Molecular Therapy
Nucleic Acids
Commentary

Inhaled aptamer therapy: A hopeful therapy for lung disease

M. Elena Martin[1]

https://doi.org/10.1016/j.omtn.2023.05.009

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), clinical syndromes with high morbidity and mortality, are characterized by progressive pulmonary deterioration usually triggered by inflammatory processes. Importantly, ALI/ARDS are major causes of COVID-19 mortality. Unfortunately, no pharmacological treatments have been found to reduce or interrupt the progression of this disease, so new therapies need to be developed to improve clinical outcomes. In a recent article published in *Molecular Therapy - Nucleic Acids*, Lei et al.[1] reported an anti-histone RNA aptamer that protects mice from ALI.

Aptamers are single-strand nucleic acids (single-stranded DNA [ssDNA] or ssRNA) that bind their targets with high affinity by folding into a three-dimensional conformation. They are isolated from oligonucleotide libraries by an *in vitro* method named SELEX (exponential enrichment in the presence of the ligand). Aptamers have high potential as therapeutic agents mainly due their important advantages including high stability, low immunogenicity and toxicity, lack of batch-to-batch variability, small size, short generation time, and quick modification.

Various insults, such as trauma, bacterial and viral infections, inhalation of toxic substances, or aspiration of gastric contents, cause endothelial and/or pulmonary epithelial cell death, leading to the massive release of histones into extracellular spaces. Here, extracellular histones act as damage-associated molecular pattern (DAMP) molecules that generate an inflammatory response. Available anti-histone therapies have failed in clinical trials due to off-target effects. Due to the aforementioned characteristics, aptamers are excellent therapeutic candidates with reduced toxicity. Thus, with the aim of finding a specific anti-histone therapy, in a previous study, the authors selected and characterized RNA aptamers against histones.[2] One of these aptamers, HBA7 (previously named KU7) has been used by Lei et al.[1] to demonstrate its efficacy in two animal models, neutralizing histones injury when co-administered and in a model of ALI from inhaling wood smoke particulate, where HBA7 alleviates lung injury. One of the major contributions of this study is the route of administration. There are very few studies using administration of aptamers by inhalation, which allows, as demonstrated in this study, targeted delivery to the lung and greater retention of the aptamer at the site of injury. Although, as they themselves state, the efficacy of the aptamer was only tested with oropharyngeal aspiration, it is to be expected that with aerosolization administration, a more clinically relevant route of drug administration, the efficacy of the aptamer would be even greater.

Throughout the initial response to injury during ARDS, known as the exudative phase of ARDS, resident alveolar macrophages are activated through pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides (LPSs; due to the presence of bacterial components) or DAMPs (due to tissue injury), that activate Toll-like receptors (TLRs), resulting in the release of potent proinflammatory mediators and chemokines.[3] As stated above, extracellular histones also act as DAMPs, activating TLRs. Lai et al.[4] obtained a DNA aptamer against the tumor necrosis factor α (TNF-α) that attenuated the severity of LPS-induced ALI in mice. The antagonist activity of a DNA aptamer against TLR4, ApTOLL, has been clearly demonstrated in several diseases,[5,6] and its efficacy for the treatment of COVID-19 is going into clinical trial phase 1 (ClinicalTrials.gov: NCT05293236). Excessive neutrophilic inflammation is also a major contributor to lung injury in ARDS. Activated neutrophils contribute to injury by releasing inflammatory mediators and proteinases such as neutrophil elastase. As early as 1997, Bless et al.[7] selected an aptamer against elastase, NX21909, capable of inhibiting lung injury and neutrophil influx in an animal model of acute inflammatory lung disease. This study was the first to demonstrate the efficacy of an aptamer in an animal model. Angiopoietin-2 (ANGPT2), which is produced by activated endothelial cells, competes with ANGPT1 for binding to receptor tyrosine kinase TIE2, destabilizing vascular junction formation. Elevated plasma levels of ANGPT2 demonstrated that an ANGPT2-neutralizing aptamer partially attenuated alveolar cell infiltration while exacerbating vascular leakage in ANGPT2-overexpressing mice exposed to LPS. All these aptamers have been administered systemically, which may produce undesirable effects. Their administration by inhalation, which allows direct delivery to the target site of action, thus minimizing systemic exposure, is a hopeful therapy for lung injury.

DECLARATION OF INTERESTS

The authors declare no competing interests

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[1]Grupo de Aptámeros, Departamento de Bioquímica-Investigación, IRYCIS-Hospital Universitario Ramón y Cajal, Carretera de Colmenar Viejo Km. 9.100, 28034 Madrid, Spain

Correspondence: M.E. Martin, Grupo de Aptámeros, Departamento de Bioquímica-Investigación, IRYCIS-Hospital Universitario Ramón y Cajal, Carretera de Colmenar Viejo Km. 9.100, 28034 Madrid, Spain.
E-mail: m.elena.martin@hrc.es

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