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Review

Checking the garbage bin for problems in the house, or how autophagy assists in antigen presentation to the immune system

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ABSTRACT

Macroautophagy was originally discovered as a nutrient salvage pathway during starvation. By now it has not only become clear that degradation of cytoplasmic constituents via transport by autophagosomes to lysosomes can be used for innate and adaptive immunity, but that the core machinery assists antigen presentation to the immune system by a variety of vesicular transport pathways. All of these rely on the presentation of small protein waste fragments, which are generated by a variety of catabolic pathways, including macroautophagy, on major histocompatibility complex (MHC) molecules. In this review, we will point out how classical macroautophagy, as well as phagocytosis and exocytosis, which both benefit from the core autophagic machinery, assist in antigen presentation on MHC class I and II molecules to CD8+ and CD4+ T cells, respectively. Finally to high-light that macroautophagy is always intimately interconnected with cell death in addition to the various supported vesicular transport function, its role in lymphocyte, especially T cell, development and function will be discussed. From this body of work a picture is emerging that the core machinery of macroautophagy can be used for a variety of vesicular transport pathways and to modulate cell survival, besides its classical role in delivering intracellular material for lysosomal degradation.

1. Introduction

The adaptive immune system hinges on the orchestration by CD4+ helper T cells and cytotoxic CD8+ T cells as main effectors of cell-mediated immunity. These lymphocyte populations do not recognize antigen directly, but their T cell receptors detect antigen fragments on major histocompatibility (MHC) class I molecules for CD8+ T cells and MHC class II for CD4+ T cells. These fragments, peptides of eight or nine amino acids in length for MHC class I and longer, often N- and C-terminal extensions of a nonameric core sequence for MHC class II, are generated and loaded onto MHC class I and II molecues in different cellular compartments [1,2]. MHC class I ligands are in their majority generated by the proteasome, a multicatalytic protease in cytosol and nucleus. In contrast, peptides for MHC class II loading are primarily produced in lysosomes. Loading of MHC class I and II molecules occurs primarily in the endoplasmic reticulum (ER) and late endosomes, respectively. Both molecules are co-translationally inserted into the ER. MHC class I ligands of proteasome origin get transported into the ER by the transporter associated with antigen processing (TAP) and loaded onto MHC class I molecules in the MHC class I loading complex, containing aminopeptidases, chaperones and protein disulfide isomerases. Once a high affinity peptide is loaded into the peptide binding groove of MHC class I, the complex is transported to the cell surface for CD8+ T cell recognition. Peptide binding to MHC class II molecules in the ER is prevented by the chaperone invariant chain (Ii), which blocks the peptide binding groove and contains in its cytosolic domain motifs that will facilitate the transport to late endosomes, either via the cell membrane or directly. These late endosomes that are equipped with the MHC class II loading machinery are called MHC class II containing compartments (MIICs). Lysosomal proteolysis within these compartments degrades Ii until only the peptide binding groove contains the last Ii remnant, called MHC class II associated invariant chain peptide (CLIP). CLIP is then exchanged for a high affinity peptide with the help of the chaperone HLA-DM or H2-M. In some cell types like B cells the negative regulator HLA-DO or H2-O modifies this event. MHC class II complexes, stabilized by high affinity peptides, then migrate to the cell surface in order to engage CD4+ T cells.

Access to MIICs or proteasomes, maybe even specific immunoproteasomes, decides how efficient antigens can be loaded onto MHC molecules for T cell stimulation. Due to their co- localization, cytosolic and nuclear antigens are preferentially processed for MHC class I presentation, and endocytosed antigens efficiently reach MIICs. Thus, in the classical paradigm of antigen processing,

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intracellular antigens are loaded onto MHC class I, while extracellular antigens are preferentially processed for MHC class II presentation. However, there are exceptions to this rule. In specialized antigen presenting cells, like dendritic cells (DCs), extracellular antigens can gain access to MHC class I presentation. This pathway is called cross-presentation [3]. During cross-presentation, antigen is thought to escape from early endosomes or even after endosome fusion with the ER into the cytosol for proteasomal degradation. Vice versa, intracellular antigen fragments can be found on MHC class II molecules and autophagy contributes to this processing as will be discussed in the next chapter.

2. Delivery of intracellular antigens for MHC class II presentation via autophagy

Evidence of intracellular antigen processing onto MHC class II molecules originally came from peptide elution studies, which were aimed at characterizing the ligand repertoire that is presented to CD4+ T cells. These studies revealed that up to one third of eluted MHC class II ligands originate from cytosolic and nuclear source proteins [4–6]. MHC class II presentation of these cytosolic and nuclear antigens can be enhanced by starvation, which upregulates macroautophagy [4]. Among these peptides, the essential autophagy proteins LC3 and GABARAP were found [4,7]. These are mammalian orthologs of the ubiquitin-like autophagy related gene (Atg) 8 protein that get coupled to the membranes of autophagosomes, the characteristic double-membrane vesicles of macroautophagy, during its formation around its substrates [8]. This conjugation is mediated by the E3-like ligase composed of Atg5, Atg16L and the ubiquitin like protein Atg12. Interestingly, Atg8 is the only macroautophagy protein that stays with the completed autophagosome, specifically on the inner autophagosome membrane, while all Atgs are recycled from the outer membrane upon autophagosome completion (Fig. 1). Therefore, the Atg8 homologues LC3 and GABARAP are in part degraded with the autophagosome cargo in late endosomes or autolysosomes by lysosomal hydrolases and can reach MHC class II loading. Accordingly, LC3 can be used to deliver antigens to autophagosomes, which frequently fuse with MIICs [9]. This targeting enhances antigen presentation on MHC class II molecules up to 20fold [9,10]. A physiological condition, under which this self-antigen processing by macroautophagy seems to play a role is thymic selection. Both positive and negative T cell selection was affected in Atg5 negative thymi [11]. During these processes intracellular self-proteins are thought to be presented on MHC class II molecules of thymic epithelial cells (TECs) to ensure low affinity interactions of the selected T cell receptors during positive selection, and eliminating high-affinity T cell receptors against self- proteins during negative selection [12]. Macroautophagy deficiency changes the repertoire of MHC class II presented ligands so that some T cell receptor specificities no longer efficiently survive positive selection, and an autoreactive T cell repertoire emerges from faulty negative selection. Accordingly, autophagosomes fuse frequently with MIICs in TECs [13], and macroautophagy substrates, like mitochondrial proteins and LC3 fusion proteins can induce negative selection [14]. Thus, self-antigens gain access to MHC class II presentation in part via macroautophagy, and this process assists thymic T cell selection.

Following these indications that macroautophagy might contribute to intracellular self- antigen loading onto MHC class II molecules, several viral and bacterial antigens have been investigated for their processing via macroautophagy for CD4+ T cell stimulation. Among these, the nuclear antigen 1 of the Epstein Barr virus (EBNA1) was found to be intracellularly processed for MHC class II presentation [15]. This processing involved lysosomal degradation, and upon inhibition of lysosome acidification EBNA1 accumulated in double membrane vesicles [16]. Moreover, siRNA

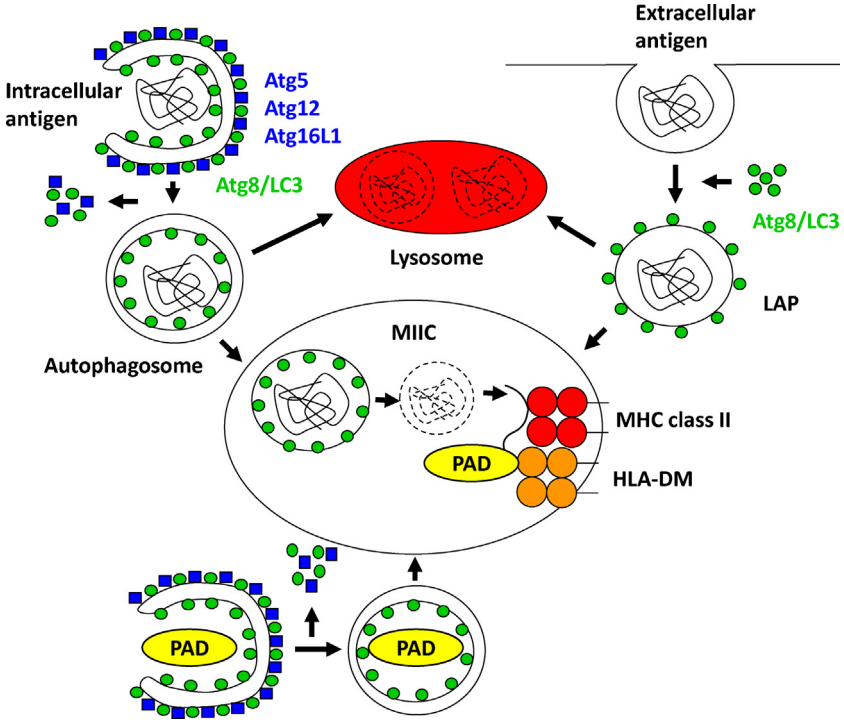

Fig. 1. Contributions of macroautophagy to MHC class II antigen processing.
Macroautophagy can deliver intracellular antigens to MHC class II containing compartments (MIICs) for lysosomal antigen processing and loading of antigen fragments onto MHC class II molecules (top left). In addition, the macroautophagy core machinery modifies phagosomes for LC3-associated phagocytosis (LAP). This can facilitate extracellular antigen processing for MHC class II presentation (top right). Finally, macroautophagy delivers cytosolic hydrolases, like peptidylarginine deiminases (PADs) to endosomal compartments for antigen modification, resulting in MHC class II presentation of altered peptide ligands, like citrullinated peptides (bottom).