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EDITORIAL

Biology, evolution, and history of antigen processing and presentation: *Immunogenetics* special issue 2019

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In 1986, Jan Klein, the previous editor-in-chief of *Immunogenetics*, wrote his opus magnum, "The Natural History of the Major Histocompatibility Complex (John Wiley and Sons: New York)." Each chapter encompassed a major feature of the MHC on its genetics, evolution, and function, and it was written in a comprehensive yet lucid style, accessible even to novices. The first chapter is ageless, recounting the history of MHC from its discovery by Peter Gorer in 1936 to the determination of MHC function by Zinkernagel and Doherty in 1974. This treatise is a must-read for all immunologists interested in how the field progressed glacially from studies of "histocompatibility" to the true function of MHC, providing a context for T cell recognition of foreign antigen. Remarkably, the year 1986 was also a key turning point for the MHC. Around this time and shortly thereafter there were major discoveries in the field that we continue to study now in 2019: the role of peptides in the function of MHC class I and class II; crystal structures of class I and class II molecules; determination of natural peptides bound to class I and class II; identification of the antigen processing machinery for class I presentation; and identification of class II-like molecules involved in class II antigen processing. The three of us were fortunate to have lived through this era as young immunologists, awestruck by each new paper that modified our view of antigen presentation. In this special issue of *Immunogenetics,* we take you from Jan Klein's 1986 history chapter entitled "The Story" to the modern-day perspectives of antigen processing and presentation.

Two heroes of the post-1986 era, John Trowsdale and Peter Cresswell, have written reviews detailing the seminal discoveries mentioned above leading to an understanding of the molecular mechanisms underlying antigen processing and presentation. Accumulated evidence indicates that many key molecules involved in antigen processing, such as TAP (transporter associated in antigen processing), immunoproteasome subunits, tapasin, and DO/DM molecules, are encoded in the MHC region. John Trowsdale and Adrian Kelly (Kelly and Trowsdale 2018) review a history of the genetic approaches, both traditional and modern, that have been highly successful in the quest to understand antigen processing and presentation. Peter Cresswell's review (Cresswell 2019) is a personal retrospective focusing on the biochemistry of antigen presentation. His seminal work on class I and class II processing, as well as on cross-priming, are written like detective stories, recounting how he and his colleagues progressed step by step in deciphering the pathways defining adaptive immunity. Every immunology student should read these two reviews in order to appreciate the creative experiments behind the textbook figures that focus on antigen presentation. These reviews are on a par with Jan Klein's chapter mentioned above, and are also destined to become ageless.

Advances in mass spectrometry technology have enabled detailed examination of MHC class II immunopeptidomes. Based on this development, Jurewicz and Stern (2018) review recent progress in our understanding of the MHC class II antigen processing and presentation pathway, focusing on HLA-DM and HLA-DO and their role in shaping the MHC class II immunopeptidome. They also discuss that the nature of immunopeptidomes presented by MHC class II molecules is influenced by the type of antigen-presenting cells, their

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maturation state, and environmental conditions such as inflammation. In their opinion piece, Welsh et al. (2019) challenge the conventional view that DO is an inhibitor of DM, and propose from their data that DO and DM work together to regulate class II epitope selection. They argue that work accumulated from several labs for over 20 years on DO function should be reexamined, and they discuss their own studies showing that DO can interact directly with peptide-receptive class II molecules.

Ishido and Kajikawa (2018) summarized recent progress in the study of March family proteins, which ubiquitinate MHC class II and regulate MHC class II-mediated antigen presentation. One family member, MARCH-1, is expressed in secondary lymphoid tissues, while the other, MARCH-8, is expressed by thymic epithelium. Although it has been difficult to determine the definitive roles for these enzymes in the immune system, the authors offer testable models to examine MARCH function in T cell development and in germinal center reactions.

Santambrogio and Rammensee (2018) discuss a new area of immunology: the peptidome and degradome found in biological fluids, such as lymph and plasma. Such analyses offer a new way to examine homeostasis and pathology in a non-invasive manner: for example, by collecting lymphatic fluid draining infected or damaged tissues. This review, which details the array of peptides that can be examined as well as the potential enzymes that generate the peptidome, is useful for all immunologists, especially those who think outside the box.

It is becoming clear that the thymic cortex displays unique self-peptides generated by a thymus-specific form of proteasomes, the thymoproteasome, as well as expressing specific enzymes that generate peptides bound to class II molecules. Based on this background, Takahama and colleagues (Takahama et al. 2018) revisit the “peptidic self” hypothesis, in which high-affinity recognition of foreign epitopes by developing thymocytes was suggested to drive positive selection. They argue that thymoproteasome-dependent self-peptides unique to the thymic cortex may be recognized as foreign. As the authors point out, the “peptidic self” hypothesis is not concordant with the current consensus that low-affinity interactions between TCR and peptide-MHC complex mediate positive selection. Nevertheless, viewing the thymoproteasome-dependent self-peptides as “deemed foreign” may generate interesting ideas among researchers in this field. Guerder and colleagues (Guerder et al. 2018) discuss the thymus-specific serine protease (TSSP), which contributes to the generation of MHC class II-associated peptides displayed in the thymus, both by thymic epithelial cells and thymic APC. Their studies have shown that TSSP modifies the repertoire of CD4 T cells, perhaps by limiting central tolerance. A model is proposed on how TSSP-dependent selection of CD4 T cells impacts autoimmunity and adaptive immunity.

Adaptive immunity occurs in all vertebrates including jawless vertebrates. However, adaptive immunity based on MHC molecules and TCR/BCR is unique to jawed vertebrates. Dijkstra and Yamaguchi (2018) review the evolution of the MHC class II antigen presentation system in jawed vertebrates. They argue that MHC class II type structures likely represent the ancestral structure of MHC molecules. They also show that the CLIP region of the MHC class II invariant chain also known as Ii or CD74 has sequence motifs conserved throughout jawed vertebrates, and that DM molecules hitherto identified only from the level of amphibians are also present in the lungfish. Kasahara and Fjajnik (2019) review the evolution of immune-specific proteasomes. Gene duplications, both at the level of the entire genome and *cis* duplications, provided the raw material for the specific β subunits and proteasome regulators involved in adaptive immunity in jawed vertebrates. Special attention is given to the β5 subunit family, which gave rise to the thymic-specific subunit mentioned above and the β5i immunoproteasome member, which is required for the assembly of immunoproteasomes and forms lineages in almost all cold-blooded vertebrates examined. Birds lack all of the immune-specialized subunits including PA28α and PA28β that regulate immunoproteasome function; further study of the bird CTL and NK systems may shed light on why all of these subunit genes were lost in birds. Specific inhibition of the immunoproteasome has emerged as a promising treatment for immunity-related diseases such as autoimmune disease and allograft rejection. Basler and colleagues (Balser et al. 2018) comprehensively reviewed the effects of immunoproteasome inhibition in allograft transplantation, providing specific hypotheses on which mechanism—antigen presentation, production of cytokines (by APC and/or T cells), T-helper cell skewing, and/or T cell activation—is most important in such inhibition.

For many years, Jenny Ting examined the regulation of MHC class II genes. Surprisingly, she found that a master regulator of class II expression, CIITA, is a member of the NLR (nucleotide-binding domain, leucine-rich-repeat containing) family. Recently, another member of the NLR family, NLRC5, was found to regulate class I presentation and processing gene expression. Vijayan and colleagues (Vijayan et al. 2019) review the major features of these transactivators, and a perspective on future work. Evolutionarily, it is of interest to ask why members of this innate-gene family are involved in MHC class I and class II regulation.

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