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T Cell Receptor Signaling Pathways: New Targets for Herpes Simplex Virus*

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Abstract: Herpes simplex viruses (HSV-1 and HSV-2) cause global morbidity and synergistically correlate with HIV infection. HSV exists life-long in a latent form in sensory neurons with intermittent reactivation, in despite of host immune surveillance. While abundant evidence for HSV interfering with innate immune responses so as to favor the replication and propagation of the virus, several lines of evidence declare that HSV attenuates adaptive immunity by various mechanisms, including but not limited to the ablation of antigen presentation, induction of apoptosis, and interruption of cellular signaling. In this review, we will focus on the perturbative role of HSV in T cells signaling.

Key words: Herpes simplex virus ; T cell receptor, Signaling

Abbreviations: **TCR**, T cell receptors; **HSV**, Herpes simplex viruses; **HVEM**, Herpesvirus entry mediator; **ICP**, infected cell protein; **LAT**, linker for activation of T cells, or latency-associated transcript; **DCs,** Dentritic cells; **MHC-I** or **MHC-II**, major histocompatibility complex class I or II; **CTL**, cytotoxic T cells; **ICOS**, inducible T cells co-stimulator; **PLC-γ1**,phospholipase C-γ1; **SLP-76**, Src-homology 2 domain leukocyte protein of 76kDa; **SOS**, son of sevenless; **MAPKs**, mitogen-activated protein kinase; **NFAT,** nuclear factor of activated T cells; **AP-1**, activator protein 1; **APCs,** antigen presenting cells; **BTLA**, B and T lymphocyte attenuator; **ERK**, extracelluar signal-regulated kinase; **JNK**, c-Jun N-terminal kinase; **EBV**, Epstein-Barr virus.

Herpes simplex viruses (HSV-1 and HSV-2) are prevalent human pathogens with a wide host cell range (54). They belong to alpha *herpesviridae* sub-family classified on the basis of biological properties. One of the unique characteristics of HSV is the establishment of latency after primary infection. The reactivation of HSV occurs intermittently through lifetime, and causes substantial morbidity and increased risk for HIV transmission (8, 14, 16). The fact that HSV infection proceeds to latency and re-occurrence regardless of the host immune surveillance suggests the ability HSV possesses not only to counteract the innate immunity, but also to disturb adaptive immunity via variety of approaches. Indeed, HSV has evolved several mechanisms to evade adaptive immune

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responses: ⅰ) ICP47 inhibits antigen presentation via blocking the processed peptide binding to MHC-I (18); ⅱ) HSV ICP22 and gB interrupt B cell presenting MHC-II antigen to T cells (4, 46); ⅲ) HSV Us3 provides inhibitory signals to CTL (60); and ⅳ) in a more general aspect, HSV infection induces apoptosis of T cells (25, 32). Besides interfering with T cell recognition and inducing T cells to death, several lines of evidence suggest that HSV can infect T lymphocytes and attenuate the T cell function by inhibiting TCR- mediated activation (6, 24, 58). However, the studies of the effect of HSV on T cell activation and signal transduction is still in its infancy, and requires more detailed and intensive research. This review focuses on the current findings and understandings regarding the effects of HSV on T cells signaling.

T CELL ACTIVATION AND SIGNALING PATHWAYS

Upon HSV infection, antigen is taken up by local and peripheral Dentritic cells (DCs) which undergo maturation and migration, and which present antigen to T cells in the context of MHC molecules (62, 70). The association between DCs and T cells stimulates multiple intracellular signaling pathways, leading to the proliferation and differentiation of T cells. The activation of T cells is stringently controlled by two signals: the primary signal is triggered by the interaction of the T cell receptor (TCR) with antigen epitopes presented on MHC molecules; and the secondary signal is initiated by the ligation of co-stimulatory receptors such as CD28 and inducible T cells co-stimulator (ICOS) (31). The engagement of both TCR and co-receptors initiates the ordered and well organized activation of various kinases, adaptor proteins, and effector molecules, and induces the sequential propagation of intracellular signaling pathways.

One of the first signaling events induced by TCR stimulation is the activation of Src family tyrosine kinases, Fyn and Lck (44, 45), followed by phosphorylation and activation of a Syk family intracellular tyrosine kinase, a 70kDa zeta-associated protein kinase ZAP-70 (9). These kinases then phosphorylate specific sites on several downstream substrates, such as linker for activation of T cells (LAT), which is a transmembrane adaptor protein with four conserved and functional tyrosine residues (61, 69). The phosphorylation of LAT provides docking sites for SH2 domain containing molecules, including phospholipase C-γ1 (PLC-γ1), Grb2, Gads, and Grap, and recruits important signaling molecules, such as Src homology 2 domain-containing leukocyte protein of 76 kDa (SLP-76), son of sevenless (SOS), Vav, and c-Cbl (64). The formation of the cluster of signal proteins (also called immune synapse) results in the activation of downstream signaling pathways, such as increase of intracellular free calcium, activation of protein kinase C and mitogen-activated protein kinases (MAPKs). There are three major MAPKs in T cells: the SOS-Ras induced ERK, and Vav-Rac activated JNK and p38. As consequences, transcription factors, such as nuclear factor of activated T cells (NFAT), NFκB, and activator protein 1 (AP-1), are activated, leading to the expression of genes that determine the fate of T cells towards proliferation, differentiation, anergy, or apoptosis.

Secondary signals are delivered via an array of co-stimulatory or inhibitory receptors that contribute

to the extent, quality, and magnitude of the T cell response. On the basis of their structure components, these co-factors fall into two categories: the immunoglobulin family, i.e. stimulatory CD28 and ICOS, inhibitory CTLA4, PD1, and BTLA; and the TNFR superfamily, i.e. CD27 and herpes virus entry mediator (HVEM) (43). The Ig family members interact with B7 family molecules expressed by antigen presenting cells (APCs), whereas the TNFR family members associate only with TNF family ligands,with the exception of HVEM.

Co-stimulatory signals augment the activation of transcription factors in cooperation with TCR signals. Ligation of CD28 recruits the regulatory subunit of PI3K which binds Tec family member Itk and facilitates activation of the Ras/ERK pathway (48, 51). In addition, CD28 can activate Vav So as to evoke the Rac/JNK pathway independent of TCR (52). All these events promote T cell proliferation and effector functions. On the other hand, the co-inhibitory receptors, CTLA4 , PD1, and recently discovered BTLA(65) attenuate TCR signaling by mechanisms that are not-yet clear, perhaps via recruiting phosphatases, such as SHP-1, SHIP-1 and/or SHIP(2, 11, 19, 47, 49). Among the TNFR family co-receptors, HVEM is highly expressed on naive T cells and providing unique ligand tropism. Besides the ability to bind HSV gD, from which the name of HVEM was derived, this receptor was reported to associate with LIGHT. Ligation of HVEM recruits TNFR-association factors TRAF1, TRAF2, and TRAF3 (28, 35, 39, 41), and activates transcription factors NF-κB and AP1. Direct interaction was also identified between HVEM and BTLA by functional screening (56), and the binding sites are distinct from those for LIGHT.

Overall， TCR and an array of co-stimulatory receptors facilitate the assembly of immune synapse and activation of T cell signaling pathways, while inhibitory receptors, phosphatases, and ubiquitin ligases may attenuate T cell signaling. Thereby, the homeostasis of host immune system is achieved.

HSV AFFECTS T CELL ACTIVATION VIA CO-RECEPTORS

Herpes simplex virus can infect a wide range of cells. The primary pathway of virus entry involves the binding of glycoproteins to cell surface receptors. The interaction of HSV glycoprotein gD plays an important role on the fusion of envelope with plasma membrane. HSV gD interacts with three types of receptors, including nectins, HVEM, and a type of heparin sulfate (54). HVEM was first identified by screening an cDNA expression library for proteins that allow HSV1 entry (41). It is a co-stimulatory receptor of the TNF receptor family and is highly expressed in naive T cells (43). The ligation of HVEM with its natural ligand LIGHT enhances T cell response (40), on the contrary, the interaction with a recently discovered ligand, B and T lymphocyte attenuator (BTLA), was reported to be inhibitory (56).

Structural analysis of HVEM and its ligands by co-crystallography revealed that HSV gD binds to the cysteine-rich domain CRD1 and CRD2 of HVEM, overlapping the binding region for BTLA (12), but is distinct from LIGHT(7). This notion was also confirmed by a competition binding assay with soluble HSV1 gD (21, 13). Therefore HSV gD can compete HVEM for binding BTLA, but not LIGHT. However, both purified or cell expressed HSV gD are capable of blocking the activation of NF-κB and T cell proliferation

(36). Both HVEM and BTLA are expressed on resting T cells (30). HSV gD may function as dual antagonist: 1) binding HVEM directly to block the stimulatory effect of LIGHT, thus diminishing pro- inflammatory signals of T cells; and 2) competitively preventing HVEM from binding to BTLA, and as a result, counteracting its inhibitory role. Since HSV latency in human trigerminal ganglia is associated with a local, persistent T cell response (63), keeping a balanced minimal level of activation may be necessary. The net results of the differential interactions remain to be tested *in vivo*.

HSV TARGETS T CELL SIGNALING AT PROXIMAL INNERMEMBRANE

T lymphocytes play important roles in controlling HSV infection and eliminate evading pathogens by activation and production of cytokines and differentiation into effector cells. Despite the powerful responses by T cells, HSV-infected cells adopt multiple mechanisms to avoid T cell recognition and inhibit T-cell induced apoptosis (3, 22, 57, 66). HSV was reported to infect both primary T cells and cultured T cell lines (25), and it is not surprising that HSV may also inhibit TCR activation, the most essential mechanisms of adaptive immunity. Indeed scattered evidence demonstrates HSV infection alters gene expression profiles which contains many proteins involved in immune response and cell signaling (50) and T cell function was manipulated towards Th2 differentiation (59). Besides, cytolytic function and IFNγ production were significantly reduced in cytotoxic T cells (CTL) that come into contact with HSV-infected fibroblasts (60). All these data manifest that the TCR signal transduction is modulated by HSV infection.

As described above, TCR stimulation evokes a wave of protein phosphorylation events, especially on the tyrosine residues of several key enzymes and adapter proteins at the plasma membrane. Immortalized Jurkat T cells have been used as a model to study T cell signaling (1). When incubated with HSV-infected fibroblasts, Jurkat cells appear to be inert to TCR stimulation by OKT3 mAb, shown as low level of IL2 secretion and non-provokable calcium flux. Glycoproteins for HSV entry (gB, gD, gH, and gL) are all indispensable as HSV mutants lacking one of the glycoproteins failed to inactivate T cells (58). gE and gI, which are responsible for juxta-cellular transmission of HSV, are also required for T cell inactivation, demonstrating that HSV entry into T cells is necessary for the inactivation of TCR signaling. HSV-infected fibroblasts may expose the virions to T cells in two ways, the direct way by HSV replication and intercellular transfering of HSV via cell junction. Despite of the inhibitory signal produced by gD-HVEM, ligation of HVEM is not the trigger for inactivating T cells, because gD mutants which defect in HVEM binding showed the same extent of inactivation as wild type virus (58). Further more, T cells directly infected with HSV confirmed that the inactivation of T cells was a consequence of HSV entry and independent of the route of infection (58).

The inactivation of T cells by HSV was resolved by the reduced level of tyrosine phosphorylation of LAT (linker for activation of T cells), an important adaptor in TCR signal transduction (58). The affected phosphorylation occurs at Tyr-191 and Tyr-132, and both residues are critical for sufficient activation of downstream events, such as calcium mobilization and

MAPK activation (27, 71). Indeed, the association of LAT to Grb2, GADS, and PLCγ1were diminished by treating Jurkat T cells with HSV-infected fibroblasts (59). It is obvious that the downstream calcium release and MAPK cascade are ablated. Nevertheless an independent report showed that HSV triggers calcium release by integrin-mediated IP_3R activation in epithelial cells and increasing calcium release from intracellular store renders effective entry of virus (10). It was reported that HSV infect and replicate in activated T cells (25, 53). The molecular mechanism of HSV-induced decrease in LAT phosphorylation remains to be explored. Treating cells with phosphatase inhibitor prior to exposure to HSV reversed inactivation of T cells, suggesting that HSV entry could activate phosphatases that counteract LAT phosphorylation by TCR stimulation(58).

HSV AFFECTS MAPK ACTIVATION IN T CELLS

Mitogen-activated protein kinases (MAPKs) pathways are involved and play pivotal roles in many cellular signaling pathways. The three major MAPKs in TCR induced signaling are extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 kinase (38). As expected, down regulation of LAT by HSV during TCR stimulation significantly decreased the amount of activated form (phosphorylated) ERK, JNK, and MEK as analyzed using phospho-specific antibodies (58). However, prior to TCR stimulation, the basal levels of the JNK and p38 were elevated upon HSV infection, indicating a TCR-independent MAPK activation by HSV (59). A more complicated situation was revealed however when a LAT-independent activation of p38 was discovered in TCR-stimulated cells, that relies on TCR-induced ZAP70 phosphorylation (55). In general, p38 and JNK is activated by stress and pro-inflammatory cytokines, the mechanism that bridging the signal transmission from TCR/ZAP70 to p38 is still to be clarified. Regardless, TCR-induced ZAP70 phosphorylation remains intact in HSV infected T cells (58). It is noted that phosphorylation and activation of p38 and JNK were also observed in infection with other subfamily of herpesviruses, such as Epstein-Barr virus (EBV) and CMV (26). Therefore the HSV induced phosphorylation of p38 is not HSV-specific and may be attributed by a yet-to be defined stress-like stimulus. HSV-1 infection did affect the activation of stress associated kinase PERK (42), and induce cellular DNA damage-sensing machinery such as ataxia-telangiectasia mutated (ATM) and DNA-dependent protein kinase (37).

HSV gene products responsible for the activation of the MAPK pathways are not fully understood. TCR-induced LAT phosphorylation and ERK activation requires neither HSV gene expression nor replication, as acyclovir and UV treatment did not affect the T cell inactivation by HSV(58). Whereas HSV-encoded ICP27 (26), UL54 (67), and perhaps Us3 (5), may be involved in p38 activation. The possibility that other virion components, such as viral RNA may also participate in inactivation of T cell signaling cannot be ruled out . Recent findings in neuron cells found that miRNA of latent-associated transcript (LAT) inhibits apoptosis by regulation of TGF-β signaling (23), and HSV-2 protein ICP10PK exerts regulatory roles in cell apoptosis (20). It will be interesting to examine if similar actions exist in T lymphocytes.

HSV ALTERS GENE EXPRESSION IN T CELLS

HSV (Type 1 and Type 2) can block T cell signal transduction and reform the orchestra of transcription factors necessary for gene expression, which ultimately measures the output of HSV immunomodulatory effects. In HSV infected T cells, inhibition of TCR signaling diminished calcium release (58), and thus NFAT transcription activity was abolished. Similarly, TCR-stimulated NF-κB activation was ablated (59), as it requires LAT-dependent activation of PKC_{θ} (15) and calmodulin-dependent kinase CaMKII (29). In contrast, HSV-1 infection increased the activation of MAPKs p38 and JNK, which are responsible for activating transcription factors ATF2 and c-Jun, respectively (17, 68). Out of a few cytokines tested in HSV-infected human $CD4^+$ T cells, TCR induced Th2 cytokine, IL-10, was selectively retained. As IL-10 is to immuno-suppressive, it is plausible that HSV manipulates T cells to secrete cytokine that favors its persistent infection.

In recent years, intensive studies have demonstrated that HSV plays both protective and promotive roles in cell apoptosis. Some HSV genes and host cellular targets have been identified. Gene expression was altered due to HSV infection, implicating the regulation of gene transcription and expression by HSV. It was noted that HSV-1 infection induce phosphorylation of another ubiquitous transcription factor Sp1 (34), and ATM is responsible for the modification of Sp1 (33). Profiling of HSV-induced gene expression in lymphocytes would accelerate studies on the potential mechanism for HSV modulating adaptive immune responses.

CONCLUDING REMARKS

In addition to the impact on antigen recognition and induce apoptosis, HSV also directly inhibits TCR-induced cell signaling. We have outlined the recent findings in this respect and attempted to explore the possible mechanisms for HSV modulated T cell function. The direct effect that HSV has on T cell signaling is not well understood. One can predict that inhibition of T cell signaling by HSV favors the establishment of latency and reactivation. However, this feature of HSV is specific to T cells, as blocking of antigen-stimulated signaling occurs only in T cells infected by HSV-1 or HSV-2, not in HSV-infected B cells. Understanding the detailed mechanisms and *in vivo* relevance of HSV inhibition of TCR signaling will provide more efficient approaches to better manipulate HSV infection and perhaps improve the control of HIV.

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