

# Regulation of MHC Class I by Viruses

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## 1. Introduction

Originally recognized for their role in triggering T cell responses that caused the rejection of transplanted tissue, it is now known that MHC-encoded molecules are involved in immune-surveillance and antigen presentation to T lymphocytes. These MHC molecules act as “signposts” that displays fragmented pieces of an antigen (viral proteins in virus-infected cells or mutated proteins in tumor cells) on the host cell surface. Because viruses can infect virtually all nucleated cells, class I molecules are constitutively expressed on almost all nucleated cells. The association of antigenic peptides and MHC molecules is a saturable interaction and once formed, persist for a sufficiently long time to be recognized by the few T cells specific for the antigen as they circulate through. The outcome of T<sub>C</sub> cells-mediated killing of the virus-infected cells is usually via apoptosis.

## 2. Antigen processing and presentation

The cellular pathways of antigen processing are designed to generate peptides that have structural characteristics required for associating with MHC molecules and to place these peptides in the same cellular location as the appropriate MHC molecules with the available peptide-binding cleft. Peptide binding to MHC molecules is essential for stable assembly and surface expression of the MHC molecules.

Class I MHC-associated peptides may be the products of viruses or other intracellular microbes that infect cells or protein antigens produced by mutated oncogenes in tumour cells (Rammensee 1995). They are produced by proteolytic degradation of cytosolic proteins in the proteasome, a large multiprotein enzyme complex found in the cytoplasm (Tanaka and Kasahara 1998). Two catalytic subunits of the proteasome, called low molecular weight protein 2 (LMP-2) and LMP-7 are encoded by genes in the MHC locus (York and Rock 1996). Peptides generated in the cytosol are translocated into the endoplasmic reticulum (ER) by specialized transport associated with antigen processing (TAP) proteins encoded by the TAP1 and TAP2 genes, also in the MHC gene complex. They mediate active ATP-dependent ferrying of peptides from the cytosol into the ER lumen (Spiliotis et al. 2000; Momburg et al. 2001).

Class I  $\alpha$  chains and  $\beta_2$ -microglobulin are synthesized in the ER and remain attached to the TAP complex by an ER chaperone protein linker called tapasin until they are loaded with high-affinity peptides (Momburg and Tan 2002). These components collectively form the

peptide-loading complex. The class I molecules, once loaded, exit the ER at unique exit sites, transit through the Golgi apparatus, and reach the cell surface to display their bound peptides for recognition by specific CD8<sup>+</sup> T<sub>C</sub> cells. T<sub>C</sub> cell-mediated killing is usually via apoptosis, mediated mainly by granule exocytosis, which releases granzymes and perforin. MHC molecules that fail to obtain high affinity peptides are either subjected to immediate degradation or short term expression at the cell surface followed by endocytosis and degradation (Spiliotis et al. 2000).

Antigen presentation via MHC class I is regulated by interferon (IFN)- $\gamma$  which increases expression of the class I molecules, transporter proteins (TAP1 and TAP2) and immunoproteasome subunits (LMP2 and LMP7) via transcriptional regulation (Momburg et al. 2001). The induction of TAP by IFN- $\gamma$  is more rapid than that of MHC class I molecules, which is consistent with the view that the constitutive level of TAP expression is insufficient to support inducible increases of MHC class I (Lobigs et al. 2003).

### 3. Immune evasion strategies of MHC class I antigen presentation by viruses

The ability of the MHC class I molecules to sample intracellular milieu and present antigens to T<sub>C</sub> cells poses great threat to viruses. To freely replicate in infected cells, viruses have evolved numerous strategies that target key stages of the MHC class I antigen presentation pathway, with the goal of preventing the presentation of viral peptides to T<sub>C</sub> cells. In order to circumvent this problem, many viruses have evolved strategies to interfere with the antigen presentation pathway. If a virus could inhibit the MHC presentation pathway, that virus would become invisible to T<sub>C</sub> cells and would be able to replicate.

Since the first descriptions of adenovirus protein binding to MHC Class I molecules over 20 years ago, there have been many reports of virus counter-attack strategies aimed at the cellular immune response. The main aim of immune-evasion strategies by viruses is to *decrease the cell surface expression* of the MHC molecules. Numerous viral proteins have been found to inhibit components of the MHC class I assembly pathway. Several stages of the antigen presentation pathway have been identified as common target sites for these viral proteins.

#### 3.1 Viral interference with gene transcription

Transcription of key players of the class I antigen presentation pathway is commonly targeted by many viruses such as human oncogenic adenovirus 12 (Ad12), human immunodeficiency virus 1 (HIV-1) and bovine papillomavirus (BPV) (Ambagala et al. 2005). Many viral genes which encode proteins that modulate host immune responses have been identified. The E1A viral protein of Ad12 inhibits transcription of nearly all components of the MHC class I pathway, including  $\alpha$ -heavy chain,  $\beta_2m$ , TAP1, TAP2, LMP2, LMP7 and tapasin (Friedman and Ricciardi 1988; Rotem-Yehudar et al. 1994). Similarly, the human cytomegalovirus (HCMV) and murine cytomegalovirus (MCMV) also inhibit gene transcription by disrupting the IFN- $\gamma$  induced up-regulation of the expression of genes encoding many components of the MHC class I heavy complex (Miller et al. 1999).

The E7 protein of oncogenic human papillomavirus (HPV) type-18 has been shown to downregulate the TAP1 gene transcription by repressing its promoter activity. The E1A

protein of adenovirus (Ad) type-12 also has similar inhibitory activity on the TAP1 gene transcription (Abele and Tampé 2006). Although both DNA viruses belong to different virus classes, the resemblance in structure and functions of the two proteins may be mediating the effects.

The human immunodeficient virus type 1 (HIV-1) Tat gene encodes a protein that transactivates transcription of the viral long terminal repeat of HIV-1. It is essential for HIV-gene expression, replication and infectivity. The Tat protein is also able to repress several cellular gene promoters including the heavy chain of the class I molecule and the  $\beta_2m$  genes of the MHC class I (Carroll et al. 1998; Cohen et al. 1999). Bovine papillomavirus E5 and E7 proteins also inhibit transcription of class I heavy chain (Ashrafi et al. 2006).

### 3.2 Viral interference with peptide generation

The central cytoplasmic processing unit for the generation of peptides for the MHC class I antigen presentation pathway is the proteasome. The degradation of viral proteins into short peptides in the proteasome is a highly complex process and proteolysis is regulated in an ATP-dependent manner. The proteasome recognizes and unfolds ubiquitylated proteins through its 19S subunit and target deubiquitylated forms of these substrates to the 20S proteolytic subunit.

Several viruses interfere with the generation of high affinity peptides to be loaded onto and expressed by the MHC class I complex. These include Epstein-Barr virus 1 (EBV), Kaposi's sarcoma herpesvirus (KSHV), murine leukemia virus (MuLV) and again, HIV-1 Tat protein. The EBV genome encodes EBV nuclear antigen 1 (EBNA-1) protein that contains long repeats of glycine and alanine residues that are resistant to proteasomal processing (Dantuma 2002). It was shown that these repeats may interfere with the recognition and unfolding functions of the 19S subunit, rather than inhibiting ubiquitylation or proteolytic activity.

KSHV encodes a protein known as latency-associated nuclear antigen 1 (LANA1) which resembles the inhibitory properties of EBNA1. However, the repetitive acidic sequence is rich in glutamine, glutamic acid and aspartic acid residues; differing from that of EBNA1. As LANA1 and EBNA1 have no sequence homology, one possible explanation may be that the two have similar structural features with related inhibitory properties. Nonetheless, because the mechanism of antigen processing by the proteasome is the least well-characterized event in the MHC class I presentation pathway, it may be that the inhibition is occurring at a step in the proteasomal degradation that is yet to be identified (Hansen and Bouvier 2009).

The Tat regulatory protein produced by HIV-1 very early after infection that is capable of repressing gene transcription, also has a role in inhibiting the generation of peptides. This protein competes with the IFN- $\gamma$  inducible 11S regulator for binding to the 20S proteasome. Binding of Tat to the 20S proteasome inhibits the peptidase and proteolytic activity of 20S proteasome (Gavioli et al. 2004). The MuLV, an oncogenic retrovirus, takes advantage of the peptide cleavage specificity of the proteasome in order to prevent the generation of specific immunodominant epitopes and this is achieved only via a single amino acid change in a target protein of MuLV (Beekman et al. 2000).

### 3.3 Viral inhibition of peptide transport mechanisms

The translocation of peptides into the ER by TAP represents a key stage in the assembly of the MHC class I molecule, since only peptide-loaded class I molecules can leave the ER for transport to the cell surface (Paulsson and Wang 2004). The TAP complex is composed of TAP1 and TAP2, each with an amino-terminal transmembrane domain and a carboxy-terminal nucleotide-binding cytoplasmic domain. The two helices form a pore across the ER membrane through which antigenic peptides can be transported. Peptide transport by TAP consists of two basic steps: ATP-free binding of peptide to TAP and ATP-dependent translocation of peptide into the ER lumen (Abele and Tampé 2006). It is thought that binding of peptides to the cytoplasmic domains triggers a conformational change that stimulates ATP hydrolysis, thereby providing energy required for peptide translocation. However, the mechanism underlying this process is not completely understood.

The human herpes simplex virus (HSV)-encoded protein, ICP47 (infected cell protein 47) inhibits the first step of peptide transport (Ambagala et al. 2005). By binding with high affinity to the cytoplasmic domain of human TAP, ICP47 inhibits peptide binding to and thereby ATP hydrolysis of TAP. In addition, evidence also suggests that ICP47 may act as a competitive inhibitor by binding with high affinity and induces a conformational change in TAP. This effect may be sufficient to cause destabilization and inactivation of TAP, thus turning off ATP hydrolysis and peptide translocation (Orr et al. 2005). ICP47 is highly species specific, since it inhibits with high affinity peptide binding to human TAP but not to TAP from mice, rabbit or guinea pigs. The region of TAP that interacts with ICP47 is, however, yet to be determined.

Human cytomegalovirus (HCMV)-encoded protein, US6, also targets the TAP but through a mechanism that differs from that of ICP47. US6 is an ER-resident integral membrane protein that binds to the ER-luminal domain of TAP and inhibits ATP binding. Like ICP47, US6 prevents peptide-stimulated ATP hydrolysis by inducing long range conformational rearrangements in TAP across the ER membrane (Hewitt et al. 2001). This subsequently inhibits peptide translocation and prevents MHC class I assembly. Unlike ICP47, however, interaction of US6 to TAP does not affect the peptide binding.

Another recently identified protein by EBV, BNLF2a, was shown to prevent the binding of peptides and ATP to TAP (Horst et al. 2011). Another HIV-1 protein, Nef, blocks the TAP transport of peptides into the ER (Cohen et al. 1999; Williams et al. 2002b). Despite the different strategies used by ICP47, US6 and BNLF2a to block peptide transport, the common goal of these proteins is to block peptide-dependent, ATP-induced conformational changes in TAP, thereby exploiting the conformational flexibility of TAP, which is normally required for peptide translocation. This will decrease the available peptide for binding to the MHC class I heavy chains that are waiting in the ER; thereby reducing the generation of completely assembled class I molecules.

### 3.4 Inhibition of tapasin

Tapasin is a transmembrane glycoprotein that is a crucial component of the peptide-loading complex. It has a key role in influencing the generation of peptide repertoire and expression of stable MHC class I molecules on the cell surface. Similar to TAP, tapasin is also targeted by a number of viral immunoevasins. Tapasin has a chaperone-like function that stabilizes

peptide transport, facilitates the removal of peptides weakly bound to MHC class I molecules and ensures high affinity peptide access to MHC class I molecules (Williams et al. 2002a). Only those peptides that can form long-lived complexes with MHC class I molecules become part of the presented repertoire at the end of this so-called peptide-editing process.

The mK3 protein of murine gammaherpesvirus-68 interacts with TAP without affecting peptide transport (Boname et al. 2004). The mK3 is located in the ER and Golgi and belongs to a large group of proteins named the K3 family that inhibits the surface expression of glycoproteins such as MHC class I, ICAM-1 and CD4. The mK3 binds via its C-terminal tail to tapasin and TAP, thereby positioning the N-terminal with ubiquitin ligase activity to the cytoplasmic tail of the MHC class I for subsequent ubiquitylation and proteosomal degradation.

In addition, mK3 also induces the degradation of both TAP subunits and tapasin via direct interactions. In fact, the assembly complex proteins TAP and tapasin are absolutely required for mK3's effect on MHC class I. The absence of TAP or tapasin, or MHC class I mutations abrogating interaction with TAP or tapasin, prevents mK3 from binding to MHC class I and down-regulating its surface expression (Lybarger et al. 2003).

The E3/19K protein of the Adenovirus E3 is a transmembrane glycoprotein that inhibits the ability of tapasin to bridge TAP to MHC class I molecules by binding to TAP, without blocking peptide transport (Bennett et al. 1999). The association of E3/19K with TAP inhibits the formation of TAP-tapasin complex and this impairs the inclusion of TAP into the peptide-loading complex. This competitive inhibition of the bridging function of tapasin delays maturation of tapasin-dependent MHC class I molecule. Thus, the disturbance in the MHC-tapasin interaction ultimately prevents the assembly of MHC class I loading complex.

HCMV also encodes another immediate early protein US3 that directly binds to and inhibits the action of tapasin (Park et al. 2004). The association of US3 with tapasin inhibits tapasin-dependent peptide-loading, thereby preventing optimization of the peptide repertoire presented by the class I molecules. This subsequently leads to retention of the MHC class I molecules in the ER, although substantial amounts of the class I molecules can still reach the cell surface (Park et al. 2004).

### **3.5 Viral interference with cell surface expression**

Down-regulation of the cell surface display of class I molecules is an important mechanism of immune evasion. Technically, once loaded with peptides, the class I MHC molecules leave the ER and translocate to the cell surface through the Golgi apparatus. Many viruses have the ability to interfere with these MHC class I trafficking processes (Ambagala et al. 2005).

In addition to inhibition of tapasin activity, the E3/19k adenovirus protein directly associate with the class I heavy chain and this blocks their transport out of the ER (Bennett et al. 1999). This association is mediated by the ER-luminal domains of both proteins and the retention effect is mediated by the cytoplasmic domains of E3/19k. Interaction between E3/19k and residue 56 of the MHC class I that appears to have crucial roles in modulating the association and ER retention of the class I molecule by the E3/19k (Hansen and Bouvier 2009).

MHC class I chaperones are remarkably efficient in only allowing mature MHC molecules to exit the ER. The elimination of incompletely assembled or misfolded nascent glycoproteins, including MHC molecules, occurs by a process collectively called ER-associated degradation (ERAD) (Vembar and Brodsky 2008). During ERAD, misassembled or misfolded proteins are recognized in the ER lumen and retrotranslocated to the cytoplasm, where they are degraded by the ubiquitin-proteasome machinery.

The HCMV invests heavily in products able to interfere with the MHC class I. Apart from US3 and US6 that have abilities to inhibit TAP, there are also other unique short genes encoded by the virus: US2, US11, US8 and US10. The US2 and US11 are small membrane glycoproteins that target human MHC class I molecules for ERAD. US2 and US11 cause ejection of MHC class I heavy chain into the cytoplasm, which results in their proteasomal degradation. The US2 cytoplasmic domain appears to have major involvement in this process. Besides inhibiting TAP functions previously described, the US3 also possesses a novel, non-contagious ER retention sequence that binds to nascent MHC class I heavy chains in the ER and targets it to ERAD. This prevents its egress of the assembled class I molecules to the cell surface (Park et al. 2004).

Another HCMV viral product, US8 binds MHC class I molecules in the ER and influence the MHC class I-restricted antigen presentation via a mechanism that is yet to be identified (Petersen et al. 2003). Lastly, the US10 also shares many features with US3. It associates with MHC class I heavy chain and delays the trafficking of peptide-loaded class I molecules out of the ER.

The p12(I) protein of human T-cell leukemia virus type 1 (HTLV-1) also redirects MHC class I heavy chains into the cytosol. This protein is localized in the ER and/or Golgi compartments, bind to the heavy chain products of the class I molecules, thus preventing association of the heavy chain with  $\beta_2m$ . This reroutes the MHC class I heavy chain into the cytosol for proteasomal degradation (Ambagala et al. 2005).

The mK3 protein encoded by murine herpesvirus-68, that inhibits TAP and tapasin, also induces rapid turnover of MHC class I molecules by a mechanism not involving endocytosis. The mK3 protein has been demonstrated to assist the virus in the escape from T cells during latent phase of infection. It specifically ubiquitylates MHC class I heavy chains and targets them for ERAD. During infection, the expression of mK3 allows the virus to maintain a higher level of latency and reduces the number of antiviral T<sub>C</sub> cells. The mK3 associates with nascent MHC class I heavy chains only in the presence of TAP, its main binding partner. Subsequently, the complex awaits entry onto the peptide-loading complex and ubiquitylates the C-terminal tail of the heavy chain, thereby targeting for ERAD (Lybarger et al. 2003).

Apart from downregulating the expression of MHC class I molecules, the HIV-1 Nef protein is also known to disrupt the trafficking of MHC class I molecules via two mechanisms. First, Nef uses the clathrin adaptor AP1 (adaptor protein 1) to divert the trafficking of MHC class I molecules directly from the Golgi network to an endocytic compartment before they reach the cell surface. This ultimately leads to degradation of the assembled class I molecules in the lysosomes (Lorenzo et al. 2001). MCMV m152gene product gp40 protein too may have similar effect on the trafficking of the class I molecules. The second mechanism of Nef-mediated MHC class I down-regulation is enhancement of endocytosis of the class I molecules from the cell surface.

K3 and K5 proteins of KSHV inhibit the transport of class I molecules to the cell surface and induce rapid internalization of class I molecules from the cell surface via endocytosis (Cohen et al. 1999; Coscoy and Ganem 2000). Although the two proteins are predominantly located in the ER, K3 and K5 do not affect the assembly or transport of MHC class I molecules through the secretory pathway. Instead, they mediate ubiquitination of the cell surface MHC class I molecules by an unknown mechanism. Once ubiquitinated, internalized class I chains are then delivered to endolysosomal vesicles where they undergo degradation.

#### **4. Multiple targets versus multiple immunoevasin**

While some viruses encode a single immunoevasin to interfere with one or more steps of the MHC class I pathway, others encode multiple immunoevasins, targeting at different stages of the antigen presentation pathway. A good example of this is the US proteins of HCMV that can inhibit gene transcription, TAP and tapasin functions and also the surface expression of the MHC class I molecules. The HIV-1 also has three distinct proteins that target different site of inhibition, namely the Tat protein that inhibits peptide generation, the vpu protein interferes with the synthesis of class I while the Nef protein takes advantage of a cellular sorting pathway to pirate MHC class I molecules away from the cell surface. The likely reason for producing multiple immunoevasins is to overcome the resistance exerted by certain MHC class I alleles. Other reasons could be the cell and/or tissue specific adaptations of immunoevasins or that multiple immunoevasins, when expressed simultaneously, act synergistically to the benefit of the virus.

Considering the fact that the virus genome size is somewhat restricted, it would be advantageous for a virus to encode a single protein that can interfere with more than one mechanism to counter-attack the MHC class I antigen presentation as methods of immune evasion. The E3/19K of adenovirus can cause direct retention of MHC class I in the ER, inhibits TAP and tapasin functions and also inhibits surface expression. The murine herpesvirus mK3 protein also has multiple actions at the peptide generation and TAP functions in addition to its interference of the surface expression step.

#### **5. Consequences of inhibition of MHC class I antigen presentation by viruses**

Inhibition of antigen processing and presentation blocks the assembly and expression of stable class I molecules and the display of viral peptides. As a result, cells infected with such viruses cannot be recognized or killed by CD8<sup>+</sup> T<sub>C</sub> cells. Natural Killer (NK) cells may be a host adaptation to kill these infected cells because NK cells are activated by the absence of class I MHC molecules (Brutkiewicz and Welsh 1995). Viruses try to evade recognition by T<sub>C</sub> cells by inhibiting the class I MHC expression, but NK cells have evolved to respond specifically to the absence of class I MHC on virus-infected cells. Not surprisingly, there is emerging evidence that some viruses may produce proteins that act as ligands for NK inhibitory receptors and thus inhibiting NK cell activation.

In many cases, the viral defense strategies against T<sub>C</sub> cells and NK cells are intertwined. The ability of NK cells to recognize and kill infected cells arises from its capacity to distinguish dangerous targets from healthy 'self' (Brutkiewicz and Welsh 1995; Biron et al. 1999). This is in turn dependent on the expression of both inhibitory and activating receptors. Inhibitory receptors on NK cells recognize class I molecules, which are constitutively expressed on

most healthy cells but are often not expressed by cells infected with virus. The activity of NK cells is down-regulated when inhibitory receptors interact with 'self' MHC class I (Lanier 1998). Activating receptors on NK cells recognize ligands present on both NK-susceptible target cells and normal cells, but the influence of inhibitory pathways dominates when class I MHC is recognized.

## 6. Regulation of MHC class I by flaviviruses

In contrast to viruses that avoid the host immune response by down-regulating cell surface MHC complex expression, it is now recognized that Flaviviruses such as JEV, DV and WNV increase the cell surface expression of the MHC molecules (Lobigs et al. 2004; Lin et al. 2006; King et al. 2007; Othman et al. 2010). This peculiar phenomenon of the MHC class I immune modulation by Flaviviruses poses potential threats to both the replicating virus and host.

Numerous experiments related to this have been conducted in various cell types and species. One particular experiment on mouse embryonic fibroblasts showed six- to ten-fold increase in the expression of H-2K and H-2D MHC antigens after infection with WNV, MVE and JEV (King 2003). Up-regulation of class I cell surface expression by WNV has also been demonstrated in human skin fibroblast cells, accounted for by both cytokine-dependent and cytokine-independent mechanisms (Arnold 2004; King et al. 2007). The exact mechanism of the up-regulation remains unclear but evidence of increased mRNAs for HLA-A, HLA-B, HLA-C, LMP-2 and TAP-1 have been observed, suggesting viral-induced transcription of genes involved in the MHC class I complex.

An alternate mechanism for the up-regulation of MHC class I cell surface expression in flavivirus-infected cells, is via the TAP-dependent increase in peptide supply for assembly with MHC class I molecules (Momburg et al. 2001; Lobigs et al. 2003). Flavivirus-mediated peptide import into the ER lumen is time- and virus dose-dependent and takes place during the latent or early productive phase of virus replication (Momburg et al. 2001). Recombinant expression of flaviviral proteins in the absence of productive virus replication is unable to mimic this effect, establishing the importance of viral RNA replication in the induction of MHC class I expression, through both TAP-dependent and independent mechanisms (Hershkovitz et al. 2008). The involvement of NF $\kappa$ B, instead of interferons, has been demonstrated (Kesson and King 2001); yet no particular viral protein has been implicated in the mechanism of action of flaviviral-induced MHC class I surface expression.

## 7. Consequences of MHC class I induction by flaviviruses to the human host

Up-regulation of MHC class I expression by Flaviviruses has obvious potential disadvantage to the human host, that is increased susceptibility to attack by class I restricted cytotoxic T cells (Douglas and Kesson 1994; Lobigs et al. 2003). Increased cell surface expression of MHC class I molecules on infected cells would generally result in more efficient killing by T<sub>C</sub> cells, yet this phenomenon is not observed in flaviviral infections. It has been hypothesized that enhancement of MHC class I expression by flaviviruses enhances the avidity of the cytotoxic T cell-target interaction. Nevertheless, the mechanisms are yet unclear.

With the additional up-regulation of co-stimulatory molecules induced by flaviviruses, the increase in avidity would be expected to recruit a wider range of low affinity T cells, which would otherwise be below the recognition threshold with normal expression of such surface

molecules. This could therefore result in the generation of larger range of  $T_C$  clones than is usual for antiviral responses, with accordingly varying affinities for MHC class I-virus peptide. This may divert the cytotoxic T cells system to infected cells in  $G_0$  of the cell cycle phase (that express high cell surface MHC concentrations) in preference to infected, most-virus-productive cycling cells (with relatively low MHC) (King 2003; King and Kesson 2003). The latter produces more virus and does not up-regulate MHC and adhesion molecules to the same extent, hence resulting in higher viral propagation and poor viral clearance that become part of the viral survival strategy.

Viral evasion from NK cell recognition involves the selective up-modulation of viral MHC class I homologues with structural similarity to endogenous host class I, mimicking 'self' antigens, that bind inhibitory receptors on NK cells (Orange et al. 2002). WNV- and Hepatitis C virus (HCV)-induced up-regulation of MHC class I cell surface expression has a pronounced effect on the susceptibility of target cells to NK cell lysis and may lead to insufficient induction of the adaptive immune response (Momburg et al. 2001; Herzer et al. 2003). DV-infected cells expressing high levels of cell surface class I molecules are capable of evading lysis by NK cells through higher binding of MHC molecules to low-affinity inhibitory receptors of NK cells.

Clearly, such immunopathological response would result in the destruction of uninfected tissues; in virus encephalitis, such damage would exacerbate the encephalitic syndrome (King 2003). In the case of DV infection, T-cell responses seem to have both protective and pathogenic effects in mouse models. Cytotoxic  $CD8^+$  T cells that are cross-reactive among DV serotypes are thought to be immunopathological during secondary infections in humans, exacerbating DHF and causing liver damage through cytotoxic effects (An et al. 2004).

## 8. Conclusions

Viruses and their hosts have coevolved for millions of years. Viruses are obligate intracellular pathogens that enter permissive cells, hijack cellular metabolic pathways to generate progeny viruses that then leave the cells. At the same time, the human hosts have developed an intricate and fine-tuned adaptive immune system designed to combat these invaders. However, viruses have evolved a diverse array of strategies to evade the human's immune responses and these strategies are as diverse as the viruses themselves. The down-regulation of the MHC class I antigen presentation pathway is a strategy used by many viruses and this however, is counter-attacked by the presence of NK cells of the host.

On the other hand, some viruses prefer to up-regulate the cell surface expression of the class I molecules. Although the opposite is expected, this strategy also appears to favour the virus and results in interference of both the  $T_C$  cells-mediated cytolysis and the killing by NK cells. As the battle between viruses and human immune system continues, the discovery of novel immunoevasins and revelations of their modes of actions will continue to broaden the horizons of biology.

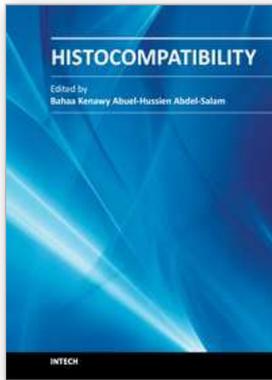
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## **Histocompatibility**

Edited by Dr. Bahaa Abdel-Salam

ISBN 978-953-51-0589-3

Hard cover, 188 pages

**Publisher** InTech

**Published online** 02, May, 2012

**Published in print edition** May, 2012

This book presents some recent researches related to histocompatibility for scientists interested in this field. It includes 10 chapters, in different topics, prepared by Sundararajulu Panneerchelvam and Mohd Nor Norazmi; Giada Amodio and Silvia Gregori; Adema Ribic; Bahaa K. A. Abdel-Salam; Kai-Fu Tang; Roberto Biassoni, Irene Vanni and Elisabetta Ugolotti; Wei-Cheng Yang, Lien-Siang Chou and Jer-Ming Hu; Shatrah Othman and Rohana Yusof; Masahiro Hirayama, Eiichi Azuma and Yoshihiro Komada; Gustav Roder, Linda Geironson, Elna Follin, Camilla Thuring and Kajsa Paulsson.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Shatrah Othman and Rohana Yusof (2012). Regulation of MHC Class I by Viruses, Histocompatibility, Dr. Bahaa Abdel-Salam (Ed.), ISBN: 978-953-51-0589-3, InTech, Available from:  
<http://www.intechopen.com/books/histocompatibility/regulation-of-mhc-class-i-by-viruses>

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