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Review

The role of endosomes in innate and adaptive immunity

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ABSTRACT

The regulation of the immune system is critical for the generation of effective immune responses to a range of pathogens, as well as for protection against unwanted responses. The regulation of many immune response pathways are directly dependent on the organisation and activities of intracellular endosomal compartments associated with cargo sorting, membrane trafficking and signalling. Over the last 5–10 years, the appreciation of the important contribution of the endosomal system has expanded dramatically to include antigen presentation of MHC class I, MHC class II and CD1 molecules, as well as the regulation of antigen receptor signalling and pattern recognition receptor signalling of the innate immune system. This review summarises some of the very diverse and key roles played by endosomes in generating effective innate and adaptive immune responses.

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1. Introduction

Advances in the field of immunology over the past four decades were intrinsically associated with the capacity to sort immune cells into distinct populations by flow cytometry. Leonard Hertzenberg, who died in October 2013, pioneered the development of the modern flow cytometer that allowed separation of cells using fluorescent markers [1]. Fluorescence activated cell sorting (FACS) has become a fundamental tool and exploits cell surface markers in the analysis and separation of different viable cell populations, for example thymocytes in different stages of T cell development and lymphocyte subsets with different immune functions from peripheral lymphoid organs, for subsequent analyses and functional studies. The use of flow cytometry and associated technologies focused immunologists on the plasma membrane and the markers present at the cell surface, and until recently little attention was given to the membrane trafficking of these cell surface markers and their intracellular itineraries. Indeed there was tendency by the field to consider the level of cell surface markers to reflect the

Abbreviations: FACS, fluorescence activated cell sorting; MHCI, MHC class I molecules; MHCII, MHC class II molecules; APC, antigen-presenting cells; DC, dendritic cells; TCR, T cell receptor; MVB, multi-vesicular body; ILV, intraluminal vesicles; MARCH, membrane-associated RING-CH; ERAD, ER-associated degradation; NOX2, NADPH oxidase 2; TAP, transporter associated with antigen processing; MTOC, microtubule organising centre; ITAM, tyrosine-based activation motifs; unc119, Uncoordinated 119; BCR, B cell antigen receptor; TLR, toll-like receptor; HOPS, homotypic fusion and vacuole protein sorting.

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total level of expression by the cell and, furthermore, the process of internalisation from the cell surface into the endosomal system was initially considered a pathway to access the lysosomes for degradation and turnover of molecules. On the other hand, work by cell biologists over the intervening period demonstrated that many cell surface molecules, including important immune molecules, are dynamically trafficking between intracellular compartments and the cell surface. The convergence of these two fields over the past decade have now witnessed a more cell biological approach in dissecting the functional properties of immune cells, approaches which have highlighted major roles for the endosomal system in the regulation of both innate and adaptive immune responses.

Initial interest in the intracellular events and compartment organisation of immune cells was sparked when it was appreciated more than 20 years ago that MHC class II molecules (MHCII) bind antigenic peptides derived from extracellular antigens. Molecular immunologists focused their attention on the process of antigen uptake, degradation of antigen in endosomal compartments, the binding of the antigenic peptides to MHCII molecules and transport of the MHCII/peptide complex to the cell surface for recognition by the T cell receptors on the surface of CD4+ T cells. It became clear that to identify the cell biology of this pathway it was imperative that the relevant specialised cells were examined, namely professional antigen presenting cells (APC), as these specialised immune cells had features associated with their endosomal system that were optimised for the pathways relevant to antigen presentation. It also became clear that the paradigm that extracellular antigens were exclusively presented on MHCII molecules was not correct; whereas the majority of MHC class I (MHCI) molecules are loaded with peptides derived from endogenous intracellular antigens, it was also possible for MHCI molecules to be loaded with extracellular (foreign) antigen. Loading of extracellular antigens onto MHCI molecules was initially inferred from *in vivo* experiments and coined cross-priming by Bevan and colleagues in 1976 [2], with the current terminology of cross presentation now denoting the antigen loading process itself. How the internalised antigens were released/transferred to the cytosol from the endosomal compartments to access the proteasome machinery and the MHCI loading machinery became a central question to understand the mechanism(s) of cross-presentation. Nonetheless, during the 1980s and 1990s the importance of endosomal compartments in immunology was mostly restricted to questions concerning antigen presentation.

The last decade has witnessed major advances in understanding the cell biology associated with innate immune responses, inflammation and adaptive immune responses. The nexus between pattern recognition of infectious agents by innate immune cells and the activation of adaptive immune responses has been a pivotal conceptual discovery [3]. At the same time, cell biologists have revealed the relevance of endosomes as compartments at the intersection of both the endocytic and anterograde pathways, the importance of endosomes in recycling of membrane receptors, and the ability of endosomes to contribute to signal transduction. Intracellular endosomal signalling is particularly relevant to initiate innate immune responses. These recent studies have revealed many surprises and highlight the importance in understanding the convergence of endocytic traffic containing endocytosed pathogens with traffic from the secretory pathway to delivery pattern recognition receptors which can respond to "danger signals" within endocytic compartments [4]. Hence, the understanding of cargo sorting signals, trafficking machinery, and the communication of endosomal components with signalling networks have become key issues. These findings are particularly important to consider for the development of novel inhibitors which influence the activation of immune responses [5].

Endosomes are not only important in initiating innate and adaptive responses, but also for the transport of newly synthesised cargo for delivery to the cell surface. Secretion of cytokines and chemokines by activated immune cells is critical for the effector phase of an activated immune response. Recycling endosomes have been shown to be critical to the anterograde pathway and the post-Golgi delivery to the cell surface of a number of inflammatory and regulatory cytokines, as well as the regulation of membrane flux between the endosome compartments and the cell surface [6,7]. However the role of endosomes in anterograde transport is beyond the scope of this review, which will focus predominantly on examples to illustrate the role of early and late endosomes in immune responses (see Fig. 1 for overview). Adaptive immune responses will be discussed first, as the importance of endosomal events in antigen presentation has had a long association, followed by the more recent discoveries on the role of endosomes in innate immune responses.

2. Adaptive immunity

2.1. Antigen presentation to CD4+ T cells

Adaptive immune responses are initiated by the recognition of antigen presented by MHCII molecules on APCs to CD4+ T cells. MHCII expression is restricted to professional APCs that include B cells, macrophages and dendritic cells (DCs). Of the three cell types, DCs are considered the predominant APC for activating naïve CD4+ T cells. As professional APCs, DCs are highly efficient at internalising antigen by fluid phase macropinocytosis or by receptor-mediated endocytosis [8]. These pathways converge on the endosomal system, where internalised antigens are hydrolysed by proteases, of which the cathepsins are the major group, in an acidic environment and the resulting peptides of variable lengths compete for binding to MHCII molecules in the MHCII loading compartment. The peptides loaded are defined by the specificity of the binding cleft of individual MHCII alleles. It is likely that antigen processing by exoproteolysis can continue after MHCII loading (see [8]) and then the stable MHCII/peptide complexes are transported from the loading compartment to the cell surface. The general pathway is now well understood and the reader is referred to a number of outstanding reviews on this topic [8–12].

An important issue identified early in this field was the importance of using specialised APCs, rather than surrogate transfected cells, to dissect the pathway of antigen presentation and the identity of the MHCII loading compartment(s). A key factor in understanding the endosomal events in antigen presentation is that DCs undergo a maturation programme in response to pathogens or inflammatory stimuli [8,11]. The maturation of DCs is associated with a dramatic increase in expression of MHCII and co-stimulatory molecules at the cell surface [11,13]. In addition there is altered intracellular trafficking of MHCII which impacts on the re-distribution of MHCII resulting in an elevated delivery of MHCII to the cell surface coupled with an extension of half-life of MHCII. Moreover, maturation of DCs is associated with a transient increase in macropinocytosis to maximise uptake of the antigens associated with the inflammatory stumuli [14]. The pathways and molecular mechanisms that regulate the trafficking of MHCII molecules in APC involve generic mechanisms found in most cell types; however, pathways for MHCII trafficking have been elaborated in DCs to handle the load of specialised MHCII cargo, resulting in an optimised system for maximising the presentation of exogenous antigens following an inflammatory stimuli mediated by an invading pathogen.

The late endosomes/lysosomes represent the major loading compartment where the majority of MHCII is loaded with antigen.

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