# Gut-lymph-lung pathway mediates sepsis-induced acute lung injury

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**Abstract**

This review attempts to unveil the possible mechanisms underlying how gut lymph affects lung and further gives rise to acute respiratory distress syndrome, as well as potential interventional targets under the condition of ischemia-reperfusion injury. We searched electronic databases including PubMed, MEDLINE, Cochrane Central Register of Controlled Trials, Google Scholar, Web of Science, and Embase to identify relevant literatures published up to December 2019. We enrolled the literatures including the Mesh Terms of "gut lymph or intestinal lymph and acute lung injury or acute respiratory distress syndrome." Gut is considered to be the origin of systemic inflammation and the engine of multiple organ distress syndrome in the field of critical care medicine, whereas gut lymph plays a pivotal role in initiation of ischemia-reperfusion injury-induced acute respiratory distress syndrome. In fact, in the having been established pathologic model of sepsis leading to multiple organ dysfunction named by *Gut Lymph* theory, a variety of literatures showed the position and role of changes in gut lymph components in the initiation of systemic inflammatory response, which allows us to screen out potential intervention targets to pave the way for future clinic and basic research.

**Keywords:** Gut lymph; Ischemia-reperfusion injury; Acute respiratory distress syndrome; Multiple organ dysfunction syndrome

## Introduction

The gut lymph (GL) theory, first put forward by Deitch *et al* in 2006,[1] roots from the pathophysiology of critical illness [Figure 1]. Derived from intestinal ischemia-reperfusion injury (IRI), which usually occurs with restored reperfusion of microcirculation in critically ill patients with injury-induced shock, intestinal toxic substances are first absorbed into the mesenteric lymphatic (ML) system. They are then transported into blood circulation to activate the monocyte-macrophage system (MMS), which triggers a systemic inflammatory response that further aggregates intestinal injury.[2] This process of successive iteration gives rise to cascade amplification of inflammation. Early studies indicated that bacterial translocation resulting from the destruction of intestinal mucosal integrity poses the threat of multiple organ dysfunction syndrome (MODS).[3] However, the latest experimental evidence suggests that GL acts as a carrier of danger-associated molecular patterns to systemic blood circulation and different organs, leading to MODS.[4] Acute respiratory distress syndrome (ARDS) can be induced in healthy rats by injecting GL fluid (GLF) from rat models of traumatic/hemorrhagic shock (T/HS), which involves severe abdominal infection.[5-7] However, simultaneous ligation of GL vessels or drainage of GLF in this model alleviated the conditions of ARDS.[8] Therefore, the gut is considered to be the origin of systemic inflammation responses[9] and the engine of MODS,[10] and plays an essential role in initiation of ARDS. This review attempts to unveil the potential mechanisms underlying how GL affects the lung and further gives rise to ARDS, as well as potential interventional targets under the condition of IRI.

## Bioactive Substances

### *From mediator to molecule*

In response to injuries such as shock, extensive burn, severe infection, and severe trauma, the gut (as the origin of systemic inflammation) releases a large number of inflammatory mediators, cytokines, and bioactive substances such as exosomes, high mobility group protein B1, tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), arachidonic acid metabolite leukotriene (LTB4), and hypoxia inducible factor-1α (HIF-1α), all of which play a pivotal role in ARDS [Table 1].

The biologic function of exosomes, which are extracellular vesicles secreted by immune cells approximately 40 to

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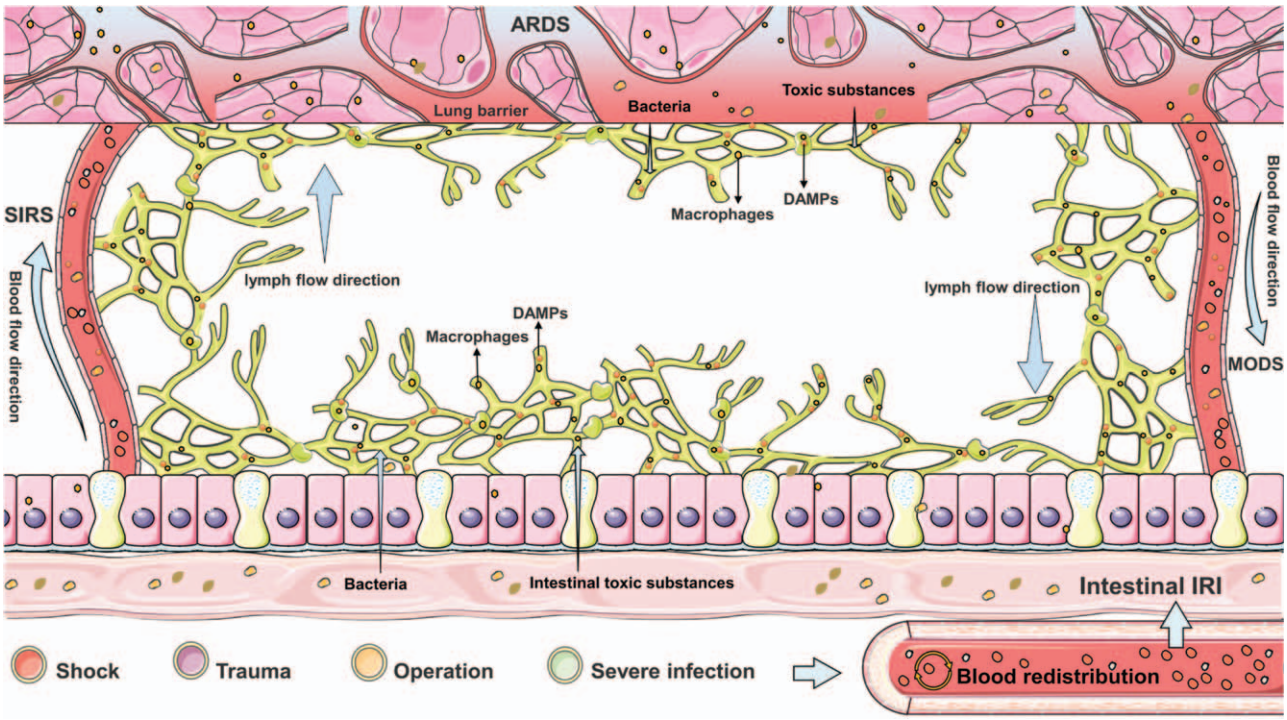


**Figure 1:** Pathophysiologic mechanism of gut-origin sepsis and acute respiratory distress syndrome in critically ill patients. ARDS: Acute respiratory distress syndrome; MODS: Multiple organ distress syndrome; IRI: Ischemia-reperfusion injury; SIRS: Systemic inflammatory response syndrome; DAMPs: Damage associated molecular patterns.

100 nm in size, is determined by its cell source and contents of lipid, protein, RNA, microRNA, and other bioactive components, which may have inflammatory and immunoregulatory effects on target cells.[11] Exosomes are able to transfer lipid mediators such as fatty acids, prostaglandins, and leukotrienes (LTs) from host to target cells, which play an important role in the activation of target cells.[12] Furthermore, the number of exosomes in body fluids is altered by various injuries such as inflammation, trauma, and infection.[5]

Kojima *et al*[13] first identified ML exosomes in rats by means of vesicle flow cytometry. Upon evaluating their cell source and changes in response to T/HS, it was found that they are able to express high levels of epithelial cell adhesion molecule before and after T/HS shock, while CD31 and CD61 expression were reduced compared with the control group. Therefore, ML exosomes may primarily originate from intestinal epithelial cells and be unaffected by T/HS. The occurrence of intestinal IRI leads to neutrophil aggregation and release of granules containing exosomes through endoplasmic reticulum stress mediated by complement 5a receptor, which promotes the development of ARDS.[14]

IL-8 homologues are the major cytokines for neutrophil aggregation. Kojima's[15] results showed that exosomes obtained from ML after T/HS treatment had significantly increased IL-8 expression. Furthermore, they confirmed that injection of ML exosomes into neonatal mice after T/HS could increase secretion of MIP-2 (a rat IL-8 homologue) and numbers of infiltrating neutrophils in bronchoalveolar lavage fluid (BALF), leading to ALI. Moreover, after intestinal IRI, ML exosomes triggered activation of nuclear factor kappa B (NF-κB) in monocytes and macrophages,[15] and induced the production of pro-inflammatory cytokines by monocytes and macrophages *via* a Toll-like receptor (TLR)-dependent signaling pathway.[16] Sakamoto *et al*[17] reported that the lung captured most exosomes from being injected into ML catheters, suggesting that the lung is the principal target for ML to carry exosomes. To verify whether exosomes can reach the lung and absorb immune cells *in vivo*, Kojima *et al*[15] injected ML exosomes into immature mice before and after shock. ML exosomes had moved to the alveolar cavity and pulmonary parenchyma 6 h after injection, and were absorbed by macrophages and $CD68^+$ pulmonary macrophages, indicating that exosomes could reach the lung and be absorbed by macrophages *in vivo*. After T/HS, the alveolar capillary barrier was destroyed by ML injection, as indicated by alveolar Evans blue dye content, protein leakage of BALF, lung wet dry ratio, and other measures. Moreover, histologic lung injury scores increased significantly, and inflammatory cells aggregated in the alveolar cavity and lung parenchyma. However, injection of ML supernatant with or without ML exosomes before shock did not cause pulmonary inflammation.

As the central link of the immune response, dendritic cells (DCs) are powerful antigen-presenting cells that can absorb, process, and present antigens.[18,19] Another study by Kojima *et al*[20] showed that after T/HS, expression of immunoregulatory molecules such as major histocompatibility complex II was significantly increased in ML exosomes. Compared with ML exosomes before shock, co-incubation of DCs with ML exosomes after T/HS increased the apoptotic rate of DCs two-fold. Additionally, ML exosomes after T/HS inhibited the antigen-presenting

**Table 1: Inflammatory mediators in lymph following ischemia-reperfusion injury that contributes to ARDS/MODS.**

| Inflammatory mediators | Function and meaning |
|---|---|
| Exosome | 1. Transfers lipid mediators such as fatty acids, prostaglandins and leukotrienes from host cells to target cells.<br>1. Triggers activation of NF-κB in monocytes and macrophages.<br>2. Increases expression of immunoregulatory molecules such as major histocompatibility complex II.<br>3. Inhibits the antigen-presenting ability, maturation, and antigen-expression function of DCs, and promotes their apoptosis. |
| TLR4 | 1. Identifies endogenous risk types and alarm factors and respond to endogenous ligands.<br>2. TLR4 signaling pathway was necessary for ML exosomes to induce macrophage activation.<br>3. iNOS expression in the lungs. |
| C5a receptor | Mediates endoplasmic reticulum stress and causes neutrophils aggregation and release of granules containing exosomes. |
| IL-1, IL-6, IL-8, and TNF-α | 1. Aggregate the neutrophils.<br>2. Increase the adhesion of PMN to vascular endothelial cells, produce and release TNF, oxygen-free radicals, and nitric oxide near the alveolar epithelium.<br>3. Increase the permeability of intestinal mucosa, forming a vicious cascade of inflammatory amplification that ultimately results in MODS. |
| IL-4 | IL-4 is an anti-inflammatory factor whose presence suggests inflammation or an immune reaction. |
| LPS | Activates TLR4, which in turn activates NF-κB and activating protein 1. |
| NF-κB and activator protein 1 | Induce the release of interferon, intercellular adhesion molecules, and cytokines. |
| HIF-1α | Stimulates neutrophils to modulate ischemia/hypoxia. |
| Neutrophils | Lead to endothelial and erythrocyte dysfunction. |
| Trypsin | leads to excessive protein catabolism and aggravation of cellular damage. |
| Arachidonoyls | Metabolized by the 5-LO pathway to produce leukotrienes. |
| LTs | Regulate PMN transport in IRI by regulating the expression of adhesion molecules. |
| Myeloperoxidase, linoleoyl, LPCs, LPEs, and PLA2 | Induce cytotoxic reactions, which in turn can induce persistent superoxide anion (O2-) production. |
| Macrophage | Produces oxygen-free radicals, lysine, and LTs, but also directly affects pulmonary vascular endothelial cells. |

ARDS: Acute respiratory distress syndrome; MODS: Multiple organ distress syndrome; NF-κB: Nuclear factor kappa B; DCs: Dendritic cells; TLR4: Toll-like receptor 4; ML: Mesenteric lymphatic; iNOS: Inducible nitric oxide synthase; C5a: Complement; IL: Interleukin; TNF: Tumor necrosis factor; PMN: Polymorphonuclear neutrophils; LPS: Lipopolysaccharide; HIF: Hypoxia inducible factor; 5-LO: 5-Lipoxygenase; LTs: Leukotrienes; IRI: Ischemia-reperfusion injury; LPCs: Lysophosphatidylcholines; LPEs: Lysophosphatidylethan olamines; PLA2: Phospholipase A (2).

ability, maturation, and antigen-expression function of DCs, and promoted their apoptosis. Thus, ML exosomes are a novel mediator of post-injury immunosuppression.

When intestinal IRI occurs, lipopolysaccharide (LPS) in circulating blood activates TLR4. With the assistance of extracellular LPS-binding protein and CD14 myeloid differentiation protein 2, the LPS-stimulating signal is transduced intracellularly, whereby it induces a signal cascade reaction through two myeloid differentiation factor 88-dependent factors to increase expression of inflammatory factors, ultimately triggering an inflammatory response.[21] The inflammatory mediator high mobility group protein B1, as well as cytokines (TNF-α, IL-6, etc) and LTB4, plays an important role in the GL theory of MODS. However, the key component of this mechanism is still activation of MMS by endotoxin. LPS-activated MMS mainly depends on TLR4, which can transmit the LPS extracellular signal into intracellular signaling with the help of LPS-binding protein, which further activates transcription factors such as NF-κB and activator protein 1. Activation of NF-κB and activator protein 1 also induces the release of interferon, intercellular adhesion molecules, and cytokines such as TNF-α and IL-6. The presence of TNF-α, IL-6, and other inflammatory factors in circulating blood can further increase the permeability of intestinal mucosa,[22] thereby increasing intestinal bacteria and endotoxin entering the interstitial space of intestinal mucosa by GL absorption into the lymphatic circulation. This process starts a new round of MMS activation, thus forming a vicious cascade of inflammatory amplification that ultimately results in distant organ injury.

Zhang *et al*[23] showed that levels of TLR4, NF-κB, and human IL-1 receptor-related kinase 4 were increased in the ileum of rats with abdominal infection compared with sham-operated rats. Indeed, levels of TNF-α, IL-6, IL-4, monocyte chemotactic proteins, and intracellular adhesion molecule 1 in plasma, lymph, and BALF, as well as intestinal and lung tissues, were increased by abdominal infection. Furthermore, GL drainage decreased levels of these factors in BALF and lung tissue. These results are consistent with the reduction of lung injury observed in rats infected by GL drainage.

Abnormal oxygen metabolism and cascade amplification of the inflammatory response are important pathophysiologic features of sepsis-induced ALI.[24] HIF-1α, a transcription

factor, is considered to be the principal regulator of ischemia/hypoxia.[25] Studies have shown that HIF-1α could be activated by an inflammatory state, suggesting that HIF-1α is closely related to the inflammatory process. Sun *et al*[24] injected septic lymph (SL) of rats and saline into the jugular vein of healthy rats. Injection of SL could obviously induce HIF-1α production, and levels of lung injury scale and myeloperoxidase were considerably increased compared with saline-injected rats. These results indicate that HIF-1α has potential a stimulatory effect on neutrophils in lymph node ALI of sepsis. Activation of neutrophils could lead to endothelial and erythrocyte dysfunction, which may contribute to ALI. Furthermore, preoperative intra-tracheal drip of 3-(50-hydroxymethyl-20-furan)-1-benzylamphetazole (YC-1) in SL-infused rats showed a tendency to reduce the signs of pulmonary inflammation injury, especially the level of myeloperoxidase. These results suggest that YC-1 can inhibit HIF-1α expression and the progress of inflammation induced by HIF-1α. Thus, HIF-1α plays an important role in hypoxia and inflammation.

### Proteins and lipids

GL contains a large number of proteins and lipids, which have an essential impact on biologic activity. Research from Fang *et al*[26] indicated an increased abundance of serum albumin precursors, creatine kinase B, and actin in ML nodes after shock; most notably, the abundance of serum albumin precursors increased by 8.5-fold. Previous studies have shown that in some inflammatory conditions, such as mycotic keratitis, serum albumin precursors in body fluids are increased, and increased creatine kinase B, a component of the cytoskeleton network, in the circulation after muscle injury is considered to result from passive or active release.[27] Actin is a central component of cytoskeletal structures. Previous studies demonstrated that HS could result in selective destruction of the intestinal actin cytoskeleton.[26] Collectively, these results indicate that serum albumin precursor, creatine kinase B, and actin are associated with the process of inflammation and injury.

Trypsin, a proteolytic enzyme released from damaged cells, can lead to excessive protein catabolism and aggravation of cellular damage.[28] Zhao *et al*[29] found that injecting post-HS mesenteric lymph (PHSML) from rats into the veins of normal rats could significantly increase trypsin activity in plasma, suggesting that toxic components in PHSML cause damage to cells and increase the release of trypsin.

Previously, Mittal *et al*[30] showed that ALI could be significantly reduced by blocking or neutralizing pancreatic enzymes entering the intestinal cavity in rats with acute pancreatitis. Upon analyzing the histology of GLF after T/HS, Morishita *et al*[31] observed a variety of lipids in PHSML, including phosphatidylcholine, lysophosphatidylcholine (LPC), phosphatidylethanolamine, lysophosphatidylethan olamine (LPE), and sphingomyelin. Compared with the sham shock group (T/SS), levels of linoleoyl, arachidonoyls, docosahexaenol LPCs, and LPEs were significantly increased in PHSML of the T/HS group. Significantly increased LPCs and LPEs containing polyunsaturated fatty acids in PHSML can induce cytotoxic reactions, which in turn can induce persistent superoxide anion ($O^{2-}$) production. Increased $O^{2-}$ production and elastase release have been shown to lead to ARDS/MODS.[31]

Gut phospholipase A (2) (PLA 2), a neutral lipid, was extracted from PHSML. It is responsible for the initiation of pro-inflammatory lipids in PHSML, which is why the cytotoxicity is increased after polymorphonuclear neutrophils (PMNs) oxidative burst.[32] The physiologic concentration of PHSML lipids will trigger PMN respiratory bursts, and the production of superoxide is twice that of lymphatic cells before shock. The systemic use of gut PLA 2 inhibition before HS eliminated the neutrophil initiation effect of PHSML, suggesting that T/HS may be at the core of the pathogenesis of ARDS/MODS,[33] provides a potentially therapeutic mechanism for acute lung injury after shock.

### Bacteria and endotoxins

Intestinal IRI results in impaired intestinal mucosal barriers, intestinal bacterial translocation, and release of inflammatory mediators and cytokines.[34] Early studies suggested that when intestinal IRI occurred, intestinal barrier function was impaired and intestinal permeability increased, leading to bacterial and endotoxin translocation. Bacteria and endotoxin primarily enter systemic blood circulation through the portal vein system and GL system, leading to distant organ injury. Adams *et al*[35] found that the GL of rats with HS and burn was sterile, and no endotoxin was detected. Our unpublished results indicate increased endotoxin levels in GL of rats with IRI compared with sham-operated rats. Reasons underlying these conflicting experimental results may be related to differences in bacterial detection techniques and/or use in different laboratories. Deitch *et al*[36] suggested that translocation of bacteria and endotoxins may not exist in GL, but instead be a property of intestinal walls and ML nodes, which induce local inflammation and stimulate production of a large number of cytokines; thus aggravating systemic inflammatory response syndrome and leading to MODS.

## Bio-mechanism

### From phenomenon to mechanism

In addition to identifying endogenous risk types and alarm factors, TLR4 has been shown to identify and respond to endogenous ligands, which suggests that it can be used as a sensor for tissue damage and microbial invasion.[37] Cells carrying TLR4 *in vivo* include innate immune system cells such as macrophages, neutrophils, and DCs.[38] Kojima *et al*[13] showed that TLR4 was the subject receptor of ML exosome and could induce macrophage inflammation; moreover, the TLR4 signaling pathway was necessary for ML exosomes to induce macrophage activation. Reino *et al*[39] showed that the lung permeability of wild-type mice transfused with T/HS lymph was 2.5-times higher than that of mice transfused with T/SS lymph; however, the lung permeability of TLR4-deficient mice injected with T/

HS lymph did not increase significantly. There was no difference in myeloperoxidase levels in TLR4-deficient mice injected with T/HS or T/SS lymph nodes. Compared with wild-type mice, inducible nitric oxide synthase (iNOS) expression in the lungs of TLR4-deficient mice injected with T/HS lymphocytes decreased significantly, suggesting that T/HS lymphokines mediate lung injury through TLR4 activation. Moreover, lack of TLR4 attenuates the lung iNOS response to T/HS lymph-induced lung injury.

PHSML contains large amounts of arachidonic acid when they return to the systemic circulation. LTs are products of arachidonic acid metabolized by the 5-lipoxygenase (5-LO) pathway. 5-LO is a rate-limiting enzyme for LT synthesis, and is an important factor causing lung dysfunction after secondary T/HS. 5-LO activation is considered to be an important regulator of the pathogenesis of multi-cellular organisms.[40] Monteiro *et al*'s study[41] have shown that IRI and even sepsis patients treated with 5-LO inhibitors are significantly protected from lung inflammation and injury. It can be seen that 5-LO products play an important role in lung injury caused by sepsis, and also suggest that the application of 5-LO inhibitors may have clinical therapeutic value.[42,43] LTs mainly regulate PMN transport in IRI by regulating the expression of adhesion molecules.[44]*In vitro* studies show that PHSML activate neutrophils, increase endothelial cell monolayer permeability, and may even cause endothelial cell death.[2] Mesenteric lymph enters the sub-clavian vein through the thoracic duct, which directly flows into the heart and lungs. The lung is the first organ that contacts the mesenteric lymph.[45] Adams *et al*[46] demonstrated that T/HS-induced PMN activation is caused by factors carried in intestinal lymph fluids by enhancing PMN's response to inflammatory mediators. These results support PMN in mediating the conversion of physiologic shock to immune inflammation. Play a leading role in startup. Moreover, the activation of macrophages in the lung not only produces oxygen-free radicals, lysine, and LTs, but also directly affects pulmonary vascular endothelial cells. In addition, TNF, IL-1, IL-6, and IL-8 can increase the adhesion of PMN to vascular endothelial cells, produce and release TNF, oxygen-free radicals, and nitric oxide near the alveolar epithelium, and cause damage to the alveolar epithelium.

## Potential Interventional Targets

### Gut-lymph pathway blockage

A large number of studies have confirmed that GL ligation or drainage could effectively prevent intestinal toxic substances from entering systemic circulation in rats with IRI, thereby effectively reducing damage to distant organs, such as ALI. However, both interventions are anti-physiologic and require abdominal surgery, which makes them difficult to be performed when intra-abdominal hypertension occurs in acute pancreatitis. The GL pathway is the most direct damage associated molecular patterns pathway. We will use the GL pathway block as our key research direction in the future to overcome ARDS induced by GL after IRI.

### 5-Aminoimidazole-4-carboxyimide nucleoside

Idrovo *et al*[47] showed that 5-aminoimidazole-4-carboxyimide nucleoside (AICAR), an anti-inflammatory cell-penetrating compound, could alleviate organ injury and inflammation after IRI. AICAR treatment significantly reduced intestinal injury scores and water content, improved histologic integrity, alleviated tissue damage and release of pro-inflammatory cytokines, and decreased intestinal bacterial translocation. Attenuated neutrophil chemotaxis and infiltration into the lungs resulted in decreased levels of TNF-α and IL-6 in the lungs. Pulmonary iNOS and COX-2 protein levels decreased, and apoptosis of lung cells was markedly decreased after AICAR treatment.

### 3-(50-Hydroxymethyl-20-furan)-1-benzylamphetazole

As a specific inhibitor of HIF-1α, YC-1 inhibits HIF-1α expression in an inflammatory state. Intra-tracheal administration of YC-1 could substantially reduce neutrophil activation, pulmonary interstitial edema, and alveolar exudation in lung tissue, thereby reducing lung injury.

### Vagus nerve stimulation

CPSI-121 is a derivative of ornithine hydrazide, which can activate the parasympathetic nervous system through an unknown mechanism. Krzyzaniak *et al*[48] confirmed that CPSI-121 could prevent intestinal barrier dysfunction after skin burns through a vagus nerve-dependent mechanism. After injecting CPSI-121 intravenously into T/HS rats, Morishita *et al*[49] found that the discharge rate of the vagus nerve increased, and both intestinal and lung injuries were prevented. Therefore, CPSI-121 could be used as a vagal-stimulating drug to limit end organ dysfunction after injury as a potential therapeutic strategy for ALI or ARDS.

### Low-level laser therapy

Low-level laser therapy (LLLT) generally involves the application of low-power laser or light-emitting diode light in the range of 1 to 500 mW to promote tissue regeneration and reduce inflammation and pain.[50] In animal experiments, lasers have an inhibitory effect on pneumonia. Carvalho *et al*[51] showed that pulmonary vascular permeability, peribranchial edema, neutrophil accumulation, pro-inflammatory factor IL-8, and anti-inflammatory factor IL-10 increased dramatically after IRI in mice. After LLLT intervention, pulmonary vascular permeability and IL-8 were decreased, the level of anti-inflammatory factor IL-10 was increased, and peribranchial edema, neutrophil accumulation, and pulmonary inflammation were inhibited. LLLT has exhibited advantages for immune function in various studies.[52-54]

## Conclusions

In summary, GL plays a major role in the pathologic process of IRI-induced ARDS after intestinal IRI. Inflammatory mediators, cytokines, proteins, and lipids in GL and the TLR4 signaling pathway play a universal role in initiation of ARDS. Although recent studies have indicated

that the treatment of GL has some therapeutic effect, there is still a lack of definite treatment measures to block lung injury after intestinal IRI. Thus, more research is required to identify prevention and treatment methods for IRI-induced ARDS. Gut is considered to be the origin of systemic inflammation, and the engine of MODS, while GL plays a pivotal role in initiation of extrapulmonary ARDS. Gut lymph purification, as a new technology deriving from continuous blood purification therapy, will become the next potential interventional target.

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## Conflicts of interest

None.

## References

1. Deitch EA, Xu D, Kaise VL. Role of the gut in the development of injury- and shock induced SIRS and MODS: the gut-lymph hypothesis, a review. Front Biosci 2006;11:520–528. doi: 10.2741/1816.
2. Deitch EA. Role of the gut lymphatic system in multiple organ failure. Curr Opin Crit Care 2001;7:92–98. doi: 10.1097/00075198-200104000-00007.
3. Moore EE. Mesenteric lymph: the critical bridge between dysfunctional gut and multiple organ failure. Shock 1998;10:415–416. doi: 10.1097/00024382-199812000-00006.
4. Assimakopoulos SF, Triantos C, Thomopoulos K, Fligou F, Maroulis I, Marangos M, *et al*. Gut-origin sepsis in the critically ill patient: pathophysiology and treatment. Infection 2018;46:751–760. doi: 10.1007/s15010-018-11*78-5.
5. Moon HG, Cao Y, Yang J, Lee JH, Choi HS, Jin Y. Lung epithelial cell-derived extracellular vesicles activate macrophage-mediated inflammatory responses via ROCK1 pathway. Cell Death Dis 2015;6:e2016. doi: 10.1038/cddis.2015.282.
6. Wohlauer MV, Moore EE, Harr J, Eun J, Fragoso M, Banerjee A, *et al*. Cross-transfusion of postshock mesenteric lymph provokes acute lung injury. J Surg Res 2011;170:314–318. doi: 10.1016/j.jss.2011.03.045.
7. Zhang YM, Zhang SK, Cui NQ. Intravenous infusion of mesenteric lymph from severe intraperitoneal infection rats causes lung injury in healthy rats. World J Gastroenterol 2014;20:4771–4777. doi: 10.3748/wjg.v20.i16.4771.
8. Tong H, Chen R, Yin H, Shi X, Lu J, Zhang M, *et al*. Mesenteric lymph duct ligation alleviating lung injury in heatstroke. Shock 2016;46:696–703. doi: 10.1097/SHK.0000000000000660.
9. de Jong PR, Gonzalez-Navajas JM, Jansen NJ. The digestive tract as the origin of systemic inflammation. Crit Care 2016;20:279. doi: 10.1186/s13054-016-1458-3.
10. Druml W. Intestinal cross-talk: The gut as motor of multiple organ failure [in German]. Med Klin Intensivmed Notfmed 2018;113:470–477. doi: 10.1007/s00063-018-04*75-1.
11. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 2013;200:373–383. doi: 10.1083/jcb.201211138.
12. Subra C, Grand D, Laulagnier K, Stella A, Lambeau G, Paillasse M, *et al*. Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins. J Lipid Res 2010;51:2105–2120. doi: 10.1194/jlr.M003657.
13. Kojima M, Gimenes-Junior JA, Chan TW, Eliceiri BP, Baird A, Costantini TW, *et al*. Exosomes in postshock mesenteric lymph are key mediators of acute lung injury triggering the macrophage activation via Toll-like receptor 4. FASEB J 2018;32:97–110. doi: 10.1096/fj.201700488R.
14. Hu R, Chen ZF, Yan J, Li QF, Huang Y, Xu H, *et al*. Endoplasmic reticulum stress of neutrophils is required for ischemia/reperfusion-induced acute lung injury. J Immunol 2015;195:4802–4809. doi: 10.4049/jimmunol.1500073.
15. Kojima M, Gimenes-Junior JA, Langness S, Morishita K, Lavoie-Gagne O, Eliceiri B, *et al*. Exosomes, not protein or lipids, in mesenteric lymph activate inflammation: unlocking the mystery of post-shock multiple organ failure. J Trauma Acute Care Surg 2017;82:42–50. doi: 10.1097/TA.0000000000001296.
16. Bonjoch L, Casas V, Carrascal M, Closa D. Involvement of exosomes in lung inflammation associated with experimental acute pancreatitis. J Pathol 2016;240:235–245. doi: 10.1002/path.4771.
17. Sakamoto W, Masuno T, Yokota H, Takizawa T. Expression profiles and circulation dynamics of rat mesenteric lymph microRNAs. Mol Med Rep 2017;15:1989–1996. doi: 10.3892/mmr.2017.6259.
18. van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol 2017;17:407–420. doi: 10.1038/nri.2017.36.
19. Girardot T, Rimmele T, Venet F, Monneret G. Apoptosis-induced lymphopenia in sepsis and other severe injuries. Apoptosis 2017;22:295–305. doi: 10.1007/s10495-016-13*25-3.
20. Kojima M, Costantini TW, Eliceiri BP, Chan TW, Baird A, Coimbra R. Gut epithelial cell-derived exosomes trigger posttrauma immune dysfunction. J Trauma Acute Care Surg 2018;84:257–264. doi: 10.1097/TA.0000000000001748.
21. Park JH, Jeong SY, Choi AJ, Kim SJ. Lipopolysaccharide directly stimulates Th17 differentiation in vitro modulating phosphorylation of RelB and NF-kappaB1. Immunol Lett 2015;165:10–19. doi: 10.1016/j.imlet.2015.03.003.
22. Watson AJ, Hughes KR. TNF-alpha-induced intestinal epithelial cell shedding: implications for intestinal barrier function. Ann N Y Acad Sci 2012;1258:1–8. doi: 10.1111/j.1749-6632.2012.06523.x.
23. Zhang Y, Zhang S, Tsui N. Mesenteric lymph duct drainage attenuates acute lung injury in rats with severe intraperitoneal infection. Inflammation 2015;38:1239–1249. doi: 10.1007/s10753-014-00*91-z.
24. Sun HD, Liu YJ, Chen J, Chen MY, Ouyang B, Guan XD. The pivotal role of HIF-1alpha in lung inflammatory injury induced by septic mesenteric lymph. Biomed Pharmacother 2017;91:476–484. doi: 10.1016/j.biopha.2017.04.103.
25. Watts JA, Kline JA, Thornton LR, Grattan RM, Brar SS. Metabolic dysfunction and depletion of mitochondria in hearts of septic rats. J Mol Cell Cardiol 2004;36:141–150. doi: 10.1016/j.yjmcc.2003.10.015.
26. Fang JF, Shih LY, Yuan KC, Fang KY, Hwang TL, Hsieh SY. Proteomic analysis of post-hemorrhagic shock mesenteric lymph. Shock 2010;34:291–298. doi: 10.1097/SHK.0b013e3181ceef5e.
27. Ananthi S, Chitra T, Bini R, Prajna NV, Lalitha P, Dharmalingam K. Comparative analysis of the tear protein profile in mycotic keratitis patients. Mol Vis 2008;14:500–507. doi: 10.1038/onc.2008.11.
28. Thrower EC, Gorelick FS, Husain SZ. Molecular and cellular mechanisms of pancreatic injury. Curr Opin Gastroenterol 2010;26:484–489. doi: 10.1097/MOG.0b013e32833d119e.
29. Zhao Y, Zhang L, Han R, Si Y, Zhao Z. Intravenous injection of post-hemorrhagic shock mesenteric lymph induces multiple organ injury in rats. Exp Ther Med 2019;17:1449–1455. doi: 10.3892/etm.2018.7048.
30. Mittal A, Phillips AR, Middleditch M, Ruggiero K, Loveday B, Delahunt B, *et al*. The proteome of mesenteric lymph during acute pancreatitis and implications for treatment. JOP 2009;10:130–142.
31. Morishita K, Aiboshi J, Kobayashi T, Mikami S, Yokoyama Y, Ogawa K, *et al*. Lipidomics analysis of mesenteric lymph after trauma and hemorrhagic shock. J Trauma Acute Care Surg 2012;72:1541–1547. doi: 10.1097/TA.0b013e318256df15.
32. Gonzalez RJ, Moore EE, Ciesla DJ, Biffl WL, Offner PJ, Silliman CC. Phospholipase A2-derived neutral lipids from posthemorrhagic shock mesenteric lymph prime the neutrophil oxidative burst. Surgery 2001;130:198–203. doi: 10.1067/msy.2001.115824.
33. Gonzalez RJ, Moore EE, Ciesla DJ, Meng X, Biffl WL, Silliman CC. Post-hemorrhagic shock mesenteric lymph lipids prime neutrophils for enhanced cytotoxicity via phospholipase A2. Shock 2001;16:218–222. doi: 10.1097/00024382-200116030-00008.
34. Orrenius S, Gogvadze V, Zhivotovsky B. Calcium and mitochondria in the regulation of cell death. Biochem Biophys Res Commun 2015;460:72–81. doi: 10.1016/j.bbrc.2015.01.137.

35. Adams CA Jr, Xu DZ, Lu Q, Deitch EA. Factors larger than 100 kd in post-hemorrhagic shock mesenteric lymph are toxic for endothelial cells. Surgery 2001;129:351–363. doi: 10.1067/msy.2001.111698.
36. Deitch EA, Lu Q, Feketeova E, Hauser CJ, Xu DZ. Intestinal bacterial overgrowth induces the production of biologically active intestinal lymph. J Trauma 2004;56:105–110. doi: 10.1097/01.TA.0000054650.15837.1B.
37. Mollen KP, Anand RJ, Tsung A, Prince JM, Levy RM, Billiar TR. Emerging paradigm: toll-like receptor 4-sentinel for the detection of tissue damage. Shock 2006;26:430–437. doi: 10.1097/01.shk.0000228797.41044.08.
38. Janeway CA Jr, Medzhitov R. Innate immune recognition. Annu Rev Immunol 2002;20:197–216. doi: 10.1146/annurev.immunol.20.083001.084359.
39. Reino DC, Pisarenko V, Palange D, Doucet D, Bonitz RP, Lu Q, *et al*. Trauma hemorrhagic shock-induced lung injury involves a gut-lymph-induced TLR4 pathway in mice. PLoS One 2011;6:e14829. doi: 10.1371/journal.pone.0014829.
40. Nunns GR, Stringham JR, Gamboni F, Moore EE, Fragoso M, Stettler GR, *et al*. Trauma and hemorrhagic shock activate molecular association of 5-lipoxygenase and 5-lipoxygenase-activating protein in lung tissue. J Surg Res 2018;229:262–270. doi: 10.1016/j.jss.2018.03.023.
41. Monteiro APT, Soledade E, Pinheiro CS, Dellatorre-Teixeira L, Oliveira GP, Oliveira MG, *et al*. Pivotal role of 5-lipoxygenase pathway in lung injury after experimental sepsis. Am J Respir Cell Mol Biol 2014;50:87–95. doi: 10.1165/rcmb.2012-0525OC.
42. Steinhilber D, Hofmann B. Recent advances in the search for novel 5-lipoxygenase inhibitors. Basic Clin Pharmacol Toxicol 2014;114:70–77. doi: 10.1111/bcpt.12114.
43. Boudreau LH, Lassalle-Claux G, Cormier M, Blanchard S, Doucet MS, Surette ME, *et al*. New hydroxycinnamic acid esters as novel 5-lipoxygenase inhibitors that affect leukotriene biosynthesis. Mediators Inflamm 2017;2017:6904634. doi: 10.1155/2017/6904634.
44. Rossi A, Pergola C, Cuzzocrea S, Sautebin L. The role of 5-lipoxygenase and leukotrienes in shock and ischemia-reperfusion injury. Sci World J 2007;7:56–74. doi: 10.1100/tsw.2007.34.
45. Deitch EA. Gut lymph and lymphatics: a source of factors leading to organ injury and dysfunction. Ann N Y Acad Sci 2010;1207 (Suppl 1):E103–E111. doi: 10.1111/j.1749-6632.2010.05713.x.
46. Adams CA Jr, Hauser CJ, Adams JM, Fekete Z, Xu D-Z, Sambol JT, *et al*. Trauma-hemorrhage-induced neutrophil priming is prevented by mesenteric lymph duct ligation. Shock 2002;18:513–517. doi: 10.1097/00024382-200212000-00005.
47. Idrovo JP, Yang WL, Jacob A, Aziz M, Nicastro J, Coppa GF, *et al*. AICAR attenuates organ injury and inflammatory response after intestinal ischemia and reperfusion. Mol Med 2015;20:676–683. doi: 10.2119/molmed.2014.00134.
48. Krzyzaniak M, Ortiz-Pomales Y, Lopez N, Reys LG, Cheadle G, Wolf P, *et al*. CPSI-121 pharmacologically prevents intestinal barrier dysfunction after cutaneous burn through a vagus nerve-dependent mechanism. J Trauma Acute Care Surg 2012;72:355–361. doi: 10.1097/TA.0b013e31824484fe.
49. Morishita K, Costantini TW, Ueno A, Bansal V, Eliceiri B, Coimbra R. A pharmacologic approach to vagal nerve stimulation prevents mesenteric lymph toxicity after hemorrhagic shock. J Trauma Acute Care Surg 2015;78:52–58. doi: 10.1097/TA.0000000000000489.
50. Bjordal JM, Johnson MI, Iversen V, Aimbire F, Lopes Martins RA. Low-level laser therapy in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. Photomed Laser Surg 2006;24:158–168. doi: 10.1089/pho.2006.24.158.
51. Carvalho JL, Britto A, de Oliveira AP, Castro-Faria-Neto H, Albertini R, Anatriello E, *et al*. Beneficial effect of low-level laser therapy in acute lung injury after i-I/R is dependent on the secretion of IL-10 and independent of the TLR/MyD88 signaling. Lasers Med Sci 2017;32:305–315. doi: 10.1007/s10103-016-2115-4.
52. Chow RT, Heller GZ, Barnsley L. The effect of 300 mW, 830 nm laser on chronic neck pain: a double-blind, randomized, placebo-controlled study. Pain 2006;124:201–210. doi: 10.1016/j.pain.2006.05.018.
53. Chow RT, Johnson MI, Lopes-Martins RA, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. Lancet 2009;374:1897–1908. doi: 10.1016/S0140-6736(09)61522-1.
54. Xavier M, David DR, de Souza RA, Arrieiro AN, Miranda H, Santana ET, *et al*. Anti-inflammatory effects of low-level light emitting diode therapy on Achilles tendinitis in rats. Lasers Surg Med 2010;42:553–558. doi: 10.1002/lsm.20896.

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