

Editorial overview: New proteins, cellular processes and intercellular interactions involved in antigen presentation

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The 2019 edition of the *Current Opinion in Immunology* issue on *Antigen Processing and Presentation* comprises seven pieces that update exciting developments in this ever-expanding field. The subjects extend from protein structure through intracellular mechanisms regulating protein expression and trafficking to cell–cell interactions within lymphoid organs.

Our understanding of the mechanisms of antigen presentation has always gone hand-in hand with structural analysis. Seminal crystallography studies were first centred on the antigen presenting molecules themselves. With the realisation that formation of MHC-ligand complexes involves multiple chaperones that stabilise the empty MHC molecules and assist with ligand loading, the focus of the structural studies turned to these accessory proteins, first in isolation and then in higher-order assemblies of increasing complexity. [Thomas and Tampe](#) now describe how the inclusion of cryo-electron microscopy to the suite of techniques available to structural biologists has contributed to illuminating the three-dimensional interactions of the components of the MHC I peptide-loading complex, and the association of MHC I with TAPBPR, with unprecedented detail. These studies help understand how these ‘molecular machines’ edit peptide binding to the MHC I binding site to promote the formation of diverse complexes while ensuring each MHC I-peptide combination meets a minimum stability threshold.

[Fahmy et al.](#) describe a recently discovered pathway of mitochondrial antigen presentation termed MitAP, and its consequence in settings of neurological disease. MitAP is a pathway by which mitochondrial antigens are presented by MHC I while its role in MHC II presentation is currently unexplored. The authors discuss the body of evidence in support of the notion that MitAP contributes to Parkinson’s disease. While controversial, MitAP is regulated by PINK1, with mutations in this protein causing Parkinson’s disease with almost 100% penetrance. As [Fahmy et al.](#) discuss, the new discoveries in pathways of mitochondrial antigen presentation raise the intriguing possibility that in some scenarios Parkinson’s disease may be linked to autoimmunity.

Turning to more traditional forms of antigen presentation, [Perrin et al.](#) describe the machinery and trafficking itineraries involved in the dynamic changes elicited in the endolysosome architecture of antigen presenting cells following pathogen encounter. Specifically, this review largely focuses on the complex trafficking patterns of MHC II and how it is motored to different cellular compartments including the plasma membrane for peptide display. Intriguing recent studies implicate new roles for autophagy and the C-type lectin Clec16A in MHC II trafficking. In discussing these findings, [Perrin et al.](#) propose a new perspective that argues how alterations in the

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MHC II endocytic pathway can promote immune evasion and lead to autoimmune disease.

The review of [Liu, Mintern and Villadangos](#) addresses the role of ubiquitination on two distinct aspects: regulation of immune receptor trafficking and interference with viral infection. They describe the varied roles of a family of ubiquitin ligases, called MARCHs, that have the peculiarity of being embedded in membranes, a property that enables them to play specialised roles in regulation of transmembrane protein trafficking and expression. While the role of MARCH proteins on MHC II antigen presentation now seems well established, emerging roles in the regulation of other families of immune receptors and in interference with viral protein expression indicates this will be an expanding area of research in coming years.

The post-translational modifications, trafficking pathways and changes in organelle architecture that optimize antigen presentation are supported by the metabolic pathways that provide the building blocks and energy required to drive these processes. [Patente, Pelgrom and Everts](#) summarise the complex changes in metabolic pathways that accompany DC maturation from cells dedicated to pathogen detection and capture to cells committed to T cell activation and polarization. Strikingly, different triggers of DC maturation stimulate distinct metabolic pathways that are matched to the promotion of Th1, Th2, Th17 or Treg differentiation. This is a vigorous area of research which we anticipate will be revisited in future issues of these series.

[Chudnovskiy et al.](#) probe the interaction between DCs and T cells and describe advances in technology that have led to our improved understanding of this response. The authors outline the conceptual leaps that intravital multi-photon laser scanning microscopy has generated including insights into the location of T cell priming niches and the longevity of DC-T cell interactions during infection and/or in tumour tissue. In addition, [Chudnovskiy et al.](#) discuss new technologies that are pioneering further insights into DC-T cell interactions. This includes histocytometry that enables mapping of the anatomical distribution of multiple cell subsets within a tissue, *in situ* photoactivatable proteins and LIPstic (labeling immune partnerships by sortagging intercellular contacts) whereby cells undergoing ligand-receptor interaction are enzymatically labelled.

Immunologists normally associate antigen presentation with T cell immunity, but this concept has been extended in recent years to encompass the recognition of intact antigen by B cells on the surface of other cells. Which cells? This is the question addressed in the review authored by [Heath et al.](#) They argue that, in addition to the well-known role of follicular dendritic cells (a non-hematopoietic cell type), and the more recently established participation of macrophages, conventional DCs play an unappreciated role in the initial encounter of antigen by naïve B cells. This review will prompt other scientists to test this hypothesis in different scenarios of infection and vaccination, which may reveal important new insights into the complex multicellular interactions involved in the establishment of protective immunity.

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