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Autophagy and MHC-restricted antigen presentation

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ABSTRACT

Major histocompatibility complex (MHC) molecules present peptide antigens to T lymphocytes and initiate immune responses. The peptides loaded onto MHC class I or MHC class II molecules can be derived from cytosolic proteins, both self and foreign. A variety of cellular processes, including endocytosis, vesicle trafficking, and autophagy, play critical roles in presentation of these antigens. We discuss the role of autophagy, a major intracellular degradation system that delivers cytoplasmic constituents to lysosomes in both MHC class I and II-restricted antigen presentation. We propose the new term "Type 2 cross-presentation" (CP2) to define the autophagy-dependent processes leading to MHC II-restricted presentation of intracellular antigens by professional antigen presenting cells. A better understanding of Type 2 cross-presentation may guide future efforts to control the immune system through autophagy manipulation.

1. Antigen processing and presentation

Adaptive immune response has to be instructed to identify and eliminate specific pathogens or foreign entities defined by their antigenic determinants. Processed antigenic peptides are loaded on major histocompatibility complexes (MHC) and presented by professional antigen presenting cells (APC) to cognate T cells for priming and activation. MHC class II (MHC II) and its associated molecular machinery are naturally expressed by professional APC or upon exposure to interferon (IFN)-γ by other cells (Bania et al., 2003). One of the most prominent types of APCs are dendritic cells (DC), cells capable of orchestrating the immune response (Blum et al., 2013) by presenting antigenic peptides to naïve T cells. Recognition of peptides by these naïve T cells promotes their activation and initiates adaptive immune responses. Upon activation, T cells proliferate and differentiate into effector T cells, which migrate to inflamed tissues, where they exert their functions and contribute to the eradication of invading pathogens.

MHC class I (MHC I) is expressed by all nucleated cell types and displays peptides to primed $CD8^+$ cytotoxic T lymphocytes (CTL), which can kill target cells (*e.g.* tumours or virally infected cells) upon recognition of the right antigen-MHC combination (Blum et al., 2013). MHC I-restricted antigens originate predominantly from endogenous neosynthesized proteins (Fig. 1, green arrows). These intracellular antigens are processed by the proteasome into short peptides that are translocated by the TAP transporters into the lumen of the endoplasmic reticulum (ER) (Powis et al., 1991), where they can be loaded onto freshly translated MHC I complexes. Peptide-loaded MHC I complexes then follow the secretory pathway reaching the trans-Golgi network (TGN), from which they are mostly and directly addressed to the cell surface, while a minority reaches specific sorting endosomes, potentially serving cross-presentation of endocytosed antigens (De Angelis Rigotti et al., 2017; Nair-Gupta et al., 2014). Surface peptides/MHC I complexes displayed by activated DCs to naïve CTLs promote their proliferation and differentiation. These circulating CTLs, then, survey the occurrence of abnormalities in the MHC I-presented peptidome at the surface of other nucleated cells to kill transformed or infected ones and limit disease spreading.

MHC II-restricted antigens are mostly of extracellular origin (Fig. 1, blue arrows). Extracellular antigens are captured by receptor mediated endocytosis, phagocytosis or macropinocytosis. Phagosome and endosome content gets digested during their progression towards MHC II-containing late endosomal compartments (MIIC), which display the biochemical features of multivesicular bodies (MVB) (Schmid et al., 2007). Newly synthetized MHC II complexes, with their antigen-binding groove shielded by the invariant chain chaperone (Ii), are also addressed to MIIC. There, Ii is degraded by specialized endosomal proteases, such as cathepsin S (Bania et al., 2003), and the remaining Ii peptide (CLIP), still occupying the groove, is exchanged by the HLA-DM

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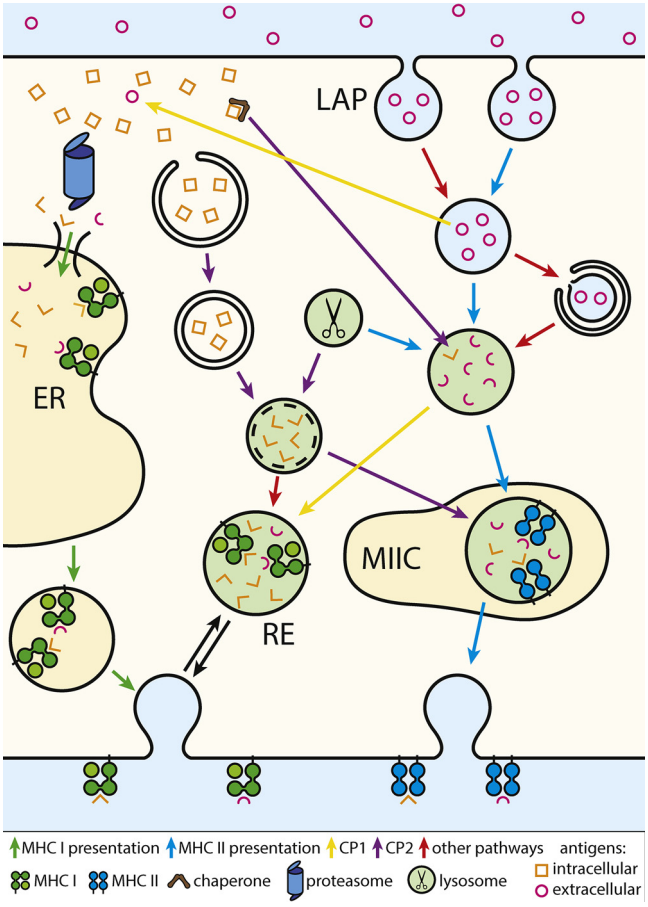

Fig. 1. Different routes of antigen processing for MHC presentation. Intracellular antigens are processed for presentation on MHC I (green arrows) and extracellular antigens for presentation on MHC II (blue arrows). Type 1 cross-presentation (CP1, yellow arrows) enables presentation of extracellular antigens on MHC I, either by transporting internalized antigens to the cytosol, or by allowing peptide loading in MHC I-containing endosomes. Type 2 cross-presentation (CP2, violet arrows) mediates presentation of intracellular antigens on MHC II, either by the autophagosome playing the processing and transport role of phagosomes in classical MHC II presentation pathway, or by chaperone-mediated translocation of antigens into lysosomes. Autophagy can also have other roles in antigen presentation (red arrows). It is an alternative pathway for MHC I presentation by delivering intracellular antigens to the recycling endosome (RE). Furthermore, the autophagy machinery enhances MHC II presentation of extracellular antigens by acquiring specific antigens through LC3-associated phagocytosis (LAP) or by autophagy-mediated disposal of ruptured phagosomes. MIIC (MHC II-containing late endosomal compartment), ER (endoplasmic reticulum) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

dimers for peptides derived from internalized antigens (Blum et al., 2013). Peptide-loaded MHC II are then transported to the plasma membrane through a complex recycling pathway involving ubiquitination and members of the MARCH E3-ligases family (De Gassart et al., 2008; Shin et al., 2006; van Niel et al., 2006). In DCs, activation by microbial products or inflammatory cytokines alters traffic of MHC II and co-stimulatory molecules, enhancing CD4 + T cell (T helper) stimulatory capacity of the DCs.

Although the specificity of MHC I and MHC II is well known, restrictions are not absolutely tight and extracellular antigens can be presented by MHC I in a process known as cross-presentation (Amigorena and Savina, 2010), while MHC II can be associated with endogenous antigens. Cross-presentation (CP) allows cells such as DCs to prime CTLs without the need for being infected or transformed to display pathogen- or tumour-derived antigens (Cruz et al., 2017). CP occurs notably in the XCR1$^+$ DC subtype and is favoured by microbial or type-I interferon-dependent activation (Vu Manh et al., 2015). To deliver antigens to MHC I, two main pathways have been implicated (Fig. 1, yellow arrows). The cytosolic pathway, in which phagocytosed proteins are transported to the cytoplasm through an ill-defined molecular mechanism, enabling proteasome-mediated processing into peptides, which are translocated to the ER and loaded on MHC I (Kovacsovics-Bankowski and Rock, 1995). Alternatively, the vacuolar pathway allows direct loading of antigenic peptides from lysosomes on MHC I in specific endosomal compartments involving recycling endosomes (Di Pucchio et al., 2008).

Although CP has been an important research subject in the field of antigen processing and presentation, the mechanisms of presentation of intracellular antigens by MHC II received considerably less attention. Interestingly, pioneering work by the Münz laboratory has pointed to an involvement of autophagy in this process (Fig. 1, violet arrows), raising numerous questions on the impact of autophagy regulation on different aspects of endogenous antigen processing and MHC II-restricted presentation by APCs (Argüello et al., 2016; Münz, 2016a, 2016b, 2015).

2. Autophagy and antigen presentation

Macroautophagy (hereafter referred to as autophagy) is a physiological phenomenon that allows cells to degrade and recycle different cytoplasmic components. Numerous review articles have recently described the detailed molecular mechanism regulating autophagy (*e.g.* Dikic and Elazar, 2018) and we provide here only a brief summary of these findings. The mTOR Complex 1 (mTORC1) is a nutrient/energy/redox sensor and controller of protein synthesis. that upon inactivation (*e.g.* upon starvation) induces autophagy by stimulation of the autophagy initiator complex kinases ULK1/2 (Mizushima, 2010). Activated ULK recruits phophatidylinositol-3 kinase Vps34 complex to the endoplasmic reticulum (ER) and activates it to produce phosphatidylinositol-3-phosphate (PI3P) in the pre-autophagosomal membrane (Dooley et al., 2014). Subsequently, PI3P effectors mediate lipidation of the Atg8-family members (*e.g.* LC3, GABARAP), that promotes autophagosome formation upon sequestration of cytoplasmic content by an engulfing double-membrane. Autophagosomes then fuse with lysosomes in a tightly regulated biochemical process, and all their content, including the inner autophagosomal membrane, is digested by lysosomal enzymes.

In APCs, autophagosome fusion with MIIC allows access of cytosolic antigens to the MHC II loading machinery (Fig. 1, violet arrows). This autophagy-mediated antigen processing and presentation pathway allows stimulation of CD4$^+$ T cells specific for intracellular antigens. This process is particularly important for negative T cell selection in the thymus (Nedjic et al., 2008), as well as for induction of an efficient antiviral immune response (Münz, 2016a). Autophagy-dependent antigen presentation may also be relevant during autoimmunity. Expression of the autophagy related protein Atg5 by DCs is required for the presentation of myelin antigen that promotes experimental immune encephalomyelitis (EAE) in the murine model of multiple sclerosis (Keller et al., 2017). Thus, autophagy-mediated antigen presentation is clearly an immunologically relevant process, which, has not yet been semantically defined. To facilitate its description, we propose the term “Type 2 cross-presentation” (CP2), to define the molecular activities leading to all types of autophagy-dependent MHC II-restricted presentation of intracellular antigens by APCs. In contrast, traditional MHC I-restricted cross-presentation of extracellular antigens should be termed “Type 1 cross-presentation” (CP1). The numbering also conveniently matches the MHC class used in the respective processes and the chronology of their discovery.