The Latent Membrane Protein 1 (LMP1)

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Abstract Almost exactly twenty years after the discovery of Epstein-Barr virus (EBV), the latent membrane protein 1 (LMP1) entered the EBV stage, and soon thereafter, it was recognized as the primary transforming gene product of the virus. LMP1 is expressed in most EBV-associated lymphoproliferative diseases and malignancies, and it critically contributes to pathogenesis and disease phenotypes. Thirty years of LMP1 research revealed its high potential as a deregulator of cellular signal transduction pathways leading to target cell proliferation and the simultaneous subversion of cell death programs. However, LMP1 has multiple roles beyond cell transformation and immortalization, ranging from cytokine and chemokine induction, immune modulation, the global alteration of gene and microRNA expression patterns to the regulation of tumor angiogenesis, cell–cell contact, cell migration, and invasive growth of tumor cells. By acting like a constitutively active receptor, LMP1 recruits cellular signaling molecules associated with tumor necrosis factor receptors such as tumor necrosis factor receptor-associated factor (TRAF) proteins and TRADD to mimic signals of the costimulatory CD40 receptor in the EBV-infected B lymphocyte. LMP1 activates NF-κB, mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3-K), IRF7, and STAT pathways. Here, we review LMP1's molecular and biological functions, highlighting the interface between LMP1 and the cellular signal transduction network as an important factor of virus–host interaction and a potential therapeutic target.

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Abbreviations

AP1	Activator protein 1
CTAR	C-terminal activating region
cIAP	Cellular inhibitor of apoptosis
EBV	Epstein-Barr virus
ERK	Extracellular signal-regulated kinase
GCM	Germinal center model
Id	Inhibitor of DNA binding
IFNγ	Interferon-γ
IL	Interleukin
IRF7	Interferon regulatory factor 7
IκB	Inhibitor of NF-κB
IKK	IκB kinase
IRAK1	Interleukin 1 receptor-associated kinase 1
JAK3	Janus kinase 3
JNK	c-Jun N-terminal kinase
LMP1	Latent membrane protein 1
LCL	Lymphoblastoid cell line
MAPK	Mitogen-activated protein kinase
MEF	Mouse embryonic fibroblast
NF-κB	Nuclear factor of kappa light polypeptide gene enhancer in B cells
NIK	NF-κB-inducing kinase
NPC	Nasopharyngeal carcinoma
UPR	Unfolded protein response

PI3-K	Phosphatidylinositol 3-kinase
PKCδ	Protein kinase C δ
PTLD	Post-transplant lymphoproliferative disease
Rb	Retinoblastoma protein
RIP1	Receptor-interacting protein 1
RING	Really interesting new gene, protein domain with E3 ubiquitin ligase activity
STAT	Signal transducers and activators of transcription
SUMO	Small ubiquitin-like modifier
TAK1	Transforming growth factor β-activated kinase 1
TAB	TAK1-binding protein
TES	Transformation effector site
TNF-R	Tumor necrosis factor receptor
TNIK	TRAF2- and Nck-interacting kinase
TM	Transmembrane domain
TRAF	Tumor necrosis factor receptor-associated factor

1 LMP1 Expression

The first hint to latent membrane protein 1 (LMP1)'s existence arose in the year 1984 when sequencing of an mRNA transcribed in primary lymphocytes, which had been latently infected with B95.8 Epstein-Barr virus (EBV), suggested the existence of a so far unknown viral transmembrane protein. The protein translated from this mRNA was predicted to consist of a short cytoplasmic N-terminus of 24 amino acids, six transmembrane spanning domains of 162 amino acids, and a cytoplasmic C-terminus of 200 amino acids (Fennewald et al. 1984). The first available LMP1 antibodies allowed the determination of LMP1's apparent molecular weight to approximately 63 kDa and confirmed its localization within the cell membrane (Hennessy et al. 1984; Mann et al. 1985; Modrow and Wolf 1986). Later, it was recognized that the largest fraction of LMP1 actually locates to intracellular membranes where it is biologically active as well (Lam and Sugden 2003). LMP1 is a phosphoprotein, although the functional relevance of LMP1 phosphorylation at serine and threonine residues remains unclear (Baichwal and Sugden 1987; Mann and Thorley-Lawson 1987; Moorthy and Thorley-Lawson 1993b). LMP1 expression is detectable as early as four days after infection of human B lymphocytes with EBV, the viral LMP1 promoter being induced by the transcription factor Epstein-Barr virus nuclear antigen 2 (EBNA2) (Allday et al. 1989; Fahraeus et al. 1990).

Once expressed, several positive and negative autoregulatory loops balance LMP1 protein levels. In cells with low amounts of LMP1, the unfolded protein response (UPR) pathway, which is triggered at the transmembrane domains of LMP1, induces activation transcription factor 4 (ATF4). ATF4, in turn, promotes transcription of the LMP1 promoter (Lee and Sugden 2008b). Furthermore,

cellular signal transduction pathways activated at the carboxy-terminal signaling domain of LMP1 such as interferon regulatory factor 7 (IRF7), NF-κB, and p38 mitogen-activated protein kinase (MAPK) contribute to the positive autoregulation of LMP1 expression (Ning et al. 2003, 2005; Demetriades and Mosialos 2009; Johansson et al. 2009, 2010). At high physiological levels, LMP1 causes cytostasis and autophagy, which limits cellular LMP1 amounts (Hammerschmidt et al. 1989; Lee and Sugden 2008a). Overexpression of LMP1 is deleterious for the cell. The LMP1 transmembrane domains alone have the potential to trigger apoptosis via the UPR pathway, which is suppressed at physiological LMP1 levels by signal transduction events initiated at LMP1's signaling domain (Pratt et al. 2012). LMP1 overexpression also induces high cellular levels of the death receptor Fas, leading to Fas autoactivity and apoptosis (Le Clorennec et al. 2008). LMP1 remains expressed throughout viral latency type III, which is found in EBV-transformed B cell lines, so-called lymphoblastoid cell lines (LCLs), post-transplant lymphoproliferative disease (PTLD), X-linked proliferative disease, and infectious mononucleosis. EBV-associated Hodgkin's disease, peripheral T cell lymphoma, and undifferentiated nasopharyngeal carcinoma (NPC), which display viral type II latency, are characterized by the presence of LMP1 protein as well (Niedobitek 1999; Cohen 2000; Yoshizaki et al. 2013). During type II latency, where EBNA2 is absent, cytokine-induced activity of signal transducers and activators of transcription (STAT) is responsible for LMP1 expression (Chen et al. 2001, 2003; Kis et al. 2006, 2010, 2011). Also, transcription factors of the C/EBP family are involved in maintaining LMP1 expression in the absence of EBNA2 (Noda et al. 2011). Apart from pleiotropic effects on its target cell, which will be discussed in the forthcoming paragraphs, LMP1 contributes to the stabilization of viral latency by suppressing activation of the EBV-derived transcription factor BZLF1, which controls EBV's entry into the lytic cycle, and by inducing IRF7, which represses the Qp promoter of EBV in type III latency (Zhang and Pagano 2000; Adler et al. 2002; Prince et al. 2003).

2 Biological Functions

2.1 Transformation of Epithelial Cells and Fibroblasts

The first breakthrough toward LMP1's biological functions was the discovery of its transforming potential in rodent fibroblasts, identifying LMP1 as a genuine herpesviral oncogene. Mouse and rat fibroblasts transfected with LMP1 show phenotypic changes typical for transformed cells such as anchorage- and serum-independent cell growth. Moreover, LMP1-transformed rat fibroblasts turned out to be tumorigenic in nude mice (Wang et al. 1985; Baichwal and Sugden 1988). Also, terminal differentiation of human epithelial cells is inhibited by LMP1, a mechanism by which LMP1 might contribute to multistep pathogenesis of EBV-associated undifferentiated NPC (Dawson et al. 1990). In nasopharyngeal

epithelial cells and rodent fibroblasts, LMP1 upregulates basic helix-loop-helix (bHLH) transcription factors of the inhibitor of DNA-binding (Id) family such as Id-1, which mediates epithelial cell cycle progression by downregulation of the retinoblastoma protein (Rb)/$p16^{INK4a}$ pathway (Everly et al. 2004; Li et al. 2004). The tumor necrosis factor receptor-associated factor (TRAF)-binding domain located within the signaling domain is required for rat fibroblast transformation and upregulates cell cycle markers linked to G1/S-phase transition of the cell cycle (Mainou et al. 2005, 2007). Notably, fibroblast transformation by LMP1 is dependent on the PI3-K/AKT and c-Jun N-terminal kinase (JNK) pathways, but independent of NF-κB (Mainou et al. 2005; Kutz et al. 2008). Cell immortalization is fostered by LMP1 through telomerase activation via the $p16^{INK4a}$/Rb, PI3-K/AKT, and JNK pathways (Ding et al. 2007; Yang et al. 2014). Moreover, LMP1 aids NPC cells to evade apoptosis, for instance induced by TNF-related apoptosis-inducing ligand (TRAIL), a factor with potential therapeutic relevance for cancer (Li et al. 2011).

2.2 B cell Transformation

EBV primarily infects and transforms human B lymphocytes (Young and Rickinson 2004). Virions lacking functional LMP1 loose the capability of efficiently transforming B cells, underscoring LMP1's critical role as the primary oncogene of EBV (Kaye et al. 1993; Dirmeier et al. 2003). LMP1 is also oncogenic in the B cell compartment of transgenic mice. Expression of LMP1 from the immunoglobulin heavy chain promoter/enhancer results in the sporadic development of B cell lymphomas of follicular center cell phenotype (Kulwichit et al. 1998). The conditional activation of LMP1 from the pro/pre-B cell stage in mice causes a rapid and fatal lymphoproliferation with high efficiency, if T lymphocytes are depleted at the same time. This result highlights the transforming potential of LMP1 in vivo as well as its role in immune surveillance of EBV-positive B cells (Zhang et al. 2012).

Activation of naive B cells depends on the stimulation of their B cell receptor by antigen and the costimulatory receptor CD40 by T helper cells. Several in vitro and in vivo studies have demonstrated that LMP1 mimics signals that are physiologically induced by CD40, a member of the TNF-R family (Zimber-Strobl et al. 1996; Hatzivassiliou et al. 1998; Kilger et al. 1998; Busch and Bishop 1999; Uchida et al. 1999; Stunz et al. 2004; Rastelli et al. 2008; Zhang et al. 2012). Accordingly, primary human B cells infected with LMP1-deficient EBV are only able to induce lymphomas in immunodeficient mice if they are supplied with CD40-mediated T cell help (Ma et al. 2015). Together with LMP2A, which generates B cell receptor-like signals, LMP1 drives B cell proliferation and survival, rendering the infected B cell independent of B cell receptor and CD40 stimulation (Mancao and Hammerschmidt 2007). In particular, activation of the NF-κB pathway by LMP1 contributes essential survival signals for the transformation of B

cells in type III latency (Cahir-McFarland et al. 1999; Feuillard et al. 2000; Cahir-McFarland et al. 2004). LMP1 even possesses general antiapoptotic potential as it protects EBV-negative Burkitt's lymphoma cells from programmed cell death by upregulation of antiapoptotic genes such as *bcl-2*, *mcl-1*, and *bfl*-1, or downregulation of proapoptotic genes such as *bax* (Henderson et al. 1991; D'Souza et al. 2004; Grimm et al. 2005). Moreover, LMP1 disrupts expression or function of tumor suppressors such as DOK1 in EBV-infected primary B cells (Li et al. 2012; Siouda et al. 2014).

Simultaneous promotion of proliferation, cell cycle progression, and cell growth of B cells can be attributed to LMP1's potential of inducing the expression of c-Myc and the epidermal growth factor receptor (EGF-R) and to upregulate cell cycle-regulating kinases such as Cdk2 and Cdc2 (Miller et al. 1995; Dirmeier et al. 2005; Shair et al. 2007; Kutz et al. 2008). Splenic B cells of LMP1 transgenic mice display increased levels of Cdk2 and phosphorylated Rb protein, a key substrate of Cdk2 and master regulator of G1- to S-phase transition of the cell cycle (Shair et al. 2007). Cdc2, which is essential for G2- to M-phase transition, is upregulated in LCLs by LMP1 via the JNK signaling pathway (Kutz et al. 2008). Notably, chemical inactivation of JNK by a small molecule inhibitor caused a proliferation defect in LCLs in vitro and strongly retarded tumor growth of EBV-transformed human B cells in a tumor xenograft model in mice (Kutz et al. 2008). Recent data point to an additional role of IRF7 in B cell transformation by EBV, because the knockdown of this transcription factor in LCLs causes a defect in cell growth (Xu et al. 2015).

2.3 Global Effects on Chromatin and Gene Expression

Accumulating evidence suggests that LMP1 also impacts the chromatin of its target cell. A first hint toward this direction came from studies, revealing that LMP1 upregulates expression of the DNA methyltransferase DNMT1 via the JNK pathway. LMP1-induced DNMT1 forms a transcriptional repression complex together with histone acetylase at the E-cadherin promoter (Tsai et al. 2006). LMP1 also induces recruitment of a DNMT1-containing repression complex to the promoter of the tumor suppressor DOK1, resulting in histone H3 trimethylation at lysine 27 (H3K27me3) and gene silencing (Siouda et al. 2014). Moreover, LMP1 stimulates phosphorylation of histone H3 at serine 10, which is an important factor in carcinogenesis of NPC (Li et al. 2013). It is tempting to speculate that additional regulatory links between LMP1 and the chromatin will emerge with more studies to be conducted.

Considering the diversity of biological processes and signal transduction pathways regulated by LMP1, it was not surprising to learn that LMP1 has an extensive impact on the gene expression pattern of its target cell. Several studies reported global analyses of LMP1-regulated gene expression in different cell types ranging from NPC cells to primary B cells infected with EBV. LMP1-regulated

genes include for instance transcription factors, cytokines, chemokines, growth factors, receptors and signaling mediators, genes involved in apoptosis and survival regulation, metabolism, and structural proteins as well as genes involved in cell motility and immune modulation (Kwok Fung Lo et al. 2001; Cahir-McFarland et al. 2004; Dirmeier et al. 2005; Morris et al. 2008; Vockerodt et al. 2008; Faumont et al. 2009; Gewurz et al. 2011; Shair and Raab-Traub 2012; Xiao et al. 2014). In primary human germinal center B cells, LMP1 induces a transcriptional pattern characteristic for Hodgkin/Reed–Sternberg tumor cells including the downregulation of B cell receptor components (Vockerodt et al. 2008). LMP1 affects cell metabolism by deregulation of glycolytic genes such as hexokinase 2, which results in increased glycolysis (Xiao et al. 2014). Moreover, it has become evident recently that not only genes translated into proteins but also genes encoding small non-coding RNA species such as microRNAs or vault RNA are regulated by LMP1 (Motsch et al. 2007; Amort et al. 2015).

2.4 Functions Beyond Cell Transformation

Apart from affecting cell survival and proliferation pathways, LMP1 influences many other processes involved, for instance, in immune modulation or the dissemination of tumor cells in the body. Due to space limitations, only some examples can be given here. The first transmembrane domain of LMP1 harbors the immunosuppressive peptide LALLFWL, which strongly inhibits T cell proliferation and NK T cell cytotoxicity, likely upon LMP1 release from EBV-positive cells via exosomes (Dukers et al. 2000; Middeldorp and Pegtel 2008).

Mice expressing LMP1 as a transgene in the skin develop epidermal hyperplasia associated with inflammatory processes, which are mediated by LMP1-induced cytokine and chemokine expression (Wilson et al. 1990; Curran et al. 2001; Hannigan et al. 2011). Like many other tumors, also NPC is accompanied by heavy chronic inflammation that adds to the severity of the disease. Several studies have shown that upregulation of proinflammatory cytokines such as interleukin (IL)-1α/β, IL-6, IL-8, chemokine (C-X-C) motif ligand 1 (CXCL-1), or granulocyte-macrophage colony-stimulating factor (GM-CSF) is related to EBV infection and LMP1 expression in undifferentiated NPC (Eliopoulos et al. 1999b; Huang et al. 1999; Li et al. 2007; Lai et al. 2010; Hannigan et al. 2011). Moreover, LMP1 activity is linked to tumor angiogenesis by upregulating angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and IL-8 (Yoshizaki et al. 2001; Murono et al. 2001; Wakisaka et al. 2002).

LMP1 promotes cell motility, migration, and tumor metastasis by inducing anchorage-independent and invasive growth of human epithelial and nasopharyngeal cells (Tsao et al. 2002; Yoshizaki 2002; Chew et al. 2010). Cell motility and migration are fostered through activation of the MAPK extracellular-regulated kinase (ERK) and PI3-K/AKT pathways and of the Rho-GTPase Cdc42 (Dawson et al. 2008; Shair et al. 2008; Liu et al. 2012). LMP1 furthermore interacts

with the SUMO-conjugating enzyme Ubc9, which mediates LMP1-induced SUMOylation of cellular target proteins. Disruption of the LMP1::Ubc9 interaction affected cell migration (Bentz et al. 2011). In NPC tissues, LMP1 expression is directly correlated with ezrin phosphorylation, a linker between the cell membrane and the actin cytoskeleton that mediates cell migration. LMP1 increases ezrin phosphorylation and its activation through a protein kinase C (PKC)-dependent pathway, which is required for LMP1-induced cell motility and invasion of nasopharyngeal cells (Endo et al. 2009). Also, upregulation of alpha(v) integrins by LMP1 contributes to cell migration (Huang et al. 2000). Recent data further showed that LMP1 induces the TNFα-induced protein 2 (TNFAIP2), whose expression correlates with metastasis and poor survival of NPC patients, via the NF-κB pathway. TNFAIP2 associates with actin and promotes the formation of membrane protrusions (Chen et al. 2014).

Tumor cells must be able to degrade and invade the extracellular matrix to migrate through surrounding tissue and to penetrate lymphatic or blood vessels, a prerequisite for tumor metastasis. LMP1 upregulates a panel of factors that are associated with cell invasiveness such as matrix metalloproteinases (Lu et al. 2003; Yoshizaki et al. 1998; Kondo et al. 2005). Furthermore, LMP1 increases invasive properties of tumor cells by downregulation of E-cadherin, a Ca^{2+}-dependent adhesion molecule at the cell surface responsible for cell–cell contact (Tsai et al. 2002). LMP1 also regulates invasive migration of lymphocytes by upregulating the tumor marker Fascin, a stabilizer of filamentous actin in filopodia of migrating cells, via the NF-κB pathway (Mohr et al. 2014).

2.5 The Role of LMP1 for EBV Infection

The germinal center model (GCM) of EBV infection explains EBV biology as well as the pathogenesis of lymphoma (Thorley-Lawson et al. 2013). According to this model, EBV exploits normal B cell biology to establish a lifelong latency in the body. After infection of naive B cells, EBV pushes the cells into proliferating lymphoblasts expressing LMP1, LMP2, and EBNA2, which then transit the germinal center as centroblasts and centrocytes to finally become long-lived resting memory B cells (Babcock et al. 2000). From the centroblast stage, EBV-infected cells express a restricted pattern of latent genes comprising LMP1, LMP2, and EBNA1, but not EBNA2 (Babcock et al. 2000). It has long been assumed that LMP1 (together with LMP2) allows the EBV-infected cells to pass the germinal center in the absence of antigen, T cell help and CD40 signaling. However, EBV-positive memory B cells apparently underwent antigen selection as their EBV-negative counterparts, suggesting that the impact of LMP1 (and LMP2) on the cells during their passage through the germinal center may be moderate (Souza et al. 2005). LMP1 likely supports the survival of EBV-infected cells in this competitive environment and favors their differentiation into memory B cells rather than plasma cells (Thorley-Lawson et al. 2013). So far, this model is largely based

upon expression analyses of EBV genes in B cell subsets of infected individuals. Due to the lack of appropriate in vivo models for EBV infection, it has been nearly impossible to test this model experimentally. This may now change due to the availability of infection models in mice carrying a reconstituted human immune system (Chatterjee et al. 2014). Recent experiments in highly immunocompetent hNSG(thy) mice engrafted with human fetal CD34-positive cells and human thymus showed that EBV lacking LMP1 can still establish long-term viral latency in vivo, but is unable to induce lymphomas (Ma et al. 2015). However, long-term latency in this model may rather resemble latency III of LCLs than the latency program found in resting memory B cells of EBV-positive individuals, because the latently infected B cells in the spleens of these animals still expressed EBNA2. This finding is in line with in vitro data demonstrating that LMP1-deficient EBV supports the establishment of LCLs at a very low frequency if the cells are supplied with a favorable environment such as a fibroblast feeder layer (Dirmeier et al. 2003).

3 Structure–Function Relationship

3.1 Amino-terminus and Transmembrane Domain

The LMP1 molecule consists of a short cytoplasmic amino-terminus (amino acids 1–24), six transmembrane domains (amino acids 25–186), and a carboxy-terminal signaling domain (amino acids 187–386), which is located in the cytoplasm (Fig. 1). There are no crystal or NMR structures of the LMP1 protein available, which is

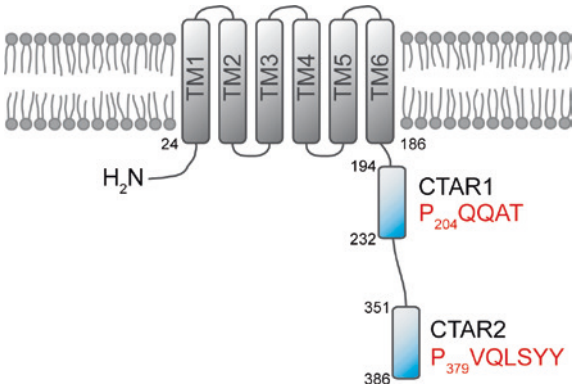

Fig. 1 Structure of the LMP1 molecule. Six transmembrane domains connect a short amino-terminal domain with a carboxy-terminal signaling domain which is located in the cytoplasm of the infected cell. The signaling domain contains the two effector sites CTAR1 and CTAR2, also called TES1 and TES2, respectively. CTAR1 harbors the TRAF interaction motif PxQxT and CTAR2 the motif PYQLSYY that is critical for JNK and canonical NF-κB signaling

partly due to its unfavorable chemical properties as a hydrophobic transmembrane protein with a signaling domain that seems to be highly unstructured, at least in the absence of a binding partner. LMP1 functions like a constitutively active receptor that is independent of ligand binding. The transmembrane domain of LMP1 has the intrinsic property to form homo-oligomers in the membrane, which replaces cross-linking by a ligand and leads to the initiation of signal transduction events at the signaling domain of the molecule (Gires et al. 1997). Intermolecular interactions between transmembrane domains (TM) 3–6 and an FWLY motif in TM1 mediate oligomerization and are thus required for LMP1 signaling (Yasui et al. 2004; Soni et al. 2006). LMP1 is distributed between lipid rafts and non-raft regions of the membrane (Ardila-Osorio et al. 1999; Higuchi et al. 2001). Also, lipid raft localization of LMP1 is mediated by the FWLY motif (Coffin et al. 2003; Yasui et al. 2004). In addition, a leucine heptad motif located within TM1 contributes to the efficient homing of LMP1 to lipid rafts (Lee and Sugden 2007). Lipid rafts are membrane subdomains enriched in sphingolipids and cholesterol that are actively involved in signal transduction processes. LMP1 specifically recruits cellular signaling molecules such as TRAF2 and 3, the TNF receptor-associated death domain protein (TRADD), or PI3-K into lipid rafts, suggesting a role for these membrane domains in LMP1 signaling (Ardila-Osorio et al. 1999; Brown et al. 2001; Schneider et al. 2008; Meckes et al. 2013).

The amino-terminus is responsible for correct insertion and orientation of LMP1 within the membrane, mediates association of LMP1 with the cytoskeleton, and is involved in the regulation of LMP1 degradation and turnover (Wang et al. 1988b; Martin and Sugden 1991; Izumi et al. 1994; Aviel et al. 2000; Coffin et al. 2001). Ubiquitination and proteasome-dependent degradation of LMP1 is further dependent on the TRAF-binding site within the carboxy-terminus of LMP1 (Rothenberger et al. 2003; Hau et al. 2011). Mutation of the amino-terminus showed that this domain does not contribute critical signals for B cell transformation (Izumi et al. 1994; Dirmeier et al. 2003).

3.2 Carboxy-terminal Signaling Domain

Extensive mutational analysis revealed the central importance of the carboxy-terminal domain and the two functional subdomains it harbors, for cell transformation and the initiation of signal transduction. The so-called transformation effector sites (TES) 1 (amino acids 187–231) and 2 (amino acids 351–386) have been defined by their essential functions in initial B cell transformation or long-term outgrowth of EBV-infected B cells, respectively (Kaye et al. 1995, 1999; Dirmeier et al. 2003). Transformation of rat fibroblasts depends on these effector sites as well (Moorthy and Thorley-Lawson 1993a; Mainou et al. 2005). Soon, it has been recognized that TES1 and 2 coincide with two regions named C-terminal activating regions (CTAR) 1 and 2, respectively, that are responsible for interaction of LMP1 with cellular signaling molecules of the TRAF family and TRADD, and the

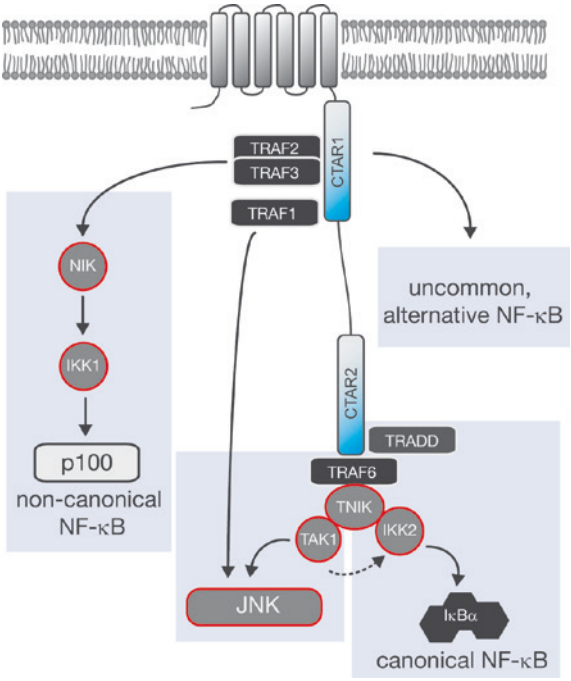

Fig. 2 NF-κB and JNK signaling by LMP1

activation of NF-κB and JNK/AP1 signaling (Fig. 2) (Huen et al. 1995; Mitchell and Sugden 1995; Mosialos et al. 1995; Devergne et al. 1996; Brodeur et al. 1997; Izumi et al. 1997; Izumi and Kieff 1997; Kieser et al. 1997; Eliopoulos and Young 1998).

The TRAF interaction motif P_{204}xQxT is critical for CTAR1 domain function and was shown to directly bind TRAF1, 2, and 3, whereas the molecular basis of TRAF5 interaction with CTAR1 remains unclear (Devergne et al. 1996; Brodeur et al. 1997; Sandberg et al. 1997; Miller et al. 1998). The crystal structure of TRAF2 in complex with the CTAR1-derived peptide P_{204}QQATDD revealed a conserved binding mode of TRAF2 to LMP1 and its cellular counterpart, CD40 (Ye et al. 1999).

CTAR2 activity depends on the presence of a minor TRAF-binding motif P_{379}VQLSYY in order to induce signaling, although direct binding of TRAF proteins to this site has never been demonstrated (Floettmann and Rowe 1997; Kieser et al. 1999; Schneider et al. 2008). Instead, it was the death domain protein TRADD that was first described to interact directly with CTAR2, the motif Y_{384}Y of CTAR2 being essential for TRADD recruitment (Izumi and Kieff 1997). This interaction, however, is unique and differs from cellular TRADD-interacting receptors, as it (i) does not require the death domain of TRADD and (ii) dictates an LMP1-specific, transferable, and non-apoptotic type of TRADD signaling (Kieser et al. 1999; Kieser 2008; Schneider et al. 2008). LMP1 is thus another impressive example of a viral protein that reprograms and thereby exploits cellular

proteins and functions for its own purposes, in this case the subversion of cellular pathways regulating cell survival. In contrast to CTAR1, CTAR2 relies on TRAF6 as the essential signaling mediator (Schultheiss et al. 2001; Luftig et al. 2003; Wan et al. 2004; Schneider et al. 2008). However, despite its central role in LMP1 signaling, it has been unclear by which mechanism LMP1 is recruiting TRAF6. Our own unpublished data now suggest that TRAF6 in fact binds to the P_{379}VQLSYY motif of CTAR2 directly. Other factors such as BS69 or TRADD might then further stabilize the complex at CTAR2 (Wan et al. 2006; Schneider et al. 2008).

The region between CTAR1 and CTAR2 is dispensable for cell transformation (Izumi et al. 1999). The functional relevance of CTAR3 (amino acids 275–330) comprising two box 1 and one box 2 Janus kinase 3 (JAK3) interaction and activation motifs, respectively, for JAK/STAT activation by LMP1 remains controversial (Gires et al. 1999; Higuchi et al. 2002). However, LMP1 can induce STAT3 via autocrine loops involving cytokines such as IL-6 (Chen et al. 2003). STAT1 activation has been linked to LMP1-dependent IFNγ secretion in PTLD-derived B cells (Vaysberg et al. 2009). Recent studies demonstrated that CTAR3 in fact exists and that it regulates Ubc9-mediated SUMO modification of cellular proteins including the transcription factor IRF7 (Bentz et al. 2011, 2012).

Most experimental data on molecular biology and the biological functions of LMP1 have been generated using the "prototype" LMP1 derived from the B95.8 strain of EBV (Hudson et al. 1985). In addition to B95.8-LMP1, a large number of LMP1 sequence variants have been isolated predominantly from NPC samples or healthy carriers of different geographical regions of the world (Hu et al. 1991; Miller et al. 1994; Sandvej et al. 1997; Hatton et al. 2014; Lorenzetti et al. 2012; Renzette et al. 2014). Due to space limitations, a detailed description of such LMP1 variants cannot be given here. Some of these variants, for instance the CAO-LMP1 variant derived from a Chinese NPC, exhibit altered signaling properties as compared to B95.8-LMP1 (Hu et al. 1991; Blake et al. 2001; Fielding et al. 2001; Stevenson et al. 2005; Mainou and Raab-Traub 2006).

4 Signal Transduction by LMP1

4.1 NF-κB Pathway

The first cellular signaling pathway identified as an LMP1 target was NF-κB (Fig. 2) (Laherty et al. 1992). The transcription factor NF-κB is a key regulator of lymphocyte development, immunity, inflammation, and cancer. The NF-κB family comprises five proteins, p65 (RelA), c-Rel, RelB, p50 (and its precursor p105), and p52 (and its precursor p100), which are kept inactive in the cytoplasm either by complex formation with inhibitory proteins of the inhibitor of NF-κB (IκB) family or as precursors (Vallabhapurapu and Karin 2009). Two major NF-κB pathways have been described, the canonical and the non-canonical pathway (Fig. 2). The canonical pathway involves phosphorylation of IκB proteins by IκB kinase 2

(IKK2) and the subsequent degradation of IκB, which liberates NF-κB dimers usually including p65. The non-canonical pathway depends on IKK1 and leads to the processing of p100 to p52 and the subsequent translocation of p52::RelB dimers to the nucleus (Vallabhapurapu and Karin 2009). Early studies revealed that both CTAR1 and CTAR2 contribute to the activation of NF-κB (Huen et al. 1995; Mitchell and Sugden 1995). However, CTAR1 induces multiple forms of NF-κB dimers, whereas CTAR2 activates complexes containing p65 (Paine et al. 1995). Later, it became evident that CTAR1 primarily activates the non-canonical NF-κB pathway including p100 to p52 processing and p50::p52 and p52::p65 dimers as well as atypical p50::p50::Bcl3 complexes, while CTAR2 is responsible for canonical NF-κB activation (Atkinson et al. 2003; Eliopoulos et al. 2003a; Saito et al. 2003; Thornburg et al. 2003; Luftig et al. 2004; Thornburg and Raab-Traub 2007). The canonical NF-κB pathway is essential for most CTAR2-dependent gene regulation (Gewurz et al. 2011). However, the recent global ChIP-seq analysis of the NF-κB-binding landscape in LCLs revealed a pattern of NF-κB complexes, which does not fully reflect the paradigm of canonical and non-canonical NF-κB pathways (Zhao et al. 2014). This result may indicate that our current view of LMP1-induced NF-κB activity still requires further refinement.

In the uninduced state, TRAF2 and TRAF3 are key inhibitors of the non-canonical NF-κB pathway leading to permanent degradation of NF-κB-inducing kinase (NIK). Upon activation, TRAF3 is cleared from the cytosol in a TRAF2 and cIAP1/2-dependent mechanism, which leads to NIK stabilization and NIK-mediated activation of IKK1 (Vallabhapurapu and Karin 2009). Overexpression of either TRAF was shown to reduce CTAR1-dependent NF-κB activation as well as processing of p100, and dominant-negative TRAF2 inhibited CTAR1 signaling, indicating that both TRAF2 and TRAF3 are involved in the regulation of non-canonical NF-κB by LMP1 (Devergne et al. 1996; Kaye et al. 1996; Song and Kang 2010). Accordingly, the siRNA-mediated knockdown of TRAF2 caused a marked reduction of total NF-κB activity and the concomitant induction of apoptosis in LCLs (Guasparri et al. 2008). However, and in contrast to CD40 signaling, TRAF3 is eliminated by LMP1 through a mechanism independent of the proteasome (Brown et al. 2001). Also, a non-essential role for TRAF6 in CTAR1 signaling has been suggested but still requires further validation (Schultheiss et al. 2001; Arcipowski et al. 2011).

Although dominant-negative TRAF2 had mild negative effects on CTAR2-induced NF-κB as well (Kaye et al. 1996), it is nowadays widely accepted that CTAR2 signaling does not depend on TRAF2 or its close relative TRAF5. Ligation of a CD40-LMP1 chimera in TRAF2-deficient mouse B cells still resulted in the degradation of IκBα (Xie and Bishop 2004). The double knockout of TRAF2 and TRAF5 in mouse embryonic fibroblasts did not impair CTAR2-induced IKK2 activation or translocation of canonical p65 NF-κB into the nucleus, excluding the possibility that TRAF2 deficiency was rescued by TRAF5 (Luftig et al. 2003; Wu et al. 2006). Instead of TRAF2, activation of canonical NF-κB by LMP1 requires TRAF6 and its function as an E3 ubiquitin ligase (Schultheiss et al. 2001). CTAR2-dependent NF-κB activation is blocked upon expression

of dominant-negative TRAF6 lacking its RING domain, and the deficiency of TRAF6 significantly reduces p65 translocation and NF-κB-dependent gene transcription induced by CTAR2 (Schultheiss et al. 2001; Luftig et al. 2003; Schneider et al. 2008; Boehm et al. 2010). TRADD was one of the first factors found to be involved in CTAR2-induced NF-κB signaling, albeit its interaction with LMP1 does not require the TRADD death domain (Izumi and Kieff 1997; Kieser et al. 1999; Schneider et al. 2008). Accordingly, a TRADD deletion mutant lacking the TRADD death domain, which is required for downstream signaling, acted as a dominant-negative allele in NF-κB signaling by LMP1 (Kieser et al. 1999). The genetic knockout of TRADD in human B cells delivered the definitive proof for an important role of TRADD in canonical NF-κB signaling by LMP1, because LMP1 was unable to activate IKK2 in the absence of TRADD in these cells (Schneider et al. 2008). However, the precise molecular function of TRADD in CTAR2 signaling is still not understood. TRADD might aid to stabilize the holocomplex at CTAR2, probably in a cell type-dependent manner depending on the abundance of other factors involved in CTAR2 signaling. In human B cells, TRADD seems to be required for the recruitment of IKK2 into the LMP1 complex (Schneider et al. 2008).

Further downstream in the cascade, TRAF6 recruits the germinal center kinase family member TRAF2- and Nck-interacting kinase (TNIK) to LMP1, which mediates canonical NF-κB and JNK signaling by the viral oncoprotein (Fig. 2) (Shkoda et al. 2012). TNIK is involved in the assembly of the TRAF6/TAB/TAK1/IKK2 complex and the bifurcation of the NF-κB and JNK pathways. The amino-terminal kinase domain of TNIK is required for NF-κB but not JNK signaling, whereas its carboxy-terminal germinal center kinase homology domain mediates JNK but not NF-κB activation (Shkoda et al. 2012). Interestingly, CTAR2 alone is able to induce an association between TNIK and TRAF2 as well, an interaction whose relevance for CTAR2 function is unclear (Shkoda et al. 2012). The TAK1 protein, but not its kinase activity, seems to be important for canonical NF-κB induction by LMP1, because the knockdown of TAK1, but not the chemical inhibition of its kinase activity, interfered with IKK2 activation by CTAR2 (Uemura et al. 2006; Wu et al. 2006). The IKK complex consisting of IKK1, IKK2, and the regulatory subunit NEMO (IKKγ) is the central mediator of the NF-κB pathway (Vallabhapurapu and Karin 2009). This is also true for LMP1 signaling, although the mode of NEMO utilization seems to differ from cellular receptors such as TNF-R1 or CD40 (Boehm et al. 2010). NEMO lacking its Zn-finger domain or part of the coiled coil region is capable of mediating NF-κB activation upon LMP1 expression, but not upon CD40 or TNF-R1 ligation in Jurkat T cells. However, the complete lack of NEMO blocks LMP1-induced canonical NF-κB in different cell types, underscoring its critical role in LMP1 signaling (Boehm et al. 2010). Likewise, inhibition or lack of IKK2 abolishes LMP1-induced NF-κB activity, confirming the essential role of this IKK isoform in LMP1 signaling (Luftig et al. 2003; Boehm et al. 2010). However, recent knockdown experiments suggested that IKK1 and IKK2 have partially redundant roles in this pathway (Gewurz et al. 2012).

Interleukin 1 receptor-associated kinase 1 (IRAK1), a coplayer of TRAF6 in Toll-like/IL-1 receptor signaling, is also involved in canonical NF-κB activation by LMP1, albeit its kinase activity seems to be dispensable for this pathway (Luftig et al. 2003; Song et al. 2006). IRAK1 deficiency does not interfere with IKK2 activation or p65 translocation induced by LMP1 but rather with p65 phosphorylation at serine 536, suggesting that IRAK1 plays a different role in LMP1 signaling compared to cellular receptors (Song et al. 2006). IRAK1 function in this pathway requires its association with Ca^{2+}/Calmodulin-dependent kinase II (CaMKII), which phosphorylates p65 (Kim et al. 2014).

4.2 MAPK Pathways—JNK, ERK, and P38 MAPK

It was in the year 1997 when JNK/AP1 was identified as the second major pathway activated by LMP1 in epithelial cells and LCLs (Kieser et al. 1997). AP1 is a dimeric transcription factor composed of members of the Jun and Fos proto-oncoprotein families. AP1 was found induced by LMP1 through the JNK signaling cascade, involving JNK1-mediated phosphorylation and activation of c-Jun (Kieser et al. 1997). JNK belongs, together with ERK and p38 MAPK, to the MAPK family of kinases. JNK1 activation critically relies on CTAR2 and its P_{379}VQLSYY motif (Fig. 2) (Kieser et al. 1997, 1999; Eliopoulos and Young 1998). It has long been unclear which signaling mediators at CTAR2 are involved in JNK activation. The use of dominant-negative TRAF2 alleles yielded conflicting results regarding a potential role of TRAF2 in this pathway (Eliopoulos et al. 1999a; Kieser et al. 1999). Several years later, experiments in TRAF2-deficient fibroblasts and B cells finally excluded a critical function of TRAF2 in JNK activation by LMP1, because the pathway was fully functional in cells lacking TRAF2 (Wan et al. 2004; Xie et al. 2004). JNK signaling is also intact in mouse embryonic fibroblasts devoid of both TRAF2 and TRAF5 (own unpublished data). A potential function of TRADD in JNK signaling by LMP1 had been subject of discussion for quite some time. Although overexpression of TRADD enhanced JNK signaling by LMP1, dominant-negative TRADD did not block the pathway in HEK293 cells (Eliopoulos et al. 1999a; Kieser et al. 1999). The issue was clarified when neither the knockdown of TRADD in HeLa cells nor the genetic knockout of TRADD in human B cells impaired JNK signaling by LMP1, demonstrating that TRADD is not critical for this pathway (Wan et al. 2004; Schneider et al. 2008). As with canonical NF-κB signaling, it turned out that TRAF6 is in fact the essential mediator of CTAR2-induced JNK activity (Wan et al. 2004). The pathway further involves TAB1, TAK1, and TNIK, the latter orchestrating the bifurcation of canonical NF-κB and JNK (Wan et al. 2004; Uemura et al. 2006; Shkoda et al. 2012).

It seems as if LMP1 is able to eventually make use of different panels of TRAF molecules to establish its signaling network, likely depending on the investigated cell type. Usually, JNK activation by LMP1 is exclusively triggered at CTAR2.

In some cell lines, however, CTAR1 contributes to JNK activity as well. JNK1 activation in Rat-1 cells was equally mapped to CTAR1 and CTAR2 (Kutz et al. 2008). Likewise, CTAR1 alone can induce JNK in BJAB cells, which is due to the very strong expression of TRAF1 in these cells. Accordingly, JNK1 activation by CTAR1 was possible after overexpression of TRAF1 in HEK293 cells (Eliopoulos et al. 2003b). Also, TRAF3 can eventually have a role in JNK signaling, as was demonstrated in TRAF3-deficient mouse B lymphoblastic leukemia cells (Xie et al. 2004). Likely, LMP1 constitutes a versatile viral oncoprotein that is variable in establishing its signaling network dependent on the cellular context it comes across.

LMP1 induces the ERK pathway (Fig. 3) (Liu et al. 2003). ERK activity in epithelial cells is mainly initiated at CTAR1 via the canonical Raf-MEK-ERK pathway independent of Ras (Dawson et al. 2008). The mechanism of ERK activation at CTAR1 is still unresolved. An involvement of TRAF2 and TRAF3 in ERK activation has been proposed, because expression of dominant-negative TRAF2 and TRAF3 reduced ERK phosphorylation induced by LMP1 (Mainou et al. 2007). At the same time, mutation of P_{204}xQxT to A_{204}xAxA abolished ERK activation (Mainou et al. 2007). However, mutation of this motif to A_{204}xAxT, which is incapable of binding TRAF2 (Devergne et al. 1998), was not sufficient to reduce pathway activation, indicating that the mechanism of ERK activation might involve other molecules besides of TRAFs. Another component of the pathway is the isoform δ of protein kinase C (PKCδ). Inhibition of this kinase by the PKCδ inhibitor Rottlerin abolished ERK activation after LMP1-CTAR1 expression in C33A cells

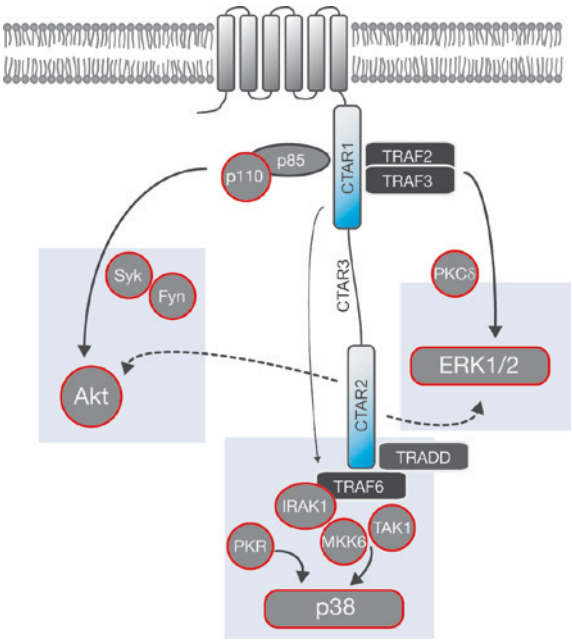

Fig. 3 PI3-K/AKT, p38 MAPK, and ERK signaling by LMP1

(Kung et al. 2011). In HEK293 cells, also CTAR2 can activate ERK (Gewurz et al. 2011). Particularly, the latter result suggests that also the ERK pathway may be regulated by different mechanisms in different cell types.

The p38 MAPK pathway is induced by LMP1 as well, mediating upregulation of IL-6, IL-8, and IL-10 (Fig. 3) (Eliopoulos et al. 1999b; Vockerodt et al. 2001). Both CTAR1 and CTAR2 are involved in the pathway, although the contribution of CTAR2 to p38 MAPK activation is more prevalent (Schultheiss et al. 2001). TRAF6 is the key component of this pathway as was demonstrated by defective LMP1 signaling to p38 MAPK in TRAF6-deficient MEFs (Schultheiss et al. 2001). Also, the lack of IRAK1 causes a defect in p38 MAPK signaling by LMP1 (Song et al. 2006). Other kinases involved in p38 MAPK signaling by LMP1 include MKK6, TAK1, and PKR (Schultheiss et al. 2001; Wan et al. 2004; Lin et al. 2010).

4.3 PI3-K/AKT Pathway

The PI3-K/AKT pathway is induced by a wide range of cellular receptors and is an important mitogenic stimulus in many cell types. Activation of the PI3-K/AKT pathway was first linked to LMP1 in the year 2003, when Dawson and colleagues immunoprecipitated the p85α regulatory subunit of PI3-K together with LMP1 from HeLa cells (Fig. 3) (Dawson et al. 2003). Although it is still unclear whether this interaction is direct, expression of LMP1-CTAR1 caused (i) an enrichment of the PI3-K substrate phosphatidylinositol-3,4,5-trisphosphate (PIP3) in the plasma membrane and (ii) the phosphorylation and activation of AKT kinase, also known as protein kinase B, at serine 473 (Dawson et al. 2003). Dominant-negative p85 or the PI3-K inhibitor LY294002 blocked LMP1-induced stress fiber formation and actin remodeling as well as transformation of rat fibroblasts (Dawson et al. 2003; Mainou et al. 2005). It is accepted that CTAR1 and the TRAF-binding site P_{204}xQxT are involved in activation of the PI3-K/AKT pathway (Dawson et al. 2003; Mainou et al. 2007; Lambert and Martinez 2007). However, CTAR2 alone was as efficient as CTAR1 in inducing AKT phosphorylation in C666-1 cells, indicating the existence of a CTAR2-dependent PI3-K/AKT pathway (Shair et al. 2008). The precise mechanism of PI3-K/AKT activation by LMP1 has not been fully elucidated but may involve the Src family tyrosine kinases Fyn and Syk (Hatton et al. 2012).

4.4 IRF7 Pathway

The transcription factor IRF7 is a critical regulator of type I interferon and thus adaptive and innate immune responses as well as of EBV latency (Zhang and Pagano 2001). LMP1 induces IRF7 expression and facilitates its ubiquitination,

phosphorylation, and nuclear translocation (Zhang and Pagano 2000; Ning et al. 2003; Huye et al. 2007). CTAR2 is involved in recruiting IRF7 to LMP1, which is a function of LMP1 that is independent of the TRADD and TRAF6 interaction site $Y_{384}Y$ (Song et al. 2008). CTAR2 then mediates IRF7 ubiquitination in a receptor-interacting protein 1 (RIP1)- and TRAF6-dependent mechanism (Huye et al. 2007; Ning et al. 2008; Song et al. 2008). TRAF6 is involved in IRF7 activation by acting as E3 ubiquitin ligase, which mediates linkage of ubiquitin chains at the carboxy-terminal lysines 444, 446, and 452 of IRF7 (Ning et al. 2008). Two major mechanisms have been identified, aiding the negative regulation of IRF7 activity. First, LMP1 induces expression of A20, which acts as a deubiquitinase for IRF7 and thus negatively regulates its activity as a transcription factor (Ning and Pagano 2010). Furthermore, SUMOylation of IRF7 at lysine 452 was shown to decrease DNA-binding and transcriptional activity of IRF7. Interestingly, this mechanism is dependent on CTAR3 and its interaction with the SUMO-conjugating enzyme Ubc9 (Bentz et al. 2011, 2012).

5 Future Perspectives

Despite thirty years of research and more than 2000 papers on the molecular and biological functions of LMP1, many important questions still remain unanswered. The molecular signaling mechanisms at the effector sites CTAR1 and CTAR2 have not been fully elucidated. Particularly, the composition and precise architecture of the signaling complex at CTAR2 including the intermolecular interactions between the components of this complex is still unresolved. The situation is getting more complex by the fact that LMP1 molecules reside within large clusters and several LMP1 molecules might be involved in forming functional CTAR1 or CTAR2 complexes of higher order. This could mean that not all components of the CTAR2 complex must necessarily interact with the same LMP1 molecule to form an active signaling complex. Also, molecular interactions between CTAR1 and CTAR2 have been suggested, although both domains can function independently from each other (Floettmann et al. 1998). The elucidation of an LMP1 crystal structure, possibly in complex with LMP1-binding partner(s), will certainly be very important to answer these questions.

Other urgent questions concern the functions of LMP1 during EBV infection and the establishment of latency in vivo. Usually and due to the lack of appropriate in vivo infection models for EBV, the analysis of LMP1's functions has largely been restricted to its role in cell transformation in cell culture. It is likely that some LMP1-induced pathways have so far unrecognized functions in the establishment of latent infection in vivo and in immune modulation. The role of LMP1 during early infection of B cells is also unclear. LMP1 expression starts four days post-infection with EBV. Surprisingly, LCL expression levels are reached only three weeks after infection, and LMP1-induced NF-κB seems to be dispensable during that time (Price et al. 2012).

LMP1 is present in exosomes that are secreted from EBV-positive B cell and NPC lines (Dukers et al. 2000; Meckes et al. 2010). The functions of secreted LMP1 in immune modulation, cell–cell communication, tumor microenvironment, and potential other processes will also be interesting topics of future research.

Another enigma are the biological and molecular functions of a truncated variant of LMP1, the so-called lytic LMP1, which is highly expressed during the lytic cycle from the ED-L1A promoter located within the first intron of the LMP1 gene (Hudson et al. 1985; Modrow and Wolf 1986; Baichwal and Sugden 1987; Erickson and Martin 1997). Due to the lack of the first four transmembrane domains, lytic LMP1 is incapable of oligomerization and, thus, likely unable to signal (Mitchell and Sugden 1995; Gires et al. 1997). Lytic LMP1 rather inhibits the activity of full-length LMP1 (Erickson and Martin 2000). In contrast to full-length LMP1, the lytic variant has no transforming capacity in fibroblasts and is not essential for B cell transformation by EBV (Wang et al. 1988a; Dirmeier et al. 2003).

Due to its proven critical importance for cell transformation and pathogenesis, LMP1 constitutes an excellent therapeutic target for intervention strategies against EBV-associated malignancies. By inhibiting LCL tumor growth with a small molecule JNK inhibitor, we have already delivered proof of principle that targeting of LMP1's signaling network is a feasible strategy (Kutz et al. 2008). However, to be more specific for LMP1, future approaches shall rather target the LMP1 molecule itself or exploit the unique interface between LMP1 and its critical cellular signaling molecules such as CTAR1::TRAF2 or CTAR2::TRAF6 as targets for small molecule inhibitors. For instance, DNAzymes targeting LMP1 expression have antitumor effects and sensitize NPC cells for radiotherapy (Cao et al. 2014). Our own laboratory is involved in the screening for inhibitors of CTAR1::TRAF2 interaction, which shall block this interaction and uncouple LMP1 from critical parts of its transforming signaling network.

References

Adler B, Schaadt E, Kempkes B, Zimber-Strobl U, Baier B, Bornkamm GW (2002) Control of Epstein-Barr virus reactivation by activated CD40 and viral latent membrane protein 1. Proc Natl Acad Sci USA 99(1):437–442

Allday MJ, Crawford DH, Griffin BE (1989) Epstein-Barr virus latent gene expression during the initiation of B cell immortalization. J Gen Virol 70(Pt 7):1755–1764

Amort M, Nachbauer B, Tuzlak S, Kieser A, Schepers A, Villunger A, Polacek A (2015) Expression of the vault RNA protects cells from undergoing apoptosis. Nat Com 6:7030

Arcipowski KM, Stunz LL, Graham JP, Kraus ZJ, Vanden Bush TJ, Bishop GA (2011) Molecular mechanisms of TNFR-associated factor 6 (TRAF6) utilization by the oncogenic viral mimic of CD40, latent membrane protein 1 (LMP1). J Biol Chem 286(12):9948–9955

Ardila-Osorio H, Clausse B, Mishal Z, Wiels J, Tursz T, Busson P (1999) Evidence of LMP1-TRAF3 interactions in glycosphingolipid-rich complexes of lymphoblastoid and nasopharyngeal carcinoma cells. Int J Cancer 81(4):645–649

Atkinson PG, Coope HJ, Rowe M, Ley SC (2003) Latent membrane protein 1 of Epstein-Barr virus stimulates processing of NF-kappa B2 p100 to p52. J Biol Chem 278(51):51134–51142

Aviel S, Winberg G, Massucci M, Ciechanover A (2000) Degradation of the Epstein-Barr virus latent membrane protein 1 (LMP1) by the ubiquitin-proteasome pathway. Targeting via ubiquitination of the N-terminal residue. J Biol Chem 275(31):23491–23499

Babcock GJ, Hochberg D, Thorley-Lawson AD (2000) The expression pattern of Epstein-Barr virus latent genes in vivo is dependent upon the differentiation stage of the infected B cell. Immunity 13(4):497–506

Baichwal VR, Sugden B (1987) Posttranslational processing of an Epstein-Barr virus-encoded membrane protein expressed in cells transformed by Epstein-Barr virus. J Virol 61(3):866–875

Baichwal VR, Sugden B (1988) Transformation of Balb 3T3 cells by the BNLF-1 gene of Epstein-Barr virus. Oncogene 2(5):461–467

Bentz GL, Whitehurst CB, Pagano JS (2011) Epstein-Barr virus latent membrane protein 1 (LMP1) C-terminal-activating region 3 contributes to LMP1-mediated cellular migration via its interaction with Ubc9. J Virol 85(19):10144–10153

Bentz GL, Shackelford J, Pagano JS (2012) Epstein-Barr virus latent membrane protein 1 regulates the function of interferon regulatory factor 7 by inducing its sumoylation. J Virol 86(22):12251–12261

Blake SM, Eliopoulos AG, Dawson CW, Young LS (2001) The transmembrane domains of the EBV-encoded latent membrane protein 1 (LMP1) variant CAO regulate enhanced signalling activity. Virology 282(2):278–287

Boehm D, Gewurz BE, Kieff E, Cahir-McFarland E (2010) Epstein-Barr latent membrane protein 1 transformation site 2 activates NF-kappaB in the absence of NF-kappaB essential modifier residues 133–224 or 373–419. Proc Natl Acad Sci USA 107(42):18103–18108

Brodeur SR, Cheng G, Baltimore D, Thorley-Lawson DA (1997) Localization of the major NF-kappaB-activating site and the sole TRAF3 binding site of LMP-1 defines two distinct signaling motifs. J Biol Chem 272(32):19777–19784

Brown KD, Hostager BS, Bishop GA (2001) Differential signaling and tumor necrosis factor receptor-associated factor (TRAF) degradation mediated by CD40 and the Epstein-Barr virus oncoprotein latent membrane protein 1 (LMP1). J Exp Med 193(8):943–954

Busch LK, Bishop GA (1999) The EBV transforming protein, latent membrane protein 1, mimics and cooperates with CD40 signaling in B lymphocytes. J Immunol 162(5):2555–2561

Cahir-McFarland ED, Izumi KM, Mosialos G (1999) Epstein-barr virus transformation: involvement of latent membrane protein 1-mediated activation of NF-kappaB. Oncogene 18(49):6959–6964

Cahir-McFarland ED, Carter K, Rosenwald A, Giltnane JM, Henrickson SE, Staudt LM, Kieff E (2004) Role of NF-kappa B in cell survival and transcription of latent membrane protein 1-expressing or Epstein-Barr virus latency III-infected cells. J Virol 78(8):4108–4119

Cao Y, Yang L, Jiang W, Wang X, Liao W, Tan G, Liao Y, Qiu Y, Feng D, Tang F, Hou BL, Zhang L, Fu J, He F, Liu X, Jiang W, Yang T, Sun LQ (2014) Therapeutic evaluation of Epstein-Barr virus-encoded latent membrane protein-1 targeted DNAzyme for treating of nasopharyngeal carcinomas. Mol Ther 22(2):371–377

Chatterjee B, Leung CS, Munz C (2014) Animal models of Epstein Barr virus infection. J Immunol Methods 410:80–87

Chen H, Lee JM, Zong Y, Borowitz M, Ng MH, Ambinder RF, Hayward SD (2001) Linkage between STAT regulation and Epstein-Barr virus gene expression in tumors. J Virol 75(6):2929–2937

Chen H, Hutt-Fletcher L, Cao L, Hayward SD (2003) A positive autoregulatory loop of LMP1 expression and STAT activation in epithelial cells latently infected with Epstein-Barr virus. J Virol 77(7):4139–4148

Chen CC, Liu HP, Chao M, Liang Y, Tsang NM, Huang HY, Wu CC, Chang YS (2014) NF-kappaB-mediated transcriptional upregulation of TNFAIP2 by the Epstein-Barr virus oncoprotein, LMP1, promotes cell motility in nasopharyngeal carcinoma. Oncogene 33(28):3648–3659

Chew MM, Gan SY, Khoo AS, Tan EL (2010) Interleukins, laminin and Epstein-Barr virus latent membrane protein 1 (EBV LMP1) promote metastatic phenotype in nasopharyngeal carcinoma. BMC Cancer 10:574

Coffin WF 3rd, Erickson KD, Hoedt-Miller M, Martin JM (2001) The cytoplasmic amino-terminus of the Latent Membrane Protein-1 of Epstein-Barr virus: relationship between transmembrane orientation and effector functions of the carboxy-terminus and transmembrane domain. Oncogene 20(38):5313–5330

Coffin WF 3rd, Geiger TR, Martin JM (2003) Transmembrane domains 1 and 2 of the latent membrane protein 1 of Epstein-Barr virus contain a lipid raft targeting signal and play a critical role in cytostasis. J Virol 77(6):3749–3758

Cohen JI (2000) Epstein-Barr virus infection. N Engl J Med 343(7):481–492

Curran JA, Laverty FS, Campbell D, Macdiarmid J, Wilson JB (2001) Epstein-Barr virus encoded latent membrane protein-1 induces epithelial cell proliferation and sensitizes transgenic mice to chemical carcinogenesis. Cancer Res 61(18):6730–6738

Dawson CW, Rickinson AB, Young LS (1990) Epstein-Barr virus latent membrane protein inhibits human epithelial cell differentiation. Nature 344:777–780

Dawson CW, Tramountanis G, Eliopoulos AG, Young LS (2003) Epstein-Barr virus latent membrane protein 1 (LMP1) activates the phosphatidylinositol 3-kinase/Akt pathway to promote cell survival and induce actin filament remodeling. J Biol Chem 278(6):3694–3704

Dawson CW, Laverick L, Morris MA, Tramoutanis G, Young LS (2008) Epstein-Barr virus-encoded LMP1 regulates epithelial cell motility and invasion via the ERK-MAPK pathway. J Virol 82(7):3654–3664

Demetriades C, Mosialos G (2009) The LMP1 promoter can be transactivated directly by NF-kappaB. J Virol 83(10):5269–5277

Devergne O, Hatzivassiliou E, Izumi KM, Kaye KM, Kleijnen MF, Kieff E, Mosialos G (1996) Association of TRAF1, TRAF2, and TRAF3 with an Epstein-Barr virus LMP1 domain important for B-lymphocyte transformation: role in NF-kappaB activation. Mol Cell Biol 16(12):7098–7108

Devergne O, Cahir-McFarland ED, Mosialos G, Izumi KM, Ware CF, Kieff E (1998) Role of the TRAF binding site and NF-kappaB activation in Epstein-Barr virus latent membrane protein 1-induced cell gene expression. J Virol 72(10):7900–7908

Ding L, Li L, Yang J, Zhou S, Li W, Tang M, Shi Y, Yi W, Cao Y (2007) Latent membrane protein 1 encoded by Epstein-Barr virus induces telomerase activity via p16INK4A/Rb/E2F1 and JNK signaling pathways. J Med Virol 79(8):1153–1163

Dirmeier U, Neuhierl B, Kilger E, Reisbach G, Sandberg ML, Hammerschmidt W (2003) Latent membrane protein 1 is critical for efficient growth transformation of human B cells by Epstein-Barr virus. Cancer Res 63(11):2982–2989

Dirmeier U, Hoffmann R, Kilger E, Schultheiss U, Briseno C, Gires O, Kieser A, Eick D, Sugden B, Hammerschmidt W (2005) Latent membrane protein 1 of Epstein-Barr virus coordinately regulates proliferation with control of apoptosis. Oncogene 24(10):1711–1717

D'Souza BN, Edelstein LC, Pegman PM, Smith SM, Loughran ST, Clarke A, Mehl A, Rowe M, Gelinas C, Walls D (2004) Nuclear factor kappa B-dependent activation of the antiapoptotic bfl-1 gene by the Epstein-Barr virus latent membrane protein 1 and activated CD40 receptor. J Virol 78(4):1800–1816

Dukers DF, Meij P, Vervoort MB, Vos W, Scheper RJ, Meijer CJ, Bloemena E, Middeldorp JM (2000) Direct immunosuppressive effects of EBV-encoded latent membrane protein 1. J Immunol 165(2):663–670

Eliopoulos AG, Young LS (1998) Activation of the cJun N-terminal kinase (JNK) pathway by the Epstein-Barr virus-encoded latent membrane protein 1 (LMP1). Oncogene 16(13):1731–1742

Eliopoulos AG, Blake SM, Floettmann JE, Rowe M, Young LS (1999a) Epstein-Barr virus-encoded latent membrane protein 1 activates the JNK pathway through its extreme C terminus via a mechanism involving TRADD and TRAF2. J Virol 73(2):1023–1035

Eliopoulos AG, Gallagher NJ, Blake SM, Dawson CW, Young LS (1999b) Activation of the p38 mitogen-activated protein kinase pathway by Epstein-Barr virus-encoded latent membrane protein 1 coregulates interleukin-6 and interleukin-8 production. J Biol Chem 274(23):16085–16096

Eliopoulos AG, Caamano JH, Flavell J, Reynolds GM, Murray PG, Poyet JL, Young LS (2003a) Epstein-Barr virus-encoded latent infection membrane protein 1 regulates the processing of p100 NF-kappaB2 to p52 via an IKKgamma/NEMO-independent signalling pathway. Oncogene 22(48):7557–7569

Eliopoulos AG, Waites ER, Blake SM, Davies C, Murray P, Young LS (2003b) TRAF1 is a critical regulator of JNK signaling by the TRAF-binding domain of the Epstein-Barr virus-encoded latent infection membrane protein 1 but not CD40. J Virol 77(2):1316–1328

Endo K, Kondo S, Shackleford J, Horikawa T, Kitagawa N, Yoshizaki T, Furukawa M, Zen Y, Pagano JS (2009) Phosphorylated ezrin is associated with EBV latent membrane protein 1 in nasopharyngeal carcinoma and induces cell migration. Oncogene 28(14):1725–1735

Erickson KD, Martin JM (1997) Early detection of the lytic LMP-1 protein in EBV-infected B-cells suggests its presence in the virion. Virology 234(1):1–13

Erickson KD, Martin JM (2000) The late lytic LMP-1 protein of Epstein-Barr virus can negatively regulate LMP-1 signaling. J Virol 74(2):1057–1060

Everly DN Jr, Mainou BA, Raab-Traub N (2004) Induction of Id1 and Id3 by latent membrane protein 1 of Epstein-Barr virus and regulation of p27/Kip and cyclin-dependent kinase 2 in rodent fibroblast transformation. J Virol 78(24):13470–13478

Fahraeus R, Jansson A, Ricksten A, Sjoblom A, Rymo L (1990) Epstein-Barr virus-encoded nuclear antigen 2 activates the viral latent membrane protein promoter by modulating the activity of a negative regulatory element. Proc Natl Acad Sci USA 87(19):7390–7394

Faumont N, Durand-Panteix S, Schlee M, Gromminger S, Schuhmacher M, Holzel M, Laux G, Mailhammer R, Rosenwald A, Staudt LM, Bornkamm GW, Feuillard J (2009) c-Myc and Rel/NF-kappaB are the two master transcriptional systems activated in the latency III program of Epstein-Barr virus-immortalized B cells. J Virol 83(10):5014–5027

Fennewald S, van Santen V, Kieff E (1984) Nucleotide sequence of an mRNA transcribed in latent growth-transforming virus infection indicates that it may encode a membrane protein. J Virol 51(2):411–419

Feuillard J, Schuhmacher M, Kohanna S, Asso-Bonnet M, Ledeur F, Joubert-Caron R, Bissieres P, Polack A, Bornkamm GW, Raphael M (2000) Inducible loss of NF-kappaB activity is associated with apoptosis and Bcl-2 down-regulation in Epstein-Barr virus-transformed B lymphocytes. Blood 95(6):2068–2075

Fielding CA, Sandvej K, Mehl A, Brennan P, Jones M, Rowe M (2001) Epstein-Barr virus LMP-1 natural sequence variants differ in their potential to activate cellular signaling pathways. J Virol 75(19):9129–9141

Floettmann JE, Rowe M (1997) Epstein-Barr virus latent membrane protein-1 (LMP1) C-terminus activation region 2 (CTAR2) maps to the far C-terminus and requires oligomerisation for NF-kappaB activation. Oncogene 15(15):1851–1858

Floettmann JE, Eliopoulos AG, Jones M, Young LS, Rowe M (1998) Epstein-Barr virus latent membrane protein-1 (LMP1) signalling is distinct from CD40 and involves physical cooperation of its two C-terminus functional regions. Oncogene 17(18):2383–2392

Gewurz BE, Mar JC, Padi M, Zhao B, Shinners NP, Takasaki K, Bedoya E, Zou JY, Cahir-McFarland E, Quackenbush J, Kieff E (2011) Canonical NF-kappaB activation is essential for Epstein-Barr virus latent membrane protein 1 TES2/CTAR2 gene regulation. J Virol 85(13):6764–6773

Gewurz BE, Towfic F, Mar JC, Shinners NP, Takasaki K, Zhao B, Cahir-McFarland ED, Quackenbush J, Xavier RJ, Kieff E (2012) Genome-wide siRNA screen for mediators of NF-kappaB activation. Proc Natl Acad Sci USA 109(7):2467–2472

Gires O, Zimber-Strobl U, Gonnella R, Ueffing M, Marschall G, Zeidler R, Pich D, Hammerschmidt W (1997) Latent membrane protein 1 of Epstein-Barr virus mimics a constitutively active receptor molecule. EMBO J 16(20):6131–6140

Gires O, Kohlhuber F, Kilger E, Baumann M, Kieser A, Kaiser C, Zeidler R, Scheffer B, Ueffing M, Hammerschmidt W (1999) Latent membrane protein 1 of Epstein-Barr virus interacts with JAK3 and activates STAT proteins. EMBO J 18(11):3064–3073

Grimm T, Schneider S, Naschberger E, Huber J, Guenzi E, Kieser A, Reitmeir P, Schulz TF, Morris CA, Sturzl M (2005) EBV latent membrane protein-1 protects B cells from apoptosis by inhibition of BAX. Blood 105(8):3263–3269

Guasparri I, Bubman D, Cesarman E (2008) EBV LMP2A affects LMP1-mediated NF-κB signaling and survival of lymphoma cells by regulating TRAF2 expression. Blood 111(7):3813–3820

Hammerschmidt W, Sugden B, Baichwal VR (1989) The transforming domain alone of the latent membrane protein of Epstein-Barr virus is toxic to cells when expressed at high levels. J Virol 63(6):2469–2475

Hannigan A, Qureshi AM, Nixon C, Tsimbouri PM, Jones S, Philbey AW, Wilson JB (2011) Lymphocyte deficiency limits Epstein-Barr virus latent membrane protein 1 induced chronic inflammation and carcinogenic pathology in vivo. Mol Cancer 10(1):11

Hatton O, Lambert SL, Krams SM, Martinez OM (2012) Src kinase and Syk activation initiate PI3K signaling by a chimeric latent membrane protein 1 in Epstein-Barr virus (EBV)+ B cell lymphomas. PLoS ONE 7(8):e42610

Hatton OL, Harris-Arnold A, Schaffert S, Krams SM, Martinez OM (2014) The interplay between Epstein-Barr virus and B lymphocytes: implications for infection, immunity, and disease. Immunol Res 58(2–3):268–276

Hatzivassiliou E, Miller WE, Raab-Traub N, Kieff E, Mosialos G (1998) A fusion of the EBV latent membrane protein-1 (LMP1) transmembrane domains to the CD40 cytoplasmic domain is similar to LMP1 in constitutive activation of epidermal growth factor receptor expression, nuclear factor-kappa B, and stress-activated protein kinase. J Immunol 160(3):1116–1121

Hau PM, Tsang CM, Yip YL, Huen MS, Tsao SW (2011) Id1 interacts and stabilizes the Epstein-Barr virus latent membrane protein 1 (LMP1) in nasopharyngeal epithelial cells. PLoS ONE 6(6):e21176

Henderson S, Rowe M, Gregory C, Croom-Carter D, Wang F, Longnecker R, Kieff E, Rickinson A (1991) Induction of bcl-2 expression by Epstein-Barr virus latent membrane protein 1 protects infected B cells from programmed cell death. Cell 65(7):1107–1115

Hennessy K, Fennewald S, Hummel M, Cole T, Kieff E (1984) A membrane protein encoded by Epstein-Barr virus in latent growth-transforming infection. Proc Natl Acad Sci USA 81(22):7207–7211

Higuchi M, Izumi KM, Kieff E (2001) Epstein-Barr virus latent-infection membrane proteins are palmitoylated and raft-associated: protein 1 binds to the cytoskeleton through TNF receptor cytoplasmic factors. Proc Natl Acad Sci USA 98(8):4675–4680

Higuchi M, Kieff E, Izumi KM (2002) The Epstein-Barr virus latent membrane protein 1 putative Janus kinase 3 (JAK3) binding domain does not mediate JAK3 association or activation in B-lymphoma or lymphoblastoid cell lines. J Virol 76(1):455–459

Hu LF, Zabarovsky ER, Chen F, Cao SL, Ernberg I, Klein G, Winberg G (1991) Isolation and sequencing of the Epstein-Barr virus BNLF-1 gene (LMP1) from a Chinese nasopharyngeal carcinoma. J Gen Virol 72(Pt 10):2399–2409

Huang YT, Sheen TS, Chen CL, Lu J, Chang Y, Chen JY, Tsai CH (1999) Profile of cytokine expression in nasopharyngeal carcinomas: a distinct expression of interleukin 1 in tumor and CD4+ T cells. Cancer Res 59(7):1599–1605

Huang S, Stupack D, Liu A, Cheresh D, Nemerow GR (2000) Cell growth and matrix invasion of EBV-immortalized human B lymphocytes is regulated by expression of alpha(v) integrins. Oncogene 19(15):1915–1923

Hudson GS, Farrell PJ, Barrell BG (1985) Two related but differentially expressed potential membrane proteins encoded by the EcoRI Dhet region of Epstein-Barr virus B95-8. J Virol 53(2):528–535

Huen DS, Henderson SA, Croom-Carter D, Rowe M (1995) The Epstein-Barr virus latent membrane protein-1 (LMP1) mediates activation of NF-kappa B and cell surface phenotype via two effector regions in its carboxy-terminal cytoplasmic domain. Oncogene 10(3):549–560

Huye LE, Ning S, Kelliher M, Pagano JS (2007) Interferon regulatory factor 7 is activated by a viral oncoprotein through RIP-dependent ubiquitination. Mol Cell Biol 27(8):2910–2918

Izumi KM, Kieff ED (1997) The Epstein-Barr virus oncogene product latent membrane protein 1 engages the tumor necrosis factor receptor-associated death domain protein to mediate B lymphocyte growth transformation and activate NF-kappaB. Proc Natl Acad Sci USA 94(23):12592–12597

Izumi KM, Kaye KM, Kieff ED (1994) Epstein-Barr virus recombinant molecular genetic analysis of the LMP1 amino-terminal cytoplasmic domain reveals a probable structural role, with no component essential for primary B-lymphocyte growth transformation. J Virol 68(7):4369–4376

Izumi KM, Kaye KM, Kieff ED (1997) The Epstein-Barr virus LMP1 amino acid sequence that engages tumor necrosis factor receptor associated factors is critical for primary B lymphocyte growth transformation. Proc Natl Acad Sci USA 94(4):1447–1452

Izumi KM, Cahir-McFarland ED, Riley EA, Rizzo D, Chen Y, Kieff E (1999) The residues between the two transformation effector sites of Epstein-Barr virus latent membrane protein 1 are not critical for B-lymphocyte growth transformation. J Virol 73(12):9908–9916

Johansson P, Jansson A, Ruetschi U, Rymo L (2009) Nuclear factor-kappaB binds to the Epstein-Barr virus LMP1 promoter and upregulates its expression. J Virol 83(3):1393–1401

Johansson P, Jansson A, Ruetschi U, Rymo L (2010) The p38 signaling pathway upregulates expression of the Epstein-Barr virus LMP1 oncogene. J Virol 84(6):2787–2797

Kaye KM, Izumi KM, Kieff E (1993) Epstein-Barr virus latent membrane protein 1 is essential for B-lymphocyte growth transformation. Proc Natl Acad Sci USA 90(19):9150–9154

Kaye KM, Izumi KM, Mosialos G, Kieff E (1995) The Epstein-Barr virus LMP1 cytoplasmic carboxy terminus is essential for B-lymphocyte transformation; fibroblast cocultivation complements a critical function within the terminal 155 residues. J Virol 69(2):675–683

Kaye KM, Devergne O, Harada JN, Izumi KM, Yalamanchili R, Kieff E, Mosialos G (1996) Tumor necrosis factor receptor associated factor 2 is a mediator of NF-kappa B activation by latent infection membrane protein 1, the Epstein-Barr virus transforming protein. Proc Natl Acad Sci USA 93(20):11085–11090

Kaye KM, Izumi KM, Li H, Johannsen E, Davidson D, Longnecker R, Kieff E (1999) An Epstein-Barr virus that expresses only the first 231 LMP1 amino acids efficiently initiates primary B-lymphocyte growth transformation. J Virol 73(12):10525–10530

Kieser A (2008) Pursuing different 'TRADDes': TRADD signaling induced by TNF-receptor 1 and the Epstein-Barr virus oncoprotein LMP1. Biol Chem 389(10):1261–1271

Kieser A, Kilger E, Gires O, Ueffing M, Kolch W, Hammerschmidt W (1997) Epstein-Barr virus latent membrane protein-1 triggers AP-1 activity via the c-Jun N-terminal kinase cascade. EMBO J 16(21):6478–6485

Kieser A, Kaiser C, Hammerschmidt W (1999) LMP1 signal transduction differs substantially from TNF receptor 1 signaling in the molecular functions of TRADD and TRAF2. EMBO J 18(9):2511–2521

Kilger E, Kieser A, Baumann M, Hammerschmidt W (1998) Epstein-Barr virus-mediated B-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated CD40 receptor. EMBO J 17(6):1700–1709

Kim JE, Kim SY, Lim SY, Kieff E, Song YJ (2014) Role of Ca2+/Calmodulin-dependent Kinase II-IRAK1 interaction in LMP1-induced NF-kappaB activation. Mol Cell Biol 34(3):325–334

Kis LL, Takahara M, Nagy N, Klein G, Klein E (2006) IL-10 can induce the expression of EBV-encoded latent membrane protein-1 (LMP-1) in the absence of EBNA-2 in B lymphocytes and in Burkitt lymphoma- and NK lymphoma-derived cell lines. Blood 107(7):2928–2935

Kis LL, Salamon D, Persson EK, Nagy N, Scheeren FA, Spits H, Klein G, Klein E (2010) IL-21 imposes a type II EBV gene expression on type III and type I B cells by the repression of C- and activation of LMP-1-promoter. Proc Natl Acad Sci USA 107(2):872–877

Kis LL, Gerasimcik N, Salamon D, Persson EK, Nagy N, Klein G, Severinson E, Klein E (2011) STAT6 signaling pathway activated by the cytokines IL-4 and IL-13 induces expression of the Epstein-Barr virus-encoded protein LMP-1 in absence of EBNA-2: implications for the type II EBV latent gene expression in Hodgkin lymphoma. Blood 117(1):165–174

Kondo S, Wakisaka N, Schell MJ, Horikawa T, Sheen TS, Sato H, Furukawa M, Pagano JS, Yoshizaki T (2005) Epstein-Barr virus latent membrane protein 1 induces the matrix metalloproteinase-1 promoter via an Ets binding site formed by a single nucleotide polymorphism: Enhanced susceptibility to nasopharyngeal carcinoma. Int J Cancer 115(3):368–376

Kulwichit W, Edwards RH, Davenport EM, Baskar JF, Godfrey V, Raab-Traub N (1998) Expression of the Epstein-Barr virus latent membrane protein 1 induces B cell lymphoma in transgenic mice. Proc Natl Acad Sci USA 95(20):11963–11968

Kung CP, Meckes DG Jr, Raab-Traub N (2011) Epstein-Barr virus LMP1 activates EGFR, STAT3, and ERK through effects on PKCdelta. J Virol 85(9):4399–4408

Kutz H, Reisbach G, Schultheiss U, Kieser A (2008) The c-Jun N-terminal kinase pathway is critical for cell transformation by the latent membrane protein 1 of Epstein-Barr virus. Virology 371(2):246–256

Laherty CD, Hu HM, Opipari AW, Wang F, Dixit VM (1992) The Epstein-Barr virus LMP1 gene product induces A20 zinc finger protein expression by activating nuclear factor kappa B. J Biol Chem 267(34):24157–24160

Lai HC, Hsiao JR, Chen CW, Wu SY, Lee CH, Su IJ, Takada K, Chang Y (2010) Endogenous latent membrane protein 1 in Epstein-Barr virus-infected nasopharyngeal carcinoma cells attracts T lymphocytes through upregulation of multiple chemokines. Virology 405(2):464–473

Lam N, Sugden B (2003) LMP1, a viral relative of the TNF receptor family, signals principally from intracellular compartments. EMBO J 22(12):3027–3038

Lambert SL, Martinez OM (2007) Latent membrane protein 1 of EBV activates phosphatidylinositol 3-kinase to induce production of IL-10. J Immunol 179(12):8225–8234

Le Clorennec C, Ouk TS, Youlyouz-Marfak I, Panteix S, Martin CC, Rastelli J, Adriaenssens E, Zimber-Strobl U, Coll J, Feuillard J, Jayat-Vignoles C (2008) Molecular basis of cytotoxicity of Epstein-Barr virus (EBV) latent membrane protein 1 (LMP1) in EBV latency III B cells: LMP1 induces type II ligand-independent autoactivation of CD95/Fas with caspase 8-mediated apoptosis. J Virol 82(13):6721–6733

Lee J, Sugden B (2007) A membrane leucine heptad contributes to trafficking, signaling, and transformation by latent membrane protein 1. J Virol 81(17):9121–9130

Lee DY, Sugden B (2008a) The latent membrane protein 1 oncogene modifies B-cell physiology by regulating autophagy. Oncogene 27(20):2833–2842

Lee DY, Sugden B (2008b) The LMP1 oncogene of EBV activates PERK and the unfolded protein response to drive its own synthesis. Blood 111(4):2280–2289

Li HM, Zhuang ZH, Wang Q, Pang JC, Wang XH, Wong HL, Feng HC, Jin DY, Ling MT, Wong YC, Eliopoulos AG, Young LS, Huang DP, Tsao SW (2004) Epstein-Barr virus latent membrane protein 1 (LMP1) upregulates Id1 expression in nasopharyngeal epithelial cells. Oncogene 23(25):4488–4494

Li J, Zhang XS, Xie D, Deng HX, Gao YF, Chen QY, Huang WL, Masucci MG, Zeng YX (2007) Expression of immune-related molecules in primary EBV-positive Chinese nasopharyngeal carcinoma: associated with latent membrane protein 1 (LMP1) expression. Cancer Biol Ther 6(12):1997–2004

Li SS, Yang S, Wang S, Yang XM, Tang QL, Wang SH (2011) Latent membrane protein 1 mediates the resistance of nasopharyngeal carcinoma cells to TRAIL-induced apoptosis by activation of the PI3K/Akt signaling pathway. Oncol Rep 26(6):1573–1579

Li L, Li W, Xiao L, Xu J, Chen X, Tang M, Dong Z, Tao Q, Cao Y (2012) Viral oncoprotein LMP1 disrupts p53-induced cell cycle arrest and apoptosis through modulating K63-linked ubiquitination of p53. Cell Cycle 11(12):2327–2336

Li B, Huang G, Zhang X, Li R, Wang J, Dong Z, He Z (2013) Increased phosphorylation of histone H3 at serine 10 is involved in Epstein-Barr virus latent membrane protein-1-induced carcinogenesis of nasopharyngeal carcinoma. BMC Cancer 13:124

Lin SS, Lee DC, Law AH, Fang JW, Chua DT, Lau AS (2010) A role for protein kinase PKR in the mediation of Epstein-Barr virus latent membrane protein-1-induced IL-6 and IL-10 expression. Cytokine 50(2):210–219

Liu LT, Peng JP, Chang HC, Hung WC (2003) RECK is a target of Epstein-Barr virus latent membrane protein 1. Oncogene 22(51):8263–8270

Liu HP, Chen CC, Wu CC, Huang YC, Liu SC, Liang Y, Chang KP, Chang YS (2012) Epstein-Barr virus-encoded LMP1 interacts with FGD4 to activate Cdc42 and thereby promote migration of nasopharyngeal carcinoma cells. PLoS Pathog 8(5):e1002690

Lo AKF, Liu Y, Wang X, Wong YC, Lee CKF, Huang DP, Tsao SW (2001) Identification of downstream target genes of latent membrane protein 1 in nasopharyngeal carcinoma cells by suppression subtractive hybridization. Biochim Biophys Acta 1520(2):131–140

Lorenzetti MA, Gantuz M, Altcheh J, De Matteo E, Chabay PA, Preciado MV (2012) Distinctive Epstein-Barr virus variants associated with benign and malignant pediatric pathologies: LMP1 sequence characterization and linkage with other viral gene polymorphisms. J Clin Microbiol 50(3):609–618

Lu J, Chua HH, Chen SY, Chen JY, Tsai CH (2003) Regulation of matrix metalloproteinase-1 by Epstein-Barr virus proteins. Cancer Res 63(1):256–262

Luftig M, Prinarakis E, Yasui T, Tsichritzis T, Cahir-McFarland E, Inoue J, Nakano H, Mak TW, Yeh WC, Li X, Akira S, Suzuki N, Suzuki S, Mosialos G, Kieff E (2003) Epstein-Barr virus latent membrane protein 1 activation of NF-kappaB through IRAK1 and TRAF6. Proc Natl Acad Sci USA 100(26):15595–15600

Luftig M, Yasui T, Soni V, Kang MS, Jacobson N, Cahir-McFarland E, Seed B, Kieff E (2004) Epstein-Barr virus latent infection membrane protein 1 TRAF-binding site induces NIK/IKK alpha-dependent noncanonical NF-kappaB activation. Proc Natl Acad Sci USA 101(1):141–146

Ma SD, Xu X, Plowshay J, Ranheim EA, Burlingham WJ, Jensen JL, Asimakopoulos F, Tang W, Gulley ML, Cesarman E, Gumperz JE, Kenney SC (2015) LMP1-deficient Epstein-Barr virus mutant requires T cells for lymphomagenesis. J Clin Invest 125(1):304–315

Mainou BA, Raab-Traub N (2006) LMP1 strain variants: biological and molecular properties. J Virol 80(13):6458–6468

Mainou BA, Everly DN, Raab-Traub N (2005) Epstein-Barr virus latent membrane protein 1 CTAR1 mediates rodent and human fibroblast transformation through activation of PI3K. Oncogene 24(46):6917–6924

Mainou BA, Everly DN Jr, Raab-Traub N (2007) Unique signaling properties of CTAR1 in LMP1-mediated transformation. J Virol 81(18):9680–9692

Mancao C, Hammerschmidt W (2007) Epstein-Barr virus latent membrane protein 2A is a B-cell receptor mimic and essential for B-cell survival. Blood 110(10):3715–3721

Mann KP, Thorley-Lawson D (1987) Posttranslational processing of the Epstein-Barr virus-encoded p63/LMP protein. J Virol 61(7):2100–2108

Mann KP, Staunton D, Thorley-Lawson DA (1985) Epstein-Barr virus-encoded protein found in plasma membranes of transformed cells. J Virol 55(3):710–720

Martin J, Sugden B (1991) Transformation by the oncogenic latent membrane protein correlates with its rapid turnover, membrane localization, and cytoskeletal association. J Virol 65(6):3246–3258

Meckes DG Jr, Shair KH, Marquitz AR, Kung CP, Edwards RH, Raab-Traub N (2010) Human tumor virus utilizes exosomes for intercellular communication. Proc Natl Acad Sci USA 107(47):20370–20375

Meckes DG Jr, Menaker NF, Raab-Traub N (2013) Epstein-Barr virus LMP1 modulates lipid raft microdomains and the vimentin cytoskeleton for signal transduction and transformation. J Virol 87(3):1301–1311

Middeldorp JM, Pegtel DM (2008) Multiple roles of LMP1 in Epstein-Barr virus induced immune escape. Semin Cancer Biol 18(6):388–396

Miller WE, Edwards RH, Walling DM, Raab-Traub N (1994) Sequence variation in the Epstein-Barr virus latent membrane protein 1. J Gen Virol 75:2729–2740

Miller WE, Earp HS, Raab-Traub N (1995) The Epstein-Barr virus latent membrane protein 1 induces expression of the epidermal growth factor receptor. J Virol 69(7):4390–4398

Miller WE, Cheshire JL, Raab-Traub N (1998) Interaction of tumor necrosis factor receptor-associated factor signaling proteins with the latent membrane protein 1 PXQXT motif is essential for induction of epidermal growth factor receptor expression. Mol Cell Biol 18(5):2835–2844

Mitchell T, Sugden B (1995) Stimulation of NF-kappa B-mediated transcription by mutant derivatives of the latent membrane protein of Epstein-Barr virus. J Virol 69(5):2968–2976

Modrow S, Wolf H (1986) Characterization of two related Epstein-Barr virus-encoded membrane proteins that are differentially expressed in Burkitt lymphoma and in vitro-transformed cell lines. Proc Natl Acad Sci USA 83(15):5703–5707

Mohr CF, Kalmer M, Gross C, Mann MC, Sterz KR, Kieser A, Fleckenstein B, Kress AK (2014) The tumor marker Fascin is induced by the Epstein-Barr virus-encoded oncoprotein LMP1 via NF-kappaB in lymphocytes and contributes to their invasive migration. Cell Commun Signal 12(1):46

Moorthy RK, Thorley-Lawson DA (1993a) All three domains of the Epstein-Barr virus-encoded latent membrane protein LMP-1 are required for transformation of rat-1 fibroblasts. J Virol 67(3):1638–1646

Moorthy RK, Thorley-Lawson DA (1993b) Biochemical, genetic, and functional analyses of the phosphorylation sites on the Epstein-Barr virus-encoded oncogenic latent membrane protein LMP-1. J Virol 67(5):2637–2645

Morris MA, Dawson CW, Wei W, O'Neil JD, Stewart SE, Jia J, Bell AI, Young LS, Arrand JR (2008) Epstein-Barr virus-encoded LMP1 induces a hyperproliferative and inflammatory gene expression programme in cultured keratinocytes. J Gen Virol 89(Pt 11):2806–2820

Mosialos G, Birkenbach M, Yalamanchili R, VanArsdale T, Ware C, Kieff E (1995) The Epstein-Barr virus transforming protein LMP1 engages signaling proteins for the tumor necrosis factor receptor family. Cell 80(3):389–399

Motsch N, Pfuhl T, Mrazek J, Barth S, Grasser FA (2007) Epstein-Barr Virus-encoded latent membrane protein 1 (LMP1) induces the expression of the cellular microRNA miR-146a. RNA Biol 4(3):131–137

Murono S, Inoue H, Tanabe T, Joab I, Yoshizaki T, Furukawa M, Pagano JS (2001) Induction of cyclooxygenase-2 by Epstein-Barr virus latent membrane protein 1 is involved in vascular endothelial growth factor production in nasopharyngeal carcinoma cells. Proc Natl Acad Sci USA 98(12):6905–6910

Niedobitek G (1999) The Epstein-Barr virus: a group 1 carcinogen? Virchows Arch 435(2):79–86

Ning S, Pagano JS (2010) The A20 deubiquitinase activity negatively regulates LMP1 activation of IRF7. J Virol 84(12):6130–6138

Ning S, Hahn AM, Huye LE, Pagano JS (2003) Interferon regulatory factor 7 regulates expression of Epstein-Barr virus latent membrane protein 1: a regulatory circuit. J Virol 77(17):9359–9368

Ning S, Huye LE, Pagano JS (2005) Interferon regulatory factor 5 represses expression of the Epstein-Barr virus oncoprotein LMP1: braking of the IRF7/LMP1 regulatory circuit. J Virol 79(18):11671–11676

Ning S, Campos AD, Darnay BG, Bentz GL, Pagano JS (2008) TRAF6 and the three C-terminal lysine sites on IRF7 are required for its ubiquitination-mediated activation by the tumor necrosis factor receptor family member latent membrane protein 1. Mol Cell Biol 28(20):6536–6546

Noda C, Murata T, Kanda T, Yoshiyama H, Sugimoto A, Kawashima D, Saito S, Isomura H, Tsurumi T (2011) Identification and characterization of CCAAT enhancer-binding protein (C/EBP) as a transcriptional activator for Epstein-Barr virus oncogene latent membrane protein 1. J Biol Chem 286(49):42524–42533

Paine E, Scheinman RI, Baldwin AS Jr, Raab-Traub N (1995) Expression of LMP1 in epithelial cells leads to the activation of a select subset of NF-kappa B/Rel family proteins. J Virol 69(7):4572–4576

Pratt ZL, Zhang J, Sugden B (2012) The latent membrane protein 1 (LMP1) oncogene of Epstein-Barr virus can simultaneously induce and inhibit apoptosis in B cells. J Virol 86(8):4380–4393

Price AM, Tourigny JP, Forte E, Salinas RE, Dave SS, Luftig MA (2012) Analysis of Epstein-Barr virus-regulated host gene expression changes through primary B-cell outgrowth reveals delayed kinetics of latent membrane protein 1-mediated NF-kappaB activation. J Virol 86(20):11096–11106

Prince S, Keating S, Fielding C, Brennan P, Floettmann E, Rowe M (2003) Latent membrane protein 1 inhibits Epstein-Barr virus lytic cycle induction and progress via different mechanisms. J Virol 77(8):5000–5007

Rastelli J, Homig-Holzel C, Seagal J, Muller W, Hermann AC, Rajewsky K, Zimber-Strobl U (2008) LMP1 signaling can replace CD40 signaling in B cells in vivo and has unique features of inducing class-switch recombination to IgG1. Blood 111(3):1448–1455

Renzette N, Somasundaran M, Brewster F, Coderre J, Weiss ER, McManus M, Greenough T, Tabak B, Garber M, Kowalik TF, Luzuriaga K (2014) Epstein-barr virus latent membrane protein 1 genetic variability in peripheral blood B cells and oropharyngeal fluids. J Virol 88(7):3744–3755

Rothenberger S, Burns K, Rousseaux M, Tschopp J, Bron C (2003) Ubiquitination of the Epstein-Barr virus-encoded latent membrane protein 1 depends on the integrity of the TRAF binding site. Oncogene 22(36):5614–5618

Saito N, Courtois G, Chiba A, Yamamoto N, Nitta T, Hironaka N, Rowe M, Yamaoka S (2003) Two carboxyl-terminal activation regions of Epstein-Barr virus latent membrane protein 1 activate NF-kappaB through distinct signaling pathways in fibroblast cell lines. J Biol Chem 278(47):46565–46575

Sandberg M, Hammerschmidt W, Sugden B (1997) Characterization of LMP-1's association with TRAF1, TRAF2, and TRAF3. J Virol 71(6):4649–4656

Sandvej K, Gratama JW, Munch M, Zhou XG, Bolhuis RL, Andresen BS, Gregersen N, Hamilton-Dutoit S (1997) Sequence analysis of the Epstein-Barr virus (EBV) latent membrane protein-1 gene and promoter region: identification of four variants among wild-type EBV isolates. Blood 90(1):323–330

Schneider F, Neugebauer J, Griese J, Liefold N, Kutz H, Briseno C, Kieser A (2008) The viral oncoprotein LMP1 exploits TRADD for signaling by masking its apoptotic activity. PLoS Biol 6(1):e8

Schultheiss U, Puschner S, Kremmer E, Mak TW, Engelmann H, Hammerschmidt W, Kieser A (2001) TRAF6 is a critical mediator of signal transduction by the viral oncogene latent membrane protein 1. EMBO J 20(20):5678–5691

Shair KH, Raab-Traub N (2012) Transcriptome changes induced by Epstein-Barr virus LMP1 and LMP2A in transgenic lymphocytes and lymphoma. mBio 3(5). doi:10.1128/mBio.00288-12

Shair KH, Bendt KM, Edwards RH, Bedford EC, Nielsen JN, Raab-Traub N (2007) EBV latent membrane protein 1 activates Akt, NFkappaB, and Stat3 in B cell lymphomas. PLoS Pathog 3(11):e166

Shair KH, Schnegg CI, Raab-Traub N (2008) EBV latent membrane protein 1 effects on plakoglobin, cell growth, and migration. Cancer Res 68(17):6997–7005

Shkoda A, Town JA, Griese J, Romio M, Sarioglu H, Knofel T, Giehler F, Kieser A (2012) The germinal center kinase TNIK is required for canonical NF-kappaB and JNK signaling in B-cells by the EBV oncoprotein LMP1 and the CD40 receptor. PLoS Biol 10(8):e1001376

Siouda M, Frecha C, Accardi R, Yue J, Cuenin C, Gruffat H, Manet E, Herceg Z, Sylla BS, Tommasino M (2014) Epstein-Barr virus down-regulates tumor suppressor DOK1 expression. PLoS Pathog 10(5):e1004125

Song YJ, Kang MS (2010) Roles of TRAF2 and TRAF3 in Epstein-Barr virus latent membrane protein 1-induced alternative NF-kappaB activation. Virus Genes 41(2):174–180

Song YJ, Jen KY, Soni V, Kieff E, Cahir-McFarland E (2006) IL-1 receptor-associated kinase 1 is critical for latent membrane protein 1-induced p65/RelA serine 536 phosphorylation and NF-kappaB activation. Proc Natl Acad Sci USA 103(8):2689–2694

Song YJ, Izumi KM, Shinners NP, Gewurz BE, Kieff E (2008) IRF7 activation by Epstein-Barr virus latent membrane protein 1 requires localization at activation sites and TRAF6, but not TRAF2 or TRAF3. Proc Natl Acad Sci USA 105(47):18448–18453

Soni V, Yasui T, Cahir-McFarland E, Kieff E (2006) LMP1 transmembrane domain 1 and 2 (TM1-2) FWLY mediates intermolecular interactions with TM3-6 to activate NF-kappaB. J Virol 80(21):10787–10793

Souza TA, Stollar BD, Sullivan JL, Luzuriaga K, Thorley-Lawson DA (2005) Peripheral B cells latently infected with Epstein-Barr virus display molecular hallmarks of classical antigen-selected memory B cells. Proc Natl Acad Sci USA 102(50):18093–18098

Stevenson D, Charalambous C, Wilson JB (2005) Epstein-Barr virus latent membrane protein 1 (CAO) up-regulates VEGF and TGF alpha concomitant with hyperlasia, with subsequent up-regulation of p16 and MMP9. Cancer Res 65(19):8826–8835

Stunz LL, Busch LK, Munroe ME, Sigmund CD, Tygrett LT, Waldschmidt TJ, Bishop GA (2004) Expression of the cytoplasmic tail of LMP1 in mice induces hyperactivation of B lymphocytes and disordered lymphoid architecture. Immunity 21(2):255–266

Thorley-Lawson DA, Hawkins JB, Tracy SI, Shapiro M (2013) The pathogenesis of Epstein-Barr virus persistent infection. Curr Opin Virol 3(3):227–232

Thornburg NJ, Raab-Traub N (2007) Induction of epidermal growth factor receptor expression by Epstein-Barr virus latent membrane protein 1 C-terminal-activating region 1 is mediated by NF-kappaB p50 homodimer/Bcl-3 complexes. J Virol 81(23):12954–12961

Thornburg NJ, Pathmanathan R, Raab-Traub N (2003) Activation of nuclear factor-kappaB p50 homodimer/Bcl-3 complexes in nasopharyngeal carcinoma. Cancer Res 63(23):8293–8301

Tsai CN, Tsai CL, Tse KP, Chang HY, Chang YS (2002) The Epstein-Barr virus oncogene product, latent membrane protein 1, induces the downregulation of E-cadherin gene expression via activation of DNA methyltransferases. Proc Natl Acad Sci USA 99(15):10084–10089

Tsai CL, Li HP, Lu YJ, Hsueh C, Liang Y, Chen CL, Tsao SW, Tse KP, Yu JS, Chang YS (2006) Activation of DNA methyltransferase 1 by EBV LMP1 Involves c-Jun NH(2)-terminal kinase signaling. Cancer Res 66(24):11668–11676

Tsao SW, Tramoutanis G, Dawson CW, Lo AK, Huang DP (2002) The significance of LMP1 expression in nasopharyngeal carcinoma. Semin Cancer Biol 12(6):473–487

Uchida J, Yasui T, Takaoka-Shichijo Y, Muraoka M, Kulwichit W, Raab-Traub N, Kikutani H (1999) Mimicry of CD40 signals by Epstein-Barr virus LMP1 in B lymphocyte responses. Science 286(5438):300–303

Uemura N, Kajino T, Sanjo H, Sato S, Akira S, Matsumoto K, Ninomiya-Tsuji J (2006) TAK1 is a component of the Epstein-Barr virus LMP1 complex and is essential for activation of JNK but not of NF-kappaB. J Biol Chem 281(12):7863–7872

Vallabhapurapu S, Karin M (2009) Regulation and function of NF-kappaB transcription factors in the immune system. Annu Rev Immunol 27:693–733

Vaysberg M, Lambert SL, Krams SM, Martinez OM (2009) Activation of the JAK/STAT pathway in Epstein Barr virus+-associated posttransplant lymphoproliferative disease: role of interferon-gamma. Am J Transplant 9(10):2292–2302

Vockerodt M, Haier B, Buttgereit P, Tesch H, Kube D (2001) The Epstein-Barr virus latent membrane protein 1 induces interleukin-10 in Burkitt's lymphoma cells but not in Hodgkin's cells involving the p38/SAPK2 pathway. Virology 280(2):183–198

Vockerodt M, Morgan SL, Kuo M, Wei W, Chukwuma MB, Arrand JR, Kube D, Gordon J, Young LS, Woodman CB, Murray PG (2008) The Epstein-Barr virus oncoprotein, latent

membrane protein-1, reprograms germinal centre B cells towards a Hodgkin's Reed-Sternberg-like phenotype. J Pathol 216(1):83–92

Wakisaka N, Murono S, Yoshizaki T, Furukawa M, Pagano JS (2002) Epstein-barr virus latent membrane protein 1 induces and causes release of fibroblast growth factor-2. Cancer Res 62(21):6337–6344

Wan J, Sun L, Mendoza JW, Chui YL, Huang DP, Chen ZJ, Suzuki N, Suzuki S, Yeh WC, Akira S, Matsumoto K, Liu ZG, Wu Z (2004) Elucidation of the c-Jun N-terminal kinase pathway mediated by Estein-Barr virus-encoded latent membrane protein 1. Mol Cell Biol 24(1):192–199

Wan J, Zhang W, Wu L, Bai T, Zhang M, Lo KW, Chui YL, Cui Y, Tao Q, Yamamoto M, Akira S, Wu Z (2006) BS69, a specific adaptor in the latent membrane protein 1-mediated c-Jun N-terminal kinase pathway. Mol Cell Biol 26(2):448–456

Wang D, Liebowitz D, Kieff E (1985) An EBV membrane protein expressed in immortalized lymphocytes transforms established rodent cells. Cell 43(3 Pt 2):831–840

Wang D, Liebowitz D, Kieff E (1988a) The truncated form of the Epstein-Barr virus latent-infection membrane protein expressed in virus replication does not transform rodent fibroblasts. J Virol 62(7):2337–2346

Wang D, Liebowitz D, Wang F, Gregory C, Rickinson A, Larson R, Springer T, Kieff E (1988b) Epstein-Barr virus latent infection membrane protein alters the human B-lymphocyte phenotype: deletion of the amino terminus abolishes activity. J Virol 62(11):4173–4184

Wilson JB, Weinberg W, Johnson R, Yuspa S, Levine AJ (1990) Expression of the BNLF-1 oncogene of Epstein-Barr virus in the skin of transgenic mice induces hyperplasia and aberrant expression of keratin 6. Cell 61:1315–1327

Wu L, Nakano H, Wu Z (2006) The C-terminal activating region 2 of the Epstein-Barr virus-encoded latent membrane protein 1 activates NF-kappaB through TRAF6 and TAK1. J Biol Chem 281(4):2162–2169

Xiao L, Hu ZY, Dong X, Tan Z, Li W, Tang M, Chen L, Yang L, Tao Y, Jiang Y, Li J, Yi B, Li B, Fan S, You S, Deng X, Hu F, Feng L, Bode AM, Dong Z, Sun LQ, Cao Y (2014) Targeting Epstein-Barr virus oncoprotein LMP1-mediated glycolysis sensitizes nasopharyngeal carcinoma to radiation therapy. Oncogene 33(37):4568–4578

Xie P, Bishop GA (2004) Roles of TNF receptor-associated factor 3 in signaling to B lymphocytes by carboxyl-terminal activating regions 1 and 2 of the EBV-encoded oncoprotein latent membrane protein 1. J Immunol 173(9):5546–5555

Xie P, Hostager BS, Bishop GA (2004) Requirement for TRAF3 in signaling by LMP1 but not CD40 in B lymphocytes. J Exp Med 199(5):661–671

Xu D, Zhang Y, Zhao L, Cao M, Lingel A, Zhang L (2015) Interferon regulatory factor 7 is involved in the growth of Epstein-Barr virus-transformed human B lymphocytes. Virus Res 195:112–118

Yang L, Xu Z, Liu L, Luo X, Lu J, Sun L, Cao Y (2014) Targeting EBV-LMP1 DNAzyme enhances radiosensitivity of nasopharyngeal carcinoma cells by inhibiting telomerase activity. Cancer Biol Ther 15(1):61–68

Yasui T, Luftig M, Soni V, Kieff E (2004) Latent infection membrane protein transmembrane FWLY is critical for intermolecular interaction, raft localization, and signaling. Proc Natl Acad Sci USA 101(1):278–283

Ye H, Park YC, Kreishman M, Kieff E, Wu H (1999) The structural basis for the recognition of diverse receptor sequences by TRAF2. Mol Cell 4(3):321–330

Yoshizaki T (2002) Promotion of metastasis in nasopharyngeal carcinoma by Epstein-Barr virus latent membrane protein-1. Histol Histopathol 17(3):845–850

Yoshizaki T, Sato H, Furukawa M, Pagano JS (1998) The expression of matrix metalloproteinase 9 is enhanced by Epstein-Barr virus latent membrane protein 1. Proc Natl Acad Sci USA 95(7):3621–3626

Yoshizaki T, Horikawa T, Qing-Chun R, Wakisaka N, Takeshita H, Sheen TS, Lee SY, Sato H, Furukawa M (2001) Induction of interleukin-8 by Epstein-Barr virus latent membrane

protein-1 and its correlation to angiogenesis in nasopharyngeal carcinoma. Clin Cancer Res 7(7):1946–1951

Yoshizaki T, Kondo S, Wakisaka N, Murono S, Endo K, Sugimoto H, Nakanishi S, Tsuji A, Ito M (2013) Pathogenic role of Epstein-Barr virus latent membrane protein-1 in the development of nasopharyngeal carcinoma. Cancer Lett 337:1–7

Young LS, Rickinson AB (2004) Epstein-Barr virus: 40 years on. Nat Rev Cancer 4(10):757–768

Zhang L, Pagano JS (2000) Interferon regulatory factor 7 is induced by Epstein-Barr virus latent membrane protein 1. J Virol 74(3):1061–1068

Zhang L, Pagano JS (2001) Interferon regulatory factor 7: a key cellular mediator of LMP-1 in EBV latency and transformation. Semin Cancer Biol 11(6):445–453

Zhang B, Kracker S, Yasuda T, Casola S, Vanneman M, Homig-Holzel C, Wang Z, Derudder E, Li S, Chakraborty T, Cotter SE, Koyama S, Currie T, Freeman GJ, Kutok JL, Rodig SJ, Dranoff G, Rajewsky K (2012) Immune surveillance and therapy of lymphomas driven by Epstein-Barr virus protein LMP1 in a mouse model. Cell 148(4):739–751

Zhao B, Barrera LA, Ersing I, Willox B, Schmidt SC, Greenfeld H, Zhou H, Mollo SB, Shi TT, Takasaki K, Jiang S, Cahir-McFarland E, Kellis M, Bulyk ML, Kieff E, Gewurz BE (2014) The NF-kappaB genomic landscape in lymphoblastoid B cells. Cell reports 8(5):1595–1606

Zimber-Strobl U, Kempkes B, Marschall G, Zeidler R, Van Kooten C, Banchereau J, Bornkamm GW, Hammerschmidt W (1996) Epstein-Barr virus latent membrane protein (LMP1) is not sufficient to maintain proliferation of B cells but both it and activated CD40 can prolong their survival. EMBO J 15(24):7070–7078