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Synthetic messenger RNA-based therapeutic strategy for treatment of alpha-1-antitrypsin deficiency

Tatjana Michel
University Hospital Tuebingen, Germany

Alpha-1-antitrypsin deficiency (AATD) is one of the most common monogenic diseases worldwide. A mutation in alpha-1-antitrypsin (AAT) protein causes the protein to misfold and accumulate in hepatocytes instead of being secreted into the blood stream. This deprives the lungs from AAT protein, which plays a protective role against neutrophil elastase proteolytic activity. Both the accumulation in the hepatocytes and absence from lung lead to permanent irreversible tissue damage in the form of cirrhosis and pulmonary emphysema. Currently, AATD patients receive an AAT protein replacement therapy but it comes at undesirable side effects and high costs. In addition, gene therapy approaches are tested in clinical trials but with serious immunogenic, mutagenic and carcinogenic consequences. Therefore, a novel therapeutic strategy based on messenger RNA (mRNA) was established, which can be used to achieve a targeted and controllable induction of AAT expression in target cells. First, an AAT-encoding mRNA was generated and tested *in vitro*. Here, it could be shown that the AAT mRNA is translated into a bioactive protein capable of efficiently inhibiting neutrophil elastase. Furthermore, the encapsulation of mRNA into nanoliposomes was optimized for later *in vivo* use. These nanoliposomes were prepared from a cationic and a neutral lipid and analyzed for mRNA encapsulation capacity, transfection efficiency, immunogenicity, biocompatibility and hemocompatibility. Compared to Lipofectamine 2000, a significantly higher translation of the AAT protein was detected during the *in vitro* experiments using prepared nanoliposomes. In addition, after incubation with the liposomes, cells showed no adverse effects on viability and no upregulation of innate immune defense genes. Furthermore, no negative effects could be observed in the form of complement system, leukocyte and platelet activation. This work lays the foundation for comprehensive mRNA-based therapeutic strategy for AATD patients and could serve as an alternative to protein replacement therapy and gene therapy in clinical use.

Recent Publications

1. T Michel, D Luft, M-K Abraham, S Reinhardt, M L. Salinas Medina, J Kurz, M Schaller, M Avci-Adali, C Schlensak, K Peter, H P Wendel, X Wang, S Krajewski (2017) Nanoliposomes meet mRNA: Efficient delivery of modified mRNA using hemocompatible and stable vectors for therapeutic applications, Molecular Therapy – Nucleic Acids
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5. Avci-Adali M, Hann L, Michel T, Steinle H, Stoppelkamp S, Stang K, Narita M, Schlensak C, Wendel HP (2015) *In vitro* test system for evaluation of immune activation potential of new single-stranded DNA-based therapeutics, Drug Testing and Analysis
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Biography

Tatjana Michel works with synthetic modified mRNA treatment strategy since 2013. Her work is focused on the development and evaluation of mRNA-based drugs for rare monogenetic diseases like alpha-1-antitrypsin deficiency or familial hypercholesterolemia. Prior to that, she worked on strategies for cell transdifferentiation for heart regeneration and investigated immunogenic effects caused through synthetic nucleic acids.

tatjana.michel@uni-tuebingen.de