**Tumor Necrosis Factor (TNF) and Phorbol Ester Induce TNF-related Apoptosis-inducing Ligand (TRAIL) under Critical Involvement of NF-κB Essential Modulator (NEMO)/IKKγ**

Received for publication, July 9, 2001, and in revised form, September 12, 2001

Published, JBC Papers in Press, September 13, 2001, DOI 10.1074/jbc.M106422200

Daniela Siegmund, Angelika Hausser, Nathalie Peters, Peter Scheurich, and Harald Wajant†‡

From the Institute of Cell Biology and Immunology, University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany

We show that tumor necrosis factor (TNF) and phorbol 12-myristate 13-acetate (PMA) induce TNF-related apoptosis-inducing ligand (TRAIL) in T cells. In cells deficient for NF-κB essential modulator (NEMO)/IKKγ, an essential component of the NF-κB-inducing IκB kinase (IKK) complex, induction of TRAIL expression was completely abrogated but was recovered in cells restored for IKKγ expression. In cells deficient for receptor-interacting protein expression TNF, but not PMA-induced TRAIL expression was blocked. Inhibition of protein synthesis with cycloheximide blocked PMA, but not TNF-induced up-regulation of TRAIL. As both TNF and PMA rapidly induce NF-κB activation this suggests that NEMO/IKKγ-dependent activation of the NF-κB pathway is necessary but not sufficient for up-regulation of TRAIL in T cells. The capability of the NF-κB pathway to induce the potent death ligand TRAIL may explain the reported proapoptotic features of this typically antiapoptotic pathway.

Tumor necrosis factor (TNF)1-related apoptosis-inducing ligand (TRAIL)/Apo2L belongs to the TNF ligand family and induces apoptosis in a broad range of tumor cells with apparently no cytotoxic activity on most nontransformed cells. TRAIL mRNA was found in a variety of tissues, in particular in activated T cells, and is often induced by interferons (1). TRAIL interacts with five different members of the TNF receptor superfamily: TRAIL-R1/DR4, TRAIL-R2/DR5/TRICK2/Killer, TRAIL-R3/TRID/Dr1/R1/LIT, TRAIL-R4/TRUND/DcR2 and osteoprotegerin (2). TRAIL-R1 and TRAIL-R2 contain a death domain and mediate the apoptotic response toward TRAIL. TRAIL-R3, lacking a cytoplasmic domain, is anchored to the cell surface by modification with glycosphospholipids and is regarded as a decoy receptor for TRAIL. TRAIL-R4 has an incomplete cytoplasmic death domain and is therefore incapable of signaling apoptosis but is still able to activate the antiapoptotic NF-κB pathway. Thus, TRAIL-R4 is maybe involved in regulation of the apoptotic TRAIL response at the cellular level. The soluble receptor osteoprotegerin, which otherwise has a critical role in regulation of osteoclastogenesis, may act as a systemic negative regulator of TRAIL-induced apoptosis (1).

TRAIL is involved in the induction of cell death by activated CD4+ T cells (3, 4), dendritic cells (5), and NK cells (6). TRAIL may also play a role in activation-induced T cell death during HIV infection (7–9). Inhibition of endogenous TRAIL enhances proliferation of autoreactive lymphocytes or synovial cells, thereby contributing to the exacerbation of arthritic inflammation and joint tissue destruction (10). These data argue for an in vivo function of TRAIL in the maintenance of immune homeostasis by counteracting autoimmune responses. However, in contrast to FasL, TRAIL inhibits autoimmune inflammation by inhibition of cell cycle progression instead of induction of T cell apoptosis (10). In accordance with its remarkable tumoricidal activity in vitro, several studies point to a role of TRAIL in anti-tumoral immunity. In this regard, it has been recently shown that TRAIL is the sole principle mediating antitumorigenic activity of interferon-activated human monocytes (11). Moreover, up-regulation of TRAIL plays a central role in IFNγ-mediated antimetastatic effects of interleukin-12 and α-galactosylceramide (12, 13). Further, aside from the capability of dendritic cells to acquire antigen from apoptotic cells to cross-present these antigens to cytotoxic T cells (14, 15), dendritic cells directly mediate cellular apoptosis via TRAIL after stimulation with IFNα or IFNγ (5). Of interest, a recent study indicates that type I IFNs induce the rapid maturation of monocytes into short-lived TRAIL-expressing dendritic cells (16). Moreover, type I IFNs up-regulate TRAIL expression on anti-CD3-stimulated human peripheral blood T cells suggesting that TRAIL contributes to the indirect cytotoxic activity of type I IFNs used in cancer therapy for the treatment of chronic myelogenous leukemias and renal cell carcinomas (17). In accordance with an antitumoral function of TRAIL, the death domain-containing TRAIL receptors (18) and (19) have been identified as targets of p53. In this study we show that TRAIL is induced by TNF and treatment with phorbol ester under critical involvement of NEMO/IKKγ, an essential component of the NF-κB signaling pathway, may account for some of the apoptotic effects described for NF-κB in the literature (20–24).

MATERIALS AND METHODS

Materials and Cell Lines—Chemicals and secondary antibodies were obtained from Sigma, and cell culture reagents from Life Technologies, Inc. The FLIP-specific rat mAb was from Apotech Biochemicals Ltd. (Epalinges, Switzerland). The broad spectrum caspase inhibitor benzylxoyacylron VAD/Fmk was purchased from Bachem (Heidelberg, Germany). The TRAIL-specific mAbs RIK-2, 2G9, and 2E11 were kind gifts from Hideo Yagita (RIK-2, Jun- tendo University, Tokyo, Japan) and Avi Ashkenazi (2G9 and 2E11; Genentech Inc.). TRAIL-R2-Fc, FLAG-tagged TRAIL and FasL were kind gifts of Pascal Schneider (University of Lausanne, Epalinges, Switzerland). The abbreviations used are: TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis inducing ligand; FasL, Fas ligand; IFN, interferon; mAb, monoclonal antibody; RIP, receptor-interacting protein; IκK, IκB kinase; PMA/I, phorbol 12-myristate 13-acetate/ionomycin; PHA, phytohemagglutinin; CHX, cycloheximide.
Switzerland) and Davide Mauri (Apoptech Biochemicals Ltd., Epalinges, Switzerland). BJAB-, Raji-, and DII/23–7 cells as well as all Jurkat cells were maintained in RPMI 1640 medium containing 10% heat-inactivated fetal calf serum in a humidified 5% CO₂ environment. The IKK-β-deficient Jurkat cell line was a gift from S.-C. Sun (Pennsylvania State University) and is described elsewhere (25). The RIP-deficient Jurkat T-cell line was a gift from B. Seed (Massachusetts General Hospital) and was described in Ting et al. (26).

**RNase Protection Assay—**Cells (10 × 10⁶) were treated as indicated, and after the given time supernatants were collected or lysisates were prepared in RIPA buffer supplemented with a protease inhibitor mixture stock solution (Roche Molecular Biochemicals). For preparation of cell lysates, cell debris was removed by centrifugation (10,000g, 10 min), and the protein concentration of the obtained supernatants was determined using the Bradford assay. To relieve Western blot detection of TRAIL-R2-Fc at 4 °C, and finally TRAIL/TRAIL-R2-Fc complexes were precipitated with 25 μl of protein A-Sepharose (1 h, 4 °C) and washed three times in RIPA buffer. TRAIL/TRAIR2-R2-Fc complexes, cell lysates (50 μg), and cell supernatants were resolved by SDS-polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes by electro-blotting. Blots were blocked for 1 h at room temperature in Tris-buffered saline containing 0.5% Tween 20 and 3% (w/v) dry milk, washed, and incubated with anti-TRAIL mAb mix (mAbs RIK-2, 2G9, 2E11; each 0.5 μg/ml) for at least 1 h at room temperature. TRAIL-mAb complexes were visualized with alkaline phosphatase-conjugated goat anti-mouse-IgG (Sigma) and nitro blue tetrazolium and 5-bromo-4-chloro-3-indolyl phosphate as substrate.

**Determination of NF-κB Activity by Electrophoretic Mobility Shift Assay and Reporter Gene Assays—**For preparation of nuclear extracts 5 × 10⁶ Jurkat cells were seeded in 100-mm culture dishes and cultivated overnight. Next day cells were stimulated with TNF or phorbol 12-myristate 13-acetate and ionomycin (PMA/I) for the indicated time, washed once with cold phosphate-buffered saline, resuspended in 0.4 ml of buffer A (10 mM KCl, 10 mM HEPES, pH 7.9, 0.1 mM EDTA, 0.1 mM EGTA, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride) and incubated on ice for 20 min. Subsequently, 25 μl of 10% Nonidet P-40 (for 2 min), and nuclei were pelleted and resuspended in buffer B (20 mM HEPES, pH 7.9, 400 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM dithiothreitol). After 20 min of shaking and subsequent centrifugation, the lysates containing the nuclear proteins in the supernatant were used for the electrophoretic mobility shift assay after protein digestion (Bio-Rad) with bovine serum albumin as standard. High pressure liquid chromatography-purified NF-κB-specific oligonucleotides (5'-ATCGGGCAGCTCCGGGACCTCCGGGACCTCCGGGAC-3') were end-labeled with [γ-3₂P]ATP and electrophoretic mobility shift assays were performed by incubating 10 μg of nuclear extracts with 4 μg poly(dI-dC) in binding buffer (5 mM HEPES, pH 7.8, 5 mM MgCl₂, 50 mM KCl, 0.2 mM EDTA, 5 mM dithiothreitol, 10% glycerol). The double-stranded, end-labeled, purified oligonucleotide probe (2 × 10⁹ to 5 × 10⁹ cpm) was added to the reaction mixture for 10 min at room temperature. The samples were separated by native polyacrylamide gel electrophoresis in low ionic strength buffer, and gels were analyzed using a PhosphorImager with the ImageQuant software (Molecular Dynamics). For monitoring PMA/I- and TNF-induced NF-κB activation in lysates derived thereof. However, three anti-TRAIL-mAb-reactive bands were detectable by Western blotting in lysates of PMA/I-stimulated Jurkat cells whereas no TRAIL was detectable in the supernatants. When Jurkat cells were treated with PMA/I during the last 30 min of PMA/I stimulation a significant amount of all three TRAIL-mAb-reactive proteins were found in the supernatant (Fig. 1D). TRAIL protein was also detectable in lysates of TNF-treated cells after immunoprecipitation with TRAIL-R2-Fc and protein A-Sepharose (Fig. 1F). The size of the smallest anti-TRAIL-mAb reactive band (19 kDa, Fig. 1, E and F) corresponds to the size of the already described soluble TRAIL product comprising the extracellular receptor-binding domain of the ligand (27). The sizes of the two slower migrating anti-TRAIL-mAb-reactive proteins (32 and 34 kDa) are in good accordance with that of complete TRAIL, suggesting that these two bands represent two isofoms of full-length TRAIL. PHA-stimulation lead to the secretion of all three anti-TRAIL-mAb reactive proteins, suggesting that PHA induces the release of TRAIL containing microvesicles as described elsewhere (28) rather than inducing proteolytic processing of cell-bound TRAIL. In PMA/I-treated T cells we also observed up-regulation of FasL and TRAIL in the B cell lines BJAB and Raji suggesting that TRAIL up-regulation by TNF and PMA/I is cell type-specific (Fig. 1C). PMA/I and TNF showed a capacity to induce TRAIL expression in the same range as the well established TRAIL inducers IFNα/β/γ (Fig. 1D). In all cases two protected TRAIL-specific fragments of slightly different sizes were observed, suggesting that TRAIL-mRNA exists in at least two different splice forms. In accordance with the barely detectable TRAIL-mRNAs levels in untreated Jurkat cells (Fig. 1A), we were unable to detect TRAIL protein in non-stimulated cells or cell culture supernatants derived thereof. However, three anti-TRAIL-mAb-reactive protein bands were detectable by Western blotting in lysates of PMA/I-stimulated Jurkat cells whereas no TRAIL was detectable in the supernatants. When Jurkat cells were treated with PHA during the last 30 min of PMA/I stimulation a significant amount of all three TRAIL-mAb-reactive proteins were found in the supernatant (Fig. 1D). TRAIL protein was also detectable in lysates of TNF-treated cells after immunoprecipitation with TRAIL-R2-Fc and protein A-Sepharose (Fig. 1F). The size of the smallest anti-TRAIL-mAb reactive band (19 kDa, Fig. 1, E and F) corresponds to the size of the already described soluble TRAIL product comprising the extracellular receptor-binding domain of the ligand (27). The sizes of the two slower migrating anti-TRAIL-mAb-reactive proteins (32 and 34 kDa) are in good accordance with that of complete TRAIL, suggesting that these two bands represent two isofoms of full-length TRAIL. PHA-stimulation lead to the secretion of all three anti-TRAIL-mAb reactive proteins, suggesting that PHA induces the release of TRAIL containing microvesicles as described elsewhere (28) rather than inducing proteolytic processing of cell-bound TRAIL. In PMA/I-treated T cells we also observed up-regulation of FasL and TRAIL-R2 mRNA, and in the B-cell lines PMA/I-induced TRAIL-R1 and TRAIL-R2 (Fig. 1). Analyses of Jurkat cells exclusively stimulated with PMA or TNF (data not shown).
IKKγ/NEMO-deficient Jurkat cells are unable to respond with NF-κB activation to a variety of NF-κB inducers including TNF and PMA, but show normal activation of NF-AT and AP1 (30). As shown in Fig. 2B, both TNF and PMA/I-induced up-regulation of TRAIL was completely prevented in this mutant Jurkat cell line. However, in a clone derived from the IKKγ/NEMO-deficient Jurkat cell line, in which NF-κB responsiveness had been restored by retransfection with an IKKγ expression construct (30), responsiveness of the TRAIL gene toward PMA/I and TNF was partly restored (Fig. 2A, right panel). Further, PMA/I-induced up-regulation of TRAIL-R2, but not FasL induction, was significantly inhibited in the IKKγ/NEMO-deficient Jurkat cells (Fig. 2A). Involvement of the NF-κB pathway in PMA/I-induced TRAIL-R2 expression is in good agreement with some recent studies showing a critical role of the cRel subunit of NF-κB in expression of TRAIL-R1 and TRAIL-R2 (24). Lack of requirement of the NF-κB pathway for FasL gene induction in IKKγ/NEMO-deficient Jurkat cells has already been described elsewhere (30) and suggests that the death ligands TRAIL and FasL are up-regulated during T cell activation by at least partially distinct signaling pathways. In the case of TNF-induced TRAIL expression we analyzed the involvement of the NF-κB pathway in a second independent genetic model, i.e. Jurkat T-cells deficient in RIP expression (26). The RIP kinase was originally isolated as a Fas interacting death domain-containing kinase, but is also part of the TNF-R1 signaling complex and plays an essential role in TNF-R1-mediated NF-κB activation (31). Lack of RIP expression impaired TNF-induced up-regulation of TRAIL (Fig. 2C) but had no significant effect on PMA/I-induced up-regulation of TRAIL and TRAIL-R2 (data not shown).

Thus, our data clearly argue for an essential involvement of IKKγ/NEMO and therefore most likely the NF-κB pathway in TNF- and PMA/I-induced TRAIL expression. However, the data described so far let open the question whether TRAIL induction occurs directly or not. We therefore analyzed the capability of TNF and PMA/I to induce TRAIL-mRNA in the presence of high concentrations of the translation inhibitor cycloheximide (CHX). While PMA/I-induced TRAIL expression was almost completely inhibited in the presence of 50 μg/ml CHX (Fig. 3A) TNF-mediated up-regulation was not affected by this treatment (Fig. 3B). Thus, while PMA/I engages TRAIL transcription indirectly, TNF induces TRAIL expression directly. As interferons are major inducers of TRAIL, we looked for an involvement of endogenous interferons in PMA/I-induced up-regulation of TRAIL. However, we found no evidence for an involvement of interferons in PMA/I-induced up-regulation of TRAIL. So, neutralizing mAbs against IFNα receptor chain 2 or interferon-β failed to inhibit TRAIL-induction (data not shown). Moreover, IFNγ is most likely also not involved in PMA/I-induced up-regulation of TRAIL because even saturating concentrations of recombinant IFNγ only marginally up-regulate TRAIL-mRNA (Fig. 1E). As both PMA/I and TNF rapidly activate NF-κB under essential involvement of IKKγ/NEMO (Fig. 2, A and B), the differential need for protein synthesis challenges the concept of NF-κB dependent up-regulation of TRAIL (see above). A possible explanation could be the existence of a second pathway that synergistically acts with the
NF-κB pathway to induce TRAIL and is directly induced by TNF but only indirectly triggered by PMA/I. However, we cannot rule out the possibility that TRAIL induction occurs by an IKK/NEMO-dependent pathway being distinct from the NF-κB pathway, which becomes differentially activated by PMA/I and TNF. With respect to the latter possibility, we found no evidence for a NF-κB dependence of an IFN-responsive reporter gene construct containing about 1 kilobase of the TRAIL promoter (data not shown). Although PMA/I stimulation induced the cytotoxic ligand TRAIL and one of its corresponding death receptors the viability of the PMA/I-treated cells was not affected 1 day after treatment. However, upon prolonged incubation time the PMA/I-treated cells started to die. This transient apoptosis resistance observed in the early phase of PMA/I treatment might be due to the concomitant induction of anti-apoptotic factors. Indeed, we have recently shown that PMA/I induces up-regulation of cFLIP, a potent inhibitor of death receptor signaling (Ref. 32, Fig. 3C). Moreover, 6 h of pretreatment with PMA/I protected Jurkat cells from a subsequent 16-h challenge with TRAIL or FasL with an efficiency comparable with the broad range caspase inhibitor Z-VAD-fmk (Fig. 3D). While TRAIL-induced apoptosis was almost completely blocked by Z-VAD-fmk and PMA/I pretreatment, FasL-induced cell death was only partially inhibited by both treatments. This is in good accordance with some recent findings showing that in the absence of CHX, TRAIL induces cell death only via the caspase-dependent Fas-associated death domain protein/caspase-8 pathway, whereas FasL in addition signals necrotic cell death via a caspase-independent RIP-mediated pathway (33, 34). Although PMA/I treatment efficiently blocked TRAIL-induced apoptosis, PMA/I treatment per se induced cell death in a significant fraction (20–40%) of the cells (Fig. 3D and Ref. 30). This per se cytotoxicity of PMA/I might reflect killing of a subpopulation of Jurkat cells in which unbalanced amounts of TRAIL/FasL and FLIP (and maybe additional anti-apoptotic factors) were induced.
Acknowledgments—We thank Brian Seed (Massachusetts General Hospital) for the RIP-deficient Jurkat clone and S.-C. Sun (Pennsylvania State University) for the IKK-deficient Jurkat cell line as well as for the IKK-retransfected clone derived thereof. FLAG-tagged TRAIL and FasL were a kind gift of Pascal Schneider (University of Lausanne, Epalinges, Switzerland) and Davide Mauri (Apotech Biochemicals Ltd., Epalinges, Switzerland).

REFERENCES

1. Wang, Q., Ji, Y., Wang, X., and Evers, B. M. (2000) Biochem. Biophys. Res. Commun. 276, 466–471
2. Locksley, R. M., Killeen, N., and Lenardo, M. J. (2001) Cell 104, 487–501
3. Thomas, W. D., and Hersey, P. (1996) J. Immunol. 161, 2195–2200
4. Kayagaki, N., Yamaguchi, N., Nakayama, M., Kawasaki, A., Akiba, H., Okumura, K., and Yagita, H. (1999) J. Immunol. 162, 2639–2647
5. Fanger, N. A., Maliszewski, C. R., Schooley, K., and Griffith, T. S. (1999) J. Exp. Med. 190, 1155–1164
6. Zamai, L., Ahmad, M., Bennett, I. M., Azzoni, L., Alnemri, E. S., and Perussia, B. (1998) J. Exp. Med. 188, 2575–2580
7. Katsikis, N. P., Garcia-Ojeda, M. E., Torres-Roca, J. F., Tijoe, I. M., Smith, C. A., Herzenberg, L. A., and Herzenberg, L. A. (1997) J. Exp. Med. 186, 1365–1372
8. Jeremias, I., Herr, I., Boehler, T., and Debatin, K. M. (1998) Eur. J. Immunol. 28, 143–152
9. Miura, Y., Misawa, N., Maeda, N., Inagaki, Y., Tanaka, Y., Ito, M., Kayagaki, N., Yamamoto, N., Yagita, H., Mizusawa, H., and Koyanagi, Y. (2000) J. Exp. Med. 192, 651–660
10. Song, K., Chen, Y., Goke, R., Wilmen, A., Seidel, C., Goke, A., and Hiliard, B. (2000) J. Exp. Med. 191, 1095–1104
11. O’Hare, T. S., Wiley, S., Riano, M., Sedger, L. M., Maliszewski, C. R., and Fanger, N. A. (1999) J. Exp. Med. 189, 1343–1354
12. Takeda, K., Hayakawa, Y., Smyth, M. J., Kayagaki, N., Yamaguchi, N., Kakuta, S., Iwakura, Y., Yagita, H., and Okumura, K. (2001) Nat. Med. 7, 94–100
13. Smyth, M. J., Cretney, E., Takeda, K., Wiltrout, R. H., Sedger, L. M., Kayagaki, N., Yagita, H., and Okumura, K. (2001) J. Exp. Med. 193, 661–670
14. Albert, M. L., Sauter, B., and Bhardwaj, N. (1998) Nature 392, 86–89
15. Albert, M. L., Pearce, S. P., Francisco, L. M., Sauter, B., Roy, P., Silverstein, R. L., and Bhardwaj, N. (1998) J. Exp. Med. 188, 1359–1368
16. Santini, S. M., Lapenta, C., Logozzi, M., Parlato, S., Spada, M., Di Puechio, T., and Belardelli, F. (2000) J. Exp. Med. 191, 1777–1788
17. Kayagaki, N., Yamaguchi, N., Nakayama, M., Eto, H., Okumura, K., and Yagita, H. (1999) J. Exp. Med. 189, 1451–1460
18. Barik, T., Siegmund, D., Peters, N., Reichwein, M., Henkler, F., Scheurich, P., and Wajant, H. (2001) Oncogene 20, 571–580
19. Wu, G. S., Burns, T. F., McDonald, E. R., III, Jiang, W., Meng, R., Krantz, I. D., Kao, G., Gan, D. D., Zhou, J. Y., Muschel, R., Hamilton, S. R., Spinner, N. B., Markowitz, S., Wu, G., and El Deiry, W. S. (1997) Nat. Genet. 17, 141–143
20. Dog, A. A., Sha, W. C., Bronson, H. T., and Baltimore, D. (1995) Genes Dev. 9, 2736–2746
21. Abbadi, C., Kabrun, N., Bouali, F., Smardova, J., Stehelin, D., Vandenbunder, B., and Enrietto, P. J. (1993) Cell 75, 899–912
22. Ryan, K. M., Ernst, M. K., Rice, N. R., and Vousden, K. H. (2000) Nature 404, 892–897
23. Lipton, S. A. (1997) Nat. Med. 3, 22–29
24. Ravi, R., Bedi, G. C., Engstrom, L. W., Zeng, Q., Mookerjee, B., Gelin, C., Fuchs, E. J., and Bedi, A. (2001) Nat. Cell Biol. 3, 409–416
25. Harhaj, E. W., Good, L., Xiao, G., Uhlik, M., Cvijic, M. E., Rivera-Walsh, L., and Sun, S. C. (2000) Oncogene 19, 1448–1456
26. Ting, A. T., Pimentel-Munoz, F. X., and Seed, B. (1996) EMBO J. 15, 6189–6196
27. Mariani, S. M., and Kramer, P. H. (1998) Eur. J. Immunol. 28, 973–982
28. Martinez-Lorenzo, M. J., Axel, A., Gamen, S., Monléon, I., Lasier, P., Larrad, L., Fierro, A., Alava, M. A., and Naval, J. (1999) J. Immunol. 163, 1274–1281
29. Kari, M., and Ben Neriah, Y. (2000) Annu. Rev. Immunol. 18, 621–663
30. Rivera-Walsh, L., Cvijic, M. E., Xiao, G., and Sun, S. C. (2000) J. Biol. Chem. 275, 25222–25230
31. Wajant, H., Grell, M., and Scheurich, P. (1999) Cytokine Growth Factor Rev. 10, 15–26
32. Kreuz, T. S., Siegmund, D., Scheurich, P., and Wajant, H. (2001) Mol. Cell. Biol. 21, 3984–3973
33. Holler, N., Zar, R., Micheau, O., Thou, M., Attinger, A., Valitutti, S., Bodmer, J. L., Schneider, P., Seed, B., and Tschopp, J. (2000) Nat. Immunol. 1, 489–495
34. Matsumura, H., Shimizu, Y., Ohsawa, Y., Kawahara, A., Uchiyama, Y., and Nagata, S. (2000) J. Cell Biol. 151, 1247–1256
Tumor Necrosis Factor (TNF) and Phorbol Ester Induce TNF-related Apoptosis-inducing Ligand (TRAIL) under Critical Involvement of NF-κB Essential Modulator (NEMO)/IKK γ

Daniela Siegmund, Angelika Hausser, Nathalie Peters, Peter Scheurich and Harald Wajant

J. Biol. Chem. 2001, 276:43708-43712.
doi: 10.1074/jbc.M106421200 originally published online September 13, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M106421200

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 33 references, 17 of which can be accessed free at http://www.jbc.org/content/276/47/43708.full.html#ref-list-1