Upsetting the Balance: When Viruses Manipulate Cell Polarity Control

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Abstract

The central importance of cell polarity control is emphasized by the frequency with which it is targeted by many diverse viruses. It is clear that in targeting key polarity control proteins, viruses affect not only host cell polarity, but also influence many cellular processes, including transcription, replication, and innate and acquired immunity. Examination of the interactions of different virus proteins with the cell and its polarity controls during the virus life cycles, and in virally-induced cell transformation shows ever more clearly how intimately all cellular processes are linked to the control of cell polarity.

Introduction

The control of cell polarity is a fundamental characteristic of multicellular organisms. Correct cell polarity leads to the ordered orientation of cells, both internally and with respect to one another, that is essential for the development of ordered systems, from intracellular organelles such as the endoplasmic reticulum, to the highly complicated networks of the brain. This being so, it is inevitable that the mechanisms and controls of cellular polarity will both affect and be affected by the presence of intracellular parasites such as viruses.

The control of normal cell polarity and tissue structure essentially defines most multicellular organisms, and its loss or misregulation essentially defines most tumors [1]. Cell polarity can be divided into four main types (shown in Fig. 1) that are highly conserved throughout evolution, with many vital regulatory elements being conserved from *Drosophila melanogaster* and *Caenorhabditis elegans* through to mice and humans [2]: *apico-basal polarity* (ABP), which describes the orientation of cells perpendicular to the basement membrane; *planar cell polarity* (PCP), describing their orientation parallel to it; *migrating cell polarity* (MCP), defining the leading and lagging edges of a migrating cell; and *cell division polarity*, defined by the difference between symmetric and asymmetric cell division in tissue differentiation.

Additional, more tissue-specific, forms of polarity control include *neuronal cell polarity*, defining the direction of neuronal signal transmission, and immune cell polarity (ICP) induced in activated cells of the immune system, such as T lymphocytes, macrophages or dendritic cells [3].

PCP is controlled by factors in the non-canonical Wnt/PCP pathway and by the interplay of a large number of signaling pathways in response to mechanical and biochemical forces [4], and PCP is established through the asymmetric and mutually exclusive localization of a highly conserved core set of proteins. These include the Scribble (Scrib) complex proteins, Scribble (Scrib) and Discs Large 1 (Dlg1), which are also critical regulators of ABP (see below), and which may represent the intersection of PCP and ABP controls [5]. PCP is essential for oriented cell division, collective cell migration and the development and function of many tissues [6].

ABP is a defining characteristic of epithelial cells and is also controlled by the intersection of several pathways, but at its core is a multi-macromolecular interaction network (Fig. 2) of three distinct protein complexes: the Scrib, Partitioning defective (Par) and Crumbs (Crbs) complexes [2,7,8]. These connect cell polarity with the control of cell–cell contacts via multiple scaffolding proteins at tight junctions (TJs) [9] and cadherins at adherens junctions (AJs) [10,11]. They also connect ABP with cell proliferation
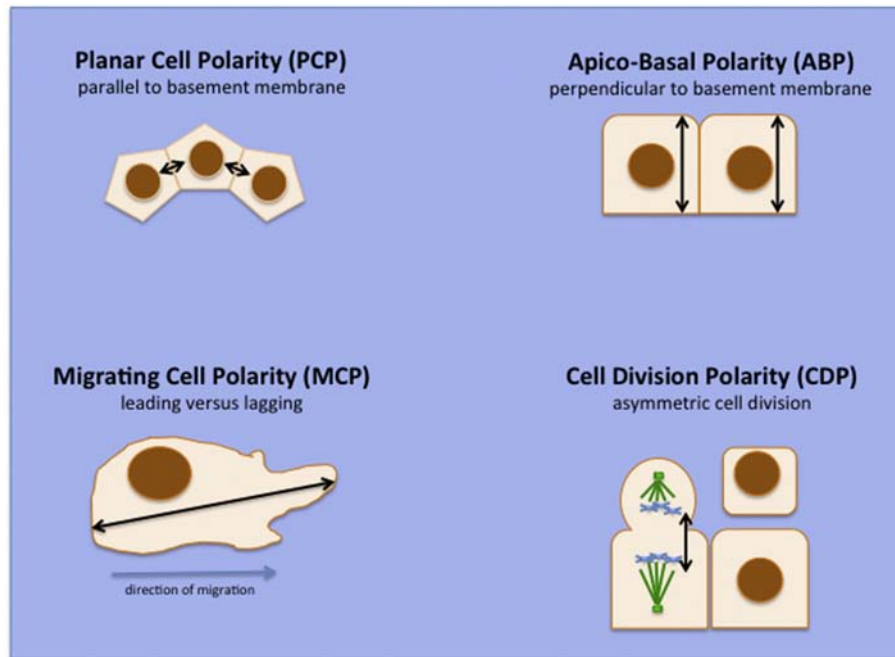
Fig. 1. Some types of cellular polarity control.

control through mitogen-activated signaling pathways [12,13], the control of cell size through the Hippo pathway [14,15], and directional cell migration and apoptosis through small GTPase signaling [16–18]. The function of this network is critically dependent on a number of factors, including precise regulation of the expression level and post-translational modifications of the network components [2]. ABP regulation is fundamentally dependent on the mutually exclusive localization of different network components, which depends, at least in part, upon differential phosphorylation of the Scrib and Par complex proteins, some of which is regulated through the atypical protein kinase C [19,20]. This differential localization of components divides the cell into different zones, each defined by the presence of one of the three complexes of the pathway (Fig. 2 and other chapters in this volume); perturbation of the correct spatio-temporal localization of the individual components has profoundly deleterious effects on the functioning of the whole complex.

Studies in lower eukaryotes, such as *Drosophila* and *C. elegans*, show that perturbing any one of the proteins that function in this network can have very adverse effects on the overall functioning of the ABP pathway and have defined many of these proteins as potential tumor suppressors [21]. However, in higher eukaryotes, the picture is more confused; although expression of many polarity regulators is lost in tumors [22,23], it is often unclear whether this is a cause or a consequence of the tumor development.

However, in recent years, studies have shown that many human viruses, both oncogenic and not, target certain key polarity regulators, demonstrating the fundamental involvement of the ABP control network not only in different viral replication strategies, but also in in tumor suppression and tumorigenesis. Targeting of many of these cell polarity regulators by oncogenic viruses, such as human papillomaviruses (HPV), has focused attention on the cell proliferative regulating activities of these proteins, and how this is connected to the control of polarity. However, many non-oncogenic viruses target many of the same pathways as a means of avoiding immune detection, both through innate and acquired mechanisms. This therefore highlights the incredible multifunctional nature of these cell polarity regulators and emphasizes why viruses targeting these pathways can achieve multiple aims, all of which contribute to a successful virus infection: the generation of a replication-permissive environment, and the avoidance of immune detection. In rare cases, the combination of such perturbation of cellular homeostasis with a long-term persistent infection can give rise to events that ultimately result in malignancy.

Tumor Viruses and Polarity Control

Tumor viruses have been estimated to cause up to 12% of all human cancers [24,25]. These viruses, as stated above, are from widely differing evolutionary backgrounds and cause many different malignancies.
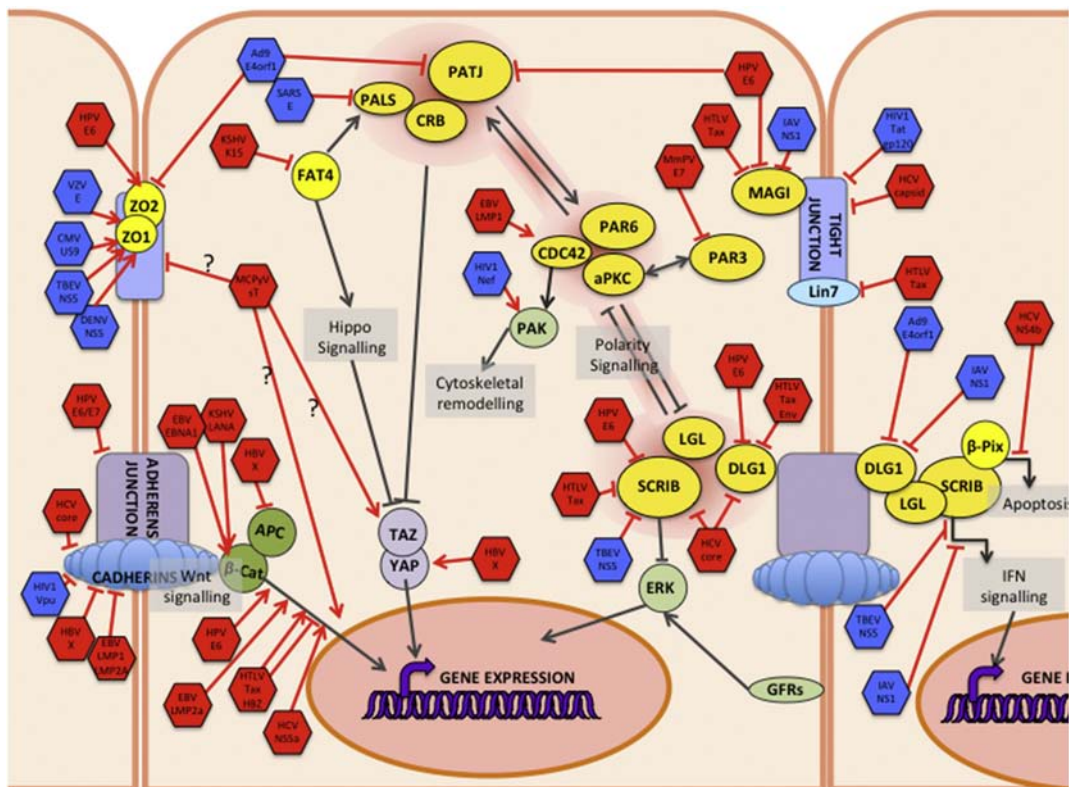
Fig. 2. Cell polarity pathways are targeted by diverse human viruses. Interplay between the Scribble (SCRIB), PAR, and Crumbs (CRB) complexes is central to the control of cell polarity. These link to the TJ and AJs that control cell–cell contacts, and to the Wnt signaling pathway, through the SCRIB complex and cadherins. The CRB complex links to cell growth and proliferation through the Hippo signaling pathway and YAP/TAZ. The SCRIB complex also links to apoptotic pathways through β-PIX, and to growth factor signaling-induced proliferation through ERK, and to interferon-activated innate immune responses through STAT activation. The virus proteins are indicated by hexagons: red for cancer-associated virus proteins or blue for non-cancer causing.

However, they commonly attack the same pathways, targeting, either directly or indirectly, some of the central elements of polarity control [26,27] (see Fig. 2). The purpose of this targeting, from the point of view of the virus, is to render the cellular environment more conducive to viral replication, and any resulting malignancy is a rare event and often prevents an effective viral life-cycle. This emphasizes the importance of host cell polarity regulation to the replication strategy of the virus.

The majority of tumor viruses exhibit long-term persistent infections in the host, infecting precursor cells and using the cellular differentiation program for their replication. Examples include B-cell precursors infected by Epstein–Barr virus (EBV), endothelial precursors infected by Kaposi's sarcoma herpesvirus (KSHV), and epithelial precursors infected by the HPVs [28–30]. Long-term or persistent infections may continue for years and in some cases are lifelong, allowing the viral oncoproteins, or the oncogenic by-products of the viral life cycles, to interact with the cellular environment over long periods and to initiate the processes that lead eventually to malignant transformation and cancer.

HPV

HPVs are major carcinogens, being responsible for around 5% of all human cancers worldwide [31]. HPV-related malignancies are characterized by their addiction to the two viral oncoproteins, E6 and E7, which contribute directly to the development and maintenance of the tumor and of cells derived therefrom [32,33], even after many years in tissue culture [34]. They act together to immortalize keratinocytes [35], which are the natural target cells of the virus, and have been shown to cause tumors in transgenic mouse models [36–38]. Thus, E6 and E7 have the potential to be excellent therapeutic targets [39].

HPV replication occurs in terminally differentiating keratinocytes and is completely dependent upon the differentiation program of the epithelium [40]. The E6 and E7 proteins cooperate to reactivate the cell cycle in these cells; E7 induces cell cycle re-entry, while E6 abrogates the resulting pro-apoptotic responses [39,41,42]. While usually resulting in a productive infection of a few months' duration, this perturbation of cellular

controls can initiate the steps that lead eventually to malignant transformation.

Polarity targeting by HPV E6

Of the nearly 200 known papillomavirus types, only a few high-risk HPV types are defined as cancer causing and, of these, HPV types 16 and 18 are the most clinically important. These viruses all have a PDZ (*P*SD-95/*D*lg1/*Z*O1)-binding motif (PBM) at the C-terminus of their E6 proteins, which is largely absent from those of low-risk viruses, which cause only benign lesions. The high-risk E6 proteins are thus able to bind to a number of polarity control proteins that contain PDZ domains. These include core components of ABP cell polarity control—hDlg1, hScrib, and PATJ—and the TJ protein MAGI-1, which are targeted by E6 for ubiquitin-mediated degradation at the proteasome, thus disrupting the stoichiometric equilibrium of these complexes [43–46]. However, it is becoming very clear that all HPV E6 PBMs are not equal, and that subtle differences in the exact amino acid sequence of the PBM can markedly alter the substrate selection, as can be seen from Table 1, the HPV E6 PBMs, whilst all having a core consensus PBM, have significant variation in the non-canonical amino acid residues. Indeed these differences can profoundly affect substrate selection, and the molecular basis for these differences has been extensively explored [47–49], showing the effect that even minor changes can have; for example, HPV-16 E6 was shown to preferentially interact with hScrib, and HPV-18 E6 with Dlg, and swapping the final amino acid also swaps these preferences [50]. More recently, the greater functional flexibility of the E6 PBM (i.e., the greater the number of different PDZ domain-containing proteins that it can bind) has been found to correlate with the degree of association of that HPV type with cervical cancer [51]. Interestingly, all of the PBMs tested in that study, including those from HPV types rarely (HPV-26, HPV-66), or never (HPV-40), found in cancer, were able to interact with hDlg, suggesting that this is a fundamental requirement for the replication of this group of HPV types. Interaction with hScrib and the TJ protein ZO2, however, was limited to the PBMs of virus types with a strong cancer association (HPV types 16, 18, 31, 33, 35, 51), suggesting that the greater disruption of the Scrib complex caused by the combined loss of hScrib and hDlg1, particularly in the context of a long-term persistent infection, has a greater risk of disrupting cellular polarity in a manner that favors malignant transformation. Indeed, this has been recently confirmed in cellular transformation assays [52]. Human cervical keratinocytes exogenously expressing activated Ras, plus HPV-16 wild-type E6 and E7, are capable of anchorage-independent growth and are tumorigenic in nude mice. Expression in this system of an E6 defective in PDZ-binding prevents this, but the tumorigenic phenotype can be slightly rescued by the individual ablation of DLG1 or DLG4 (also known as PSD-95) and partially rescued by ablation of either hScrib, MAGI-1 or PAR3. However, ablation of hScrib plus DLG1 and DLG4, or hScrib plus MAGI1 and PAR3 in this system actually enhances the tumorigenic phenotype above that of cells expressing the wild-type HPV-16 E6 [52], demonstrating the pivotal importance of hScrib targeting in HPV-induced malignancy.

It is interesting to note that in the rhesus papillomavirus (MmPV1), which causes cervical cancer in rhesus macaques (*Macaca mulata*), E6 has no PBM but instead the E7 oncoprotein has a PBM [53]. This has a very different sequence from that of the HPV E6 PBMs and structurally would appear to be quite diverse [47,49]. Not surprisingly, proteomic and biochemical analyses showed that it binds to a different polarity regulator, the PAR3 protein [53], part of the PAR complex. Thus, MmPV1 targets the same overall polarity regulatory pathway as HPVs, and through the same mechanism, but using a different viral protein and with different cellular partners, demonstrating a marked evolutionarily conserved requirement for these viruses to target this pathway for viral replication, and most likely for their ability to cause cancer.

Evolutionary conservation of the polarity proteins is also illustrated in a new animal model for HPV E6 activity, where HPV E6 can bind to the *Drosophila* MAGI protein in a PBM-dependent fashion, and, if exogenously supplied with a human UBE3A (E6AP) ubiquitin-protein ligase, can induce its degradation [54]. Intriguingly, this model shows that a key factor in HPV-induced malignancy is the E6AP, which is used by E6 for substrate degradation, but is also required for E6 stability [55]. The *Drosophila* E6AP lacks the E6 interaction motif, and hence, human E6AP is required for E6 to exert a phenotype in flies. Notably, although both Dlg and MAGI would appear to be perturbed in this model by E6, it is MAGI that appears to play the critical role in the tumor phenotype [54].

Cell polarity and the HPV life cycle

The life cycle of HPVs is completely dependent on the differentiation program of the infected epithelium, and studies of infection in organotypic raft cultures show that viruses defective in binding the polarity proteins produce fewer progeny virus and their genomes are more unstable and prone to integration in the host DNA [56–58].

The reason for loss of correct virus genome segregation in the absence of the E6 PBM is as yet unknown, although it may be related to the levels of cell proliferation in the lesion. The E6 PBM plays a

Table 1. The PBMs of viral proteins targeting cell polarity and their potential phospho-control. Many of the viral proteins that target cell polarity control do so by binding the PDZ domains of polarity control proteins through a PBM. The table shows the sequences of such viral PBMs, their cellular targets, and the potential of the PBM to be modified by phosphorylation. The T/S amino acid residues in green have been shown to be phosphorylated by the indicated kinase [76,263]; those in blue have consensus kinase recognition sites, but phosphorylation has not been formally demonstrated.

Virus protein	PBM sequence	Cellular target protein	Outcome of interaction	℗-Site
HPV-16 E6	SSRTRRETQL	Dlg1,	AJ/ABP disrupted	AKT
HPV-18 E6	RLQRRRETQV	hScrib	cell cycle ↑	PKA
HPV-31 E6	WRRPRTETQV	MAGI, PATJ,		AKT
HPV-33 E6	WRSRRRETAL	MUPP, ZO2	TJ disrupted	PKA
HPV-66 E6	TSRQATESTV	Dlg1		CK2 AKT
HPV-26 E6	RPRRQTETQV			CK2 AKT/PKA
HPV-40 E6	EKGQRSETLC	Dlg1	AJ disrupted	CK2 AKT
MmPV-1 E6	IVCPSCASRV	PAR3		None
HCV Core	RRSQSRESQC	E-cad, Dlg1, hScrib ↓	AJ & TJ disrupted	CK2 AKT
HCV NS5A	MLVWRDDLVV	?	AJ disrupted	None
HCV NS4B	INEEDCSTPC	hScrib	Apoptosis ↓	None
HTLV-1 Tax	SEKHFRETEV	Dlg1, hScrib, MAGI, Tax1BP3, Lin7	AJ/ABP disrupted cell cycle ↑	CK2
HTLV-1 Env	YSLINPESSL	Dlg1	AJ disrupted	None
Ad9 E4ORF1	FPSVKIATLV			
	-monomer	MUPP, MAGI, ZO2	TJ disrupted	None
	-trimer	Dlg1	Cell cycle ↑	None
Influenza A				
- avian	KMARTIESEV	Dlg1, Scrib, MAGI, PDLim, Dlg4	Apoptosis ↓ / Immune evasion	None
- human	KMARTARSKV	?		None
TBEV NS5	WELRLESSII	hScrib	Immune evasion	CK2 AKT
WNV NS5	DTIVVEDTVL			None
DENV NS5	EEEEEAGVLW	ZO1	TJ disrupted	None
SARS-CoV E	SSEGVPDLLV	PALS	?Virus entry/budding	None
MERS-CoV E	KPPLPPDEWV	?	?	None
RaV G				
- virulent	SYKSGGQTRL	MAST2	↑Akt →cell survival	None
- attenuated	SYKSGGETRL	Dlg2, MUPP, PTPN4	↑Apoptosis→virus release	None

key role in expanding the number of proliferating cells (i.e., those capable of replicating viral DNA), by targeting the polarity proteins to uncouple the link between cell polarity control and cell proliferation control. The orderly asymmetric cell division seen in the normal differentiating epithelium is maintained by strict control of mitotic spindle orientation, maintenance of ABP, and correct formation of the cell–cell junctions [59,60]. The HPV E7 protein inappropriately stimulates cell cycle progression in the epithelial mid-layer, while E6 perturbs the Scrib and Par complexes to expand the population of infected cells capable of replicating the viral DNA. Expression of E7 alone has been shown to induce the formation of aberrant spindle poles [61,62], while disruption of Dlg and the Par complex also perturbs mitotic spindle orientation [63,64], all of which

contributes to enhanced symmetrical cell division, thus expanding the population of replication-competent cells and accounting for the disordered epithelium observed in viral lesions.

As noted above, cell–cell communication through cell junctions is also affected in HPV-infected cells. MAGI-1 is targeted for degradation by high-risk HPV E6 proteins [65], possibly to counteract the signaling role of non-junctional MAGI-1 in the induction of apoptosis [66]. Indeed, when a mutant MAGI-1, which was no longer susceptible to E6-induced degradation, was re-expressed in HeLa cells, it was found to induce cell growth arrest and apoptosis [67]. On the other hand, E6 induces the stabilization of the TJ protein ZO-2, which appears to increase cell proliferation and enhance the wound healing ability of HeLa cells [68,51]. In addition, both E6 and E7

target AJs by downregulation of E-cadherin, at least partly through the induction of Cdc6 [69–72], thus increasing proliferative signaling. Potentially, this disruption of cell junction control, combined with enhanced proliferation and decreased apoptotic signaling, could also contribute to the disordered epithelial structure characteristic of HPV lesions and, further, increase the risk of pro-oncogenic mutations arising in those lesions.

Regulation of PBM/PDZ binding

It is becoming very clear that PBM/PDZ binding, while allowing proteins a wide flexibility in choice of binding partners, is subject to a greater level of specificity and control than was originally thought [73]. The steric and electrostatic characteristics of the respective PBM and PDZ sequences give an irreducible level of specificity to the interactions of the papillomavirus PBMs [47–49]. However, the HPV PBMs are also bi-functional: there is a phospho-acceptor site embedded within the PBM, which, when phosphorylated, prevents PDZ binding [74] and instead confers affinity for proteins of the 14-3-3 family [75]. Examples of phospho-acceptor sites on the PBMs of diverse viral proteins are shown in Table 1. These proteins link to a variety of different pathways, including Hippo and p53 regulation, while kinases such as AKT and PKA have been implicated in regulating E6 interaction with the cell polarity regulators [76]. Recent data also suggest that the E6 PBM may be phosphorylated by DNA damage response kinases, allowing E6 to modulate p53's transcriptional transactivation activity [77]. It seems likely that this would reduce p53's apoptotic response, while allowing the cellular DNA damage repair enzymes to enhance viral genome replication [78,79]. Taken together with studies that show phospho-regulation of Dlg for E6 regulation [80,81], these findings highlight a complex pattern of phospho-regulation controlling the E6 PBM interactions. Perturbation of these controls is likely to have profound consequences for successful viral life cycles, and for the potential progression to malignancy.

HPV-induced malignancy and cell polarity

As mentioned above, the productive HPV life cycle occurs in the differentiating squamous epithelium: the virus infects cells in the basal layer of the stratified epithelium and progeny virions are shed as the surface layer of cells sloughs off. There is considerable debate surrounding the identity of the cells that are subject to malignant transformation: are they squamous cells in which a normally productive infection has stalled and become persistent? or are they cells that do not stratify, such as the columnar cells of the simple epithelium of the endocervix? It is clear that the majority of cervical

($>$99%) and anal ($>$90%) tumors occur at the transformation zone between the stratified and columnar epithelia [82], and many cervical tumor cells have an embryonic stem cell expression signature [83]. It has been suggested that many cervical tumors may have their origin in the cuboidal cells of the squamocolumnar junction: these cells are more accessible than the endocervical cells; they are highly susceptible to infection by HPV, but are unable to stratify and permit a productive infection; and they are located in an anatomical site that appears to be somewhat immune-privileged. Thus, they appear to be convincing candidates for malignant transformation [84,85], and interestingly, a similar population of cells has been described at the anorectal junction [84], where HPV is also a potent carcinogen. However, other studies suggest that they arise in a population of stem cells, known as reserve cells, that maintain both stratified and columnar epithelia, depending upon tissue context [86,87,30]. Interestingly, while the majority of HPV-16-induced cervical cancers are derived from the squamous cells of the ecto-cervix, HPV-18 is found in a very high proportion of adenocarcinomas [88], which would be consistent with infection of the columnar epithelium of the endocervix. These differences may reflect the finding that E6 PBMs from different HPV types have distinct binding profiles with respect to their cellular PDZ-containing targets, many of which are polarity control proteins [51], and it would be interesting to further determine whether the E6 PBM has any role in the frequency with which different HPV types are found associated with adenocarcinomas.

Studies in transgenic mice have shown that the E6–PDZ interaction is required for the ability of E6 and E7 to induce hyperplasia and tumors in the skin and in the cervix [89,90], suggesting that deregulation of polarity control contributes to malignant transformation. This is further confirmed by the finding that E6 proteins mutated in the PBM lose the ability to induce an epithelial-to-mesenchymal transition (EMT) in keratinocytes and fail to cooperate with E7 in inducing cell transformation in certain *in vitro* settings [91]. E7 downregulates E-cadherin expression by epigenetic modification [70] and E6 also has a downregulatory effect, probably through the degradation of PDZ domain-containing polarity complex proteins leading to the perturbation of cell–cell adhesion complexes [91,92].

Up to 20 different PDZ domain-containing targets of high-risk E6 proteins have been described [93], many of them targeted by E6 for ubiquitin-mediated degradation, and it is not clear which of these losses is/are associated with the induction of malignancy. Dlg1 was the first PDZ-containing target of HPV E6s to be identified [43] and seemed for some years to be a likely candidate, but recent work suggests that E6

PBMs from many HPV types can bind to Dlg1, regardless of the degree of association with cancer [51]. As shown in Fig. 3, this may point more to this association being an adaptation for the viral life cycle and replication at mucocutaneous anatomical sites, rather than to an association with malignancy [94], and suggests that the ability to target hDlg1 may be a necessary but not sufficient feature of cancer-causing HPV types. Other E6 PBM degradation targets that have also been validated *in vivo* [44,95], such as MAGI-1 and hScrib, are also associated with polarity control, and the ability to bind to hScrib appears to be confined to those HPV types with highest cancer risk [49]. The key element here appears to be the degree of flexibility of the E6 PBM,

with the ability to bind multiple PDZ-containing cell polarity regulators conferring the ability to target multiple signaling pathways.

Interestingly, it has recently been shown that hScrib expression in HeLa cells is required to maintain E6 expression levels, through hScrib regulation of mTORC signaling [96]. In the development of HPV-induced tumors, disruption of polarity control appears to drive malignancy, with both hDlg1 and hScrib being mislocalized, and often overexpressed, in medium- to high-grade lesions [97,98]. This suggests that in certain cellular locations, both hDlg1 and hScrib might have pro-oncogenic properties: studies that ablated each protein individually would seem to support this [96,99], and this effect has also been
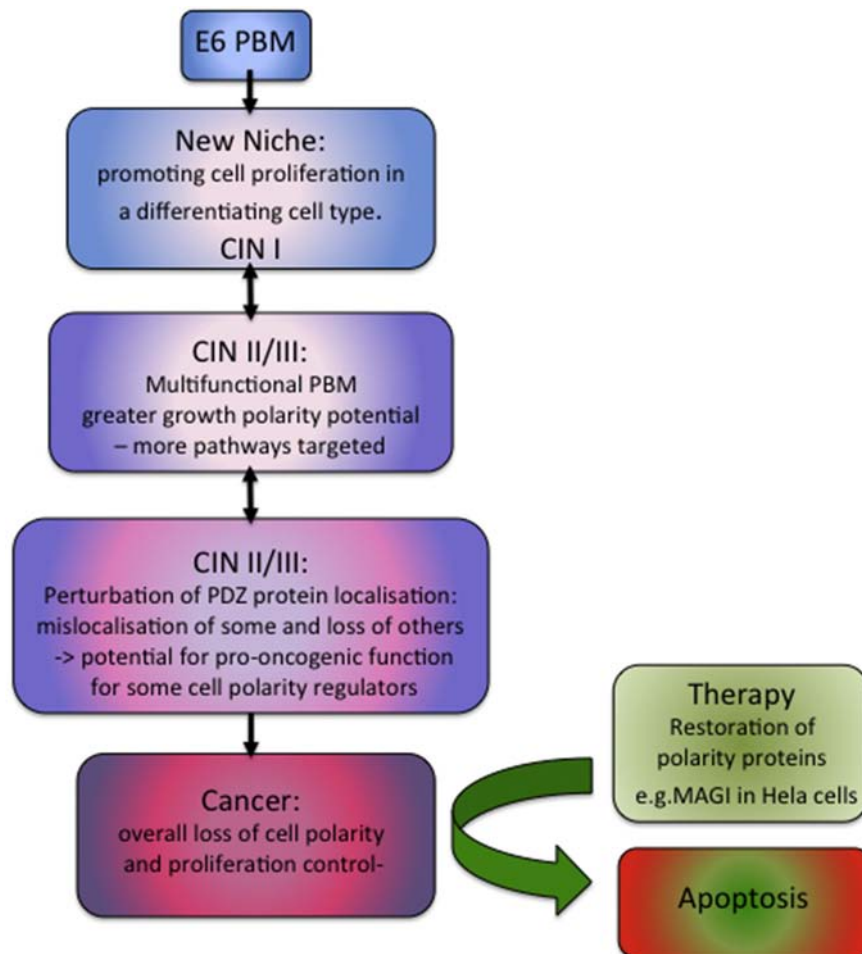

Fig. 3. The contribution of HPV E6 PBM target selection to HPV-induced carcinogenesis. The evolutionary acquisition of a PBM on HPV E6 proteins is probably associated with the colonizing of a new niche—and is associated with Dlg1 binding, but not with oncogenicity. Further adaptations of the PBM allow binding to more diverse polarity proteins, thus targeting more pathways to enhance the viral life cycle, but potentially also perturbing controls of epithelial differentiation, seen clinically as CIN I (cervical intraepithelial neoplasia, grade 1). Further adaptation of the PBM leads to a more flexible target binding profile, greater polarity perturbation, mislocalization or deletion of PDZ polarity proteins, and the acquisition of pro-oncogenic properties by Dlg1 and hScrib, manifest as CIN III (cervical intraepithelial neoplasia, grade 3) and its potential progression to cancer. Restoration of functional polarity proteins can lead to apoptosis of cervical cancer cells and may indicate a possible direction for therapeutic strategies.

seen in non-HPV related tumor development [100–102]. However, in late-stage cancers, hDlg1, hScrib, and E-cadherin are often lost, which is consistent with data from various experimental settings showing that under certain conditions, they can act as tumor suppressors [97,100,103].

Human Herpesviruses

The human herpesviruses are large, enveloped, double-stranded DNA viruses that establish lifelong latent infections, which can be periodically reactivated by various stimuli to cause a productive lytic infection.

Tumor-associated herpesviruses

There are two human tumor viruses in the herpesvirus family: KSHV, which causes cancers only infrequently, and mainly in immunosuppressed patients; and EBV, which causes a large number of diverse tumor types. A number of the viral proteins that are expressed to maintain the latent phase of infection have oncogenic potential [24].

KSHV can infect a wide range of cells, including lymphoid cells, endothelial cells, and keratinocytes [24]; it also expresses a number of potentially oncogenic proteins [29]. These include LANA, which is essential for the establishment and maintenance of KSHV latency [24]; LANA expression upregulates Par3 and SNAIL, leading to the downregulation of E-cadherin and the promotion of EMT [104,105] In addition, the latency protein K15 upregulates miR-31 to inhibit the FAT4 cadherin [106], which has been implicated in the control of both apico-basal and planar polarity [107,108], and is a component of the Hippo pathway [109]; thus, expression of the K15 protein is likely to have wide-ranging effects on ABP and PCP cellular polarity.

EBV infection is generally found in B-lymphocytes, but the virus is also thought to infect polarized epithelium through the formation of direct adhesions between the B cells and the basolateral surface of epithelial cells [110,111], utilizing the endocytic recycling pathways of both donor and recipient cell to facilitate direct cell–cell transmission of the virus [112,113]. It has also been suggested that the virus exploits the endosomal machinery to cross the epithelial cells of the oral mucosa, without initiating an infection, to directly infect the B lymphocyes in the underlying dermis [112,114].

EBV, like all herpesviruses, persists latently for the life of the host in memory B cells and different latency states, characterized by specific gene-expression profiles, are associated with the development of specific tumor types [24]. None of the transforming proteins of EBV—EBNA1, LMP1, and LMP2a—has been detected in direct interaction with cell polarity

regulators, but through upregulation of the TWIST, SNAIL, and SLUG transcription repressors, they severally downregulate expression of E-cadherin [115–119] and upregulate β-catenin [116,120,121]. In addition LMP1 stimulates CDC42 activation [122], leading to increased cell motility, and potentially to invasion, through CDC42's RhoGTPase activity, which is required for Scrib's ability to control polarized cell migration through actin remodeling [123–125]. Thus, although there is no direct interaction between KSHV or EBV proteins and the core cell polarity control proteins, they perturb many peripheral aspects of the pathway, leading to increased cell proliferation and an increased risk of malignant transformation.

Non-oncogenic herpesviruses

Herpes simplex viruses (HSV1 and HSV2), cytomegalovirus, and the varicella zoster virus (VZV) infect epithelial cells where the lytic, or productive, virus life cycle occurs and it is not clear whether the polarity of these cells is involved in the virus replication cycle. However, in plaque assays, HSV infection has been shown to induce polarized cell migration (MCP) in uninfected keratinocytes, which migrate toward the site of infection, and become infected in their turn, [126], while VZV glycoprotein E expression colocalizes with the ZO1 TJ protein and can increase cell–cell contacts and enhance TJ formation in low calcium, presumably to allow cell-to-cell spread of the virus particles [127]. The cytomegalovirus gpUS9 protein has similarly been reported to colocalize with cell junction components such as ZO1 and E-cadherin in polarized epithelial cells [128], although this finding has been disputed [129]. In addition to their lytic cycle, HSV and VZV form latent infections in the dorsal ganglia, forming reactivated lesions at the original site under certain stimuli, which argues a very sophisticated interaction with the neuronal cell polarity determinants of the neuronal cell. The glycosylated US9 and gE/gI proteins of both HSV and VZV, and also the rodent pseudorabies virus (PsRV) have been implicated in the microtubule-mediated ferrying of the virus capsid within the axon [130–132].

Thus, it appears that effects on the core regulators of cell polarity are seen unequivocally only with the tumorigenic herpesviruses, confirming again that perturbation of the correct functioning of polarity control is one of the primary features of malignancy.

Hepatitis Viruses

Hepatitis viruses are the major cause of hepatitis worldwide (World Health Organization) and chronic infections of hepatocytes with hepatitis B virus (HBV; a double-stranded DNA hepadnavirus) and hepatitis

C virus (HCV; a single-stranded RNA flavivirus) are associated with over 80% of hepatocellular carcinomas (HCCs) [24]. Hepatocytes are polygonal multipolar cells, with multiple apical and basal surfaces and hepatic function is dependent upon the maintenance of hepatocyte PCP and the correct functioning of the hepatocyte's numerous TJs [133]. The high rates of cell division and double-strand DNA breaks characteristic of chronic hepatitis are thought to be the means by which HBV DNA integrates into the cellular genome, where it is found in more than 85% of HBV-induced HCCs [134]. Studies suggest that the integration site is random, but may promote the inappropriate activation of neighboring cellular genes, with potentially pro-oncogenic sequelae.

HBV expresses a protein, X (Hbx), that contributes to tumorigenesis through its effects on many cellular mechanisms, including polarity control pathways. The virus uses the various activities of Hbx to optimize viral replication through epigenetic modification and transcriptional reprogramming of the cell. It suppresses E-cadherin expression though epigenetic modification [135], as well as upregulating SNAIL expression and downregulating miR-373 expression [136], while also perturbing the β-catenin interaction with the APC tumor suppressor, thus increasing β-catenin levels [137], which, in turn, further downregulates E-cadherin. Hbx also upregulates YAP expression, thus stimulating cell proliferation [138]. The resulting perturbation of PCP promotes the EMT, which, in combination with the increased cell division, thus contributes to the development of HCC.

HCV is a very different virus from HBV, but given the similarity of their replicative environments and clinical outcomes, it is not surprising that they target a number of similar cellular pathways [139]. It is clear that HCV targets certain proteins of the TJ, including claudin, occludin, and the interferon-induced transmembrane protein 1 [140–142], during virus entry into the basolateral membrane of the hepatocyte [143]. In contrast, intact TJs have also been shown to be instrumental in defending the cell against HCV entry [144,145]; however, virus envelope components have been shown to relocalize TJ components, possibly to prevent superinfection of the cell, but potentially leading to the compromise of junctional integrity [146,147].

During infection, the HCV core protein has been shown to inhibit the SHIP2 phosphatase, leading to downregulation of Dlg1 and Scrib at the basolateral membrane. This disrupts both apico-basal and PCP and morphology and causes the formation of multilumen cysts, which compromise hepatocyte function [148,149]. The core protein also induces methylation of the E-cadherin promoter, leading to its downregulation [150], while the viral NS5A protein activates PI3 kinase activity, leading to increased β-catenin stability and upregulating c-Myc expression [151,152], these activities together tending to promote EMT-associated changes in cell polarity. Such changes are further promoted by the synergy between NS5A activation of TWIST2 [153], while the viral core and Env proteins induce increased TGF-β signaling [154]. It has recently been reported that the NS4B protein binds to Scrib, through at least three PDZ domains, and induces its proteasome-mediated degradation [155]. This appears to protect the infected cell from Scrib-mediated apoptosis, a result that also appears to contribute directly to an increased likelihood of cell transformation. Thus, the virus uses multiple ways to manipulate host cell polarity control, which, in combination with chronic hepatic inflammation and hence accelerated cell division, can contribute to drive malignant transformation.

Merkel Cell Polyomavirus

MCPyV is the first polyomavirus found to be associated with a human cancer [156,157], and over 80% of Merkel cell carcinomas have been found to harbor viral DNA sequences [156]. Although MCPyV infection is widespread in normal skin, a number of characteristics define it as a probable causative agent: clonal integration of the viral genome into the host cell DNA appears to precede tumor development [158,159]; the tumor cells require persistent expression of the viral small T antigen (sT) to survive [160,161]; and the association with immunesuppression strongly supports a viral etiology for the cancer [158].

Interactome analysis has shown that the MCPyV sT binds to a wide range of cellular proteins, most relevantly including CD44 and emerin [162]. CD44 is a widely expressed protein, involved in stabilizing the TJ, thus regulating epithelial barrier function and cell–cell communication [163]. Knockout of CD44 has been shown to result in mislocalization of Par3 to the cell membrane and disruption of the TJ barrier function in mouse skin. Emerin is a component of the LINC complex, which connects the nuclear lamina to the actin cytoskeleton [164]; it binds β-catenin, restricting its nuclear entry [165] and, at least in certain cell types, constraining the Wnt/β-catenin signaling [166] that is required for the MCPyV life cycle in human dermal fibroblasts [167]; and it therefore seems probable that the sT interaction with emerin would relieve this inhibition.

T Lymphotrophic Tumor Viruses

Two retroviruses that infect T lymphocytes, HIV-1 (human immunodeficiency virus-1) and HTLV-1 (human T lymphotrophic virus-1) are known to be cancer-causing.

HIV-1 is defined as tumorigenic owing to the tumors that develop as a direct result of its immunosuppressive impact on the host, but although tumors are

common in HIV patients, HIV-1 is not a tumor virus in the classic sense. The cancers most commonly associated with HIV-1-infection are induced by other viruses: Kaposi's sarcoma, induced by KSHV; ano-genital carcinomas induced by HPV; and lymphomas, induced mainly by EBV.

To further its life cycle, HIV-1 impinges upon several aspects of the cellular polarity control machinery. The virus envelope protein gp120 has been reported to decrease the ZO-1 levels at the TJ, and this may contribute to efficient virus entry [168]. Normal T-cell activation depends on cell polarity pathways, with Rac1, cdc42 and the Scrib/β-Pix complex signaling downstream to PAK at the immune synapse [169]. However, in HIV-1-infected T cells, the viral Nef protein activates PAK indepen-dently [170], inducing a pseudo-activated state that is favorable for viral replication [171], but which also induces anti-apoptotic signals [172], leading to increased survival of the infected cell and enhanced viral pathogenesis [173]. Late in infection, the viral Vpu protein has been shown to sequester β-TrCP in the cytoplasm [174], preventing its E3 ligase activity and thereby stabilizing Snail and β-catenin [175], destabilizing E-cadherin, and enhancing the release of progeny virus particles [176]. β-TrCP is similarly targeted by the Vaccinia virus A49 protein [177] and by the Rotavirus NSP1 protein [178]; these con-served virus strategies indicating a key point at which viral activity can redirect host cell functions to serve the virus's end. Fresh cycles of virus infection may also be enhanced by secreted HIV-1 Tat protein from already-infected cells, which can also result in decreased ZO-1 expression at the TJ in uninfected cells [179,180].

HIV-1 thus perturbs ICP cellular polarity to enhance the efficiency of virus infection, leading to host immunosuppression and increased susceptibil-ity to cancers induced by other viruses.

Unlike HIV-1, HTLV-1 is a true tumor virus, being a direct cause of adult T-cell leukemia, and maintenance of the malignancy, as with HPV-induced tumors, depends on the continued expression of a viral oncogene, in this case the viral HBZ gene. The Tax oncoprotein, although lost in many later-stage T-cell leukemia cells, is required for viral replication and is implicated in many of the steps that lead to tumor development. It has a C-terminal PBM, through which, like HPV E6, it binds a number of proteins involved in cell polarity control, including Dlg, hScrib, MAGI-1, MAGI-3, and Lin7 [181–186]. Tax binding to these proteins results, at least in part, in their aggregation or mislocalization within the cell [184,187,188]. Since Tax competes with PTEN for binding to Dlg [189], this attenuates PTEN-mediated restriction of the PI3K/Akt pathway [190], increasing Akt activation and enhanc-ing cell proliferation. As with HPV E6, the Tax PBM has been shown to be required for persistent viral infection [191], for IL2-independent growth of HTLV-1-infected T

cells [192], and also for its transforming potential in cooperation with NF-κB [193,194]. The importance of the PBM to the carcinogenic phenotype of HTLV-1 is underlined by its absence from the Tax protein of non-oncogenic HTLV-2 [182].

The viral envelope glycoprotein Env also has a PBM, through which it binds hDlg1 [195] and recruits it to the virological synapse that forms between neighboring T cells, and which is thought to be a means of transmitting virus directly from cell to cell. It is thought that the recruitment of hDlg1 may stabilize these synapses to enhance viral transmission [196]. This process is also enhanced by Tax, which is closely associated with the microtubule organizing center (MTOC) on the cell surface, to which it recruits intercellular adhesion molecule 1 (ICAM-1) [197,198], thus activating MEK/ERK signaling and inducing the reorganization of MTOC polarity to form the virological synapse [199]. The involvement of ERK signaling may also suggest a role for hScrib in this process [13]. Thus, the virus exploits the normal cell polarity machinery to enhance its ability to enter cells directly, while evading any risk of immune detection [200].

Non-tumorigenic Viruses

Adenoviruses

Adenoviruses (AdVs) are large DNA viruses with linear double-stranded genomes; they usually cause self-limiting, lytic respiratory or gastrointestinal in-fections in humans. AdV infection occurs through the virion binding to the coxsackie and adenovirus receptor (CAR), which is located on the basolateral cell surface and is essential for TJ integrity [201]. CAR has a C-terminal PBM that mutational studies suggest is not involved in CAR's basolateral target-ing, but is required for interactions with other PDZ domain-containing TJ proteins: MAGI-1, ZO-1, and DLG4, amongst others [202]. Thus, the initial steps of AdV infection involve interaction with proteins essential in maintaining correct cell–cell interactions and polarity.

AdVs are not usually associated with any tumor-igenic activity in humans; however, the human adenovirus 9 (AdV9) has, uniquely, been long been known to have transformation potential in animal cells and can cause tumors in laboratory rodents [203]. In human cells, it has no such effect, but it has been used as a model for virus-induced tumorigenesis [204].

The main oncoprotein of AdV 9 is the early-expressed E4-ORF1 protein, which has at its C-terminus the first virus PBM to be discovered [181,205]. Through this, E4-ORF1, like high-risk HPV E6, binds to Dlg, MUPP, MAGI-1, ZO-2, and PATJ [45,181,206–208]. Unlike E6, E4-ORF1 does

not induce the degradation of its PDZ-containing targets, but sequesters or relocates them. The E4-ORF1 protein exists in either monomeric or trimeric states, with different binding specificities. Monomeric E4-ORF1 binds to its PDZ-containing targets associated with the TJ (MUPP1, MAGI-1, and ZO-2), and with the Crumbs cell polarity complex (MUPP1 and PATJ), sequestering them in insoluble complexes within the cytoplasm, thus disrupting ABP control and compromising the TJ barrier function [209]. In contrast, the trimeric form of E4-ORF1 binds only to Dlg, relocating it to the plasma membrane and, as with the HTLV-1 Tax/Dlg interaction [189], resulting in the constitutive activation of the PI3K signaling pathway [210,211]. Thus, under certain circumstances, perturbation of Dlg by E4-ORF1 turns Dlg into a pro-oncogenic factor [212,213], resulting in increased cell cycle turnover, and thus probably an enhanced environment for AdV9 replication; however, it is likely to also increase the potential for EMT and the risk of malignant transformation. Thus, in enhancing the virus life cycle, the AdV9 E4-ORF1 can compromise both cell junction integrity and cell polarity control. There is a clear parallel here with the early stages of HPV-induced cervical cancer [98], where mislocalization and upregulation of Dlg may also play a pro-oncogenic role. Both of these cases thus underline the multifunctional nature of the polarity control proteins, and the contribution that the complex interplay of their function and location makes to the determination of cell fate.

Orthomyxoviruses

These are negative-strand RNA viruses, of which the best-studied is Influenza A virus, which infects the respiratory epithelia of many birds and mammals [214]. Indeed, the frequent transmission of different influenza virus serotypes between host species renders it a major global health risk for many species of economic importance, such as chickens and pigs, as well as humans.

The influenza A virus non-structural protein NS1 is a multifunctional virulence factor that has a number of protein interaction domains, including an SH3 domain, through which it binds and activates PI3K [215–217], leading to Akt activation and enhanced cell growth, and also inhibiting pro-apoptotic factors, thus extending the life-span of the infected cell to allow enhanced viral replication [218–220].

The vast majority of NS1 proteins analyzed also have a C-terminal PBM, the presence and sequence of which correlate with viral virulence, since it is often mutated or lost in attenuated viruses [221–223]. Interestingly, the avian and human subtypes of influenza A virus have quite different and characteristic PBM sequences (ESEV and RSKV, respectively), which differ in their target specificities, and with their virulence in mammalian cells [224,225]. The avian-type PBM binds strongly to the cellular polarity proteins Scrib, Dlg, MAGI-1, MAGI-2, MAGI-3, PDLIM2, and PSD-95 (Dlg4) [226–229], while the human-type PBM binds more weakly or not at all. The interaction with Scrib relocalizes Scrib from the plasma membrane to cytoplasmic puncta, protecting infected cells from Scrib's pro-apoptotic functions [226], and reducing interferon-induced STAT activation [227], an effect also seen with the Tick-Borne Encephalitis virus (TBEV) NS5 protein [230]. Dlg has also been shown to localize with Scrib in these cytoplasmic puncta, disrupting cell–cell junctions and ABP and PCP polarity control [231]. The NS1 PBM binding also colocalizes MAGI-1 in these puncta, potentially perturbing its regulation of interferon-β signaling [232]. The Dlg/Scrib interaction has also recently been suggested to be involved in dendritic cell maturation, and to be targeted there by NS1, thus potentially leading to evasion of both innate and acquired immune systems [219,233].

Flaviviruses

These are single-stranded RNA viruses that are mainly zoonotic and transmitted to mammals by insect vectors. TBEV causes a severe encephalitis in humans, with a high mortality rate (20%–30%). The TBEV NS5 protein, and that of the closely related West Nile Virus (WNV), is an RNA-dependent RNA polymerase that is essential for replication of the virus genome, but it also has a rare internal PBM, through which it binds to Scrib and relocates to the plasma membrane. Binding Scrib blocks interferon-mediated JAK/STAT signaling, presumably to evade the host's innate immune response [230]. TBEV and WMV NS5 also bind to ZO-1, apparently stabilizing it at the TJ, and also binds to the RIMS2 protein [234–236], a PDZ-containing neurone-specific protein, [237] reflecting the viruses' neuronal etiology. However, it is not yet clear what role this NS5/ZO-1/RIMS complex may play in the virus infectious cycle.

Dengue virus (DENV), which causes the severe febrile illness Dengue fever, is also insect-borne and has an NS5 protein very similar to the TBEV NS5, and which also binds ZO-1 through its internal PBM [234], but in the case of DENV, ZO-1 appears to be sequestered in the nuclear or perinuclear regions of the infected endothelial cell. DENV infection also increases the expression of macrophage inhibitory factor, probably to evade the host immune response and this may also displace ZO-1 from the TJ [238]. The resulting TJ impairment is probably responsible for the vascular leakage that is a hallmark of severe Dengue infection [239,240].

These studies highlight unexpected roles for ABP cell polarity regulation in the control of immune signaling, and it seems likely that some of the well-studied human oncogenic viruses which target these cell polarity regulators are also taking advantage of

the immune avoidance opportunities that these interactions provide, and not just promoting an increase in cell proliferation.

Coronaviruses

Coronaviruses are large single- and positive-stranded enveloped RNA viruses which infect the gastrointestinal and respiratory tracts of birds and mammals. The most studied human coronavirus, SARS-CoV, causes severe acute respiratory syndrome (SARS) and its original major outbreak is thought to have originated as a zoonosis from a bat coronavirus. Like most coronaviruses, SARS-CoV infects polarized epithelium specifically through the apical cell membrane [241–243]. The virus envelope protein (E) has a C-terminal PBM, through which it binds to the cellular PALS protein [244], a component of the Crumbs polarity complex that defines the apical domain, and controls the establishment of apicobasal polarity and the formation of TJs. In infected cells, PALS relocalizes specifically to the perinuclear regions of the Golgi, where virus assembly occurs. Although the location of other TJ proteins, such as ZO-1, does not appear to be affected, the formation of TJs was shown to be aberrant in SAR-CoV-infected cells, and apicobasal polarity is defective in cyst formation of MDCK cells ectopically expressing E, but not EΔPBM. It is not clear whether SARS-CoV requires the E/PALS interaction for virus entry, but the interaction may contribute to virus budding. The importance of the Crumbs complex [245,246] in the control of polarity is shown clearly here; the mislocalization of just one Crm component completely disrupting the epithelial integrity, which may, in turn, be one cause of the particularly severe pathology of SARS.

The MERS (Middle East respiratory syndrome)-CoV, in contrast, can enter and exit cells through both apical and basolateral membranes [247], and viral release occurs through inducing apoptosis in the infected cell, but no specific interactions with the polarity proteins have been reported.

Paramyxoviruses

These are enveloped, negative-, and single-strand RNA viruses, which include the highly contagious measles, mumps and (now-eradicated) Rinderpest viruses. The measles virus (MV) is spread by aerosols, but curiously does not directly infect the respiratory epithelium. Instead, in the alveoli it infects activated, and hence polarized, myeloid cells, through binding of the virus H glycoprotein to the signaling lymphocyte activation molecule on the cell surface [248]. The virus then replicates extensively in myeloid cells in the lymphatic organs, and ultimately the circulating infected myeloid cells deliver the viral genomes directly to the columnar epithelial cells of the upper airway. Making use of the ABP of these cells, the virus enters via their basolateral surfaces, through binding to the AJ protein Nectin 4 [249,250]. The Nectin 4 connection, via Afadin, to the actin cytoskeleton is then required for MV infection to spread directly from cell to cell through the formation of pores in the lateral surfaces of adjacent epithelial cells [251]. This results in the formation of large infectious centers in the tracheal epithelium, which are thought to eventually detach and be expelled in aerosols, facilitating transmission of the virus. Thus, the life cycle of MV uses both the ICP of activated myeloid cells in the lungs to infect the host and the ABP of tracheal epithelium as a means of egress and further cycles of contagion.

The mumps virus (MuV) differs from MV, as its receptor, sialic acid, is expressed on both apical and basolateral membranes, allowing its initial infection via the apical surface of airway epithelia, and its secondary infection in the viremic phase through the basolateral surfaces of the epithelia of the various target organs of MuV. Virus release, however, occurs solely from the apical surface of epithelial cells and requires the Rab11 protein, a protein found in recycling endosomes and characteristic of differentiated epithelium [252,253], again showing virus exploitation of normal cellular mechanisms.

Rhabdoviruses

Rabies virus (RaV) is a small single- and negative-strand RNA virus that infects the neuronal tissue of a very wide host range, causing an acute, and usually fatal, encephalitis. The virus infects the peripheral nervous tissue from wounds or bites, and travels along the axon to the central nervous system. The RV glycoprotein (G) has a C-terminal PBM [254] that appears to be a virulence factor, depending upon its amino acid sequence, similar to that of the Influenza A virus NS1. The PBM of virulent RaV strains (QTRL) has only one known binding partner: it binds with very high specificity to the MAST2 serine–threonine kinase. MAST2 is a normal binding partner of PTEN, which it phosphorylates, allowing phospho-PTEN to enter the nucleus and inhibit the PI3kinase/Akt pathway, limiting neurosurvival. The virulent RaV G protein binds to MAST2 preventing PTEN phosphorylation and leading to Akt activation, thus promoting neuronal cell survival [255]. The PBM of attenuated RaV (ETRL) is more promiscuous in its binding: it does not compete with PTEN for MAST2 binding, instead it binds to a number of PDZ-containing proteins, including Dlg2 (PSD-93) and MUPP1. It also binds to the tyrosine phosphatase PTPN4, which binding promotes apoptosis and neuronal cell death [256,257]. Interestingly, in the absence of any binding ligand, the PDZ domain of PTPN4 inhibits the catalytic activity of the PTP domain, while ligand binding activates the PTP

activity [258]. This lends further weight to the notion that certain PDZ domains may not be simply molecular interactors, but might also act in the dynamic regulation of signaling pathways, suggesting yet another means by which viruses may exert control over specific cellular processes.

The identification of the differences in virus targets between virulent and non-virulent strains of RaV has practical applications: studies are ongoing to identify peptides that could be used therapeutically, either binding MAST2 to promote neuro-regeneration or binding PTPN4 as oncolytic therapies in neuronal tumors [259,260]. The apoptotic bodies induced by non-virulent RaV are strong potentiators of the antiviral immune response [261], which may potentially contribute to vaccine design [256]. In addition, they are being examined as predictors of neurovirulence in the safety testing of live viral vaccines, such as those against yellow fever, polio, or measles [262].

Conclusions

The central importance of cell polarity control is emphasized by the frequency with which it is targeted

by many diverse viruses. Figure 4 shows an overview of the role of polarity protein targeting in persistent and lytic virus infections. It is clear that in targeting key polarity control proteins, viruses not only affect host cell polarity, but also influence many cellular processes, including transcription, replication, and innate and acquired immunity. Examination of the interactions of different virus proteins with the cell and its polarity controls during the virus life cycles, and in virally-induced cell transformation, shows ever more clearly how intimately all cellular processes are linked to the control of cell polarity. Viruses act as signposts, indicating the key cellular pathways and controls that maintain cellular and tissue homeostasis.
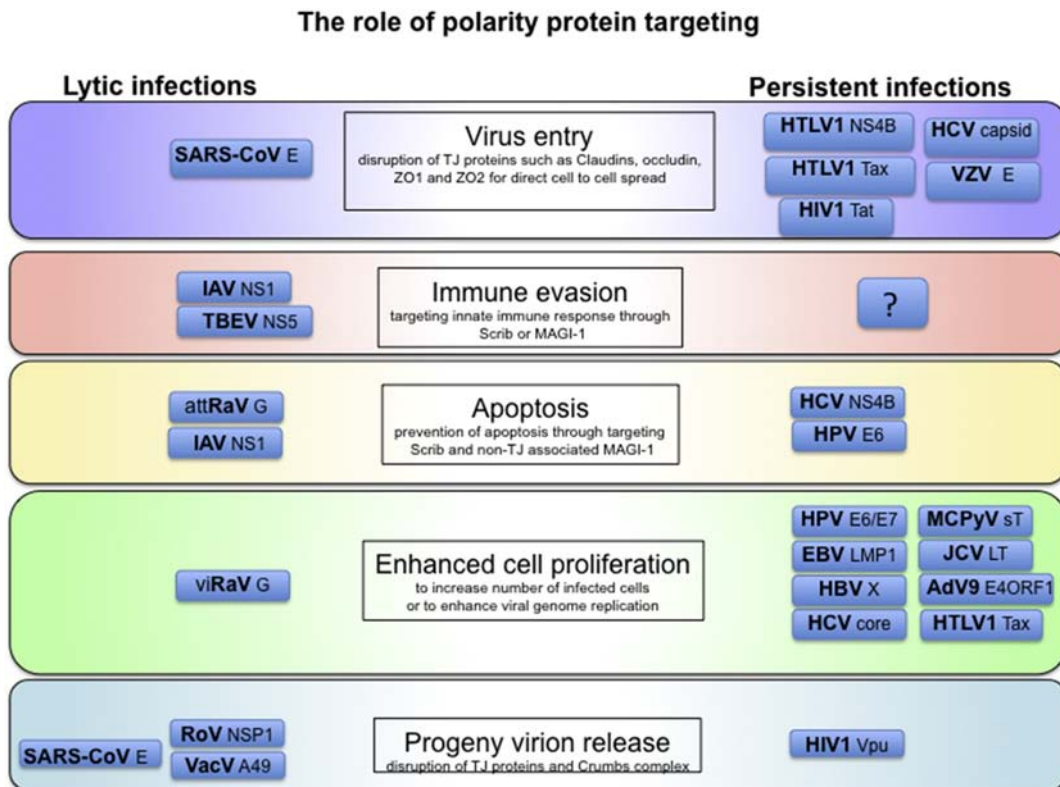
Acknowledgments

Fig. 4. The role of polarity targeting in virus life cycles. Cellular polarity control is targeted by many diverse virus types to enhance their productive life-cycle. However, the effects of the targeting are somewhat different. Lytic viruses, such as influenza A virus (IAV), tend to have a short replication cycle within each infected cell, and the polarity targeting contributes to immune evasion and virus release. Persistent viruses, such as HPVs, have a long replicative cycle, and the polarity targeting tends more towards activating the life-span and proliferation of the infected cell to increase the pool of cells harboring viral genomes and thus to increase the productivity of infection.

Declarations of Interest: None.

Abbreviations used:
ABP, apico-basal polarity; PCP, planar cell polarity; MCP, migrating cell polarity; ICP, immune cell polarity; Scrib, Scribble; Dlg1, Discs Large 1; Par, Partitioning defective; TJs, tight junctions; AJs, adherens junctions; HPV, human papillomavirus; EBV, Epstein–Barr virus; KSHV, Kaposi's sarcoma herpesvirus; PBM, PDZ-binding motif; EMT, epithelial-to-mesenchymal transition; HSV, herpes simplex virus; VZV, varicella zoster virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV-1, human immunodeficiency virus-1; HTLV-1, human T lymphotrophic virus-1; AdV, adenovirus; CAR, coxsackie and adenovirus receptor; TBEV, tick-borne encephalitis virus; DENV, Dengue virus; SARS, severe acute respiratory syndrome; MV, measles virus; RaV, rabies virus; CMV, cytomegalovirus; MCPyV, Merkel cell polyoma virus; IAV, Influenza A virus; WNV, West Nile virus; MuV, mumps virus.

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