MAIT cells boost adenovirus-induced CD8+ T cells

Mucosal-associated invariant T (MAIT) cells are unconventional T cells that can act as innate sensors for viruses in mucosal tissues. Wang et al. now demonstrate that the ChAdOx1 virus, of recent fame as a vector for one of the first approved vaccines against SARS-CoV-2, robustly activates MAIT cells and that these cells play a central role in activating CD8+ T cell responses to vaccine-encoded antigens.

MAIT cells specifically recognize microbiobly derived metabolites of vitamin B, synthesis but can also be activated via cytokines produced by virus-infected antigen-presenting cells. For example, they are known to amplify the early local immune responses to influenza infection. The authors hypothesized that these cells may also play a role in the immunogenicity of vaccines based on replication-incompetent adenoviral vectors like ChAdOx1.

Indeed, they found that stimulation of human peripheral blood mononuclear cells (PBMCs) with ChAdOx1 induced a dose-dependent upregulation of CD69, granzyme B and IFNγ in MAIT cells, indicating activation. Significant MAIT cell activation was detected after immunization of human volunteers with ChAdOx1, which correlated with an increase in plasma levels of IFNγ. RNA sequencing of human MAIT cells after ChAdOx1 stimulation revealed a strong induction of type 1 interferons and the IL-1, IL-12 and IL-2 family signalling pathways.

Next, the authors sought to investigate how these MAIT cells are activated. They found that ChAdOx1 mainly infects monocytes, conventional dendritic cells and CD123+ plasmacytoid dendritic cells (pDCs). Using in vitro analysis and various knockout mice,

Mutant p53 chills tumours by turning off cGAS

The tumour microenvironment can be referred to as ‘hot’ or ‘cold’ depending on whether it contains immune cells with anti-tumour or pro-tumour functions. A recent study in Cancer Cell has found that mutant p53 (mtp53) proteins can promote tumorigenesis by inhibiting the cGAS–STING signalling pathway and rendering tumours immunologically cold.

Cancer cells have aberrantly high levels of cytoplasmic DNA and these can be detected by cGAS; this leads to downstream formation of STING–TBK1–IRF3 complexes, in which IRF3 is phosphorylated and activated by TBK1. Activated IRF3 enters the nucleus to upregulate type I interferons or can translocate to the mitochondria to induce apoptosis, and these IRF3-driven responses protect against tumorigenesis.

However, in some cancer cells the cGAS–STING pathway cannot activate IRF3 (despite high levels of cytoplasmic DNA) and instead promotes metastasis. Ghosh et al. assessed whether mtp53 proteins with mutations affecting the DNA-binding domain (which typically inactivate the tumour suppressor function of p53 and cause gain-of-function oncogenic activity) interfere with the cGAS–STING pathway and found that mtp53 proteins can indeed inhibit STING activation by interfering with cGAS and STING signalling.

This finding is significant because it suggests that targeting cGAS–STING could be a viable strategy for treating p53-mutant cancers, which are notoriously difficult to treat. In addition, these findings highlight the importance of understanding the role of cGAS–STING in cancer biology and the potential for developing novel therapeutics to target this pathway.

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