorption in models of pulmonary edema associated with infection and asthma (8-10).

How can we understand the apparently contradictory results concerning the effect of TNF on lung liquid clearance?

Rudolf Lucas: The answer to this could possibly be provided by the recent observation that TNF is a moonlighting molecule, displaying at least two functional domains with opposite action on edema reabsorption, *i.e.* the receptor binding sites *versus* the lectin-like domain. Indeed, spatially distinct from its receptor binding sites, TNF carries a lectin-like domain (11,12), which can be mimicked by a circularised 17 AA peptide (the tip peptide). This domain was originally identified

because of its capacity to mediate the trypanolytic activity of the cytokine in extracellular African trypanosomes (12), but later on, it was also shown to be implicated in the TNF-mediated activation of sodium uptake in A549 cells (6). Interestingly, in a flooded rat lung model *in vivo*, in conditions where TNF inhibits lung liquid clearance, complexation of the cytokine with its soluble TNF receptor 1, which blocks the receptor binding sites, but not the lectin-like domain (12), shifts this activity towards activation of edema reabsorption (13). This activity of the soluble receptor/ligand complex can be blocked by sugars binding to the lectin-like domain, such as *N,N'*-diacetylchitobiose (13). Taken together, these results thus indicate that in healthy lungs the receptor binding sites of TNF inhibit, whereas its lectin-like domain activates edema reabsorption.

Could the edema reabsorption activating activity of the lectin-like domain of TNF be therapeutically interesting?

Rudolf Lucas: The TNF-derived Tip peptide, mimicking the lectin-like domain of the cytokine, was

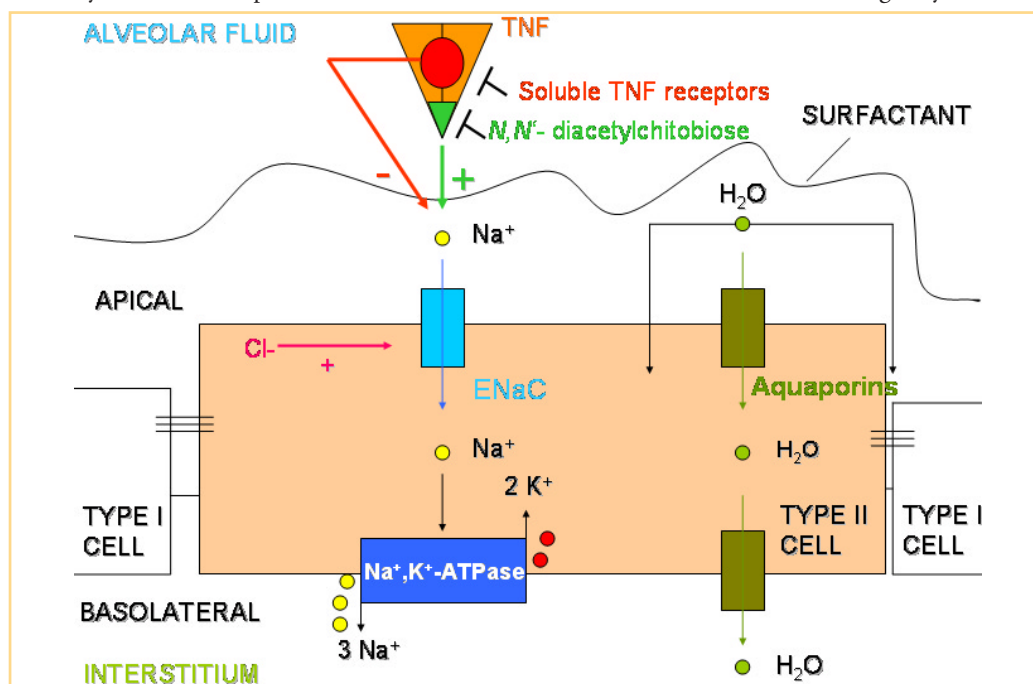


Figure 1: Dichotomous role of TNF on alveolar fluid clearance: the TNF receptor binding sites (red ellipses) inhibit Na⁺-uptake in type II alveolar epithelial cells, whereas the cytokine's lectin-like domain (green triangle), either directly or indirectly, activates Na⁺ uptake in these cells.

shown to efficiently activate alveolar liquid clearance in a blood-perfused isolated flooded rat lung model *ex vivo* (14) as well as in a flooded rat lung model *in vivo* when applied intratracheally, but not intravenously, to the same extent as the β 2-adrenergic agonist terbutaline (13). In contrast to the native cytokine, the Tip peptide of TNF, no longer exerts pro-inflammatory

activities (13). Therefore, we can conclude that the TNF-derived Tip peptide is able to activate lung liquid clearance in healthy lungs, stressing the need for a further pre-clinical evaluation of this substance as an alternative anti-edema agent. We are currently investigating whether this peptide can also activate edema reabsorption in injured lungs.

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