MEMBRANE TRAFFICKING

# IFT proteins play a new game

> IFT is part of the membrane trafficking pathway that orchestrates signalling at the immune synapse

Primary cilia are present on most eukaryotic cells, where they function as sensory organelles to relay information from the external environment into the cell. Cilia are assembled by means of intraflagellar transport (IFT) — a process carried out by multimeric IFT particles and molecular motors. Finetti *et al.* now reveal an unexpected new role of IFT in cells lacking cilia, by showing that IFT is part of the membrane trafficking pathway that orchestrates signalling at the immune synapse — a platform that can integrate, fine-tune and terminate signalling.

When naive T cells encounter antigen-presenting cells (APCs), membrane and cytosolic molecules rearrange at the T cell–APC contact area to form the immune synapse. During this process, the microtubule organizing centre (MTOC) and the Golgi reorient towards the APC to ensure targeted delivery of signalling molecules, such as the T cell receptor (TCR)–CD3 (which is composed of four chains) complex, from intracellular pools to the immune synapse.

Finetti *et al.* observed that IFT20 (an IFT component that is essential for ciliary assembly) colocalizes with the MTOC and the Golgi in lymphoid and myeloid cells, which lack primary cilia. Notably, IFT20 clusters with TCR at the immune synapse, concomitant with MTOC and Golgi reorientation, and it associates with the ζ- and ε-chains of CD3 in response to TCR engagement.

To study the potential role of IFT20 in immune synapse formation, the authors knocked down *IFT20* by RNA interference in T cells. Immunostaining of CD3ζ and CD3ε showed that *IFT20* knockdown impairs the clustering of TCR–CD3 at the immune synapse. Furthermore, protein tyrosine kinase activation and upregulation of the surface activation marker CD69, which occur in response to TCR engagement, are reduced in *IFT20*-knockdown cells. These results suggest that IFT20 controls the extent and duration of TCR signalling at the immune synapse.

TCR–CD3 assembly is initiated in the endoplasmic reticulum and completed in the Golgi, from where it is translocated to the cell surface through the canonical exocytic route. The complex then undergoes several rounds of recycling, before being targeted for degradation. The authors observed that less CD3 was expressed at the surface of *IFT20*-knockdown cells than control cells, even though the total CD3 levels were similar, which suggests a role for IFT20 in trafficking TCR–CD3 to the membrane. Indeed, by monitoring CD3 recovery at the cell surface after treatment with phorbol esters, which stimulate TCR–CD3 recycling, they found that this process is impaired in *IFT20*-knockdown cells. So, IFT20 is dispensable for the internalization of TCR–CD3, but is required for TCR–CD3 recycling back to the cell surface. Notably, other IFT components are also expressed by T cells and participate in T cell activation as a complex with IFT20.

These important findings suggest that IFT proteins might participate in intracellular membrane trafficking in all eukaryotic cells. As the defects in IFT particles associated with various human diseases have been attributed to impaired ciliogenesis, it will be important to study their role in intracellular protein trafficking in these pathologies.

*Francesca Cesari*

**ORIGINAL RESEARCH PAPER** Finetti, F. *et al.* Intraflagellar transport is required for polarized recycling of the TCR/CD3 complex to the immune synapse. *Nature Cell Biol.* **11**, 1332–1339 (2009)