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A new insight into viral proteins as Immunomodulatory therapeutic agents. KSHV vOX2 a homolog of human CD200 as a potent anti-inflammatory protein

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ABSTRACT

The physiologic function of the immune system is defence against infectious microbes and tumour cells, Therefore, need to have precise modulatory mechanisms to maintain the body homeostasis. The mammalian cellular CD200 (OX2)/CD200R interaction is one of such modulatory mechanisms in which myeloid and lymphoid cells are regulated. CD200 and CD200R molecules are membrane proteins that their immunomodulatory effects are able to suppress inflammatory responses, particularly in the privilege sites such as CNS and eyes. Kaposi's sarcoma-associated herpesvirus (KSHV), encodes a wide variety of immunoregulatory proteins which play central roles in modulating inflammatory and anti-inflammatory responses in favour of virus dissemination. One such protein is a homologue of the human CD200, encoded by open reading frame (ORF) K14 and therefore called vOX2/vCD200. Based on gene expression profile during the KSHV life cycle, it is hypothesised that vOX2 modulates host inflammatory responses. Moreover, it seems that vOX2 involves in cell adhesion and modulates innate immunity and promotes Th2 immune responses. In this review the activities of mammalian CD200 and KSHV CD200 in cell adhesion and immune system modulation are reviewed as potential therapeutic agents.

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Introduction

The organism is protected against both foreign pathogens and internal harmful stimuli by the immune system. However, the immune system activities are regulated by inhibitory mechanisms for maintenance of the body homeostasis. To modulate the immune responses, a variety of molecules and receptors are involved. The CD200/CD200R interaction is one the inhibitory mechanisms in which myeloid and lymphoid cells are down-regulated, properly (1). CD200 and CD200R molecules are membrane proteins that their immunomodulatory effects are able to suppress inflammatory responses and induce immune tolerance in some circumstances. CD200 is expressed on the surface of many cell types whereas CD200R expression is restricted mainly to myeloid cells (2-4).

CD200 structure

Cellular CD200 protein, also called OX2, belongs to a group of leukocyte IgSF glycoproteins including neural cell adhesion molecule (NCAM) and thymocyte differentiation antigen 1 (Thy-1) (5). Recently its structure has been identified and the main pattern is containing IgV and IgC domains (6). Due to the short intra-cytoplasmic tail, CD200 lacks the signal transmission capacity (7, 8).

Cellular CD200 is particularly expressed on a broad range of cell types, such as thymocytes, B cells, activated T cells, follicular dendritic cells, neurons and vascular endothelium (2, 3). CD200 is an adhesion molecule that negatively regulates functions of macrophage lineage, and probably T cell responses (9). Thus, CD200 might be involved in the delivery of tolerizing signals to T cells (10).

In contrast to CD200 which is expressed on a wide range of cells, in humans the distribution of the CD200 receptors (CD200R) is restricted to myeloid and lymphoid cells (1, 4). Recently, CD200R1 expression in human trophoblast cells has also been

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reported (11). Several groups have described evidences for the existence of members of the CD200R family (including in the mouse, CD200R1, R2, R3 and R4, and in man CD200R1 and R2) (4, 12). Mammalian CD200R1 subtypes, including the human varieties have an intra- cytoplasmic tail consisting of at least 60 amino acid residues that may transfer negative signals through receptor ligation in macrophages and T cells (4, 13). It should be noted that vOX2 signals via binding to CD200R (14); therefore, it presumably activates CD200 employed signalling pathway.

There have been controversies regarding the functions of CD200R family members. Although, Barclay's group have shown that mouse CD200 mainly binds to the inhibitory receptor CD200R1 (15), Gorczynski *et al* have demonstrated that different isoforms of CD200R bind to CD200, although, the functional consequences of CD200 interaction are different (12). Genes encoding CD200 and CD200R are located on chromosome 3, 3q12‑13 and 3q13, respectively (16, 17).

The immunomodulatory potent of CD200

The immune-modulatory effects of CD200/-CD200R system have been confirmed in many studies. This immunosuppressive activity was shown in CD200-/- knockout mice (18), when macrophage numbers were elevated and their phenotype was activated. Moreover, microglia of these mice, including retinal microglia (19), were hyperactivated in response to injury and the animals succumbed rapidly to collagen-induced arthritis. It has also been shown that the severity of the disease and inflammation are increased during influenza virus infection in CD200-/- mice (20).

Since positive costimulatory signals are essential in T cell activation, blocking either these signals alone or downstream signaling events is important for induction of immunological unresponsiveness. It has been reported that some dendritic cells (DCs) expressing CD200, triggered an immunoregulatory function which leads to increased allograft survival (21). Moreover, blocking CD200/CD200R interaction by anti-CD200R antibody has been resulted in microglial activation and intensified neuro-degeneration in animal model of Parkinson's disease (22).

In close cell-cell contact, it seems that the CD200/CD200R1 interaction provides modulatory signals that contribute to setting signalling thresholds at an appropriate level at the site of an immune response. Therefore, the CD200/CD200R1 interaction may influence locally on immune-response to modulate immune cell activities at the sites of infection.

CD200 delivers immunosuppressive signals to myeloid cells by ligating its cognate receptors; the three principal mitogen activated protein kinases (MAPks) (ERK, JNK and p38 MAPk) are inhibited after CD200R1 ligation by CD200, through the recruitment of RasGAP, *via* adapter proteins Dok1 and Dok2 (23).

Therefore, T cell function may also be impaired by ligation of the CD200 receptor family. Cellular stimulation by anti-CD200R2 in thymocytes or bone marrow *via* maturation of dendritic cells having the capacity to induce T regulatory cells in favor of inhibitory activities (24). Inflammatory stimuli invoke several intracellular signalling pathways, including the NF-κB pathway and the three MAPk pathways. Indeed, these pathways represent targets for anti-inflammatory therapeutic intervention of such inhibitory signals in the treatment of inflammatory diseases, such as rheumatoid arthritis, psoriasis and Crohn's disease, as well as haematological malignancies (25-27).

Therapeutic application of CD200

CD200 in the central nervous system (CNS) and the eye

CD200 has been identified as an immuno-regulatory molecule in immune privileged organs such as the CNS and eye. The immune status of the CNS and eye is strictly regulated and kept to a minimum. The professional phagocytes of the nervous system, microglial cells, are in a quiescent state in the intact CNS by local interaction of CD200 and CD200R1. While neurones express the CD200, the corresponding ligand was detected on microglial cells (28).

Although distribution of CD200 is widespread on the endothelium of many organs, its constitutive expression on neurones within the CNS and eye may confer additional protection against immune destruction through regulation of macrophage activity *via* CD200R1. In support of these findings, the phenotype of a CD200-deficient mouse showed defects in myeloid cell biology within tissues that normally express CD200 (18). One of these defects was an increase in the number and activation state of microglial cells in the brain. In addition, these animals showed an increased susceptibility to experimental autoimmune encephalitis (EAE). Furthermore, CD200-deficient mice showed increased expression of inducible nitric oxide synthase in inflammatory microglia and macrophages during EAE progression (18). It therefore, seems that CD200 provides a steady-state control mechanism for microglia in the brain.

Furthermore, The attenuated expression of CD200 in neuro-degenerative diseases has been reported (29). In this case, increased microglia activation was seen in Parkinson and Alzheimer patients because of down regulating of CD200 expression (30). CD200R blocking antibody injection into striatum of 6-hydroxydopamine (6-OHDA)-lesioned rats model of Parkinson's disease increased microglia activation and neurodegeneration compared to control groups (31). Hippocampus function is related to long term potentiation and could be affected with aging or LPS treatment. It has been shown that MHC class II and CD40 expression and inflammation –associated long term potentiation are reduced after CD200Fc injection into hippocampus of aged or LPS treated rats (32). Methamphetamine is a dopaminergic neuronal toxin that can induce inflammation and microglia activation in striatum. Injection of both methamphetamine and CD200Fc in rats resulted in decreasing the number of activated microglia and reducing loss of dopamine compared to rats without CD200Fc treatment (33).

It has been also demonstrated that CD200 is expressed on retinal vascular endothelium and some types of neurones in the retina and optic nerve. However, within normal retina, CD200R1 is not detected on myeloid–derived cells (34), both CD200 and CD200R1 are expressed during experimental autoimmune uveitis (EAU), on infiltrating leukocytes (34). The data from knock out mice together with functional data suggested that the CD200/ CD200R1 interaction is a novel pathway that suppresses and limits inflammatory reactions within the retina (31).

CD200 in pregnancy

The mammalian reproductive system has highly regulated immune components, in which anatomic alterations, such as inflammation, injury, and trauma lead to autoimmune reaction. On the other hand, the mammalian fetus is a natural allograft for the mother. Nevertheless, the mother does not normally reject the fetus. Several experimental observations have demonstrated various mechanisms for this immunological tolerance, such as anatomic location, lack of MHC class II molecules on trophoblast cells, and an immunologically-privileged site (35). Evidence now suggests that CD200 may contribute in providing either immunological privilege or constitutively suppressed immune responses in reproductive tissues, as in the brain and eye. CD200 is highly expressed on the syncytiotrophoblast cells (36), capillaries of the fallopian tube, and cells of the ovarian germinal epithelium (37). These data implicate the CD200 and CD200R interaction in the regulation of myeloid cells in the female reproductive organ and during the maintenance of maternal tolerance (38, 39).

CD200 has been found on the trophoblasts during normal pregnancy in humans and its expression is inhibited by proinflammatory cytokines, such as TNF-α, which triggers spontaneous abortion (39). Therefore, one effect of TNF leading to abortion could be down-regulation of CD200 expression. In mice, abortions can be completely abrogated by administration of the soluble CD200 fusion protein, CD200Fc (38, 39).

It has been confirmed that CD200R is located on the surface of myeloid and lymphoid cells although CD200R1 expression by villus trophoblast and by decidual cells has recently been reported. However the biological importance of CD200/CD200R signalling in non-hematopoietic cells is not clear; it maybe required for human pregnancy success (11, 40).

Role of CD200 in transplantation

Allograft survival in mice is increased following donor-specific portal vein (pv) immunization (41). Using a DNA subtractive hybridisation approach, tolerance in pv-immunised mice was found to be associated with increased expression of a number of distinct mRNA species, one of which encoded CD200 (41). Furthermore, either increased expression of CD200 or soluble CD200 administration to mice receiving allograft was associated with immune suppression and altered cytokine production, leading to increased graft survival (10, 21, 41, 42). In these circumstances, prolongation of allograft survival is associated with preferential activation of type 2 cytokine (IL-4, IL-10 and TGF-β) rather than type 1 cytokine (IL2, IFN-γ) producing cells. These effects are enhanced by simultaneous infusion of soluble CD200Fc and donor CD200R1 bearing macrophages to transplant mice (21, 43).

However CD200Fc injection subconjunctivally after corneal allografts in rats has not been an efficient therapeutic strategy for suppression CD200/CD200R axis in macrophages and could not inhibit corneal graft rejection (44). Gorczynski and his colleagues produced a hybrid molecule named CD200Fc(Gly)6TGFβ (45). This molecule can bind to both T cell through TGFβ and APC through CD200R1 and result in activity suppression of leukocytes by its strong inhibitory effect (46).

Role of CD200 in malignancies

An important consideration is whether the CD200 molecule is also implicated in immunity to tumour cells. It has been found that infusion of CD200Fc suppresses tumour immunity, leading to increased tumour growth (47). There is a positive correlation between both CD200R expression and the level of soluble form of CD200 with proliferation and metastasis in some malignancies (48, 49). Increased CD200 expression in acute myeloid leukaemia and multiple myeloma patients is associated with a poor prognosis (50, 51).

Role of CD200 in allergy

Mast cells and basophils play a crucial role in allergic reactions in body tissues and blood respectively. It has been confirmed that

CD200/CD200R interaction reduces their degranulation and attenuates the allergic inflammation (23, 52). Administration of intratracheal CD200 recombinant to experimental asthmatic rats was also reported to inhibit airway hyperresponsiveness by local alterations of T cell responses and the cytokine secretion (53).

Role of CD200 in autoimmune diseases

Multiple sclerosis as an autoimmune disease is a serious neurological disorder with axonal demyelination. Using animal models of MS, EAE, it is confirmed that CD200/CD200R interaction suppresses inflammatory responses by microglia inhibition (54). The severity and disease progression during the chronic phase of EAE in mice was decreased by CD200Fc injection (54). Rheumatoid arthritis is another autoimmune disorder that is associated with synovial damages while its progression was increased in CD200-/- mice (55). Injection of CD200Fc also decreased the level of proinflammatory cytokines and induced slow progression in rats with rheumatoid arthritis. Thus CD200/CD200R interaction promotes non-responsiveness to autoantigens (56).

Taken together, it is more likely that CD200 family and their microbial homologs are very important molecules for modulation of inflammatory reactions in immunopathological diseases.

KSHV vOX2

The establishment of viral infection is a complex process in which both host immune responses and viral factors contribute to the outcome of infection. Innate immune system including antiviral effector mechanisms, interferons, phagocytes, natural killer (NK) cells and complement, along with adaptive immune antiviral responses such as antibodies and cytotoxic T lymphocytes, protect the host from viral infection. The establishment of infection depends on viral evasion strategies from host immune system effector functions.

Herpesviridae family, all are enveloped and double stranded DNA viruses which consists of eight species (57); Kaposi's sarcoma-associated herpesvirus (KSHV) belongs to the subfamily of *Gammaherpesvirinae* and is called human herpesvirus 8 (HHV-8). KSHV worldwide has infected several hundred millions of humans with the highest incidence in central regions of Africa in which more than 50% of population is infected (58, 59). Our study in Northeast Iran among prisoners showed that KSHV seroprevalence is less than 5% (unpublished data). KSHV contributes to tumor induction and the infection is associated with three human malignancies: Kaposi's sarcoma (KS) (60), multicentric Castleman's disease (MCD) (61) and primary effusion lymphoma (PEL) (62). In 2002, 65,000 KS cases were identified which represents 1% of detected cancers (63). In last decades, high prescription of immunosuppressive drugs (iatrogenic immunodeficiency), transplantation and HIV infection have increased the incidence of KSHV infection. Therefore, it was brought to the attention by inducing the most common neoplasm in acquired immune deficiency syndrome (AIDS) patients (64); KSHV and HIV-1 co-infection could increase the KS risk by 60% (65).

Herpesviruses vary in their genome (66) and particle size (120 nm to 300 nm) (67), specific proteins, and pathogenesis; however, they share a characteristic architecture in which all of them have a similar virion structure and genome characteristics. Their genomes encode 60 to 120 genes. KSHV genome encodes 86 genes (Figure 1; GenBank accession no. AF148805), of which, 25% (about 22 genes) are involved in immune system modulation (68, 69). Two groups of viral immunomodulatory genes, homologues of cellular genes and non-homologues, help the virus to evade immune system. The effects of viral immune modulation are implemented through chemokines, cytokines, cell surface receptors, signal transduction and antigen presentation. Effective anti-KSHV immune responses have been demonstrated in neutralising antibody responses (70), virion endocytosis (71), cytotoxic lymphocyte (72) and NK cells (73).

KSHV encodes several molecules which affect innate immunity and helps virus to evade from destructive host responses. Among them, open reading frame (ORF) 4 encodes a protein which inhibits complement mediated lysis of infected cells (74) and therefore is called KSHV complement control protein (KCP). Several viral homologs of interferon regulatory factors (vIRFs) encoded by KSHV (75, 76) restrain the expression of IFN-inducible genes, induce decay of activated IRF3 and prevent the activation of protein kinase R (PKR) (69). Other factors affecting innate immunity include: three viral chemokines (vCCL1, vCCL2 and vCCL3), viral CD200 which is called vCD200 or vOX2 (it will be discussed in details in next sections), viral interleukin-6 (vIL-6) and viral G protein-coupled receptor (vGPCR) (77). KSHV K3 and K5 induce down-regulation of MHC class I which help the virus evade destruction mediated by $CD8^+$ cytotoxic T cells (78). Furthermore, K5 reduces B7-2 and ICAM-1 surface expression and interferes in T helper cells activation (77).

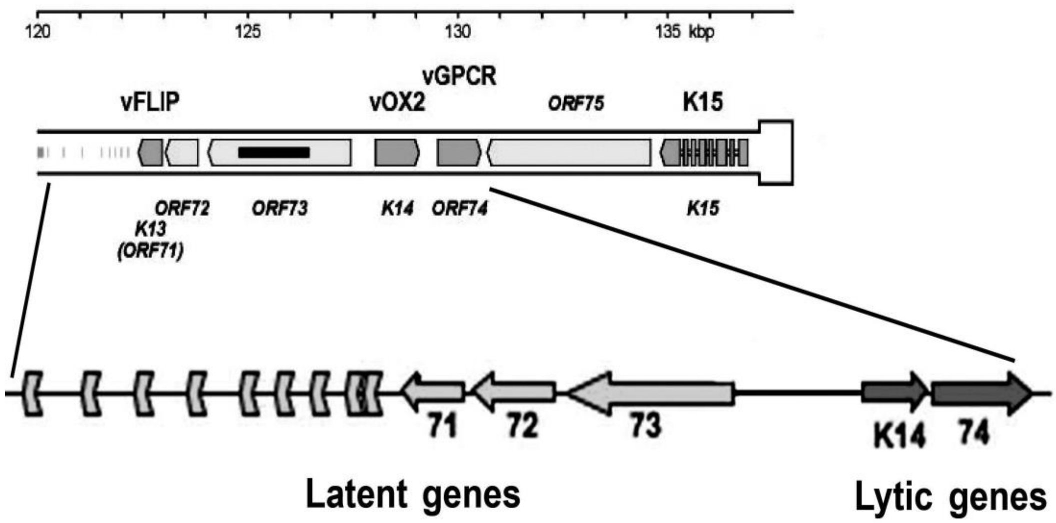

Figure 1. The last part of KSHV gene map (From GenBank accession no. AF148805 [21]); the orientation of identified ORFs is denoted by the direction of arrows. KSHV genome encodes 86 genes, 25% of them are involved in immune system modulation. The CD200/vOX$_2$ protein, which is encoded by ORF K$_{14}$, is a bicistronic transcript which also encodes vGPCR (ORF $_{74}$). vOX$_2$ is an early-lytic gene which upon virus activation, its expression increases over 100-fold. This part of Figure is taken from [21] with radical modification

Several human herpesviruses including HHV-6 (79), HHV-7 (80), rat Cytomegalovirus (CMV) (81), Rhesus macaque rhadinovirus (RRV) (82) and KSHV (83), as well a yaba-like disease poxviruses (YLDV) (84), Shope (85) and myxoma virus (86) encode CD200 homologues. It is most likely that distinct viral families have independently captured the cellular CD200 immunoregulatory gene (87), presumably to provide a selective microenvironment that protects infected cells from host inflammatory and immune responses. Considering the shared mechanisms of immuno-modulation with cellular CD200, KSHV vOX2 should bind to CD200R (14, 88) to activate signalling pathways which might be involved in suppressing some aspects of immune system. Indeed, KSHV encodes a long list of immunomodulators; however, since KSHV vOX2 has a broad range of activities on immune responses, the modulatory effects of the protein will be highlighted in the next sections. In this review, considering its homology with CD200 and shared receptors and some identical functions, , CD200 function have been discussed and now structural and functional properties of vOX2 will be considered. Finally, potential use of viral proteins (like vOX2) in clinical applications will be discussed.

vOX2 structure

The KSHV vOX2 protein, encoded by ORF K14, is a bicistronic transcript which also encodes vGPCR (Figure 1). This protein has been brought to the attention of researchers for its immunoregulatory activities. vOX2 is a type I transmembrane glycoprotein with 271 amino acids (89). This protein is a member of immunoglobulin superfamily (IgSF) containing IgV and IgC domains in N- and C-terminal fragments of the protein, respectively (5). It is constructed mainly from beta sheets with a small alpha helix in N-terminal domain; moreover, all five potential glycosylation sites are exposed on protein surface (90). The vOX2 protein is homologous to the rat and human CD200 molecule, various NCAMs, the poliovirus receptor-related protein (PRR1) and ORF U85 of HHV-6 and -7 (83) (Figure 2).

vOX2 adhesive function

Integrins are heterodimers of α and β subunits and their family could be divided into four main classes: leukocyte-specific receptors, collagen receptors, laminin receptors and Arg-Gly-Asp (RGD) receptors (91). In addition to the integrin, cadherin, and selectin gene families, members of the IgSF are responsible for many homophilic as well as heterophilic binding interactions. Integrins posse-ssing RGD play a widespread role in cell adhesion, angiogenesis, tumor cell invasion and metastasis (92, 93).

	Sequences producing significant alignments	Score (Bits)	E-value	Similarity (%)
A	gi|14627175|gb|AAB62632.2| K_{14} [Human herpesvirus 8] >gi|2715...	528	7e-149	100
	gi|5669895|gb|AAD46502.1| ORF K_{14} [Human herpesvirus 8] >gi|1...	526	3e-148	100
	gi|32451726|gb|AAH54759.1| CD_{200} protein [Mus musculus] >gi|3...	135	2e-30	31
	gi|7340143|gb|AAF61105.1| cell surface glycoprotein OX_2 [Mus musc…	133	5e-30	33
	gi|58477722|gb|AAH89793.1| Antigen OX-2 [Rattus norvegicus)	133	7e-30	34
	gi|1335216|emb|CAA28943.1| MOX_2 [Homo sapiens]	124	3e-27	36
	gi| 12002014|gb|AAG43150.1 | brain my_{033} protein [Homo sapiens]	124	3e-27	32
	gi|47716665|gb|AAT37533.1| CD_{200} antigen [Homo sapiens]	124	5e-27	32
	gi|51988918|ref|NP_001004196.1| CD_{200} antigen isoform b [Homo sap…	123	5e-27	36
	gi|34500093|gb|AAO45420.1| vOX_2 [Murid herpesvirus 2]	119	7e-26	38
	gi|18653887|ref|NP_570821.1| R_{15} [Cercopithecine herpesvirus ...	108	3e-22	36
	gi|66476707|ref|YP_238461.1| JM_{158} [Macaca fuscata rhadinovir...	106	9e-22	35
	Sequences producing not significant alignments			
B	gi|10312085|gb|AAG16648.1| HVEC cell-cell adhesion molecule/hum	63.9	5e-09	29
	gi|42560237|ref|NP_002846.3| poliovirus receptor-related 1 (hum	63.5	6e-09	29
	gi|11558775|emb|CAA53980.2| nectin 1 [Homo sapiens]	63.5	7e-09	29
	gi|7441746|pir||JE0099 neural cell adhesion molecule 1 - Afri...	50.1	8e-05	30

Figure 2. vOX_2 homologues according to NCBI BLASTN (see the score, similarity, and e-value). The NCBI BLAST (blastn) program (http://www.ncbi.nlm.nih.gov/BLAST/) was used to search homologues of vOX_2 protein. (A). Seven CD_{200} like proteins were identified with E-value less than 10^{-20}. B). A molecule with E-value less than 10^{-9}; nectin-1 (which also called HveC and poliovirus receptor-related 1), and a molecule with e-value less than 10^{-5}, neural cell adhesion molecule (NCAM), were also identified. Hypothetical and predicted proteins were excluded. The score, e-value, and percentage of similarity are shown at the left of the proteins

Evidences suggest that RGD motif may play an important role in KSHV life cycle. KSHV glycoprotein B (gB) contains RGD which facilitates virus entry (94). In addition, synthetic peptides possessing RGD sequences inhibits KSHV infection (94).

KSHV vOX2 contains RGD motif (83) which is located at residues 191-193 and our data has shown that this portion is exposed on protein surface (90). Besides RGD-integrin interactions, surprisingly, vOX2 might be involved in homophilic binding, both may influence cell adhesion. Lymphoblastoid Jurkat cell line transfected with native vOX2 forms large aggregates (unpublished data) and the same observation was reported in soluble vOX2 treated dendritic cells (89). RGD mediated cell adhesion might be involved in KSHV spreading, since anti-vOX2 antibody or vOX2:Fc were able to inhibit virus spreading in KSHV infected cells (unpublished data).

Modulation of immune system by KSHV vOX2

vOX2 modulates several aspects of immune responses which may prevent inducing of inflammatory reactions during lytic phase of virus replication (Table 1). Studies with soluble form of vOX2 in which viral protein was fused to C-terminal domains of IgG1 (vOX2:Fc), have been revealed this protein suppresses neutrophils oxidative burst and inhibits IL-8 production by monocyte/macrophage cell line (95) and primary monocytes (unpublished data). Moreover, basophils treatment with vOX2:Fc or CD200 suppress histamine release and CD11b up-regulation induced by the engagement of FcεRI (96), a condition which lessens effector functions of this kind of cells. In addition, CD200R transfected human NK cell line shows reduced cytotoxicity against CD200 or vOX2 transfected target cells (96) which represents another clue for inhibitory effect of KSHV vOX2. Recently, it has been demonstrated that vOX2 exerts negative effect on antigen-specific T cells (97). In this case, vOX2 transfected antigen-presenting cells (APCs) prohibited IFN-γ production and reduced exocytosis of cytotoxic T lymphocytes granule components. Furthermore, by suppressing Th1 cytokines and slight effect on Th2 cytokines, vOX2 favours Th2 immune response (unpublished data) which is not protective immune response in a viral infection.

In addition, *in vivo* studies on an animal model of rheumatoid arthritis in David Blackbourn Lab has shown that vOX2:Fc could inhibit the incidence and the severity score of autoimmune diseases (unpublished data), it also suppressed the acute inflammatory response in carrageenan induced inflammation (95).

Despite suppressive effects of vOX2 on neutrophils, NK cells, lymphocytes and basophils, its effect on macrophages has been remained controversial and it is not clear whether this effect is inhibitory or stimulatory. In Foster-Cuevas *et al.* study, vOX2 or CD200 expressing cells inhibited pro-inflammatory cytokines (i.e. TNF-α) secretion by activated macrophages (88), while the results were not confirmed by others (89). In another study by Salata *et al.*, both activatory and inhibitory functions of vOX2 have been revealed (98); they showed that in the presence of vOX2, IFN-γ activated primary monocyte-derived macrophages (MDMs) shows reduced cytokine secretion and phagocytosis, while in the absence of IFN-γ, these cells release inflammatory cytokines and intensify the

Table 1. KSHV vOX_2 immunomodulatory functions

	Target cell	Immunomodulatory functions	Effects
vOX_2	Neutrophil	Oxidative burst	High suppression
		Phagocytic activity	No effect
		Chemotaxis	Inhibited due to IL-8 reduction
	Monocyte/macrophage cell line; primary monocytes	IL-8 production	Highly reduction
		MCP-1 production	Moderately reduction
	Basophil	Histamine release	Suppression
		CD11b up-regulation	Reduction
	CTLs and NK	Cytotoxicity	Reduction
	Th1 and CTL lymphocytes	IFN-γ production	Reduction
		Th1/Th2 responses	Suppression of Th1 responses
		Immunological synapse	Negative signaling to Th cells and macrophages
		Exocytosis of granule components	Reduction
		Pro-inflammatory cytokines secretion (i.e. TNF-α)	Reduction
		Killing mechanisms	Suppression
	Macrophages	MHC-I and MHC-II expression	Reduction
		Inflammatory cytokines release	Controversial (both induction and reduction)
		Phagocytosis	Controversial (both induction and reduction)

CTL: cytotoxic T lymphocytes, NK: natural killer

phagocytosis. Furthermore, this study revealed that MHC-I and MHC-II expression in unstimulated MDMs reduce around 50 and 45%, respectively, while the MHC down-regulation is lower in IFN-γ stimulated MDMs (30% and 25% in MHC-I and MHC-II, respectively); these findings were not observed in our study using monocyte/macrophage cell lines (U937 and J774.2) and human monocyte primary cells (unpublished data). By considering the present results, it seems that activatory or inhibitory functions of vOX2 depend on macrophage maturation or activation phase or different signalling pathways might be involved. Salata *et al.* suggested that by down-regulating CD200R, vOX2 deliver a pro-inflammatory signal to MDMs (98). This probably means that vOX2 activates macrophages indirectly by down-regulating an inhibitory receptor (CD200R), but the mechanism is not yet clear. Moreover, this study showed that MDMs treatment with IFN-γ is resulted in increased CD200R expression which leads to anti-inflammatory responses (98).

Therapeutic application of viral immune-modulatory proteins

We are living with viruses from the time humans appeared. Viruses have co-evolved with their host and learned how to infect and also survive in a challenging environment like human body. To avoid destructive immune system responses, viruses use several methods (99) and secretion of immune-modulatory proteins like vOX2 is one of them. The immune-regulatory viral products help virus to downregulate or shift immune responses to a direction which is not destructive for virus survival. Some viruses like KSHV by establishing latency, are able to hide themselves. In a lytic phase, they are vulnerable to immune responses since their antigenic proteins are exposed and immune system could identify them. In this phase, proteins like vOX2 are produced to temper immune responses. In fact upon virus activation, vOX2 expression as an early-lytic protein increases over 100 fold (100) which indicates its importance to immune response deviation.

Even though immune system protects host against pathogens, it promotes many problems in human life such as autoimmunity diseases. Rates of some autoimmune diseases, for example multiple sclerosis (MS), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), are increasing over the time (101-103). In non-pathological conditions such as organ transplantation, control of the immune responses is pivotal. In this field, non-steroidal anti-inflammatory drugs (NSAID), cyclosporine A, tacrolimus and rapamycin for instance, are widely used albeit with extensive side effects (104, 105). Formulating of target specific immune-suppressor agents is the main aim of new studies. At the present, some anti-inflammatory agents (i.e. TNFR-Ig and CTLA4-Ig) are FDA approved and numerous agents including monoclonal antibodies targeting immune system modules (i.e. anti-CD28, anti-CD80 and anti-TNF-α) are working out (106).

However, for thousands of years viruses have been evading immune responses and have gained capability to selectively suppress immune system. They encode several proteins which interfere with some aspect of immune responses (see introduction). When viruses use them, why we not? Employing viral proteins, as anti-inflammatory agents is an up-coming tool which might have broad applications. Although, there is a huge holdup: immune system which identifies viral proteins and attempts to remove them especially by constructing antibodies. In fact viral proteins are immunogenic and our immune system considers them as a non-self. Any success in employing viral products as a medicinal treatment will depend on overcoming antigenicity problem.

There are not many options for increasing viral proteins bio-compatibility. Previously mouse and other animals produced antibodies were humanized. The same way might be applied to viral proteins. By keeping only receptor binding fragment and if needed binding capacity to appropriate host protein, it might help to reduce immune responses; despite it does not remove it. Identifying antigenic epitopes and substituting them with similar amino-acids might be another option to increase immune-compatibility. Protein encapsulation might be other option. By targeting the tissue for drug delivery which decreases the applied dose, it might assist to reduce the encounter of viral protein and host immune system and also reduces anti-viral protein responses.

As previously mentioned, many studies (88, 95-97) have stated the inhibitory effects of vOX2 on inflammatory reactions and this protein have been introduced as an appropriate candidate for modulation of immune system which might be used as a therapeutic agent.

Conclusion

Taken together, vOX2 is one of the KSHV strategies to modulate host inflammatory reactions in favor of virus dissemination. Many researchers have stated the inhibitory effects of vOX2 on inflammatory reactions and this protein has been introduced as an appropriate candidate for therapeutic agent. However, vOX2 is a viral protein and is able to elicit human immune responses. Due to antigenicity of viral products in humans and some controversial results, it is uncertain that viral proteins can be used as suitable medications. However, Dr. Blackbourn lab and our new *in vitro* and *in vivo* findings demonstrated that it can suppress acute and chronic inflammation. Prophylaxis and treatment of neutrophil driven diseases by vOX2:Fc may therefore represent an inventive step. The *in vivo* studies in carrageenan model of acute inflammation and autoimmune models (94) and unpublished data) demonstrated that if bio-incompatibility for human could be resolved, vOX2 may be suitable immunomodulator for immunopathologic diseases.

Conflict of interest

There is no conflict of interest.

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