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Liponucleotides: Promises and Unknowns as Novel Therapeutics for Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is the clinical manifestation of a diffuse lung injury that can result from a multitude of etiologies. Despite significant advances in management of patients with ARDS, morbidity and mortality from ARDS remain high (1). Respiratory infections, including those caused by emerging viruses, represent a major clinical risk factor for ARDS. Our continuing struggle against the coronavirus disease (COVID-19) pandemic highlights the societal burden presented by this syndrome and the critical need for novel strategies in the prevention and management of ARDS.

The biology of type II alveolar epithelial cells (AEC II) has gained significant interest because of their role in a number of pathways associated with ARDS pathophysiology. Direct infection and local inflammation can lead to cellular dysfunction in AEC II, resulting in impaired alveolar fluid clearance, increased alveolar permeability, and impaired regeneration of injured epithelium (2). AEC II are also the predominant sources of surfactant components, including proteins and phospholipids. In ARDS, disturbances in the composition of surfactants and their biophysical properties exacerbate derangements in pulmonary physiology (3). Moreover, surfactant depletion by serial saline lavage is a well-established experimental model of ARDS (reviewed in Reference 4). Phosphatidylcholine (PC) and phosphatidylglycerol are among the phospholipids that are significantly decreased in pulmonary surfactants during ARDS (3). Indeed, in a mouse model of ARDS by H1N1 influenza (IAV) infection, AEC II exhibit defective PC biosynthesis (5).

In this issue of the *Journal*, Rosas and colleagues (pp. 677–686) tested the hypothesis that supplementation with parenteral liponucleotides (LPNs) in IAV-infected mice would attenuate acute lung injury by reversing defective phospholipid synthesis in AEC II (6). The specific LPN tested was cytidine-5′-diphosphocholine (CDP-Cho), an intermediate in the biosynthesis of PC from choline, with or without coadministration of another LPN, cytidine diphosphate-diacylglycerol (CDP-DAG). CDP-Cho has been shown to exhibit neuroprotective properties in preclinical models of acute and chronic brain ischemia; however, its benefits in clinical trials have not been demonstrated to date (7, 8). CDP-Cho is also used in the management of glaucoma to slow vision decline and in select cases of cognitive impairment/memory loss in adults. It is believed that CDP-Cho is quickly catabolized into cytidine and choline upon injection, with a significant portion of newly generated choline absorbed by the liver, thus minimizing the cholinergic activity of CDP-Cho. Indeed, its toxicity in animals is minimal (LD_{50} 4,600 mg/kg in mice by an intravenous route and 8 g/kg in mice by the enteric route) (7). CDP-Cho is sold as dietary supplements (citicoline) in the United States and prescribed in other parts of the world. The commercial availability and favorable toxicity profile of CDP-Cho make it an attractive pharmacologic candidate for adoption in the treatment of ARDS.

Rosas and colleagues report finding significant improvements in physiologic parameters in IAV-infected mice supplemented with parenteral LPN. LPNs reduced hypoxemia, pulmonary edema, and histological measures of lung damage 6 days after virus inoculation (days post inoculation [dpi]). The effect was observed when LPNs were delivered as a postexposure prophylaxis (daily for 5 d) or as a single dose at 5 dpi. Furthermore, measures of alveolar inflammation, including BAL fluid macrophage and neutrophil counts and BAL chemokine and cytokine concentrations, were all markedly attenuated or altered with LPN administration. The coadministration of CDP-Cho and CDP-DAG enhanced the beneficial effect of CDP-Cho. Interestingly, LPNs did not restore normal pulmonary surfactant composition; specifically, although PC concentrations were restored as predicted based on lipidomic analysis, decreases in major surfactant proteins were not reversed.

The benefit from LPN supplementation in preventing ARDS in this preclinical model was striking; however, the report leaves a number of important questions unanswered. Given the modest effect on surfactant composition and the improvements in the measure of inflammation, the most likely explanation for the beneficial effects observed is immune modulation associated with LPNs. Alternatively, LPNs may affect alveolar epithelial regeneration, although this was not assessed in their report. The mechanism by which LPNs suppress alveolar inflammation in IAV infection remains unclear. As LPNs were administered systemically, the effect of LPNs on systemic inflammation will also be critical to understand. Could the beneficial effects observed be tied to the cholinergic antiinflammatory pathway? Attenuation of acute lung injury was seen in CDP-Cho alone or in combination with CDP-DAG but not CDP-DAG alone. CDP-Cho and its catabolite, choline, may have agonist activity on cholinergic receptors on relevant effector cells. Cholinergic stimulation of immune effector cells (for example, signaling *via* the α7 subunit of the nicotinic acetylcholine receptor on macrophages) suppresses cytokine production and has been shown to reduce capillary leak in animal models of sepsis (9–11).

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It is curious that administration of choline and cytidine triphosphate in the IAV model had no beneficial effect, whereas CDP-Cho resulted in improvement even though CDP-Cho is believed to be rapidly catabolized to choline and cytidine in the vascular compartment before uptake by target cells. Better characterization of the pharmacokinetics of CDP-Cho *in vivo* will help shed light on this conundrum. In addition, daily coadministration of CDP-Cho and CDP-DAG after IAV inoculation resulted in significantly elevated viral titers from lung homogenates compared with saline treatment or CDP-Cho alone at 2 and 4 dpi. What the enhanced viral titers in early IAV infection means in clinical practice will have to be carefully considered. Finally, the report is focused on the IAV model of ARDS. Whether CDP-Cho has similar benefits in other infectious and noninfectious models of ARDS has yet to be determined.

The deadly COVID-19 pandemic created an urgent need to adapt established therapeutics in other conditions for use in the management of COVID-19. Antivirals, steroids, biologics, and other immunosuppressives have been tried, but few clinically proven therapeutics have been identified. While the world awaits the broad implementation of vaccination programs, novel therapies that prevent the development of ARDS will continue to be needed. Although this report only establishes a proof of concept for the use of LPNs to prevent ARDS after IAV exposure, the striking results position CDP-Cho as a tantalizing candidate for a clinical trial in the prevention, and perhaps treatment, of virus-induced ARDS, with potential application beyond the limits of the current pandemic. ■

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