LMP1 Protein from the Epstein-Barr Virus Is a Structural CD40 Decoy in B Lymphocytes for Binding to TRAF3*

Received for publication, March 7, 2005, and in revised form, June 9, 2005 Published, JBC Papers in Press, July 11, 2005, DOI 10.1074/jbc.M502511200

ShuangDing Wu‡, Ping Xie§1, Kate Welsh§1, Chenglong Li‡2, Chao-Zhou Ni‡1, Xiwen Zhu‡1, John C. Reed‡3, Arnold C. Satterthwait‡4, Gail A. Bishop§1, and Kathryn R. Ely‡3

From the ‡Cancer Center, The Burnham Institute, La Jolla, California 92037 and the §Departments of Microbiology and Internal Medicine, University of Iowa, and the Veterans Affairs Medical Center, Iowa City, Iowa 52242

Epstein-Barr virus is a human herpesvirus that causes infectious mononucleosis and lymphoproliferative malignancies. LMP1 (latent membrane protein-1), which is encoded by this virus and which is essential for transformation of B lymphocytes, acts as a constitutively active mimic of the tumor necrosis factor receptor (TNFR) CD40. LMP1 is an integral membrane protein containing six transmembrane segments and a cytoplasmic domain at the C terminus that binds to intracellular TNFR-associated factors (TRAFs). TRAFs are intracellular co-activators of downstream signaling from CD40 and other TNFRs, and TRAF3 is required for activation of B lymphocytes by LMP1. Cytoplasmic C-terminal activation region 1 of LMP1 bears a motif (PQQAT) that conforms to the TRAF recognition motif PVQET in CD40. In this study, we report the crystal structure of this portion of LMP1 C-terminal activation region-1 (204PQQATDD210) bound in complex with TRAF3. The PQQAT motif is bound in the same binding crevice on TRAF3 where CD40 is bound, providing a molecular mechanism for LMP1 to act as a CD40 decoy for TRAF3. The LMP1 motif is presented in the TRAF3 crevice as a close structural mimic of the PVQET motif in CD40, and the intermolecular contacts are similar. However, the viral protein makes a unique contact: a hydrogen bond network formed between Asp210 in LMP1 and Tyr395 and Arg393 in TRAF3. This intermolecular contact is not made in the CD40-TRAF3 complex. The additional hydrogen bonds may stabilize the complex and strengthen the binding to permit LMP1 to compete with CD40 for binding to the TRAF3 crevice, influencing downstream signaling to B lymphocytes and contributing to dysregulated signaling by LMP1.

The success of viral infection depends on effective evasion of the cell death machinery of the host. This is a formidable task for the pathogen because the response to infection is complex in mammals. The immune response to viruses may involve apoptosis, or, in some cases, the host defense may incorporate the expression of survival and pro-inflammatory genes to avoid the serious side effects associated with the apoptotic response. One evasion tactic used by the oncogenic herpesviruses is a viral protein makes a unique contact: a hydrogen bond network formed between Asp210 in LMP1 and Tyr395 and Arg393 in TRAF3. This intermolecular contact is not made in the CD40-TRAF3 complex. The additional hydrogen bonds may stabilize the complex and strengthen the binding to permit LMP1 to compete with CD40 for binding to the TRAF3 crevice, influencing downstream signaling to B lymphocytes and contributing to dysregulated signaling by LMP1.

* This work was supported in part by National Institutes of Health Grants CA69381, AI28847, AI49993, and CA99997 and a Veterans Affairs career award (to G. A. B.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

† Special Fellow of the Leukemia and Lymphoma Society.

‡ To whom correspondence should be addressed: The Burnham Inst., 10901 North Torrey Pines Rd., La Jolla, CA 92037. Tel.: 858-646-3135; Fax: 858-646-3105; E-mail: ely@burnham.org.

‡1 The atomic coordinates and structure factors (code 1ZMS) have been deposited in the Protein Data Bank, Research Collaboratory for Structural Bioinformatics, Rutgers University, New Brunswick, NJ (http://www.rcsb.org/).

‡2 Present address: The Scripps Research Inst., La Jolla, CA 92037.

‡3 To whom correspondence should be addressed: The Burnham Inst., 10901 North Torrey Pines Rd., La Jolla, CA 92037. Tel.: 858-646-3135; Fax: 858-646-3105; E-mail: ely@burnham.org.

‡4 The abbreviations used are: EBV, Epstein-Barr virus; TNFRs, tumor necrosis factor receptors; TRAFs, TRAF, tumor necrosis factor receptor-associated factors; JNK, c-Jun N-terminal kinase; LTβR, lymphotixin-β-receptor; BAFF-R, BAFF receptor; CCT, cytoplasmic C-terminal tail; CTAR, C-terminal activation region; MES, 4-morpholineethanesulfonic acid; HPLC, high pressure liquid chromatography; SOEing, splicing by overlap extension; hCD40, human CD40; Ab, antibody.
LMP1 Protein Binds TRAF3 as a Structural CD40 Decoy

TABLE ONE

| Summary of crystallographic data and refinement statistics |
|----------------------------------------------------------|
| Values for the highest resolution shell (2.9 to 2.8 Å) are given in parentheses. R.m.s.d., root mean square deviation. | |
| Crystallographic data | |
| Space group | P321 |
| Unit cell dimensions (Å) | a = b = 83.7, c = 78.0 |
| Molecules/asymmetric unit | 1 monomer |
| Resolution range (Å) | 39.0 to 2.8 |
| Data completeness (%) | 100 (100) |
| Observed reflections | 41,024 (4141) |
| Unique reflections | 8103 (794) |
| R:sym (%) | 7.9 (38) |
| R/σ(f) | 8.6 (4.0) |
| Refinement statistics | |
| R factor (%) | 20.6 (27.0) |
| Rfree (%) | 25.6 (25.7) |
| Average B factor (Å²) | 36.9 |
| No. protein atoms | 1532 |
| No. peptide atoms | 54 |
| R.m.s.d. bond length (Å) | 0.008 |
| R.m.s.d. bond angle | 1.31° |

EXPERIMENTAL PROCEDURES

Crystallographic Analysis—For co-crystallization of LMP1 with TRAF3, crystals of TRAF3 were grown as described previously (40) after tryptic digestion of the protein to shorten the long N-terminal helix. Crystals formed in space group P321 in hanging drops from solutions of 0.1 M MES (pH 6.5) containing 15% polyethylene glycol 4000. The crystals grew to a size of 500 × 500 × 25 μm at room temperature and diffracted to 2.7-Å resolution.

To form the complex, synthetic peptides of various lengths representing the minimal region in CTAR1 of LMP1 implicated for TRAF3 recognition were soaked into TRAF3 crystals. Each peptide contained the PQQAT TRAF recognition motif of LMP1, but differed in the number of flanking residues. The peptides were 202PHQQATDDGSHEDSNSN-amide, 202PHQQATDDGSHEDSNSN-amide, and 203PHQQATDD210. Each peptide was tested in separate experiments. Peptides were dissolved in water and soaked into TRAF3 crystals, and then the crystals were cryoprotected with 25% polyethylene glycol and 20% glycerol and flash-frozen for data collection. Diffraction data were collected at the Stanford Synchrotron Radiation Laboratory beamline 11-3 at −175 °C using a Q4 image plate detector. The data were processed using DENZO and SCALEPACK (41). The data collection statistics are summarized in TABLE ONE.

The structure of the complex was refined using the atomic coordinates of native truncated TRAF3 (40) implementing simulated annealing in CNS (59). An iterative process of refinement in CNS and model building in the program O (42) was used to construct the model of the complex. After refinement, difference maps (F₁ − F₀ and 2F₁ − F₀) and OMITMAPS (43) were used to fit the peptide. Clear electron density was visible for only the shortest peptide, in the TRAF3 binding crevice for backbone atoms. After several rounds of refinement, annealing, and model adjustment, all atoms were clearly placed in density for residues 204–210. These residues were included in the final model. Refinement statistics for the complex are presented in TABLE ONE. For the final structure, the R factor and Rfree values were 20.6 and 25.6%, respectively. Graphic images and electrostatic surfaces presented in the figures were prepared with MOLMOL (44) and SPOCK (45).

Peptide Synthesis—Peptides for the complex were designed to correspond to the sequence in LMP1 that contains the binding site for TRAF3. The peptides acetyl-HFQQATDD-amide, acetyl-PHQQATDDGSHEDSNSN-amide, and acetyl-PHQQATDDGSHEDSNSN-EGRRH-amide were synthesized using Fmoc (N-(9-fluorenyl)methoxycarbonyl) chemistry with diisopropylcarbodiimide/hydroxybenzotriazole coupling on Rink’s amide (methoxybenzhydrylamine) resin with an Advanced ChemTech 350 multiple peptide synthesizer. The peptides were cleaved from the resin and deprotected by treatment with trifluoroacetic acid/water/triisopropylsilane (95:2.5:2.5) for 2 h at room temperature. The cleaved peptides were precipitated and washed with cold diethyl ether. After drying, the peptides were dissolved in aqueous acetonitrile and purified on a preparative C₁₈ column (Cosmosil 5C₁₈-AR, 20 × 250 mm; Phenomenex, Torrance, CA) with detection at 210 nm using a Gilson HPLC apparatus. The peptides were separated from impurities using a linear gradient of 0–40% solvent B over 40 min (solvent A = 0.1% trifluoroacetic acid in water and solvent B = 0.1% trifluoroacetic acid in 90% acetonitrile) at a flow rate of 8 ml/min. Pure peptides, as judged by their elution as single peaks by HPLC on analy-
LMP1 Protein Binds TRAF3 as a Structural CD40 Decoy

RESULTS AND DISCUSSION

TRAF adaptor proteins are trimeric assemblies that are stabilized by coiled-coil interactions of elongated N-terminal α-helices. At the end of these helices, a conserved C-terminal TRAF domain exists with a folding pattern that is structurally maintained in TRAF3 (27), TRAF2 (51, 52), and TRAF6 (53). This independently folded domain is an eight-stranded β-sandwich formed by two layers of β-sheet that each contain four antiparallel strands and that enclose a hydrophobic core (Fig. 1). In the TRAF3 crystals, one monomer is the asymmetric unit, and the three structurally identical subunits are related by crystallographic 3-fold symmetry.

Residues 348–504 in TRAF3 form the TRAF domain. In the mushroom-shaped molecule, intermolecular contacts are made between the C-terminal TRAF domain at one end of the trimer and typical coiled-coil interactions at the other end. Because of the shape of the molecule, there are large solvent channels in the crystal lattice along the length of the extended helices. To form the complex, synthetic peptides corresponding to the TRAF-binding region of LMP1 were soaked into existing TRAF3 crystals. These peptides varied in length from 24 to 8 residues, but each contained the PQQAT motif for TRAF3 binding: 202HPQQATDSDSNSNNEGRHRH225, 202HPQQATDSDSGH-ESDNSN220, 202HPQQATDSD210. The structure of each complex was solved, but density for the peptide was strong and clearly defined only for the short 8-residue fragment. In the case of the longer peptides, some density was apparent in the TRAF3 binding cleft, but there was no evidence of ordered peptide, and residues could not be placed with confidence (data not shown). Furthermore, there was no extra non-protein density anywhere around the TRAF3 surface. This was surprising because we have shown in several previous studies that peptides as long as 24 residues in length can be accommodated in TRAF3 crystals in a restricted solvent “cave” located at the binding cleft on the TRAF domain (27, 28, 31). The structure presented here is the complex with the short peptide representing residues 203–210.

Structure of the LMP1–TRAF3 Complex—The structure of the LMP1-TRAF3 complex at 2.8 Å resolution is presented in Fig. 1 (A and B). One LMP1 peptide was bound to each of the three subunits in TRAF3, and the structure of the peptide was identical at each of the three sites in the trimer, related by strict crystallographic 3-fold symmetry. The binding site for LMP1 is located in the same cleft on TRAF3 that accommodates other TNFRs, including CD40, LTβR, and BAFF-R (27–29). There was clear density for the polypeptide backbone atoms of LMP1 peptide 204PQQATDD210, and residues in the PQQAT motif could be positioned unambiguously in the electron density (Fig. 1C). Density for the N-terminal histidine was weak and fragmented, so this residue was omitted from the model. Density was clear and continuous for the rest of the peptide, except for the side chain of Asp209, where the density was broken and poorly defined, probably because this residue does not make contact with TRAF3 and is flexible in the complex. In contrast, the...
density for the side chain of the adjacent aspartic acid, Asp\textsuperscript{210}, was strong and clearly defined.

**LMP1-TRAF3 Intermolecular Contacts**—The detailed intermolecular contacts that mediate LMP1-TRAF3 recognition are shown in Fig. 1D. In the complex, Pro\textsuperscript{204} is within van der Waals distance of the phenyl rings of Phe\textsuperscript{448} and Phe\textsuperscript{457} in TRAF3. The side chain of Gln\textsuperscript{206} forms a hydrogen bond with the hydroxyl group of Ser\textsuperscript{454} and is within hydrogen bonding distance of the hydroxyls of Ser\textsuperscript{455} and Ser\textsuperscript{456}. Thr\textsuperscript{208} participates in a hydrogen bond network. The side chain hydroxyl forms a hydrogen bond with O-\textsuperscript{81} of Asp\textsuperscript{399} in TRAF3, whereas the main chain imino group of the threonine is hydrogen-bonded to O-\textsuperscript{82} of Asp\textsuperscript{399}. In addition to intermolecular interactions, Thr\textsuperscript{208} also participates in an intramolecular hydrogen bond between the threonine hydroxyl and O-\textsuperscript{82} of Asp\textsuperscript{210} (2.87 Å), 2 residues away in LMP1. The last contact residue in LMP1, Asp\textsuperscript{210}, also participates in a hydrogen bond network forming hydrogen bonds with two side chains in TRAF3: between O-\textsuperscript{82} and the phenolic hydroxyl of Tyr\textsuperscript{395} (2.98 Å) and between O-\textsuperscript{81} and N-\textsuperscript{2} in Arg\textsuperscript{393} (2.78 Å). No intermolecular contacts were observed involving Gln\textsuperscript{205}, Ala\textsuperscript{207}, or Asp\textsuperscript{209}.

The intermolecular contacts between TRAF3 and LMP1 observed in the crystal structure were further examined by site-directed mutagenesis. LMP1 self-aggregates through its six transmembrane domains and thus is constitutively active when it is expressed on cells (15, 33, 54). It has been shown previously that only the CCT of LMP1 is required for post-aggregation delivery of signals (18, 22, 33, 54). To better determine the recruitment and binding of TRAF molecules by LMP1 signaling in B cells, we previously generated a chimeric molecule (hCD40-LMP1) composed of the extracellular and transmembrane domains of hCD40.

![Figure 1: Structure of the LMP1-TRAF3 complex.](image-url)
LMP1 Protein Binds TRAF3 as a Structural CD40 Decoy

LMP1 triggered by anti-hCD40 Ab stimulation in live cells and thus may recruit TRAF3 in the lysates during the immunoprecipitation procedure. Therefore, the amount of TRAF3 that co-immunoprecipitated with each mutant in both lanes of the Brij-58-soluble fraction stimulated with the isotype control Ab (iso, S) and the Brij-58-insoluble raft fraction stimulated with anti-hCD40 Ab (α-h, I) shown in Fig. 2 reflects the ability of this mutant to bind to TRAF3. Our results demonstrate that, in M12.4.1 mouse B cells, recruitment and binding of TRAF3 were dramatically diminished by substitution of Ala for Pro204, Gln206, and Thr208 and moderately decreased by substitution of Ala for Asp210, but were not affected by the D209A mutation (Fig. 2). Corroborating our co-immunoprecipitation data, a previous study using in vitro pull-down experiments with glutathione S-transferase fusion proteins also showed that mutations of Pro204, Gln206, Thr208, and Asp210 have important effects in dampening TRAF3 association (50). These findings indicate that Pro204, Gln206, Thr208, and Asp210 (but not Asp209) of LMP1 are critical for binding TRAF3. Gln206, Thr208, and Asp210 participate in hydrogen bond interactions with TRAF3, whereas Pro204 participates in van der Waals interaction in a hydrophobic pocket in the TRAF3 binding crevice. Substitution of alanine for the 3 polar residues in the LMP1 motif would prevent formation of key hydrogen bonds. Substitution of Ala for Pro204 apparently affects the strength of the hydrophobic interactions at that site in the motif or perhaps may affect the folding pattern of the LMP1 motif in a more general manner that diminishes binding.

Comparison of LMP1 Versus CD40 Contacts with TRAF3—LMP1 mimics signaling events and effector functions of CD40 in B lymphocytes (18, 19, 46, 54), and TRAF3 appears to be a major adaptor protein required to transmit LMP1 signals while acting as a negative regulator for CD40 signals (56, 57). We demonstrated recently that TRAF3 is actually required for activation of B cells by LMP1 and that CD40 and LMP1 use TRAF3 in different ways (39). The cytoplasmic C-terminal regions of CD40 and LMP1 each bear a TRAF recognition motif (PXXQXT) that binds in the same binding crevice on the surface of TRAF3. The sequences are closely similar, PVQQT in CD40 and PQQAT in LMP1, and the structural features of the pentapeptide motifs are also similar (Fig. 3). LMP1 and CD40 bind in the same crevice on TRAF3, and the intermolecular interactions involving proline and glutamine in the motif are the same. Although the recognition motifs are accommodated in a similar mode, there is a molecular adaptation of the TRAF3 surface illustrated by changes in the electrostatic surface of

Figure 2. Recruitment and binding of TRAF3 by the CCT of LMP1 with single amino acid mutations of the PQQATDD motif in B cells. A, co-immunoprecipitation assay of hCD40-LMP1 mutants with TRAF3. M12.4.1 B cells stably transfected with wild-type (WT) hCD40-LMP1 and hCD40-LMP1 mutants P204A, Q206A, T208A, D209A, and D210A were stimulated with 10 μg/ml anti-hCD40 Ab (α-h) to trigger signaling through these chimeric receptors or with an isotype control Ab (iso) for 10 min. Detergent-soluble (S) and insoluble (I) raft lysates were prepared. The lysates were incubated with anti-hCD40 Ab (clone G28-5) to immunoprecipitate the chimeric receptors. The immunoprecipitates were analyzed by immunoblotting for TRAF3 and LMP1. B, histogram analysis of TRAF3 binding to hCD40-LMP1 mutants. TRAF3 and hCD40-LMP1 bands on immunoblots were quantitated using a low light imaging system. The amount of TRAF3 in each lane was normalized to the intensity of the corresponding hCD40-LMP1 band. The graph depicts the results of two independent experiments (mean ± S.D.).
TRAF3 calculated when bound to LMP1 versus CD40 (Fig. 3). This is consistent with our previous observations that the TRAF3 binding crevice contains structurally adaptive “hot spots” that undergo conformational adjustments in the binding crevice to provide a unique shape and electrostatic characteristic for each binding partner (32).

The overall structural similarity of the recognition motifs in LMP1 and CD40 facilitates docking in the binding crevice, but there are also distinct differences in the binding patterns that must be considered in light of the functional differences that are known to result from binding events with these two proteins. It should be noted that extensive comparisons are not possible because the segment of LMP1 that has been structurally defined is short (8 residues) compared with the portion of the cytoplasmic domain of CD40 (20 residues) that was determined in complex with TRAF3 (27). With the longer segment from CD40 as well as similar fragments from LTβR (28) and BAFF-R (29), secondary structural features of the peptides were determined to define binding of the receptors in the context of either a hairpin or extended “boomerang” conformation. CD40 binds to TRAF3 in a hairpin or reverse turn configuration. The hairpin is stabilized by an intramolecular contact made by the threonine in the consensus motif (27). In LMP1, the equivalent threonine (Thr208) does make an intramolecular contact with the side chain of the neighboring residue Asp210. It is not possible with the present data to predict whether LMP1 also assumes a hairpin/reverse turn configuration upon binding TRAF3, as we observed for CD40 (27). Both CD40 and LTβR bind TRAF3 in reverse turn configurations, and each of these receptors bears 1 or 2 prolines at the turn. LMP1 does not have proline(s) in the equivalent sequence and, in this respect, is more like the sequence pattern seen in BAAF-R and the downstream regulator TANK, which bind to TRAF3 as extended chains. This is of particular interest given the recent report that, like LMP1, BAAF-R utilizes TRAF3 as a positive signal regulator and shows unique binding features (58).

**LMP1 Makes Unique Contacts with TRAF3**—LMP1 makes two additional key contacts at or near the recognition motif that are not made by CD40. Thr208 in the consensus pentapeptide forms a hydrogen bond with Asp209 in TRAF3. This hydrogen bond is also made by the conserved threonine in the motif in TANK (31). In CD40, the equivalent of this threonine is engaged in the stabilizing intramolecular interaction within the hairpin and does not make any direct contacts with TRAF3 (27). Another interesting contact is made between LMP1 Asp210 and 2 residues (Tyr399 and Arg395) in TRAF3. The hydrogen bonds formed in this network apparently provide stability to the complex because substitution of Ala for Asp210 diminished binding to TRAF3 (Fig. 2). In CD40, the equivalent residue (2 residues downstream of the recognition motif) is histidine, which does not contact TRAF3. Interestingly, Asp209 does not make an intermolecular contact with TRAF3. This observation was confirmed by mutagenesis in which substitution of Ala for Asp209 did not affect binding.

Our results contrast with those from studies with TRAF2 (30) in which Asp209 in LMP1 was reported to be the contacting residue, whereas Asp210, which is in close proximity, did not form hydrogen bonds with residues 393 and 395. Although binding of LMP1 to TRAF2 is considerably weak, our LMP1 mutant D210A also showed reduced binding to TRAF2, whereas D209A retained binding (data not shown), consistent with our results for TRAF3 and implicating Asp210 as the key contact for both TRAF2 and TRAF3.

**Stabilizing Interactions with TRAF3**—It is possible within the TRAF crevice for hydrogen bonds to form with an aspartic acid adjacent to the PXQXT motif, as we have shown in crystal structures of LTβR and TANK complexes with TRAF3 (28, 31). In LTβR, within the context of the sequence IPEEGD, the aspartic acid participates as a sixth residue for recognition by forming a hydrogen bond with Tyr215 in TRAF3. In

the complex of TANK and TRAF3, we noted that, within the context of the sequence PIQCTD, the aspartic acid makes hydrogen bonds with Tyr395 and Arg395 in TRAF3, similar to the pattern we have reported here for Asp210 in LMP1. The additional hydrogen bonds provided by these aspartic acids may serve to strengthen binding over contacts made only by residues in the consensus motif, as seen with CD40. In the case of TANK, this downstream regulator competes with CD40 for binding to the same binding crevice on TRAF3. Stronger binding affinity was proposed to have important implications for release of TRAFs from CD40 or for modulation of TANK-mediated inhibition of NF-κB activation by CD40.

The question of whether LMP1 competes with CD40 for the TRAF3 binding crevice awaits future experiments in cell-based assays, which are beyond the scope of this study. But our work to date has already given us some insight that stronger binding of LMP1 to TRAF3 compared with CD40 is critical for the ability of LMP1 to transform B lymphocytes. We have demonstrated previously that LMP1 exhibits stronger binding to TRAF3 relative to CD40. In B lymphocytes, LMP1 recruits the majority (~80%) of cellular TRAF3, whereas CD40 engagement recruits only ~30% of cellular TRAF3 (39, 46, 50). Furthermore, the amount of TRAF3 that co-immunoprecipitates with CD40 is dramatically reduced by the presence of LMP1, suggesting that LMP1 may sequester cellular TRAF3, making it unavailable for CD40 (39). The additional hydrogen bonds provided by Asp210 in the LMP1-TRAF3 complex strengthen binding and stabilize the complex and thus may represent the molecular basis for understanding these binding properties.

In summary, we have reported the structural details of the molecular interactions that are made when LMP1 binds to TRAF3 and have shown that more hydrogen-bonded contacts are formed than exist in the CD40-TRAF3 complex. In particular, Asp210 forms key intermolecular hydrogen bonds that do not exist when CD40 binds to TRAFs. The stability of the LMP1-TRAF3 complex may play a role in the dysregulated signaling and sustained B cell activation caused by LMP1. Presentation of LMP1 as a structural mimic of CD40 may be an effective viral strategy to introduce a molecular decoy for the CD40-binding site on TRAF3, influencing downstream signaling in B lymphocytes.

**Acknowledgments**—We are grateful to the staff at the Stanford Synchrotron Radiation Laboratory for assistance at the beamline and to L. O’Brien for skillfully preparing the manuscript for publication.

**REFERENCES**

1. Henderson, S., Huen, D., Rowe, M., Dawson, C., Johnson, G., and Rickinson, A. (1993) *Proc. Natl. Acad. Sci. U. S. A.* 90, 8479–8483
2. Marshall, W. L., Datta, R., Hanify, K., Teng, E., and Finkel, R. W. (1999) *Virology* 256, 1–7
3. Sarid, S., Sato, T., Bohenzky, R. A., Russo, J. J., and Chang, Y. (1997) *Nat. Med.* 3, 293–298
4. Cheng, E. H., Nicholas, J., Bellows, D. S., Hayward, G. S., Guo, H. G., Reitz, M. S., and Hardwick, J. M. (1997) *Proc. Natl. Acad. Sci. U. S. A.* 94, 690–694
5. Neilan, J. G., Lu, Z., Aforion, C. L., Kutish, G. F., Sussman, M. D., and Rock, D. L. (1993) *J. Virol.* 67, 4391–4394
6. Miura, M., Friedlander, R. M., and Yuan, J. (1995) *Proc. Natl. Acad. Sci. U. S. A.* 92, 8318–8322
7. Talley, A. K., Dewhurst, P., Perry, S. W., Dollard, S. C., Gomulski, S., Fine, S. M., New, D., Epstein, L. G., Gendelman, H. E., and Gellard, H. A. (1995) *Mol. Cell. Biol.* 15, 2359–2366
8. Tewari, M., and Dixit, V. M. (1995) *J. Biol. Chem.* 270, 3255–3260
9. Benedict, C. A., Norris, P. S., and Ware, C. F. (2002) *Nat. Immunol.* 3, 1013–1018
10. Benedict, C. A., Banks, T. A., and Ware, C. F. (2003) *Curr. Opin. Immunol.* 15, 59–65
11. Bishop, G. A., and Busch, L. K. (2002) *Curr. Opin. Immunol.* 15, 59–65
12. Lyons, S. F., and Liebowitz, D. N. (1995) *Microbes Infect.* 4, 855–875
13. Thorley-Lawson, D. A., Miyashita, E. M., and Khan, G. (1996) *Trends Microbiol.* 4, 204–208
14. Cahir McFarland, E. D., Izuimi, K. M., and Mosialos, G. (1999) *Oncogene* 18, 6959–6964
LMP1 Protein Binds TRAF3 as a Structural CD40 Decoy

15. Eliopoulos, A. G., and Young, L. S. (2001) Semin. Cancer Biol. 11, 435–444
16. Kaye, K. M., Izumi, K. M., and Kieff, E. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 9150–9154
17. Kilgler, E., Kieser, A., Baumann, M., and Hammerschmidt, W. (1998) EMBO J. 17, 3700–3709
18. Busch, L. K., and Bishop, G. A. (1999) J. Immunol. 162, 2555–2561
19. Uchida, J., Yasui, T., Takaoka-Shichijo, Y., Muraoka, M., Kulwichit, W., Raab-Traub, N., and Kikutani, H. (1999) Science 286, 300–303
20. Kuhne, M. R., Robbins, M., Hambor, J. E., Mackey, M. F., Kosaka, Y., Nishimura, T., Gigley, J. P., Noelle, R. J., and Calderhead, D. M. (1997) J. Exp. Med. 186, 337–342
21. Chung, J. Y., Park, Y. C., Ye, H., and Wu, H. (2002) J. Cell Sci. 115, 679–688
22. Hostager, B. S., and Bishop, G. A. (2001) Immunol. Res. 24, 97–109
23. Clark, E. A., and Ledbetter, J. A. (1994) J. Biol. Chem. 269, 50523–50529
24. Banchereau, J., Bazan, F., Blanchard, D., Briere, F., Galizzi, J. P., van Kooten, C., Liu, Y. J., Rousset, F., and Saeland, S. (1994) Annu. Rev. Immunol. 12, 881–922
25. Ni, C.-Z., Welsh, K., Zheng, J., Havert, M., Reed, J. C., and Ely, K. R. (2002) Proc. Natl. Acad. Sci. U. S. A. 99, 10395–10399
26. Li, C., Norris, P. S., Ni, C.-Z., Havert, M. L., Chiong, E. M., Tran, B. R., Cabezas, E., Reed, J. C., Satterthwait, A. C., Cheng, G., and Ely, K. R. (2000) Mol. Cell. Biol. 20, 10395–10399
27. Ni, C.-Z., Welsh, K., Leo, E., Chiou, C. K., Wu, H., Reed, J. C., and Ely, K. R. (2000) J. Biol. Chem. 275, 50523–50529
28. Ye, H., Park, Y. C., Kershman, M., Kieff, E., and Wu, H. (1999) Mol. Cell. Biol. 19, 321–330
29. Li, C., Ni, C.-Z., Havert, M. L., Cabezas, E., He, J., Kaiser, D., Reed, J. C., Satterthwait, A. C., Cheng, G., and Ely, K. R. (2002) Structure 10, 403–411
30. Ely, K. R., and Li, C. (2002) J. Mol. Recognit. 15, 286–290
31. Ni, C.-Z., Welsh, K., Leo, E., Chiou, C. K., Wu, H., Reed, J. C., and Ely, K. R. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 10395–10399
32. Li, C., Norris, P. S., Ni, C.-Z., Havert, M. L., Chiong, E. M., Tran, B. R., Cabezas, E., Reed, J. C., Satterthwait, A. C., Ware, C. F., and Ely, K. R. (2000) J. Biol. Chem. 275, 50523–50529
33. Ye, H., Park, Y. C., Kershman, M., Kieff, E., and Wu, H. (1999) Mol. Cell. Biol. 19, 321–330
34. Li, C., Ni, C.-Z., Havert, M. L., Cabezas, E., He, J., Kaiser, D., Reed, J. C., Satterthwait, A. C., Cheng, G., and Ely, K. R. (2002) Structure 10, 403–411
35. Ely, K. R., and Li, C. (2002) J. Mol. Recognit. 15, 286–290
36. Gilmore, P. E., and Kieff, E. (1998) J. Immunol. 160, 12592–12597
37. Clark, E. A., and Ledbetter, J. A. (1994) Nature 367, 7098–7108
38. Busch, L. K., and Bishop, G. A. (2001) J. Mol. Cell. Biol. 16, 7098–7108
39. Park, Y. C., Burkitt, V., Villa, A. R., Tong, L., and Wu, H. (1999) Nature 396, 533–538
40. McWhirter, S. M., Pullen, S. S., Holton, J. M., Clute, J. J., Kehry, M. R., and Alber, T. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 8408–8413
41. Ho, S. N., Hunt, H. D., Horton, R. M., Pullen, J. K., and Pease, L. R. (1989) Gene (Amst.) 81, 319–329
42. Hostager, B. S., and Bishop, G. A. (2001) J. Exp. Med. 193, 943–954
43. Hostager, B. S., and Bishop, G. A. (2001) J. Immunol. 167, 5805–5813
44. Erle, W. D., Zhou, Y., and Warren, G. L. (1998) Acta Crystallogr. Sect. D 54, 905–921
LMP1 Protein from the Epstein-Barr Virus Is a Structural CD40 Decoy in B Lymphocytes for Binding to TRAF3
ShuangDing Wu, Ping Xie, Kate Welsh, Chenglong Li, Chao-Zhou Ni, Xiuwen Zhu, John C. Reed, Arnold C. Satterthwait, Gail A. Bishop and Kathryn R. Ely

J. Biol. Chem. 2005, 280:33620-33626.
doi: 10.1074/jbc.M502511200 originally published online July 11, 2005

Access the most updated version of this article at doi: 10.1074/jbc.M502511200

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 57 references, 29 of which can be accessed free at http://www.jbc.org/content/280/39/33620.full.html#ref-list-1