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REVIEW

Class II MHC antigen processing in immune tolerance and inflammation

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Abstract
Presentation of peptide antigens by MHC-II proteins is prerequisite to effective CD4 T cell tolerance to self and to recognition of foreign antigens. Antigen uptake and processing pathways as well as expression of the peptide exchange factors HLA-DM and HLA-DO differ among the various professional and non-professional antigen-presenting cells and are modulated by cell developmental state and activation. Recent studies have highlighted the importance of these cell-specific factors in controlling the source and breadth of peptides presented by MHC-II under different conditions. During inflammation, increased presentation of selected self-peptides has implications for maintenance of peripheral tolerance and autoimmunity.

Keywords Major histocompatibility complex · MHC protein · Antigen presentation · Immunopeptidome

Introduction

Presentation of peptide antigens by class II Major Histocompatibility Complex (MHC-II) molecules is critical for maintenance of self-tolerance and for initiation of effective immune responses. Immunological tolerance to antigens presented on MHC-II molecules begins at the selection stage of T cell development in the thymus and continues in the periphery. CD4 T cells necessarily interact with self-ligands presented by MHC-II molecules in the thymus for positive selection and also require tonic stimulation by MHC-II-peptide complexes in the periphery for survival. During the process of thymic negative selection, development of T cells with T cell receptor specificities overtly reactive to self is prevented, and cells with borderline reactivity are directed into the CD4 T regulatory lineage. A peripheral immune response is initiated when antigen-presenting cells (APCs) present peptides that alert the adaptive immune system to mount a targeted response against invading pathogens. Entry of self- and foreign antigens into the endo/lysosomal pathway, proteolytic processing, and selection of peptides for presentation are influenced by APC type, maturation state, and external environment. Thus, the set of peptides presented by MHC-II molecules, known as the MHC-II immunopeptidome, is determined by these factors.

In this review, we discuss the details of MHC-II presentation and processing, with particular focus on the nonclassical MHC-II molecules HLA-DM and HLA-DO and their role in shaping the MHC-II immunopeptidome. We also discuss the influence of APC type and maturation state on the immunopeptidome and how the peptides presented may change under inflammatory conditions. Finally, we explore implications of these changes in generation of immune responses to pathogens and maintenance of tolerance to self-antigens.

Overview of MHC-II synthesis and peptide loading pathways

MHC-II molecules are constitutively expressed on professional APCs, such as dendritic cells, macrophages, and B cells, as well as thymic epithelia, and are upregulated on many other cell types by IFN-γ. The study of MHC-II synthesis and peptide loading pathways has been performed predominantly in B cells and dendritic cells. Expression of MHC-II genes is primarily regulated by the class II transactivator (CIITA), which interacts with multiple DNA-binding proteins to initiate transcription of MHC-II genes and MHC-II antigen processing pathway components (Masternak et al. 2000; Reith et al.

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2005). The MHC-II antigen processing pathway is depicted schematically in Fig. 1, and expression of antigen processing components in various APCs is summarized in Table 1. Following synthesis of MHC-II α and β subunits in the ER, nascent MHC-II molecules bind the invariant chain (Ii) protein, allowing for stabilization of the MHC heterodimer, spatial restriction of peptide loading, and transport to the endocytic compartment for peptide loading (Elliott et al. 1994; Roche and Cresswell 1990). The MHC-II-Ii complex then translocates through the Golgi complex into the endocytic pathway by way of a dileucine targeting motif present in the cytoplasmic domain of Ii (Cresswell 1996; Lotteau et al. 1990; Pieters et al. 1993). As endocytic vesicles acidify, endolysosomal proteases termed cathepsins acquire increased proteolytic activity and cleave the MHC-II-bound invariant chain until only a residual peptide (CLIP or class II-associated invariant chain peptide) remains bound in the MHC-II peptide-binding site (Blum et al. 2013; Riese et al. 1998, 1996). Proteins transported into the lumen of the endosome unfold and are digested by endosomal proteases to allow for MHC-II binding (Hsieh et al. 2002; van Kasteren and Overkleeft 2014; Villadangos et al. 1999; Villadangos and Ploegh 2000). The nonclassical MHC-II peptide exchange factor HLA-DM (H2-M in mice, hereafter referred to as DM) also resides in endosomal/lysosomal compartments and catalyzes the removal of CLIP from the peptide-binding groove of MHC-II molecules with resultant exchange of CLIP for endosomal peptides (Pos et al. 2012; Sloan et al.

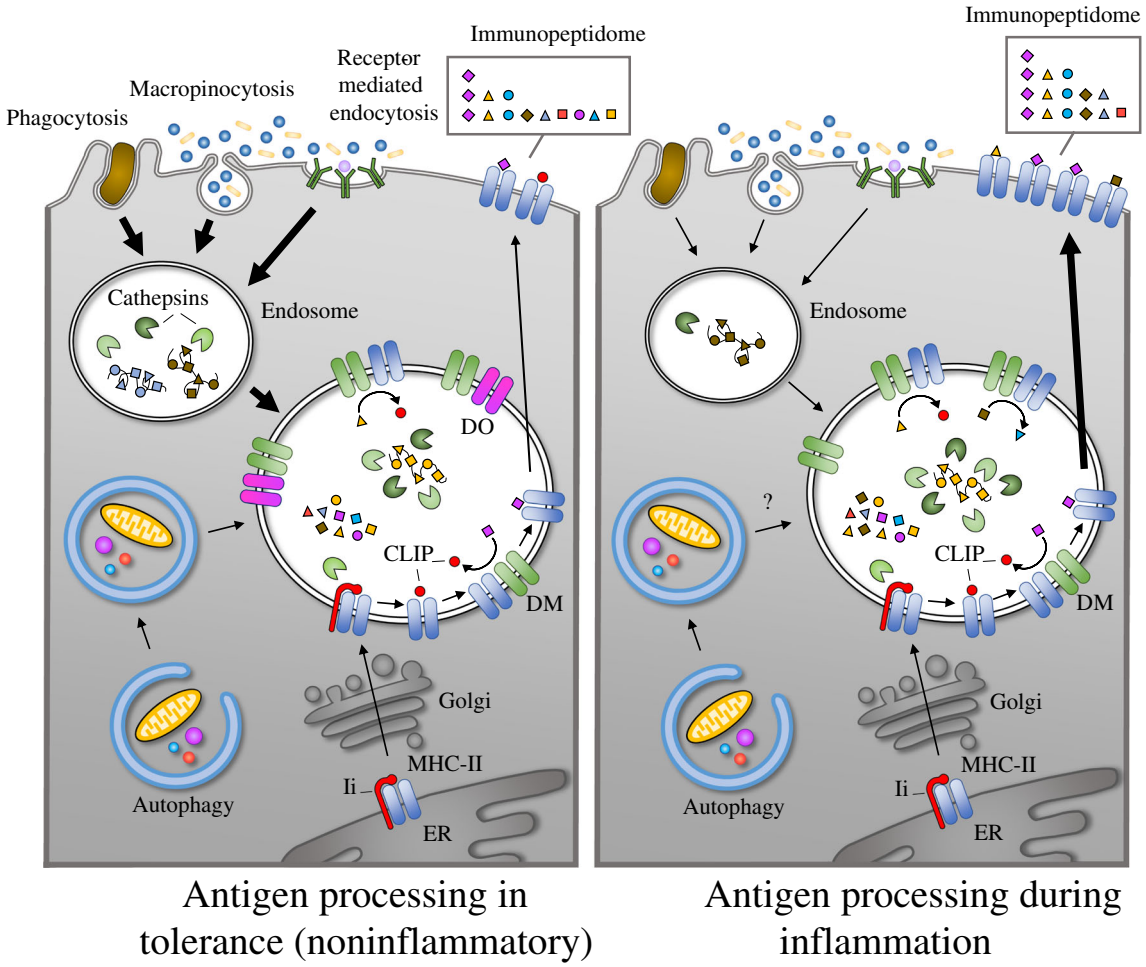

Fig. 1 MHC class II dimers are synthesized in the ER and loaded with invariant chain, after which they traffic to the endosome. Cathepsins cleave the invariant chain (Ii) to the residual peptide CLIP, which is then removed by the peptide exchange factor DM and exchanged for peptides derived from proteolyzed self- and foreign antigens. The MHC-II-peptide complex traffics to the cell surface for presentation to CD4 T cells. To maintain tolerance in noninflammatory conditions (left panel), the immunopeptidome in APCs is comprised of diverse self-peptide antigens acquired through extracellular uptake pathways as well as autophagy. Components of the antigen processing machinery including the DM inhibitor DO further enhance the diversity of the peptides presented. Upon activation and initiation of an inflammatory response (right panel), antigen sampling is reduced, endosomal proteases are redistributed to late endosomes, DO expression is downregulated, and MHC-II expression is substantially increased. (The effects of inflammation on the process of autophagy in APCs are incompletely understood.) During inflammation, these changes result in greater efficiency of MHC-II antigen presentation as well as reduced diversity in the MHC-II peptidome in an immune response

Table 1 Expression of antigen processing components in mouse and human APCs

Cell type	MHC-II expression	Endosomal proteases[b]	DM	DO	Ratio of DM:DO	Refs. (human)	Refs. (mouse)
Immature DCs	+++	**Cat S**, Cat D, Cat E, Cat H, SPPL2A (mu) **Cat D**, **Cat G**, **Cat S**, **AEP** (hu)	✓	✓	Low	Burster et al. (2005); Cella et al. (1997); Hornell et al. (2006); Nijman et al. (1995); Sallusto and Lanzavecchia (1994); Stoeckle et al. (2009)	Immgen[e]; Bergmann et al. (2013); Chain et al. (2005); Chen et al. (2006); Driessen et al. (1999); Fallas et al. (2004); Moss et al. (2005); Nakagawa et al. (1998); Nakagawa et al. (1999); Pierre et al. (1997); Trombetta et al. (2003); Villadangos et al. (2001); West et al. (2013)
Mature DCs	+++++	Cat D, Cat H, Cat L, AEP (ms), **Cat S** (hu and ms), Cat B (hu)	✓	–	High	Sallusto and Lanzavecchia (1994); Cella et al. (1997); Fiebiger et al. (2001); Hornell et al. (2006)	Immgen; Chen et al. (2006); Pierre and Mellman (1998); Pierre et al. (1997); Trombetta et al. (2003); Villadangos et al. (2001)
Macrophages	++	**Cat B**, **Cat E**, **Cat F**, **Cat L**, **Cat S**, **AEP**	✓	–	High	Barascuk et al. (2010); Pires et al. (2016); Ranella et al. (2005); Reilly et al. (1990); Santin et al. (1999)	Immgen; Baumgart et al. (1998); Beers et al. (2003); Driessen et al. (2001); Kakehashi et al. (2007); Manoury et al. (2002); Nakagawa et al. (1999); Shi et al. (2000); Walter et al. (1999)
Monocytes	+	Cat B[c], Cat G, Cat K[c], Cat L[c], Cat S[c] (hu)	✓	–	High	Gren et al. (2015); Lee et al. (2017); Nijman et al. (1995); Senior and Campbell (1984); Zawada et al. (2011)	Immgen
Mature B cells	++	**Cat B**, **Cat D**, **Cat L**, **Cat S**, SPPL2A (ms), **Cat E**, **Cat G**, AEP (hu)	✓	✓	Low	Arunachalam et al. (2000); Burster et al. (2004); Burster et al. (2008); Chalouni et al. (2003); Glazier et al. (2002); Manoury et al. (1998); Riese et al. (1996)	Immgen; Bergmann et al. (2013); Fallas et al. (2007); Honey et al. (2001); Nakagawa et al. (1999); Pluger et al. (2002); Rausch et al. (2010)
GC B cells	+++	Cat S	✓	–	High	Chalouni et al. (2003); Chen et al. (2002); Glazier et al. (2002)	Immgen; Fallas et al. (2007); Shi et al. (1999)
cTECs[a]	++	**Cat L**, TSSP (ms) Cat G, **Cat V** (hu)	✓	–	High	Douek and Altmann (2000); Rouse et al. (1982); Stoeckle et al. (2009); Tolosa et al. (2003)	Immgen; Gommeaux et al. (2009); Kasai et al. (1998); Nakagawa et al. (1998); Yang et al. (2006)
mTECs[a]	++	Cat L[c], Cat S[c]	✓	✓	Low	Douek and Altmann (2000); Karlsson et al. (1991); Rouse et al. (1982)	Immgen; Douek and Altmann (1997); Kasai et al. (1998); Surh et al. (1992); Yang et al. (2006)
Thymic DCs[a]	+++	**Cat S** (hu and ms), **AEP** (ms)	?	?	?	Stoeckle et al. (2012); Vandenabeele et al. (2001)	Manoury et al. (2002); Nakagawa et al. (1998); Yang et al. (2006)
Endothelium/ epithelium[d]	++	Cat B, Cat D, Cat L (hu), **Cat S** (hu and ms)	✓	?	?	Bania et al. (2003); Barrera et al. (2001); Daar et al. (1984); Hershberg et al. (1997); Lin et al. (2005); Pober et al. (1983); Scott et al. (1980); Wiman et al. (1978)	Beers et al. (2005); Kreisel et al. (2010); Muzaki et al. (2016)

DCs, dendritic cells; GC, germinal center; cTECs, cortical thymic epithelial cells; mTECs, medullary thymic epithelial cells; Cat, cathepsin; SPPL2A, signal peptide peptidase-like 2a; AEP, asparagine endopeptidase; TSSP, thymus-specific serine protease; hu, human; ms, mouse

[a] Relative MHC-II expression is estimated based on data in references included. For thymic DCs, no published data is available regarding DM and DO expression

[b] Proteases in which enzymatic activity is reported are in bold (demonstrated via active site labeling or through effects on antigen presentation of specific epitopes). Of note, endosomal proteases have been shown in many instances to exhibit redundancy in their activity and specificity

[c] mRNA expression demonstrated only

[d] Human endothelium and epithelium basally express MHC-II, while MHC-II has been reported both to be expressed basally on mouse epithelium and endothelium as well as only in response to inflammation (e.g., exposure to IFN-γ). MHC-II levels shown are in the context of inflammation. No published data are currently available on DO expression in human or mouse endothelium/epithelium in the periphery

[e] Immunological Genome Project (www.immgen.org)

1995; Vogt et al. 1996). DM can act on other peptides in addition to CLIP, such that multiple cycles of peptide exchange can occur (Kropshofer et al. 1996; Weber et al. 1996). The DM-MHC-II interaction has been shown to be transient (Anders et al. 2011; Narayan et al. 2009; Painter et al. 2011), increasing the rates of peptide binding to and peptide release from MHC-II without altering the equilibrium affinity, consistent with an enzyme-like catalytic activity (Vogt et al. 1996; Zarutskie et al. 2001). Because the efficiency of DM-mediated catalysis varies for different MHC-II-peptide complexes, the net effect of DM activity is to exchange peptides that interact more weakly with MHC-II for those that interact with greater affinity. The precise features of the MHC-II-peptide interaction that are targeted by DM are controversial, with recent work focusing on conformational flexibility as an important determinant (Alvaro-Benito et al. 2018; Busch et al. 2012; Pos et al. 2012; Yin et al. 2014; Zhou et al. 2017). Overall, DM thus serves an editing function, selecting for peptides with optimal interaction with MHC-II. DM activity is competitively inhibited by another nonclassical MHC-II molecule, HLA-DO (H2-O in mice, hereafter referred to as DO), which tightly binds to DM in the endoplasmic reticulum and traffics together with DM into the endocytic pathway, preventing a fraction of the DM from interacting with MHC-II (Denzin et al. 1997; Deshaies et al. 2005; Guce et al. 2013; Kropshofer et al. 1998; Painter et al. 2011; Xiu et al. 2011; Yoon et al. 2012; Zarutskie et al. 2001). The implications of this inhibition are discussed in the subsequent texts. Following removal of CLIP and loading of antigenic peptide, the MHC-II-peptide complex then traffics to the plasma membrane for presentation at the cell surface to CD4 T cells. While the basic mechanism of peptide loading appears to be shared by all cells that constitutively express MHC-II, the acquisition and processing of MHC-II antigens can occur via diverse pathways (Fig. 1) to promote presentation of epitopes from a broad range of antigens.

The nonclassical MHC-II molecules HLA-DM and HLA-DO in immunopeptidome selection

The expression of DM has been shown to be critical for effective processing and presentation of MHC-II antigens. In mice deficient in DM, CLIP removal and peptide exchange are impaired, resulting in both a restricted MHC-II peptidome as well as defective negative selection of CD4 T cells (Fung-Leung et al. 1996; Martin et al. 1996; Miyazaki et al. 1996; Surh et al. 1997). In human transfected cell systems, reduced expression of DM leads to presentation of a set of peptides with lower MHC-II-peptide affinity (Alvaro-Benito et al. 2018; Zhou et al. 2017). Certain HLA-DQ alleles genetically linked to autoimmune disease exhibit reduced susceptibility to DM editing, suggesting that efficient DM editing is required for generation of a self-tolerant T cell pool (Busch et al. 2012; Fallang et al. 2008; Hou et al. 2011; Nguyen et al. 2017; Zhou et al. 2016). DO deficiency, while shown to have a significantly less dramatic effect on the peptide and T cell repertoires, lifts inhibition of DM and has been demonstrated to alter presentation of select epitopes, to affect CD4 T cell responses and to result in mild autoimmunity and enhanced neutralizing antibody generation (Alfonso et al. 2003; Denzin et al. 2017, 1997; Kremer et al. 2012; Liljedahl et al. 1998; Perraudeau et al. 2000; Yi et al. 2010). The net DM activity resulting from the ratio of DM to DO protein levels is posited to influence the content of the immunopeptidome presented on MHC-II-expressing cells, such that presentation of particular epitopes is reduced by the presence and/or levels of DM (Ferrante et al. 2015; Kropshofer et al. 1996; Lovitch et al. 2003; Yin et al. 2012). These observations have led to the development of a model of epitope immunodominance governed by DM, whereby epitopes resistant to DM-mediated exchange become more prevalent in the MHC-II peptidome as DM activity increases (Kim et al. 2014; Sant et al. 2005, 2013; Yin et al. 2012). Due to differing spatiotemporal levels of DM and DO in different APC subsets and during different stages of maturation (Table 1), the immunopeptidome presented on MHC-II may thus qualitatively vary with respect to its breadth and diversity (Denzin 2013). Differences in the particular peptides selected for presentation as well as the relative amounts of peptides that are selected are both expected to be important in APC interactions with T cells. In particular, DO may play a role in negative selection in the thymus, based on its expression in medullary thymic epithelial cells (mTECs) (Douek and Altmann 1997, 2000; Karlsson et al. 1991; Kasai et al. 1998; Surh et al. 1992), where a diverse set of self-peptides would be most advantageous for efficient clonal deletion of autoreactive T cells. Expression of DM and DO can also modulate the density of particular epitopes, potentially further influencing clonal deletion or affecting diversion of CD4 T cells into the T regulatory (Treg) population. An alternative model for DO action suggests that rather than broadening the immunopeptidome through inhibition of DM editing, the primary function of DO is to focus antigen presentation on late endosomal compartments, based on the fact that the interaction of DM and DO is pH-sensitive (Jiang et al. 2015; Kropshofer et al. 1998; Liljedahl et al. 1996; Liljedahl et al. 1998; van Ham et al. 2000; Yoon et al. 2012). By tightly binding DM until the endosome becomes very acidic, DO has been suggested to prevent efficient peptide exchange from occurring in early endosomes, resulting in preferential loading of foreign antigens trafficking to late endosomes or lysosomes (Gondre-Lewis et al. 2001; Jiang et al. 2015; van Ham et al. 2000; Yi et al. 2010). A focus on late endosomes or lysosomes has been postulated to allow B cells to focus attention on antigens internalized through the B cell receptor (BCR), which presumably would not release bound cargo until relatively low pH (Alfonso et al. 2003; Denzin et al. 2005). These proposed functions of DO are not necessarily mutually exclusive,

and further experimentation may prove that the mechanism of DO action in fact integrates the two models, such that inhibition of epitope selection by DO and pH susceptibility of the DM/DO interaction together shape the immunopeptidome.

Acquisition of antigens for processing in MHC-II pathways

MHC-II-expressing cells acquire antigen by distinct cellular processes that allow professional APCs to sample their external environment. Classically, extracellular proteins were thought to predominate as antigenic sources in MHC-II presentation, but many studies have demonstrated that the MHC-II peptidome largely consists of peptides derived from endogenous—rather than exogenous—source proteins (Bergseng et al. 2015; Mommen et al. 2016; Sofron et al. 2016). These endogenous peptides can derive from proteins expressed at the plasma membrane and in endo/lysosomal compartments, as expected from location of the MHC-II loading machinery in the endocytic pathway, but peptides from other intracellular compartments, such as the nucleus, mitochondria, ER/Golgi, and cytosol, also are found in abundance. The predominance of endogenous peptides has been shown to persist in inflammatory conditions (Draheim et al. 2017; Fugmann et al. 2017; Strug et al. 2008) and thus may have implications for maintenance of tolerance during an immune response. The fact that very low fractional occupancy of MHC-II by pathogen-derived peptides in virally infected cells (Strug et al. 2008), which is also observed for MHC-I peptides (Schellens et al. 2015), is sufficient to elicit effective immunity demonstrates that minimal shifts in the immunopeptidome can have important immunological consequences.

Canonical acquisition and processing of MHC-II antigens

Capture of extracellular antigen occurs via multiple processes with varying degrees of efficiency in different types of antigen-presenting cells. Macropinocytosis, a nonspecific and actin-dependent endocytic process that allows for fluid-phase uptake of extracellular material via invagination of the cell membrane, serves as a primary means of exogenous antigen internalization in immature DCs and macrophages (Sallusto et al. 1995; Steinman et al. 1976; West et al. 2000). Macropinocytotic activity has been shown to be predominantly regulated in response to growth factor stimulation and results in incorporation of extracellular solute into large vesicles termed macropinosomes, which mature before converging with the endocytic pathway (Lim and Gleeson 2011). Phagocytosis, an additional fundamental uptake mechanism that occurs principally in DCs and macrophages, is characterized by internalization of relatively large (> 0.3 μm) particulate antigens (Savina and Amigorena 2007). In contrast to the nonspecific process of macropinocytosis, phagocytosis primarily occurs following recognition of surface receptors, such as the C-type lectin pattern-recognition receptor DEC-205 or the opsonic Fcγ receptors (Allavena et al. 2004; Guilliams et al. 2014; Jiang et al. 1995; Linehan et al. 1999). Signal transduction following ligation of different surface receptors varies but has been shown in all cases to culminate in actin polymerization and phagosome formation (Underhill and Goodridge 2012). The phagosome, derived primarily from the plasma membrane, then fuses with lysosomes to form phagolysosomes (Flannagan et al. 2012). Proteolysis of internalized proteins within the phagolysosome is accomplished in DCs by cathepsins and other endosomal proteases, while NOX2 is recruited to the phagosomal membrane to regulate antigen proteolysis (Savina et al. 2009). In macrophages, increased acidification of this compartment favors pathogen eradication through effects of antimicrobial factors (e.g., ROS, RNI, and lysozyme) (Myers et al. 2003; Wolf et al. 2011). In comparison, B cells principally depend upon receptor-mediated endocytosis to capture extracellular antigen (Adler et al. 2017; Lanzavecchia 1985; Rock et al. 1984). Antigen is internalized during this process after binding to the BCR, or to surface Fc or complement receptors, after which endocytosis—most often mediated by entry via clathrin-coated vesicles—occurs (Malhotra et al. 2009; Roche and Furuta 2015). Each APC subset thus preferentially adopts a particular mode or modes of internalization, all of which converge in the endocytic pathway for generation of peptides and presentation on MHC-II.

Nonconventional pathways of MHC-II processing

Evidence for acquisition of MHC-II antigenic source proteins via alternate pathways has accumulated over the past two decades. Perhaps chief among these is the process of autophagy, whereby cytoplasmic components are digested by the cell for degradation and processing (Klionsky 2007). Incorporation of the cytosol into autophagosomes was initially described in yeast as the cellular response to starvation, and as such, an essential energy source for cell survival (Takeshige et al. 1992). Since its discovery, however, autophagy has been determined to be critical for myriad cellular and organismal processes, including aging and development, as well as for antigen presentation (Brazil et al. 1997; Dengjel et al. 2005; Levine and Klionsky 2004). All forms of autophagy (macro-, micro-, or chaperone-mediated) intersect with the endocytic pathway and thus deliver nuclear, microsomal, and cytoplasmic proteins for presentation on MHC-II (Crotzer and Blum 2009; Kaushik and Cuervo 2018; Veerappan Ganesan and Eisenlohr 2017). Processing of antigens via macroautophagy has been demonstrated to be important in DCs, in which constitutive formation of autophagosomes has been shown, as

well as in B cells, for presentation of both self- and foreign antigens (Crotzer and Blum 2009; Ireland and Unanue 2011; Schmid et al. 2007; Zhou et al. 2005). Although antigen-processing pathways in thymic epithelial cells (TECs) are considerably less well-examined than in professional APCs, TECs are thought to rely primarily upon constitutive macroautophagy to present MHC-II antigens (Liang et al. 2018; Nedjic et al. 2008; Wu et al. 2013). In mTECs, incorporation of antigens into autophagosomes has been shown to allow for presentation of the many tissue-specific antigens under the transcriptional control of AIRE (Aichinger et al. 2013). Colocalization of the autophagosomal marker LC3 with DM was demonstrated nearly a decade ago in cryosections of thymus samples (Kasai et al. 2009), and it was recently shown that clonal deletion of conventional T cells specific for the model antigens pigeon cytochrome c and (a GFP-LC3 fusion of) human C-reactive protein is dependent upon processing through the macroautophagy pathway (Aichinger et al. 2013). Another group reported that specific deletion of Atg7 in mTECs had little effect on selection of thymocytes (Sukseree et al. 2012), but this discrepancy may be due to differences in the autophagic machinery that intersects with the antigen presentation pathway, as Klein and colleagues examined the effect of Atg5 rather than Atg7 ablation (Aichinger et al. 2013). Antigen transfer via trogocytosis, in which an immune synapse forms between cells to mediate intercellular transfer of proteins, has also been shown to allow for capture and presentation of MHC-peptide complexes by both APCs and non-APCs (Cone et al. 1972; Joly and Hudrisier 2003; Nakayama 2014). In the thymus, peptides presented as a result of trogocytosis between DCs and mTECs is posited to aid in increasing presentation of rare thymic antigens by MHC-II (Klein et al. 2009; Kroger et al. 2017; Millet et al. 2008). Intercellular MHC-II transfer has been shown to occur in a number of other peripheral immune cell subsets as well, including between DCs and NK cells (Nakayama 2014; Nakayama et al. 2011). While the mechanism of transfer from DCs to many cell types remains unclear, MHC-II-peptide uptake by T cells has been demonstrated to be mediated via the T cell receptor (TCR) and the costimulatory molecule CD28 (Hwang et al. 2000). Recycling of MHC-II molecules also serves as an alternative means of presentation of MHC-II epitopes; peptide loading on recycled MHC-II following endocytosis has been shown to occur in early endosome compartments (Li et al. 2005; Pathak and Blum 2000; Reid and Watts 1990; Villadangos et al. 2000). Of note, the antigen acquisition processes of trogocytosis and recycling in early endosomes in most cases seem to be independent of DM and cathepsin activity, such that peptide species loaded or exchanged on recycled or trogocytosed MHC-II may be comprised of epitopes absent from the MHC-II peptidome generated by canonical pathways (Griffin et al. 1997; Lindner and Unanue 1996; Villadangos et al. 2000), although in some cases DM-mediated editing has been observed (Pathak et al. 2001). Yet another mechanism capable of generating antigens presented on MHC-II molecules relies on components of MHC-I machinery, including the proteasome, TAP, and ERAP (Spencer et al. 2013; Tewari et al. 2005); however, the mode of intersection of the MHC-I and MHC-II processing pathways has not been determined. It has thus become clear that the MHC-II immunopeptidome can be influenced by multiple processing pathways that serve to present antigens from endogenous and exogenous sources and that canonical MHC-II acquisition and processing is not the sole determinant of the MHC-II-bound peptide repertoire.

Source proteins in the MHC-II peptidome

Recent advances in mass spectrometry technology have significantly improved both accuracy and sensitivity of detection of peptides eluted from purified MHC proteins, allowing for qualitative and quantitative characterization of MHC peptidomes. Mass spectrometry can thus be leveraged as a powerful tool to identify source proteins from which MHC-II peptides derive in order to assess effects of perturbations in MHC processing, such as cellular maturation or infection, and the relative contributions of different processing pathways. Increases in the sensitivity of mass spectrometry have allowed studies of APCs characterized ex vivo (Clement et al. 2016; Fugmann et al. 2017; Olsson et al. 2018), likely reflective of in vivo peptidomes, as compared to classical immunopeptidome studies of cultured cells. Recent work has demonstrated that the MHC-II peptidome is substantially comprised of peptides derived from nuclear or cytosolic proteins (25–55% of total peptides eluted from HLA-DR) (Clement et al. 2016; Mommen et al. 2016), presumably largely due to the self-degradative autophagic process. Several studies have quantified peptides derived from extracellular source proteins as constituting only ~ 10–20% of the MHC-II peptidome, with the remaining peptides derived from endogenous source proteins located in various cellular compartments, including the plasma membrane, mitochondria, endosomes or lysosomes, and ER/Golgi (Bergseng et al. 2015; Clement et al. 2016; Mommen et al. 2016; Sofron et al. 2016). A caveat of these analyses is that classification of peptides as sourced from endogenous proteins does not preclude acquisition of (at least a portion of) these proteins via uptake of necrotic or apoptotic cells. Recent work examining source proteins in the peptidome of mouse lymphatic fluid compared to the HLA-DR1-bound peptidome of splenic dendritic cells posited that lymph-derived epitopes were loaded at the surface or in early endosomal compartments based on their sensitivity to DM-mediated exchange and endosomal digestion, suggesting a DM-independent mechanism for presentation of low-affinity autoantigens derived from extracellular sources (Clement et al. 2016). In the context of infection

or inflammation, the MHC-II peptidome has been shown to include only a very small fraction of foreign peptide sequences present within a much larger set of host-derived sequences, as characterized in the settings of experimentally induced colitis in mice (~0.2% of 2188 total sequences), a mouse model of malaria infection (42 malaria derived out of 372 sequences), or vaccinia infection of cultured B cells (1% of the peptidome, as estimated by comparing intensities of several hundred peaks) (Draheim et al. 2017; Fugmann et al. 2017; Strug et al. 2008). Further quantitative analysis is required to determine the proportion of foreign peptides presented on MHC-II molecules with respect to total peptide component (as compared to the fraction of different sequences), but these studies suggest that even during inflammation or infection, the MHC-II peptidome largely consists of peptides derived from self.

Implications of MHC-II processing for immune tolerance

Positive and negative selection of T cells in the thymus depends on interactions of developing T cells with local antigen-presenting cells, and so antigen presentation events in the thymus play a key role in guiding selection of CD4 T cells as well as in development of regulatory CD4 T cells. Differential processing and presentation pathways in various cell populations can result in distinct peptidomes in different tissues. Restraint of autoimmunity to tissue-restricted antigens produced in this manner presents a challenge for central and peripheral tolerance mechanisms.

MHC-II presentation in central tolerance

Somatic gene arrangement of the T cell receptor (TCR) occurs in the thymus and generates T cells with diverse specificities for different MHC-II-peptide complexes. Presentation of self-ligands on MHC-II in the thymus positively selects only those T cells that express TCRs capable of recognizing the peptide-MHC complex (Huseby et al. 2005). Positive selection is mediated by cortical thymic epithelial cells (cTECs), which have been posited to present a unique MHC-II ligandome due to proteolytic activities of cathepsin L and thymus-specific serine protease (TSSP) (Gommeaux et al. 2009; Klein et al. 2009; Nakagawa et al. 1998) (Table 1). Evidence for a requirement for distinct peptide species in the positively-selecting MHC-II peptidome was demonstrated by rescue of the defect in CD4 T cell selection observed in cathepsin L-deficient mice (Nakagawa et al. 1998) via reconstitution with MHC-II-deficient bone marrow (Honey et al. 2002). These results suggested that in mice deficient in cathepsin L, the efficiency of negative selection of T cells is increased due to overlapping immunopeptidomes of MHC-II-expressing hematopoietic APCs and cTECs. A substantially reduced MHC-II peptide repertoire in H2-M-deficient mice demonstrated a similar effect on the CD4 T cell compartment (Martin et al. 1996; Miyazaki et al. 1996), highlighting the importance of (at least somewhat) distinct peptides presented by positively and negatively selecting APCs in effective thymic selection of CD4 T cells.

If positive selection is required to ensure that developing CD4 T cells can recognize MHC-II-peptides, the process of negative selection is necessary to remove CD4 T cells that are overtly reactive with self-ligands (Klein et al. 2014). By deleting T cells with exceedingly high affinity for MHC-II bound to peptide autoantigens in the thymus, peripheral immune responses to self-antigens can be subverted. MHC-II presentation by mTECs of peptides derived from self-peptides is mediated by promiscuous expression of tissue-restricted antigens by AIRE, which allows for deletion of CD4 T cells with high affinity for autoantigens expressed in peripheral tissues (Mathis and Benoist 2009). MHC-II processing and presentation of tissue-restricted antigens has been shown to involve nonconventional pathways, such as macroautophagy and trogocytosis (discussed previously). Recent analysis of thymus MHC-II peptidomes has confirmed the diverse spectrum of source proteins presented by thymic APCs (Adamopoulou et al. 2013; Collado et al. 2013), but whether the thymus-associated MHC-II immunopeptidome is comparatively unique relative to other tissues remains a subject for future work.

Presentation of ligands by MHC-II in the thymic medulla also controls development of thymocytes into an alternative CD4 T cell fate. Selection of the suppressive Foxp3-expressing T regulatory (Treg) population occurs in the thymic medulla through recognition of MHC-II-peptide complexes, at a threshold of affinity/avidity thought to lie above the threshold for conventional T cell selection but below the threshold for clonal deletion (Aschenbrenner et al. 2007; Benoist and Mathis 2012; Hsieh et al. 2012; Klein and Jovanovic 2011). Examination of T cell activation by the Hogquist group using reporter mice expressing Nur77, which is rapidly upregulated following TCR signaling, demonstrated the importance of TCR specificity in selection of Tregs (Moran et al. 2011). The consequence of Treg selection within a high affinity or avidity window is suggested to result in activation of Tregs in the periphery at low agonist doses, so that they may outcompete conventional T cells for MHC-II ligand binding (Gubser et al. 2016; Onishi et al. 2008). Seminal work from the Hsieh group demonstrated through TCR retrogenic technology that Treg self-reactivity is observed over a broad range of affinity, indicating Tregs are likely to participate in suppression of immunity to both self and non-self (Lee et al. 2012). MHC-II peptide ligands responsible for Treg selection have not yet been determined, and identification of these peptides may provide greater

understanding of the determinants of Treg selection, particularly with regard to ligand avidity and affinity.

Peripheral tolerance and the MHC-II immunopeptidome

Following thymic egress, mature CD4 T cells migrate to the periphery and populate the secondary lymphoid organs. A portion of clonotypes that exit the thymus are reactive to self, owing to the fact that negative selection is an imperfect process (Xing and Hogquist 2012). Peripheral tolerance mechanisms serve to dampen or eliminate autoreactive T cells by inducing anergy or mediating clonal deletion. T cells that bind their cognate ligands in the absence of positive costimulatory molecules become hyporesponsive (or anergic), thereby circumventing autoimmune attack of healthy tissue (Mueller 2010). Other costimulatory molecules, such as PD-1, provide negative signals that inhibit T cell activation, effectively suppressing self-reactivity (Fife et al. 2009); in mouse models deficient in PD-1, autoimmune disease develops with features of lupus, including arthritis and glomerulonephritis (Nishimura et al. 1999). CD4 T cells also require tonic stimulation by MHC-II ligands to survive, and the absence of tonic signals results in clonal deletion by apoptotic cell death (Fletcher et al. 2011; Steinman et al. 2003). A third mechanism of peripheral tolerance occurs via Treg-mediated suppression of effector T cells. Thymic Tregs enter the periphery endowed with suppressive function, and peripheral induction of Tregs, particularly in sites such as the gut where naïve CD4 T cells encounter commensal and food-derived antigens, can help to restrain overactive or self-reactive T cell responses (Kanamori et al. 2016; Yadav et al. 2013). The precise mechanism(s) by which Treg-mediated suppression occurs is a matter of some debate (Shevach 2006; Vignali 2012), but models of Treg deficiency conclusively demonstrate the vital function of these cells in regulating the development of autoimmunity and in preventing excessive immunopathology during infection (Belkaid 2007; Gambineri et al. 2003; Ramsdell and Ziegler 2014; Sakaguchi et al. 1995).

Alterations in the MHC-II peptidome that can occur in specific tissues or in certain disease states have the potential to compromise the efficacy of peripheral tolerance mechanisms. Tissue- or cell-specific differences in antigenic sources, processing, or peptide loading may generate distinct peptide repertoires presented by particular APCs in particular locations. Local sources of captured exogenous antigen are likely to vary considerably in different organs, and disparate metabolic or gene expression profiles of tissue-specific APCs may further diversify the immunopeptidome in various locations throughout the body (Calderon et al. 2014; Fortier et al. 2008; Fugmann et al. 2017; Muixi et al. 2012). Such differences may have implications in maintenance of tolerance based on the weak expression of tissue-restricted antigens mediated by AIRE in mTECs (Derbinski and Kyewski 2010; Villasenor et al. 2008), in cases where TCR agonist density increases sufficiently enough in the periphery to activate a T cell selected in the thymus with only weak affinity for its cognate antigen. In addition, post-translational modifications of self-peptides in the periphery can lead to generation of novel epitopes capable of binding and activating T cells that then initiate an autoimmune response. In such cases, if epitopes fail to be generated in the thymus, developing T cells with specificity for these antigens may escape negative selection. For example, citrullination of peptides or proteins has been observed in rheumatoid arthritis, multiple sclerosis, and type 1 diabetes (T1D) and has been implicated in the etiology of disease (Nguyen and James 2016; Sipila et al. 2017). Trans-splicing of peptides derived from proteins present in the insulin secretory granule has been suggested to generate new epitopes that can be loaded onto MHC-II and presented by pancreatic beta cells and recognized by diabetogenic CD4 T cells (Babon et al. 2016; Delong et al. 2016; Jin et al. 2015). Differential proteolytic activity in different cells or different cellular locations could alter proteolysis of antigens and result in a qualitatively different immunopeptidome, as suggested by altered processing of myelin basic protein (MBP) and insulin proteins in thymic APCs due to cathepsin S activity (Stoeckle et al. 2012). Differential expression of DM, or differential trafficking of antigens through DM-containing compartments, in the periphery as compared to thymus could further influence the content of the MHC-II peptidome and impact autoimmunity (Mohan et al. 2011; Mohan and Unanue 2012). Lastly, regulation of the MHC-II peptidome may also be conferred by differential resistance of MHC alleles to editing by DM, and this has been suggested to contribute to the genetic association of certain HLA-DR and HLA-DQ allotypes with autoimmunity in diabetes and celiac disease (Busch et al. 2012; Nguyen et al. 2017; Zhou et al. 2017).

MHC-II processing in inflammation

Professional APCs undergo a maturation process in the context of inflammation that results in alterations in MHC-II processing and presentation pathways. Changes in multiple components of the MHC-II presentation pathway in addition to upregulation of MHC-II expression may serve to focus the peptide repertoire by amplifying presentation of stable MHC-II-peptide complexes, which has been shown to be a feature of immunodominant epitopes derived from foreign antigens (Ferrante et al. 2015; Lazarski et al. 2005; Yin et al. 2012). Induction of CIITA by IFN-γ in non-professional APCs such as endothelial cells—which often do not constitutively express MHC-II molecules—results in substantial surface expression of MHC-II (McDouall et al. 1996; Pober et al. 1983). Such changes allow for efficient and widespread presentation

of inflammation-associated epitopes derived from invading pathogens or autoantigens. Due to the preponderance of self-ligands in the MHC-II peptidome, however, these changes may also have implications for breakdown of tolerance under inflammatory conditions.

Effects of inflammation on antigen acquisition pathways

During an immune response, targeted and precise activation of T cells is necessary to eliminate pathogenic insult. Some processes of antigen acquisition are down-modulated when APCs are activated, representing a shift in priority from antigen sampling to more efficient antigen presentation (Fig. 1). Macropinocytotic activity in activated DCs has been shown to be reduced in some contexts and unaffected in others (Drutman and Trombetta 2010; Garrett et al. 2000), while activation of macrophages has been demonstrated to reprogram antigen uptake to favor macropinocytosis over receptor-mediated phagocytosis (Bosedasgupta and Pieters 2014). In contrast, DC activation appears not to affect the efficiency of antigen capture via receptor-mediated phagocytosis (Platt et al. 2010), although MHC-II trafficking pathways are altered to prevent MHC-II ubiquitination and targeted degradation in lysosomes, preserving captured MHC-II-peptide complexes for recycling (Cho et al. 2015). With regard to nonconventional antigen acquisition by autophagy in the context of inflammation, presentation of many bacterial and viral antigens has been shown to be dependent on macroautophagy (Jagannath et al. 2009; Lee et al. 2010; Paludan et al. 2005), supporting a continued role for this process during an immune response. The dominant EBV antigen EBNA-1 was shown to colocalize with LAMP-1 in EBV-transformed lymphoblastoid cells, and blockade of autophagy resulted in decreased EBNA-1-specific CD4 T cell activation (Paludan et al. 2005). Lysosomal degradation of *Mycobacterium tuberculosis* is enhanced by induction of autophagy and aids in eradication of the mycobacteria (Alonso et al. 2007). Some pathogens have been shown to be eliminated through noncanonical functions of the autophagy machinery, such as LC3-associated phagocytosis, which has been demonstrated to be necessary for clearance of the fungal pathogen *Aspergillus fumigatus* (Martinez et al. 2015). Altogether, the autophagic pathway has been shown to be necessary for efficient presentation of a multitude of foreign antigens to induce an effective CD4 T cell response.

Inflammation-associated alterations in MHC-II processing and presentation

Changes in the antigen processing and presentation machinery during inflammation serve to poise APCs to most efficiently orchestrate an effective immune response (Fig. 1). Concurrent with alterations in antigen sampling, synthesis of MHC molecules is also regulated in APCs to maximize presentation of MHC-II epitopes during inflammation. Surface MHC-II levels are 10-fold higher in mature DCs compared to immature DCs, owing to a transient burst in MHC-II biosynthesis upon DC activation (Cella et al. 1997; Pierre et al. 1997). IFN-inducible CIITA-mediated upregulation of MHC-II and associated processing and loading machinery also confers antigen-presenting ability to endothelium and epithelium (Abrahimi et al. 2016; Cella et al. 1997; Chang et al. 1994; Thelemann et al. 2014). Redistribution of MHC-II molecules from endosomes and lysosomes to the plasma membrane in DCs and macrophages further maximizes antigen-presenting efficiency, as does the enhanced stability of surface peptide-MHC complexes upon DC maturation (Cella et al. 1997; Chow et al. 2002; Pierre et al. 1997). In addition to overall enhanced MHC-II presentation and upregulation of costimulatory molecules, inflammatory signals result in changes in antigen processing and peptide loading machinery that likely affect the spectrum of peptides presented on MHC-II. Cathepsins are redistributed to MHC-containing compartments, and antigen processing efficiency is enhanced in DCs exposed to TLR ligands (Blander and Medzhitov 2006; Lautwein et al. 2002). Acquisition of cathepsin E activity has been shown in primary B cells activated with PMA or *Staphylococcus aureus* in vitro (Burster et al. 2008; Sealy et al. 1996). DO expression is down-modulated following DC maturation and B cell entry into germinal centers (Chen et al. 2002, 2006; Fallas et al. 2004; Glazier et al. 2002; Hornell et al. 2006), effectively increasing DM activity. Removing inhibition of DM has the potential to allow for editing of a subset of the MHC-II peptidome, although the determinants that dictate sensitivity vs. resistance of peptides to DM-mediated editing remains a topic of active investigation (Alvaro-Benito et al. 2018; Chou and Sadegh-Nasseri 2000; Ferrante and Gorski 2010, 2012; Pos et al. 2013; Raddrizzani et al. 1999; Yin et al. 2014; Zhou et al. 2009). These alterations, together with overall reduction in antigen acquisition during inflammation, result in augmentation of antigen-presenting capacity and presentation of stable MHC-peptide complexes to T cells.

Potential effects of inflammation on peripheral tolerance

MHC-II peptide elution studies suggest that epitopes derived from pathogens comprise only a small fraction of the overall peptide repertoire. Due to the predominance of self-ligands in the MHC-II peptidome, increased surface expression of MHC-II on APCs during inflammation will likely result in increased peptide density of certain self-peptides. In addition, proteins up-regulated by the inflammatory process, for example by induction of IFN-stimulated genes, can enter the endo/lysosomal pathway and represent an additional source of antigens potentially

upregulated in inflammatory immunopeptidomes. Thus, during an immune response, the increased expression of MHC-II molecules carrying particular self-peptides together with increased expression of costimulatory molecules, as well as enhanced secretion of cytokines and chemokines, may result in unwanted activation of T cells that under homeostatic conditions are only mildly reactive to self. Consistent with this idea, the etiology of autoimmune disorders has been linked to exposure to pathogens; initial onset of autoimmunity is shown in many instances to coincide with recent viral infection (Christen and von Herrath 2005; Fujinami 2001). Associations have been demonstrated between type 1 diabetes and Coxsackie virus, herpesvirus, and retrovirus, as well as between multiple sclerosis and EBV, HHV-6, and rubeola virus (Cusick et al. 2012). The mechanism whereby inappropriate activation of autoreactive T cells occurs in these contexts is often attributed to molecular mimicry (Cusick et al. 2012; Fujinami et al. 2006). Degenerate TCR specificity has indeed been shown in studies of MBP-reactive T cell clones, which were found to bind pathogen-derived peptides (Fujinami and Oldstone 1985; Hemmer et al. 1997; Wucherpfennig and Strominger 1995), and TCRs cross-reactive for self- and foreign antigens have been observed in other contexts as well (Colf et al. 2007; Harkiolaki et al. 2009). Yet, given the considerable levels of self-pMHC on the surface of APCs during inflammation (Fugmann et al. 2017; Strug et al. 2008), activation of autoreactive T cell clones may also occur in an antigen-specific manner, such that increased ligand density in combination with costimulatory molecule expression initiates an inappropriate response to self. This idea shares features with the concept of bystander activation (Fujinami et al. 2006) associated with breakdown of tolerance but is distinct in that additional uptake of self-antigen appears not to be required, given the predominance of self-pMHC in the immunopeptidome in both homeostatic and inflammatory conditions. Moreover, Tregs selected with higher affinity or avidity for self-antigen may be similarly activated by upregulated presentation of self-peptides, particularly if selection of Tregs is mediated by ubiquitous proteins or by antigens commonly overexpressed during inflammation. Thus, in addition to suppressing autoreactive T cell proliferation under homeostatic conditions, thymically-derived Tregs may in an inflammatory context have an important role in suppressing unwanted self-reactivity. Identification of thymic Treg peptide ligands could lend support for this proposed function, as well as reinforce the basis for selection of Tregs within an avidity/affinity window above that of conventional T cells.

Conclusions and perspective

Antigen uptake, processing, and presentation pathways differ among the various types of antigen-presenting cells, their developmental states, and their tissue location. Self-peptides comprise the bulk of the MHC-II peptide in both resting and activated antigen-presenting cells. Substantial alterations in antigen processing pathways occur during inflammation in addition to upregulation of immune response genes and costimulatory functions, including changes in antigen acquisition and in the relative expression of the nonclassical MHC-II proteins DO and DM that mediate peptide editing/selection. Thus, inflammation is expected to result in considerable changes in the MHC-II self-peptidome, although detailed qualitative and quantitative studies will be required to elucidate these changes. Minor shifts in the peptide repertoire can have substantial effects on activation of pathogen-reactive T cells, suggesting possible immunological consequences of altered MHC-II peptidomes under inflammation, but whether the extreme sensitivity to peptide dose observed for pathogen-specific T cells also applies to self-reactive conventional T cells and to Tregs is unclear. The mechanisms whereby tolerance to upregulated or peripherally modified self-antigens is maintained or lost during inflammation are incompletely understood, and further knowledge of this process may provide insights into the etiology of autoimmune disease.

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Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

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