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Role of Viral Cytokines (Virokines) in Viral Infections-Mini Review

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Abstract: The vertebrate body is an ideal breeding ground for viruses and provides the conditions that promote their growth, survival and transmission. Vertebrates have developed immunity and at the same time the invading viruses have discovered elegant ways to circumvent the host's immune mechanisms. One of the defense strategies that counteract the immune responses of the infected host exploits viral immunomodulators that directly interfere with the host's cytokine system. Virus encoded immunomodulators (Virokines), enables viruses to create favorable habitat, which preserves them by protecting against damage from the inflammatory response, as well as by blocking apoptosis, until the virus replicates to high titers and finds another host. Virokines are clinically and therapeutically beneficial to the medical field and also having potential implications in viral epidemiology, treatment or prevention of viral and inflammatory diseases and for the development of safer vaccines. The endogenous secretion of the virus immunomodulators is thus emerging as an important mechanism of viral control, which is potentially inducible by effective vaccines. The in depth knowledge of the interactions between viruses and the virokines may lead to novel therapeutic and preventive strategies for the control of viral inflammatory diseases. There is no doubt that these virokines will serve as useful starting points for the development of new treatment tools in the new millennium.

Key words: Viral Infections, immunomodulators

INTRODUCTION

By co-evolving with the immune system of the hosts for untold millennia under constant selective pressure, viruses have developed their own defenses to counteract a broad variety of antiviral immune effectors molecules that would impede their successful propagation[1]. One such strategy of immune evasion by viruses is the expression of immuno-modulatory proteins in the infected host cells. The secretion of the virus-encoded immuno-modulatory molecules from the infected cells gives rise to the possibility of synergistic interaction between viruses within a co-infected host. The origin of these viral immuno-modulatory proteins is from ancestral homologous that were hijacked from the infected host cells during the process of co-evolution[2,3]. These viral genes are thought to have been captured from host cells during viral evolution and modified to confer an advantage in viral replication, survival or transmission[1,4]. Analysis of various viral proteins demonstrates that these virus-encoded proteins are often smaller and more powerful than the highly homologous host immune proteins[1]. Viral immuno-modulatory proteins can be grouped into several categories based on their targets and mechanisms of action[5].

Viroceptors are secreted or cell surface viral glycoproteins homologous to cellular receptors that generally act by competitively binding ligands of cytokines thereby short-circuiting an immune or inflammatory signal[5,7].

Viromitigators are intracellular viral proteins aimed at disrupting specific signal transduction cascades. The most recently studied group of these *Viromitigators* are the viral proteins involved in mitigating apoptosis of the infected cells[5,7].

Virostealth refers to the general strategy by which the virus seeks to hide its presence from the immune system by specifically down regulating specific cell surface markers such as class 1 MHC molecules that act as the window for the immune system to detect and target virus infected cells[5].

Virokines are virally encoded proteins that are secreted from the infected host cell, which mimics or modulate different aspects of the host immune system, including cytokines, chemokines, complement regulatory proteins and growth factors to better maintain a

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suitable habitat for viral replication[2,6,7]. The expression of these virokines is important for virus survival and to persist in the host. Since the discovery of virokines in the 1980s, much time and research has been dedicated to exploring their potential use as therapeutic agents[1].

Several viruses are known to express virokines, all of which are restricted to members of families' of *Herpesviridae, Poxviridae, Retroviridae* and *Adenoviridae*[2,3,6,9]. These larger DNA viruses are of particular interest because they use their larger genetic encoding capacity to produce a range of viral proteins aimed to disabling the host immune response. Many of these proteins are currently being investigated for use as novel therapeutic immunomodulators in manage immune disorders, viral diseases inflammation after trauma, graft rejection and autoimmune diseases[1].

These viral immunomodulators have been subject to extensive scrutiny because it is now apparent that an understanding of the viral mechanisms used to perturb virokine function might lead to novel therapeutic applications for the treatment or prevention of a wide spectrum of inflammatory or viral diseases[6].

TYPES OF VIROKINES

Virus-encoded cytokines: vIL-6 has capable of stimulating leukocyte cell growth, thus vIL-6 play a role in KSHV pathogenesis by stimulating B cells leads to B cell lymphomas. The vIL-6 interacts with IL-6 receptors and stimulates cell growth to enhance KSHV replication and survival. vIL-6 has been shown to activate the signaling pathways of cytokines involving STAT proteins and Janus kinases via interactions with the gp130 signal transducing subunit. This interaction is independent of the IL-6 receptor alpha chain and may influence disease pathogenesis upon KSHV infection by interfering with signaling through gp130 in response to native cytokines[2] are listed in (Table 1).

Cytokines such as interferon (IFN)-α/IFN-β, IFN-γ and Tumor Necrosis Factor (TNF)-α, have potentiality to trigger the activation of intracellular antiviral pathways. Once after they bind to specific receptors on the surface of the infected cells, other cytokines such as IL-1α, IL-1β, IL-2, IL-6, IL-12, IL-13 and IL-18 also contribute to the antiviral response indirectly, by modulating various aspects of the immune response, including the autocrine or paracrine up regulation of IFN-α, IFN-β, IFN-γ and TNF-α[1]

The IFN-induced antivital pathways involve , the induced synthesis of a family of enzymes called 2-5-oligoadenylate synthetases, which polymerizes ATP into 2'-5'-linked oligoadenylates that in turn activate cellular ribonucleases to degrade viral RNA and the induced synthesis of RNA dependent protein kinases (PKR), which phosphorylates and inactivates the translation elongation factors 2 alpha (eIF2α). Both these pathways require double-stranded RNA (dsRNA) produced during viral replication as a cofactor and the net effect of these pathways is the inhibition of cellular (and also viral) protein synthesis. Other IFN-induced mechanisms are known to directly inhibit viral replication, or promote lysis of infected cells by enhancement of MHC class I expression and viral peptide presentation. Other cytokines such as TNF-β and IL-1 have also been shown to inhibit viral replication through IFN-like mechanisms or through the up regulation of MHC class1 or class II antigens. Since cytokines are so important in regulating immunity to pathogens, it is not surprise that many viruses have developed mechanisms to evade cytokine by expression of viral cytokines. Some of the viral cytokines are

viral IL-10(vIL-10): The vIL-10 is 70 % homologous to murine IL-10 and 84 % homologous to human IL-10, indicating that vIL-10 is more closely related to human-IL-10[2,12]. IL-10 is a cytokine normally secreted by Th2 CD4 helper T cells and from activated B cells and macrophages and vIL-10 has retained many of the functions of IL-10, such as, inhibition of other cytokines synthesis from macrophages, monocytes, natural killer cells and T cells and stimulation of B cell growth and differentiation

viral IL-6(vIL-6): IL-6 is a multifunctional cytokines that is important for various cell types and stimulate B-cell differentiation. vIL-6 shows 62 % homologous to human IL-6. The Kaposi's sarcoma-associated herpes virus (KSHV) open reading frame K2 encodes a vIL-6, which retains at least one of the functions of IL-6. The vIL-6 has capable of stimulating leukocyte cell growth, thus vIL-6 play a role in KSHV pathogenesis by stimulating B cells leads to B cell lymphomas. The vIL-6 interacts with IL-6 receptors and stimulates cell growth to enhance KSHV replication and survival. vIL-6 has been shown to activate the signaling pathways of cytokines involving STAT proteins and Janus kinases via interactions with the gp130 signal transducing subunit. This interaction is independent of the IL-6 receptor alpha chain and may

Table 1: Virus-encoded cytokines

Virus	Coding Genes	Virokines	Homolog of host cytokines
Epstein-Barr virus	BCRF1	vIL-10	IL-10
Herpes virus papio	BCRF1	vIL-10	IL-10
Equine herpes virus type-2	BCRF1	vIL-10	IL-10
Cytomegalovirus	CmvIL-10	vIL-10	IL-10
Orf virus	OrfvirusIL-10	vIL-10	IL-10
Kaposi's sarcoma-associated herpes virus	K2	vIL-6	IL-6
Herpes virus saimiri	HVS13	vIL-17	IL-17

Table 2: Virus-encoded chemokines

Virus	Coding gene	Virokines	Homolog of host chemokines
Murine cytomegalovirus	m131	MCK-1	CC chemokines (vCC)
Human herpes virus-8	K6	vMIP-1	
(HHV-8/KSHV)	K4	vMIP-2	MIP-1α
Human herpes virus-6 (HHV-6)	U83	vMIP-1α	MIP-1α
HHV-8	K4.1	vMIP-3/vMIP-1β	MIP-1β
Molluscum contagiosum virus	MC148R	vMIP-1β	MIP-1β
		vMCC-1	MCP-1
Human cytomegalovirus	UL146	vIL-8 (vCXC-1)	
(HHV-5)	UL147	vIL-8(vCXC-2)	IL-8
Marek's disease virus	Unmapped	vIL-8	IL-8
Respiratory syncytial virus	SCYD1	RVS Glycoprotein G	Fractalkine
Stealth virus	Unmapped	GRO-α	Not determined

MIP-Macrophage Inflammatory Protein; MCP-Monocyte Chemoattractant Protein; GRO-growth-related gene

Table 3: Virus encoded growth factors

Virus	Coding gene	Virokines	Homologue to host growth factors
Vaccinia virus	19K	Vaccinia Growth Factor (VGF)	EGF and TGF-α
Variola virus	----	Pox virus growth factor	EGF
Shope fibroma virus	----	Shope Fibroma Growth Factor (SFGF)	EGF
Myxoma virus	----	Myxoma virus Growth Factor (MGF)	EGF and TGF-α
Cow pox virus	----	Cow pox virus Growth Factor (CGF)	EGF and TGF-α
Orf virus	A2R	vVEGF	VEGF
Human Immuno deficiency Virus (HIV)	----	tat protein	VEGF

influence disease pathogenesis upon KSHV infection by interfering with signaling through gp130 in response to native cytokines[2].

viral IL-17(vIL-17): vIL17 exhibits 72% homologous to human IL-17 and 63% with murine CTLA-8 (IL-17). It is encoded by Herpes Virus Simplex (HVS)-13, an Open Reading Frame (ORF13) from the genome of the T-lymphotropic Herpesvirus saimiri[13]. vIL-17 stimulates secretion of IL-6 in fibroblasts, activation of NFκ-B and co-stimulates T-cell proliferation[14]. It was reported that the gene is not required for the induction of T-cell lymphomas but that it may contribute to apathogenic viral persistence in the natural host, the squirrel monkey[14].

Virus-encoded chemokines: Chemokines constitute a super family of inter-cellular messengers that play multiple roles in the development and homeostasis of different organ systems (particularly the hematopoietic system), as well as in the generation of both innate and adaptive immune responses. Chemokines are key regulators of innate and adaptive immune responses against invading microorganisms, including viruses. They are not only as immune system traffic officers (controlling leukocyte migration under both physiological and pathological conditions), but also as fine orchestrators that modulate induction, amplification and cytokine-secretion pattern of antiviral responses[15]. However, viruses have succeeded in turning the chemokine system into an ally by expressing virus-encoded chemokines[2] (Table 2). Currently there are three modes of chemokine modulation known to be used by the viral immuno-modulatory proteins such as:

Viral CC chemokines

vMIP-1; vMIP-2; vMIP-3: KSHV genome K6 encodes vMIP-1, which exhibits 37.9% homologuous to MIP-1-α and K4 encodes vMIP-2, which exhibits 41.1% homologuous to MIP-1-α. Both vMIP-1 and vMIP-2 are expressed in latently infected lymphoma cells and their expression is induced by phorbol esters[16]. Human Herpes Virus (HHV)-8 genome K4.1 encodes viral MIP-1β (vMIP-3). HHV-8 encodes vMIP-1, vMIP-2 and vMIP-3. Most of these molecules act as functional agonists, at least on selected receptors; for example, vMIP-1 selectively acts on CCR8, vMIP-2 on CCR3[16] and vMIP3 on CCR4 [7]. Since all of these receptors have been linked to Th2 responses towards a Th2-like pattern, thereby hindering Th1-polarised antiviral responses[3]. Viral MIP-2 has been shown to bind with high affinity to various chemokines receptors (CCR-1, CCR-2, CCR-5, CCR-8, CXCR4 and US28). Binding of viral MIP-2 to the chemokine receptors has been shown to block calcium mobilization induced by endogenous chemokines rather than being associated with the normal rapid mobilization of calcium from intracellular stores. The vMIP-2 also acts as a broad-spectrum chemokine antagonist, with ability to reduce inflammatory responses[3,18]. All the HHV-8 encoded chemokines exhibits highly angiogenic in the chicken chorioallanotic membrane assay[16]. The viral MIP-1 and viral MIP-2 helps KSHV to produce a polyclonal lymphoproliferation associated with prominent vascularity.

HHV-6 genome U83 also encodes viral MIP-1α, which competing directly with cellular MIP-1α for binding to CCR8 and prevents the action of the cellular MIP-1α. Molluscum Contagiosum virus genome MC148R encodes viral MIP-1β. The vMIP-1β has retained the correct cysteine positioning important for overall structure of the protein, but lacks a significant segment of the N-terminal region. This N-terminal lack vMIP-1β can bind to chemokine receptors but are unable to trigger an intracellular signal. Thus vMIP-1β function as a chemokine inhibitor by competing directly with cellular MIP-1β for binding with receptors and preventing the subsequent activation of leukocytes[2,19].

viral IL-8 (vIL-8): IL-8 is secreted by macrophages and endothelial cells. IL-8 chemotactically attracts neutrophils and induces adherence to vascular endothelium and extravasations into tissues. Human cytomegalovirus genome UL146 encodes vIL-8 (vCXC-1) and UL147 encodes vIL-8 (vCXC-2) is homologous to host IL-8. Viral IL-8 is IL-8 homologue of 134 amino acids shares closest homology to mammalian and avian IL-8 and is encoded within the genome of Marek's Disease Virus (MDV). vIL8 is a Chemoattractant for chicken peripheral blood mononuclear cells but not for heterophils. Lytic infection of cells with a viral vIL8 deletion mutant is less pronounced than infection with the wild type virus. The mutant virus is also less oncogenic[3].

Virus-encoded complement control proteins: The complement system serves as one of the host's initial defenses against microbial pathogens[20]. Activation of complement leads to a cascade of events that inactivate or destroy the invading organisms. Complement deposition on the foreign particle can result in its efficient opsonization and phagocytosis. The mammalian complement system, composed of over 25 proteins, is divided into two pathways of activation. Both pathways are typical cascades, which enormously amplify the initiating event. The classical pathway relies on antibody-antigen complex to initiate the cascade whereas the alternate pathway may be activated in the absence of antibody. Both the two pathways make coverage of a fragment of the third surface bound, component of complement, C3b and the subsequent common steps lead to the formation of a membrane attack complex [20].

Virokine - vaccina virus Complement Control Protein (VCP), which is the major secretory protein of cells infected with vaccina virus[21]. VCP in vaccina virus is also known as Inflammation Modulatory Protein (IMP). Vaccina virus genome B5R encodes VCP. VCP is structurally related to the family of complement control proteins (human C4-binding protein). VCP is the first immuno-modulatory protein to be discovered in early 1990s[21]. It was found that VCP plays important role in evasion of the host complement system through various functions like, down regulation of the inflammatory response elicited during viral infection, exerting control measures in preserving viral habitat, Inhibition of the antibody-dependent activation of the classical and alternative pathways of complement via the C-terminus of the amyloid precursor protein and preservation of the virus by protecting against damage from the inflammatory response, as well as by blocking apoptosis, which favors viral replication[21].

Virus-encoded growth factors: The capture and expression of cellular growth factors by numerous viruses mostly of *Poxviridae* family has been reported[2]. The viral-encoded growth factors (Table 3) stimulate the

proliferation of their host cells, thereby ensuring their own replication. Virus encoded proteins that mimic the activities of Epidermal Growth (EGF); Transforming Growth Factor-α (TGF-α) and Vascular Endothelial Growth (VEGF) have been identified. Mostly tumor viruses are the best adopt these strategies.

Shope Fibroma Growth Factor (SFGF) shows 37% identity with VGF and TGF-α. Myxoma virus Growth Factor (MGF) is an 85-residue polypeptide that shares 80% identity with SFGF. All the poxviral EGF homologous, including VGF, MGF, Cowpox virus Growth Factor (CGF) and SFGF, are predicated to have similar secondary and tertiary structures to their cellular counter parts, as indicated by the conserved six cysteine residues that form three intramolecular disulfide bonds. EFG activates tyrosine kinase on erbB receptors (EGF receptors) via autophosphorylation and initiates mitogenesis in the responsive cells. Since native MGF and SFGF are heavily glycosylated, it does not require any glycosylation to acquire biochemical functions. MGF possesses genuine EGF function and stimulates mitogenesis, proliferation and differentiation of responsive cells. Poxvirus EGF homologous (VGF, MGF, SFGF, CGF) has interchangeable biological functions with the cellular counterparts. The pox virus-encoded EGF homologous appears to stimulate biosynthesis in both infected and uninfected cells, thus provide a more suitable environment for the viral replication.

Potential roles for poxviral EGF-like growth factors (VGF, MGF, SFGF, CGF) are like; reduction in dependence on cellular S phase prior to infection, up regulation of cellular macromolecular synthesis useful for virus morphogenesis (Example, nucleotide polls, ribosomes, translational factors, etc.), stimulation of EGF receptor signal transduction pathway which, might directly facilitate virus replication in the cytoplasm, maintaining an increased virus titer in certain cell types within complex tissues might potentiate virus transmission (Example, increased replication in skin might assist spread by arthropod vectors) and induction of tissue remodeling might assist the spread of virus by decreasing effectiveness of host cellular immune responses in infected cells.

Orf virus encoding vVEGF: Orf virus genome A2R encodes vVEGF, which is functional homologue to VEGF. The biological activities of VEGF are not species-specific. VEGF is a highly specific mitogen for vascular endothelial cells. VEGF does not appear to enhance the proliferation of other cell types. VEGF significantly influence vascular permeability and is a strong angiogenic protein in several bioassays and probably also plays a role in neovascularisation under physiological conditions. It has been suggested that VEGF released from smooth muscle cells and macrophages may play a role in the development of arteriosclerotic diseases. In endothelial cells VEGF induces the synthesis of Von Willebrand factor. It is also a potent chemoattractant for monocytes and thus has procoagulatory activities. In microvascular endothelial cells VEGF induces the synthesis of plasminogen activator and plasminogen activator inhibitor type-1[1].

Since VEGF is an important regulator of angiogenesis, the expression of VEGF from orf virus infected cells is consistent with the presence of lesions at the primary site of infection that are characterized by capillary proliferation and oedema. To date, mimics of EGF and VEGF growth factors that favour virus replication have only been observed in members of the poxvirus family and in HIV; however, the presence of these growth factors in other viruses is a distinct possibility[2].

CONCLUSION

The invading virus must evade the defense mechanisms of the invaded host. Vertebrates have developed immunity: the invading viruses have discovered interesting and elegant ways to circumvent the immune mechanisms. Some of the interaction clearly favors the invading virus and were probably evolved by it for that purpose. One of the defense strategies that counteract the immune responses of the infected host exploits viral immunomodulators that directly interfere with the host's cytokine system. Viruses encoded immunomodulators, enables viruses to create favorable habitat, it preserves the virus by protecting against damage from the inflammatory response, as well as by blocking apoptosis, until the virus can replicate to high titers and find another host. The virus encoded immunomodulators makes virus as a trinity of (1) the creator, example, all pox viruses seem to be able to create a habitat for viral replication by at least blocking first line of defense, as the complement control protein is conserved; (2) the preserver, example, CPV has a very wide natural host reservoir and complete repertoire on intact ORFs for immunomodultory proteins; and (3) the destroyer, example, small pox virus, which is unable to employ their repertoire of immunomodulatory proteins to protect their habitat and elicit a response that is

destructive to the host.

Such knowledge about virokines has potential implications for viral epidemiology, treatment or prevention of viral and inflammatory diseases and for the development of safer vaccines. Viruses are extensively educated in regard to the innermost working of the vertebrate immune system and therefore viewed as educational tools for the study of immunology. Thus viruses can be used as potential probes for understanding and manipulating the immune system. There is no doubt that these virokines will be serving as a useful starting point for the treatment of viral infections in the new millennium.

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