The Structure of CD3εγ in Complex with the Therapeutic antibody, OKT3

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The T cell receptor (TCR) is responsible for the recognition of peptide antigens presented by MHC class I molecules. Upon recognition of a presented peptide, the TCR induces the cytotoxic T cell response. CD3 is a multisubunit complex that performs a fundamental role in T cell signalling, T cell development and surface expression of the αβ TCR. The CD3 complex is composed of a CD3εγ heterodimer, a CD3εδ heterodimer and a CD3ζζ homodimer and, together with the TCR, are key molecules of the T cell immunological synapse. A focus of the T cell signaling function of the CD3 complex is the interaction of the CD3ε extracellular domain with the TCR constant domains. The importance of the CD3ε extracellular domain in signal transmission is also emphasized by the binding of OKT3, a therapeutic monoclonal antibody used successfully as an immunosuppressive agent in tissue transplantation.

We solved the crystal structure of the human CD3εγ heterodimer in complex with a Fab fragment of OKT3. The mode of CD3εγ dimerization together with the OKT3 epitope provides a general structural basis for CD3 assembly and maps potential sites of interaction with TCR. Despite the important influence of OKT3 on the activity of the immunological synapse OKT3 binds to an atypically small area and has a low affinity for the isolated CD3εγ heterodimer.

Keywords: immunobiology, therapeutic antibodies, T cell receptors