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WHAT IS THE ROLE OF ALTERNATE SPLICING IN ANTIGEN PRESENTATION BY MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I MOLECULES ?

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Abstract

The expression of Major Histocompatibility Complex (MHC) Class I molecules on the cell surface is critical for recognition by cytotoxic T lymphocytes (CTL). This recognition event leads to destruction of cells displaying the MHC class I - viral peptide complexes or cells displaying MHC class I - mutant peptide complexes. Before they can be transported to the cell surface, MHC class I molecules must associate with their peptide ligand in the endoplasmic reticulum (ER) of the cell. Within the ER numerous proteins assist in the appropriate assembly and folding of MHC class I molecules. These include the heterodimeric transporter associated with antigen processing (TAP1, TAP2), the heterodimeric chaperone-oxidoreductase complex of tapasin and ERp57 and the general ER chaperones calreticulin and calnexin. Each of these accessory proteins have a well defined role in antigen presentation by MHC class I molecules. However, alternate splice forms of MHC class I heavy chains, TAP and tapasin have been reported suggesting additional complexity to the picture of antigen presentation. Here we review the importance of these different accessory proteins and the progress in our understanding of alternate splicing in antigen presentation.

Keywords

antigen presentation; HLA antigens; tapasin; alternate splicing

Almost all nucleated cells of the body display Major Histocompatibility Complex (MHC or HLA in humans) class I molecules at the cell surface. MHC class I molecules sample intracellular peptides and display them on the cell surface in order to report on the cellular ‘health’ to immune cells such as cytotoxic T lymphocytes (CTLs). CTL recognition of viral peptides or mutant peptides on the surface of infected or mutant cells leads to their destruction. In the case of malignancy, CTLs are considered the surveyors of malignant cells, recognizing and destroying cells expressing mutant peptides in association with MHC class I molecules possibly before any clinical manifestation of disease. However, if tumor cells reduce their expression of MHC class I-peptide complexes on the cell surface, they may avoid destruction by CTLs. Numerous examples of HLA class I antigen defects have been described and in some cases, correlation with disease progression has been reported (reviewed elsewhere (1)). Therefore, expression of MHC class I-peptide complexes is important for efficient anti-tumor CTL responses. Many proteins function together to assist in the assembly and folding of MHC class I-peptide complexes in the endoplasmic reticulum prior to their export to the cell surface.

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Here we first discuss the process of MHC class I assembly followed by the genetic regulation of each player in the process and finally we review the literature regarding alternate splicing of the genes involved in antigen presentation.

ASSEMBLY OF CLASSICAL MHC CLASS I MOLECULES WITH PEPTIDE IN THE ER

Classical MHC class I molecules exert their function in antigen presentation at the cell surface where they are recognized by $CD8^+$ T cells. In order for these molecules to be shuttled to the cell surface they must first be folded and loaded with peptide in the ER. The interactions that end in the successful loading and transport of classical MHC class I molecules take place in a macro-molecular complex known as the peptide loading complex (PLC). Newly synthesized MHC class I heavy chains and beta-2 microglobulin (β_2m) proteins are guided to the ER by their amino-terminal signal sequences. Both are translocated by the Sec61 macro-molecular complex into the ER where the signal sequences are cleaved (2,3). Following translocation, the MHC class I heavy chain is glycosylated and the two intra-chain disulfide bonds are formed (4,5). The MHC class I heavy chain then interacts with calnexin (6-8), facilitating its association with β_2m, its soluble partner (9). Following the formation of MHC class I: β_2m heterodimers, calnexin is replaced by calreticulin (10) and interactions with other accessory proteins including TAP, tapasin and ERp57 take place to form the PLC (11-13). The loading of processed peptides required for the stabilization of the MHC class I:β_2m heterodimer is enhanced by the concerted action of TAP, tapasin, and ERp57. Following the interaction with disulfide linked tapasin and ERp57, MHC class I:β_2m heterodimers are loaded with peptides generated in the cytosol (11,14-19).

Cytosolic peptides are generated from degraded proteins (20,21) degraded by the proteasome —a multicatalytic protease located throughout the cell (22). Cytosolic peptides are translocated into the ER in an ATP-dependent manner by the ABC transporter TAP, a heterodimer composed of TAP1 and TAP2 (23,24). Upon entering the ER, peptides are trimmed by the heterodimeric aminopeptidase ERAAP1/ERAAP2 (or ERAP1/ERAP2) (25-30). Processed peptides are brought in close proximity to the MHC class I heavy chain:β_2m by a preformed complex composed of TAP and tapasin (31,32).

Tapasin, tethers MHC class I:β_2m heterodimers to TAP facilitating their binding of a peptide forming a stable trimer (33,34). Stable MHC class I molecules dissociate from TAP heterodimers (35,36) and are transported through the Golgi apparatus to the cell surface (37-39) with the assistance of the B cell Associated Protein 31kDa (BAP31) (40). Absence of MHC class I heavy chain, β_2m or peptide results in an unstable complex that is rapidly degraded (41,42).

DIFFERENTIAL REQUIREMENT FOR PEPTIDE LOADING COMPLEX MEMBERS IN ASSEMBLY AND EXPORT OF MHC CLASS I MOLECULES

Evidence for the contribution of several of the proteins involved in classical MHC class I loading and assembly has been provided by cell lines or mice deficient for some of these proteins. Although each component of the peptide loading complex is required for the optimal assembly and transport of classical MHC class I molecules to the cell surface. Defects in TAP or tapasin show the most marked defects (34,43).

β_2m deficiency

The role of β_2m was studied in Daudi cells, a human B cell lymphoma cell line which has low surface expression of classical MHC class I molecules due to β_2m deficiency (44). β_2m is

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necessary for the proper folding of MHC class I molecules, thus virtually extinguishing their export from the ER (44).

Calnexin and calreticulin deficiency

In human CEM cells calnexin protein expression is undetectable, yet they maintain comparable cell surface expression of classical MHC class I molecules when compared to CEM cells transfected with calnexin (45,46). This may be the case because there seems to be redundancy in the ER and other chaperones bind to free MHC class I heavy chains such as immunoglobulin binding protein (BiP) (47). Additionally, calreticulin, a soluble protein that is homologous to calnexin, can interact with heavy chains compensating for the calnexin deficiency (10). Contrary to calnexin, in the absence of calreticulin, classical MHC class I molecules are not loaded with optimal peptides (48) thus having a lower stability.

TAP deficiency

TAP1 knockout animals, have defective transport of peptides into the ER and consequently, the level of stable peptide MHC class I complexes is barely detectable. Thus, development of T lymphocytes is impaired in the thymus given the low classical MHC class I expression at the cell surface (49,50).

Similar to mice, patients with defective TAP function are immunocompromised and diagnosed with bare lymphocyte syndrome (BLS) type I, a disease characterized by low surface expression of classical MHC class I molecules, sinusitis and chronic bronchitis (51). In the absence of TAP, immature classical MHC class I molecules or those bound to a low affinity peptide are transported to the cell surface albeit their stability is drastically reduced.

In *in vitro* experiments, the stabilization of suboptimally loaded classical MHC class I molecules can be rescued by exogenous pulsing with optimal binding peptides which replace the endogenous low affinity bound peptides (52-54). Surface level of classical MHC class I molecules is also enhanced *in vitro* by lowering the temperature subphysiologically. Ploegh and colleagues came across the observation that in RMA-S, a TAP2 deficient murine cell line (55), lowering the temperature from 37°C to 26°C prevents the rapid degradation of classical MHC class I molecules at the cell surface (54).

Tapasin deficiency

Similar to TAP1/2 knock out animals, tapasin deficient mice, have a reduced ability to mount $CD8^+$ T cell responses against viral infections and other processes that rely on expression of cell surface classical MHC class I molecules, such as $CD8^+$ T cell development or cross-presentation by dendritic cells. Additionally, the only tapasin deficient individual identified to date had a reduction of surface classical MHC class I expression level. She exhibited a history of herpes infections reflecting the importance of tapasin in anti-viral immune responses (56). Until recently, most of the studies that have focused on the function and importance of tapasin have examined the 721.220 B-LCL, the only available tapasin deficient human cell line until our characterization of M553, a human melanoma cell line, also tapasin deficient (57). In 721.220 cells, classical MHC class I : TAP association and peptide loading is defective as tapasin is absent (10) Tapasin facilitates the expression of surface bound classical MHC class I molecules by stabilizing the peptide loading complex (58) acting as a bridge between TAP heterodimers and immature classical MHC class I molecules (34), and by providing immature MHC class I molecules with a high affinity peptide to stabilize them (59). Further experimentation in the 721.220 cell line revealed that different HLA class I alleles had different sensitivities to tapasin. It was discovered that while HLA-B*2705 alleles are expressed appreciably at the cell surface, HLA-B*0801 alleles are moderately expressed and HLA-B*4402 are barely detectable by flow cytometric analysis in the absence of tapasin (60). In

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spite of the variable sensitivity to tapasin between the three studied alleles, transfection with a wild type tapasin cDNA enhanced the expression of all the alleles including that of the presumably tapasin independent allele HLA-B*2705 (61), suggesting that although considered tapasin 'independent', these are still 'more stable' in the presence of tapasin.

It has been proposed that the amino acid residue at position 116 is responsible for the classical MHC class I : TAP interaction thus affecting peptide loading (62-67). However, a report by Raghavan and colleagues argues that both tapasin dependent and independent alleles interact with TAP, but detection of this interaction at steady state is confounded by the kinetics of the interaction. They studied HLA-B*4402 and HLA-B*4405 as representatives of tapasin dependent and independent classical MHC class I alleles respectively, only differing at position 116 in the presence or absence of peptides. In the presence of functional TAP, peptide loading, dissociation from TAP, and ER export of HLA-B*4405 was more rapid than for HLA-B*4402, which showed a greater retention in the ER. In the absence of peptides both HLA-B*4405 and HLA-B*4402 were detectable in association with TAP and tapasin in the ER. Furthermore, the exogenous addition of peptides nine amino acids long conferred higher thermostability to HLA-B*4405 than to HLA-B*4402 suggesting that both alleles are capable of interacting with TAP and tapasin comparably well, but in the case of HLA-B*4405 the loading is not optimal in the absence of tapasin and their stability at the surface is reduced (68).

REGULATION OF ANTIGEN PRESENTATION COMPONENTS

Classical MHC class I expression is modulated by cytokines acting on the many interacting partners involved in their assembly and loading. The successful up-regulation of these components facilitates the activation of pathogen specific T cell subsets (69).

In *in vitro* studies, cells incubated with interferon (IFN)-alpha(α), -beta(β) or -gamma(γ), leads to an increase in the transcription of proteasome subunits, MHC class I heavy chain, β_2m, transporter-associated with antigen processing (TAP) and TAP-associated protein (tapasin) (70-74). Together with the fact that in *in vivo* models, viral infections lead to the rapid production of interferons (75,76), these data suggest that the early induction of antigen presentation components by interferons has been selected through evolution. The development of an immune response against a potentially lethal pathogen was the only means by which to survive infection especially until the advent of antibiotics or antivirals (77).

Genetic regulation of MHC class I molecules

Classical MHC class I molecules are expressed constitutively in most nucleated cell types and can be further induced by multiple cytokines. Similar to other genes, the MHC class I promoter has the general control elements TATAA-, CCAAT-, Inr like motifs and a CA/GT region to which Sp1 binds (78). Upstream of these are binding sites for transcription factors that control tissue expression and restriction as well as cytokine mediated stimulation. These promoter elements are the enhancer A, Interferon-stimulated response element (ISRE) and the SXY module.

Enhancer A—The enhancer A comprises two nuclear factor-kappa B (NF-κB) binding sites, κB1 and κB2 to which members of the NF-κB/rel family of transcription binding factors and certain zinc finger proteins bind to (79-83). Due to slight sequence differences in the κB1 and κB2 sites of different HLA alleles, members of the NF-κB family bind as homo- or heterodimers resulting in different transcription rates for different alleles (84,85).

Zinc finger proteins myeloid zinc finger (MZF)-1 and zinc finger protein X-linked (ZFX) bind with high affinity to the NF-κB binding sites (82,83). While ZFX has been reported to play a

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critical role in the regulation of HLA-A*11 which was dependent on the 3′ half of the κB2 site (83), a role for MZF-1 is yet to be described.

Interferon-stimulated response element—Stimulation with interferons, in particular IFNγ results in a robust induction of MHC class I molecules due to this cytokines' direct effects on its structural components, the classical MHC class I heavy chain and β_2m genes, as well as in the induction of other endoplasmic reticulum (ER) resident proteins required for the efficient assembly and loading of immature classical MHC class I molecules like TAP and tapasin (86). IFNγ binds to the IFNγR and signals through Janus activated kinases (JAKs) and signal transducer and activator of transcription 1 (STAT-1) inducing the expression of interferon regulatory factor-1 (IRF-1) and IRF-2 (87). Both IRF-1 and IRF-2 bind to the ISRE site present in the promoter of the MHC class I gene with opposing effects (88). Whereas IRF-1 activates its transcription (89,90), IRF-2 represses it (91,92). Induction of classical MHC class I molecules by interferons is successful due to the different kinetics of IRF-1 and IRF-2 (93), as IRF-1 is initially in excess of IRF-2 and out-competes it for binding to the ISRE resulting in the transactivation of MHC class I genes (94).

SXY regulatory module—The SXY module consists of four regulatory elements: S or W box, X1 box, X2 box and the Y box and is also referred to as the MHC enhanceosome (95). The SXY module is bound by a multiprotein complex containing 1) Regulatory factor X (RFX), 2) X2 binding protein (X2BP) and nuclear factor Y (NFY). RFX is a trimer composed of RFX5, RFXB/activating transcription factor (ATF) RFXB/ATF and RFXAP; X2BP is a complex of cAMP response element binding protein (CREB), CREB/ATF3); and NFY is a trimer composed by NFYa, NFYb and NFYc (96,97).

The X1 box mediates the transactivation by the RFX complex (98). The X2 box is bound by several members of the CREB/ATF family of transcription factors including CREB1, ATF, cAMP response element modulator 1 and ATF1 (99). The Y box is bound by an NFY-like complex (95,100).

Additionally, MHC class I and at least β_2m are regulated by MHC class II transactivator (CIITA) (101). Its activity being influenced by the general co-activators CREB binding protein (CBP), E1A binding protein p300 (p300), general control of amino-acid synthesis 5 (GCN5) and p300/CBP-associated factor (PCAF) (95).

Genetic Regulation of Tapasin

The murine tapasin promoter is G-C rich and lacks a TATAA transcriptional start site. Various transcription factor binding sites have been localized 500-624 base pairs upstream of the translational start site. These include interferon stimulatory response element (ISRE)/IRF-E site most proximal to the translational start codon (102,103). IRF-E sites are recognized by the transcription factors IRF1 or IRF2 to promote transcription in response to IFN-gamma. Further upstream are a gamma-activating site (GAS), two NF-kB binding sites, and an Sp1 binding site. GAS elements are bound by STAT1 homodimers, which promote transcription after signaling from the IFN-gamma receptor. Each of the cis elements is conserved with the putative human tapasin promoter. Although tapasin is known to be upregulated by IFN-gamma, TNF-alpha and toll like receptor ligation, little is known about how tapasin might be downregulated. A recent report (104) demonstrated that Blimp1 (also called PRDM1) represses tapasin promoter activity in HeLa cells by binding to the IRF-E site. In our investigations of tapasin in the melanoma cell line, M553, we find that tapasin protein is undetectable and mRNA levels are very low. Full-length tapasin mRNA can be recovered suggesting that the defect in this cell line is not due to a genetic deletion. Current investigations are focused on the regulation of tapasin promoter in this cell line.

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POTENTIAL REGULATION OF ANTIGEN PRESENTATION BY ALTERNATE SPLICING OF HEAVY CHAINS, TAP AND TAPASIN

Alternative splicing can provide a gene with many functions by selectively removing exons. This process can also result in truncated non-functional proteins that are rapidly degraded or those that compete with the properly spliced products acting as a dominant negative if highly expressed. Additionally, alternate splicing is a mechanism that regulates the level and function of certain proteins (105). For example, patients with thalassemia have an abnormally low level of hemoglobin due to improper splicing of globin RNA transcript, leading to non-functional proteins inefficient at carrying oxygen. On the other hand, alternate splicing may provide a single gene with distinct functions. One example is the IG20 gene often over-expressed in human tumors. The IG20 gene encodes several splice variants, which control cell proliferation, apoptosis, while other splice forms have unknown functions (106).

Alternate splicing of classical MHC class I heavy chains, TAP and tapasin has been described (34,107-109). These splice variants often result in abolished function and commonly occur due to mutations at the genomic level. Conserved consensus sequences recognized by the spliceosome machinery that specify the splicing of exons from introns are located at the 5′ and 3′ end of intron / exon boundaries of mammalian genes. Such sequences may also be located distant from the splicing sites in intron or exons (110,111). Mutations in these consensus sequences results in their inactivation and often lead to the use of alternative cryptic sites present in introns or to the splicing of exons, process known as exon skipping (112,113).

Heavy chain alternate splicing

The classical MHC class I heavy chain gene is organized into eight exons with distinct functional domains. Exon 1 encodes the signal peptide and exons 2, 3 and 4 encode the α1, α2 and α3 domains respectively. Exon 5 encodes the transmembrane domain and the cytoplasmic tail is encoded by the remaining three exons. Thus alternative splicing of a given exon may yield an altered yet functional protein.

In the T leukemic cell line HPB-ALL, an alternate splice mechanism removed exon 5, which encodes the transmembrane domain resulting in a soluble HLA allele. Both HLA-A alleles, HLA-A*24 and HLA-A*09, were found in supernatants in soluble form. Furthermore, Krangel and colleagues detected similar size proteins in PBLs obtained from normal donors suggesting that this mechanism does not exclusively happen in cancerous cells or particular HLA class I alleles (114). In general, activated T and B lymphocytes secrete HLA class I molecules. This property is utilized in leukemia and lymphoma patients as a marker of disease since the serum levels of β_2m correlate with disease burden. However, the basic functional significance of secreted HLA class I molecules is unclear.

Secretion of HLA class I molecules could theoretically provide a mechanism of tolerance by delivering a signal to the T cell receptor without costimulatory or accessory signals. Experimental systems to address this question have revealed that soluble MHC molecules do not induce tolerance to membrane bound MHC molecules (115,116). Rather, mice expressing secreted, soluble forms of MHC class I allotypes show CD8+ T cell responses to membrane bound allotypes, but not to peptides from the soluble MHC molecule (115,116). More recent studies suggest that tolerance may be induced by oligomeric assemblies (tetramers or dimers) of soluble MHC class-peptide complexes and alter the course of diseases (117-119). Thus, while soluble MHC class I molecules (in dimeric or tetrameric forms) have shown promise for practical applications, our fundamental understanding of why soluble MHC class I molecules are generated *in vivo* is still lacking.

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In a human melanoma cell line, 624MEL28, two alternate splices of HLA-A2 have been identified. One of them results from the skipping of exon 2 while the other is a product of the failure to excise the second intron. Preservation of the second intron causes a reading frameshift, generating an early stop codon. The exon 2 deficient splice variant is maintained in frame but is not expressed at the cell surface. Sequencing analysis revealed a mutation in the 5′ splice donor responsible for both the skipping of the second exon and the retention of the second intron in 624MEL28 (120).

TAP alternate splicing

In the case of the TAP heterodimer, both TAP1 and TAP2 have been shown to be alternatively spliced to yield different products. Studies of patients with BLS type I revealed a point mutation at the splice acceptor site of the 3′ end of the first intron. The point mutation in TAP1 results in abnormal splicing and undetectable levels of TAP1 protein (107).

The human TAP2 gene has a reported splice variant in which exon 11 and its 3′ UTR is deleted and replaced by a new exon, exon 12 and an also new 3′ UTR. This splice variant is capable of restoring the peptide translocation deficiency of T2 cells and rescues classical MHC class I levels at the cell surface to the same extent as wild type TAP2 (108). However, although surface expression of classical MHC class I molecules is restored, the peptides supplied by the TAP heterodimer are different between the wild type and the alternate splice variant of TAP2 (108).

Tapasin alternate splicing

Two reports of alternate splicing of the tapasin gene have been described. In the human B-LCL 721.220, a single genomic point mutation results in aberrant splicing of tapasin lacking exon 2. In the absence of the second exon, part of the signal sequence and the first fifty amino acids of the N-terminus are deleted. Since the N-terminus is required for the interaction with the immature classical MHC class I heavy chains, this genomic point mutation results in a significant loss of surface expression of tapasin dependent alleles. This defect is restored upon transfection with a wild type tapasin cDNA (34).

Elliott and colleagues have identified an additional alternate splice variant of tapasin that fails to exclude introns 4 through 6. When this mutated splice form of tapasin is transfected into 721.220 cells, it is processed to remove the 4th and the 6th intron but the 5th intron remains as part of the translated product, introducing an early stop codon prior to the transmembrane domain generating a soluble tapasin protein. This soluble tapasin protein, although unable to interact with TAP (as its TMD is missing), is able to restore surface presentation of HLA-B*05 in 721.220 cells. However, their stability is significantly enhanced when a wild type tapasin cDNA is used in place of soluble tapasin, suggesting that the peptide bound by the HLA-B*05 allele in the ER is suboptimal (109). To date, tapasin alternative splicing has been reported exclusively as a result of genomic mutations at splice sites. Our laboratory has observed an alternate splice of tapasin in the absence of any genetic mutations. Current investigations are focused on determining the functional significance and frequency of this alternate splice in different tumor cells.

Overall, the regulation and function of alternate splicing in antigen presentation by MHC class I molecules remains largely unknown. MHC class I alternate splicing has been well established for several years, however the functional impact remains less clear. The difficulties in tackling this problem stem from the difficult task of determining how the alternate splice form of MHC class I molecules regulate T cell responses in the face of full length MHC class I expression which is required for T cell development in the first place. In the case of alternate splicing of TAP2, more progress has been made in the sense that functional differences of the different

splice forms have been determined. However, the overall biological significance of two splice forms of TAP2 is unclear. Finally, in the case of tapasin alternate splicing, one alternate splice has been deposited in the genbank database however the reproduction of this isolated event has not been reported. Thus, sporadic reports of alternate splicing in MHC class I structural genes, TAP2 and tapasin have been reported, but these reports await further studies for clarification of biological significance in normal and disease states.

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