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Grand challenges in molecular antigen-presenting cell-biology

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All adaptive immune responses are initiated by dedicated antigen-presenting cells (APCs), mainly dendritic cells (DC), whose principal purpose is the activation of T-cells. To this end, APCs need to correctly perform a series of complex functions: First, they need to home to tissues to be available for collecting antigens. Then they need to transport the antigen to secondary lymphatic organs, where naïve T-cells await activation. The antigen must be endocytosed and loaded onto MHC molecules to be visible to T-cell receptors, necessitating the existence of a specialized antigen processing machinery. Antigenic peptides for presentation to $CD4^+$ T helper and $CD8^+$ T effector cells have their own rules of Ag-processing: to generate MHC class II-peptides for T helper cell activation, APCs take up *exogenous* protein Ags, proteolytically process it in late endosomes, load nascent MHC class II molecules with "fitting" peptides, and export the MHC class II-peptide complex to the cell membrane for presentation to T helper cells. In contrast, canonical MHC class I-peptides for $CD8^+$ T-cell activation are generally derived from intracellularly synthesized (endogenous) proteins that first undergo a proteasomal processing pathway before fitting peptides are loaded on MHC class I molecules and presented to $CD8^+$ T-cells. This restriction of MHC class I loading, however, can be overcome by a process termed "cross-presentation," which allows exogenous Ag to "cross" into the MHC class I pathway for activation of CD8 T-cells. The recent clarification of some underlying molecular mechanisms has ended the long controversy regarding cross-presentation. It was shown that only distinct DCs characterized by expression of CD8α, XCR1, and the transcription factor Batf3, can cross-present. Such DC's sequester the MHC class I loading machinery for exogenous Ag to phagosomes and early (recycling) endosomes that are supplied with Ag by specific receptors such as the mannose receptor or Clec9a. Especially the research field of DC subsets is developing rapidly.

In addition to antigen, APCs also need to deliver co-stimulatory signals that are required for immunogenic T-cell activation. These signals are expressed depending on recognition of molecular patterns indicating the presence of microbes or any forms of danger, implying that APCs must possess a range of sensors to detect such patterns. The lack of such patterns, and consequently of co-stimulation, is thought to result in T-cell tolerance. As this is the situation for self-antigens, it has been speculated that induction of peripheral T-cell tolerance is another central function of APCs. The classical "signal 1/2" theory by Cohn and Bretscher is still used to explain how APCs induce either immunity or tolerance. Subsequently, it has been realized that APCs not merely switch on T-cells, but in addition program them to perform distinct functions appropriate for defense against the great variety of viruses, bacteria, fungi, and parasites we are facing incessantly. The signals determining T-cell functional differentiation have been referred to as "signal 3." The recent discovery that APCs use distinct chemokines to attract naïve T-cells has been interpreted as a distinct signal for T-cell activation acting before signals 1, 2, and 3, which therefore has been coined "signal 0." Finally, APCs also affect the functions of effector T-cells infiltrating infected or inflamed tissues, for example by producing cytokines and chemokines.

This short summary of APC-function may create the impression that most of the complex functions of APCs in the induction of adaptive immunity and in avoiding autoimmunity are well understood. However, on closer inspection there can be no doubt that our knowledge on the exact mechanisms governing APC-function is superficial at best. For example, many different classifications of DCs currently co-exist, which partially overlap, and not always reflect on true cellular lineages, but are sometimes based only on cell surface markers. The nomenclature of DCs has been developed separately from that of macrophages, which also possess potent antigen-presenting functionality. Furthermore, the definitions of DCs and macrophages overlap, and it is unclear whether a line can be drawn and where. "The enigmatic signal 2" that decides between immunogenic and tolerogenic T-cell activation includes, but is not equal to B7 molecules, and thus remains to be identified. So do the pattern-recognition and interpretation mechanisms that APCs use to decide whether to express signal 2 or not, and to produce signal 3. Furthermore, if an APC carries both self-antigens and microbial antigens that have caused its maturation, will its maturation state also apply to the self-antigen, so that it is presented in an immunogenic manner? This and many other central questions remain unresolved.

We challenge the field to tackle our top 10 unresolved questions in APC biology:

1. Advancing methodology and techniques to study APC-function, for example single immune cell tracking techniques.
2. Understanding ontogenesis of APC types and subsets; developing a simplified classification based on functional and ontogenic, rather than phenotypic qualities.
3. Understanding Cell-biology and Biochemistry of antigen processing, especially for MHC I-restricted cross-presentation; for example how are antigens transported over organelle membranes within APC's?
4. Identifying signal 2 that decides between immunity and tolerance; for example clarify the role of DC-derived IL-2.

5. Unravel the pattern-recognition and interpretation mechanism of APCs resulting in the expression of signal 2.
6. Deciphering "pattern-recognition" signal pathways that result in signal 3: APC-driven Th-1, Th-2, Th-17, and Treg polarization.
7. Understanding the mechanisms governing APC migration from BM through blood into tissues, and on to secondary lymphatics.
8. Clarify the role of tissue-resident APCs during the T-cell effector phase, including non-hematopoietic cells with APC-functionality.
9. Develop prospects of DC cell therapies.
10. Most likely the development of rationale vaccines will be one of the key paradigms of the twenty-first century. We anticipate that deciphering the molecular APC Biology will be precondition to realizing this most challenging objective.

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