



GÖTEBORGS UNIVERSITET

Structural analyses of immune cell receptor signalling and activation

MARIA SALINE

Institutionen för kemi och molekylärbiologi
Naturvetenskapliga fakulteten

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ABSTRACT

Structural biology is a scientific field where the aim is to observe macromolecules on a atomic level to understand their functions. Often these macromolecules are proteins that make, almost, everything happen within the cells; from hormones and enzymes to building blocks and controlling gene expression. With structural biology tools, scientists can visualize structures, interactions and mobility within the proteins to get an insight in the chain of events in a cell.

In this thesis, the function of signalling has been in focus. Both signalling within the immune system through a membrane bound receptor that finds an invading pathogen and signals into the cells “alert, we have an invader” where the immune system reacts. How the signalling passes from the outside of the cell to the inside is still not revealed. One part of this thesis investigates the outside of an immune cell and the other, the inside, past the membrane.

Proteins are chains of amino acids that are predestined to either fold into a stable structure or stay loose and flexible. Superantigens are very stable proteins; they are toxins, made to last and conquer. The opposite are the intracellular flexible domains of the immune receptors which belong to a class of proteins, so-called intrinsically disordered proteins, IDPs, which are less investigated but omnipresent. In this thesis some flexible domains of the immune receptors have efficiently been produced in a cell free protein synthesis and examined by NMR, using a new setup of acquisition and analysis. All domains are lacking secondary structure and a well-defined three-dimensional structure. The proteins investigated more in depth within the work of this thesis, show tendency for α -helical regions, most likely of functional significance.

Viruses are evolved to use its host and get a free ride. Here we explore the interaction of one SIV (orthologous to HIV) protein with one of the intracellular flexible domains of the T-cell receptor, which leads to down regulation of the receptor resulting in immune deficiency. This interaction is unique in that no changes in the very sensitive NMR spectra are seen; yet other techniques indicate specific interaction.

As the SIV protein is abusing the immune system, superantigens hijack the immune system by crosslinking the T-cell receptor to an antigen-presenting cell displaying pieces of an invading pathogen on it's surface, and by this start an extreme immune response, sometimes lethal. This superantigen can circumvent the intricate, specific and effective immune system and they are up to date thought to interact with the β -chain of the T-cell receptor. We show in this thesis by structural biology techniques such as x-ray and NMR that a superantigen interacts with the α -chain of the TCR. This is the first structure structurally determined ternary complex of an antigen-MHC-superantigen-TCR, a paradigm shift in superantigen biology.