of MHC-restricted and non-autoreactive TCRs, the specific response to an antigen is characterized by the expression of a limited TCR repertoire with preferred gene segment usage. We focused our studies on the T cell response against the human beta-herpesvirus cytomegalovirus (HCMV) that infects 60 to 90% of the population and can cause life-threatening diseases in immunocompromised patients. In most individuals sharing the widespread MHC allele HLA-A*0201 (A2), HCMV-specific T cells target the same epitope NLV, derived from the viral protein pp65. While the NLV-specific TCR repertoire is heterogeneous in healthy donors, a dramatic diversity reduction and a high affinity TCR selection occur in chronic inflammation and immunodepression. To provide new insights into the structural basis of antigen recognition by T cells and generation of protective immune response against a major infectious agent in human, we have determined the crystal structure of the ternary complex between NLV, A2 and a TCR expressed by a predominant clone (RA14) derived from a rheumatoid arthritis patient. These data, with binding and activation experiments, provide evidences of constrains for preferred TCR gene usage in this viral peptide recognition. Contrasting with known structures of public TCRs, a novel antigen read-out is observed with the recognition of three peptide and one A2 specific hot spots.

Keywords: structures of T-cell receptor complexes, HLA, X-ray crystallography of proteins

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Crystal structure of a pattern recognition protein required for fungal detection in *Drosophila*

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In *Drosophila*, the synthesis of antimicrobial peptides in response to microbial infections is under the control of the Toll and Imd signaling pathways. The Toll signaling pathway responds mainly to gram-positive bacterial and fungal infection while the Imd pathway mediates the response to gram-negative bacteria. Microbial recognition upstream of Toll involves peptidoglycan recognition proteins (PGRPs) and glucan binding proteins (GNBP). The sensing of gram-positive bacteria is mediated by PGRP-SA and GNBP1 that cooperate to detect the presence of lysine-type peptidoglycan in the host. Recently it has been shown that the pattern recognition receptor GNBP3 is required for the detection of fungal cell wall components. We have solved the crystal structure of the N-terminal domain of GNBP3 at 1.8 Å by single wavelength anomalous dispersion (SAD) method using a Sm derivative. This structure together with the functional studies contributes to improve understanding of the molecular mechanisms underlying innate immune system in *Drosophila*.

Keywords: innate immunity, pattern recognition, molecular recognition

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Structure-function correlations in vertebrate defensins

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Defensins are small (3-5 kD), cysteine-rich cationic proteins, mostly recognized for their antimicrobial properties. The last several years of research have also revealed the ability of defensins to interact specifically with a range of cellular receptors, including chemokine receptors. Using X-ray crystallography, functional assays, and other biophysical methods, we attempted to correlate the biological activities of defensins with their structural characteristics. We were able to demonstrate that the N-terminal fragment of human beta-defensin is critical for productive signaling through the chemokine receptor CCR6. Specifically, we can explain why human beta-defensins 1 through 3 activate CCR6, whereas beta-defensin 4 does not. We also demonstrated that the human receptor CCR6 can be activated by non-human defensins, if the molecules contain the required structural determinants. Our data suggest that for most (possibly for all) biological activities of defensins that belong to both alpha and beta subfamilies, specific oligomerization is irrelevant. Furthermore, we have established specific roles for highly-conserved residues in human alpha-defensins. We explained the functional/structural roles of a salt bridge (Arg-Glu) or of the presence of a Gly residue, both nearly invariant in alpha-defensins. Although all alpha-defensins studied to date appear to form conserved dimers in solution, we have found the first case of a native alpha-defensin in which mutual arrangement of monomers is strikingly different from all examples reported previously. Our conclusions are supported by nearly 30 high-resolution crystal structures, accompanied by thorough biological studies in vitro, and, for selected proteins, additional studies in solution.

Keywords: defensins, chemotaxis, antimicrobial

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Molecular recognition of the natural killer cell receptors 2B4 and Ly49 with their respect ligands

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Natural killer (NK) cells eliminate virally infected and tumor cells. Among the receptors regulating NK cell function we are interested in 2B4, a member of the signaling lymphocyte activation molecule (SLAM) family that binds CD48; and the Ly49 family, regulating NK cell function by sensing major histocompatibility complex class I (MHC-I) molecules on target cells. 2B4 is the only heterophilic receptor of the SLAM family. The complex structure between the N-terminal domains of mouse 2B4 and CD48 displayed an association mode related to, yet distinct from, that of the NK-T-B-antigen dimer, suggesting a model that permits intermixing of SLAM receptors with MHC-specific receptors in the NK cell immune synapse. The crystal structures of Ly49C, Ly49G and Ly49C－H-2Kb complex, combined with mutational analysis of Ly49A, permitted a structure-based classification of Ly49s that we used to dissect the binding site into three distinct regions, each having different roles in MHC recognition. One region, located at the center of the binding site, has a similar structure across the Ly49 family and mediates conserved interactions with MHC-I that contribute most to binding. However, the preference of individual Ly49s for particular MHC-I molecules is governed by two regions that flank the central