

mRNA vaccines engage unconventional pathways in CD8⁺ T cell priming

Abstract

Vaccines composed of mRNA and lipid nanoparticles (LNPs) activate B cells and T cells by inducing in vivo production of specific protein antigens. While B cells can be activated directly by antigens, T cell activation requires antigen processing and presentation by MHC molecules on specialized antigen-presenting cells (APCs). In response to viral infections, tumours, and protein- and cDNA-based vaccines, antigen presentation to CD8⁺ T cells is particularly dependent on type 1 conventional dendritic (cDC1) cells, which are specialized for efficient cross-presentation of exogenous antigens^{1,2,3,4}. However, whether similar mechanisms have a role in mRNA–LNP vaccination is unclear. Here we report that mRNA–LNP vaccines do not require cDC1 cells or the WDFY4-dependent cross-presentation pathway for CD8⁺ T cell priming but instead engage both cDC1 and cDC2 cells redundantly. While CD8⁺ T cells primed exclusively by either cDC1 or cDC2 cells showed phenotypic differences, both could mediate anti-tumour responses and memory formation. Importantly, acquisition by cDCs of peptide–MHC-I complexes from non-haematopoietic cells, called cross-dressing, provides a substantial component of CD8⁺ T cell priming, in a manner dependent on type I interferon. mRNA–LNP induction of cross-dressing might explain their ability to activate CD8⁺ T cells against antigens not encoded by the vaccine.

Data availability

The scRNA-seq and TCR-seq data underlying Fig. 5 and Extended Data Fig. 7 is openly available in the National Center for Biotechnology Information Gene Expression Omnibus (GEO) under accession number GSE296093. All data in this study are available in the published Article and its Supplementary Information.

News Source:

<https://www.nature.com/articles/s41586-026-10353-6>