

Recognition and signaling by immunoreceptors

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We aim at understanding, in molecular and quantitative terms, the mechanisms of ligand recognition by the Multi-chain ImmunoRecognition Receptors (MIRR), and of the processes that couple them to the respective cellular response.

Ligand recognition by the T-cell receptor

Antigen recognition by T-cells takes place in a process whereby peptides (self and pathogen derived) are bound to proteins encoded by the Major Histocompatibility Complex (MHC). Direct measurements of the interactions between class I MHC encoded molecules and peptides, mainly by fluorescence methods, yielded detailed thermodynamic and kinetic understanding of the assembly and dissociation of mouse H2-K^d and H2-K^b as well as human A-2 ternary complexes, all of which exhibit allosteric control. We are now pursuing the analysis of the binding process of such MHC-peptide complexes to their respective T-cell receptors. This is again, done by spectroscopic methods, including fluorescence correlation spectroscopy.

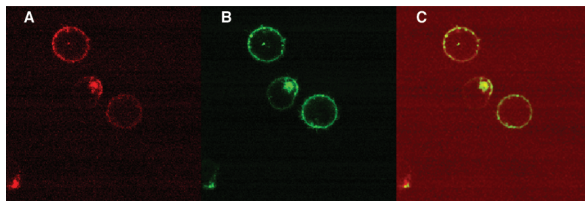


Fig. 1 Heterogeneous clustering pattern of TCR induced upon H-2K^d/PbCS^{ABA}-PE binding (A). Redistribution of the membrane rafts induced by H-2K^d/PbCS^{ABA}-PE binding; the rafts are stained with Cholera toxin-FITC (B). Overlap of the TCR enriched areas and the rafts (Panel C).

Coupling of the Fc-epsilon receptor stimulus to mast cells response

Our main model system for investigating cell stimulation via a MIRR family member is the mast cells. The mast secretory response is coupled to the stimulus of the type 1 Fc-ε receptor (Fc-epsilon RI). We have discovered that immobilization of these receptors is one requirement for production of the above stimulus. Immobilization is most probably a more general

constraint pertaining to all MIRRs and is rationalized by the need for producing a 'transdusosome', i.e. a nucleus of binding sites on the MIRR cytosolic tails for interaction with downstream components of the signaling cascade.

Modulation of the Fc-epsilon receptor stimulus

We are investigating the modulation of the response to the Fc-epsilon RI by a C-type lectin discovered in our lab. This lectin, a glycoprotein named Mast cell function-associated antigen (MAFA) has recently been shown to have binding capacity to terminal manosides. In MAFA's intracellular tail, an Immunoreceptor Tyrosine-based Inhibitory Motifs (ITIM) is present. Investigation of the mechanism of MAFAs' action and the identity of cellular components with which it is interacting has established that two phosphatases are involved in this process: The protein tyrosine phosphatase SHP-2 and the inositol 5-phosphatase SHIP. The latter was shown to play the major role in the MAFA's regulatory action.

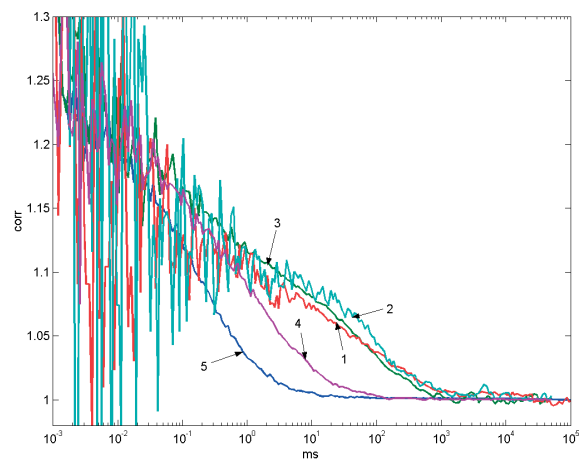


Fig. 2 Lateral diffusion of TCR and CD8 monitored by Fluorescence Correlation Spectroscopy of their bound ligands. Monomeric (1) and tetrameric H-2K^d/PbCS^{ABA}-TMR (2), anti-CD3 CyChrome (3) and anti-CD8-SPRD (4) on the cell surface, and monomeric H-2K^d/PbCS^{ABA}-TMR in PBS (5).

A novel modulation mechanism of the Fc- ϵ RI stimulated secretory response of mucosal mast cells by the complement component C3a has been discovered in collaboration with Prof. Anna Erdei of the Budapest University, Hungary. The unexpected inhibitory capacity of the C3a molecule, known as an anaphylotoxin (for serosal-type mast cells), was now shown to be mediated via its interactions with the beta subunit of the Fc- ϵ RI, apparently representing a novel control process performed by this receptor itself.

Electron Transfer Mechanisms Through Protein Matrices

The mechanism of electron transfer via polypeptide matrices is investigated in two types of systems: (1) Single-site mutants of the electron-carrier single blue copper protein azurin. (2) In the multi-centered redox enzymes, cytochrome c oxidase, ascorbate oxidase, and nitrite reductases.

Selected Publications

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