MINIREVIEW

Emerging Theme: Cellular PDZ Proteins as Common Targets of Pathogenic Viruses[▽]

Ronald T. Javier* and Andrew P. Rice*

Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas 77030

More than a decade ago, three viral oncoproteins, adenovirus type 9 E4-ORF1, human T-lymphotropic virus type 1 Tax, and high-risk human papillomavirus E6, were found to encode a related carboxyl-terminal PDZ domain-binding motif (PBM) that mediates interactions with a select group of cellular PDZ proteins. Recent studies have shown that many other viruses also encode PBM-containing proteins that bind to cellular PDZ proteins. Interestingly, these recently recognized viruses include not only some with oncogenic potential (hepatitis B virus, rhesus papillomavirus, cottontail rabbit papillomavirus) but also many without this potential (influenza virus, Dengue virus, tick-borne encephalitis virus, rabies virus, severe acute respiratory syndrome coronavirus, human immunodeficiency virus). Examination of the cellular PDZ proteins that are targets of viral PBMs reveals that the viral proteins often interact with the same or similar types of PDZ proteins, most notably Dlg1 and other members of the membrane-associated guanylate kinase protein family, as well as Scribble. In addition, cellular PDZ protein targets of viral PBMs commonly control tight junction formation, cell polarity establishment, and apoptosis. These findings reveal a new theme in virology wherein many different virus families encode proteins that bind and perturb the function of cellular PDZ proteins. The inhibition or perturbation of the function of cellular PDZ proteins appears to be a widely used strategy for viruses to enhance their replication, disseminate in the host, and transmit to new hosts.

The PDZ domain is a protein-protein interaction module that is widespread throughout evolution, being found in bacteria, fungi, and metazoans (76). PDZ domains generally consist of approximately 90 amino acid residues that adopt a structure composed of six β -strands and two α -helices (reviewed in reference 57). The term PDZ is an abbreviation for the first three proteins found to share this structural domain: PSD-95, Dlg, and ZO-1. PDZ domains are typically found in cytoplasmic and membrane adapter proteins that are involved in a variety of cellular processes of significance to viral infection: maintenance of cell-cell junctions, cellular polarity, and signal transduction pathways. In metazoans, PDZ proteins often contain multiple PDZ domains and additional protein-protein interaction elements, such as SH3, L27, or leucine-rich repeat (LRR) domains. In the mouse genome, over 700 individual PDZ domains are found in over 300 proteins, while in the human genome, over 900 PDZ domains are found in over 400 proteins (103).

PDZ domains usually bind to a specific peptide sequence located at the extreme carboxyl terminus of a target protein, although in some cases, the peptide sequence can have an internal location. The peptide sequence that binds to a PDZ domain is referred to as the PDZ domain-binding motif, or PBM. Carboxyl-terminal PBMs have been grouped into three general specificity classes: type I PBM ($-X-S/T-X-\Phi_{\text{COOH}}$),

type II PBM ($-X-\Phi-X-\Phi_{\text{COOH}}$), and type III PBM ($-X-D/E-X-\Phi_{\text{COOH}}$), where X is any residue and Φ is a hydrophobic residue (36, 76). However, a recent comprehensive study that scanned a very large random peptide library showed that PDZ proteins can recognize up to the last seven residues at the carboxyl termini of proteins and that 16 distinct specificity classes can be identified (117). Carboxyl-terminal and internal PBMs bind to a groove between the $\beta\alpha$ -helix and the $\beta\beta$ -sheet of the PDZ domain (57). The equilibrium dissociation constant (K_D) for PDZ domains and peptides comprising carboxyl-terminal PBMs are generally in the 1 to 50 μM range (44).

The initial discoveries of PBMs in viral proteins arose over a decade ago from studies of three viral oncoproteins, human adenovirus (Ad) E4-ORF1, human T-lymphotropic virus type 1 (HTLV-1) Tax, and human papillomavirus (HPV) E6 (49, 59, 94). In recent years, however, nontransforming viruses, such as influenza A virus and tick-borne encephalitis virus (TBEV), have been found to encode proteins with PBMs that target many of the same PDZ proteins as do the PBMs from viral oncoproteins. This has led to the realization that a select set of PDZ proteins are commonly targeted during infections by different viruses with quite distinct replication cycles. As discussed below, the association of some viral PBMs with PDZ proteins results in their loss of function, either through proteasome-mediated degradation or aberrant sequestration in cellular structures. In other cases, however, the association of viral PBMs with their PDZ protein targets results in an apparent gain of function of the cellular protein. In both cases, the targeting of PDZ proteins and modulation of the cellular processes that these PDZ proteins regulate are likely to enhance

* Corresponding author. Mailing address: Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030. Phone for Ronald T. Javier: (713) 798-3898. Fax: (713) 798-3586. E-mail: rjavier@bcm.edu. Phone for Andrew P. Rice: (713) 798-5774. Fax: (713) 798-3490. E-mail: arice@bcm.edu.

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TABLE 1. Known cellular PDZ protein targets of viral proteins

Adenoviridae	Hepadnaviridae	Orthomyxoviridae	Papillomaviridae	Retroviridae
Human Ad E4-ORF1 proteins PBM: ASLI, ATMI, ASNV, ATLV <u>PDZ targets</u> • Dlg1 • MAGI-1 • MUPP1 • PATJ • ZO-2 (Ad9 only)	HBV Core protein PBM: SQAR <u>PDZ target</u> • TIP-2/GIPC	Influenza A NS1 proteins Avian PBM: ESEV <u>PDZ targets</u> • Dlg1 • MAGI-1 • MAGI-2 • MAGI-3 • Scribble • PDLIM2	HPV E6 proteins HPV-16 PBM: ETQL HPV-18 PBM: ETQV <u>PDZ targets</u> • CAL/GOPC • Dlg1 • Dlg4 • MAGI-1 • MAGI-2 • MAGI-3 • MUPP1 • PATJ • PTPN3 • PTPN13 • Scribble • TIP-1 • TIP-2/GIPC	HTLV I Tax protein PBM: ETEV <u>PDZ targets</u> • β 1-syntrophin • Dlg1 • Dlg4 • Erbin • MAGI-3 • pro-IL-16 • Scribble • TIP-1 • TIP-2/GIPC • PDLIM2* <u>Env protein</u> PBM: ESSL <u>PDZ target</u> • Dlg1 HIV Gag protein PBM: None <u>PDZ target</u> • Dlg1* • PDZD8*
Flaviviridae	Rhabdoviridae	Coronaviridae		
TBEV NS5 protein PBM: internal <u>PDZ targets</u> • RIMS2 • Scribble • ZO-1 DV NS5 protein PBM: internal <u>PDZ target</u> • ZO-1	Rabies G proteins PBM: ETRL <u>PDZ targets</u> • Dlg1 • MAST2 • MUPP1 • PTPN4	SARS E protein PBM: DLLV <u>PDZ target</u> • PALS1	RhPV E7 protein PBM: ASRV <u>PDZ target</u> • Par3 CRPV LE6 and SE6 proteins PBM: Not identified <u>PDZ target</u> • Dlg1	

viral replication, dissemination in the host, or transmission to new hosts.

EIGHT VIRUS FAMILIES TARGET CELLULAR PDZ PROTEINS DURING AN INFECTION

We summarize below studies which have shown that viral proteins from eight virus families target cellular PDZ domain-containing proteins (Table 1). The domain structures of the most frequently targeted PDZ proteins are shown in Fig. 1. The best-studied virus families are *Adenoviridae*, *Papillomaviridae*, and *Retroviridae*, as the human adenovirus E4-ORF1, high-risk human papillomavirus E6, and human T-cell leukemia virus type 1 Tax genes encode the first identified viral PBMs and have been actively studied due to their role in cellular transformation (see references 43 and 115 for detailed reviews). These initial discoveries of viral PBMs have been followed by more recent work showing that nononcogenic viruses likewise code for PBM-containing proteins, suggesting that functional perturbations of cellular PDZ proteins are of wide importance to viruses.

(i) ADENOVIRIDAE

Human adenovirus. Human adenovirus (Ad) is associated with acute, self-limiting infections of the respiratory and gastrointestinal tracts or the eye. These viruses additionally pos-

sess cellular growth-transforming potential in rodent cells, and some are tumorigenic in laboratory animals under experimental conditions. For example, adenovirus type 9 (Ad9) causes eye infections in people, but it also elicits estrogen-dependent mammary tumors in experimentally infected female rats (43). The E4-ORF1 protein is the primary determinant for tumorigenesis induced by Ad9, and amino acid residues located at the extreme carboxyl terminus of E4-ORF1 were shown to be crucial for its oncogenic potential (124). To identify cellular proteins that bind to this carboxyl-terminal element, Lee et al. screened a cDNA expression library with an E4-ORF1 protein probe (59). This work led to the discovery of the first virus-encoded PBM (type 1 sequence -ATLV_{COOH}) and to the identification of Dlg1 as the first cellular PDZ protein target of a viral PBM. Dlg1 PDZ domains 1 and 2 mediate this interaction (Fig. 1).

Subsequent studies revealed that the E4-ORF1 PBM mediates binding not only to Dlg1 but also to at least four additional cellular PDZ proteins: MUPP1, PATJ, MAGI-1, and ZO-2 (24, 25, 55, 58). Like Dlg1, one or more specific PDZ domains in these proteins bind to E4-ORF1. All of these PDZ proteins lack a catalytic domain and instead consist of multiple protein-protein interaction modules. Dlg1, MAGI-1, and ZO-2 are members of the membrane-associated guanylate kinase (MAGUK) protein family that contains PDZ, SH3, or WW, and guanylate kinase homology domains, while MUPP1 and PATJ are closely

FIG. 1. Domain structures of PDZ proteins frequently targeted by viruses. For proteins having more than one PDZ domain, the most amino-terminal PDZ domain is defined as domain number 1 and domain numbers increase sequentially toward the carboxyl terminus.

related multi-PDZ domain family members containing 13 and 10 PDZ domains, respectively, as well as an amino-terminal L27 domain (43). As suggested by their domain structures (Fig. 1), these PDZ proteins function as scaffolds to assemble large protein complexes that regulate signal transduction. They also control formation of membrane junctions at regions of cell-cell contact, such as the tight junction (TJ) or adherens junction (AJ) (18, 32, 50, 53, 54, 60, 69, 97, 107, 120, 121). In polarized epithelial cells, MUPP1, PATJ, MAGI-1, and ZO-2 associate with the TJ (27, 46, 82, 97), whereas Dlg1 localizes to the AJ (54, 107).

E4-ORF1 exists as both monomers and trimers in cells. Monomeric E4-ORF1 binds only to MUPP1, PATJ, MAGI-1, and ZO-2, whereas the trimeric protein binds only to Dlg1 (9). The fact that E4-ORF1 sequesters MUPP1, PATJ, MAGI-1, and ZO-2 within detergent-insoluble complexes, possibly in association with cytoplasmic membrane vesicles, but instead promotes Dlg1 translocation to the plasma membrane, indicates that monomeric and trimeric forms of E4-ORF1 evolved to have differential functional effects on their PDZ protein

targets (20, 24, 25, 55, 58). In epithelial cells, individual small interfering RNA (siRNA)-mediated knockdown of MUPP1, PATJ, ZO-2, and MAGI-1 disrupts the TJ (32, 50, 53, 97), demonstrating an essential function for these proteins in TJ assembly. By a PBM-dependent mechanism, E4-ORF1 causes nearly identical TJ defects in epithelial cells without producing discernible effects on AJ structure (55), suggesting that E4-ORF1 sequestration of its TJ-associated PDZ targets results in their functional inactivation. The effect of E4-ORF1 on Dlg1 also possibly contributes to E4-ORF1-induced TJ defects, as Dlg1 knockdown functionally disrupts the TJ (54, 107).

PATJ, ZO-2, and Dlg1 also function to control establishment of proper cell polarity, a cellular property that involves the differential distribution of macromolecules within a cell. Cell polarity is crucial for development and normal cell functions, and it can be classified into three general types, apical-basal, anterior-posterior, and planar cell polarity, which represent vertical, horizontal, and tissue organizational cell polarity, respectively (68, 73, 84, 99). In epithelial cells, establishment of

FIG. 2. Cellular PDZ proteins that function in cell polarity establishment and cell junction formation are commonly targeted by viruses. Shown on right is a polarized epithelial cell divided into its apical, tight junction (TJ), and lateral regions. Shown on left are cellular PDZ proteins that localize to one of these epithelial cell regions and that function to regulate formation of the tight junction or adherens junction (AJ) and/or establishment of cell polarity establishment. Viral proteins known to interact with these PDZ proteins are indicated. Flu A, influenza A virus.

proper apical-basal polarity depends on three evolutionarily conserved protein polarity complexes: Crumbs (Crumbs-Pals1-PATJ), Par (Par3-Par6-atypical protein kinase C [aPKC]), and Scribble (Scribble-Dlg1-Lgl) (84) (Fig. 2). ZO-2 has recently also been implicated in establishment of apical-basal cell polarity (32). Scribble, Dlg1, and PATJ also control establishment of anterior-posterior cell polarity (16, 35, 52, 63, 81, 90, 93, 98). By a PBM-dependent mechanism, Ad9 E4-ORF1 causes a loss of apical-basal polarity in epithelial cells (55), similar to siRNA knockdown of PATJ or ZO-2, and also prevents establishment of anterior-posterior cell polarity (K. Kong, L. Waldron, and R. T. Javier, unpublished results). Thus, E4-ORF1 uses its PBM to disrupt the TJ and to cause a loss of cell polarity, two hallmarks of epithelium-derived cancer cells (10, 100). As discussed below, viral proteins that target cellular PDZ proteins involved in the control of cell junction formation and cell polarity establishment have emerged as a common theme of viral infections (Fig. 2).

The phosphatidylinositol 3-kinase (PI3K) signaling pathway is required for many cellular processes, and dysregulation of this pathway is widely implicated in the development of human cancers (15). By a PBM-dependent mechanism, Ad9 E4-ORF1 promotes constitutive growth factor-independent PI3K activation in cells, and this activity is crucial for the oncogenic potential of E4-ORF1 (21). Interestingly, this E4-ORF1 activity, which is conserved between different human Ad serotypes, enhances virus production in human adenovirus type 5-infected cells and also is a major determinant for obesity asso-

ciated with human adenovirus type 36 infections (21, 80, 91). PI3K activation by Ad9 E4-ORF1 specifically depends on its interaction with Dlg1, as *Dlg1*-null cells cannot support this activity, yet *MAGI-1*-null or *MUPP1*-null cells can (20). These findings revealed the first known viral activity mediated by Dlg1 and also demonstrated that E4-ORF1 has a gain-of-function effect on this PDZ protein, despite evidence suggesting that Dlg1 is tumor suppressor (1, 75).

In summary, current evidence indicates that E4-ORF1 monomers functionally inactivate MUPP1, PATJ, MAGI-1, and ZO-2 to disrupt the TJ and cause a loss of cell polarity, whereas E4-ORF1 trimers exert a gain-of-function effect on Dlg1 to constitutively activate the PI3K signaling pathway. In future studies, it will be important to investigate how these E4-ORF1 activities contribute to Ad replication and Ad-associated human diseases.

(ii) *PAPILLOMAVIRIDAE*

Human papillomavirus. Human papillomaviruses (HPVs) cause warts in cutaneous and mucosal epithelial cells. Additionally, infections by some mucosal HPVs termed high-risk viruses, such as HPV type 16 (HPV-16) and HPV-18, can trigger the development of cervical cancer. Two HPV gene products, the E6 and E7 proteins, cooperate to promote uncontrolled cellular proliferation and viral genome amplification and represent the major oncogenic determinants of high-risk HPVs. A functional class I PBM located at the carboxyl

terminus of high-risk but not low-risk HPV E6 proteins was first reported in 1997 by Lee et al. and shortly thereafter by Kiyono et al. (49, 59). The HPV-18 and -16 E6 PBMs have the sequences -ETQV_{COOH} and -ETQL_{COOH}, respectively.

It was subsequently shown that in keratinocytes, the normal target cells for HPV replication and carcinogenesis, the PBM is also important for HPV-16 and HPV-18 E6 to promote epithelial-to-mesenchymal transition-like changes (104, 123), a hallmark of cancer development. The PBM is also important for HPV-16 E6 to immortalize and induce anchorage-independent growth in human tonsil keratinocytes (104, 105) and to inhibit apoptosis in human airway epithelial cells (42). A role for the HPV E6 PBM in HPV-induced tumorigenesis has also been strongly suggested by studies conducted with transgenic mice carrying an expression cassette containing the HPV-16 *E6* and *E7* genes driven by the cellular keratin 14 promoter, which directs expression within physiologically relevant basal cells of stratified epithelium, including those of the cervix. Dual *E6* and *E7* gene expression in these transgenic mice promotes epithelial neoplasia at a high frequency, as well as cervical cancer following treatment with estrogen. Using this transgenic animal system, the Lambert laboratory has demonstrated that the E6 PBM is crucial for increased tumor size and frequency mediated by the cooperation of the *E6* gene with the *E7* gene in both the cervix and other epithelial locations (74, 95, 96). The E6 PBM is a marker for carcinogenic mucosal HPVs because it is the sole protein-interaction element unique to high-risk HPVs (115). Additionally, organotypic raft cultures infected by HPV-31 encoding an E6 gene with a deleted PBM lack the typical pathological features associated with a wild-type HPV-31 infection, such as a thickened basal epithelial layer and the presence of nuclei throughout the suprabasal layers (56).

As for Ad E4-ORF1, Dlg1 was the first identified cellular PDZ protein target for the E6 PBM of high-risk HPVs (49, 59). Two PDZ domains in Dlg1, PDZ1 and PDZ2, mediate the interaction with the E6 PBM, and this interaction promotes proteasome-mediated degradation of Dlg1 (23), implying functional inactivation of Dlg1 by E6. Degradation is the outcome for most cellular proteins that interact with E6 due to its ability to recruit the cellular E6AP ubiquitin ligase into protein complexes. However, E6 reduces but does not completely eliminate its target proteins in cells, and in the case of Dlg1, this is due to specific E6 targeting of a subset of Dlg1 that is nuclear and hyperphosphorylated (65, 66). Mucosal HPVs also express splice-variant E6 mRNAs coding for carboxyl-terminal truncated proteins referred to as E6* proteins, which lack the PBM. Interestingly, despite lacking any detectable interaction with Dlg1, E6* promotes degradation of Dlg1 phosphoforms that associate with the cytoskeleton (85), in contrast to the specificity of full-length E6 for nuclear Dlg1 phosphoforms.

Biochemical purification of proteins associated with E6-E6AP complexes revealed that high-risk HPV E6 proteins also bind to the Scribble polarity protein that functions upstream of Dlg1 in the same polarity pathway (71). This interaction is mediated by the E6 PBM and at least two Scribble PDZ domains, and it promotes ubiquitin-mediated degradation of Scribble. The observation that HPV-16 E6-mediated degradation of Scribble is linked to reduced membrane localization of the TJ-associated protein ZO-1 in epithelial cells suggests that

Scribble degradation may contribute to a loss of TJ integrity (71). Protein expression of Scribble and Dlg1 is reduced or absent in cervical cancers, and E6 PBM-mediated degradation of these two polarity proteins may therefore contribute to carcinogenesis (8, 72, 114, 122).

High-risk E6 also binds to the multi-PDZ domain proteins MUPP1 and PATJ in a PBM-dependent manner and targets them for degradation (55, 58, 106). The interaction with the PATJ polarity protein requires PDZ domains 4 and 5, and PATJ degradation by E6 is mediated by an E6AP-independent mechanism (106). Although HPV-18 E6* lacks a PBM, it also can bind to PATJ and target it for degradation (106). The findings described above have established that high-risk HPV E6 proteins promote degradation of at least three different cell polarity proteins, Dlg1, Scribble, and PATJ, suggesting an important role for their inactivation and possibly loss of cell polarity in the HPV life cycle and HPV-induced carcinogenesis.

The HPV-16 and HPV-18 E6 proteins also bind to the PDZ proteins MAGI-1, MAGI-2, and MAGI-3 and target them for proteasome-mediated degradation (111, 113). Among E6-binding PDZ proteins, MAGI family proteins exhibit the strongest binding to and most efficient degradation by E6 (115, 132). Recent findings indicate that E6-mediated degradation of MAGI-1 promotes TJ disruption in epithelial cells (50). Purification of cellular proteins that associate with the glutathione *S*-transferase (GST)-HPV-16 E6 fusion protein *in vitro* led to the finding that high-risk HPV E6 PBMs also mediate binding to the single PDZ domain in the cystic fibrosis transmembrane regulator-associated ligand (CAL) and target it for degradation (45). Given the suspected involvement of CAL in vesicle trafficking, an activity crucial for cell polarity establishment (109), it will be interesting to examine whether this PDZ protein is also involved in this cellular process.

Yeast two-hybrid system studies showed that the HPV-16 E6 PBM mediates binding to Tax-interacting protein-1 (TIP-1) (28, 79), which is involved in both Rho A and Wnt signaling (48, 89) and, as its name implies, also binds to human T-lymphotropic virus type 1 (HTLV-1) Tax (see below) (94). TIP-1 is an unusual example of an E6-binding protein not targeted for degradation in cells, suggesting that its interaction with E6 may result in gain of function rather than loss of function, as is likely to occur with proteins that E6 targets for degradation. Consistent with this idea, siRNA depletion of TIP-1 prevented HPV-16 E6 from increasing the motility of HPV-negative human C33A cervical cancer cells (28). The HPV-18 E6 PBM also mediates binding to and triggers proteasome-mediated degradation of the PDZ protein GIPC/Tax-interacting protein-2 (TIP-2) (19) which is involved in transforming growth factor- β (TGF- β) signaling. siRNA depletion of GIPC in HeLa cells inhibited TGF- β -induced *Id3* gene expression and antiproliferative activity, whereas siRNA depletion of E6 increased *Id3* gene expression and blocked cell proliferation (19). These data suggest that downregulation of GIPC by E6 diminishes the cytostatic effect of TGF- β .

In addition to the *Dlg1* gene, mammals encode five other Dlg-related genes (*Dlg2* to *Dlg6*). The HPV-16 and -18 E6 PBM mediates binding to and proteasomal degradation of Dlg4/PSD95 in cervical cancer cell lines (29). Whether high-risk HPV E6 proteins similarly target the remaining Dlg family

members is not yet known. High-risk HPV E6 proteins also bind to and promote degradation of two different nonreceptor FERM domain-containing protein tyrosine phosphatases, PTPN3/PTPH1 (47, 118) and PTPN13 (105). PTPN3, which has a single PDZ domain, regulates tyrosine phosphorylation of growth factor receptors and is mutated in some cancers. The ability of HPV-16 E6 to confer reduced growth factor requirements in keratinocytes, an activity dependent on the E6 PBM, can in part be phenocopied by siRNA depletion of PTPN3. PTPN13, which has five PDZ domains, is reported to function as a tumor suppressor in human colon carcinogenesis (43) and is also implicated in several cell survival pathways involving I κ B α , EphrinB, β -catenin, and *c-src* (15a). In tonsil epithelial cells, HPV-16 E6 promotes PBM-dependent anchorage-independent growth and, in cooperation with RasV12, invasive growth *in vivo*. siRNA depletion of PTPN13 recapitulated these E6 activities, whereas PTPN13 overexpression reversed the effects. The findings described above argue strongly that functional perturbations of the PDZ proteins TIP-1, GIPC, Dlg4, PTPH1, and PTPN13 contribute to cancers induced by high-risk HPV E6 oncoproteins.

Cottontail rabbit papillomavirus. Cottontail rabbit papillomavirus (CRPV), which causes papillomas that progress to carcinomas at a high frequency in domestic rabbits, encodes three transforming proteins, long E6 (LE6), short E6 (SE6), and E7, each of which is essential for papilloma formation. The 176-residue SE6 protein is identical to the carboxyl-terminal region of the longer, 273-residue LE6 protein; however, their mechanisms of transformation and papilloma formation are unknown. Du et al. reported that both CRPV E6 proteins utilize an unknown carboxyl-terminal motif to associate with Dlg1 via the PDZ2 and PDZ3 domains (12). In addition, while this interaction was indirect and did not target Dlg1 for degradation in *in vitro* assays, a CRPV SE6 mutant having a truncated carboxyl terminus was unable to bind Dlg1 and was defective for papilloma formation.

Rhesus papillomavirus type 1. Natural infections of rhesus macaques with rhesus papillomavirus type 1 (RhPV-1), which is sexually transmitted and closely related to HPV-16, can result in cervical malignancy. Despite being a high-risk papillomavirus, the RhPV-1 E6 protein lacks any recognizable PBM. Interestingly, Tomaic et al. recently showed that the RhPV-1 E7 protein possesses a class I carboxyl-terminal PBM (-ASRV_{COOH}) that mediates binding to and proteolytic degradation of the PDZ domain-containing polarity protein Par3 (116). Furthermore, an RhPV-1 E7 PBM mutant unable to bind Par3 exhibited a reduced capacity to cooperate with EJ-Ras and transform primary rodent cells. Interestingly, Par3 interacts with Par6 and aPKC to form the Par complex, which in conjunction with the Crumbs and Scribble complexes, represents a key regulator of apical-basal polarity establishment in epithelial cells (85) (Fig. 2). Interference with the function of these evolutionarily conserved cell polarity complexes appears to be of central importance to the papillomavirus life cycle.

(iii) RETROVIRIDAE

Human T-lymphotropic virus type 1. (a) **Tax protein.** Human T-lymphotropic virus type 1 (HTLV-1) is a deltaretrovirus that replicates primarily in CD4⁺ T lymphocytes and causes

T-cell leukemia and lymphoma in adults. HTLV-1 encodes a transcriptional activator protein termed Tax that potently stimulates gene expression directed by the HTLV-1 long terminal repeat (LTR). Tax is the major oncogenic determinant of HTLV-1, and like adenovirus E4-ORF1 and high-risk HPV E6, was first reported by Lee et al. and later by Rousset et al. to have a class I carboxyl-terminal PBM (-ETE_V_{COOH}) (59, 94). The Tax PBM plays a crucial role in cellular transformation as evidenced by its requirement for Tax to cooperate with NF- κ B to transform mouse CTLL-2 T cells and to promote anchorage-independent growth in Rat-1 cells (33, 34). The PBM is also required for Tax-induced proliferation of human T cells and micronucleus formation in HeLa cells, as well as in HTLV-1 virus persistence in a rabbit model (128). *In vitro* assays show that the pleiotropic protein kinase CK2 phosphorylates Tax threonine-351, a crucial residue within the PBM, suggesting that phosphorylation of the PBM may regulate Tax binding to PDZ proteins (5).

Dlg1 was the first PDZ protein identified as a target of Tax (59), and this interaction occurs in HTLV-1-infected T cells and requires the Tax PBM and at least one of the three Dlg1 PDZ domains (108). Dlg1 overexpression inhibits progression of mouse 3T3 cells into the S phase of the cell cycle, and wild-type but not a PBM-mutant Tax protein ablates this Dlg1 activity (108). Consistent with the idea that Tax inactivates Dlg1, Dlg1 is sequestered by Tax within detergent-insoluble complexes in cells (34). Given that the growth-inhibitory activity of Dlg1 is linked to its interaction with the adenomatous polyposis coli protein (APC) tumor suppressor (39), which like Tax requires a carboxyl-terminal class I PBM to bind Dlg1 PDZ domains (67), it may be relevant that a peptide containing the Tax PBM blocks Dlg1-APC complex formation *in vitro*. A more recent study sought to test the importance of Dlg1 inactivation in Tax-induced transformation of interleukin-2 (IL-2)-dependent mouse CTLL-2 T cells (40), where expression of wild-type Tax but not PBM-mutant Tax promotes IL-2-independent growth. In this system, if the crucial transformation function of the Tax PBM is to inactivate Dlg1, then siRNA-mediated Dlg1 depletion should complement the transformation defect of PBM-mutant Tax. However, Tsubata et al. found that Dlg1 depletion fails to enhance transformation by PBM-mutant Tax, though it does augment transformation by wild-type Tax (119). This unexpected finding suggests that in this system, Tax-induced transformation does not require Tax PBM-mediated Dlg1 inactivation and instead requires Tax PBM-mediated functional perturbation of another undetermined cellular PDZ protein target(s) or, alternatively, requires both of these Tax PBM-mediated activities.

A yeast two-hybrid system screen revealed that HTLV-1 Tax binds to the Scribble polarity protein and that this interaction requires the Tax PBM and Scribble PDZ domains 2 and 4 (3). The Tax-Scribble complex was also detected in HTLV-1-infected human T cells, where Tax mislocalized Scribble to puncta, which may reflect Tax sequestration of Scribble within detergent-insoluble complexes (2). Dlg1 blocks T-cell receptor (TCR)-induced activation of NFAT (92, 127), a key regulator of T-cell activation and differentiation (70). Consistent with the fact that Dlg1 and Scribble act in the same polarity and signaling pathways (62), Scribble overexpression also blocked TCR-induced NFAT activation in human T cells, and this

Scribble activity was inhibited by expression of wild-type but not PBM-mutant Tax (3). Also pertinent is that unlike normal T cells, HTLV-1-infected T cells fail to establish proper anterior-posterior polarity (4). This finding hints that Tax binding to Dlg1 and Scribble, which control cell polarity, immune synapse formation, migration, and signaling in T cells (52, 62, 88, 90, 92, 93, 127), may disrupt these normal T-cell processes in order to stimulate cell proliferation and to block host T-cell-mediated viral clearance, both of which could be envisioned to aid the establishment of HTLV-1 persistent infections in T cells.

Sequence similarity between the three PDZ domains of Dlg1 and those of the precursor of interleukin-16 protein (pro-IL-16) led Wilson et al. to demonstrate that the first PDZ domain of pro-IL-16 binds HTLV-1 Tax via its PBM in both human T cells and COS African green monkey cells, where Tax and pro-IL-16 colocalize in the nucleus (126). In COS cells, overexpression of pro-IL-16 promoted cell cycle arrest, and wild-type but not PBM-mutant Tax allowed these cells to reenter the cell cycle, thereby reversing the antiproliferative effect of pro-IL-16. It remains to be determined, however, whether these findings also extend to human T cells.

The yeast two-hybrid system was used to identify six other Tax-interacting proteins: Dlg4, β 1-syntrophin, Lin-7, TIP-1, TIP-2/GIPC, and TIP-40 (94). In addition, a differential display analysis identified the *MAGI-3* gene as a Tax-inducible gene in Rat-1 cells but not in human T cells (78); in human 293T cells, overexpressed wild-type but not PBM-mutant Tax also interacted with MAGI-3 to alter its subcellular localization. A Scribble-related PDZ protein named Erbin forms a complex with the ErbB2 receptor and negatively regulates its ability to activate ERK (11). By screening a human T-cell cDNA library for binding partners of the single Erbin PDZ domain, Song et al. discovered that Erbin also interacts with Tax via the PBM (101). These *in vitro* results were extended to human MCF-7 breast epithelial cells, where endogenous Erbin coimmunoprecipitated with wild-type but not PBM-mutant Tax. The functional consequences of the interactions of Tax with these PDZ proteins are presently unclear.

Interestingly, the PDZ domain-containing ubiquitin E3 ligase PDLIM2 associates directly with Tax and transports it to the nuclear matrix for proteasome-mediated proteolysis, thereby suppressing Tax's transforming activity (129). Binding of Tax to PDLIM2 is not mediated by a PBM-PDZ domain interaction, but rather by multiple regions in Tax and a α -helical motif in PDLIM2 (22).

(b) Envelope glycoprotein. HTLV-1 is transmitted almost exclusively by direct cell-cell contact. Upon stable interaction of an HTLV-1-infected cell with a target cell, the viral Gag protein, envelope (Env) glycoprotein, and RNA concentrate at a specific membrane region at the site of cell-cell contact, whereupon virus is subsequently transmitted to the target cell (37). This specialized cell contact area is referred to as the virological synapse (13, 37), based on its similarity to the immunological synapse formed between immune cells during antigen recognition (7). Prompted by the requirement of the Env cytoplasmic domain in virological synapse formation, a yeast two-hybrid screen with this HTLV-1 domain led to the discovery that the Env glycoprotein possesses a class I carboxyl-terminal PBM that mediates binding to Dlg1 in HTLV-1-in-

fecting primary T cells, where Dlg1 together with viral Env and Gag become clustered at the virological synapse (6). Furthermore, Dlg1 binds to and promotes membrane clustering of the cellular GLUT1 receptor for HTLV-1 via a class I carboxyl-terminal PBM in GLUT1 (130). This observation, together with the observation that cell syncytium formation was additively blocked by siRNA depletion of Dlg1 in both HTLV-1-infected and target human T-cell lines, supports the idea that Dlg1 clusters both HTLV-1 Env and the cellular GLUT1 receptor by a PBM-dependent mechanism at the virological synapse to facilitate cell-to-cell transmission of HTLV-1. A more recent study by Ilinskaya et al. reported that the PBM of HTLV-1 Env additionally functions to stabilize this viral glycoprotein by antagonizing endocytosis-induced protein turnover; however, this PBM activity does not require Dlg1 (38).

Human immunodeficiency virus. Human immunodeficiency virus type 1 (HIV-1) is a lentivirus that causes AIDS, a disease characterized by immune system failure and life-threatening opportunistic infections. A recent study reported that the cellular PDZ protein Dlg1 restricts HIV-1 virion infectivity (83). In both adherent cells and T cells, Dlg1 overexpression and siRNA depletion of Dlg1 reduces or enhances virion infectivity, respectively, with the latter effect correlating with increased viral envelope (Env) glycoprotein levels in both infected cells and virions and with redistribution of Env and Gag proteins to CD63- and CD82-positive vesicles. Additional results linked this Dlg1-mediated inhibition of HIV virion infectivity to an interaction between Dlg1 and the HIV-1 Gag protein. Unlike most other viral proteins that target cellular PDZ proteins, the HIV-1 Gag protein does not encode a PBM and instead the Gag NC domain interacts with the Dlg1 SH3 and I3 domains. These findings identify Dlg1 as a novel antagonist of a late step in the HIV-1 life cycle. Additionally, a yeast two-hybrid study identified a PDZ protein known as PDZD8 that binds to the HIV-1 Gag polyprotein and promotes infection at an early step in the viral life cycle following entry into the cell (30). Again, the association between Gag and PDZD8 does not involve a PBM-PDZ domain interaction, but instead requires a coiled-coiled motif in PDZD8.

(iv) HEPADNAVIRIDAE

Hepatitis B virus. Hepatitis B virus (HBV) is an *Orthohepadnavirus* that causes acute and chronic hepatitis, and the latter is a major risk factor for development of cirrhosis or hepatocellular carcinoma. A recent yeast two-hybrid study reported that the HBV core protein interacts with the PDZ protein GIPC1 (87). This interaction is mediated by a variant class III carboxyl-terminal PBM (-SQAR_{COOH}) in the viral core protein and the single PDZ domain in GIPC1. While it is not yet known whether this *in vitro* interaction occurs in HBV-infected cells or whether this plays an important role in the HBV life cycle, it is intriguing that the PBM of high-risk HPV E6 and HTLV-1 Tax likewise mediate binding to cellular GIPC1 (19, 94). Given that the GIPC1 adaptor protein tethers proteins to myosin VI and also participates in vesicle recycling of membrane receptors, one possible function for the HBV core-GIPC1 complex may be to facilitate transport of HBV capsids from the cytoplasm into the nucleus.

(v) *RHABDOVIRIDAE*

Rabies virus. Rabies virus is a neurotropic virus that causes fatal encephalitis in mammals. The neurovirulence of wild-type rabies virus depends on survival of infected neurons. Attenuated rabies virus strains, on the other hand, trigger neuronal death by apoptosis, which potentiates an immune response that limits viral replication and spread. A recent study showed that survival or death of rabies virus-infected neurons depends on which cellular PDZ proteins are able to bind the class I PBM at the carboxyl terminus of viral envelope glycoprotein G (86). The wild-type G protein PBM (-QTRL_{COOH}) from virulent rabies virus interacts with the PDZ domain of the serine-threonine kinase MAST2 to mediate both antiapoptotic AKT activation and neuronal survival, whereas a G protein from attenuated rabies virus with a point mutant PBM (-ETRL_{COOH}) displayed expanded PDZ interactions that included Dlg2, MUPP1, and the tyrosine phosphatase PTPN4, the latter of which was found to promote neuronal death. Consistent with the role of PTPN4 in cell death, siRNA depletion of PTPN4 ablated cell death induced by the point mutant G protein. These findings provide a molecular explanation for the attenuation of rabies virus by revealing a PBM mutation that allows the viral G protein to bind a cellular PDZ protein that triggers neuronal death.

(vi) *ORTHOMYXOVIRIDAE*

Influenza A virus. Influenza A virus infects the respiratory tracts of birds and mammals. Influenza A virus encodes the NS1 protein, which is an important virulence determinant and whose general function is to counteract antiviral mechanisms of the innate immune system (26, 51). A large-scale sequencing study of influenza A virus isolates identified a PBM at the carboxyl terminus of NS1 and further showed that the avian and human viruses display distinct PBM sequences (77). While both avian and human viruses encode a class I PBM (-X-S/T-X-Φ_{COOH}), the avian virus PBM has the consensus sequence ESEV (78% of viral isolates) whereas that of the human virus PBM is RSKV (85% of isolates). The same study also examined *in vitro* binding of recombinant full-length NS1 proteins to 123 different individual cellular PDZ domains and demonstrated that ESEV and RSKV PBMs possess distinct binding properties (77). Subsequent studies showed that the influenza A NS1 PBM functions as a virulence determinant in mice, where infections with H1N1 or H7N1 recombinant viruses encoding an avian ESEV PBM produced more severe disease in mice than did infections with recombinant viruses encoding a human RSKV PBM (41, 102). An additional study which examined H5N1 recombinant viruses failed to detect a role for the NS1 PBM in virulence, indicating that other viral determinants may either mask or regulate this PBM activity during an infection (133).

GST pulldown assays were used to show that the ESEV but not the RSKV PBM specifically mediates association *in vitro* with at least five cellular PDZ proteins: Scribble, Dlg1, MAGI-1, MAGI-2, and MAGI-3 (61, 112). A functional study focused on the interaction between the NS1 ESEV PBM and Scribble and found that binding was direct and required two

Scribble PDZ domains (61). A recombinant influenza A virus expressing an avian virus NS1 protein with the ESEV PBM replicated to approximately 4-fold higher levels in mammalian cells than did the same virus expressing NS1 with a mutant ESEA PBM unable to bind Scribble. In addition, NS1 with the ESEV PBM relocalized Scribble from the plasma membrane into cytoplasmic puncta and also protected virus-infected cells from apoptosis. The observation that siRNA-mediated depletion of Scribble abrogated this protection demonstrates that the NS1 ESEV PBM functions in part to block the proapoptotic function of Scribble during a viral infection.

A recent study found that Dlg1 colocalizes with both Scribble and NS1 containing an ESEV PBM in cytoplasmic puncta of influenza A virus-infected cells (25a). This study also observed that infections with the ESEV NS1 virus resulted in TJ disruption, which was similarly seen by siRNA depletion of either Dlg1 or Scribble, suggesting that the ESEV PBM-mediated binding of NS1 to Scribble and Dlg1 functions to disrupt cellular TJs and that this effect may contribute to viral pathogenesis. In the future, it will be important to evaluate roles for the interactions of the ESEV PBM with the PDZ proteins MAGI-1, MAGI-2, and MAGI-3 during a viral infection, as well as to identify cellular PDZ proteins that bind to the human RSKV PBM.

A recent study used the yeast two-hybrid system to demonstrate that the PDZ protein PDLIM2 also associates directly with ESEV NS1 (131). The interaction is specific because PDLIM2 failed to bind NS1 with an RSEV PBM. This work characterized the interaction between the single PDZ domain of PDLIM2 and the NS1 ESEV PBM by solving the crystal structure of the PDLIM2 PDZ domain complexed with the NS1 carboxyl-terminal 6-amino-acid residues that include the ESEV PBM. The functional importance of this complex to the viral life cycle or virus-induced disease has not been determined.

(vii) *FLAVIVIRIDAE*

Tick-borne encephalitis virus. Tick-borne encephalitis virus (TBEV), an arthropod-borne flavivirus, causes a febrile illness in humans that often progresses to encephalitis, with mortality rates as high as 20 to 30%. The TBEV NS5 protein is a methyltransferase and RNA-dependent RNA polymerase involved in viral genome replication (64). Yeast two-hybrid and GST pulldown assays revealed that an internal PBM within the methyltransferase domain of TBEV NS5 binds the fourth PDZ domain of Scribble (125). NS5 expressed from a plasmid vector in mammalian cells coimmunoprecipitates with Scribble, and an immunofluorescence analysis indicates that this interaction directs NS5 to the plasma membrane. Importantly, the binding of NS5 to Scribble inhibits interferon-mediated JAK-STAT signaling, demonstrating that this interaction functions at least in part to counter innate immunity, though the mechanism responsible for this activity is yet to be determined.

In vitro binding assays showed that the TBEV NS5 additionally utilizes its internal PBM to bind to the cellular TJ-associated PDZ protein ZO-1 and also the neuron-specific RIMS2 PDZ protein (14). Results from immunofluorescence assays with mammalian cells expressing TBEV NS5 protein from a plasmid vector suggest that this viral protein associates with ZO-1 at the plasma membrane. The functional significance of

TABLE 2. Consequences ascribed to the interactions of viral proteins with cellular PDZ proteins

Virus	Consequences
Adenovirus	TJ disruption, cell polarity loss, PI3K activation, viral replication, transformation/tumorigenesis
HPV	TJ disruption, cell motility, block apoptosis and TGF- β signaling, transformation/tumorigenesis
CRPV	Papilloma formation
RhPV-1	Transformation
HTLV-1	NFAT activation, pro-IL16 inhibition, virological synapse formation, viral persistence, transformation
HIV	Virion infectivity
Rabies virus	Block apoptosis, viral virulence
Influenza A virus	Block apoptosis, TJ disruption, viral replication, viral virulence
TBEV	Inhibit host innate immune responses
SARS virus	Delay TJ formation and cell polarity establishment

the complex formed between TBEV NS5 and ZO-1, or the putative RIMS2 target, is not yet known.

Dengue virus. Dengue virus (DV), another arthropod-borne flavivirus, causes Dengue fever and the more severe Dengue hemorrhagic fever in tropical and subtropical regions. *In vitro* binding assays showed that, similar to TBEV NS5, DV NS5 uses an internal PBM to bind to ZO-1 (14). Interestingly, unlike TBEV NS5, DV NS5 appears to associate with ZO-1 in the nucleus.

(viii) CORONAVIRIDAE

SARS coronavirus. The severe acute respiratory syndrome (SARS) coronavirus is the causative agent of SARS. The E envelope protein of SARS coronavirus contains a carboxyl-terminal class II DLLV PBM that may mediate binding to the single PDZ domain of cellular PALS1 (110), a key component of the Crumbs polarity complex that controls tight junction formation and apical-basal polarity establishment in epithelial cells (Fig. 2). In SARS-infected epithelial cells, the viral E envelope protein redistributes PALS1 to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) and the Golgi region. This altered PALS1 localization is associated with delayed TJ formation and polarity establishment in SARS-infected MDCK epithelial cells, hinting at a potential role in the pathology of lung epithelia observed for SARS patients.

PERSPECTIVES

It is remarkable that PBMs from diverse families of pathogenic viruses target many of the same cellular PDZ proteins (Table 1; Fig. 2). Given that just four residues at the carboxyl terminus of a protein can constitute a functional PBM, appending a PBM at the end of viral proteins has posed only a limited challenge to viral evolution. The insertion of a PBM at internal locations of some viral proteins, such as the NS5 proteins of TBEV and Dengue virus, and the finding of PBM swapping from the E6 to E7 protein of RhPV-1 further illus-

trate the evolutionary pressure on viruses to bind and perturb the function of key cellular PDZ proteins. Thus, it is almost a certainty that other viruses not listed in Table 1 also encode PBMs, and we anticipate that future studies will identify these viruses and their cellular PDZ targets.

Findings summarized here reveal that diverse families of viruses target similar cellular PDZ proteins. This observation parallels a well-known common theme in virology in which many otherwise unrelated proteins from DNA and RNA tumor viruses share common abilities to target the cellular pRb and p53 tumor suppressors. For example, simian virus 40 (SV40) large T antigen, Ad E1A and E1B, and HPV E7 and E6 target both pRb and p53, whereas mouse polyomavirus large T antigen and hepatitis C virus (HCV) NS5B target pRb and HBV X, HTLV-1 Tax, and HCV NS5A target p53. These interactions serve to dysregulate the cell cycle and inhibit apoptosis, indicating that such effects are fundamentally important to the replication of many viruses. Likewise, the many viral PBMs that target common PDZ proteins, such as Dlg1, Scribble, and the MAGI proteins, suggest that the cellular processes regulated by these PDZ proteins, especially cellular polarity and apoptosis (see below), are of fundamental importance to viral replication.

Although the interactions of viral proteins with their cellular PDZ protein targets have many different functional consequences (Table 2), some common patterns emerge. For example, viral proteins commonly target PDZ proteins that control cell polarity establishment and TJ formation (Fig. 2), and most of these cellular proteins are members of the MAGUK family (Fig. 1). Consistent with functional inactivation of these cellular targets during viral infections, cells expressing PBM-containing proteins encoded by Ad, HPV, influenza A virus, and SARS coronavirus show loss of TJ integrity and cell polarity (Fig. 2; Table 2). This observation argues that these activities are of central importance to virus-host interactions. In this regard, disruption of the TJ barrier in epithelial and endothelial cells might benefit viruses by enhancing local spread, systemic dissemination, and transmission of viruses. TJ disruption

might also contribute to viral virulence and disease by increasing tissue damage and/or heightening inflammatory responses, the latter of which was suggested for the NS1 protein of influenza A virus (41). Loss of cell polarity, on the other hand, could be envisioned to block polarized cellular responses, such as immune synapse formation required for host immune surveillance, and/or to enhance virus-mediated cell polarization responses, such as the virological synapse formation required for efficient viral spread.

Another striking observation is that viral protein targeting of cellular PDZ proteins commonly functions to dysregulate apoptotic pathways. For example, studies show that PBM-dependent interactions of rabies virus G protein with PTPN4 and of influenza A virus NS1 protein with Scribble modulate apoptosis in infected cells. In addition, a conserved activity among Ad E4-ORF1 proteins is PBM-dependent activation of the PI3K signaling pathway, which functions to inhibit apoptosis, as does the PBM of high-risk HPV E6. Given the latter observations, an intriguing possibility is that inhibition of apoptosis represents a common function for the PBM of tumor virus oncoproteins. Thus, viral PBMs may play a central role in regulating apoptosis, which is well known to influence viral replication and pathogenesis, as well as tumorigenesis.

Evidence suggests that cellular PDZ proteins also indirectly influence viral infections. For example, HCV is a flavivirus that infects an estimated 180 million people worldwide, in many cases resulting in fibrosis or cirrhosis of the liver. A PDZ protein known as PDZK1 facilitates HCV entry into hepatocytes through its association with scavenger receptor class B type 1 (SR-B1), which is a cellular receptor for HCV (17). Despite its key role in HCV entry, however, PDZK1 apparently is not directly targeted by HCV. A recent study also reported that the PDZ protein PDZD8 suppresses herpes simplex virus 1 (HSV-1) replication (31), though PDZD8 has not been shown to bind an HSV-1 protein. Few studies have reported a role for PDZ proteins in infections by the *Herpesviridae* family, so this may be a particularly productive area of investigation.

Future research will provide insights into the mechanisms whereby the targeting of cellular PDZ proteins by viral PBMs benefits viral replication, dissemination in the host, or transmission to new hosts. This research may lead to the development of novel therapeutics to prevent viral infections and to treat viral diseases.

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Ronald T. Javier received his B.S. degree in Biochemistry and his Ph.D. degree in Microbiology and Immunology from the University of California at Los Angeles. He completed his postdoctoral studies at Princeton University. His current position is Associate Professor in the Department of Molecular Virology and Microbiology at Baylor College of Medicine. Dr. Javier's research interests include viral pathogenesis and oncogenesis. He studied the pathogenesis of herpes simplex virus infections for his Ph.D. thesis research and mechanisms of mammary tumorigenesis induced by human adenovirus type 9 for his postdoctoral and current research.

Andrew P. Rice received his B.A. degree in Biology from the University of California at Santa Cruz and his Ph.D. degree in Biology from Brandeis University. He carried out postdoctoral studies at the University of Cambridge and the Imperial Cancer Research Fund (now Cancer Research UK). Following his postdoctoral studies, he was Staff Scientist at Cold Spring Harbor Laboratory before moving to Baylor College of Medicine. His current position is the Nancy Chang Professor in the Department of Molecular Virology and Microbiology at Baylor College of Medicine. Dr. Rice's research has involved the study of virus-host interactions from the time of his Ph.D. thesis research to the present. His current research interests include virus-host interactions in HIV-1 and influenza virus systems.