The Role of Three-Dimensional Structures in Understanding MHC Restricted Antigen Presentation

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The Japan Prize of 1999 cites four scientific accomplishments from my research laboratory: the determination of the three dimensional structures of both Class I and Class II Major Histocompatability Glycoproteins; and, the discovery of how peptide antigens bind to both of those molecules. That research spans a period of about 15 years, from about 1979 to 1994 and involved a number of individuals other than myself. In fact scientific research is usually the combined efforts of a number of individuals, somewhat like the music produced by an orchestra. My role as leader of the laboratory may be thought of as that of an orchestra conductor.

The first and most celebrated scientific result in this series occurred in 1987 when the three-dimensional structure of the human class I MHC molecule was determined by X-ray crystallography at Harvard. This was primarily the work of a graduate student and later postdoctoral fellow in the laboratory, Pamela Bjorkman, over a period of many years. In the final year of the work Mark Saper joined and made a significant contribution as a postdoctoral fellow. The structure was extremely exciting, immediately suggesting answers to long-standing puzzles in the field of cellular immunology. It showed, although only indistinctly, how peptide antigens could be presented by class I MHC molecules on the surface of human cells to be recognized by the receptors on T-killer cells of the human immune system. The structure has been used as the framework for countless experiments in immunology often permitting more precise and informative inquiries. At the clinical level it has been useful in the design of candidate vaccines for infectious agents and for tumors.

The second discovery, showing in atomic detail how class I MHC molecules bound peptide antigens was made by Dean Madden, a graduate student in my laboratory, in collaboration with Joan Gorga, a postdoctoral fellow in Jack Strominger's laboratory, and Ted Jardetzky a postdoctoral fellow in my laboratory. Joan purified and crystallized HLA-B27 a class I molecule associated with susceptibility to autoimmune diseases in humans. Madden and Gorga determined its three dimensional structure, using the earlier results as a starting point. Ted Jardetzky supplied key data by purifying and sequencing a number of the peptides that were bound to the MHC molecule. The combination of a more distinct image of the bound antigens and the knowledge of the amino acid sequence of the bound peptides allowed construction of an atomic model of the interactions between the peptides and MHC molecules. This addressed the mystery of how one MHC molecule could bind very tightly to thousands of different peptide antigens, when the presence of interactions between parts of the peptides and MHC antigens conserved in all peptides (backbone atoms) and MHC molecules (non-polymorphic residues) were described. It also described in atomic detail, how one specific MHC molecule selectively bound specific classes of peptide antigens using polymorphic pockets described earlier by Saper, Tom Garrett, and Bjorkman at Harvard.

The third accomplishment cited was the determination of the three dimensional structure of a class II MHC molecule. These molecules are found on specialized immune cells and present peptides from antigens found outside of cells but brought into cells for presentation to T-helper cells as part of the control and regulation of the cellular immune response. In humans

different alleles of class II molecules are associated with increased susceptibility to a number of autoimmune diseases such as Rheumatoid Arthritis, Multiple Sclerosis, and Insulin Dependent Diabetes. This work was started by Joan Gorga in Jack Strominger's laboratory, who discovered how to proteolytically dissect a human class II molecule, HLA-DR1, off the surface of a human cell and purify it in a form that would crystallize. Gorga and a graduate student, Jerry Brown, in my laboratory began the X-ray structure determination, which was quite difficult until Ted Jardetzky discovered a new crystal form using their HLA-DR1. Larry Stern, another postdoctoral fellow in my laboratory, expressed HLA-DR1 in insect cells and found yet another crystal. Led by Brown and Gorga, these four collaborated to solve the three dimensional structure in 1993.

Larry Stern led the continuing collaboration with Jardetzky, Gorga, and Brown to determine how class II molecules bound peptide antigens by loading a single peptide antigen from the haemagglutinin glycoprotein of influenza virus onto "empty" HLA-DR1 that he had produced in insect cells (that lacked MHC molecules and the peptide presentation system of the vertebrate immune system). The X-ray structure they produced showed in atomic detail what HLA-DR1 looked like when presenting the Flu peptide, just as though we had been looking at the surface of a cell in a person with an influenza infection. The interactions between peptide antigens and class II molecules are different than those seen in class I molecules. The interactions discovered by Stern and colleagues have subsequently been found in all other class II/peptide complexes including those from HLA-DR2 and HLA-DR4, which contribute to increased susceptibility to Multiple Sclerosis and Rheumatoid arthritis.

So far I have named 8 scientists whose research was critical to the discoveries cited above. A number of other members of my laboratory worked on these projects and they are listed in the bibliography cited wiht the award (http://www1.mesh.ne.jp/jstf/). A difference in the metaphor of an orchestra with a research group is that the scientists in an academic research group like mine at a University are all in training; some were graduate students receiving Ph. D. degrees for participation in the research outlined and others were recent degree recipients received postdoctoral training. The research results appeared incrementally, as the result of the sequential efforts of small groups of scientists, some of whom had left the laboratory by the time others arrived, in a continuous process of renewal.