RESEARCH ARTICLE | VACCINES

Polymer nanoparticles deliver mRNA to the lung for mucosal vaccination

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Editor's summary

The ability to efficiently deliver mRNA to the lung would have applications for vaccine development, gene therapy, and more. Here, Suberi *et al*. showed that such mRNA delivery can be accomplished by encapsulating mRNAs of interest within optimized poly(amine-*co*-ester) polyplexes. Polyplex-delivered mRNAs were efficiently translated into protein in the lungs of mice with limited evidence of toxicity. This platform was successfully applied as an intranasal SARS-CoV-2 vaccine, eliciting robust immune responses that conferred protection against subsequent viral challenge. These results highlight the potential of this delivery system for vaccine applications and beyond. —Courtney Malo

Abstract

An inhalable platform for messenger RNA (mRNA) therapeutics would enable minimally invasive and lung-targeted delivery for a host of pulmonary diseases. Development of lung-targeted mRNA therapeutics has been limited by poor transfection efficiency and risk of vehicle-induced pathology. Here, we report an inhalable polymer-based vehicle for delivery of therapeutic mRNAs to the lung. We optimized biodegradable poly(amine-*co*-ester) (PACE) polyplexes for mRNA delivery using end-group modifications and polyethylene glycol. These polyplexes achieved high transfection of mRNA throughout the lung, particularly in epithelial and antigen-presenting cells. We applied this technology to develop a mucosal vaccine for severe acute respiratory syndrome coronavirus 2 and found that intranasal vaccination with spike protein–encoding mRNA polyplexes induced potent cellular and humoral adaptive immunity and protected susceptible mice from lethal viral challenge. Together, these results demonstrate the translational potential of PACE polyplexes for therapeutic delivery of mRNA to the lungs.

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