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Review

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Liver-lung axes in alcohol-related liver disease

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Alcohol-related liver disease (ALD) and alcohol-related susceptibility to acute lung injury are the leading causes of morbidity and mortality due to chronic alcohol abuse. Most commonly, alcohol-induced injury to both organs are evaluated independently, although they share many parallel mechanisms of injury. Moreover, recent studies indicate that there is a potential liver lung axis that may contribute to organ pathology. This mini-review explores established and potential mechanisms of organ-organ crosstalk in ALD and alcohol-related lung injury. **(Clin Mol Hepatol 2020;26:670-676)**

Keywords: Liver diseases; Alcoholic Liver disease; Acute lung injury; Respiratory distress syndrome, Adult

ALCOHOL-RELATED LIVER AND LUNG DISEASE

The risk of alcohol-related liver disease (ALD) increases in a dose- and time-dependent manner with consumption of alcohol. Progression of ALD is well-characterized and is actually a spectrum of liver diseases, which ranges initially from simple steatosis, to inflammation and necrosis (steatohepatitis), to fibrosis and cirrhosis. The most effective therapy for ALD is orthotopic liver transplantation.[1] However, the usefulness of liver transplantation is limited, owing to a donor organ shortage, as well as by ethical issues concerning the treatment of individuals that have inveterate alcohol dependence. In the absence of a "cure" for ALD, the major clinical focus is to treat the sequelae of a failing liver (e.g., ascites, portal hypertension, and hepatorenal syndrome).[1] Although the successful treatment of these secondary effects prolongs the life of ALD patients, this therapy is only palliative. Furthermore, since underlying cirrhosis greatly increases the risk of developing hepatocellular carcinoma (HCC),[2] success in maintaining 'stable cirrhotics' may translate into an increase in the incidence of HCC. Indeed, HCC incidence is increasing in the USA and in Europe.[3]

Alcohol abuse is known to increase the risk for lung injury. In contrast to the liver, most studies do not support a direct pathogenic effect of ethanol on the lungs. Instead, it is hypothesized that alcohol consumption enhances the risks of injury caused by other 'hits.' For example, alcohol increases the risk for the development of lung infection.[4,5] This increased risk is mediated by physical factors that increase the risk of inoculation, including aspiration of gastric contents and/or microbes from the upper respiratory track (i.e., oropharyngeal flora), as well as decreased mu-

Abbreviations:

ALD, alcohol-related liver disease; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; AUD, alcohol use disorder; BALF, bronchoalveolar lavage lavage fluid; CNS, central nervous system; DAMPs, damage-associated molecular patterns; EVs, extracellular vesicles; HCC, hepatocellular carcinoma; HMGB1, high motility group box-1; LPS, lipopolysaccharide; MTDs, mitochondrial damage-associated molecular patterns; MV, microvesicles; PAMPs, pathogen-associated molecular patterns; SIRS, systemic inflammatory response syndrome; TLR, toll-like receptor; TNFR1, tumor necrosis factor-α receptor; TNFα, tumor necrosis factor-α

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cous-facilitated clearance of bacterial pathogens from the upper airway.[6] Moreover, alcohol ingestion disrupts the normal beating motion of the cilia that is important in the clearance mechanisms aimed to help remove pathogens from the airways.[7] These abnormalities, together with documented impairments in pulmonary host defenses, likely explain the increased infection rate observed in individuals that abuse alcohol.[8] Alcohol consumption is also associated with worse outcomes after pulmonary infection. Specifically, individuals diagnosed with an alcohol use disorder (AUD) are more susceptible to the development of the acute respiratory distress syndrome (ARDS) in response to a pulmonary or systemic infection.[9] ARDS is the most severe form of acute lung injury (ALI) with an incidence close to 200,000 cases per year in the USA and with a mortality rate of around 40%.[10] ARDS occurs 3.7 times more often in people who meet the diagnostic criteria for AUD. Lastly, it was recently shown that alcohol exposure to rodents using the acute-on-chronic binge model does cause subtle functional changes to the lung,[11] bringing into question the assumption that alcohol abuse does not directly damage the lungs.

LIVER-LUNG INTERACTIONS IN ALD

End-stage ALD is well-recognized as a systemic disorder. The idea of the liver-lung axis in the setting of chronic alcohol exposure is based on clinical data demonstrating that patients with a diagnosed AUD have increased incidence of and mortality from ARDS.[9,12,13] Furthermore, in ARDS patients with hepatic failure, mortality increases to almost 100%.[9] The finding that most individuals with an AUD have at least subclinical ALD further supports coexistence of liver disease in alcohol-abusing patients with ARDS.[14] Pulmonary injury induced by lipopolysaccharide (LPS) can be altered by mediators released from the liver (e.g., tumor necrosis factor-α [TNFα]). Indeed, it was demonstrated in rats that extrathoracic LPS-induced lung damage required perfusion with the liver.[15]

POTENTIAL MECHANISMS OF INTER-ORGAN COMMUNICATION BETWEEN THE LIVER AND THE LUNGS

Although end organ diseases are often studied in isolation. Cross-talk between organs is not uncommon in the maintenance of homeostasis, as well as in mounting a coordinated response to dyshomeostasis. As mentioned above, the existence of a liver-lung axis, at least unidirectional, has been established experimentally. Below, potential mechanisms that mediate organ-organ crosstalk are discussed (Fig. 1, 2).

Cytokines and chemokines

In addition to TNFα (see above), a wide variety of hepatic cell types both produce and respond to cytokines, including inflammatory cells, such as monocytes, macrophages, and neutrophils, as well as parenchymal cells. Cytokines can be primarily classified into two groups: "proinflammatory" T helper 1 and "anti-inflammatory" T helper 2. Homeostasis mediated by these cytokines ensures appropriate immune and inflammatory responses, with minimal normal tissue damage. These mediators also facilitate a coordinated response to insults and injuries that stem well beyond the primary target organ.

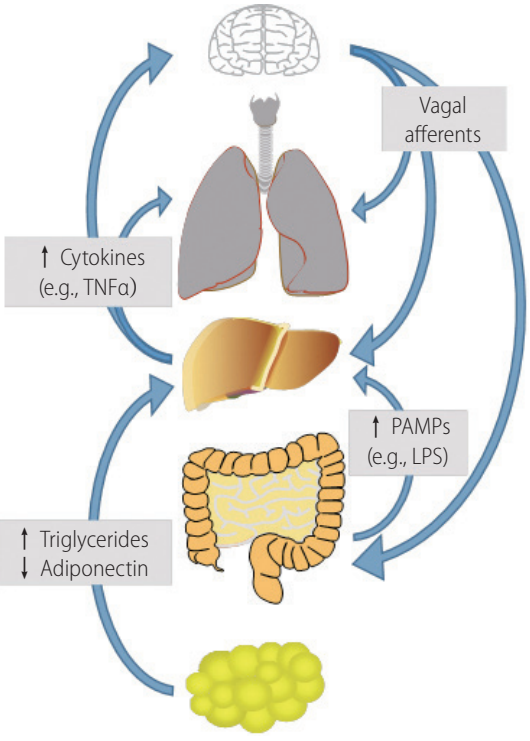

Figure 1. The liver at the center of organ-organ axes. There are several physiologic and pathophysiologic mechanisms by which inter-organ communication can be mediated, such as via nutrients, hormones and hepatokines, afferent and efferent innervation, release of extracellular vesicles, cytokines and PAMPs and DAMPs. Modified from Poole et al.[57] TNFα, tumor necrosis factor-α; PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharide; DAMPs, damage-associated molecular patterns.

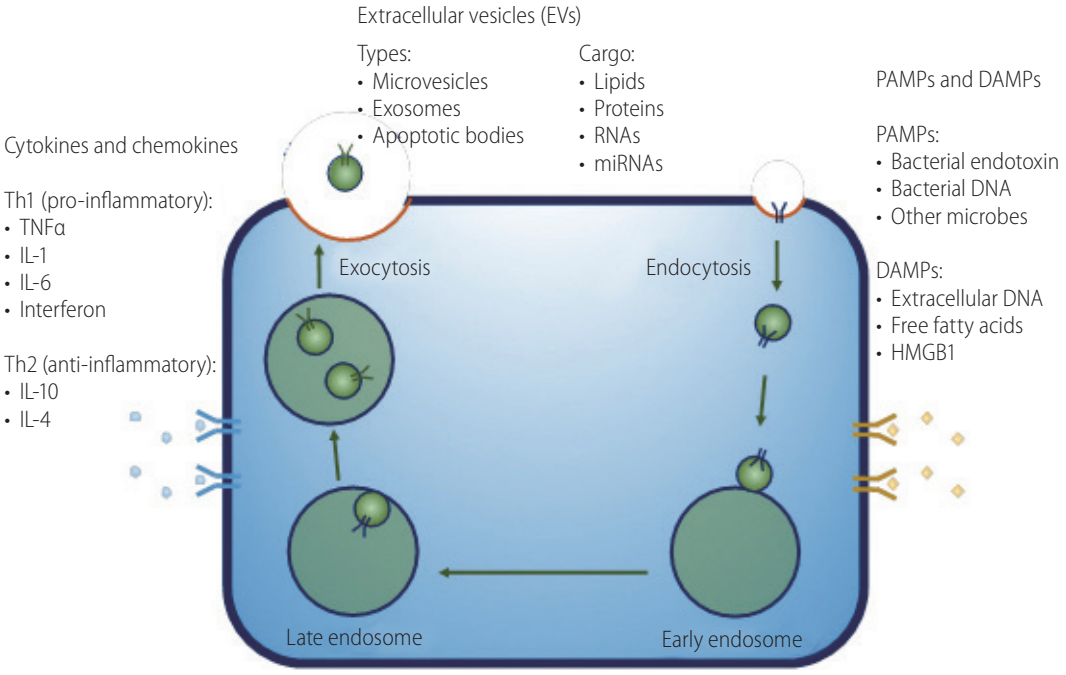

Figure 2. Specific mechanisms of communication in response to stress. Injured cells can release several signals to mediate communication between them and distal tissues. The profiles of both Th1 (i.e., proinflammatory) and Th2 (i.e., anti-inflammatory or profibrotic) cytokines is altered during hepatic injury. Additionally, the liver can respond to PAMPs (e.g., bacterial LPS) from other organs, such as the gastrointestinal tract, and/or respond or release DAMPs (e.g., HMGB1) that serve as 'danger signals' to pattern recognition receptors in other organs. Modified from Poole et al.[57] Th1, T helper 1; TNFα, tumor necrosis factor-α; IL, interleukin; Th2, T helper 2; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; HMGB1, high motility group box-1; LPS, lipopolysaccharide.

Dysregulated cytokine production has been implicated in the development and progression of ALD.[16] Kupffer cells, the resident hepatic macrophages, play a key role in monitoring, clearing and mediating responses to gut-derived toxins, such as bacterial LPS. Alcohol consumption has long been known to increase gut permeability, leading to increased LPS in the portal circulation.[17,18] LPS and other bacterial toxins interact with Kupffer cells via toll-like receptors (TLRs) including TLR4. Activation of the TLR4 signaling pathway leads to increased transcription of several pro-inflammatory cytokines. It is therefore unsurprising that patients with ALD have increased levels of several circulating cytokines, including TNFα.[19] Other cytokines also likely play key roles, but TNFα is likely the most well studied.

TNFα is widely recognized as having a potential role in organ-organ communication in alcohol-induced organ injury. TNFα is suspected to be a common mechanism of alcohol-induced pathology not only in the liver,[20,21] but also in other organs, such as the lungs and the brain. In the lung, chronic alcohol pre-exposure enhanced endotoxemia-induced ALI, which was prevented by blocking systemic TNFα with etanercept.[22] In the brain, alcohol exposure enhances the increase in TNFα levels in caused by LPS, which is also prevented by deleting the canonical TNFα receptor (TNFR1).[23] The source of this systemic TNFα ultimately remains unknown, although liver is clearly a likely key player.

TNFα has also been potentially implicated in alcohol-enhanced ALI. Lung damage was more severe in mice that were exposed to chronic alcohol subsequently injected with intraperitoneal LPS.[22] The differential effects on cytokine expression in systemic circulation and locally in the lung (i.e., bronchoalveolar lavage fluid [BALF]) were examined. Animals pre-exposed to ethanol diet had significantly elevated levels of plasma TNFα after LPS injection compared to animals fed a control diet. In the BALF, however, ethanol pre-exposed animals had elevated levels of the TNFα-responsive chemokines, macrophage inflammatory protein-2 and KC. This elevated chemokine expression also correlated with increased pulmonary neutrophil recruitment. Interestingly, blocking systemic TNFα using a TNFα-inhibiting antibody, etanercept, significantly attenuated the alcohol-enhanced pulmonary chemokine expression, and ultimately, alcohol-enhanced lung injury and inflammation after LPS (Fig. 3). While the liver is not the sole source

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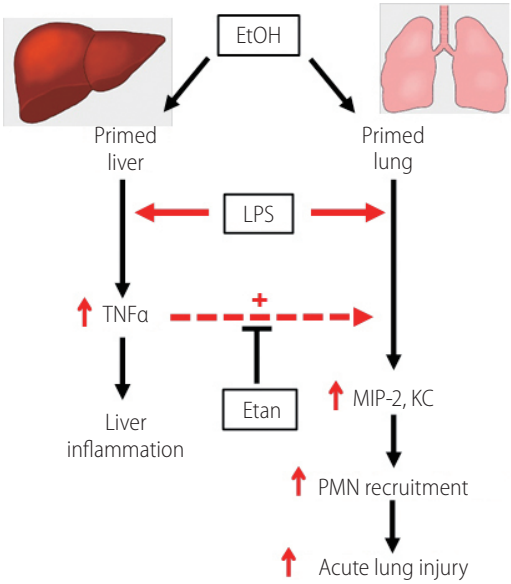

Figure 3. Potential mechanism of crosstalk between the liver and the lungs in alcohol-induced organ injury. Ethanol preexposure primes both the liver and lung to enhanced injury and inflammation caused by LPS. In the work presented here, ethanol preexposure significantly enhanced LPS induced TNFα mRNA expression in the liver but not the lung. Interestingly, ethanol preexposure enhanced LPS induced increases in the TNFα responsive genes MIL-2 and KC in the lung. Modified from Poole et al.[57] LPS, lipopolysaccharide; TNFα, tumor necrosis factor-α; MIP-2, macrophage inflammatory protein-2.

of systemic TNFα in this experimental setting, other studies have demonstrated that ablation of Kupffer cells before LPS injection decreased systemic TNFα levels by almost 90%, indicating that these cells are in fact a predominate source of plasma TNFα in experimental endotoxemia.[24]

Extracellular vesicles (EVs)

EVs, a term that includes microvesicles (MV), exosomes, and apoptotic bodies, are an emerging mechanism of organ-organ communication in many diseases, including ALD.[25] EVs can carry a diverse cargo, including lipids, proteins, RNAs, and miRNAs and are attractive therapeutic targets, due to both their potential mechanistic role in disease progression, as well as for being potential surrogate biomarkers. Over 10 years ago, it was proposed that MVs are (at least) surrogate biomarkers of advanced ALD.[26] Furthermore, alcohol exposure causes a release of hepatic EVs that contain a distinct miRNA profile.[27] It was also found that patients with ALD had elevated circulating EVs, and that these EVs also may carry a unique miRNA "barcode".[27] EVs may not only serve as surrogate biomarkers of ALD, but they may also play a mechanistic role in disease progression. In addition to mediating intra-organ communication between cells, EVs can also mediate inter-organ communication.[28] Indeed, it is now hypothesized that EVs contribute to the development and severity of ARDS.[29] Furthermore, remote preconditioning, such as the cardioprotective effect of hindlimb ischemia-reperfusion injury, is also hypothesized to be mediated by EVs (e.g.,[30,31]). The potential role of circulating EVs in mediating liver-lung communication in the context of ALD are not currently understood and would be an interesting target for further investigation.

Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs)

As mentioned above, the gut-derived toxin, LPS, has long been identified as playing a potential role in ALD. The primary receptor for LPS (TLR9) belongs to a family of pattern recognition receptors. Ligands for these receptors are grouped together as molecular "danger signals," and include PAMPs and DAMPs. PAMPs include products of microbial (e.g., bacterial endotoxin or bacterial DNA), viruses, fungi, and parasites. DAMPs, on the other hand, are endogenous danger signals released from dead or dying cells; examples include extracellular DNA or RNA, free fatty acids, and high motility group box-1 (HMGB1), among others.[32] Signals derived by PAMPs/DAMPs can span multiple organs, and are thought to contribute to systemic inflammatory responses (e.g., systemic inflammatory response syndrome [SIRS]).[33] The innate immune system surveils qualitative and quantitative changes in the spectrum of PAMPs and DAMPs as a means to mount rapid and coordinated responses to any perceived threat that is driving those changes. Although this response is important for normal immune/inflammatory function, dysregulation of this response can lead to inappropriate inflammation and tissue damage. Ethanol consumption appears to broadly dysregulate the response of these receptors and enhances expression of several TLRs, as well as their responses to stimuli.[34]

The role of PAMPs in organ-organ interaction during is perhaps best understood in the context of the gut-liver axis. As early as 1893, Pavlov observed that low levels of intestinally-derived "toxins" are normally present in the portal blood and are cleared by the liver.[35] More than half a century later, several studies suggested that experimental fibrosis caused by choline deficiency was dependent on products derived from intestinal bacteria. For example, Rutenburg and colleagues showed that non-absorbable

antibiotics protected against diet-induced cirrhosis in rats.[36] The causal role of bacterial PAMPs in liver injury was not confined to models of diet-induced cirrhosis, but was further established in studies using acute hepatotoxins such as carbon tetrachloride.[37,38] High systemic levels of the PAMP, LPS, are found in both acute and chronic liver diseases.[39,40] Aside from the liver, GI-derived PAMPs during alcohol exposure can potentially affect other organs, including the lungs.

One of the best-understood DAMPs, or "alarmins," is HMGB1. HMGB1 is a constitutively-expressed nuclear protein that is released from necrotic cells. A recent study demonstrated that HMGB1 translocation from the nucleus to the cytosol correlated with disease severity in liver biopsies from ALD patients.[41] Additionally, knocking out HMGB1 in hepatocytes protects mice against alcohol-induced liver injury. HMGB1 signaling has also been shown to be elevated in alcohol-induced injury in the brain[42,43] and pancreas.[44] However, the role of HMGB1 and other DAMPs in organ-organ crosstalk in the setting of ALD has been largely unexplored.

Although less characterized in the setting of ALD, the concept that circulating DAMPs may be involved in organ-organ crosstalk in other disease states is clearly established. For example, trauma elevates circulating mitochondrial DAMPs (MTDs), such as mitochondrial DNA, and is hypothesized to contribute to SIRS under that condition.[45] Human neutrophils exposed to MTDs have increased expression of the chemokine interleukin-8. In the same study, it was demonstrated that MTDs derived from rat liver cause lung injury in recipient rats; this injury was characterized by vascular leak, pulmonary edema, neutrophil infiltration, and accumulation of inflammatory cytokines in the alveolar space. As mentioned above, SIRS has been established as a significant risk factor for mortality from alcohol-related hepatitis.[46] Therefore, it is not unlikely that circulating DAMPs may be involved.

Other potential mechanisms

There are also less direct means by which the liver can influence other organs via axes (Fig. 2). For example, the liver plays an absolutely critical role in supplying fuel to other organs.[47] Therefore, alterations in the flux of carbohydrates and lipids through the liver can indirectly impact distal organs, as their energy sensing mechanisms respond to these changes. Nutrient levels in the liver also directly mediate responsive changes in the central nervous system (CNS) via glucose sensing afferent neurons in the liver and other organs; these sensors are hypothesized to mediate rapid central responses to short-term energy status alterations.

There is intricate crosstalk between these metabolic systems that is controlled by a complex interplay of nuclear receptors, intracellular signaling pathways and transcription factors. Hormones and other endocrine mediators play a key role in regulating these responses. The liver is well known to respond to several endocrine hormones, including insulin, glucagon, thyroid hormones and cortisol. The liver also produce several hormones that can mediate several extrahepatic effects, such insulin-like growth factor, angiotensinogen and thrombopoietin. Furthermore, it has become increasingly clear that the liver produces several endocrine-like "hepatokines" that play key roles in regulating extrahepatic responses (e.g., FGF21).[48,49] The net effect of these interactions is to generate an organ that rapidly responds to endocrine signals, as well as rapidly produces endocrine signals in response to stimuli.

The liver also has several afferent neurons that mediate and coordinate its responses with extrahepatic targets, especially the CNS. This circuitry plays a key role in metabolic homeostasis, stress responses, and inflammation.[50-52] There is evidence suggesting that ethanol and the sympathetic nervous system interact with and partially mimic each other. For example, acute alcohol intoxication increases plasma levels of adrenaline and noradrenaline.[53] Furthermore, ethanol causes a hypermetabolic state in liver that is abolished by adrenalectomy, hepatic vagotomy or by adrenoceptor blockade.[54,55] Repeated administration of ethanol also increases plasma catecholamines and gene expression of enzymes for catecholamine synthesis in the adrenal medulla.[56] Although it is understood that such networks can mediate coordination between organs in response to stress or dyshomeostasis in general, the specific impact of these interactions in the context of organ-organ crosstalk in ALD is incompletely understood.

SUMMARY AND CONCLUSIONS

In conclusion, while multiple organ failure is a hallmark of decompensated, end-stage alcoholic liver disease, there is an increasing appreciation for communication between organs during earlier stages of the disease. Organs can communicate with one another via several potential mechanisms, including EVs, cytokines and chemokines, PAMPs and DAMPs, and the nervous system. The liver is proposed to communicate with other organs, such as the gut, brain, lung, and adipose tissue using these mechanisms, as well as others. Understanding the mechanisms by which organs communicate during the inflammatory injury phase

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of ALD may allow for the development of targeted therapeutics to protect one or all of these systems from alcohol-mediated toxicities.

Conflicts of Interest

The authors have no conflicts to disclose.

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