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Monitoring peptide processing for MHC class I molecules in the endoplasmic reticulum

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Abstract

Classical MHC class I molecules open a window into the cell by presenting intracellular peptides (pMHC I) on the surface. The peptides are used for immune surveillance by circulating CD8+ T and NK cells to detect and eliminate infected or tumor cells. Not surprisingly, viruses and tumor cells have evolved immune evasion mechanisms to keep the window shades down and the cytotoxic cells oblivious to their presence. Here, we review counter mechanisms that nevertheless allow the immune system to detect and eliminate cells unable to properly process antigenic peptides in the endoplasmic reticulum.

Introduction

MHC class I molecules present intracellular peptides on the cell surface [1,2]. These peptide-MHC I complexes, referred to as pMHC I, are a reflection of the current state of the proteome in the cell. The pMHC I repertoire is used by both CD8+ T cells and Natural Killer (NK) cells to detect abnormal cellular events such as those caused by viral infection or transformation. Thus effective presentation of the pMHC I repertoire and surveillance of pMHC I is essential for eliminating virus infected and cancer cells.

The MHC class I molecules chaperone peptides generated by the antigen processing pathway to the cell surface. The antigen processing pathway generates the peptides by the concerted action of multiple cellular components in different cellular compartments. Because of the importance of pMHC I for immune surveillance, many components of the antigen processing pathway are targeted for immune evasion in virally infected or transformed cells [3]. Here we review targeting of ERAAP, the ER aminopeptidase associated with antigen processing and the counter measures used by the immune system to detect defects in ERAAP function.

The MHC class I antigen processing pathway

The MHC class I antigen processing pathway uses products of protein turn-over and degradation of newly synthesized polypeptides from a variety of translational mechanisms

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as antigenic precursors (Figure 1) [4–8]**. By a process involving the multicatalytic proteasome and several distinct chaperones, the polypeptides are fragmented and safely transported into the endoplasmic reticulum (ER) [9]. In the ER, the peptides encounter the MHC class I molecules within the peptide-loading complex (PLC) as well as ERAAP, the ER aminopeptidase associated with antigen processing [10]. The peptides are further edited in the ER for presence of appropriate carboxyl- as well as amino termini that make the peptides suitable for loading the MHC molecule [11]**. When the pMHC I complex achieves a certain stability threshold it exits the ER and reaches the cell surface to serve as a potential ligand for the TCRs of circulating CD8+ T cells [12]. Thus the antigen presentation pathway allows representation of virtually every protein in the form of a peptide chaperoned by MHC class I molecules to the cell surface.

Every known step in the antigen processing pathway is targeted by viruses or mutations in cancer cells for immune evasion (Figure 1) [3]. For example, the production of antigenic precursors is inhibited by the Epstein Barr Virus encoded nuclear antigen, EBNA1 by a stretch of glycine-alanine repeats (GAR) [13]*. Intriguingly the GAR inhibits the availability of EBNA1 derived epitopes through an intriguing RNA-based mechanism [14,15]**. Likewise, the transport of cytoplasmic peptides into the ER through TAP, the transporter associated with antigen processing, is inhibited by virus encoded protein ICP47 in herpes simplex virus [16,17], or US6 in cytomegalovirus [18,19], and by mutations in TAP1 or TAP2 genes in cancer cells.

It had long been believed that the antigenic peptides were generated solely in the cytoplasm and only loaded onto the MHC I in the ER [20]. However, the discovery of the ERAAP, and its role in peptide editing in the ER have revealed that cytoplasmic peptide emigrants are extensively edited in the ER. We next turn to the role of ERAAP in peptide editing in the ER, how ERAAP is targeted and the mechanisms used to counter interference in ERAAP function.

Peptide editing in the ER

The key features of peptides presented by classical MHC I molecules suggested a need for a mechanism for peptide trimming in the ER. The MHC I are among the most polymorphic loci known. Current estimates show that over 5500 MHC I polymorphs exist in the human (<http://www.ebi.ac.uk/ipd/imgt/hla/stats.html>). Since the first crystal of pMHC I was solved, it has been evident that the polymorphic substitutions among MHC I molecules are mostly located in the peptide binding groove and determine the structural characteristics of peptides that can bind a particular MHC I. Since then, dozens of non-overlapping sequence motifs have been found that define the unique peptide repertoires presented by each polymorphic version of the MHC class I molecule (<http://www.iedb.org>). This fundamental property of the peptide binding groove of MHC I presents a conundrum for the mechanism for peptide generation. On one hand cells could generate huge sets of peptides suitable for binding all MHC I polymorphs and select only the "best-fit" peptides for the MHC I polymorphs expressed in that cell. Alternatively, the peptide repertoires for each MHC I polymorph could be generated by editing the intermediate peptide fragments available in the ER. The discovery and function of ERAAP favored the latter mechanism.

The role of ERAAP in peptide editing

Mouse ERAAP (or ERAAP1 in human) is an ER-resident aminopeptidase critical for trimming precursors of antigenic peptides presented by MHC I [21,22]. After the discovery of ERAAP, we and others, generated mice genetically deficient in ERAAP (ERAAP-KO) [23–26]. Compared to their wild-type (WT) counterparts, ERAAP-deficient mice were found to express moderately lower levels of classical (MHC class Ia) molecules on the cells

surface [23]. The pMHC I on the surface of ERAAP-KO cells were also less stable relative to WT cells. Certain endogenous antigens were poorly presented by ERAAP-KO cells, while presentation of other antigens was enhanced or unaffected, suggesting that generation of some peptides required ERAAP, while others were destroyed in the presence of ERAAP. While the overall number of CD8 T cells was unchanged in ERAAP-ko mice, the immunodominance hierarchy of certain cellular and viral antigens was greatly altered, again demonstrating that various pMHC I have differential requirements for ERAAP function.

The *in vivo* studies with ERAAP-ko mice and its natural substrates are consistent with *in vitro* studies carried out with recombinant human ERAP1 and synthetic peptide substrates [27–30]. The aminopeptidase activity of ERAP1 and its structurally related human analog ERAP2, was affected by the peptide length as well as the nature of C-terminal residue and also internal amino acid sequence. The crystal structure of ERAP1 and its structurally similar paralog ERAP2 show that the enzyme can adopt an open conformation with a substrate pocket suitable for trimming the amino termini of peptides of a length likely to be encountered in the ER [31–33]. Furthermore, natural polymorphisms found in ERAP1 alter its enzymatic properties providing a possible explanation for its role in autoimmune disorders discussed below [34].

Unexpectedly, immunization experiments designed to reveal differences in pMHC I repertoire showed that ERAAP-deficiency resulted in a dramatically altered and highly immunogenic pMHC I repertoire [35]. WT mice are normally tolerant to self-pMHC I, but when immunized with ERAAP-ko cells the mice elicited a potent immune response against ERAAP-ko cells. Thus, the loss of ERAAP function resulted in expression of novel, immunogenic pMHC I on the cell surface recognized by WT mice. Analysis of MHC I bound peptides by mass spectrometry revealed that compared to the ERAAP-sufficient wild-type cells, ERAAP-deficiency caused large scale changes in the composition of peptides and also increased the proportion of N-terminally extended peptides [36]. This analysis suggested that many unique peptides found in absence of ERAAP were likely to have been destroyed by ERAAP in wild-type mice [37].

Alterations in ERAAP function

Independent genome wide association studies (GWAS) in patients with autoimmune ankylosing spondylitis disorder confirmed not only the expected near-perfect association with HLA-B27, but also revealed associations with loci encoding ERAP1 and the IL-23 receptor [38,39]. In other GWAS an association of ERAP1 polymorphisms was found for psoriasis [40], as well as poor prognosis of human cancers [41]. Notably, human cytomegalovirus encodes a microRNA (miR-US4) that specifically targets ERAP1, the human ortholog of mouse ERAAP [42]. Although the mechanisms of how ERAP1 polymorphisms affect the course of these diseases is unknown, it is possible that changes in the pMHC I repertoire caused by ERAAP dysfunction affect immune responses that affect disease outcomes.

Mechanisms for detecting ERAAP dysfunction

ERAAP-deficiency altered the presentation of peptides by MHC Ia molecules. A fraction of CD8 T cells elicited by immunizing WT mice with ERAAP-deficient cells fails to respond to cells lacking MHC Ia molecules [35]. Additionally, mass-spectrometric analysis of the peptides bound to MHC Ia showed that absence of ERAAP changed the overall composition of the peptide repertoire [11,36]. Nevertheless, analysis of the WT anti-ERAAP-ko T cell response unexpectedly showed that a large fraction of ERAAP-ko specific CD8⁺ T cells responded to ERAAP- and MHC Ia- double deficient antigen presenting cells [43]. The

immunogenic pMHC I in ERAAP-ko cells thus also included peptides presented by non-classical MHC Ib molecules. Notably, WT mice, previously primed with ERAAP-ko cells, rejected MHC Ia- as well as MHC Ib-expressing ERAAP-ko target cells. Thus, T cell mediated-immune surveillance for altered pMHC I can lead to the elimination of ERAAP-deficient cells.

Using a pMHC Ib-specific, lacZ inducible T cell hybridoma from WT anti-ERAAP-ko T cell lines we identified its target antigen by expression cloning [43]. This hybridoma recognized the FL9 nonapeptide encoded by the *Fam49b* gene that was presented by the Qa-1^b MHC class Ib molecule. The FL9 peptide was not detected in ERAAP-sufficient WT cells, demonstrating that the FL9 peptide was generated only in the absence of ERAAP and served as a unique flag indicating ERAAP-deficiency.

Mechanisms of altered peptide presentation in ERAAP-KO cells

Why is the FL9 peptide presented by Qa-1 molecule only in the absence of ERAAP? It is conceivable that the FL9 peptide is destroyed by ERAAP in WT cells. In the absence of ERAAP, FL9 is spared and is thus available for presentation by Qa-1. On the other hand the FL9 peptide might represent the N-terminally extended peptide intermediate that is normally cleaved by ERAAP to generate a shorter product for presentation by Qa-1 in WT cells.

The significance and function of anti - ERAAP-ko specific CD8+ T cells

The Qa-1-FL9 specific QFL T cells have several unusual properties. Not only are these cells relatively abundant the QFL T cells also express markers of antigen experience in naïve WT mice. The expression of these markers requires Qa-1 and therefore a likely peptide-Qa-1 complex [43]. However, because the Qa-1-FL9 complex is expressed only when ERAAP is absent or inhibited, where and when QFL T cells encounter a pMHC Ib complex in WT mice presents an enigma. It is possible that ERAAP function may be transiently inhibited in WT cells due to transformation, the action of commensal microbes, or localized inflammation similar to inhibition of human ERAP1 by human cytomegalovirus [42]. Such an impairment of ERAAP function could result in the expression of the Qa-1-FL9 complex and the expansion of QFL T cells. Alternatively, QFL T cells could have developed by a unique pathway, which imprints them with certain characteristics common to other MHC Ib-restricted T cell populations. Innate-like T cells, such as invariant NKT or MAIT cells, are also MHC Ib-restricted (CD1, MR1), and undergo a different program of thymic selection compared to conventional MHC Ia-specific T cells [44]. However, because QFL T cells develop in Qa-1-deficient mice, but do not have an antigen-experienced phenotype distinguishes QFL T cells from these other MHC Ib-specific T cells. Most importantly, QFL T cells detect and expand in response to a challenge with ERAAP-deficient cells and kill target cells expressing the Qa-1-FL9 ligand. Thus QFL T cells serve as monitors for detecting and eliminating ERAAP-deficient cells.

Future perspectives

Analysis of ERAAP function in the antigen processing pathway has yielded novel insights into how the peptide repertoire presented by MHC class Ia and Ib molecules is generated and regulated in autoimmune disorders and cancer. Furthermore, the discovery of the role for MHC Ib in monitoring defects in antigen processing presents a particularly fruitful area for future research. Because non-classical MHC Ib molecules are essentially non-polymorphic and highly conserved across species, understanding the mechanisms that generate pMHC Ib and the effectors cells that recognize and respond to these MHC Ib ligands could provide widely applicable approaches to immune surveillance and vaccines.

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Highlights

Current state of knowledge on the MHC class I antigen processing pathway

Molecular and immunological consequences of deficiency in ERAAP

Mechanisms for detecting ERAAP-dysfunction

Future perspectives.

Figure 1.

Schematic of the MHC class I antigen presentation pathway. The pathway begins with newly synthesized and turned-over proteins to generate peptide intermediates. The intermediates are transported into the ER where they are edited by ERAAP and the peptide loading complex (not shown). The assembled pMHC Ia and pMHC Ib complexes are presented on the cell surface for immune surveillance by CD8+ T and NK cells. Each of the major steps of the pathway are subject to interference by viral gene products or mutations in tumors. The disruptions of the pathway are detected by changes in the peptides presented by classical pMHC Ia and non-classical pMHC Ib molecules.