Dr Yuri Sykulev

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How immune receptor clustering relates to the quality of T cell responses

Research Objectives

Dr Sykulev is investigating molecular mechanisms of immune system functioning.

Detail

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Bio
Yuri Sykulev graduated from Pyrogov Medical Institute, Moscow, Russia, with MD and MS degrees. Later, he earned his PhD degree in Biology. Sykulev completed a fellowship at the Department of Experimental and Theoretical Physics, Pyrogov Moscow Medical Institute, and the International Fogerty Fellowship at the Department of Biochemistry, University of Virginia. He continued training as a postdoctoral fellow in the Department of Biology at the Massachusetts Institute of Technology and accepted a faculty position at the Department of Microbiology and Immunology, Thomas Jefferson University. Currently, Sykulev is a Full Professor at the Departments of Microbiology and Immunology and Medical Oncology at Thomas Jefferson University.

Funding
National Institutes of Health, USA

Collaborators
Dr Nadia Anikeeva, a long-standing colleague and collaborator

Acknowledgement
Dr Sykulev would like to acknowledge Nick Fisher and Craig Blanchette for contributing discoidal nanolipoprotein particles that mimic MHC membrane clusters.

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Personal Response

How do you think these findings may eventually translate to human medicine?

"The findings will provide basis to improve engineering of T cells with higher potency to fight pathogens and cancer."

How immune receptor clustering relates to the quality of T cell responses

When foreign substances enter the body, cells of the immune system must be alerted to the invader before they can mount an appropriate response. Dr Yuri Sykulev, Thomas Jefferson University, Pennsylvania, aims to better understand what factors drive T cell responses and how the spacing of immune cell receptors impacts on the immune response. He hopes that these findings will be used to establish new tools for evaluating immune cell function.

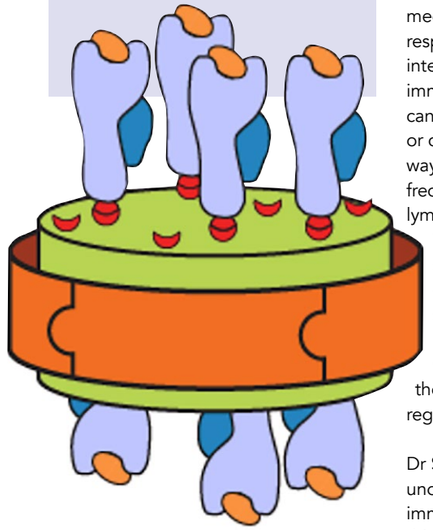

Fig. 1: The researchers model receptor clustering and interactions between MHC clusters and TCR on live T cells.

To mount the correct immune response against a particular pathogen, the immune cells must first be able to identify that there is a foreign invader in the body. Major histocompatibility complex (MHC) proteins are responsible for binding and presenting small fragments of proteins that are derived from the body's normal cells (self-antigens) or from bacteria and viruses (foreign antigens) to cells of the immune system. Once these peptides are displayed on the MHC molecules, the cells of the immune system are able to elucidate whether the source of the antigen needs to be destroyed or not.

The research of Dr Yuri Sykulev and his team at Thomas Jefferson University, Pennsylvania, explores the molecular mechanisms underlying immune responses. Dr Sykulev is particularly interested in cytotoxic lymphocytes, immune cells that are capable of killing cancer cells, cells that are infected, or cells that are modified in other ways. The group of lymphocytes most frequently recognised as cytotoxic lymphocytes are CD8+ T cells, or killer T cells. In addition to CD8+ T cells, so called because of the expression of CD8 co-receptor on the cell surface, CD4+ T cells also play an important role in immune responses. CD4+ T cells are best known for their role in antibody production and regulation activity of CD8+ T cells.

Dr Sykulev is interested in understanding more about how our immune system works, but also how this knowledge could be exploited to establish new tools to evaluate the quality of immune responses and to inform new therapeutic strategies.

The researcher has been investigating the biochemistry of receptors on the surface of T cells as well as other immune receptors. These receptors play a crucial role in T cells being able to recognise antigens (foreign substances that the immune system will try to fight off). Now, Dr Sykulev is interested in how the receptors behave when they appear on the surface of living cells.

The receptors cluster in different ways on the cell surface, either as multiple versions of the same receptor or groups of different receptors. This clustering may be responsible for triggering distinct T cell responses through the recruitment of other immune receptors and membrane molecules. This would shed light on ways that T cells are able to deliver a flexible immune response – something that is necessary when your enemy is always changing.

In particular, Dr Sykulev found that variations in the quality of T cell responses are linked to differences in the initial signalling cascades that are activated upon T cell stimulation. This variation seems to be linked to changes in the kinetics and pattern of calcium accumulation in the cytoplasm of responding T cells. It is well established that calcium signalling is crucial in eliciting immune responses and that altered calcium regulation in lymphocytes can lead to a variety of autoimmune and inflammatory syndromes. While much of the relationship between calcium molecules and T cell signalling is still unknown, it is evident that they are able to fine-tune T cell responses through complex crosstalk and feedback mechanisms. Furthermore, calcium molecules are thought to be responsible for regulating the activity of around 75% of genes involved in T cell activation.

Understanding more about patterns of calcium accumulation during T cell activation will bring about knowledge concerning the quality of T cell response against aberrant cells and will facilitate the development of diagnostic and prognostic tests. This knowledge could be utilised to incorporate T cells into T cell-based therapies to treat viral infections and cancer.

MHC CLUSTERING

MHC proteins present peptide antigens for recognition by TCRs. The MHC molecules form clusters of up to 20 molecules on the cell surfaces of antigen-presenting cells; however, it is not yet fully understood how the structure of these clusters affects T cell receptor-mediated signalling.

Dr Sykulev and his colleagues have used a technique involving discoidal nanolipoprotein particles (NLPs) that recreate membrane patches presenting immune receptors, thus enabling researchers to model receptor clustering and interactions between MHC clusters and TCR on live T cells *(see figure 1)*. They were able to use this approach to explore the impact of the MHC clustering on these interactions analysing TCR-mediated calcium signalling.

The results of the study found that it is not just the number of MHC molecules but the density of the MHC clusters that is important for regulating interactions with CD8+ T cells and calcium signalling. This suggests that variations in MHC clustering can influence interactions between MHC proteins and TCRs which subsequently regulate antigen recognition, the kinetics of intracellular calcium signalling, and the selectivity of T cell responses.

These findings support earlier work done by the group, which first suggested that MHC clustering on target cells could be used as a mechanism to regulate T cell responsiveness. MHC molecules also interact with other cell surface proteins. Therefore, future studies could serve to increase our understanding of cell surface interactions with other cellular receptors.

UTILISING DISTANCES BETWEEN IMMUNE RECEPTORS

Given that spacing of MHC molecules is now understood to be essential for TCR-mediated signalling, this knowledge can be used to inform experimental studies. For example, Dr Sykulev acknowledges that conjugating MHC molecules with nanoparticles offers a tool that can be used to examine the effects of proximity between MHC molecules on T cell receptor-mediated signalling. He explains that "variations in the separating distances may, therefore, serve to regulate T cell responses at various stages of T cell differentiation to diverse TCR ligands".

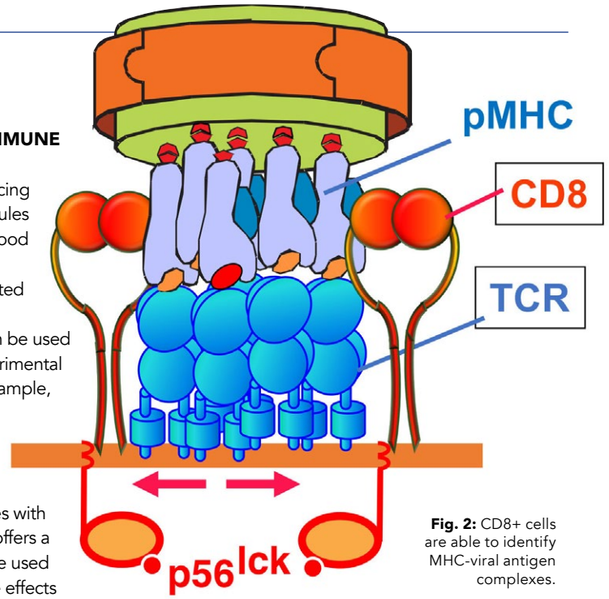

Fig. 2: CD8+ cells are able to identify MHC-viral antigen complexes.

SELF AND VIRAL ANTIGENS WORK TOGETHER

MHC proteins do not just present viral antigens; they also present self-antigens, which originate from normal proteins within the body and are distinct from external antigens derived from potentially dangerous bacteria and viruses. Somehow, cytotoxic CD8+ T cells are able to identify a few MHC-viral antigen complexes among many other MHC-self-antigen complexes, even though these self-antigens are displayed on virus-infected cells. It is widely accepted that recognition of self-antigen induces survival signal that is necessary to extend the lifespan of T cells in the body. Dr Sykulev's group has shown that TCR engagement with self-antigens also facilitates recognition of minute amounts of external antigens. Because of the MHC clustering, the signal that arises from TCR engaged by external antigens spreads to other TCRs, enhancing the ability of the CD8+ T cells to target the virus-infected cells *(see figure 2)*. This indicates that external and self MHC complexes function in concert to deliver the most effective immune response.

Dr Sykulev and colleagues used a quantum dot/peptide-MHC bio-sensor approach to reveal this phenomenon. Biosensors are used to detect the concentration of certain analytes, such as a microorganism or biomolecule. Thus, nanoparticles can be used to improve the sensitivity of such biosensors.

Understanding more about the mechanisms underlying T cell responses allows scientists to build on existing knowledge about the immune system. It also means that laboratory models can replicate the mechanisms used by live, wildtype T cells, or the mechanisms can be disrupted to investigate the impact they have on the immune response. Ultimately, understanding more about how our immune system works paves the way for better understanding and treatment of human disease, as well as the development of new experimental tools and assays.

These novel tools could be used to evaluate the quality of immune responses and inform new therapeutic strategies.

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