MS02 Infection and Disease/hot structures

MS02-1-4 Structure of the diabetogenic I-Ag7 receptor with a bound hybrid insulin peptide #MS02-1-4

E. Erausquin¹, P. Serra², D. Parras², P. Santamaria³, J. López-Sagaseta¹

¹1Unit of Protein Crystallography and Structural Immunology, Navarrabiomed, 31008, Navarra, Spain. 2Public University of Navarra (UPNA), Pamplona, 31008, Navarra, Spain. 3Navarra University Hospital, Pamplona, 31008, Navarra, Spain. - Pamplona (Spain), ²Institut D'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. - Barcelona (Spain), ³4Institut D'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. 5Julia McFarlane Diabetes Research Centre (JMDRC) and Department of Microbiology, Immunology and Infectious Diseases, Snyder Institute for Chronic Diseases and Hotchkiss Brain Institute, Cumming School of Medicine - Barcelona (Spain)

Abstract

The NY4.1 T cell clone was originally isolated from pancreatic islet-infiltrating lymphocytes from nonobese diabetic (NOD) mice¹. Recently, evidence was provided for promiscuous recognition of several different hybrid insulin peptides (HIPs) by the highly diabetogenic, I-Ag7-restricted 4.1-T cell receptor (TCR)². In TCR-transgenic NOD mice, recognition of these peptide-MHCII complexes triggers the activation and recruitment of 4.1-CD4+ T cells into pancreatic islets, leading to rapid destruction of pancreatic beta cells and over type 1 diabetes within the first few weeks of life.

To understand, at an atomic level, how this diabetogenic receptor binds HIP antigens, I solved the crystal structure of an agonistic HIP/I-Ag7 complex at 1.8 Å resolution.

The HIP39 epitope is tightly packaged into the peptide-binding groove of the MHCII molecule through a nourished net of interactions with both the I-Aad and I-Abg7. These include Van der Waals (VDW), hydrogen bonding (H-bonds), ionic interactions (salt bridges) and water bridges. Positions P5, P7 and P8 in the peptide are occupied by acidic residues (Glu/Glu/Asp) that expose side chains outwardly, making them available for potential interactions with cognate TCRs. Importantly, these acidic residues and positions are highly abundant in HIPs derived from a human lymphoblastoid cell line³.

Altogether, this crystal structure provides high-resolution data that enable an accurate definition of the HIP/I-Ag7 binding signature and contribute to a better understanding on how HIP antigens bind diabetogenic receptors. These complexes are known to trigger T cell autoreactivity to self tissues in type I diabetes.

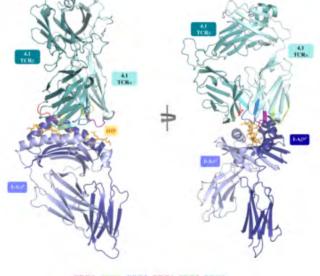
References

1. Verdaguer J., Schmidt D., Amrani A., Anderson B., Averill N., Santamaria P.; *Spontaneous Autoimmune Diabetes in Monoclonal T Cell Nonobese Diabetic Mice.* J Exp Med 17 November 1997; 186 (10): 1663–1676. doi: https://doi.org/10.1084/jem.186.10.1663

2. Parras D, Solé P, Delong T, Santamaría P, Serra P. Recognition of Multiple Hybrid Insulin Peptides by a Single Highly Diabetogenic T-Cell Receptor. Front Immunol. 2021 Aug 30;12:737428. doi: 10.3389/fimmu.2021.737428

3. Tran, M.T., Faridi, P., Lim, J.J. et al. T cell receptor recognition of hybrid insulin peptides bound to HLA-DQ8. Nat Commun 12, 5110 (2021). https://doi.org/10.1038/s41467-021-25404-x

Structure of the 4.1-TCR:HIP39/I-Ag7 complex



CDR1_CDR2_CDR3_CDR1_CDR2_CDR3