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A Glue and Zipper mechanism upholds the TCR-peptide-MHC interaction

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The immune system consists of a complex network of cells whose role is to protect the body against a large range of potential invaders or pathogens. Among these cells exists a special team of molecules: one that binds the pathogen particle (MHC) and one that recognises the pathogen particle (TCR) and eliminates the infected cells. Understanding how this team of molecules works may help us to design vaccines and drugs, such as anti-cancer agents, but also to improve the rate of transplant success.

The interaction between T-cell receptor (TCR) and the Major Histocompatibility Complex molecule (MHC) presenting the viral particle (peptide), essential as it is for the immune system to function, operates via an unclear mechanism.

Indeed, The driving force behind this weak TCR-peptide-MHC interaction is elusive so far. In this study we show by combining biophysical, structural and cellular assays, how the hot spot on the MHC molecule are spread in a manner that merely follows the TCRs gaze on the peptide. The structures of three different TCRs specific for the same peptide-MHC complex show that the peptide is the driving force of the TCRs docking, attracting the receptor like "glue", and that the MHC molecule locks the interaction like a "molecular zipper". By doing so, the hot spot on both peptide and MHC are co-localised on the peptide-MHC surface.

Keywords: immunology, epstein-barr virus, T-cell receptor.

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The assembly of c4b-binding protein via its oligomerisation domain

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C4b-binding protein (C4bp) is a soluble regulator of both the classical and lectin pathways of complement activation capable of controlling C4b-mediated reactions. Inhibition of the innate response by C4bp is achieved via three distinct mechanisms; C4bp possesses cofactor activity for proteolytic cleavage of C4b by factor I and inhibits assembly of the classical and lectin pathway C3 convertase to which it also displays decay-accelerating properties.

Human C4bp is a macromolecular assembly of alpha and beta chains each consisting of eight and three complement control protein (CCP) domains respectively. Regulation of complement is provided by the C4b binding site in CCP's 1-3 of the alpha chain. Assembly into a spider-like structure occurs via separate C-terminal oligomerisation domains with the most common stochiometry reported to be 7α1β. Recently, the C4bp oligomerisation domains from different species have shown great potential in acting as vaccine adjuvants when fused to an antigen.

Presented here are the X-ray structures of the oligomerisation domains from both human C4bp and a chicken homologue showing assembly of discrete, disulphide-bonded species. Also provided is data rationalising the stoichiometry between the alpha and beta chains and discussion of the adjuvant-like effects observed by Ogun *et al*.

Keywords: C4bp, oligomerisation, structure

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Structural and Functional Investigation of the *trans*-encoded HLA-DQ8/2

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The class II MHC molecule HLA-DQ2 (DQA1*0501-DQB1*0201) and HLA-DQ8 (DQA1*0301-DQB1*0302) confer susceptibility to type I diabetes and to celiac disease. Individuals who are heterozygous for HLA-DQ2 and HLA-DQ8 have a five-fold higher risk of developing type 1 diabetes than those who are homozygous for either HLA-DQ2 or HLA-DQ8 [1]. For celiac disease, such elevated risk for heterozygous individuals is not observed. It has been proposed that HLA-DQ2/HLA-DQ8 heterozygous individuals express disease contributing *trans*-encoded MHC molecules on the surface of antigen presenting cells. A *trans*-encoded MHC refers to a MHC heterodimer where the α-chain and β-chain are derived from HLA genes encoded on different chromosomes [2]. However, relatively little is known about the extent of *trans*-encoded HLA-DQ formation or their immunological function. Here, we report the crystal structure of HLA-DQ8/2 which is a hybrid MHC molecule made up of the HLA-DQ8 α-chain and the HLA-DQ2 β-chain. It is the first atomic structure of a *trans*-encoded HLA-DQ molecule. We also present T-cell data showing differential presentation of a celiac disease associated gliadin peptide by the *cis*-encoded HLA-DQ2 and the *trans*-encoded HLA-DQ8/2.

[1] E. Thorsby, *Hum. Immunol.* **1997**, *53*, 1-11. [2] D. J. Charron, V. Lotteau, P. Turmel, *Nature* **1984**, *312*, 157-159.

Keywords: celiac disease, trans-encoded, MHC

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Crystal Structure of HLA-DQ2.5 in complex with CLIP

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We have determined the atomic structure of HLA-DQ2.5 in complex with CLIP at 2.7 Å resolution. HLA-DQ2.5 is a class II MHC associated with type 1 diabetes and celiac disease. CLIP (Class II Invariant Chain Peptide) is a fragment of the invariant chain which is