

 VACCINES

TBK1 mediates DNA vaccine immunogenicity

In the past decade, DNA vaccines have emerged as a potential favoured strategy for inducing immunity. Not only are they cost-effective and free of infection risk, but they can elicit both strong humoral and cellular responses in mice. However, compared with conventional vaccines, which contain immune-system boosting adjuvant components, DNA vaccines only consist of plasmid DNA. So, what is the adjuvant element that stimulates immunogenicity and makes these vaccines successful? Ishii and colleagues now reveal that TBK1 (TANK-binding kinase 1) mediates the adjuvant effect of DNA vaccines and that this effect occurs independently of the TLR (Toll-like receptor) signalling pathway.

It has been suggested that the CpG-containing DNA motifs (which are TLR9 ligands) in the plasmid backbone of DNA vaccines could

function as 'built-in' adjuvants, similar to the effects of other TLR ligands in conventional vaccines. However, accumulating evidence, supported also in this study by the fact that TLR9-deficient mice can elicit equally effective responses to DNA vaccines as can wild-type mice, indicates that other TLR-independent signalling pathways must be involved. Indeed, recent evidence showing that double-stranded DNA stimulates innate immune cells to produce type I interferons (IFNs) in a TBK1- and IRF3 (interferon-regulatory factor 3)-dependent manner but independently of TLRs, suggests that the double-stranded nature of the plasmid in DNA vaccines might contribute to their immune-boosting effect.

In a study prompted by these results, the authors first showed that signalling by type I IFNs was indispensable for the induction of DNA vaccine immunogenicity, as, in contrast to their wild-type counterparts, mice that lacked type-I-IFN-mediated signalling could not elicit strong T- and B-cell responses to various antigens after immunization with the corresponding DNA vaccine.

Next, the authors generated TBK1-deficient mice in a TNF (tumour-necrosis factor)-deficient background (as TBK1 deficiency on its own is lethal) and showed that in response to DNA vaccination these mice failed to increase the frequency and cytotoxicity of antigen-specific

CD8⁺ T cells and the production of IFN γ in the spleen, compared with wild-type and control mice (*Tnf*^{-/-} mice). Similarly, a role for TBK1 in the humoral responses elicited by DNA vaccines was shown by the capacity of wild-type and control mice to augment their IgG titre in response to DNA vaccination, contrary to TBK-deficient mice, which showed no increase. In an attempt to determine whether DAI (also known as ZBP1), which was recently shown to be a candidate for double-stranded DNA recognition, might have a function in the generation of DNA vaccine immunogenicity, the authors generated DAI-deficient mice, but this molecule proved to have no essential role in immune responses to DNA vaccination.

To further understand the intercellular processes by which TBK1 might mediate immunogenicity, the authors carried out a series of bone-marrow transfer experiments to reveal that TBK1-mediated signalling in haematopoietic cells was crucial for the induction of both antigen-specific B cells and CD4⁺ T cells, and that TBK1 was required in non-haematopoietic cells for the induction of CD8⁺ T cells.

Although the element recognizing double-stranded DNA was not determined, these data show that TBK1 functions as a key molecule in DNA-vaccine-induced immunogenicity. In the future, it will be interesting to determine whether activation of the TBK1 signalling pathway can also boost the immunogenicity of other vaccines.

Marta Tufet

ORIGINAL RESEARCH PAPER Ishii, K. J. et al. TANK-binding kinase-1 delineates innate and adaptive immune responses to DNA vaccines. *Nature* **451**, 725–730 (2008)

