MINIREVIEW

Viral Modulation of T-Cell Receptor Signaling[▽]

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To successfully replicate and spread, viruses must take control of multiple cellular processes. Depending on the cell type infected, a virus may drive cellular differentiation, alter cell cycle progression, or inhibit apoptotic pathways to facilitate viral genomic replication and production of progeny virus. In addition, viruses must deal with an inherently hostile environment in the host. Infection induces intracellular antiviral responses; in addition, the immune system seeks to neutralize virus infectivity and destroy infected cells. Among the cells of the immune system, T lymphocytes (T cells) are critically important for the orchestration of the antiviral response and also for the direct killing of infected cells.

The T-cell receptor (TcR) is the central signaling pathway regulating T-cell biology. The TcR allows the T cell to recognize antigen presented in the context of major histocompatibility complex (MHC) class I or class II molecules expressed on infected cells or professional antigen-presenting cells. TcR signaling in naive T cells drives their activation and expansion. In effector or memory T cells, TcR signaling drives expansion and triggering of effector functions, such as cytokine synthesis and cytotoxicity.

Since T cells pose a threat to the successful replication of viruses, and since TcR signaling is central to the development and function of T cells, it is not surprising that many viruses have evolved mechanisms to modulate TcR signaling. For T lymphotropic viruses, the T cell itself is the major site of viral infection and replication; thus, the virus may stimulate TcR signaling to drive T-cell proliferation such that the T cell is permissive for viral replication. For other viruses, which predominantly infect nonlymphoid cells, the ability to modulate TcR signaling constitutes an immune evasion mechanism, in which the virus inhibits the ability of T cells to respond to infected cells.

As outlined in this review, many viruses modulate TcR function, either positively or negatively, to further their own propagation. However, the specific mechanisms used by each virus to modulate TcR signaling vary widely. Viruses are fascinating in their diversity, and their millennia of evolutionary probing for control points in TcR signaling can educate us regarding the normal function and regulation of this critical pathway.

TcR SIGNALING

Ligation of the TcR leads to a cascade of signaling events (Fig. 1) ultimately resulting in T-cell effector function (reviewed in references 106, 120, and 157). The earliest recognizable event after TcR ligation is the induction of tyrosine phosphorylation by Src family kinases, especially Lck. Active Lck phosphorylates immunoreceptor-based tyrosine activation motifs (ITAMs) on the TcR ζ chain and the γ , δ , and ϵ chains of CD3. This phosphorylation allows recruitment of a Syk family kinase, ZAP-70, which binds to the phosphorylated ITAMs. Once bound, ZAP-70 itself is phosphorylated by Lck and becomes an active kinase. Activated ZAP-70 can then phosphorylate linker for activation of T cells (LAT). LAT is a transmembrane protein with 10 sites of potential tyrosine phosphorylation. Phosphorylation of the C-terminal four sites allows binding and activation of a set of adapter molecules, including phospholipase C γ 1 (PLC- γ 1), growth factor receptor-bound protein 2 (Grb2), and Grb2-related adaptor downstream of Shc (GADS).

The binding and activation of PLC- γ 1 and the adapter molecules GADS and Grb2 lead to the recruitment of additional molecules and/or the triggering of downstream signaling events. Activated PLC- γ 1 cleaves phosphatidylinositol biphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3), leading to the release of Ca^{2+} from endoplasmic reticulum storage sites and, ultimately, the influx of extracellular Ca^{2+} . PIP2 cleavage to DAG activates protein kinase C (PKC), which in turn leads to the nuclear translocation of the transcription factor NF- κ B. Recruitment of Grb2 to LAT leads to activation of Ras and mitogen-activated protein kinases (MAPKs), including extracellular signal-regulated kinase (ERK). At the same time, the recruitment of GADS to LAT facilitates the phosphorylation of SLP76 and association with Vav, leading to cytoskeletal rearrangements necessary for signal propagation and formation of the immune synapse. The combination of calcium flux, MAPK activation, and cytoskeletal rearrangements leads to T-cell activation, including activation of transcription factors, cytokine synthesis, cell cycle entry, and cytotoxic activity.

Not surprisingly, in reality, TcR signal transduction is more complex than the basic scheme presented here. Signals do not necessarily propagate in a linear fashion; instead, there is significant cross talk between many of the signaling molecules involved. There also exists a recently described pathway of TcR signaling that is not dependent upon LAT (124). Instead, this alternative pathway involves activation of the kinase p38, which

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FIG. 1. TcR signaling. Major activation pathways are depicted by bold green lines, major regulatory mechanisms are depicted by thin red (inhibitory) or green (stimulatory) lines, and alternative LAT-independent TcR signaling is depicted by the dashed green line. For details, see the text.

may be directly phosphorylated by ZAP-70. p38-dependent TcR signaling appears to favor a predominantly Th2-type response, characterized by synthesis of cytokines such as interleukin-4 (IL-4), IL-5, IL-13 and, especially, IL-10 (76).

There are also a number of additional molecules that play roles as positive or negative regulators of TcR signaling. Foremost among these is the costimulatory receptor CD28 (122). In the absence of CD28 costimulation, TcR ligation induces suboptimal signaling, which can result in the induction of an anergic state. In contrast, the inhibitory receptor CTLA-4 (which competes for the same ligands as CD28) antagonizes TcR signaling, most likely via recruitment of protein phosphatase 2A (PP2A) or the SHP-2 phosphatase, which dephosphorylates molecules within the TcR pathway (149). Similarly, the programmed cell death receptor 1 (PD-1) transduces a negative signal when ligated simultaneously with the TcR, via recruitment of the SHP-2 and SHP-1 phosphatases (134). Another molecule, the ubiquitin ligase Cbl, negatively regulates TcR signaling via recruitment of ubiquitin-conjugating enzymes, thus targeting TcR pathway molecules for endosomal degradation (32). As detailed below, these and other regula-

tory molecules provide attractive targets to allow viral manipulation of TcR signaling.

MODULATION OF TcR SIGNALING BY SPECIFIC VIRUSES

HIV. No virus has been more studied for its effects on TcR signaling than human immunodeficiency virus (HIV). HIV has several proteins that can modify TcR function, including the negative factor (Nef). Nef is a 27- to 34-kDa myristylated protein that has multiple contributions to HIV pathogenesis (40, 93). Nef promotes HIV replication (26, 100, 143) and infectivity (2, 22, 100, 131). It downregulates several cell surface molecules relevant to T-cell biology, including CD4 (44), MHC class I (132), MHC class II (144), and multiple chemokine receptors (99). In addition, Nef modulates a number of intracellular signaling pathways. In T cells, Nef expression has been reported to have both inhibitory and stimulatory effects on TcR signaling.

Nef exerts its effects on T-cell activation via direct binding of multiple proteins within the TcR signaling pathway. Nef has

been reported to associate with the Src family kinases Lyn, Hck, and Lck (24, 123), Raf-1 (59), phosphatidylinositol 3-kinase (PI3K) (80, 160), PAK2 (7, 109, 121), the TcR ζ chain (161), the IP3 receptor (90), and the guanine nucleotide exchange factor Vav (37). The binding of Nef to these proteins is mediated via various motifs contained within the Nef molecule. The PXXP motif of Nef binds SH3 domains of Hck, Lyn, Lck, ζ chain, and Vav (24, 37, 123, 161). In addition, phosphotyrosine residues on Nef can interact with the SH2 domains in Lck (24) and (for the YE variant of SIV Nef) ZAP-70 (85). At least in the case of Lck, the physiological interaction involves Nef binding to the Lck SH2 and SH3 domains in a synergistic manner (24). The Nef/Lck interaction may not be direct; instead, it involves the formation of a complex between the PKC family members δ and θ and a conserved α -helix in the N terminus of Nef (13, 159). The interaction with PAK2, a positive regulator of TcR signaling (23), involves a hydrophobic binding surface on the Nef core (1). The interaction with PI3K is mediated via the carboxy terminus of Nef (80, 160), and a carboxy-terminal acidic sequence in Nef interacts with the Raf-1 kinase (59).

While the literature clearly demonstrates that Nef can bind multiple proteins involved in TcR signaling, the effects of these interactions on TcR signaling and T-cell activation have been much less consistent. In many studies, binding to Nef has been reported to activate the cellular binding partner and/or facilitate TcR signaling; in other instances, Nef binding has been predominantly inhibitory. Some of the conflicting literature is due to differences in the localization of exogenously expressed Nef. Cytoplasmic Nef appears to mediate mainly inhibitory effects upon the TcR, while Nef localizing to the cell membrane instead stimulates the TcR (14). Thus, the mixed positive and negative effects of Nef probably reflect its function as an adapter molecule, binding multiple components of the TcR signaling pathway to achieve optimal control of T-cell activation for viral replication (93). Nef expression itself can induce a T-cell transcriptional program with remarkable similarity to that induced by anti-CD3 stimulation (136). Conversely, Nef binding to TcR signaling proteins may prevent hyperstimulation of T cells by disrupting normal membrane trafficking of signaling molecules, actin remodeling, and the formation of the immunologic synapse (36, 38, 52, 150). Nef slows internalization and recycling of TcR complexes, thus inhibiting their accumulation at the immunologic synapse (150). Similarly, Nef causes the accumulation of Lck at recycling endosomes, such that translocation to the immune synapse and sustained immune signaling cannot be maintained (150). The degradation of TcR signaling molecules may be mediated in part by Nef-induced phosphorylation of c-Cbl, which regulates TcR signaling via recruitment of ubiquitin-conjugating enzymes (137, 164). Finally, the Nef proteins from related lentiviruses vary in their abilities to modulate the TcR pathway; a recent report demonstrates that Nef from HIV type 1 (HIV-1) and its close relatives is much less able to downregulate surface expression of the TcR than Nef from HIV-2 or other lentiviruses (125).

In addition to Nef, several other HIV proteins have effects on TcR signaling. Binding of the envelope glycoprotein gp120 to CD4 inhibits protein tyrosine phosphorylation and calcium mobilization after TcR ligation (47). This effect has been suggested to result from the sequestration of Lck to the cytoskel-

eton (46). However, other work suggests that gp120 acts via a Lck-independent mechanism (48). gp120 can also activate p38 MAPK and the tyrosine phosphatase SHP-2 in hepatocytes (12), and the gp160 form of envelope protein was reported to inhibit the activity of JNK and Erk2 in CD4⁺ but not CD8⁺ T cells (63). The HIV transactivator of transcription (Tat) has been reported both to inhibit and to augment (51, 110) TcR signaling. Soluble Tat or Tat peptides can inhibit TcR-induced proliferation and IL-2 production (18, 145), although certain events in the TcR pathway, including calcium flux and IP3 generation, are unaffected (18). Interestingly, this inhibitory effect can be overcome by exogenous IL-2 (18) or costimulation via CD28 (18, 145). The inhibitory effect has been associated with the binding of Tat to CD26 (dipeptidyl aminopeptidase type IV) (145). On the other hand, Tat has been reported to induce hyperactivation of T cells after stimulation via CD3 and CD28 (110). Tat affects the cellular redox balance, increasing H₂O₂ after TcR stimulation, increasing TcR-mediated upregulation of CD95L and thus activation-induced cell death (AICD) (51). As discussed above for Nef, these seemingly contradictory results probably reflect differential effects based on the localization of Tat. While soluble Tat exerts predominantly inhibitory effects, immobilized Tat can provide costimulation to T cells (173). Finally, the viral protein R (Vpr) of HIV modulates TcR signaling in a somewhat peripheral manner. Vpr leads to downregulation of the costimulatory molecule CD28 on T cells, while simultaneously upregulating CTLA-4, a CD28 homolog that negatively regulates TcR signaling (153). Vpr also interferes with NF- κ B-mediated events in TcR signaling by upregulating I κ B (leading to the formation of inactive I κ B-NF- κ B complexes) (11) and preventing nuclear translocation of NF- κ B (153).

What does this plethora of modulatory mechanisms and effects ultimately mean for the HIV/T-cell interaction? Since T cells represent the main site of HIV replication *in vivo*, perhaps it should not be surprising that HIV is a talented manipulator of T-cell function. By the same logic, given how central TcR signaling is to T-cell biology, it should not be surprising that HIV carefully controls this pathway to its own ends. Also, the relatively recent jump of HIV to the human host may mean that we are currently observing a set of virus-host interactions that may not perfectly mimic the optimum virus-host balance that evolved in its prehuman host. Overall, it appears that in the *in vivo* situation, the immune-stimulatory effects of Nef and other HIV proteins favor the entry of T cells into an activated state, allowing the production of progeny virus (172). This occurs at least in part because of similarities between HIV transcriptional regulatory elements and those of many inducible T-cell genes (4, 71). At the same time, the HIV proteins have immune-suppressive effects that suppress the response to exogenous stimulation via the TcR, thus preventing hyperactivation and induction of AICD (36). The subtle control of TcR signaling by HIV serves also as a reminder that TcR signaling is not a binary, yes-or-no event, but rather a complex process in which submaximal levels of signaling may induce some but not all TcR-mediated cellular processes. This is a lesson clearly "taken to heart" by HIV.

HTLV-1. Human T-lymphotropic virus type 1 (HTLV-1) is a deltaretrovirus that is endemic in parts of Japan, Africa, the Caribbean, and South America. In a small subset of individu-

als, infection causes a rare malignancy of human T cells known as adult T-cell leukemia/lymphoma (96). In vitro, HTLV-1 leads to transformation of T cells, with T-cell proliferation initially being dependent on exogenous IL-2 but later progressing to IL-2-independent growth. Like HIV, HTLV-1 has both activating and inhibitory effects on T cells. Activated T cells are much more susceptible to infection than are resting T cells (97). Early in infection, the HTLV-1 protein p12¹ increases cytoplasmic calcium levels, inducing activation of the transcription factor NFAT and leading to increased T-cell activation and production of IL-2 (3, 28, 30, 70). In addition, short-term expression of the viral transcription factor Tax can bypass TcR signaling to activate transcription of the genes for CD28, CD69, and CD5 (19).

At the same time, HTLV-1 uses multiple mechanisms to inhibit TcR signaling. HTLV-1 decreases cell surface expression of the TcR via transcriptional downregulation of the CD3- γ , - δ , - ϵ , and - ζ genes (27) and similarly blocks transcription of Lck (75). This ultimately leads to defects in TcR-induced calcium flux and cytotoxicity (60, 101, 102, 114, 146, 170). The effect on T-cell function may occur in vivo, as well; peripheral blood mononuclear cells from HTLV-1-infected individuals have been shown to have a reduced response to recall antigens (95). The opposing stimulatory and inhibitory effects of HTLV-1 relate at least in part to opposing functions mediated by the p12¹ protein. p12¹ localizes to the endoplasmic reticulum/Golgi apparatus, to membrane lipid rafts, and also to the immunologic synapse after TcR stimulation (29, 43, 65). While p12¹ increases intracellular calcium, this effect is PLC- γ , LAT, and PI3K independent, suggesting that this effect bypasses proximal effectors in the TcR pathway (3). Conversely, p12¹ inhibits the phosphorylation of LAT, Vav, and PLC- γ 1 after TcR ligation, leading to decreased TcR-induced activation of NFAT (43). Interestingly, although both the 8- and 12-kDa forms of p12¹ can be palmitoylated, only the smaller form localizes to rafts and downregulates TcR signaling (G. Franchini, personal communication). Overall, the situation with HTLV-1 may be reminiscent of that of HIV in that HTLV-1 increases basal T-cell activation to allow infection and viral replication while preventing excessive TcR signaling that might lead to full T-cell activation, overexpression of virus and viral antigens, and AICD.

HVS. Herpesvirus saimiri (HVS) is a T-lymphotropic virus that leads to leukemias and lymphomas in certain species of nonhuman primates (39, 151). HVS encodes at least three gene products that modulate TcR function. The most intensely studied of these, the tyrosine kinase-interacting protein (Tip), is a 40-kDa protein that is constitutively present in lipid rafts. Tip interacts with and is phosphorylated by the Src family kinase Lck (17). The interaction occurs between the SH3 domain of Lck and 38 amino acids located in the central portion of Tip, containing a C-terminal Src-kinase homology motif, a linker sequence, and a proline-rich SH3 binding motif (17, 66). As discussed above for the Nef protein of HIV, however, there is considerable controversy regarding the functional outcome of this interaction. Infection of T cells with HVS, or transient transfection with Tip, has been reported to enhance the kinase activity of Lck (54, 55, 82, 84, 158). Consistent with these stimulatory effects, Tip can induce activation of the transcription factors STAT1, STAT3, and NFAT in a Lck-dependent

manner (54, 73, 83, 84). Tip also acts synergistically with the StpC protein of HVS to induce NF- κ B activation and IL-2 production from T cells (98).

On the other hand, other experiments point to an inhibitory role for Tip. Jurkat T cells stably transfected with Tip show decreased basal levels of overall tyrosine phosphorylation and decreased levels of tyrosine phosphorylation after CD3 stimulation (67). This may occur because the interaction of Tip with Lck recruits the TcR complex to lipid rafts. The lipid rafts are then internalized, leading to downregulation of the TcR via a second interaction between Tip and the endosomal protein p80 (111, 112). In addition, binding to Tip sequesters Lck such that TcR stimulation fails to activate ZAP70 and initiate downstream signaling events (20). Thus, in the presence of Tip, ζ -chain phosphorylation and ZAP70 recruitment occur normally after TcR ligation, but ZAP70 is not phosphorylated and instead remains stably associated with the TcR complex. Interestingly, the Tip-Lck interaction also appears to block the engagement of the TcR with MHC on antigen-presenting cells, thus inhibiting formation of the immunologic synapse (20).

How, then, do we reconcile these seemingly contradictory results? Differences between transient and stable transfection experiments may result from a compensatory response to stable expression of Tip, resulting in a dampened response to TcR signaling (62). It is also likely that Tip can increase basal levels of TcR activation while simultaneously decreasing sensitivity to ligation of the receptor and subsequent AICD, as proposed for proteins of HIV and HTLV-1.

Another HVS protein, HVS ORF5, has also been shown to modulate TcR function. HVS ORF5 encodes an 89- to 91-amino-acid protein containing an amino-terminal myristylation site and six SH2 binding motifs (79). Myristylation of HVS ORF5 is necessary for its localization to the plasma membrane, where phosphorylation of tyrosine within the SH2 binding domains allows interaction with the SH2 domain-containing signaling molecules Lck, Fyn, SLP-76, and p85 (79). The expression of HVS ORF5 augments TcR signal transduction, as measured by tyrosine phosphorylation of downstream signaling molecules, calcium flux, CD69 expression, IL-2 production, and activation of cellular transcription factors. Since the membrane localization and recruitment of SH2 domain-containing proteins is reminiscent of the normal function of LAT, whether HVS ORF5 might substitute for LAT in LAT-deficient Jurkat T cells was investigated. Interestingly, HVS ORF5 is sufficient to partially restore TcR-induced calcium flux in these cells but is unable to mediate CD69 upregulation, demonstrating that HVS ORF5 can substitute only partially for LAT function.

Finally, HVS ORF14 is a 249-amino-acid, highly glycosylated protein that is secreted (165). HVS ORF14 has significant homology to a superantigen encoded by mouse mammary tumor virus (21). Since HVS ORF14 directly binds HLA-DR and induces the proliferation of human T cells, it has been suggested to act itself as a superantigen (165). However, unlike traditional superantigens that preferentially bind certain VB chains of the TcR, HVS ORF14 seems to induce polyclonal T-cell proliferation without VB dependence (34, 74).

HHV-6. Human herpesvirus 6 (HHV-6), which preferentially infects CD4⁺ T cells (49), is the cause of the benign childhood illness exanthem subitum (163). Infection of T cells with HHV-6 results in downmodulation of surface CD3 (49,

87) and the TcR α/β heterodimer (87). This downmodulation may result in part from decreased transcription of CD3 (86). However, while surface levels of TcR components are markedly decreased by HHV-6 infection, their intracellular levels remain relatively normal (87, 147), suggesting that redistribution of the TcR complex may play a more important role than transcriptional regulation. Redistribution of the TcR complex has been ascribed to the U24 protein of HHV-6, which blocks CD3 access to recycling endosomes (147). Thus, CD3 accumulates in early and late endosomes and cannot recycle back to the cell surface. Transient transfection of Jurkat T cells with U24 results in a defective response to TcR stimulation (147); thus, it is likely that the downmodulation of the TcR complex by HHV-6 results in hyporesponsiveness of T cells to external antigenic stimulation.

HSV. Like all herpesviruses, herpes simplex virus (HSV) establishes lifelong latency in the host. For HSV, latency is maintained in the neurons of the dorsal root ganglia, a site where the virus is largely hidden from the immune system. During reactivation, however, the virus travels to the epithelium, where it must contend with the immune response. T cells are clearly important in the control of HSV reactivations in the periphery (115, 174); thus, it is not surprising that HSV might modulate T-cell function. HSV has a very powerful strategy for the evasion of CD8⁺ T cells, via inhibition of peptide loading of MHC class I by TAP (41, 58). However, HSV also has immune-modulatory mechanisms targeted directly at T cells. Coincubation of T cells with HSV-infected cells leads to a loss of T-cell function, including cytotoxicity (25, 118, 140) and production of most cytokines (139, 140). The effects of HSV on T-cell function result from a modulation of TcR signaling and depend upon entry of the virus into the T cells, as deletion of any of the viral proteins required for cell-to-cell spread or fusion abrogates the effect (117, 138, 171). However, disruption of T-cell function does not require viral replication or viral gene expression (116, 140). HSV entry can also lead to apoptosis in a fraction of infected T cells (53, 64). However, the effect on T-cell function is biochemically distinct from apoptosis, since the pan-caspase inhibitor ZVAD-fmk blocks HSV-induced apoptosis but does not block the inhibition of T-cell function (53).

The functional defect of HSV-exposed T cells is caused by failure of the TcR signal to propagate beyond the adapter molecule LAT. HSV induces a state of LAT hypophosphorylation in unstimulated T cells (138). After TcR stimulation of HSV-exposed T cells, ZAP-70 phosphorylation occurs normally, but phosphorylation of LAT is not observed. Thus, the normal recruitment of PLC- γ 1, Grb2, and GADS to the LAT complex does not occur, nor do downstream signaling events, such as Ca²⁺ flux and activation of Erk and NF- κ B (138, 139). Interestingly, despite their inability to synthesize most cytokines, HSV-exposed T cells retain the ability to produce normal amounts of IL-10 after TcR ligation (139). IL-10 has a number of immunosuppressive effects (103); thus, this skewing of the outcome of TcR stimulation may represent a sophisticated method of immune modulation by the virus. The selective synthesis of IL-10 is dependent upon the activity of p38, which unlike Erk is activated normally after TcR stimulation of HSV-exposed T cells (139). Thus, HSV appears to have evolved the ability to remodel TcR signaling to selectively

activate a secondary TcR pathway that may involve the direct activation of p38 by ZAP-70 (124). The viral proteins responsible for the hypophosphorylation of LAT and the activation of the p38 pathway remain to be determined. One interesting study reported that recombinant soluble glycoprotein D (gD) or gD-expressing fibroblasts could inhibit T-cell proliferation (77). However, the effect of gD on TcR signaling was not specifically investigated. Another interesting observation is that the HSV protein UL46 is specifically phosphorylated by Lck in infected T cells (G. Zahariadis, M. J. Wagner, R. C. Doecker, J. M. Maciejko, C. M. Crider, K. R. Jerome, and J. R. Smiley, submitted for publication). However, UL46 is not required for the induction of TcR signaling defects by HSV (G. Zahariadis, et al., submitted), and the significance of this protein in T-cell biology remains to be determined.

EBV. Epstein-Barr virus (EBV) is a human herpesvirus that is the most common cause of infectious mononucleosis. EBV can also cause lymphoproliferative disease in immunocompromised individuals, nasopharyngeal carcinoma, and Hodgkin's disease. EBV predominantly infects B lymphocytes, in which it establishes latency and induces alterations in B-cell receptor signaling. However, EBV can also infect T cells and is associated with certain T-cell and NK/T-cell lymphoproliferative disorders (162). EBV-infected T cells express high levels of proinflammatory cytokines. TcR signaling in EBV-infected T cells is disrupted via the action of the latent membrane protein 2A (LMP2A). LMP2A consists of a large cytoplasmic amino-terminal domain, 12 hydrophobic transmembrane domains, and a small cytoplasmic carboxyl-terminal domain (81). LMP2A localizes to membrane lipid rafts (57). Although LMP2A is palmitoylated, palmitoylation is not required for the raft localization (69). LMP2A can bind the TcR pathway-associated kinases Lck, Fyn, and ZAP-70 via specific tyrosine phosphorylation motifs within its amino-terminal domain (61). In addition, LMP2A has two PPPY motifs that allow binding to the NEDD4 family E3 ubiquitin ligase AIP4. Thus, LMP2A mediates downregulation of the TcR, presumably by facilitating ubiquitin-mediated degradation of LMP2A-associated kinases. Stable expression of LMP2A in Jurkat cells leads to TcR downregulation and attenuation of TcR signaling; the relative contributions of decreased overall TcR expression versus sequestration of LMP2A-associated kinases remain unclear (61).

MV (and other morbilliviruses). The clinical impact of measles virus (MV) is sometimes underappreciated, despite the fact that the World Health Organization estimates that this virus caused 345,000 deaths in 2005. Infection with MV is associated with significant generalized immune suppression, which can be fatal in certain clinical settings. One prominent feature of MV-induced immunosuppression is proliferative unresponsiveness of T cells to polyclonal and antigen-specific stimulation (129). Since a relatively low proportion of T cells is infected with MV in human disease, T-cell unresponsiveness likely results, in part, from MV dysregulation of monocyte and dendritic cell maturation and cytokine production (42, 68, 133). In addition, MV has direct effects upon the T cell (128). Interaction of T lymphocytes with the MV glycoprotein complex, consisting of the fusion and hemagglutinin proteins (F/H), induces T-cell unresponsiveness, but neither protein alone is sufficient to mediate the suppression (35, 107, 126). Infectious virus is not required, since UV-inactivated MV still in-

duces T-cell unresponsiveness (8). The F and H proteins of a related morbillivirus, rinderpest virus, have similar inhibitory effects on lymphocytes (56). The ability of the MV F/H complex to inhibit T cells requires the proteolytic activation of the F protein (156). However, it does not depend on cellular fusion or the generation of soluble mediators, suggesting that the effect on lymphocytes is mediated through a surface contact mechanism (155). Infection of dendritic cells by MV may be an important contributor to this, since infected DCs form unstable immune synapses with T cells (135) and can suppress T-cell proliferation through the action of surface-expressed H and F proteins (33). MV and the F/H complex have a number of effects on lymphocytes, including cell cycle arrest at the G₀/G₁ phase, reduced expression and activity of cyclin-dependent kinase complexes, delayed degradation of p27Kip, and inhibition of actin remodeling, T-cell polarization, and TcR clustering to the site of T-cell/antigen-presenting cell contact (35, 104, 108, 130). In addition to the MV F/H protein complex, the MV nucleoprotein has been shown to inhibit antigen-specific or mitogen-induced T-cell proliferation, presumably via binding of a putative nucleoprotein binding receptor expressed upon T-cell activation (78, 91, 92).

These findings led to intense interest in the mechanisms of MV F/H complex modulation of T-cell signaling pathways. MV interacts with lipid raft membrane microdomains on the surface of T cells (10). This interaction appears to disrupt trafficking of signaling molecules to lipid rafts and is likely to be central to the ability of MV to modulate TcR signaling. The major defects after contact with the F/H complex revolve around disruption of PI3K activation and downstream signaling events. The interaction of MV with lipid rafts prevents the degradation of Cbl-b that normally occurs after CD3/CD28 stimulation of T cells (10). In normal T cells, Cbl-b prevents the recruitment of the p85 regulatory subunit of PI3K to lipid rafts; therefore, without Cbl-b degradation, downstream events triggered by PIP2 and PIP3 synthesis, including lipid raft recruitment and subsequent activation of pleckstrin-homology domain-containing proteins, such as Akt and Vav, cannot occur. Interference with Akt activation is required for the induction of immunosuppression by MV, since the overexpression of catalytically active Akt caused a marked reduction in sensitivity to the inhibitory MV signal (8). In addition, MV induces the expression of SIP110, a splice variant of the lipid phosphatase SHIP-1 lacking the N-terminal SH2 domain but retaining phosphatase activity (9). Overexpression of SIP110, which is constitutively active, counteracts tonic or stimulated PI3K-dependent PIP2 and PIP3 accumulation, thereby raising the threshold for T-cell activation after TcR ligation (9). MV also inhibits IL-2-mediated activation of Akt, as measured either by Ser473 phosphorylation or by *in vitro* kinase activity assays (8). In contrast, MV has no effect on IL-2-induced JAK/STAT signaling (8). Thus, MV, through the action of its H and F proteins, has a wide variety of effects upon the T cell and the TcR signaling pathway. The exact manner in which the F and H proteins disrupt lipid raft function and whether this is indeed the initiating event leading to other TcR signaling defects remain to be determined.

RSV. Respiratory syncytial virus (RSV) has an effect on T-cell proliferation similar to that of MV. Contact with the RSV fusion (F) protein is sufficient to inhibit the proliferation

of T cells to mitogen stimulation (127). The presumed RSV attachment protein (G), while not absolutely required for inhibition by F protein, augments its strength. Interestingly, while the RSV F protein blocks T-cell entry into the cell cycle after mitogen stimulation, it does not inhibit the expression of mitogen-induced activation markers (127). The mechanism by which the F protein mediates its effect is unclear, as is whether it exerts any direct effect on TcR signaling.

HCV. Hepatitis C virus (HCV) infects over 170 million people worldwide, yet mechanistic studies have been hampered until recently by the inability to culture the virus. *In vivo*, HCV infection causes downregulation of TcR- ζ in peripheral blood mononuclear cells relative to uninfected controls (89), although the mechanism by which this occurs is unclear. *In vitro*, HCV proteins have been reported to have both positive and negative effects on TcR signaling. The HCV envelope protein E2 binds CD81, providing costimulation and lowering the threshold for TcR signaling (154). Costimulation by E2 is Lck dependent and leads to increased and prolonged tyrosine phosphorylation of TcR- ζ , ZAP-70, and LAT, suggesting that the effect occurs at the most proximal stages of TcR signaling (142). In addition, the core (C) protein of HCV can modulate the activity of transcription factors immediately downstream of the proximal TcR pathway, apparently by increasing cytosolic Ca²⁺ and Ca²⁺ oscillations (16). In transient transfections, this results in activation of NFAT and the IL-2 promoter (15). The expression of C protein from a lentivirus vector induces the expression of a set of genes very similar to those overexpressed in ionomycin-induced anergy (31). In contrast, in stable transfections, C protein inhibits JNK signaling and IL-2 promoter activity, while inducing Erk and p38 activation and inducing promoter activity for IL-4, IL-10, gamma interferon, and tumor necrosis factor alpha (148). It is likely that these contrasting results reflect a differential response of the T cell to transient versus extended perturbations in Ca²⁺ concentration and oscillation. Recombinant C protein also has a number of inhibitory effects on TcR signaling, including impaired activation of the signaling molecules Lck, ZAP-70, Akt, ERK, and MEK, upregulation of T-cell expression of the negative regulator PD-1, and cell cycle arrest. These effects have been reported to be dependent upon the interaction of C protein with the complement receptor gC1qR (72, 166–169), which may facilitate the entry of C protein into T cells (31). In support of the importance of C protein *in vivo*, transgenic mice with C protein expression targeted to T cells by the CD2 promoter showed markedly depressed IL-2 and gamma interferon production after anti-CD3 stimulation of splenocytes (141). In humans, HCV RNA can be detected in CD4⁺ T cells during chronic infection (31). However, it is likely that only a minority of T cells is infected by HCV, and the immunosuppressive effects are more likely to be mediated by circulating C protein, which can be detected in the sera of infected patients (88, 94). Several recent reports have demonstrated increased levels of PD-1 on T cells of HCV-infected patients (45, 113, 119, 152), although it is not yet clear whether this results from the action of C protein *in vivo*.

Vaccinia virus. Vaccinia virus has received much recent attention, both as a potential vaccine vector and as a model for the immunobiology of poxvirus infections. However, relatively little work has focused on the effects of vaccinia virus on TcR

FIG. 2. TcR modulation by T-lymphotropic and nonlymphotropic viruses.

signaling. The vaccinia virus H1 protein (VH1) has been shown to efficiently block TcR-induced activation of the NFAT/AP-1 element from the IL-2 promoter (5). VH1 was the first cloned member (50) of a large group of dual specific (Ser/Thr and Tyr) phosphatases that have been shown to regulate cellular signaling pathways (105). Although the mechanism of action of VH1 has not been investigated in detail, the related cellular VHR phosphatase can inhibit activation of ERK, JNK, and reporter genes dependent on these kinases (6). In contrast, VHR has no effect on p38 or its downstream genes. Following TcR ligation, VHR is phosphorylated by ZAP-70, and this phosphorylation is required for VHR to exert its inhibitory effects on ERK and JNK (5). Whether such a mechanism is operative for VH1 remains to be determined.

BIOLOGICAL RELEVANCE OF VIRAL MANIPULATION OF TcR SIGNALING

Clearly, a large number of viruses have evolved the ability to manipulate signaling via the TcR. However, each virus seems to have evolved its own unique mechanism(s) of action. How then to synthesize these varied approaches into a cohesive view of the virus/T-cell interaction? One useful construct is to consider the two basic situations in which viruses have experienced selective pressure to modulate TcR signaling: viruses that predominantly infect and replicate in T cells and viruses that predominantly replicate in other cell types but modulate T-cell function as a mechanism of immune evasion (Fig. 2).

Viruses that preferentially replicate in T cells. Medically, the most important example of a virus that predominantly replicates in T cells is HIV, although HTLV-1 and HVS clearly fall into this category as well. Compared to many other cell types that viruses might use as their preferred host cell, T lymphocytes are profoundly sensitive to external stimuli and can rapidly move from the resting phase to a fully activated, rapidly cycling state after TcR stimulation. Thus, it is not surprising that T-lymphotropic viruses carefully control this process. HIV, HTLV-1, and HVS use aspects of the TcR signaling machinery to induce a state of constitutive low-level

activation in their host cells, allowing the viral replication cycle to occur. At the same time, full activation of the host T cell would be detrimental to the infecting virus, in that it might trigger activation-induced cell death or cause overexpression of viral antigen, thus attracting unwanted attention from the immune system. T-lymphotropic viruses therefore attenuate the ability of the TcR to respond to external triggering when encountering cells expressing cognate antigen. The simultaneous increase in basal T-cell activation, combined with reduced sensitivity to external triggering, keeps infected T cells at a stable, low level of activation, ideal for replication of the infecting viruses.

Viruses seeking to evade T-cell immunity. A different situation arises when viruses replicate predominantly in other cell types, yet seek to manipulate TcR signaling as a means of evading the attack of T lymphocytes. Some viruses in this category modulate TcR activity via the secretion of products or viral components that mediate the suppressive effects. For example, the HCV core protein is present in the sera of infected patients and mediates a number of T-cell-inhibitory effects in vitro and in vivo. Since secreted products or viral components can become diffused widely throughout the body, T-cell modulation by this mechanism tends to be widespread. In contrast, other viruses disable T cells that threaten them by contact-dependent mechanisms. For example, HSV disrupts TcR signaling by cell-to-cell spread from infected epithelial cells. The effects of contact-dependent mechanisms are by their nature highly localized compared to the systemic effects caused by secreted products or viral components. Thus, rather than inducing immunosuppression throughout the host, these viruses exquisitely target their inhibitory effects, inducing a localized area of immune privilege around the site of their own replication.

CONCLUDING THOUGHTS

The virus-host interaction is a dynamic, constantly changing process. For some viruses, such as HSV, the virus and host have evolved together for millions of years, and the virus-host

balance presumably reflects a stable balance of immune pressure versus modulation. For other viruses, such as HIV, the introduction into the human host has occurred much more recently, and the virus-host balance reflects more the "shotgun wedding" of a virus and host that have evolved separately. Nevertheless, in both extremes, the virus possesses the ability to modulate TcR signaling, and this ability appears to be important for the success of each virus in its host.

Clinically, there are many circumstances in which the ability to manipulate TcR signaling would be useful. In autoimmunity, the ability to induce a generalized desensitization to TcR stimulation might be useful, while during graft rejection, there would be great utility in inducing localized T-cell dysfunction. Conversely, in the face of tumors or chronic infectious disease, the ability to upregulate T-cell function by lowering the threshold for TcR stimulation is an attractive therapeutic concept. Even more attractive may be a subtler remodeling or skewing of the T-cell response, by selectively targeting specific parts of the TcR pathway to favor production of a specific subset of cytokines. For now, these ideas remain largely unattainable by pharmacologic means. Nevertheless, viruses have already achieved this goal, and each day, they manipulate TcR function in their human hosts to their own ends. We would do well to learn from these ancient teachers.

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