Review Article

Zahedan Journal of Research in Medical Sciences

Journal homepage: www.zjrms.ir

Viral Evasion and Subversion Mechanisms of the Host Immune System

Mehran Ghaemi-Bafghi,[1] Alireza Haghparast*[1]

1. Department of Pathobiology, Faculty of Veterinary Medicine & Institute of Biotechnology, Ferdowsi University of Mashhad, Mashhad, Iran

Article information

Article history:
Received: 16 July 2012
Accepted: 8 SEP 2012
Available online: 27 Mar 2013
ZJRMS 2013; 15 (10):1-6

Keywords:
Virus
Immune system
Evasion mechanisms

*Corresponding author at:
Department of Pathobiology, Faculty of Veterinary Medicine, & Institute of Biotechnology, Ferdowsi University of Mashhad, Mashhad, Iran
E-mail:
alireza.haghparast@gmail.com

Abstract

Viruses are the most abundant and versatile pathogens which challenge the immune system and cause major threats to human health. Viruses employ different mechanisms to evade host immune responses that we describe them under the following headings: Inhibition of humoral responses, Interference with interferons, Inhibition and modulation of cytokines and chemokines, Inhibitors of apoptosis, Evading CTLs and NKs, and modulating MHC function.

Viruses inhibit humoral immunity in different ways which contains change of viral antigens, production of regulatory proteins of complement system and receptors of the Fc part of antibodies. Viruses block interferon production and function via interruption of cell signaling JAK/STAT pathway, Inhibition of eIF-2α phosphorylation and translational arrest and 2'5'OS/RNAse L system. Also, Poxviruses produce soluble versions of receptors for interferons. One of the most important ways of viral evasion is inhibition and manipulation of cytokines; for example, Herpsviruses and Poxviruses produce viral cytokines (virokines) and cytokine receptors (viroceptors). In addition, viruses change maturation and expression of MHC I and MHC II molecules to interrupt viral antigens presentation and hide them from immune system recognition. Also, they inhibit NK cell functions.

In this review, we provide an overview of the viral evasion mechanisms of immune system. Since most viruses have developed strategies for evasion of immune system, if we know these mechanisms in detail we can fight them more successfully.

Introduction

Viruses are the most abundant, various and rapidly evolving pathogens that the host immune system must deal with them and they therefore represent a serious threat to human health. In this review, we give an overview of the different mechanisms that viruses employ to evade host immune responses.

Inhibition of humoral immune responses: One of the first identified viral immune evasion strategies was antigenic variability. Because of the low fidelity of RNA polymerases, viral RNA genomes include a collection of RNA species with random mutations. Genetic variability can also produce different peptide sequences that are either new antigens or that do not bind to major histocompatibility complex (MHC) molecules at all. For example, herpesviruses alter the number of expressed protein epitopes and the resemblance to host epitopes, in different phases of viral infection to evade the host immune system [1].

The complement system is one of the major non-specific host defense mechanism. Viruses produce secretory homologues of complement regulatory proteins that obstruct complement activation and neutralization of virus particles (Table 1). The cowpox virus (CPV) complement inhibitor, named inflammation modulatory protein (IMP), prevents immunopathological tissue damage at the site of infection, supposedly by inhibiting production of the macrophage chemoattractant factors C3a and C5a [2]. Viruses guard the membranes of infected cells and the lipid envelopes of virus particles from complement lysis by producing homologues of inhibitors of the membrane-attack complex. Viruses such as HIV, human cytomegalovirus (HCMV) and vaccinia virus (VV) employ an intelligent strategy, 'borrowing' host cellular factors, including CD59, which normally saves cells from complement lysis, and incorporating them into the viral envelope. Lastly, Fc receptors of antibodies are encoded by some viruses (Table 1). Antibodies attached to infected cells or virus particles might therefore be bound at the Fc region, thereby suppressing Fc-dependent immune activation of complement and phagocyte.

The matrix (M_1) protein of influenza A virus interacts with complement C1qA and acts as an important inhibitory factor in the classical complement pathway. The N-terminal domain of M_1 protein was necessary for its binding to the globular region of C1qA. As a consequence, M_1 blocked the interaction between C1qA and IgG and inhibited the complement-mediated neutralization of influenza virus [3].

Inhibition of cell response to Beta interferon (IFN-β): After viral infection, infected cells express Beta interferon (IFN-β) that would bind to their receptors on the cell surfaces in the autocrine or paracrine manner and cause

the expression of numerous IFN-stimulated genes (ISGs) through the janus kinase (JAK)/signal transducers and activators of transcription (STAT) signal transduction pathways. Some of the ISGs such as RIG-I (retinoic-acid-inducible gene I), MDA5 (melanoma differentiation-associated gene 5), DAI (DNA-dependent activator of IRFs), some microRNAs and the TRIM (tripartite motif-containing) family of proteins, are involved in the amplification and regulation of the IFN response.

Other ISGs such as 2'5'-oligoadenylate synthetase (OAS) and ribonuclease L (RNaseL), IFN-inducible dsRNA-dependent protein kinase (PKR) are involved in antiviral mechanisms that interfere with the life cycle of individual viruses, and also prevent the activation of IFN effector pathways that cause an anti-viral state in the cell and restrict virus replication. This is mainly acquired by inhibiting double-stranded (ds)-RNA-dependent protein kinase (PKR) activation, the phosphorylation of eukaryotic translation initiation factor 2a (eIF-2a) and the RNase L system, which might break down viral RNA and stop translation in the host cell [4].

Primarily, some viruses prevent interferon to bind their receptors using viral interferon receptors. Some of the Poxviruses produce soluble versions of receptors for IFN-α and -β (IFN-α/βR) and IFN-γ (IFN-γR), which block the immune functions of IFNs. The VV-secreted IFN-α/βR is localized at the cell surface to protect cells from IFN (Table 2) [5, 6].

Secondarily, some viruses obstruct induced transcriptional signals of ISGs from receptors of IFNs to the cell nucleus to inhibit an antiviral status and the limitation of viral replication in cells. Parainfluenza virus 5 (PIV5) induces STAT1 degradation with cellular proteasome inhibiting IFN signaling [7] and V protein of paramyxoviruses also cause ubiquitination and degradation of STAT1 [8-10]. Non structural protein of Rift Valley Fever virus activates suppressor of cytokine signaling 1 (SOCS1) to block IFN signaling pathway [11]. Hepatitis C virus (HCV) and herpes simplex virus 1 (HSV-1) also activate SOCS3 to reduce JAK and STAT phosphorilation [12, 13].

A major component of the cellular antiviral system is protein kinase R (PKR) which is activated by binding to either double-stranded RNA (dsRNA) or the cellular PACT protein. Activated PKR phosphorylates the translation initiation factor eIF2, thereby inhibiting viral and cellular protein synthesis and virus replication. So, different viruses inhibit the PKR, for example, NS1A non structural protein of Influenza virus [14], Core and E2 structural proteins, NS3/4A, NS5A and 4B nonstructural proteins of HCV all prevent PKR activation [15].

Additionally, several viruses inhibit the activity of IFN-γ, a key activator of cellular immunity, by blocking the synthesis or activity of factors required for its production, such as interleukin IL-18 or IL-12 (Table 2): CPV cytokine response modifier (Crm) A, inhibits caspase-1, which processes the mature forms of IL-1β and IL-18 [16]; various poxviruses produce soluble IL-18-binding proteins (IL-18BPs) [17]; measles virus (MeV) binds CD46 in macrophages and inhibits IL-12 production [18]; and herpesviruses and poxviruses express IL-10 homologues that diminish the Th1 response by down-regulating the production of IL-12 [19].

Inhibition and modulation of cytokines

Cytokines have a great effect on the beginning and modulation of the innate and adaptive immune responses, and viruses try hard to block cytokine production, activity and signal transduction (Table 3). African swine fever virus (ASFV) reproduces in macrophages and produces an IkB homologue that prevents cytokine expression mediated by nuclear factor (NF)-κB and the nuclear factor activated T cell (NFAT) transcription factors [20]. Many viruses obstruct signal tranduction by ligands of the tumor necrosis factor (TNF) family, whereas others purposefully initiate some cytokine pathways; for example, the Epstein-Barr virus (EBV) latent membrane protein 1 (LMP1) recruits components of the TNF receptor (TNFR) and CD40 transduction machinery to imitate cytokine responses that could be advantageous for the virus, such as cell proliferation [21] (Table 3).

One of the most interesting viral evasion mechanisms is the mimicry of cytokines (virokines) and cytokine receptors (viroceptors) by large DNA viruses (herpesviruses and poxviruses) [22]. The functions of these molecules in the animal host are varied. Soluble viral cytokine receptors might neutralize cytokine activity and cytokine homologues might redirect the immune response for the sake of the virus. For example, EBV expresses viral interleukine 10 (vIL-10) that inhibits HLA-class I, ICAM-1, and B7 expression on the monocytes/macrophages to prevent the macrophage induction of the T cell activation [23].

On the other hand, viruses that contaminate immune cells might use these homologues to induce signaling pathways in the infected cell that assist virus replication. The herpesvirus cytokine homologues vIL-6 and vIL-17 might have regulatory activity of immune system but might also augment proliferation of cells that are suitable for viral replication [1]. Secreted cytokine receptors or binding proteins are mostly produced by poxviruses [24].

These proteins were originally recognized as homologues of host TNFRs, IL-1Rs and IFN-γRs. The finding of four different soluble poxvirus TNFRs, and a membrane TNF-binding activity in VV infections, is noteworthy and proposes that viral TNFRs might have additional functions [25, 26]. By using binding and activity assays researchers have recognized secreted proteins that bind IFN-α and -β, chemokines (CKs) or granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-2, and that do not have any sequence similarity to cellular counterparts [27].

In poxviruses, three different secreted IL-18BPs that have been recognized are homologues of human and mouse secreted IL-18BPs but not of membrane IL-18Rs [17, 28]. Inactivation of poxvirus cytokine receptor genes causes virus attenuation in vivo but, interestingly, deletion of the VV IL-1βR increases virus virulence and the beginning of fever, suggesting that the target of some immune evasion mechanisms is to decrease the immunopathology induced by viral infection [24].

Evading CTLs and NKs, and modulating MHC function: How to succeed persistence in front of a strong host immune response is a problem that must be solved by viruses that establish lifelong infections. Cellular proteins are degraded by the proteasome, the major intracellular protease complex, and the resulting peptides are moved by transporters connected to antigen processing (TAP) molecules into the endoplasmic reticulum (ER), where they donate to the assembly of MHC class I molecules. MHC class I molecules exhibit the composition of cellular proteins to cells of the immune system. The demonstration of foreign peptides activates and attracts cytolytic CD8+ T cells. Interference with antigen processing [e.g. Epstein-Barr nuclear antigen A1 (EBNA1)] or TAP function [e.g. herpes simplex virus (HSV) infected cell protein 47 (ICP47) and HCMV US6 and pp65] hinders peptide production and transport either particularly or generally (Table 4).

Viruses employ different mechanisms to modify the maturation, assembly and export of MHC class I molecules. There is only restricted functional homology and no sequence homology among the different viral effectors. However, the general result of these functions is the same: down-regulation of MHC class I molecules or of some MHC class I alleles.

The investigation of MHC class I regulation has disclosed additional genes in herpesviruses of different species [29-31], which might influence many cell types or only those tissues relevant for virus maintenance. HCMV, MCMV, HHV-6,7,8 and HSV all encode multiple proteins that interfere with proper MHC class I antigen presentation. The HSV gpUS2, gpUS6, gpUS11 and gpUS3 glycoproteins bind to the MHC class I and retain it in the endoplasmic reticulum [32, 34]. The U21 open reading frame from HHV-7 and HHV-6 diverts class I MHC molecules to an endolysosomal compartment that effectively remove them from the cell surface. Also Human herpesvirus-6A and -6B encode viral immunoevasins that down-regulate class I MHC molecules [33, 34].

Although the down-regulation of MHC class I expression hinders CD8+ T-cell recognition, cells that down-regulate these molecules turn into targets for NK cells. NK cells, the first line of cellular defense against viruses, have receptors for particular MHC molecules. Some of these receptors suppress the cytolytic machinery of NK cells and work as killer cell inhibitory receptors (KIR). Other receptors, designated leukocyte immunoglobulin-like receptors (LIR), are expressed chiefly on monocytes and B cells. Engagement of an NK receptor can alternatively cause NK activation because all receptors don't have immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their intracellular domains. The HCMV protein UL18 and the MCMV m144 protein, which are homologous to MHC class I, could be connected to NK killing, and UL18 help to the identification of LIR-1. In addition, the HCMV UL40 protein supplies a peptide selectively needed for the maturation of the HLA-E molecule, an NK target [35, 36].

Effects on MHC class II expression divide in two classes, effects on transcription and posttranslational effects. Adenovirus, MCMV and HCMV control MHC class II transcription. At the post translational level, the HCMV US2 protein, which affects MHC class I, apparently translocates the DRa and the DMa chain into the cytosol in order for the proteasome to degrade them. Another target entangled with interference with MHC class II function is the transportation between endosomal peptide loading and surface expression. Human papilloma virus (HPV) and HIV Nef influence vesicle traffic as well as the function of the endocytic machinery. Therefore, in addition to MHC class II, other proteins that use this pathway, for example the CD4 molecule, are also affected.

Table 1. Viral inhibition of humoral immunity (complement and antibodies)

Function/activity	Gene/protein	Virus	Mechanism
Inhibition of soluble complement factors	vCP/C21L, IMP, SPICE, gC, ORF4, CCPH	VV, CPV, VaV, HSV-1, HSV-2 , HVS, HHV-8, MHV-68	Viral homologues of C4BP, CR1, CD46 or CD55
	gp120-gp41	HIV	Recruitment of factor H
Blockade of formation of membrane-attack complex	ORF15	HVS	Viral CD59 homolog
	Host proteins CD59, CD55 or CD46	VV, HIV, HTLV, HCMV	Host proteins incorporated into virion envelope
Viral IgG Fc receptors	gE-gI, gE, Fcr1, S peplomer	HSV-1, HSV-2, MCMV, coronavirus	Binding of IgG and inhibition of Fc-dependent immune activation

Table 2. Viral interference with IFN

Function/activity	Gene/protein	Virus	Mechanism
Inhibition of JAK/STAT pathway	EIA	Adenovirus	Decreases the levels of STAT1 and p48
	EBNA-2	EBV	Down regulates IFN-induced transcription
	Unknown	HCMV	Reduces levels of JAK1 and p48; involvement of proteasome
	Unknown	HPIV-2	Targets STAT2 for degradation
	Unknown	HPIV-3, SeV	Block STAT1 phosphorylation
	E7	HPV-16	Binds to p48

	T antigen	MPV	Binds to and inactivates JAK1
	V protein	SV5	Targets STAT1 for proteasome-mediated degradation
IFN-induced transcription	IRF homologue	HHV-8	Represses transcriptional responses to IFNs
	Capsid protein	HBV	Inhibits MxA gene expression
Inhibition of PKR	σ3, NSP3, E3L, OV20.0L, NS1	Reovirus, rotavirus, VV, OV, influenza virus	Bind dsRNA and prevent PKR activation
	VAI RNA, EBER RNA, TAR RNA	Adenovirus, EBV, HIV	RNA that binds to, but fails to activate, PKR
	PK2, NS5A and E2, US11, Tat	Baculovirus, HCV, HSV, HIV	Bind to and inhibit PKR
	Unknown	Poliovirus	Induced degradation of PKR
	Unknown	Influenza virus	Induction of p58IPK, a cellular inhibitor of PKR
Inhibition of eIF-2α phosphorylation and translational arrest	K3L	VV	eIF-2α homolog, prevents eIF-2α phosphorylation, also inhibits PKR
	ICP34.5	HSV	Redirects protein phosphatase 1 to dephosphorylate and re-activate eIF-2α
Inhibition of 2'5'OS/RNase L system	σ3,NSP3, E3L, OV20.0L, NS1	Reovirus, rotavirus, VV, OV, influenza virus	Bind dsRNA and prevent activation of 2'5'OS/RNAse L
	Unknown	EMCV, HIV	Induce RNAse L inhibitor, which antagonizes 2'5'OA binding to RNAse L
	Unknown	HSV	Synthesis of 2'5'OA antagonists

Table 3. Viral cytokines, cytokine receptors and inhibitors

Function/activity	Gene/protein	Virus	Mechanism
	M-T2	MV, SFV	Secreted, binds rabbit TNF
	CrmB	CPV, VaV	Secreted, binds TNF and LT-a
	CrmC	CPV, VV	Secreted, binds TNF
vTNFR	CrmD	CPV, EV	Secreted, binds TNF and LT-a
	CrmE	CPV	Secreted, binds TNF
	Unknown	VV	TNFR at the surface of VV-infected cells
	UL144	HCMV	TNFR homolog, unknown function
vIL-1 βR	B15R	VV	Secreted, binds IL-1 p, blocks febrile response
vIFN-γR	M-T7, B8R	MV, VV, CPV	Secreted, binds IFN-7 from various species
vIFN-α/βR	B18R	VV	Secreted and cell surface, binds type I IFN from various species
vCSF-1R	BARF-1	EBV	Secreted, binds CSF-1
vGM-CSF/IL-2BP	GIF	OV	Secreted, binds GM-CSF and IL-2
	MC54	MCV	Secreted, binds IL-18, inhibits IL-18 induced IFN-γ production
vIL-18BP	MC53	MCV	Secreted, binds IL-18, inhibits IL-18-induced IFN-γ production
	D7L	EV, VV, CPV, VaV	Secreted, binds IL-18, inhibits IL-18-induced IFN-γ production and NK response
vIFN-γ/IL-2/IL-5BP	Unknown	TPV	35 kDa, secreted, binds IFN-γ, IL-2 and IL-5
Inhibition of TNF signaling	E3 14.7K, E3 10.4/15.4K, E1B 19K	Adenovirus	Prevent TNF cytolysis and block phopholipase A2 activation
Mimicry of TNFR/CD40 signaling	LMP-1	EBV	Recruits death-domain-containing proteins and induces signals of the TNFR/CD40 pathway
IkB homologue	A238L	ASFV	Inhibition of NFkB/NFAT signaling
Inhibition of maturation of cytokines	CrmA, SPI-2, B13R, SERP-2	CPV, VV, MV	Inhibition of IL-I β converting enzyme (ICE, caspase-I), inhibition of IL-I3, and possibly IL-18, cleavage
Inhibition of IL-12 production	Hemagglutinin	MeV	Binds to CD46 and blocks induction of IL-12 by macrophages

Table 4. Viral interference with MHC functions

Function/activity	Gene/protein	Virus	Mechanism
	E3/I9K	Adenovirus	Binding and retention of class I in ER
	US3	HCMV	Binding and retention of class I in ER
	US2, US11	HCMV	Relocation of heavy chain into ER for degradation
	m4	HCMV	Binds class I molecules
Effect on MHC class I	m6	MCMV	Binding of class I molecules and transport to lysosomes for degradation
	M152	MCMV	Retains class I in ER–Golgi intermediate compartment
	K3, K5	HHV-8, MHV-68	Down-regulation of class I molecules
	Nef	HIV	Endocytosis of surface class I and CD4
	Vpu	HIV	Destabilization of class I, targets CD4 to proteasome
Effect on MHC class II	EIA	Adenovirus	Interferes with class II upregulation (IFN-7 signal transduction

			cascade)
	Unknown	HSV	Interference with class II function
	Unknown	HCMV, MCMV	Interference with class II upregulation (IFN-7 signal transduction cascade)
	US2	HCMV	Targets class II DR, DM a chain for degradation
	ORFI4	HSV	Class II binding
	E5, E6	HPV, BPV	Interference with class II processing, E5 acidification of endosomes, E6 interaction with AP complex
	Nef	HIV	Interference with class II processing
Effect on TAP	ICP-47	HSV	Prevents peptide binding to TAP in cytosol
	US6	HCMV	Prevents peptide transport through TAP pore
Effect on antigen processing	EBNA-I	EBV	A Gly-Ala repeat motif prevents proteasomal degradation
	pp65	HCMV	Modulates processing of another HCMV protein
Effect on NK cells	UL18, m144, r144	HCMV, MCMV,RCMV	Class I homolog, inhibits NK cell lysis
	MC80	MCV	Class I homolog, function unknown
	UL40	HCMV	UL40 peptide causes HLA-E upregulation

Discussion

Recognition of the novel immune evasion strategies and the analysis of their functions in the context of a viral infection should result in a more clear comprehension of the immune system and the interaction of viruses with their hosts. This will help us to deal with virus-induced pathology and to design safer and more immunogenic viruses for novel therapeutic as well as vaccination strategies.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

Funding/Support

Ferdowsi University of Mashhad.

References

1. Kotwal GJ. Poxviral mimicry of complement and chemokine system components: what's the end game? Immunol. Today 2000; 21(5): 242-248.
2. Tortorella, D. Viral subversion of the immune system. Annu Rev Immunol 2000; 18: 861-926.
3. Zhang J. Influenza A virus M_1 blocks the classical complement pathway through interacting with C1qA. J Gen Virol 2009; 90(11): 2751-8.
4. Andrew G. Bowie viral evasion and subversion of pattern-recognition receptor signaling Nature Rev. Immunol 2010; 8(12): 911-923.
5. Haller O, Kochs G, Weber F. The interferon response circuit: Induction and suppression by pathogenic viruses. Virology 2006; 344(1): 119-130.
6. Thomas A. Kraus enabled interferon signaling evasion in an immune-competent transgenic mouse model of parainfluenza virus 5 infection. Virology 2006; 371(1): 196-205.
7. Didcock, L. The V protein of simian virus 5 inhibits interferon signalling by targeting STAT1 for proteasome-mediated degradation. Virology 1999; 73(12): 9928-9933.
8. Palosaari H. STAT protein interference and suppression of cytokine signal transduction by measles virus V protein. Virology 2003; 77(13): 7635-7644.
9. Precious, B. In vitro and in vivo specificity of ubiquitination and degradation of STAT1 and STAT2 by the V proteins of the paramyxoviruses simian virus 5 and human parainfluenza virus type 2. J Gen Virol 2005; 86(1): 151-158.
10. Yokota S. Induction of suppressor of cytokine signaling-3 by herpes simplex virus type 1 contributes to inhibition of the interferon signaling pathway. Virology 2004; 78(12): 6282-6286.
11. Ulane CM. Composition and assembly of STAT-targeting ubiquitin ligase complexes: paramyxovirus V protein carboxyl terminus is an oligomerization domain. Virology 2005; 79(16): 10180-10189.
12. Bode JG. IFN-alpha antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling-3. FASEB J 2003; 17(3): 488-490.
13. Li S, Min JY, Krug RM, Sen GC. Binding of the influenza A virus NS1 protein to PKR mediates the inhibition of its activation by either PACT or double-stranded RNA. Virology 2006; 349(1): 13-21.
14. Xu J, Liu S, Xu Y, et al. Identification of the nonstructural protein 4B of hepatitis C virus as a factor that inhibits the antiviral activity of interferon-alpha. Virus Res 2009; 141(1): 55-62.
15. Smith GL. Vaccinia virus immune evasion. Immunol Lett 1999; 65(1-2): 55-62.
16. Smith GL, Symons JA, Alcami A. Poxviruses: interfering with interferons. SemVirol 1998; 8: 409-418.
17. Spriggs, MK. One step ahead of the game: viral immunomodulatory molecules. Annu Rev Immunol 1996; 14: 101-130.
18. Kotenko SV, Saccani S, Izotova LS, et al. Human cytomegalovirus harbors its own unique IL-10 homolog (cmvIL-10). Proc Natl Acad Sci USA 2000; 97(4): 1695-1700.
19. Miskin JE, Abrams CC, Goatley LC and Dixom LK. A viral mechanism for inhibition of the cellular phosphatase calcineurin. Science 1998; 281(5376): 562-565.
20. Farrell PJ. Signal transduction from the Epstein–Barr virus LMP-1 transforming protein. Trends Microbiol 1998; 6(5): 175-177.
21. Nash P, Barrett J, Coa JX, et al. Immunomodulation by viruses: the myxoma virus story. Immunol Rev 1999; 168: 103-120.
22. Lalani AS, Barrett JW, McFadden G. Modulating chemokines: more lessons from viruses. Immunol Today 2000; 21(2): 100-106.
23. Salek-Ardakani S, Arrand JR, Mackett M. Epstein–Barr virus encoded interleukin-10 inhibits HLA-class I, ICAM-1, and B7 expression on human monocytes: Implications

for immune evasion by EBV. Virology 2002; 304(2): 342-351.
24. Alcami A, Symons JA, Khanna A and Smith G. Poxviruses: capturing cytokines and chemokines. Sem Virol 1998; 8(5): 419-427.
25. Loparev VN, Parsons JM, Knight C. A third distinct tumor necrosis factor receptor of orthopoxviruses. Proc Natl Acad Sci USA. 1998; 95(7): 3786-3791.
26. Alcami A, Khanna A, Paul NL and Smith GL. Vaccinia virus strains Lister, USSR and Evans express soluble and cell-surface tumour necrosis factor receptors. J Gen Virol 1999; 80(pt4): 949-959.
27. Deane D, Mclnnes CJ, Percival A. Orf virus encodes a novel secreted protein inhibitor of granulocyte-macrophage colony stimulating factor and interleukin-2. J Virol 2000; 74(3): 1313-1320.
28. Ziegler H, Muranyi W, Burgert HG, et al. The luminal part of the murine cytomegalovirus glycoprotein gp40 catalyses the retention of MHC class I molecules. EMBO J. 2000; 19(5): 870-881.
29. Ishido S, Wang C, Lee BS, et al. Downregulation of major histocompatibility complex class I molecules by Kaposi's sarcoma-associated herpesvirus K3 and K5 proteins. J Virol 2000; 74(11): 5300-5309.
30. Coscoy L, Ganem D. Kaposi's sarcoma-associated herpesvirus encodes two proteins that block cell surface display of MHC class I chains by enhancing their endocytosis. Proc Natl. Acad Sci USA 2000; 97(14): 8051-8056.
31. Stevenson PG, Eftsthiou S, Doherty PC and Lehner PJ. Inhibition of MHC class I-restricted antigen presentation by gamma2–herpesviruses. Proc Natl Acad Sci USA 2000; 97(15): 8455-8460.
32. Besold K, Wills M, Plachter B. Immune evasion proteins gpUS2 and gpUS11 of human cytomegalovirus incompletely protect infected cells from CD8 T cell recognition. Virology 2009; 391(1): 5-19.
33. Glosson NL, Hudson AW. Human herpesvirus-6A and 6B encode viral immunoevasins that downregulate class I MHC molecules. Virology 2007; 365(1): 125-135.
34. Bullock GC, Lashmit PE, Stinski MF. Effect of the R1 element on expression of the US3 and US6 immune evasion genes of human cytomegalovirus. Virology 2001; 288(1):164-174.
35. Tomasec, P, Braud VM, Rickards C, et al. Surface expression of HLA-E, an inhibitor of natural killer cells, enhanced by human cytomegalovirus gpUL40. Science 2000; 287(5455): 1031-1033
36. Ulbrecht M, Martinozzi S, Grzeschik M, et al. The human cytomegalovirus UL40 gene product contains a ligand for HLA-E and prevents NK cell-mediated lysis. J Immunol 2000; 164(10): 5019-5022.

Please cite this article as: Ghaemi-Bafghi M, Haghparast A. Viral evasion and subversion mechanisms of the host immune system. Zahedan J Res Med Sci (ZJRMS) 2013; 15(10): 1-6.