Review Article

Specialized Pro-resolving Mediators Regulate Alveolar Fluid Clearance during Acute Respiratory Distress Syndrome

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Abstract

Objective: Acute respiratory distress syndrome (ARDS) is an acute and lethal clinical syndrome that is characterized by the injury of alveolar epithelium, which impairs active fluid transport in the lung, and impedes the reabsorption of edema fluid from the alveolar space. This review aimed to discuss the role of pro-resolving mediators on the regulation of alveolar fluid clearance (AFC) in ARDS.

Data Sources: Articles published up to September 2017 were selected from the PubMed, with the keywords of "alveolar fluid clearance" or "lung edema" or "acute lung injury" or "acute respiratory distress syndrome", and "specialized pro-resolving mediators" or "lipoxin" or "resolvin" or "protectin" or "maresin" or "alveolar epithelial cells" or "aspirin-triggered lipid mediators" or "carbon monoxide and heme oxygenase" or "annexin A1".

Study Selection: We included all relevant articles published up to September 2017, with no limitation of study design.

Results: Specialized pro-resolving mediators (SPMs), as the proinflammatory mediators, not only upregulated epithelial sodium channel, Na,K-ATPase, cystic fibrosis transmembrane conductance regulator (CFTR), and aquaporins levels, but also improved Na,K-ATPase activity to promote AFC in ARDS. In addition to the direct effects on ion channels and pumps of the alveolar epithelium, the SPMs also inhibited the inflammatory cytokine expression and improved the alveolar epithelial cell repair to enhance the AFC in ARDS.

Conclusions: The present review discusses a novel mechanism for pulmonary edema fluid reabsorption. SPMs might provide new opportunities to design "reabsorption-targeted" therapies with high degrees of precision in controlling ALI/ARDS.

Key words: Acute Lung Injury; Acute Respiratory Distress Syndrome; Alveolar Fluid Clearance; Specialized Pro-resolving Mediator

Introduction

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a common, devastating clinical syndrome that affects large numbers of patients and has a mortality of up to 40%.[1] The injury of alveolar epithelium impairs active fluid transport mechanisms in the lung, preventing reabsorption of edema fluid from the alveolar space, which is a key step in the resolution of ALI/ARDS. It is also widely accepted that edema fluid must be cleared for patients with ALI/ARDS to survive.[2]

Fluid and solute reabsorption from the alveolus is critical in clearing fluid from lungs in pathologic conditions, such as ALI/ARDS and hydrostatic pulmonary edema. The primary mechanism driving fluid clearance from the alveolus is the active transportation of Na^+ ions from airspaces into the lung interstitium.[3] This solute transportation drives osmotic water transportation and accordingly alveolar fluid clearance (AFC).[4] Na^+ ions enter alveolar epithelial cells at the apical surface, primarily through amiloride-sensitive sodium channels, such as the epithelial sodium channel (ENaC), and are pumped out on the basolateral surface by Na,K-ATPase.[5-7] Furthermore, the cystic fibrosis transmembrane conductance regulator (CFTR) and aquaporins are also important in mediating the AFC.

Specialized pro-resolving mediators (SPMs) are produced by cells of the innate immune, which are formed via the stereoselective conversion of essential fatty acids that

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include arachidonic acid, eicosapentaenoic acid, n-3 docosapentaenoic acid and docosahexaenoic acid (DHA). They are grouped into four families, lipoxins, resolvins, protectins, and maresins.[8] These mediators share basic biological effects in regulating host responses, such as inhibiting the production of proinflammatory cytokines and chemokines, regulating the neutrophils trafficking, stimulating the macrophages phagocytosis of apoptotic cells, bacteria, and cellular debris via G-protein coupled receptors (GPCRs)-dependent manner.[9-11] Recent studies[12-14] have demonstrated that SPMs could regulate the AFC in ARDS to protect the lung function. Therefore, the present review will focus on: (1) mechanisms underlying the regulation of the AFC in the normal lung and ARDS and (2) mechanisms underlying the pro-resolving mediators' regulation on the AFC.

Inflammation Resolution

The acute inflammatory response is protective, evolving to permit repair of injured tissues and eliminate foreign invaders,[15] which leads to complete resolution of leukocyte infiltrates and clearance of cellular debris. Recently, new evidences have demonstrated that the resolution of inflammation might be an active and tightly regulated process.[16-22] SPMs have been demonstrated to exert potent immune-resolving effects, such as cell proliferation, migration, clearance of apoptotic cells, and microorganisms.[23-25] Therefore, the effective and timely resolution of inflammation might be the key step to keep effective host defense and restitution of homeostasis.

Inflammation Resolution in the Lung-Alveolar Fluid Clearance

In the normal lung, vectorial ions transport across the alveolar epithelial cells to create an osmotic gradient that drives fluid from the airspaces into the lung interstitum.[3,26]

Alveolar epithelial Type I (ATI) and Type II (ATII) cells, alveolar and endothelium permeability, amiloride-sensitive sodium channels-ENaC, Na,K-ATPase, CFTR, aquaporin 5, inflammatory cytokines, and pro-resolving mediators regulate the AFC together to maintain the alveolar homeostasis.[27-30] The bacteria or exogenous microorganisms invade lung tissue, leading to lung injury and ARDS. It is well recognized that the AFC is reduced in ARDS, which is associated with the morbidity and mortality of ARDS.[31,32] Therefore, it is critical to reveal the reasons of AFC reduction to understand the pathogenesis of ARDS.

First, ARDS is characterized by large amounts of neutrophil infiltration and diffuse alveolar damage, including the damage of both lung endothelium and epithelium.[33] Excessive neutrophilic influx into the alveolar space leads to the generation of reactive oxygen species and proinflammatory factors, which could disrupt the alveolar-capillary barrier; therefore, the ability to clear alveolar edema fluid is reduced.[33,34] Alveolar and endothelium permeability is critical for AFC. If permeability is increased, it is impractical to improve AFC since the fluid will come back to the alveolar space. Active AFC is very important but the lung recovery depends on the barrier repair and AFC facilitates ALI/ARDS recovery when blood-gas barrier regains integrity. The reduction in the rate of AFC in ARDS is associated with decreased survival.[31,32] Therefore, it is critical to investigate the mechanisms underlying the reduction of AFC in ARDS in order to better understand the pathogenesis of this condition.[34]

Second, pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-8, and transforming growth factor-β1 (TGF-β1) were found in ARDS pulmonary edema fluid.[1,34-36] Under controlled conditions, this inflammatory response is important for pathogen clearance. However, when excessive levels of cytokines are present, they might cause alveolar injury and decreased AFC.[37-40] Previous study[41] showed that cytokine expression was increased and the ion transport protein expression was decreased in the ARDS edema fluid compared to a plasma control, indicating that the levels of cytokines might be increased in alveolar epithelium during ARDS, leading to a decreased expression of alveolar ion channels and accumulation of AFC.[27] Furthermore, the inflammatory pulmonary edema fluid could also cause alveolar cell injury and necrosis, leading to altered epithelial tight junctions.[42,43]

Third, the damaged lung endothelium and epithelium lead to loss of the ion channels and pumps, which are key regulators of AFC. Moreover, the alveolar epithelium damage will lead to an increase in the permeability of the alveolar-capillary barrier, which in combination with changes in hydrostatic and oncotic pressures, might lead to the formation of pulmonary edema.[44,45]

Fourth, hypoxemia that due to ventilation-perfusion mismatch, intrapulmonary shunts, and an increased lung dead spaces, might result in the need for positive pressure ventilation.[33] Otherwise, the low oxygen or high carbon dioxide could downregulate the ENaC transcription and trafficking; in addition, the Na,K-ATPase functions are also impaired.[46-48] Therefore, supplemental oxygen and correction of hypercapnia might improve the resolution of alveolar edema.[46]

Specialized Pro-Resolving Mediators for the Therapy of Acute Respiratory Distress Syndrome

Damage to the lung results in activation of the immune system, which not only leads to the release of several proinflammatory proteins and neutrophilic influx into the alveolar space but also leads to the release of pro-resolution lipids mediators, such as lipoxins, resolvins, protectins, and maresins.[33,34]

Lipoxins

Lipoxins are arachidonic acid metabolites formed during inflammation via transcellular biosynthetic routes that elicit distinct anti-inflammatory and pro-resolution bioactions, including the suppression of neutrophil activation and upregulation of monocyte ingestion of apoptotic neutrophils.[49] Lipoxins are included in the first class of lipid mediators that are "switched on" in the resolution phase of an inflammatory response and can function as "braking signals" in inflammation. Lipoxins, as potential novel therapeutic agents, have been extensively studied in various inflammatory diseases and are able to interact with the lipoxin A4 (LXA4) receptor (ALX) to mediate anti-inflammatory actions.[50-53] A previous study showed that LXA4 dramatically blocked the allergic pleural eosinophil influx, and concurrently inhibited the earlier edema and neutrophilia that was associated with allergic reaction.[54] The data clearly demonstrated that LXA4 had no effect on AFC in healthy, perfused, intact rat lungs. However, treatment with LXA4 might promote the AFC in oleic acid (OA)-induced ALI, with the outcome of decreased pulmonary edema. Furthermore, treatment with LXA4 might not only upregulate the ENaC-α and ENaC-γ subunit protein expression but also increase the Na,K-ATPase β1 subunit protein expression and Na,K-ATPase activity. Finally, evidence has shown that the BML-111 (ALX agonist) had similar effects as those of LXA4, and the beneficial effects of LXA4 could be abrogated by BOC-2 (ALX antagonist) in OA-induced ALI, suggesting that LXA4 might promote AFC by interacting with a specific GPCR, denoted ALX. The mechanism of the salutary effect of LXA4 might involve the ALX-cGMP signaling pathway.[12]

Another study[13] has demonstrated that treatment of rats with LXA4 could significantly inhibit IL-6, TNF-α production, and increase AFC with the outcome of decreased pulmonary edema in lung tissue. The inhibitor of CFTR could abolish the beneficial effects of LXA4. Furthermore, it has also been demonstrated that treatment with LXA4 could upregulate the CFTR protein expression *in vivo* and in primary ATII cells. Finally, the study has also provided evidence that lipopolysaccharide (LPS) could decrease CFTR protein expression via PI3K/Akt signaling pathway and the LXA4 could suppress LPS-stimulated phosphorylation of Akt.

LXA4 has been shown to be able to promote alveolar epithelial repair by stimulating the epithelial cells wound repair and proliferation; blocking the negative effects of soluble Fas ligand/TNF-α; and augmenting the epithelial cell proliferative response. The effects of LXA4 might be PI3K dependent and are mediated via the LXA4 receptor.[55] Higgins *et al*.[56] have shown that LXA4 might play a protective role in bronchial epithelium by stimulating tight junction repair, delaying and reducing the invasion of cystic fibrosis (CF) bronchial epithelial cells induced by *P. aeruginsosa*.

Resolvins

Resolvins are v-3 DHA-derived metabolites, and are biosynthesized during the resolution phase of inflammatory response, including halted transendothelial migration of human neutrophils,[17,57,58] upregulation of monocyte ingestion of apoptotic neutrophils, and enhanced macrophage phagocytosis of zymosan and apoptotic polymorphonuclear neutrophils (PMNs).[59] Previous studies have shown that resolvin D1 (7S,8R,17S-trihydro-xy-4Z,8E,10Z,12E,14E, 19Z-docosahexaenoic acid; RvD1) exerts potent anti-inflammatory and pro-resolving actions in several animal models of sepsis, peritonitis, taraxis, and ALI.[60,61] Furthermore, a recent study[62] has shown that RvD1 could improve the survival rate and attenuated ALI induced by LPS. It has also been shown that RvD1 could accelerate the airway mucous metaplasia in the resolution of established allergic airway responses.[63] Recently, two GPCRs of RvD1 have been identified and validated using a GPCR/arrestin-coupled system, namely, Orphan GPR32 and ALX.[59] Extracellular signals interact with GPCRs to activate adenylate cyclase/guanylyl cyclase and stimulate formation of the second messenger cyclic adenosine monophosphate/cyclic guanosine monophosphate (cAMP/cGMP), which activates protein kinase A/protein kinase C. Indeed, β_2AR agonists have been shown to enhance AFC transport via a cAMP-dependent mechanism under physiological conditions[64] and in experimental models of lung injury,[65] as well as in one prospective study of extravascular lung edema in patients with ALI.[66] In contrast, PI3K has been identified to be involved in the regulation of ENaC-mediated AFC by insulin.[67] There has been evidence for the pro-resolution actions of RvD1 in ARDS. Treatment with RvD1 could improve the AFC and decrease pulmonary edema in LPS-induced ALI in rats. RvD1 might regulate AFC via upregulating the protein expression of ENaC-α, -γ and Na,K-ATPase α1, β1 subunits and increasing the activity of Na,K-ATPase. RvD1 could increase Na^+ currents in primary ATII cells, and enhance the subcellular distribution of ENaC and Na,K-ATPase. Moreover, the beneficial effects of RvD1 were abrogated by BOC-2, LY294002, and Rp-cAMP, indicating that RvD1 might increase the ENaC expression to promote AFC via the ALX/PI3K/cAMP signaling pathway.[14] In addition, RvD1 and RvD2 could inhibit the IL-17, TNF-α, and IFN-γ production, and enhance the tissue repair.[15]

Protectins

Protectins are novel lipid mediators that are involved in anti-inflammation and resolution.[68] Protectin DX, an isomer of protectin D1,[69] is believed to have anti-inflammatory effects including inhibition of neutrophil activation and regulation of inflammatory cytokines. It is produced by double lipoxygenase-mediated reaction in murine perritonitis exudates, in suspensions of human leukocytes, or by soybean 15-lipoxygenase incubated DHA.[69,70] A recent study has demonstrated that protectin DX could block neutrophil infiltration in murine peritonitis by 20–25% at a dose of 1 ng/mouse.[69] In addition, protectin D1 could also inhibite TNF-α, IFN-γ secretion, and enhance tissue repair.[15,71]

Maresins

Maresins are newly described macrophage-derived mediators of inflammation resolution, which are produced from essential omega-3 fatty acids and biosynthesized via 12-lipoxygenase.[72,73] Maresin1 (7,14-dihydroxyd-ocosa-4Z, 8Z,10,12,16Z,19Z-hexaenoic acid, MaR1) has been shown to be a potent mediator to stop PMN infiltration and stimulate macrophages phagocytosis.[74-76] Zhang *et al*.[77] reported that MaR1 not only upregulated ENaC, Na,K-ATPase protein expression but also enhanced Na,K-ATPase activity in LPS-induced ALI, and be able to alleviate pulmonary edema, enhance AFC, and attenuate lung injury via activation of the ALX/PI3K/Nedd4-2 pathway. In addition, MaR1 was engaged in healing, tissue regeneration, and the reducing of IL-17, TNF-α, and IFN-γ production.[12]

Aspirin-Triggered Lipid Mediators

As a classic anti-inflammatory agent, aspirin induces a shift from the synthesis of proinflammatory to pro-resolving lipid mediators termed as aspirin-triggered lipoxins (ATL) and aspirin-triggered resolvins (AT-Rv).[17,78] ATL and AT-Rv share the pro-resolution effects of LXA4 and RvD1, respectively, and act via the same intracellular pathways.[63]

Previous study has shown that posttreatment with ATL could inhibit TNF-α, nitric oxide (NO), and malondialdehyde production, with the outcome of decreased pulmonary edema, lipid peroxidation, and the infiltration of neutrophils in lung tissues.[79] Another study has shown that 15-epi-lipoxin A4 could inhibit myeloperoxidase signaling and enhance resolution of ALI.[80] In addition, ATLa, an ATL synthetic analog, could inhibit the lung production of IL-1β, IL-17, TNF-α, and TGF-β in BLM-challenged mice.[81] ATLa could restore the balance of inducible NO synthase (iNOS)-positive and arginase-positive cells in the lungs, suggesting a prevalence of M2 versus M1 macrophages.[81]

Early treatment with exogenous AT-RvD1 (1 h post infection) could enhance the clearance of *Escherichia coli* and *P. aeruginosa in vivo* and lung macrophage phagocytosis of fluorescent bacterial particles *in vitro*.[82] AT-RvD1 could also increase the efferocytosis of these cells *in vitro* and accelerate neutrophil clearance during pneumonia *in vivo*.[82] Moreover, treatment with AT-RvD1 has shown a reduced level of proinflammatory cytokines IL-6 and IL-8 in IL-1β stimulated A549 cells. AT-RvD1 could reduce the IL-1β-mediated alveolar epithelial cell activation.[83] AT-RvD1 could significantly reduce the lung vascular permeability in the mice with lung injury and decrease the neutrophils, inflammatory cytokines, and chemokines in the BALF. Furthermore, secretion of TNF-α, IL-6, keratinocyte cell-derived chemokine, and MIP-1α from IgG immune complex-stimulated alveolar macrophages or neutrophils could be significantly decreased by AT-RvD1.[84] Animals treated with AT-RvD1 have been shown to have improved epithelial and endothelial barrier integrity and decreased airway resistance concomitant with increased BALF epinephrine levels. AT-RvD1 could inhibite neutrophil-platelet heterotypic interactions by downregulating both P-selectin and its ligand CD24. AT-RvD1 could also significantly decrease the levels of BALF proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, and decrease the nuclear factor-κB-phosphorylated p65 nuclear translocation.[85] Therapeutic treatment with exogenous AT-RvD1 could significantly reduce the pneumococcal load during the acute phase of infection (days 4–6 postpneumococcal inoculation).[86] AT-RvD1 could also significantly reduce the neutrophil elastase activity and restore total antimicrobial activity, reduce the number of infiltrating lung neutrophils and monocytes/macrophages, and limit the movement of excessive leukocyte chemotaxis from the infected bronchioles to distal areas of the lungs through binding ALX.[86]

Heme Oxygenase and Carbon Monxide

Heme oxygenase (HO), a ubiquitous inducible stress-response protein, is a stress response gene that has been extensively investigated in ALI/ARDS. HO-1 catalyzes the oxidative degradation of heme to biliverdin-IX alpha, iron, and carbon monoxide (CO), all exerting anti-oxidative and anti-inflammatory activities.[87] Recent studies have demonstrated that HO-1 or CO can confer cytoprotection in ARDS models, based on anti-apoptotic, anti-inflammatory, and anti-proliferative properties.[88.89]

Chiang *et al*.[90] found that resolvins and lipoxins in turn upregulated HO-1 in macrophages, demonstrating mutual amplification of these two pro-resolving pathways. ATL could promote the formation of HO-1 and its activity in the lung tissues.[79] RvD1 increased HO-1 expression, which might contribute to the protection of the tight junction. In addition, RvD1 could reduce pulmonary cellular apoptosis in LPS-induced mice. Therefore, RvD1 might possess the ability that relieves the pulmonary edema and restores pulmonary capillary permeability and reduces disruption of tight junction in LPS-induced ALI mice, at least in part, by upregulating HO-1 expression.[91]

In the lung, CO could suppress LPS-induced lung alveolitis and associated edema formation. This protection appears to be partially due to LPS-induced iNOS and NO production.[92] CO could prevent the up-regulation of iNOS and NO in the lung.[92] Studies of primary lung macrophages *in vitro* have revealed that CO could inhibit LPS-induced cytokine production in lung macrophages.[92] The administration of CO could prevent pulmonary microvascular permeability alteration noted after ischemia-reperfusion (I/R) of the lower limbs. Histologically, CO administration inhibited neutrophilic sequestration observed after I/R. Exogenous administration of CO by inhalation at low doses could prevent ALI post-I/R in this model.[93] CO could promote resolution of inflammation via enhancing bacterial kiling,[94] repressing proinflammatory cytokines such as TLR-2, -4, -5, and -9 expression, initiating the

production of anti-inflammatory cytokines such as IL-10 in macrophages,[95] enhancing efferocytosis of apoptotic cells or bacteria by macrophages,[90] and improving the expression of lipoxygenases which are key synthetases of SPMs.[90]

Annexin A1

Annexin A1 (ANXA1), a 37 kDa monomeric protein, is an endogenous regulator of anti-inflammatory and pro-resolving as well as a mediator of glucocorticoids (GCs) action.[96,97] A previous study[98] has shown that ANXA1 could potently downregulate PMN migration into inflammatory sites and accelerate their apoptosis, upregulate the monocytes migration into inflammatory sites. Administration of the active N-terminal peptide of AnxA1 (Ac2-26) in I/R-induced lung injury could significantly attenuate the lung edema and proinflammatory cytokine production recovered in BALF, and reduce oxidative stress, apoptosis, neutrophil infiltration, and lung tissue injury,[99] possibly via the activation of the N-formyl peptide receptor.[96] In addition, Ac2-26 administration could be effective to reduce pro-resolving mediators, such as IL-2, IL-4, IL-10, and IL-13,[100] and induce the release of pro-resolving mediators, such as IL-10.

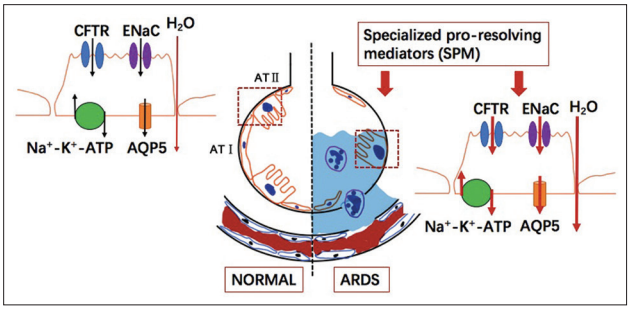

Figure 1: Mechanisms underlying the effects of specialized pro-resolving mediators on alveolar fluid clearance in acute respiratory distress syndrome. In normal lungs, ATI and ATII cells, alveolar and endothelium permeability, ion channels, and inflammatory cytokines regulate the AFC together to maintain balance and re-establish alveolar homeostasis. In ARDS, SPMs enhance the alveolar epithelium repair, inhibit the inflammatory cytokines, upregulate the ion channel activity and protein expression to improve the AFC and recovery the lung function. SPMs: Specialized pro-resolving mediators; AFC: Alveolar fluid clearance; ARDS: Acute respiratory distress syndrome; ATI/ATII cells: Alveolar epithelial Type I/Type II cells; ENaC: Epithelial sodium channel; CFTR: Cystic fibrosis transmembrane conductance regulator; AQP5: Aquaporins.

Discussion

ALI and its more severe form ARDS are relatively common syndromes in critically ill patients, and are associated with high morbidity and mortality.[1] Pulmonary edema is a hallmark in ALI/ARDS and a life-threatening condition.[62,101] It is widely accepted that resolution of alveolar edema is key for patient's survival.[2] Previously, clinical studies have shown that impaired alveolar fluid transport mechanisms contribute to the development, severity, and outcome of pulmonary edema in humans.[102] The AFC process is crucial to efficient gas exchange in the lung,[4] and ALI/ARDS patients with intact AFC have lower morbidity and mortality than those with compromised AFC.[32]

SPMs are chemical mediators that are involved in the resolution process in response to injury, infection, or allergy. Pro-resolving mediators include the arachidonic acid-derived lipoxins and the omega-3 fatty acid-derived resolvins, protectins, maresins, CO, HO-1, and ANXA1.[72] During acute inflammation, polyunsaturated fatty acid metabolism switches from pro-inflammatory mediators to pro-resolving mediators. SPMs could inhibit proinflammatory cytokine production, prevent leukocyte infiltration, and promote the removal of inflammatory leukocytes by natural killer cell-mediated leukocyte apoptosis. Moreover, SPMs also promote macrophage phagocytosis and epithelial cell repair, and improve the ENaC, Na,K-ATPase, CFTR to upregulate the AFC in ARDS.

Conclusion

In this review, we have discussed how the pro-resolving mediators regulate the AFC in both physiologic and pathologic conditions. We suggest that declined AFC in ARDS might be associated with the impaired vectorial ion transportation in injured lungs. Recent studies have also suggested that pro-resolving mediators might enhance the alveolar epithelium repair, inhibit the inflammatory cytokines, and upregulate the ion channel activity and protein expression in a receptor-dependent manner to increase the AFC, and thus may serve as promising agents for the treatment of ARDS [Figure 1].

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Conflicts of interest

There are no conflicts of interest.

References

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-49. doi: 10.1056/NEJM200005043421806.
2. Sznajder JI. Alveolar edema must be cleared for the acute respiratory distress syndrome patient to survive. Am J Respir Crit Care Med 2001;163:1293-4. doi: 10.1164/ajrccm.163.6.ed1801d.
3. Matthay MA, Clerici C, Saumon G. Invited review: Active fluid clearance from the distal air spaces of the lung. J Appl Physiol (1985) 2002;93:1533-41. doi: 10.1152/japplphysiol.01210.2001.
4. Matthay MA, Folkesson HG, Clerici C. Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 2002;82:569-600. doi: 10.1152/physrev.00003.2002.
5. Kellenberger S, Schild L. Epithelial sodium channel/degenerin family of ion channels: A variety of functions for a shared structure. Physiol Rev 2002;82:735-67. doi: 10.1152/physrev.00007.2002.
6. Rahman MS, Gandhi S, Otulakowski G, Duan W, Sarangapani A, O'Brodovich H, *et al*. Long-term terbutaline exposure stimulates alpha1-Na+-K+-ATPase expression at posttranscriptional level in rat fetal distal lung epithelial cells. Am J Physiol Lung Cell Mol Physiol 2010;298:L96-104. doi: 10.1152/ajplung.00158.2009.

7. Sznajder JI, Factor P, Ingbar DH. Invited review: Lung edema clearance: Role of Na(+)-K(+)-ATPase. J Appl Physiol (1985) 2002;93:1860-6. doi: 10.1152/japplphysiol.00022.2002.
8. Dalli J. Does promoting resolution instead of inhibiting inflammation represent the new paradigm in treating infections? Mol Aspects Med 2017;58:12-20. doi: 10.1016/j.mam.2017.03.007.
9. Serhan CN. Treating inflammation and infection in the 21st century: New hints from decoding resolution mediators and mechanisms. FASEB J 2017;31:1273-88. doi: 10.1096/fj.201601222R.
10. Serhan CN, Dalli J, Colas RA, Winkler JW, Chiang N. Protectins and maresins: New pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome. Biochim Biophys Acta 2015;1851:397-413. doi: 10.1016/j.bbalip.2014.08.006.
11. Serhan CN, Chiang N. Resolution phase lipid mediators of inflammation: Agonists of resolution. Curr Opin Pharmacol 2013;13:632-40. doi: 10.1016/j.coph.2013.05.012.
12. Wang Q, Lian QQ, Li R, Ying BY, He Q, Chen F, *et al*. Lipoxin A(4) activates alveolar epithelial sodium channel, Na, K-ATPase, and increases alveolar fluid clearance. Am J Respir Cell Mol Biol 2013;48:610-8. doi: 10.1165/rcmb.2012-0274OC.
13. Yang Y, Cheng Y, Lian QQ, Yang L, Qi W, Wu DR, *et al*. Contribution of CFTR to alveolar fluid clearance by lipoxin A4 via PI3K/Akt pathway in LPS-induced acute lung injury. Mediators Inflamm 2013;2013:862628. doi: 10.1155/2013/862628.
14. Wang Q, Zheng X, Cheng Y, Zhang YL, Wen HX, Tao Z, *et al*. Resolvin D1 stimulates alveolar fluid clearance through alveolar epithelial sodium channel, Na, K-ATPase via ALX/cAMP/PI3K pathway in lipopolysaccharide-induced acute lung injury. J Immunol 2014;192:3765-77. doi: 10.4049/jimmunol.1302421.
15. Serhan CN, Chiang N, Dalli J. New pro-resolving n-3 mediators bridge resolution of infectious inflammation to tissue regeneration. Mol Aspects Med 2017 [Epub ahead of print]. doi: 10.1016/j.mam.2017.08.002.
16. Serhan CN. A search for endogenous mechanisms of anti-inflammation uncovers novel chemical mediators: Missing links to resolution. Histochem Cell Biol 2004;122:305-21. doi: 10.1007/s00418-004-0695-8.
17. Serhan CN, Hong S, Gronert K, Colgan SP, Devchand PR, Mirick G, *et al*. Resolvins: A family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J Exp Med 2002;196:1025-37. doi: 10.1084/ jem.20020760.
18. Buckley CD, Gilroy DW, Serhan CN, Stockinger B, Tak PP. The resolution of inflammation. Nat Rev Immunol 2013;13:59-66. doi: 10.1038/nri3362.
19. Chan MM, Moore AR. Resolution of inflammation in murine autoimmune arthritis is disrupted by cyclooxygenase-2 inhibition and restored by prostaglandin E2-mediated lipoxin A4 production. J Immunol 2010;184:6418-26. doi: 10.4049/jimmunol.0903816.
20. Miki Y, Yamamoto K, Taketomi Y, Sato H, Shimo K, Kobayashi T, *et al*. Lymphoid tissue phospholipase A2 group IID resolves contact hypersensitivity by driving antiinflammatory lipid mediators. J Exp Med 2013;210:1217-34. doi: 10.1084/jem.20121887.
21. Wu SH, Liao PY, Yin PL, Zhang YM, Dong L. Elevated expressions of 15-lipoxygenase and lipoxin A4 in children with acute poststreptococcal glomerulonephritis. Am J Pathol 2009;174:115-22. doi: 10.2353/ajpath.2009.080671.
22. Serhan CN. Discovery of specialized pro-resolving mediators marks the dawn of resolution physiology and pharmacology. Mol Aspects Med 2017;58:1-11. doi: 10.1016/j.mam.2017.03.001.
23. Serhan CN, Chiang N, Dalli J. The resolution code of acute inflammation: Novel pro-resolving lipid mediators in resolution. Semin Immunol 2015;27:200-15. doi: 10.1016/j.smim.2015.03.004.
24. Headland SE, Norling LV. The resolution of inflammation: Principles and challenges. Semin Immunol 2015;27:149-60. doi: 10.1016/j. smim.2015.03.014.
25. Ungaro F, Rubbino F, Danese S, D'Alessio S. Actors and factors in the resolution of intestinal inflammation: Lipid mediators as a new approach to therapy in inflammatory bowel diseases. Front Immunol 2017;8:1331. doi: 10.3389/fimmu.2017.01331.
26. Huppert LA, Matthay MA. Alveolar fluid clearance in pathologically relevant conditions: In vitro and in vivo models of acute respiratory distress syndrome. Front Immunol 2017;8:371. doi: 10.3389/fimmu.2017.00371.
27. Flodby P, Kim YH, Beard LL, Gao D, Ji Y, Kage H, *et al*. Knockout mice reveal a major role for alveolar epithelial type I cells in alveolar fluid clearance. Am J Respir Cell Mol Biol 2016;55:395-406. doi: 10.1165/rcmb.2016-0005OC.
28. Johnson MD, Widdicombe JH, Allen L, Barbry P, Dobbs LG. Alveolar epithelial type I cells contain transport proteins and transport sodium, supporting an active role for type I cells in regulation of lung liquid homeostasis. Proc Natl Acad Sci U S A 2002;99:1966-71. doi: 10.1073/pnas.042689399.
29. Canessa CM, Schild L, Buell G, Thorens B, Gautschi I, Horisberger JD, *et al*. Amiloride-sensitive epithelial Na+ channel is made of three homologous subunits. Nature 1994;367:463-7. doi: 10.1038/367463a0.
30. Matalon S, O'Brodovich H. Sodium channels in alveolar epithelial cells: Molecular characterization, biophysical properties, and physiological significance. Annu Rev Physiol 1999;61:627-61. doi: 10.1146/annurev.physiol.61.1.627.
31. Matthay MA, Wiener-Kronish JP. Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. Am Rev Respir Dis 1990;142:1250-7. doi: 10.1164/ajrccm/142.6Pt1.1250.
32. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 2001;163:1376-83. doi: 10.1164/ajrccm.163.6.2004035.
33. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest 2012;122:2731-40. doi: 10.1172/JCI60331.
34. Laffey JG, Matthay MA. Fifty years of research in ARDS. Cell-based therapy for acute respiratory distress syndrome. Biology and potential therapeutic value. Am J Respir Crit Care Med 2017;196:266-73. doi: 10.1164/rccm.201701-0107CP.
35. Pugin J, Verghese G, Widmer MC, Matthay MA. The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 1999;27:304-12. doi: 10.1097/00003246-199902000-00036.
36. Olman MA, White KE, Ware LB, Simmons WL, Benveniste EN, Zhu S, *et al*. Pulmonary edema fluid from patients with early lung injury stimulates fibroblast proliferation through IL-1 beta induced IL-6 expression. J Immunol 2004;172:2668-77. doi: 10.4049/jimmunol.172.4.2668.
37. Roux J, Kawakatsu H, Gartland B, Pespeni M, Sheppard D, Matthay MA, *et al*. Interleukin-1beta decreases expression of the epithelial sodium channel alpha-subunit in alveolar epithelial cells via a p38 MAPK-dependent signaling pathway. J Biol Chem 2005;280:18579-89. doi: 10.1074/jbc.M410561200.
38. Fukuda N, Jayr C, Lazrak A, Wang Y, Lucas R, Matalon S, *et al*. Mechanisms of TNF-alpha stimulation of amiloride-sensitive sodium transport across alveolar epithelium. Am J Physiol Lung Cell Mol Physiol 2001;280:L1258-65. doi: 10.1152/ajplung.2001.280.6.L1258.
39. Elia N, Tapponnier M, Matthay MA, Hamacher J, Pache JC, Brundler MA, *et al*. Functional identification of the alveolar edema reabsorption activity of murine tumor necrosis factor-alpha. Am J Respir Crit Care Med 2003;168:1043-50. doi: 10.1164/rccm.200206-618OC.
40. Dagenais A, Fréchette R, Yamagata Y, Yamagata T, Carmel JF, Clermont ME, *et al*. Downregulation of ENaC activity and expression by TNF-alpha in alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 2004;286:L301-11. doi: 10.1152/ajplung.00326.2002.
41. Lee JW, Fang X, Dolganov G, Fremont RD, Bastarache JA, Ware LB, *et al*. Acute lung injury edema fluid decreases net fluid transport across human alveolar epithelial type II cells. J Biol Chem 2007;282:24109-19. doi: 10.1074/jbc.M700821200.
42. Zemans RL, Colgan SP, Downey GP. Transepithelial migration of neutrophils: Mechanisms and implications for acute lung injury. Am J Respir Cell Mol Biol 2009;40:519-35. doi: 10.1165/ rcmb.2008-

0348TR.
43. Calfee CS, Matthay MA. Clinical immunology: Culprits with evolutionary ties. Nature 2010;464:41-2. doi: 10.1038/464041a.
44. Staub NC. Pulmonary edema. Physiol Rev 1974;54:678-811. doi: 10.1152/physrev.1974.54.3.678.
45. Comellas AP, Briva A. Role of endothelin-1 in acute lung injury. Transl Res 2009;153:263-71. doi: 10.1016/j.trsl.2009.02.007.
46. Vivona ML, Matthay M, Chabaud MB, Friedlander G, Clerici C. Hypoxia reduces alveolar epithelial sodium and fluid transport in rats: Reversal by beta-adrenergic agonist treatment. Am J Respir Cell Mol Biol 2001;25:554-61. doi: 10.1165/ajrcmb.25.5.4420.
47. Vadász I, Raviv S, Sznajder JI. Alveolar epithelium and Na, K-ATPase in acute lung injury. Intensive Care Med 2007;33:1243-51. doi: 10.1007/s00134-007-0661-8.
48. Briva A, Vadász I, Lecuona E, Welch LC, Chen J, Dada LA, *et al*. High CO2 levels impair alveolar epithelial function independently of pH. PLoS One 2007;2:e1238. doi: 10.1371/journal.pone.0001238.
49. Karp CL, Flick LM, Park KW, Softic S, Greer TM, Keledjian R, *et al*. Defective lipoxin-mediated anti-inflammatory activity in the cystic fibrosis airway. Nat Immunol 2004;5:388-92. doi: 10.1038/ni1056.
50. O'Meara SJ, Rodgers K, Godson C. Lipoxins: Update and impact of endogenous pro-resolution lipid mediators. Rev Physiol Biochem Pharmacol 2008;160:47-70. doi: 10.1007/112_2006_0606.
51. Serhan CN. Resolution phase of inflammation: Novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. Annu Rev Immunol 2007;25:101-37. doi: 10.1146/annurev.immunol.25.022106.141647.
52. Serhan CN, Yacoubian S, Yang R. Anti-inflammatory and proresolving lipid mediators. Annu Rev Pathol 2008;3:279-312. doi: 10.1146/annurev.pathmechdis.3.121806.151409.
53. Bandeira-Melo C, Bozza PT, Diaz BL, Cordeiro RS, Jose PJ, Martins MA, *et al*. Cutting edge: Lipoxin (LX)A4 and aspirin-triggered 15-epi-LXA4 block allergen-induced eosinophil trafficking. J Immunol 2000;164:2267-71. doi: 10.4049/jimmunol.164.5.2267.
54. Fukunaga K, Kohli P, Bonnans C, Fredenburgh LE, Levy BD. Cyclooxygenase 2 plays a pivotal role in the resolution of acute lung injury. J Immunol 2005;174:5033-9. doi: 10.4049/jimmunol.174.8.5033.
55. Zheng S, D'Souza VK, Bartis D, Dancer RC, Parekh D, Naidu B, *et al*. Lipoxin A4 promotes lung epithelial repair whilst inhibiting fibroblast proliferation. ERJ Open Res 2016;2: 00079-2015. doi: 10.1183/23120541.00021-2016.
56. Higgins G, Fustero Torre C, Tyrrell J, McNally P, Harvey BJ, Urbach V, *et al*. Lipoxin A4 prevents tight junction disruption and delays the colonization of cystic fibrosis bronchial epithelial cells by Pseudomonas aeruginosa. Am J Physiol Lung Cell Mol Physiol 2016;310:L1053-61. doi: 10.1152/ajplung.00368.2015.
57. Sun YP, Oh SF, Uddin J, Yang R, Gotlinger K, Campbell E, *et al*. Resolvin D1 and its aspirin-triggered 17R epimer. Stereochemical assignments, anti-inflammatory properties, and enzymatic inactivation. J Biol Chem 2007;282:9323-34. doi: 10.1074/jbc.M609212200.
58. Norling LV, Dalli J, Flower RJ, Serhan CN, Perretti M. Resolvin D1 limits polymorphonuclear leukocyte recruitment to inflammatory loci: Receptor-dependent actions. Arterioscler Thromb Vasc Biol 2012;32:1970-8. doi: 10.1161/ATVBAHA.112.249508.
59. Krishnamoorthy S, Recchiuti A, Chiang N, Yacoubian S, Lee CH, Yang R, *et al*. Resolvin D1 binds human phagocytes with evidence for proresolving receptors. Proc Natl Acad Sci U S A 2010;107:1660-5. doi: 10.1073/pnas.0907342107.
60. Liao Z, Dong J, Wu W, Yang T, Wang T, Guo L, *et al*. Resolvin D1 attenuates inflammation in lipopolysaccharide-induced acute lung injury through a process involving the PPARγ/NF-κB pathway. Respir Res 2012;13:110. doi: 10.1186/1465-9921-13-110.
61. Bento AF, Claudino RF, Dutra RC, Marcon R, Calixto JB. Omega-3 fatty acid-derived mediators 17(R)-hydroxy docosahexaenoic acid, aspirin-triggered resolvin D1 and resolvin D2 prevent experimental colitis in mice. J Immunol 2011;187:1957-69. doi: 10.4049/jimmunol.1101305.
62. Wang B, Gong X, Wan JY, Zhang L, Zhang Z, Li HZ, *et al*. Resolvin D1 protects mice from LPS-induced acute lung injury. Pulm Pharmacol Ther 2011;24:434-41. doi: 10.1016/j.pupt.2011.04.001.
63. Rogerio AP, Haworth O, Croze R, Oh SF, Uddin M, Carlo T, *et al*. Resolvin D1 and aspirin-triggered resolvin D1 promote resolution of allergic airways responses. J Immunol 2012;189:1983-91. doi: 10.4049/jimmunol.1101665.
64. Sakuma T, Folkesson HG, Suzuki S, Okaniwa G, Fujimura S, Matthay MA, *et al*. Beta-adrenergic agonist stimulated alveolar fluid clearance in ex vivo human and rat lungs. Am J Respir Crit Care Med 1997;155:506-12. doi: 10.1164/ajrccm.155.2.9032186.
65. Su X, Robriquet L, Folkesson HG, Matthay MA. Protective effect of endogenous beta-adrenergic tone on lung fluid balance in acute bacterial pneumonia in mice. Am J Physiol Lung Cell Mol Physiol 2006;290:L769-76. doi: 10.1152/ajplung.00334.2005.
66. Perkins GD, McAuley DF, Thickett DR, Gao F. The beta-agonist lung injury trial (BALTI): A randomized placebo-controlled clinical trial. Am J Respir Crit Care Med 2006;173:281-7. doi: 10.1164/rccm.200508-1302OC.
67. Deng W, Li CY, Tong J, Zhang W, Wang DX. Regulation of ENaC-mediated alveolar fluid clearance by insulin via PI3K/Akt pathway in LPS-induced acute lung injury. Respir Res 2012;13:29. doi: 10.1186/1465-9921-13-29.
68. Serhan CN. Resolvins and protectins: Novel lipid mediators in anti-inflammation and resolution. Scand J Food Nutr 2006;50:68-78. doi: 10.3402/fnr.v50i0.1579.
69. Chen P, Fenet B, Michaud S, Tomczyk N, Véricel E, Lagarde M, *et al*. Full characterization of PDX, a neuroprotectin/protectin D1 isomer, which inhibits blood platelet aggregation. FEBS Lett 2009;583:3478-84. doi: 10.1016/j.febslet.2009.10.004.
70. Serhan CN, Gotlinger K, Hong S, Lu Y, Siegelman J, Baer T, *et al*. Anti-inflammatory actions of neuroprotectin D1/protectin D1 and its natural stereoisomers: Assignments of dihydroxy-containing docosatrienes. J Immunol 2006;176:1848-59. doi: 10.4049/jimmunol.176.6.3843-a.
71. Ariel A, Li PL, Wang W, Tang WX, Fredman G, Hong S, *et al*. The docosatriene protectin D1 is produced by TH2 skewing and promotes human T cell apoptosis via lipid raft clustering. J Biol Chem 2005;280:43079-86. doi: 10.1074/jbc.M509796200.
72. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature 2014;510:92-101. doi: 10.1038/nature13479.
73. Serhan CN, Yang R, Martinod K, Kasuga K, Pillai PS, Porter TF, *et al*. Maresins: Novel macrophage mediators with potent antiinflammatory and proresolving actions. J Exp Med 2009;206:15-23. doi: 10.1084/ jem.20081880.
74. Serhan CN, Dalli J, Karamnov S, Choi A, Park CK, Xu ZZ, *et al*. Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. FASEB J 2012;26:1755-65. doi: 10.1096/fj.11-201442.
75. Dalli J, Zhu M, Vlasenko NA, Deng B, Haeggström JZ, Petasis NA, *et al*. The novel 13S,14S-epoxy-maresin is converted by human macrophages to maresin 1 (MaR1), inhibits leukotriene A4 hydrolase (LTA4H), and shifts macrophage phenotype. FASEB J 2013;27:2573-83. doi: 10.1096/fj.13-227728.
76. Titos E, Rius B, López-Vicario C, Alcaraz-Quiles J, García-Alonso V, Lopategi A, *et al*. Signaling and immunoresolving actions of resolvin D1 in inflamed human visceral adipose tissue. J Immunol 2016;197:3360-70. doi: 10.4049/jimmunol.1502522.
77. Zhang JL, Zhuo XJ, Lin J, Luo LC, Ying WY, Xie X, *et al*. Maresin1 stimulates alveolar fluid clearance through the alveolar epithelial sodium channel Na, K-ATPase via the ALX/PI3K/Nedd4-2 pathway. Lab Invest 2017;97:543-54. doi: 10.1038/labinvest.2016.150.
78. Spite M, Serhan CN. Novel lipid mediators promote resolution of acute inflammation: Impact of aspirin and statins. Circ Res 2010;107:1170-84. doi: 10.1161/CIRCRESAHA.110.223883.
79. Jin SW, Zhang L, Lian QQ, Liu D, Wu P, Yao SL, *et al*. Posttreatment with aspirin-triggered lipoxin A4 analog attenuates lipopolysaccharide-induced acute lung injury in mice: The role of heme oxygenase-1. Anesth Analg 2007;104:369-77. doi: 10.1213/01.ane.0000252414.00363.c4.
80. El Kebir D, József L, Pan W, Wang L, Petasis NA, Serhan CN, *et al*. 15-epi-lipoxin A4 inhibits myeloperoxidase signaling and

enhances resolution of acute lung injury. Am J Respir Crit Care Med 2009;180:311-9. doi: 10.1164/rccm.200810-1601OC.
81. Guilherme RF, Xisto DG, Kunkel SL, Freire-de-Lima CG, Rocco PR, Neves JS, *et al*. Pulmonary antifibrotic mechanisms aspirin-triggered lipoxin A(4) synthetic analog. Am J Respir Cell Mol Biol 2013;49:1029-37. doi: 10.1165/rcmb.2012-0462OC.
82. Abdulnour RE, Sham HP, Douda DN, Colas RA, Dalli J, Bai Y, *et al*. Aspirin-triggered resolvin D1 is produced during self-resolving gram negative bacterial pneumonia and regulates host immune responses for the resolution of lung inflammation. Mucosal Immunol 2016;9:1278-87. doi: 10.1038/mi.2015.129.
83. Cox R Jr., Phillips O, Fukumoto J, Fukumoto I, Tamarapu Parthasarathy P, Mandry M, *et al*. Resolvins decrease oxidative stress mediated macrophage and epithelial cell interaction through decreased cytokine secretion. PLoS One 2015;10:e0136755. doi: 10.1371/journalone.0136755.
84. Tang H, Liu Y, Yan C, Petasis NA, Serhan CN, Gao H, *et al*. Protective actions of aspirin triggered (17R) resolvin D1 and its analogue, 17R-hydroxy-19-para-fluorophenoxy-resolvin D1 methyl ester, in C5a-dependent IgG immune complex-induced inflammation and lung injury. J Immunol 2014;193:3769-78. doi: 10.4049/ jimmunol.1400942.
85. Eickmeier O, Seki H, Haworth O, Hilberath JN, Gao F, Uddin M, *et al*. Aspirin-triggered resolvin D1 reduces mucosal inflammation and promotes resolution in a murine model of acute lung injury. Mucosal Immunol 2013;6:256-66. doi: 10.1038/mi.2012.66.
86. Wang H, Anthony D, Yatmaz S, Wijburg O, Satzke C, Levy B, *et al*. Aspirin-triggered resolvin D1 reduces pneumococcal lung infection and inflammation in a viral and bacterial coinfection pneumonia model. Clin Sci (Lond) 2017;131:2347-62. doi: 10.1042/ CS20171006.
87. Sacerdoti D, Pesce P, Di Pascoli M, Bolognesi M. EETs and HO-1 cross-talk. Prostaglandins Other Lipid Mediat 2016;125:65-79. doi: 10.1016/j.prostaglandins.2016.06.002.
88. Ryter SW, Choi AM. Heme oxygenase-1/carbon monoxide: From metabolism to molecular therapy. Am J Respir Cell Mol Biol 2009;41:251-60. doi: 10.1165/rcmb.2009-0170TR.
89. Ryter SW, Choi AM. Heme oxygenase-1/carbon monoxide: Novel therapeutic strategies in critical care medicine. Curr Drug Targets 2010;11:1485-94. doi: 10.2174/1389450111009011485.
90. Chiang N, Shinohara M, Dalli J, Mirakaj V, Kibi M, Choi AM, *et al*. Inhaled carbon monoxide accelerates resolution of inflammation via unique proresolving mediator-heme oxygenase-1 circuits. J Immunol 2013;190:6378-88. doi: 10.4049/jimmunol.1202969.
91. Xie W, Wang H, Wang L, Yao C, Yuan R, Wu Q, *et al*. Resolvin D1 reduces deterioration of tight junction proteins by upregulating HO-1 in LPS-induced mice. Lab Invest 2013;93:991-1000. doi: 10.1038/labinvest.2013.80.
92. Boutros C, Zegdi R, Lila N, Cambillau M, Fornes P, Carpentier A, *et al*. Carbon monoxide can prevent acute lung injury observed after ischemia reperfusion of the lower extremities. J Surg Res 2007;143:437-42. doi: 10.1016/j.jss.2007.02.013.
93. Sarady JK, Zuckerbraun BS, Bilban M, Wagner O, Usheva A, Liu F, *et al*. Carbon monoxide protection against endotoxic shock involves reciprocal effects on iNOS in the lung and liver. FASEB J 2004;18:854-6. doi: 10.1096/fj.03-0643fje.
94. Wegiel B, Larsen R, Gallo D, Chin BY, Harris C, Mannam P, *et al*. Macrophages sense and kill bacteria through carbon monoxide-dependent inflammasome activation. J Clin Invest 2014;124:4926-40. doi: 10.1172/JCI72853.
95. Nakahira K, Kim HP, Geng XH, Nakao A, Wang X, Murase N, *et al*. Carbon monoxide differentially inhibits TLR signaling pathways by regulating ROS-induced trafficking of TLRs to lipid rafts. J Exp Med 2006;203:2377-89. doi: 10.1084/jem.20060845.
96. D'Acquisto F, Perretti M, Flower RJ. Annexin-A1: A pivotal regulator of the innate and adaptive immune systems. Br J Pharmacol 2008;155:152-69. doi: 10.1038/bjp.2008.252.
97. Perretti M, D'Acquisto F. Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. Nat Rev Immunol 2009;9:62-70. doi: 10.1038/nri2470.
98. Perretti M, Christian H, Wheller SK, Aiello I, Mugridge KG, Morris JF, *et al*. Annexin I is stored within gelatinase granules of human neutrophil and mobilized on the cell surface upon adhesion but not phagocytosis. Cell Biol Int 2000;24:163-74. doi: 10.1006/ cbir.1999.0468.
99. Liao WI, Wu SY, Wu GC, Pao HP, Tang SE, Huang KL, *et al*. Ac2-26, an annexin A1 peptide, attenuates ischemia-reperfusion-induced acute lung injury. Int J Mol Sci 2017;18:E1771. doi: 10.3390/ ijms18081771.
100. Gimenes AD, Andrade TR, Mello CB, Ramos L, Gil CD, Oliani SM, *et al*. Beneficial effect of annexin A1 in a model of experimental allergic conjunctivitis. Exp Eye Res 2015;134:24-32. doi: 10.1016/j. exer.2015.03.013.
101. Tseng TL, Chen MF, Tsai MJ, Hsu YH, Chen CP, Lee TJ, *et al*. Oroxylin-A rescues LPS-induced acute lung injury via regulation of NF-κB signaling pathway in rodents. PLoS One 2012;7:e47403. doi: 10.1371/journal.pone.0047403.
102. Sartori C, Matthay MA. Alveolar epithelial fluid transport in acute lung injury: New insights. Eur Respir J 2002;20:1299-313. doi: 10.1183/09031936.02.00401602.

促炎症消退介质调控急性呼吸窘迫综合征肺泡液体清除率的机制

摘要

目的：急性呼吸窘迫综合征（ARDS）是一种临床急危重症，其主要特征是肺泡上皮损伤削弱肺内液体主动转运，限制水肿液从肺泡腔中重新吸收。本综述旨在探讨促炎症消退介质调控ARDS肺泡液清除（AFC）的机制。

数据来源：截止2017年9月1日，所有发表在PubMed上的文章。查询关键词为："alveolar fluid clearance"或"lung edema"或"acute lung injury"或"acute respiratory distress syndrome"和"specialized pro-resolving mediators"或"lipoxin"或"resolvin"或"protectin"或"maresin"或"alveolar epithelial cells"或"aspirin-triggered lipid mediators"或"carbon monoxide and heme oxygenase"或"annexin A1"。

研究选择：综述包含了截止2017年9月1日出版了的所有相关的文章，对研究设计无限制。

结果：作为促炎症消退介质，SPMs不仅上调ENaC，Na,K-ATPase，囊性纤维化跨膜传导调节因子（CFTR）和水通道蛋白水平，而且增强Na,K-ATPase活性，进而促进ARDS中的AFC。SPMs除了直接影响肺泡上皮的离子通道和泵外，还能抑制炎症因子的表达，改善肺泡上皮细胞的修复功能，进一步增强ARDS的AFC。

结论：本综述探讨了一种肺泡水肿液重吸收的新机制。SPMs可能为控制急性肺损伤（ALI）/ARDS提供高精确度的"重吸收靶向"治疗提供新的机会。