Structure of a key 'trigger' of immune response solved

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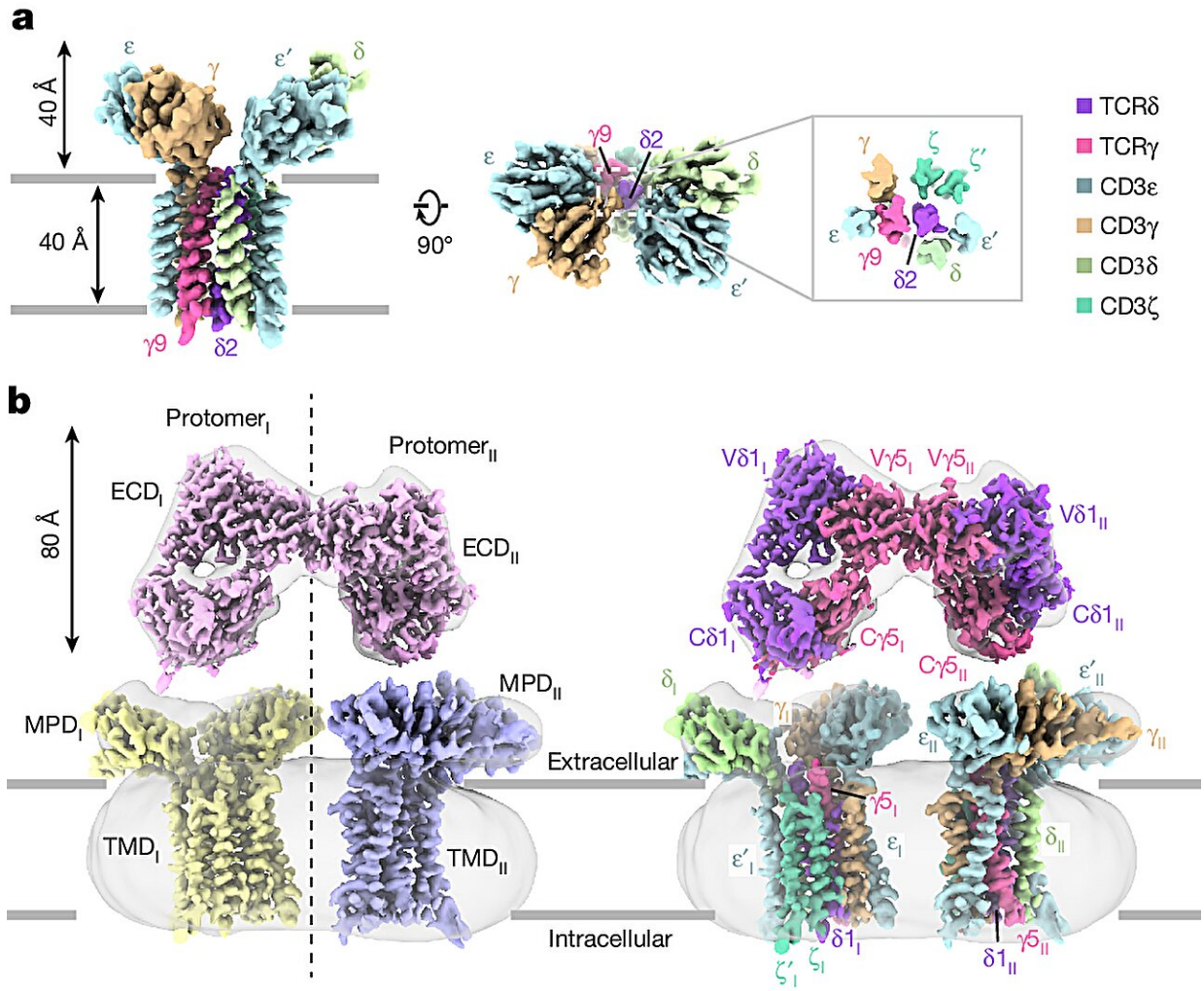

Cryo-EM reconstructions of the human Vγ9Vδ2 and Vγ5Vδ1 TCR–CD3 complexes. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07439-4

An international collaboration, involving researchers from Monash University and the University of Oxford, has led to a breakthrough in our understanding of how immune responses are started. The study has been published in *Nature*.

The human immune system comprises multiple important white blood cells (i.e., lymphocytes) including B cells and T cells that fight off infections and cancers. Basic discoveries leading to an understanding of how lymphocytes function have led to the development of immunotherapies and vaccines.

There are two types of T cells in humans, called αβ T-cells and γδ T cells, each of which expresses on their surfaces either an αβ T cell receptor (TCR) or a γδ TCR, respectively.

In 1957, Frank Macfarlane Burnet, a famous Australian immunologist, predicted the existence of these receptors and speculated that they would "trigger" clonal lymphocyte expansions, producing enough cells to fight off infections.

We now recognize that TCRs have the pivotal role of recognizing molecules derived from foreign pathogens or tumors. While less is known about γδ T cells than αβ T cells, they are emerging as key players in immune defense and are becoming increasingly important for immunotherapy.

The team, using a technique called cryogenic electron microscopy, determined the molecular structure of the TCR that is found on the surface of γδ T cells. This technically demanding project took over a decade from conception to completion and was made possible by the expertise within the Monash Ramaciotti Center for Cryo-Electron Microscopy.

The new structure unexpectedly showed that the γδ TCR is remarkably flexible, in stark contrast to relatively rigid αβ TCRs. The work also showed that the γδ TCR is very likely the more primeval receptor and completes the initial structural analysis of Burnet's "trigger" receptors, alongside a companion paper also published in *Nature*.

"This flexibility is key to the ability of the γδ TCR receptor to recognize a wide array of binding partners, which underscores the unique role it plays in the human immune system," Dr. Benjamin Gully, co-first author of the study stated.

According to Professor Simon Davis, from Oxford University and joint senior author of the study, γδ T-cells are becoming increasingly important therapeutically.

"The new structure helps constrain theories of how TCRs trigger lymphocytes, and should be helpful, especially, for re-engineering TCRs and optimizing their use in the clinic," he said.

More information: Benjamin S. Gully et al, Structure of a fully assembled γδ T-cell antigen receptor, *Nature* (2024). DOI: 10.1038/s41586-024-07920-0

Weizhi Xin et al, Structures of human γδ T cell receptor–CD3 complex, *Nature* (2024). DOI: 10.1038/s41586-024-07439-4

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