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Review

Viral immune evasion: Lessons in MHC class I antigen presentation

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ABSTRACT

The MHC class I antigen presentation pathway enables cells infected with intracellular pathogens to signal the presence of the invader to the immune system. Cytotoxic T lymphocytes are able to eliminate the infected cells through recognition of pathogen-derived peptides presented by MHC class I molecules at the cell surface. In the course of evolution, many viruses have acquired inhibitors that target essential stages of the MHC class I antigen presentation pathway. Studies on these immune evasion proteins reveal fascinating strategies used by viruses to elude the immune system. Viral immunoevasins also constitute great research tools that facilitate functional studies on the MHC class I antigen presentation pathway, allowing the investigation of less well understood routes, such as TAP-independent antigen presentation and cross-presentation of exogenous proteins. Viral immunoevasins have also helped to unravel more general cellular processes. For instance, basic principles of ER-associated protein degradation via the ubiquitin-proteasome pathway have been resolved using virus-induced degradation of MHC class I as a model. This review highlights how viral immunoevasins have increased our understanding of MHC class I-restricted antigen presentation.

1. MHC class I antigen presentation

Virtually all nucleated cells express major histocompatibility complex class I molecules (MHC I) on their cell surface. The heterotrimeric MHC I complex consists of β_2-microglobulin (β_2m), the MHC I heavy chain (HC) and a variable peptide. This peptide is usually generated within the cell by degradation of endogenously expressed proteins. The resulting peptides are loaded into the peptide binding groove of the MHC I HC – β_2m complex. At the cell surface, MHC I molecules are continuously surveyed by $CD8^+$ cytotoxic T cells (CTLs), which mount an immune response when the presented peptide is recognized by the T-cell receptor.

MHC I assembly is a highly specialized process that demands tight regulation by additional proteins. The MHC I HC is a type I membrane protein that is co-translationally inserted into the ER-membrane. Once inserted, it associates with the ER-resident chaperones calnexin and BiP, which aid in correct folding of the HC. Upon engagement with β_2m, the β_2m/HC complex dissociates from calnexin and BiP and interacts with calreticulin, ERp57, tapasin, and the transporter associated with antigen processing (TAP), which together form the MHC I class I peptide-loading complex (PLC) (Fig. 1A). The PLC promotes folding of MHC I, stabilizes the complex, and facilitates efficient loading of peptides into the binding groove of the β_2m/HC heterodimer [1]. TAP transports cytosolic peptides into the ER, thus serving as the major source of peptides loaded onto MHC I molecules. After the formation of the trimeric complex of β_2m/HC and a high-affinity peptide, the complex dissociates from the PLC and travels through the Golgi-network to the cell surface, where it presents its cargo to $CD8^+$ CTLs.

Viral inhibitors of the MHC I antigen presentation pathway have greatly advanced our understanding of this important arm of the adaptive immune system. This is illustrated by the discovery of the adenovirus 5 protein E3-19K, the first specific viral inhibitor of MHC I antigen presentation [2]. At the time, the location of MHC I peptide loading was still elusive. Using E3-19K, it was shown that retention of MHC I in the ER prevents antigen presentation of newly

Abbreviations: ABC, ATP-binding cassette; β_2m, β_2-microglobulin; DC, dendritic cell; BHV, bovine herpes virus; EBNA-1, Epstein–Barr virus nuclear antigen-1; EBV, Epstein–Barr virus; EHV, equine herpes virus; ERAD, ER-associated protein degradation; ExoA, Exotoxin A; HC, heavy chain; HCMV, human cytomegalovirus; HSV-1, herpes simplex virus-1; LANA-1, latency-associated nuclear antigen-1; KSHV, Kaposi's sarcoma-associated herpesvirus; MHC I/II, major histocompatibility complex class I/II; MARCH, Membrane-Associated RING-CH proteins; MHV, mouse herpesvirus; MIR, Modulator of Immune Recognition; NBD, nucleotide binding domain; OVA, ovalbumin; PLC, MHC class I peptide-loading complex; SP, signal peptidase; SPP, signal peptide peptidase; SRP, signal-recognition particle; TAP, transporter associated with antigen processing; TEIPP, T-cell epitope associated with impaired antigen processing; TM, transmembrane.

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Table 1
Overview of known viral immunoevasins that target the MHC class I antigen presentation pathway.

Virus name or family	Viral protein	Effects	Refs
α-herpesvirus (HSV, BHV-1, PRV)	UL41/vhs	Inhibits MHC I and pro-inflammatory cytokine synthesis through host shutoff	[166]
Varicellovirus (BHV-1; EHV-1/4; PRV)	UL49.5	Induces conformational arrest of TAP BHV: also induces conformational arrest and degradation of TAP EHV: also blocks ATP binding to TAP	[48–50]
HSV-1/2	ICP47	Binds and blocks peptide binding site of TAP	[38,39]
VZV	ORF66	Retains mature MHC I complexes in the ERGIC	[167,168]
EBV	EBNA1	Resists proteasomal degradation	[10–16]
	BNLF2a	Blocks both peptide and ATP binding to TAP	[51]
	BGLF5	Inhibits MHC I synthesis through host shutoff	[169,170]
	BILF1	Causes MHC I internalization and lysosomal degradation	[171]
hCMV	US2/gp24	Targets MHC I for ERAD	[87]
	US3/gp23	Binds tapasin and inhibits tapasin-dependent peptide loading	[66,67]
	US6/gp21	Prevents ATP binding by inducing conformational changes in TAP	[43–46]
	US10	Causes non-classical MHC I (MHC I-G) degradation	[172]
	US11/gp33	Targets MHC I for ERAD	[88]
mCMV	m4/gp34	Binds MHC I at the cell surface, thereby decreasing NK cell-mediated lysis and recognition of peptide-loaded MHC I complexes by CTLs	[173,174]
	m6/gp48	Targets MHC I to lysosomes, thereby decreasing cell-surface expression of MHC I molecules	[175]
	m27	Inhibitor of IFN-γ signaling, thereby blocking immunoproteasome formation	[176]
	m152/gp40	Causes MHC I retention in the ERGIC, thereby downregulating cell-surface MHC I molecules	[177]
RhCMV	rh178/VIHCE	Inhibits MHC I HC translation in a signal peptide-dependent manner	[5,6]
HHV-6/7	U21	Reroutes MHC I to lysosomes for degradation	[178–182]
KSHV	LANA1	Resists proteasomal degradation	[18,19]
	ORF37/SOX	Inhibits MHC I and pro-inflammatory cytokine production through host shutoff	[183,184]
	kK3/MIR1	Ubiquitinates MHC I for internalization	[120,121]
	kK5/MIR2	& lysosomal degradation	
MHV-68	mK3	Ubiquitinates MHC I HCs for ERAD	[102,103,108]
Cowpoxvirus	CPXV012	Prevents peptide transport by inhibiting ATP binding to TAP	[34–37]
	CPXV203	Retains MHC I in the ER	[35,114]
Adenovirus	E3-19K	Retains MHC I in the ER	[2,3]

synthesized peptides, thereby stressing the central role of this compartment in MHC I processing [3]. Since the discovery of E3-19K, many different viral MHC I inhibitors have been identified that together target virtually every single step within the MHC I antigen presentation pathway (Table 1). These inhibitors not only demonstrate how viruses evade the immune system, but also represent great tools to further dissect MHC I antigen presentation, including less common PLC-independent antigen presentation pathways and cross-presentation of exogenous proteins. In addition, viral MHC I inhibitors have helped unraveling more general cellular processes, including ER-associated degradation of proteins via the ubiquitin-proteasome pathway.

2. MHC I insertion into the ER

Like other type I transmembrane (TM) proteins, the MHC I HC is inserted into the ER co-translationally. This process is guided by an N-terminal signal sequence. Upon translation, the signal peptide binds to the cytosolic signal-recognition particle (SRP). This event temporarily stalls the translation process of the HC and allows binding to the SRP receptor. This interaction mediates the delivery of the ribosome and the nascent HC to the Sec61 translocation complex, which co-translationally integrates the HC into the ER membrane (for a recent review of this process see [4]).

The signal peptide of the polymorphic MHC I HC is highly homologous between haplotypes and conserved among species. Therefore, this sequence is an ideal target for viral immunoevasins. The rhesus CMV protein Rh178 specifically blocks the translation of the HC in a signal peptide-dependent manner. Although the HC mRNA engages with the ribosome and translation is initiated, full-length HC molecules are absent in cells expressing Rh178. The mechanism of inhibition is unclear, but Rh178 is suggested to interfere with chain elongation prior to engagement of the HC with the Sec61 translocon. Likely, Rh178 inhibits proper functioning of the SRP or the SRP receptor [5,6]. Future studies on Rh178 may help to further establish the mechanism by which TM proteins are inserted into the ER membrane, a process that is still incompletely understood [4].

3. Proteasomal generation of antigenic peptides

The majority of the peptides presented via MHC I is derived from ubiquitinated proteins degraded by the 26S proteasome. This large cylindrical complex of 2 MDa is composed of a 20S core unit and two 19S caps. The 19S caps recognize ubiquitinated substrates and partially unfold proteins to allow them to access the 20S core. The 20S complex contains six proteolytic sites with distinct protease activities that cleave the substrate after large hydrophobic, basic, or acidic amino acid residues. Peptides released by the proteasome can be processed further for presentation via MHC I molecules [7]. In addition to the central role of the proteasome in the MHC I antigen presentation pathway, its activity is crucial for cellular homeostasis. Inhibition of the proteasome by *e.g.* chemical compounds will ultimately lead to apoptosis. While general, *in trans* inhibition of the proteasome will therefore be detrimental for the cell, viral evasion mechanisms have been found that act *in cis*, preventing the specific generation of viral epitopes by the proteasome.

The Epstein–Barr virus (EBV) nuclear antigen-1 (EBNA-1) is essential for the persistence of the viral episome and for distribution of viral genomes to daughter cells upon cell division [8]. EBNA-1 is expressed during latent EBV infections and is found in all EBV-associated tumors, thereby making it an ideal target for $CD8^+$ T cell immunity. Initial studies showed that $CD8^+$ T cell responses against EBNA-1 cannot be detected *in vitro*, despite the presence of