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NON-INTEGRATING ALPHARETROVIRUS-BASED PARTICLES FOR EFFICIENT RNA DELIVERY AND GENE MODIFICATION

Keywords: gene therapy, CRISPR/Cas9, transient protein expression, RNA delivery, MS2CP, genome editing

INVENTION NOVELTY

The chimeric alpharetrovirus-like particles (a.Gag.MS2) are designed for specific encapsidation of non-retroviral RNA and allow its non-toxic and effective delivery into target cells by exploiting the well-evolved viral cell entry route. This technology enables the transient expression of transgenes and overcomes inefficient endosomal escape of the delivered RNA, which is currently the bottleneck of comparable nanoparticle-based technologies. In addition, the lipid envelope of a.Gag.MS2 particles can be equipped with membrane proteins to increase target cell specificity.

VALUE PROPOSITION

In addition to mRNA, also small RNA molecules, e.g. shRNA, miRNA, and lncRNA, can be transferred. Moreover, even more complex molecular genetics tools, like genome modification approaches, can effectively introduced into target cells and tissues. As an example, novel RNA-guided endonuclease genome editing technologies, like CRISPR/Cas9, became effective research tools and promising therapeutic approaches during the last decade. However, for risk mitigation and a safe application, the transient expression of DNA-modifying technologies is a prerequisite for human genome and cell therapies. a.Gag.MS2 particles enable the spatiotemporal co-delivery of CRISPR/Cas9 mRNA and single-guide RNA due to simultaneous incorporation of different RNA species into viral like all-in-one particles enabling the transient expression of the transferred mRNA.

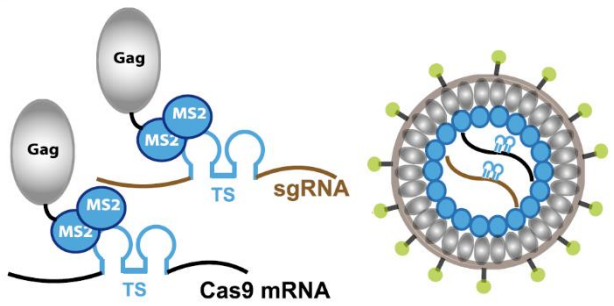

Figure 1: Non-integrating alpharetrovirus-based viral-like particles for efficient non-viral RNA delivery into target cells. As an application example, a.Gag.MS2CP VLPs can simultaneously deliver CRISPR/Cas9 RNA components to realize efficient and safe genome editing. Furthermore, other RNA species or CRISPR/Cas9-related techniques, like CRISPR/Cas9-mediated HDR, base-editing or Prime Editing can be realized (edited from Knopp et al., 2018).

TECHNOLOGY DESCRIPTION

To allow specific packaging of non-retroviral RNA into alpharetrovirus-based particles, the structural alpharetroviral Gag protein is fused to a MS2 bacteriophage coat protein (MS2CP) dimer. MS2CP binds to a ~23 nucleotide stem loop sequence (TS) which has to be present in designed RNA constructs enabling specific and efficient RNA encapsidation and VLP formation. The particles can incorporate a single RNA species or a variety of coding and non-coding RNA molecules, e.g. for gene editing, RNA interference and/or for multiplexing approaches.

COMMERCIAL OPPORTUNITY

In-licensing or collaboration is possible.

DEVELOPMENT STATUS

Initial proof-of-concept studies have been performed at Hannover Medical School.

PATENT SITUATION

International PCT-application with priority of December 2021 is pending.

FURTHER READING

Baron *et al.*, 2022, Improved alpharetrovirus-based Gag.MS2 particles for efficient and transient delivery of CRISPR-Cas9 into target cells. Mol. Ther. Nucleic Acids

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