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Giving CD4+ T Cells the Slip: Viral Interference with MHC Class II-Restricted Antigen Processing and Presentation

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Abstract

Activation of CD4+ T cells through interactions with peptides bound to Major Histocompatibility Complex Class II (MHC-II) molecules is a crucial step in clearance of most pathogens. Consequently, many viruses have evolved ways of blocking this aspect of adaptive immunity, from specific targeting of processing and presentation components to modulation of signaling pathways that regulate peptide presentation in addition to many other host defense mechanisms. Such cases of interference are far less common compared to what has been elucidated in MHC-I processing and presentation. This may be attributable in part to the complexity of MHC-II antigen processing, the scope of which is only now coming to light.

Introduction

CD8+ and CD4+ T cells, triggered by peptide-MHC-I and peptide-MHC-II complexes respectively, are frequently critical participants in adaptive immune responses. In the conventional model of MHC-II antigen processing and presentation, MHC-II $\alpha\beta$ heterodimers co-assemble in the endoplasmic reticulum (ER) with the invariant chain protein (Ii, also termed CD74) [1]. MHC-II-Ii complexes traffic through the Golgi apparatus, where signals in the cytoplasmic portion of Ii induce diversion to the endocytic compartment [2]. Therein, endosomal proteases cleave Ii, leaving the class-II-associated invariant chain peptide (CLIP) occupying the MHC-II peptide binding groove [2]. In parallel, proteins internalized from the extracellular space, both self and foreign, undergo unfolding and proteolysis. Those resulting peptides with a high affinity for the MHC-II binding groove can displace CLIP from the MHC-II binding groove through participation of the H2-DM chaperone [3]. MHC-II peptide loaded complexes then traffic to the cell surface to present peptide to cognate CD4+ T cells [3].

Only professional antigen-presenting cells (APCs), such as dendritic cells, macrophages and B cells as well as thymic epithelial cells (TECs) constitutively express MHC-II. However,

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interferon gamma (IFN γ), a pivotal inflammatory signal that activates numerous host defense programs, can confer MHC-II processing and presentation capability to many other cell types through coordinate upregulation of the aforementioned cellular components [4].

Considering the pivotal roles of CD4+ and CD8+ T cells, it should come as no surprise that pathogens have developed strategies for repressing the peptide generating and presenting systems that underlie T cell activation. While there are many examples of pathogens that interfere with a variety of steps in the MHC-I antigen presentation pathway [5–7], relatively few mechanistically understood examples exist for inhibition of MHC-II. Here we review those examples that have been elucidated, restricting focus to viruses.

We have divided these examples into two categories: broad-spectrum and targeted inhibition. In the case of broad-spectrum inhibition, interference with MHC-II processing and presentation is part of a larger program of evasion through blockade of signaling pathways that have pleiotropic effects. In contrast, targeted inhibition is defined as the obstruction of specific components in the MHC-II presentation pathway.

Broad-Spectrum Inhibition

In the case of viruses, where genomic space is limited, inhibition of host defense at a more global level may be particularly pertinent. Two means of broad-spectrum inhibition that have been extensively characterized are interference with the IFN γ pathway and stimulation of interleukin 10 (IL-10) production.

Interferon Gamma Pathway Interference

Upon interaction between IFN γ and its receptor (IFN γ R) a signal transduction pathway is induced resulting in phosphorylation of the kinases Jak1 and Jak2 and subsequent phosphorylation of Stat1 [8–10]. Phosphorylated Stat1 dimerizes, transits to the nucleus and directly activates transcription of many genes that are collectively termed ‘interferon stimulated genes’ (ISGs) [8–11]. ISGs include mediators for many different host defense mechanisms. For example, upregulation of components of the immunoproteasome increase quality and quantity of peptides that can be presented on MHC-I [8–11]. Likewise, protein synthesis down-regulators inhibit viral protein translation, and both cell cycle arrest factors and pro-apoptotic factors are upregulated to block dissemination [8–11]. Furthermore, upregulation of chemoattractants and adhesion molecules allow for increased immune cell presence at the site of infection [8–11]. In combination with these many host defense mechanisms, the Class II Transcriptional Activator (CIITA) is also upregulated after IFN γ treatment [8–11].

CIITA tightly controls MHC-II regulation at the transcriptional level. CIITA is a non-DNA binding co-activator that is recruited by the MHC-II enhanceosome and coordinates the recruitment of chromatin remodelers and transcription initiation factors [4]. CIITA is constitutively expressed in professional APCs, but only activated in non-professional APCs after IFN γ interaction due to differential promoter usage [4]. CIITA drives expression of all the MHC-II processing and presentation components enumerated above, such as MHC-II, Ii and H2-DM.

Pathogen inhibition of the IFN γ pathway results in widespread obstruction of host defense mechanisms including the MHC-II presentation pathway. Three broad mechanisms of IFN γ pathway inhibition have been described (Table 1). Firstly, poxviruses encode viral homologues of the IFN γ R that sequester soluble IFN γ [12,13]. Secondly, viruses in many families block Jak1, either by inhibiting phosphorylation or by inducing degradation [12, 14–19]. Thirdly, several viruses employ Stat1 blockade through a variety of mechanisms including inhibition of phosphorylation, degradation, inhibition of dimerization and sequestration [12, 20–22].

Type 1 interferons can also utilize Stat1 in signal transduction and so can be targets of the same viral inhibitory mechanisms discussed above; however, the impact of type 1 interferons on MHC-II expression and function is still a topic of debate [23–27].

Interleukin 10 Upregulation

Interleukin 10 (IL-10) is an immunosuppressive cytokine that can impact many cell populations [28–30]. First described as cytokine synthesis inhibitory factor (CSIF) [31], IL-10 is now known to downregulate many inflammatory cytokines including TNF α , IL-1 α , IL-1 β and IFN γ as well as both CC and CXC chemokines [24–26]. In addition, IL-10 is associated with down-regulation of surface MHC-II on monocytes, both constitutive as well as IFN γ -induced [28–32]. Furthermore, IL-10 signaling raises the pH of the endosome, thereby diminishing the activities of acid-sensitive proteases that participate in antigen processing [33].

Many viruses have coopted this cytokine, either by inducing cellular IL-10 expression or by encoding their own IL-10 homolog (Table 2). The high degree of homology between viral and host IL-10 suggests viral gene acquisition of cellular IL-10 [34].

Targeted Inhibition

Focused viral interference with processing and presentation components has been appreciated mainly in the MHC-I system. Nevertheless, there are several examples of interference in the MHC-II system via increasingly varied mechanisms (Fig. 1).

CIITA inhibition

Several members of the herpesviridae family have been shown to inhibit CIITA function directly. Kaposi's Sarcoma-Associated Herpesvirus (KSHV) encoded latency associated nuclear antigen (LANA) has long been known to downregulate CIITA transcriptional activation [30]. A mechanistic basis has been recently revealed by the Verma lab, which reported that LANA interacts with components of the CIITA associated enhanceosome to interfere with enhanceosome assembly as well as CIITA recruitment to the MHC-II promoter [35]. In addition, Epstein-Barr virus (EBV) encoded immediate-early gene BZLF1 (also called Zta, ZEBRA), represses CIITA transcription by directly binding to the CIITA promoter [36**]. Interestingly, recent work from the Tsai lab has shown that LMP2A, a crucial mediator of EBV immune evasion [37], indirectly downregulates CIITA by inhibiting two positive regulators of CIITA transcription in B cells, E47 and PU.1 [39**]. Furthermore, human cytomegalovirus (HCMV) decreases CIITA transcript levels in mature Langerhans

cells; although *de novo* viral products are implicated, an exact mechanism has not yet been identified [40].

In addition, the Human Immunodeficiency Virus (HIV) encoded transcriptional transactivator (Tat) protein is known to interfere with CIITA function [41]. One important component of the MHC-II enhanceosome that CIITA binds is cyclin T1, a subunit of the positive transcription elongation factor b (p-TEFb) complex that is necessary for productive transcription [41]. Tat acts as a competitive inhibitor of CIITA by binding the same region on cyclin T1 as CIITA [41].

Invariant Chain (Ii) interaction

Viruses have evolved ways of modulating various aspects of Ii function. For example, the HCMV protein US3 binds the α/β dimers of MHC-II resulting in decreased affinity for Ii [42]. This results in decreased, although incomplete, abrogation of MHC-II expression at the cell surface and impaired stimulation of CD4+ T cells [42].

The EBV encoded protein BZLF1 has been shown to interfere with Ii in a manner independent of its previously discussed inhibition of CIITA transcription [43]. When expressed in an inducible plasmid system, BZLF1 downregulated both cell surface and total cellular Ii [43]. Accompanying pulse-chase experiments showed that Ii was downregulated post-transcriptionally through a mechanism that has yet to be elucidated [43]. Despite downregulation of Ii it should be noted that the authors saw no significant reduction in MHC-II at the cell surface and so the impact of this process on MHC-II peptide presentation has not yet been elucidated.

Hepatitis C virus (HCV) also targets Ii, although indirectly, to repress formation of functional MHC-II complexes. The HCV core and NS5A proteins repress transcription of cathepsin S, which is critical for processing of Ii to CLIP [44]. The consequence is higher levels of Ii at the cell surface, which correlates negatively with the amount of peptide-loaded MHC-II [44]. Interpretation of this work is complicated by the fact that the experimental cell (hepatocytes) expresses low levels of MHC-II unless stimulated with IFN γ [44], which also stimulates Cathepsin S transcription.

Vaccinia, a poxvirus, has been shown to inhibit MHC-II presentation [45–47], with one potential mechanism being downregulation of Ii expression [48]. One virally encoded protein that may be responsible is the virulence factor A35, which decreases MHC-II-restricted peptide presentation [45]. While the underlying mechanism has not been fully deduced, A35 was found to localize to the endosome where it may modulate peptide-CLIP exchange [40].

In addition, the HIV encoded protein nef leads to the upregulation of Ii at the cell surface by interfering with the trafficking of peptide loading complexes. The functional consequences were not fully explored, but the expectation is that increased surface Ii will correlate negatively with the amount of surface peptide-MHC-II [49].

MHC-II degradation

Somewhat surprisingly, given the wealth of examples for MHC-I [5–7], there have been few instances of MHC-II molecules that are targeted for degradation by pathogen-encoded proteins. One exception is the HCMV US2 protein, which has roles in degrading both MHC-I and MHC-II molecules [50]. In the latter case, MHC-II α chains are targeted for proteasomal degradation via a targeting mechanism that has not yet been elucidated [50].

Similarly, recently published work from the Rowe lab has identified the EBV encoded late lytic protein BDLF3 as having a role in both MHC-I and MHC-II degradation [51*]. BDLF3 was found to act on both MHC-I and MHC-II molecules, both increasing internalization and delaying appearance on the plasma membrane [51*]. This work showed that BDLF3 induces ubiquitylation of MHC-I and MHC-II molecules [51*]. Subsequent proteasomal degradation of surface MHC proteins was the proposed mechanism, however it should be noted that intracellular levels of both MHC-I and MHC-II were unchanged.

TCR recognition inhibition

In addition to intracellular means of inhibiting MHC-II antigen presentation, EBV has also developed a strategy to block MHC-II- TCR interactions [52]. The EBV lytic phase protein gp42 binds to MHC-II complexes at the cell surface [52]. This results in steric hindrance of interactions with cognate TCRs and consequently, limited CD4+ T cell activation [52,53].

Phenotypic characterization of MHC-II Inhibition

In addition to the examples of MHC-II inhibition described above, there are studies that implicate a particular viral protein in downregulation of MHC-II or decreased CD4+ T cell activation but the host targets have not yet been identified.

The Ebola encoded protein VP35 decreases MHC-II surface expression when encoded in the genome of Herpes Virus Simplex (HSV) [54]. Furthermore, dendritic cells infected with this construct are less able to activate CD4+ T cells [54].

Recent work by the Fröh group examined the poxvirus B22 protein, which is a potent virulence factor [55]. This work demonstrated that B22 is necessary and sufficient for poxvirus inhibition of CD4+ T cell responses. In addition, while the exact mechanism is unknown, this work showed that B22 is located on the APC cell surface and proximal TCR signaling is affected. These findings led the authors to speculate that B22 engages an inhibitory co-receptor [55].

Discussion

Excluding the widespread targeting of IFN γ and IL-10 signaling, there are relatively few examples of viral interference with MHC-II presentation. One likely contributor to this trend is the historical focus on antibodies and cytolytic CD8+ T cell responses, the principal effectors of adaptive immunity. Consequently, corollary studies on evasion of CD4+ T cell responses have been limited.

The increasingly apparent complexity of MHC-II antigen processing may be another factor. For many years alternatives to the classical MHC-II processing pathway have been recognized. These include loading of “recycling” MHC-II in an early endosomal compartment [56–58] and endogenous processing, in which peptide is derived from antigen synthesized within the APC, often via processing mechanisms that extend beyond the endocytic compartment [59]. Until recently, these alternatives have been considered marginal. However, recent work from our laboratory suggests that peptides derived from endogenous processing drive the vast majority of the response to infectious influenza [60*]. Furthermore, we have observed endogenous processing to be comprised of an array of pathways, sufficiently complex for us to propose the term “processing network” [59, 60*]. Recently, a similar level of complexity has been reported for the extra-endosomal generation of the human MHC-II-restricted self-peptidome [61*]. In addition, a genome-wide siRNA screen by the Neefjes lab revealed 276 genes implicated in MHC-II antigen presentation, only 10% of which had been previously identified [62]. Importantly, almost all of the MHC-II inhibition mechanisms discussed in this review necessitate the direct infection of the MHC-II expressing cell, suggesting that, in such cases, endogenous processing is a major source of peptides for MHC-II. Thus, experimentation that focuses upon classical MHC-II antigen processing may overlook many inhibitory strategies. Alternatively, if peptide generation is possible via a variety of pathways, the extent to which CD4+ T cells responses can be blunted through inhibition of specific processing components may be limited. Consequently, broad-spectrum mechanisms may, in general, be more effective and skewing toward the more global strategies may persist even with additional investigation.

We have restricted this review to viruses, but a growing body of literature indicates that some bacteria also interfere with the MHC-II processing and presentation system [63–72]. It will be of great interest to learn the strategies employed, the relative usage of broad-spectrum vs. targeted mechanisms, and how these strategies contrast with what viruses have contrived. No doubt there is much left to uncover in this area of host-pathogen interplay.

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Research highlights

- Many viruses inhibit MHC-II presentation by targeting host defense signaling pathways
- Some viruses target specific components of the MHC-II presentation pathway
- Recent insights have greatly expanded both types of interference
- Accounting for alternative MHC-II processing may reveal additional mechanisms

Figure 1. Viral inhibition of distinct steps in the MHC-II processing and presentation pathway. 1. Inhibition of CIITA-mediated MHC-II gene transcription. 2. Interference with invariant chain functions. 3. Inhibition of acid-sensitive proteases. 4. Interference with MHC-II-TCR complex formation.

Table 1Viral Inhibition of the IFN γ - Jak-Stat Pathway

Virus	Mechanism of Inhibition
Poxviridae	
Many members ^{a,b}	Soluble IFN γ -R mimic that sequesters IFN γ
Vaccinia Virus ^a	Dephosphorylates activated Stat1
Herpesviridae	
Herpes simplex Virus 1 ^a	Interferes with Jak1 and Stat1 phosphorylation
Human cytomegalovirus ^c	Mediates Jak1 degradation
Murine cytomegalovirus ^a	Inhibits the Stat1 dimer prior to nuclear translocation
Ebstein-Barr Virus ^a	Inhibits IFN γ -R1 transcription
Varicella zoster Virus ^a	Lowers Jak2 and Stat1 levels
Paramyxoviridae	
Simian Virus 5 ^a	Mediates Stat1 degradation
Mumps Virus ^a	Destabilizes Stat1
Sendai Virus ^a	Reduces synthesis, stability and phosphorylation of Stat1
Nipah Virus ^a	Sequesters Stat1 in the cytoplasm
Adenoviruses ^a	Reduces IFN γ -R2 levels; inhibits Stat1 function; reduces Stat1 levels
Measles Virus ^d	Inhibits phosphorylated Stat1 dimerization
Flaviviridae	
Hepatitis C Virus ^a	Decreases Stat1 expression
Tick-born encephalitis viruses ^e (Langat Virus)	Inhibits Jak1 phosphorylation
Polyomaviridae	
Murine Polyoma Virus ^a	Binds to Jak1
Filoviridae	
Ebola Virus ^a	Inhibits prior to Stat1 dimer formation
Marburg Virus ^f	Inhibits Jak1 activation
Togaviridae	
Sindbis Virus ^g	Inhibits Jak1 activation
Chikungunya Virus ^h	Inhibits Stat1 phosphorylation
Venezuelan equine encephalitis virus ⁱ	Inhibits Jak1 activation
Rhabdoviridae	
Rabies Virus ^j	Retains phosphorylated Stat1 in cytoplasm

^a reviewed in [12]^b reviewed in [13]^c [14_15]

$d_{[20]}$ $e_{[19]}$ $f_{[18]}$ $g_{[17]}$ $h_{[21]}$ $i_{[16]}$ $j_{[22]}$

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Table 2Viral Expression or Induction of IL-10^a

Viruses that encode a homolog of IL-10	Viruses that induce cellular IL-10
Herpesviridae	Herpesviridae
Human cytomegalovirus	Human cytomegalovirus
Green monkey cytomegalovirus	Murine cytomegalovirus
Rhesus cytomegalovirus	Equid herpesvirus 2
Baboon cytomegalovirus	herpesvirus 6
Owl monkey cytomegalovirus	Ebstein-Barr virus
Squirrel monkey cytomegalovirus	Retroviridae
Ebstein-Barr virus	Human Immunodeficiency Virus
Bonobo herpesvirus	Papillomaviridae
Rhesus lymphocryptovirus	Human Papilloma Virus
Baboon lymphocryptovirus	Arenaviridae
Bovine herpesvirus 2	Tacaribe Virus
Equid herpesvirus 2	Bunyaviridae
	Crimean-Congo Haemorrhagic
	Fever Virus
Alloherpesviridae	Togaviridae
Cyprinid herpesvirus 3	Chikungunya Virus
Anguillid herpesvirus 3	
Poxviridae	
Orf virus	
Bovine papular stomatitis virus	
Pseudocowpox virus	
Lumpy skin disease virus	
Sheeppox virus	
Goatpox virus	
Canarypox virus	

^aReviewed in [24-27, 29]