Queen Mary Innovation

Opportunity 2023060

Boosting self-amplifying RNA vaccine efficacy by overcoming innate antiviral barriers

The cis-expression of Nodamuravirus (NoV) B2 protein, a well-known viral suppressor of RNAi, from Chikungunya virus (CHIKV) or Venezuela equine encephalitis (VEEV) genome-based saRNAs was shown to increase their ability to express a gene of interest in both embryonic stem cells and somatic cells, whilst preserving saRNA's self-adjuvant properties.

Background

The groundbreaking success of mRNA-based vaccines in combating COVID-19 has driven intense interest in RNA technologies and their optimisation. Self-amplifying mRNA (saRNA) technology represents a powerful next-generation vaccine platform. saRNA are derived from alphavirus replicons that are engineered to encode both the antigen of interest and viral replication machinery. This allows saRNA to self-replicate within host cells, leading to prolonged antigen expression at lower doses compared to conventional mRNA vaccines. Therefore, saRNA holds great promise as a novel strategy for efficient vaccine design and its ability to amplify antigen production within cells offers potential applications in gene therapy, cancer immunotherapy, and protein replacement therapies.

The Problem

saRNA self-replication generates double-stranded RNA (dsRNA) intermediates that trigger innate antiviral pathways, including the interferon (IFN) response and RNA interference (RNAi). These pathways compromise saRNA stability, replication, and translation, ultimately limiting vaccine efficacy. To fully unlock saRNA's potential, it is essential to develop innovative strategies that overcome these antiviral barriers while preserving its immunostimulatory properties.

Invention: Benefits & Application

The cis-expression of a viral suppressors of RNA interference (VSR), Nodamuravirus (NoV) B2 protein, was shown to significantly enhances saRNA-mediated gene expression in both embryonic stem cells and various somatic cell lines. Stem cells utilise an IFN-independent antiviral RNAi pathway, breaking down double-stranded RNA (dsRNA) into viral small interfering RNAs (vsiRNAs) to limit viral replication. The co-expression of NoV B2 with self-amplifying mRNA (saRNA) significantly reduces vsiRNA production, preserving saRNA integrity. This effect aligns with the known viral suppressor of RNAi (VSR) activity of NoV B2 proteins, previously observed in insect, mammalian, and neonatal mouse models.

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In somatic cells, the NoV B2 protein prevented translation inhibition mediated by protein kinase R (PKR), a key antiviral effector of the interferon (IFN) system, ensuring efficient saRNA-driven protein production. Notably, NoV B2 does not disrupt IFN induction or downstream signalling, preserving the self-adjuvant properties of saRNA critical for robust immune activation. Additionally, while dsRNA generated during saRNA replication is typically restricted to the cytoplasm, NoV B2 redistributes dsRNA to the cell periphery, unveiling a novel mechanism for modulating innate immune sensing.

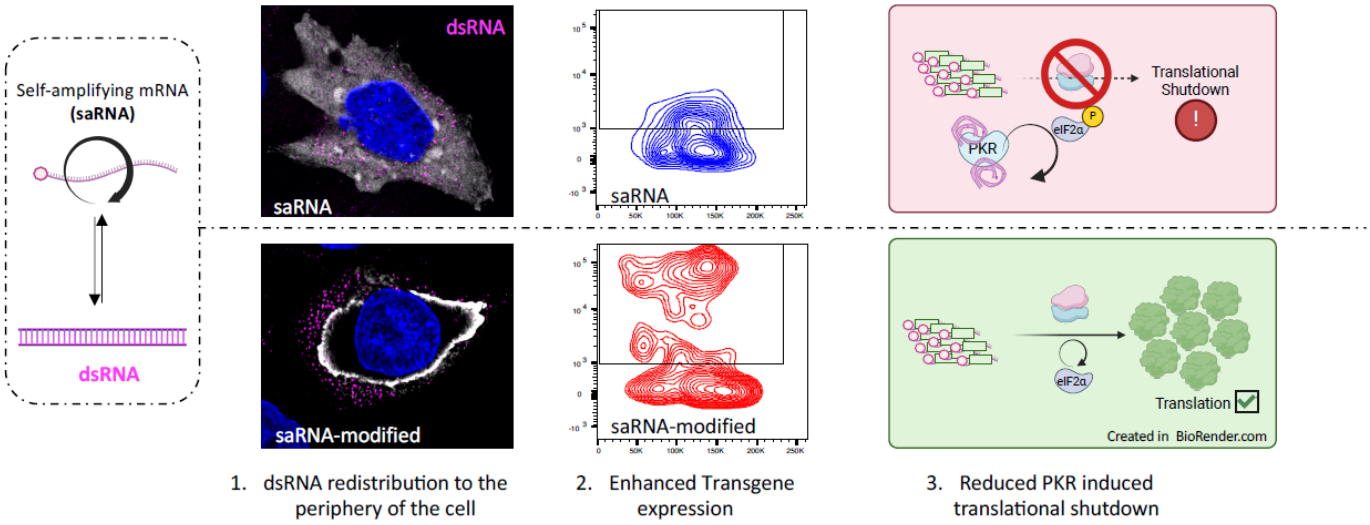

Figure 1: Enhanced activity of self-amplifying mRNA's technologies by spatial redistribution of the vectors double-stranded RNA

This presents a novel strategy to enhance saRNA vaccine efficiency by co-expressing NoV B2 protein, which boosts transgene expression while preserving self-adjuvanticity. By increasing saRNA stability and function without disrupting the interferon response, this approach holds significant promise for next-generation RNA vaccines and therapeutic applications.

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Patent

A UK patent application has been filed.

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