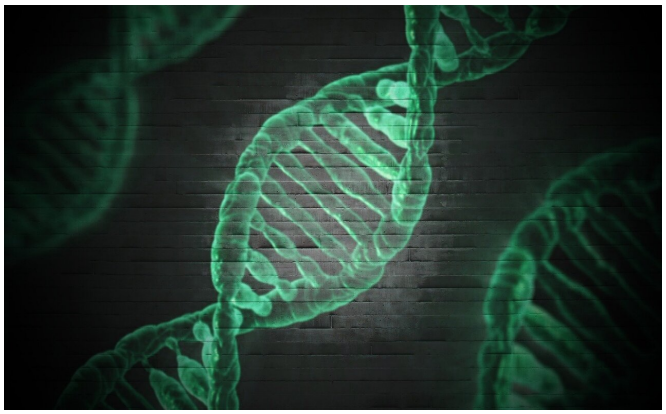
The third generation of siRNA delivery system makes RNAi therapy feasible

30 March 2021



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In a new study published in the *Cell Research*, Chen-Yu Zhang's group at Nanjing University reports "In vivo self-assembled small RNA is the new generation of RNAi therapeutics."

The development of RNAi therapy has undergone two major stages, direct injection of synthetic siRNAs and delivery with artificial vehicles; neither have realized the full therapeutic potential of RNAi in clinic. In this study, Chen-Yu Zhang's group reprogram host liver with genetic circuits to direct the synthesis and self-assembly of siRNAs into secretory exosomes. In vivo assembled siRNAs are systematically distributed to multiple tissues or targeted to specific tissues (e.g., brain), inducing potent target gene silencing in these tissues. The therapeutic value of this strategy is demonstrated in a variety of diseases ranging from cancers to metabolic diseases. Overall, in vivo self-assembled siRNA represents a next generation RNAi therapeutics, which makes RNAi therapy feasible.

The scientific significance of these findings is highlighted below:

1. The lack of a safe and efficient in vivo delivery system remains a major obstacle to the clinical translation of RNAi therapy. This study reprograms the native circulating exosome system of mammals with artificial genetic circuits to facilitate the transfer of siRNA in vivo. This strategy re-conceptualizes delivery vehicles as "medicines" instead of "agents," thus avoiding the safety and efficiency concerns associated with conventional delivery techniques.
2. Most human diseases are caused by the mutation or dysfunction of multiple genes. The design of in vivo self-assembled siRNAs offers the co-expression of tandem siRNAs and simultaneous silencing of multiple genes in vivo (e.g. EGFR and TNC in glioma), thus allowing precise control of gene expression in a purpose-driven mode.
3. Since in vivo self-assembled siRNAs are delivered by circulating exosomes, specific tissue targeting may be achieved by the co-expression of tissue-specific protein tags on exosome membrane. Thus, in vivo self-assembled siRNAs can be directed to specific tissues, especially for those with biological barriers (e.g., blood-brain-barrier).
4. This study is the first attempt to combine genetic circuits with native exosome circulating system to achieve gene silencing in vivo. Self-assembled siRNAs may be a novel gene silencing tool for studying gene function in vivo.

"With these findings," Chen-Yu Zhang added, "we believe that this study is very important for addressing the urgent topics in biomedicine and will be of broad interest to biomedical researchers and pharmaceutical industries."

More information: Zheng Fu et al, In vivo self-assembled small RNAs as a new generation of RNAi therapeutics, *Cell Research* (2021). DOI:

10.1038/s41422-021-00491-z

Provided by Nanjing University School of Life Sciences