EDITORIAL

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From fragments to immunity

Pioneering transplantation studies revealed what became a central tenet of immunology: somehow the immune system seemed to distinguish 'self' from 'nonself' and, once learned, could retain a memory of these specific interactions. Nobel Prize–winning investigations made a compelling case for the highly polymorphic major histocompatibility complex (MHC) locus as the enforcer of such distinctions, leading to the idea of 'MHC restriction'. Yet it was the discovery that MHC gene products bind to peptides, and that these peptide-MHC complexes form the ligand recognized by antigen-specific T cell receptors, that unlocked the doors to understanding how such exquisite specificity and diversity can be achieved. MHC presentation of small peptides, which represent a sampling of the local protein environment, allows roving T cells to continuously assess the intracellular and extracellular protein milieu for any hints of infection or abnormal growth.

This issue of *Nature Immunology* includes a special focus on Making Peptides for Presentation. Featured are four review articles that describe the pathways and enzymes that clip and trim proteins into ever-smaller polypeptides to generate or, in many cases, destroy mature antigenic peptide epitopes. Understanding the processes and participants that craft and display antigenic peptides provides us with crucial insights necessary for understanding basic immunology, infectious disease and immune responses to tumors and transplanted organs.

The immune system is poised to detect even subtle differences in the peptide repertoire that might signal an abnormal state. So critical is this peptide sampling process that it imposed powerful selective pressures on pathogens, which developed elaborate schemes to inhibit the machinery responsible for generating these peptides. Tumor cells also lower their capacity for antigen presentation, thus evading immune surveillance. Many autoimmune diseases are linked to altered peptide selection and presentation, suggesting that deviations from the normal antigen processing pathways might be sufficient to trigger pathologic situations. Thus, ideas arising from studies discerning how peptide epitopes are made and presented to T cells continue to affect vaccine development and the design of therapeutic strategies to bolster peptide presentation, even in the face of pathogen interference or tumor progression.

Key to any discussion on peptide presentation is the recognition that two classes of MHC molecules exist that have different functional interactions. The different structures of class I and class II MHC result in different intracellular pathways by which they acquire peptides and different length and composition criteria for suitable peptides. Class I MHC is expressed ubiquitously throughout the body and is recognized by receptors on $CD8^+$ killer T cells and natural killer cells. Class II MHC is expressed mainly on professional antigen-presenting cells (APCs) and the stromal cells of the thymus and is recognized by $CD4^+$ T cells.

Typically, MHC class I peptides are thought to be derived from endogenous proteins marked with ubiquitin for destruction by cytoplasmic protein degradation pathways. In this focus, Kloetzel reviews the interactive functions of proteasomes and tripeptidyl peptidase II (TPPII). These large multiprotein assemblies are responsible for the initial cleavage of proteins in the cytoplasm. The combination of proteasome and TPPII activities generates precursor polypeptides bearing mature carboxy termini but extended amino-terminal residues. Infection triggers cytokine-inducible changes in proteasome subunit composition and activity, which in turn can increase the availability of antigenic peptides. Because most MHC class I molecules bind to short peptides, ranging between only eight and ten residues, additional peptide trimming must occur. Rock, York and Goldberg discuss subsequent processing steps essential for MHC class I peptide generation.

The MHC class I peptide generation pathway described above poses a dilemma, because it does not explain how APCs alert naive $CD8^+$ T cells to tumors or to viral infection of cells other than the APCs. Cross-priming is probably the answer and was originally described by Bevan as requiring APCs to take up antigens from the milieu and process them for presentation by MHC class I molecules. In their review, Ackerman and Cresswell discuss recent findings on how APCs might overcome the topological obstacles that endocytosed antigens face to gain access to cytosolic proteasomes and for the peptides to be loaded onto MHC class I molecules for cross-presentation to $CD8^+$ T cells.

In contrast to peptides that bind to MHC class I proteins, those that bind MHC class II are usually derived from extracellular proteins, including soluble antigens, antibody- or complement-coated immune complexes, or cellular debris from dying cells. These exogenous proteins are engulfed by APCs and are routed into the endosomal-lysosomal compartment. Watts reviews the special challenges antigens and MHC molecules face after entry in the degradative environment of lysosomes. Lipids (and it seems some polysaccharides) are also acquired via endocytic uptake and are presented by MHC-like molecules after processing in the lysosome.

We invite you to visit us online for additional content. Throughout the month of July this focus is freely available to registered users on our focus website (http://www.nature.com/ni/focus/peptides/). The online focus includes free links to a selection of papers recently published by the Nature Publishing Group that are relevant to those interested in antigen processing and epitope generation. Updated highlights of new research as well as links to an annotated collection of classic papers are also featured. These classics have been nominated as making seminal contributions to the identification of the 'peptide code', which underlies immunological individuality, and to our understanding of how antigenic peptides are generated and presented by MHC molecules. In compiling these classics, we are indebted to Sebastian Amigorena, Peter Jensen, Peter Kloetzel, Jacques Neefjes, Ken Rock, Nilabh Shastri and Colin Watts for their gracious suggestions. We hope you find this focus, Making Peptides for Presentation, insightful. We would enjoy hearing your comments!