bZIP proteins of human gammaherpesviruses

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The human gammaherpesviruses Epstein–Barr virus (EBV) and Kaposi’s sarcoma-associated herpesvirus (KSHV) both infect lymphoid and epithelial cells and both are implicated in the development of cancer. The two viruses establish latency in B-lymphoid cells that, once disrupted, leads to a burst of virus replication during the lytic cycle. A basic leucine zipper (bZIP) transcription factor encoded by EBV, Zta (also known as BZLF1 and ZEBRA), is key to the disruption of EBV latency. KSHV encodes a related protein, K-bZIP (also known as RAP and K8x). Recent developments in our understanding of the structures and functions of these two viral bZIP proteins have led to the conclusion that they are not homologues. Two important features of Zta are its ability to interact directly with DNA and to induce EBV replication whereas K-bZIP is not known to interact directly with DNA or to induce KSHV replication. Despite these differences, the ability to disrupt cell cycle control is conserved in both Zta and K-bZIP. The interactions of Zta and K-bZIP with cellular genes will be reviewed here.

INTRODUCTION

There are two members of the gammaherpesvirus family that infect humans: Epstein–Barr virus (EBV) also known as human herpesvirus 4 (HHV4) and Kaposi’s sarcoma-associated herpesvirus (KSHV) also known as human herpesvirus 8 (HHV8). Both viruses contain genes encoding proteins related to the basic leucine zipper (bZIP) family of transcription factors. EBV encodes Zta (ZEBRA, BZLF1) from the BZLF1 gene (Baer et al., 1984; Rickinson & Kieff, 1996) and KSHV encodes K-bZIP (RAP, K8x) from the K8 gene (Russo et al., 1996; Boshoff & Chang, 2001). Interestingly, both genes are adjacent to the genes encoding another conserved viral transcription factor BRLF1 (encoding Rta) in EBV and Orf 50 (encoding Rta) in KSHV. All four viral genes are silent during virus latency and are expressed early during the virus lytic cycle. Indeed, the expression of Zta is able to disrupt EBV latency whereas K-bZIP does not share this feature. However, some structural features and several functions of Zta and K-bZIP are related as discussed below.

The structure and function of Zta has been extensively reviewed (Miller, 1989; Sinclair & Farrell, 1992; Speck et al., 1997; Schwarzmann et al., 1998) and a brief outline will suffice here. The general structure of the family of bZIP proteins is illustrated in Fig. 1. These proteins appear to be modular in nature, containing a transactivation domain, a basic region that mediates DNA contact, adjacent to a coiled-coil dimerization domain that together form the bZIP domain. The actual structure of the bZIP domain of one member of this family, GCN4, interacting with DNA is shown to illustrate the contiguous nature of the α helix within the bZIP domain (Fig. 1B). The N-terminal region of Zta contains the transactivation domain, with the bZIP region extending towards the C terminus. Zta interacts with a series of related DNA-binding sites termed Zta-response elements (ZREs). Recently, it has been demonstrated that the dimerization domain of Zta folds as a coiled-coil, although the strength of the interaction is much weaker than that of other bZIP proteins (Hicks et al., 2001). The mechanism by which Zta achieves stability as a dimer awaits further investigation.

Not all of the functions of Zta rely on its ability to interact with ZREs. A mutant of Zta that is unable to interact with DNA is also able to undertake some of the functions of Zta, such as specific transactivation of a virus reporter construct (Flemington et al., 1994). Also, a series of mutants within the basic region of Zta revealed that the basic region conferred more than just a DNA-binding function to Zta; some mutants that retain the ability to interact with ZREs fail to disrupt virus latency (Francis et al., 1997, 1999; Adamson & Kenney, 1998).

Initially, K-bZIP was identified as a potential product of one of the alternately spliced mRNAs encoded by the K8 gene of KSHV (Sun et al., 1998; Gruffat et al., 1999; Lin et al., 1999; Seaman et al., 1999; Zhu et al., 1999). The coding sequence of K-bZIP does not have much overall amino acid identity with Zta, although there is some similarity in the predicted propensity of the dimerization region to fold as a coiled-coil (Fig. 1C). Indeed, when expressed in vitro, K-bZIP is able to form homodimers through this region (Gruffat et al., 1999; Lin et al., 1999). In common with Zta, K-bZIP contains a

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nuclear localization signal (NLS) (Portes-Sentis et al., 2001). Analysis of the transcription profile of KSHV genes shows that K-bZIP RNA is expressed during the virus lytic cycle (Gruffat et al., 1999; Lin et al., 1999; Sun et al., 1999; Zhu et al., 1999). Furthermore the protein has also been detected in cells undergoing the virus lytic cycle (Polson et al., 2001).

It is important to note that K-bZIP lacks a basic DNA contact region adjacent to its dimerization domain (Fig. 1C) and it has not been demonstrated to interact with DNA directly, so that its classification as a bZIP protein is in question. However, despite these major differences in the structure and functions of Zta and K-bZIP,
they undertake several of the same functions for EBV and KSHV.

**Interaction of Zta and K-bZIP with virus replication structures and their ability to disrupt virus latency**

For EBV, both Zta and Rta are independently able to activate the virus lytic cycle following enforced expression in cells carrying latent EBV (Ragoczyn et al., 1998; Schwarzmann et al., 1998). Zta acts in part as a transcription factor and in part as a replication factor. Zta activates the expression of several viral genes by interaction with ZREs (reviewed by Miller, 1989; Speck et al., 1997; Schwarzmann et al., 1998), and possibly by other mechanisms not involving direct contact with DNA (see below). Zta also makes direct contact with the ZREs within the origin of replication of the EBV genome (Ori-Lyt) (Scheipers et al., 1996). Rta also appears to act as a classical transcription factor, interacting with Rta response elements (RREs) in the promoters of viral genes (Schwarzmann et al., 1998). The generation of EBV mutants, compromised for either Zta or Rta (Feederle et al., 2000), allowed the role of each to be defined. Each viral mutant was able to undertake some elements of the virus lytic cycle but neither was able to complete the virus lytic cycle. The pattern of viral gene expression revealed that several genes are regulated by either Zta or Rta with some genes requiring the action of both. Therefore these viral genes cooperate to disrupt virus latency. A surprising observation to emerge was the successful expression of some late viral genes in the absence of lytic DNA replication (Feederle et al., 2000).

In contrast to the function of Zta, K-bZIP is not able to disrupt KSHV latency, at least under conditions tested to date (Lukac et al., 1999; Polson et al., 2001). In contrast, RTA is able to disrupt KSHV latency (Lukac et al., 1998, 1999; Sun et al., 1998; Gradoville et al., 2000). It has recently been proposed that K-bZIP plays an opposite role to Zta in early lytic cycle control; K-bZIP is able to repress the ability of RTA to transactivate reporter constructs and to repress the ability of RTA to activate the KSHV lytic cycle (Izumiya et al., 2003). Further delineation of the role of K-bZIP for virus replication awaits the generation of KSHV mutant viruses.

The nuclear DNA genomes of many viruses associate with promyelocytic leukaemia bodies (PML bodies, ND-10s, PODs) (Everett, 2001). The relevance of this is unclear; however, it is interesting to note that PODs contain several transcription regulatory factors and that during virus lytic replication, several viral genes encode proteins that disrupt the structures of the PODs (Everett, 2001). Again the significance of this is unclear, but correlations have been drawn regarding the efficiency of disrupting PODs and the efficiency of virus replication (Everett, 2001). K-bZIP localizes to punctate spots in the nucleus associated with PODs but does not disrupt the PODs (Wu et al., 2001). This association can be reproduced in the absence of other viral genes (Wu et al., 2001) and may prove to be functionally relevant since PODs surround viral pseudo-replication compartments (Pseudo-RC) which include K-bZIP (Wu et al., 2001). The genome of EBV does not associate with PODs during virus latency (Bell et al., 2000) but, during lytic replication, PODs are dispersed (Adamson & Kenney, 2001) and the viral genome is found in close proximity to dispersed PML proteins (Bell et al., 2000). It has been demonstrated that Zta is able to disrupt PODs, when over-expressed in EBV negative cells (Adamson & Kenney, 2001). This appears to be mediated by competition between Zta and PML for limited amounts of the ubiquitin-like protein SUMO, involving amino acid residue K12 of Zta (Adamson & Kenney, 2001). However, the relevance of the disruption of PODs for EBV lytic replication will await the generation and analysis of a Zta K12 mutant virus.

The viral proteins required to mediate the replication of the EBV genome have been reviewed (Schwarzmann et al., 1998) and a recent publication addresses the contribution of KSHV proteins to lytic replication (Wu et al., 2001). These will not be discussed further here. The main difference is in the involvement of the viral origin binding protein; Zta interacts directly with Ori-Lyt and is required for the replication of the EBV genome but there is no evidence to date that K-bZIP plays a similar role for KSHV. Interestingly, both EBV and KSHV contain two lytic origins of replication (Rickinson & Kieff, 1996; Schwarzmann et al., 1998; AuCoin et al., 2002).

**Interaction of Zta and K-bZIP with cellular proteins**

The initial identification of cellular proteins that directly interact with Zta and K-bZIP was undertaken on an individual basis after analyses of the likely suspects involved in the signal transduction pathways implicated in virus-host interactions. Subsequent advances here exploited genetic screening approaches and there remains the possibility that further cellular proteins that are able to interact with Zta and K-bZIP will be identified now that we have entered the post-genomic era. Cellular proteins that can interact directly with Zta or K-bZIP are presented in Table 1. For most of these interactions, experiments to assess the relevance of the interaction have been undertaken following enforced expression of one or both components, so that it is not clear yet whether they can occur at physiological levels of protein expression and the current challenge is to understand their relevance to the biology of the viruses.

**p53**

Both Zta and K-bZIP interact with p53 in vivo and in vitro and furthermore both are able to interfere with the transactivation function of p53 (Zhang et al., 1994; Park et al., 2000; Mauser et al., 2002c). The mechanisms of down regulation of p53-dependent transcription may have similarities since in both cases the bZIP region of the viral proteins interacts with the C-terminal region of p53 (Zhang 2002, unpublished).
et al., 1994; Park et al., 2000). However, Mauser et al. have recently added complexity by showing that at least some of the negative effects of Zta on p53-dependent transcription may be effected indirectly via the TATA binding protein (TBP, see below) (Mauser et al., 2002c). Interestingly, opposing effects of Zta on p53 function have also been observed; in a T-lymphoid cell line Zta expression activates p53-dependent transcription (Dreyfus et al., 2000), and Zta induces a cell cycle arrest and enhances the expression of p53 in several cell types (Cayrol & Flemington, 1996a, b). Therefore, it is difficult to judge at present how the interactions of Zta and K-bZIP with p53 relate to the biology of the viruses and the final answer may well be dependent on the cell lineage and genetic background.

**CREB-binding protein**

An interaction between Zta and CREB-binding protein (CBP) has been demonstrated in over-expression systems and in EBV-infected cells undergoing the lytic cycle (Adamson & Kenney, 1999; Zerby et al., 1999; Hwang et al., 2001). Dissection of the region of CBP required for the interaction with Zta implicated the N-terminal half of CBP, specifically the CH/1 region (Adamson & Kenney, 1999; Zerby et al., 1999; Berge et al., 1998; Lieberman et al., 1997; Ellwood et al., 1999; Deng et al., 2001). Involvement of a region in the C-terminal half of CBP, specifically the CH/3 region, has also been indicated (Adamson & Kenney, 1999; Zerby et al., 1999; Hwang et al., 2001). Interestingly, these two domains of CBP can independently either aid the transactivation of Zta reporter constructs (CH/1) or repress the ability of Zta to activate them (CH/3) (Zerby et al., 1999). However, in its natural context, full-length CBP protein clearly cooperates with Zta both to transactivate reporter constructs and to induce the virus lytic cycle (Adamson & Kenney, 1999; Zerby et al., 1999). Identification of the region of Zta involved in the interaction with CBP is less advanced; most deletions of the protein abolish the ability to interact with full-length CBP and point mutants suggest that the dimerization region of Zta is required and that there is a further involvement of residues in the activation domain (Adamson & Kenney, 1999). The observation that CBP augments the function of Zta could be accounted for by the observed ability of Zta to stimulate the histone-acetyl transferase (HAT) activity of CBP (Chen et al., 2001), which could lead to chromatin remodelling and increase the accessibility of DNA around ZREs. However, the full picture may be more complex since the augmentation of Zta activity is also observed with the isolated CH/1 domain that does not have HAT activity.

K-bZIP is also able to interact with CBP both in vitro and in KSHV-infected cells undergoing the lytic cycle (Hwang et al., 2001). The association can occur through the CH/3 region of CBP (Hwang et al., 2001), but whether there is an additional role for the N-terminal CH/1 domain is untested at present. The region of K-bZIP required for the interaction with CBP has been mapped; the dimerization domain is not required but the basic and nuclear localization regions are (Deng et al., 2001). The functional relevance of the interaction of K-bZIP with CBP was assessed using an HIV

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**Table 1. Physical association of cellular proteins with Zta and K-bZIP**

<table>
<thead>
<tr>
<th>Cellular protein</th>
<th>Interaction with Zta</th>
<th>References</th>
<th>Interaction with K-bZIP</th>
<th>References</th>
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<tbody>
<tr>
<td>p53</td>
<td>Yes</td>
<td>Zhang et al. (1994) Mauser et al. (2002c)</td>
<td>Yes</td>
<td>Park et al. (2000)</td>
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<td>TFIIA–D</td>
<td>Yes</td>
<td>Chen et al. (2001)</td>
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<tr>
<td>NF-kB</td>
<td>Yes</td>
<td>Gutsch et al. (1994) Hong et al. (1997)</td>
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</tr>
<tr>
<td>Ubinuclein</td>
<td>Yes</td>
<td>Aho et al. (2000)</td>
<td>Unknown</td>
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<tr>
<td>RACK1</td>
<td>Yes</td>
<td>Baumann et al. (2000)</td>
<td>Unknown</td>
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A. J. Sinclair
reporter construct which is repressed by K-bZIP; the ability of CBP to relieve this repression suggests a functional interaction (Hwang et al., 2001). However, whether K-bZIP has any effect on the HAT activity of CBP awaits further investigation.

**C/EBPα**

Recently, it has been shown that both Zta and K-bZIP interact directly with C/EBPα. This appears to activate the transcriptional function of C/EBPα, leading to enhanced expression of C/EBPα and a downstream target, p21^{CIP1}, which is thought to effect cell cycle arrest (Wu et al., 2002, 2003). The ability to activate C/EBPα and p21 requires the C-terminal half of both Zta and K-bZIP (Wu et al., 2002, 2003). The interaction between C/EBPα and the viral proteins appear to be highly relevant for cell cycle arrest and are discussed below.

**Basic transcriptional machinery**

A series of elegant studies has detailed the interaction of Zta with the basic transcriptional machinery. The first indication for this came from the work of Lieberman and Berk who demonstrated that not only do Zta and TBP interact directly, but the interaction stabilizes the association of TFIIID with the TATA element (Lieberman & Berk, 1991). This was followed by studies describing the formation of stable initiation complexes containing Zta (Lieberman & Berk, 1991, 1994; Chi & Carey, 1993, 1996; Lieberman, 1994; Chi et al., 1995a, b; Ozer et al., 1996; Lieberman et al., 1997; Berk et al., 1998; Ellwood et al., 1999; Deng et al., 2001). Although it is inferred that the interaction between Zta and the general transcriptional machinery promotes transcription of ZRE-containing promoters, it remains an open question whether the interaction of Zta with the basic transcriptional machinery affects the expression of genes that do not contain a ZRE. To date there have been no reports of interactions of K-bZIP with the basic transcriptional machinery.

**Other cellular proteins**

Zta is able to interact directly with the retinoic acid receptors RAR α and RXR α (Sista et al., 1993, 1995; Pfitzner et al., 1995). Each transcription factor is able to inhibit the other when expressed at high levels. Evidence in favour of the functional relevance of this interaction comes from the observation that retinoic acid is able to inhibit the expression of C/EBPα from latency (Wu et al., 1995). Each transcription factor is able to inhibit the other when expressed at high levels. Evidence in favour of the functional relevance of this interaction comes from the observation that retinoic acid is able to inhibit the expression of C/EBPα from latency (Wu et al., 1995).

The bZIP region of Zta is also reported to bind the p65 subunit of NF-κB (Gutsch et al., 1994; Hong et al., 1997). Enhanced expression of p65 in cells is able to inhibit Zta-mediated transactivation suggesting that the interaction of p65 with Zta may be relevant in vivo (Gutsch et al., 1994; Hong et al., 1997). At present it is not known whether the inhibition occurs in a reciprocal manner or at physiological levels of expression.

One Zta-interacting protein, called Ubinuclein (Aho et al., 2000), was identified through an expression screen using Zta as probe. Binding involves the basic region of Zta and requires dimerization of Zta. A similar interaction occurs between Ubinuclein and the cellular transcription factor c-Jun (Aho et al., 2000), but the functional significance of these interactions is unclear at present.

A Zta-interacting protein, RACK1, was discovered in a two-hybrid screen in yeast using the activation domain of Zta as bait (Baumann et al., 2000). Despite a connection between RACK1 and protein kinase C and the involvement of protein kinase C in the phorbol ester-mediated disruption of virus latency, RACK1 does not affect the phosphorylation or activation status of Zta in vitro or in vivo (Baumann et al., 2000). This suggests that the interaction is not required to meditate signal transduction from phorbol esters to Zta.

Zta can interact directly with CREB, as demonstrated by co-immunoprecipitation studies on cell extracts following enhanced expression of Zta (Adamson & Kenney, 1999). Zta is also able to inhibit CREB transactivation of a reporter construct (Adamson & Kenney, 1999), suggesting a relevance in vivo. It is interesting that Zta has two potential routes to down-regulate the function of CREB: through direct interaction and via its interaction with CBP. CREB has been suggested to play a role in the regulation of the Zta promoter and the ability of Zta to repress CREB function may act as an auto-regulatory feed back mechanism to regulate transcription of the BZLF1 gene.

**Ability of Zta and K-bZIP to regulate the cell cycle**

The ability of herpesviruses to arrest or modulate cell cycle progression during the virus lytic cycle has become a recurring theme in herpesvirus biology (Flemington, 2001). Interestingly both Zta and K-bZIP recently emerged as candidates to mediate such changes. Enhanced expression of either Zta or K-bZIP causes several cell types to arrest (Cayrol & Flemington, 1996a, b; Mauser et al., 2002a, c; Wu et al., 2003).

Part of the mechanism behind the cell cycle effects involves C/EBPα (Wu et al., 2002, 2003; Wang et al., 2003). Importantly, neither Zta nor K-bZIP are able to effect a cell cycle arrest in C/EBPα knock-out fibroblasts and cell lines (Wu et al., 2002, 2003). As detailed above, both Zta and K-bZIP physically interact with C/EBPα and stimulate the ability of C/EBPα to transactivate dependent promoters (Wu et al., 2002, 2003). Zta achieves this initially by protecting C/EBPα from proteasome-dependent degradation (Wu et al., 2003). Since C/EBPα auto-regulates its own promoter, this rapidly results in enhanced C/EBPα expression. In addition, C/EBPα up-regulates the expression of p21^{WAF1}, a cyclin-dependent kinase inhibitor involved in
cell cycle regulation. Thus, both viral proteins can promote cell cycle arrest through their interaction with C/EBPz. However, the situation is more complex as both Zta and K-bZIP appear to use more than one route to halt the cell cycle. Zta-induced cell cycle arrest is associated with the up-regulation of p53, and p27KIP1, in addition to the up-regulation of C/EBPz and p21CIP1 (Cayrol & Flemington, 1996a, b; Mauser et al., 2002a; Wu et al., 2003). Genetic analysis has revealed that the basic region of Zta is required to mediate all of these events (Rodriguez et al., 1999, 2001; Wu et al., 2003). In addition, the activation domain of Zta can also contribute to the up-regulation of p53 and p27KIP1, suggesting more than one mechanism at work (Rodriguez et al., 1999).

However, this relatively simple story is not true for all cells, as Mauser and colleagues recently revealed that Zta does not cause cell cycle arrest in primary keratinocytes (Mauser et al., 2002b). Indeed, Zta induced the expression of several genes that promote S-phase transition (Mauser et al., 2002b). The authors have identified some differences in gene regulation that may account for these profoundly different effects; in the cells that do not arrest or up-regulate p53, the S-phase transcription factor E2F1 is up-regulated. It will be interesting to see whether different regulation of C/EBPz can account for the different outcomes with respect to cell cycle arrest.

### Ability to regulate the expression of cellular genes

Table 2 lists a number of genes whose expression is perturbed by Zta and K-bZIP. In each case, the regulation occurs in the absence of other viral genes (Table 2 and references therein). Regulation at the RNA level implies that Zta and K-bZIP may act as transcription factors on the cellular promoters by direct binding or via their associations with other transcription factors. However, the mechanisms of regulation of the cellular genes have not been assessed further as yet. Several of these genes have also been shown to be regulated at the protein level, suggesting relevance. Of special note is the identification of a series of cell cycle regulatory genes such as p21CIP1, p53, CDC25A and E2F1. In addition, it has recently been shown that the expression of the IFN-γ receptor is regulated by Zta (Morrison et al., 2001). Expression of the IFN-γ receptor gene is down-regulated at both the RNA and protein levels following introduction of an adenovirus vector expressing Zta.

### Table 2. Cell genes regulated by Zta and K-bZIP

(i) RNA changes

<table>
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<th>K-bZIP</th>
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<tr>
<td>TGFβ inh3</td>
<td>Yes</td>
<td>Cayrol &amp; Flemington (1995)</td>
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<td>TGFβ</td>
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<td>z1 collagen</td>
<td>Yes</td>
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<td>TKT tyrosine kinase</td>
<td>Yes</td>
<td>Lu et al. (2000)</td>
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<td>MMP1</td>
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<td>IFN-γ receptor</td>
<td>Yes</td>
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<td>E2F1</td>
<td>Yes</td>
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<td>Yes</td>
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<td>p21</td>
<td>Yes</td>
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(ii) Protein changes

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<td>p53</td>
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Moreover, this translates into an ability of Zta to functionally disrupt the IFN-γ signal transduction pathway (Morrison et al., 2001), which has implications for the ability of EBV to survive during primary infection and lytic cycle replication in vivo.

DISCUSSION

In summary, Zta and K-bZIP are not direct homologues. Despite similarities in their genome location, gene structures and dimerization domains, the proteins are not highly related. Importantly, K-bZIP has not been shown to interact directly with DNA. The C-terminal halves of the proteins, where the dimerization domains lie, are most related and not surprisingly some functions requiring this region are conserved, specifically the interaction with p53 and C/EBPα and the ability to effect cell cycle arrest. In the future, it will be interesting to further analyse the dimerization region of both viral proteins to identify how the poorly related primary sequence of the proteins can promote interaction with the same cellular proteins. Finally, the identification of cellular targets for Zta and K-bZIP is currently in the early stages. In the near future, genome-wide screens from a variety of cell lineages should inform us greatly about the mechanisms by which these two viral proteins reprogram the patterns of cellular gene expression during the disruption of virus latency.

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REFERENCES


