Save messengers -- modified mRNAs open up new therapeutic possibilities

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Defects in the genome are the cause of many diseases. Gene therapy – direct replacement of mutant genes by intact DNA copies – offers a means of correcting such defects. Now a research team based at the Medical Center of the University of Munich, and led by Privatdozent Dr. Carsten Rudolph, has taken a new approach that avoids DNA delivery. The team shows for the first time that chemical modification of mRNAs (the metabolically active molecules derived from genomic DNA that programs protein synthesis) provides a promising alternative to DNA-based procedures.

In contrast to the latter, the modified RNAs do not increase the risk of cancer, and do not induce frequently observed severe immune reactions seen with DNA or unmodified mRNA. The researchers show that the new method is life-saving in mice with a congenital lethal lung defect. "These results clearly demonstrate the therapeutic potential of our mRNAs," says Rudolph. (Nature Biotechnology, 7 February 2011)

Gene therapy offers great potential for the treatment of both congenital and acquired diseases that are otherwise not amenable to other treatments. However, the approaches that have been tested so far are associated with serious side-effects. The use of engineered viruses to introduce intact genes into the cellular genome are associated with an increased risk of developing leukaemia, and can provoke strong immune reactions. Nonviral vectors, on the other hand, tend to be inefficient delivery vehicles. The new RNA-based method displays neither of these disadvantages. "Chemical modification of the mRNA prevents it from

activating the immune system, so that no inflammatory reaction ensues," says Rudolph. "Furthermore, in contrast to conventional mRNA, the modified mRNA can be administered repeatedly, is more stable and is effective at very low doses."

The new method, referred to as Transcript Therapy by its inventors, opens up new opportunities for targeted treatments. The modified mRNAs shuttle genetic information into cells in a form that can be used directly for the production of therapeutically active proteins. In addition to their potential for the treatment of genetic diseases, they represent an alternative to established protein-based treatment regimes. The researchers demonstrated the efficacy of the latter application in a mouse model. A single intramuscular injection of mRNAs coding for the hormone erythropoetin, which stimulates the differentiation of red blood cells, led to a significant increase in erythrocyte counts four weeks later.

The team also employed a mouse model to show that the technique can effectively be used to treat a genetic disease. For this, they chose a strain with a lethal congenital lung defect, caused by its inability to make surfactant protein B (SP-B). Regular application of mRNA for SP-B, as an aerosol, to the lungs of the mutant mice restored lung function, and the effect persisted for the duration of the study. Rudolph sees great scope for transcript therapy in regenerative medicine and the treatment of metabolic diseases, and hopes to test the efficacy of modified mRNAs in a clinical setting over the next few years.

More information: Expression of therapeutic proteins after delivery of chemically modified mRNA in mice, Kormann MS, Hasenpusch G, Aneja MK, Nica G, Flemmer AW, Herber-Jonat S, Huppmann M, Mays LE, Illenyi M, Schams A, Griese M, Bittmann I, Handgretinger R, Hartl D, Rosenecker J, Rudolph C. *Nature Biotechnology*, XX. February 2011, doi:10.1038/nbt.1733

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