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Modulation of antigen presentation by intracellular trafficking

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Processing and loading of antigen into major histocompatibility complex molecules (MHC) occurs in specific intracellular compartments. Accessing MHC loading compartments requires trafficking via specific pathways, some of which have yet to be fully characterized. For MHC I, cross-presentation involves antigen trafficking to a specialised compartment. We review the features of this compartment and how it is accessed by different mechanisms of antigen capture and internalization. We also summarize advances in understanding how antigen efficiently accesses the MHC II loading compartment, with particular focus on the role of autophagy. Understanding the mechanisms that control how antigen is trafficked to specific compartments for loading and presentation is crucial if these pathways are to be manipulated more effectively in settings of vaccination.

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Introduction

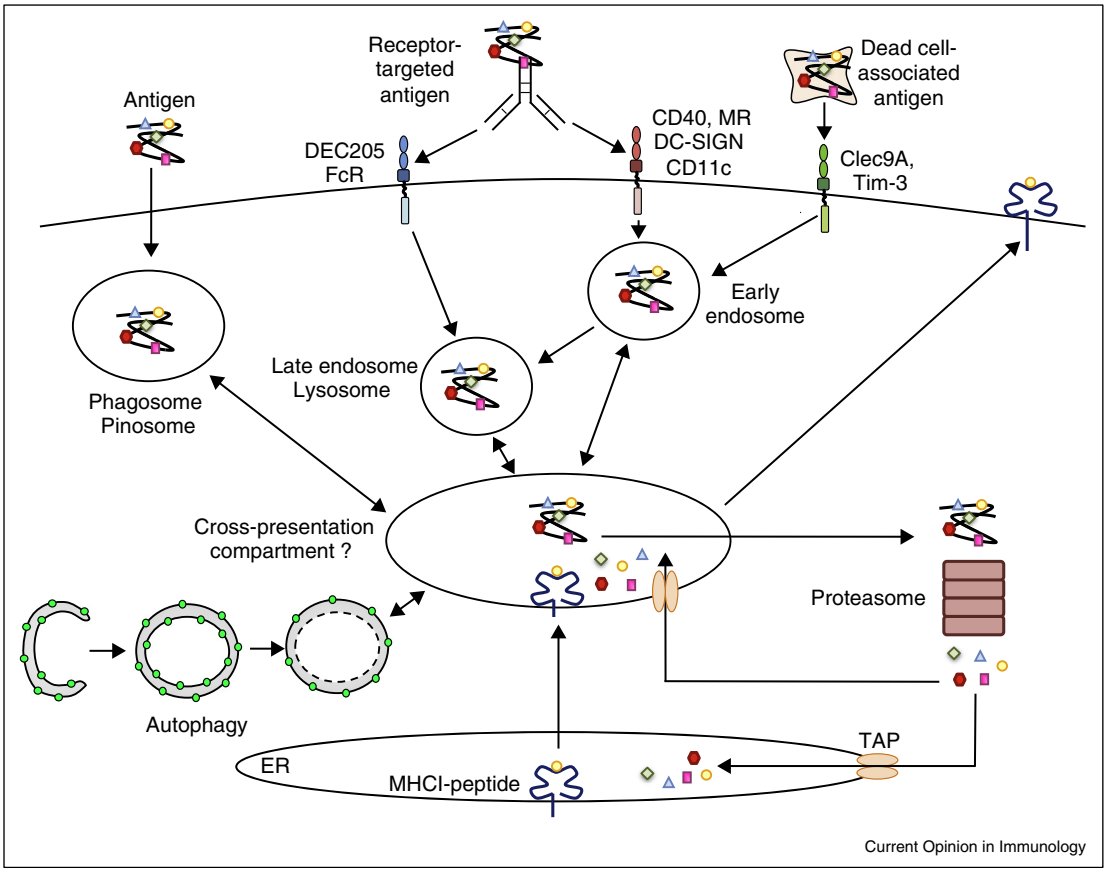
Presentation of antigens captured from extracellular sources is generally considered an attribute of MHC class II molecules (MHC II), but it is now accepted that such antigens can also be *cross-presented* by MHC class I molecules (MHC I). Conversely, presentation of antigens contained in the nucleo-cytoplasmic space was considered the domain of MHC class I, but it is now clear these antigens contribute a sizable proportion of the peptide repertoire presented by MHC II. MHC I cross-presentation of exogenous antigens, and MHC II presentation of nucleo-cytosolic antigens, entail the participation of specific endosomal organelles and intracellular trafficking pathways that are different to those involved in classical MHC I and II presentation. Here we review recent developments on the characterization of the antigen trafficking required for these mechanisms.

MHC I cross-presentation

For exogenously acquired antigen to be cross-presented by MHC I, it has to access a specific endosomal location that is equipped with the required attributes to facilitate processing and MHC I loading (Figure 1). As cross-presentation in vivo appears to be carried out predominantly, if not only by dendritic cells (DC), studies aiming to characterize this route have focused on DC. The cross-presentation compartment has been identified by several markers including Rab 5 and EEA-1 [1], Rab 14 [2,3], and RAB3b/3c [4]. A major feature of the compartment is its ability to store antigen for prolonged periods without significant proteolysis [1,5–8]. The low protease activity stems from a more neutral pH that is generated by the recruitment of NADPH oxidase complex NOX2 to the endosomal membrane [9] in a process facilitated by the GTPase Rac2 [10]. Lowering the proteolytic activity of the resident proteases consequently ensures the acquired antigen is preserved or only partially processed, facilitating its transport out of the endosome and into the cytosol where it is degraded by the proteasome. How antigen is trafficked across the endosomal membrane is not well defined, however several studies implicate a role for the endoplasmic reticulum (ER) retrotranslocation machinery in a mechanism similar to ER-associated degradation (ERAD) [11–13]. Once present in the cytosol, proteasomal degradation liberates peptides that are then imported into the ER, or returned to the endosomal compartment, for MHC I loading [14]. Import of peptides into endosomes is achieved by the ER-resident transporter associated with antigen processing (TAP), implying that for endosomal MHC I loading to occur, TAP has to be recruited to these compartments [14]. Crucial for trafficking of ER proteins to endosomes is SEC22b, an ER-resident SNARE. SEC22b is required for cross-presentation, but not endogenous MHC I antigen presentation [12].

Simply entering the endocytic route is not sufficient to ensure efficient cross-presentation. Antigen must gain access to the cross-presentation compartment (Figure 1). What is the best way to get there? One useful approach to address this is to track antigen that is fused to mAb specific for receptors with defined endosomal trafficking routes. Antigen targeted to CD40 [15•,16•], mannose receptor

Figure 1



Intracellular trafficking of antigens during MHC I cross-presentation. MHC I cross-presentation involves endocytosed antigen export from the endosomal compartment to the cytosol for proteasomal degradation. Peptide products are imported into the ER or into endosomes via TAP for MHC I loading. Antigens acquired by phagocytosis or pinocytosis gain access to the MHC I cross-presentation pathway. In addition, antigens targeted to receptors including CD40, mannose receptor (MR), DC-SIGN or CD11c traffic to early endosomes and are efficiently processed for MHC I cross-presentation. Other receptors including DEC205 and FcR-targeted antigens access late endosomes/lysosomes to elicit MHC I cross-presentation. Antigens associated to cell debris are engulfed and cross-presented following binding to specific receptors such as Clec9A or Tim-3. Autophagy has been suggested to modulate MHC I cross-presentation although the underlying mechanism remains unclear.

(MR) [1,13,16•,17,18], DC-SIGN [19] and CD11c [15•], all show preferential traffic to early endosomes and all elicit efficient cross-presentation. Likewise, soluble antigen coupled to transferrin [17] and liposome-encapsulated antigen [20] also traffic to early endosomal compartments and promote cross-presentation of their cargo antigen. Although CD40 and MR both traffic to early endosomes, CD40 is the more efficient receptor at promoting cross-presentation [16•]. It has been proposed that the slower speed of antigen internalization exhibited by CD40 receptor likely enhances the efficiency of cross-presentation, allowing for a more sustained delivery of antigen over time [16•]. Notably, early endosomes are not the only compartment from which cross-presentation can be facilitated. DEC205, a C-type lectin that traffics to late endosomes and lysosomes [15•,16•,21], can elicit efficient cross-presentation [60,61]. Indeed, targeting DEC205 on human and mouse DC has been exploited as a delivery route for cross-presentation of tumour and viral antigens (reviewed in [22]). Immunoglobulin receptor (FcR) also traffics to lysosomes and is likewise capable of promoting effective cross-presentation when targeted with antigen [23•]. Therefore, antigen traffic to either early endosomes or lysosomes can efficiently promote cross-presentation. However, not all DC appear capable of utilizing early endosomes and lysosomes as platforms for cross-presentation. Human BDCA3$^+$ DCs are superior at cross-presenting antigen targeted to late endosome/lysosomal compartments, relative to their BDCA1$^+$ counterparts, while both subsets are equivalent at cross-presenting antigen targeted to early endosomes [15•].

The type of antigen captured by a DC can influence the mechanisms engaged for its internalization, downstream trafficking and cross-presentation. Antigen acquired by pinocytosis, receptor-mediated endocytosis and phagocytosis can all be cross-presented by MHC I [24]. Notably, cell-associated antigen gains more efficient