VACCINES

Self-amplifying RNA in lipid nanoparticles: a next-generation vaccine?

Photodisc

Vaccines based on nucleic acids (both DNA and RNA) have been investigated for several decades, but have not yet resulted in a commercial product for human use. Now, reporting in *PNAS*, Geall and colleagues present a new vaccine platform based on self-amplifying RNA encapsulated in synthetic lipid nanoparticles (LNPs), which overcomes some of the limitations of earlier nucleic-acid-based approaches.

The concept of nucleic-acid-encoded vaccines was conceived over two decades ago when it was found that injection of mRNA or plasmid DNA (pDNA) into skeletal muscle of mice leads to the expression of the encoded protein. Early efforts to develop this approach into a vaccine focused on DNA, as it is more stable than RNA. However, vaccination with pDNA was found to produce insufficient antibody responses in humans, although more recent approaches to deliver pDNA by local *in vivo* electroporation have shown a promising rise in efficiency. Strategies using pDNA, mRNA or self-amplifying RNA delivered by viral vectors can induce potent immune responses in non-human primates and in humans, but are hampered by anti-vector immunity and safety concerns.

The authors took advantage of recent advances in RNA synthesis and nanoparticle technology. Encapsulation of RNA in LNPs was shown to protect it from enzymatic degradation and allowed for efficient gene delivery after intramuscular injection. Importantly, LNPs do not carry vector surface proteins and are therefore not limited by anti-vector immunity. The self-amplifying RNA was derived from the genome of an alphavirus; the genes encoding structural proteins were replaced by genes coding for the antigen of interest, whereas the RNA replication machinery was retained. As RNA amplification and protein expression take place in the cytoplasm of target cells, the risk of genomic integration is eliminated and the RNA does not need to cross the nuclear membrane (this was found to be a rate-limiting factor for DNA-based vaccines).

Using a bioluminescent reporter gene, it was shown that RNA delivery by LNPs leads to antigen expression that lasts twice as long as RNA delivery by the latest viral vector technology, viral replicon particles (VRPs).

> “This approach could provide a potentially generic platform for the rapid development of potent, versatile vaccines for the induction of both humoral and cellular immune responses.”

Proof of concept was demonstrated in a model of respiratory syncytial virus (RSV) infection. The LNP–RNA vaccine potently induced neutralizing antibodies in cotton rats, as well as antigen-specific interferon-γ-producing $CD4^+$ and $CD8^+$ T cells in mice. These responses were comparable to or exceeding those elicited by VRP delivery of RNA or electroporation of pDNA and provided protection against subsequent RSV infection.

The authors point out that the LNP–RNA vaccine is produced *in vitro* in a cell-free manner, allowing large-scale, cost-effective production while avoiding safety and manufacturing issues associated with cell culture of live viral vaccines, recombinant subunit proteins and viral vectors. Therefore, this approach could provide a potentially generic platform for the rapid development of potent, versatile vaccines for the induction of both humoral and cellular immune responses.

Alexandra Flemming

ORIGINAL RESEARCH PAPER Geall, A. J. *et al.* Nonviral delivery of self-amplifying RNA vaccines. *Proc. Natl Acad. Sci. USA* **109**, 14604–14609 (2012)