Published in final edited form as:

Curr Opin Immunol. 2017 June ; 46: v–vii. doi:10.1016/j.coi.2017.07.002.

Editorial Overview: Antigen Processing and Presentation; many fingers in many pies

Peter Cresswell¹ and Paul A Roche²

¹Yale University School of Medicine, United States

²Experimental Immunology Branch, National Cancer Institute, Bethesda, United States

The field of antigen processing is well established, but it continues to surprise and delight its practitioners as well as the wider immunological community. The selection of reviews in this edition of *Current Opinions in Immunology* reflects some basic questions that remain incompletely answered as well as larger areas impinged upon by the field, ranging from evolution to autoimmunity, tolerance and T cell selection in the thymus.

Studies of immune systems other than those in mammals have informed our understanding of both innate and adaptive immunity, going back the original definition of B lymphocytes. Parker and Kauffman provide an analysis of the MHC class II system in chickens that highlights the potential for a fundamental difference in the way birds regulate antigen processing. The MHC-I system of chickens differs from that of placental mammals in that the polymorphisms that specify variation in the peptide repertoire are focused on the TAP, TAP2, and tapasin genes rather than the MHC-I genes themselves. MHC-II genes in chickens are more limited in number than in mammals but the dominant pair resembles the DR/I-E system in that there is a monomorphic gene encoding an α -chain that may associate with two different β gene products. The chicken DM system also has two β genes, but interestingly their products have different tissue distributions, one of them dominating in the gut. The potential implications of this apparent tissue specialization are addressed in the review.

Two reviews cover areas other than the classical peptide-binding MHC molecules. Moody and Cotton address the latest developments in the CD1 field. CD1 molecules bind lipid antigens, and while mice only possess a single functional CD1 gene encoding CD1d, humans possess a family of genes encoding CD1a, b, c and d molecules, respectively. The review addresses recent progress in understanding the nature of the lipids bound by the different CD1 species, their different intracellular trafficking patterns, and how the latter regulate the former. It also covers fascinating recent developments in our understanding of how the structural properties of the different CD1 species affect not only the lipids that are bound but also their ability to be recognized by T cells. The models that have arisen, particularly for CD1a and CD1c, have added to ideas of T cell receptor recognition that have been largely shaped by analysis of MHC/T cell receptor interactions.

Rossjohn *et al.* address antigen processing functions that relate to Mucosal-Associated Invariant T cells (MAIT) cells, which are innate-like T cells that represent nearly 10% of human peripheral blood T cells. The semi-invariant T cell receptor on these cells is selected

by the MHC-I-related protein MR1. Like CD1, MR1 does not present conventional peptide antigens to MAIT cells but instead binds and presents vitamin B precursors to the T cell receptor on these cells. Like conventional MHC-I molecules, ligand-binding assists MR1 assembly and egress from the endoplasmic reticulum. The review describes recent structural studies examining ligand binding to MR1 and the attempts to identify novel compounds that can bind to MR1 to modulate MAIT cell activity *in vivo*.

Three reviews address issues pertaining to MHC-I molecules. Neerincx and Boyle discuss the functions of the tapasin homolog TAPBPR. The role of tapasin in MHC class I peptide loading is well established. As part of the peptide loading complex it facilitates the binding of TAP-transported peptides by MHC-I molecules in the endoplasmic reticulum. The role of TAPBPR is less clear. Like tapasin, it can associate with MHC class I molecules *in vitro* and can similarly facilitate peptide exchange, favoring the binding of high affinity peptides at the expense of low affinity ones. However, where in the cell TAPBPR functions, and why and when this secondary peptide editor is required, is unclear. Potential roles of this enigmatic molecule are discussed.

Mice, monkeys and man all possess genes that encode an MHC class I molecule that can bind signal peptides from self MHC-I molecules and express them on the cell surface. These molecules are recognized by inhibitory NK receptors and serve an important role in dampening NK cell activity against normal cells. McMichael and Picker describe the evidence that these molecules can also serve as more conventional antigen presenting molecules that bind viral or mycobacterial peptides. Called MHC-E, after the equivalent human gene HLA-E, they are recognized by broadly reactive SIV-specific cytotoxic T cells in rhesus monkeys immunized with a variant rhesus cytomegalovirus vector expressing SIV proteins. The work opens up the possibility of expressing HIV proteins in a similar variant of human cytomegalovirus with the ultimate goal of developing an HIV vaccine.

The initiation of MHC-I-restricted CD8-positive T cell responses generally requires cross-priming, or cross-presentation, a term coined decades ago to describe the unusual ability of some APCs, particularly specific subsets of dendritic cells, to process and present internalized exogenous antigens to MHC-I. While the phenomenon of cross-presentation is well documented, the cellular and molecular machineries involved in the process remain poorly understood. Two basic varieties have been described: the vacuolar pathway, which involves antigenic peptide generation by endocytic proteolysis of the internalized antigens, and the cytosolic pathway, which involves translocation of internalized antigens into the cytosol followed by proteasomal degradation. Grotzke *et al.* review recent studies highlighting the importance of ER and lysosomal peptidases/proteinases in antigenic peptide generation, the potential role of recycling MHC-I as the target of these peptides, and recent advances in our understanding of how exogenously acquired antigens gain access to the cytosol from endosomes/phagosomes.

One of the hallmarks of a well-balanced immune system is strong tolerance to self-antigens. Loss of tolerance can lead to autoimmunity, and Unanue and colleagues review recent advances in the processing of insulin in mice and in patients with type I diabetes. The NOD mouse is perhaps the best-studied model of an autoimmune disease, and insulin is the major

diabetogenic antigen in this mouse. The anatomic locations of insulin processing are discussed and reveal important contributions of the pancreas itself and both pancreatic draining and non-draining lymph nodes (as well as bone marrow) as sites of insulin processing and presentation to autoreactive T cells.

Central tolerance is generated in the thymus, and while the importance of antigen processing mechanisms for immune defense functions is well established these mechanisms must be replicated and regulated in the thymus for functional T cells to emerge. Takahama and colleagues review both the familiar and unusual mechanisms that operate in the thymus to ensure that potentially useful self-tolerant CD4-positive and CD8-positive T cells are released into the periphery. The promiscuous expression in medullary and cortical thymic epithelial cells of self antigens mediated by Aire and the recently discovered Fexf2 transcription factor are discussed, as are the functional implications of the variations in processing mechanisms specific to the thymus, such as the expression of thymus specific proteasome subunits for the generation of MHC-I-restricted self epitopes.

In the case of cancer patients undergoing immunotherapy, tolerance may be unwelcome. While individual tumor cells might express a tumor antigen, tolerance can reduce the tumor cell to another form of 'self that is ignored by the adaptive immune system. The high incidence of genetic mutations in cancer cells can, in some cases, lead to non-synonymous mutations that will give rise to essentially 'foreign' antigens that can serve as targets for CTL. Delamarre *et al.* discuss recent advances in attempts to identify neoantigens, how they can interact with MHC-I and influence TCR avidity, and how computational modeling can help to identify MHC-I-binding neoantigen peptides. With this information 'personalized' immunotherapies may provide highly specific cancer treatments.

From the reviews in this compendium it is clear that antigen processing, a term that includes the generation of derivatives that bind to MHC and other antigen presenting molecules as well as the intracellular processes that regulate binding, impinges on virtually all areas of research into both the normal processes of adaptive immunity and the clinical problems that result from their disturbance. Antigen presentation, or the ability of different T cell subtypes to recognize these antigenic derivatives, is similarly of critical importance to both immune defense and to tolerance. These truths, like all facts, lack alternatives and we consider them to be self-evident.

Peter Cresswell

Peter Cresswell, Ph.D., FRS, is the Eugene Higgins Professor of Immunobiology at Yale University Medical School. He was educated in the U.K., receiving his Ph.D. in London before beginning a postdoctoral fellowship with Jack Strominger at Harvard University. He was a faculty member at Duke University before moving to Yale in 1991. The major focus of

his research has been in the area of antigen processing, involving both MHC class I and class II as well as CD1 molecules. Current major interests are in the details of MHC class I peptide-loading mechanisms, CD1d functions, cross-presentation, and in the functions of the antiviral interferon-inducible protein, viperin.

Paul Roche studied chemistry and received a Ph.D. in Biochemistry from Duke University. He did post-doctoral training in the laboratories of Peter Cresswell and Eric Long before joining the Experimental Immunology Branch of the National Cancer Institute, NIH. His laboratory studies the cell biology of MHC class II antigen processing and presentation. His current focus is on the mechanisms of MHC class II-peptide transport and the regulation of MHC class II endocytosis, recycling, and degradation by ubiquitination.