We report the identification of a novel p75TNF receptor isoform termed icp75TNFR, which is generated by the use of an alternative transcriptional start site within the p75TNFR gene and characterized by regulated intracellular expression. The icp75TNFR protein has an apparent molecular mass of ~50 kDa and is recognized by antibodies generated against the transmembrane form of p75TNFR. The icp75TNFR binds the tumor necrosis factor (TNF) and mediates intracellular signaling. Overexpression of the icp75TNFR cDNA results in TNF-induced activation of NFκB in a TNF receptor-associated factor 2 (TRAF2)-dependent manner. Thus, our results provide an example for intracellular cytokine receptor activation.

TNF is a pleiotropic cytokine involved in a broad spectrum of inflammatory and immune responses including proliferation and cytotoxicity in a variety of different cell types. Two distinct receptor molecules with an apparent molecular mass of 55 kDa (p55TNFR, TNFR type 1) and 75 kDa (p75TNFR, TNFR type 2) have been identified, and their corresponding cDNAs have been cloned (1–4). The p55TNFR is expressed rather constitutively in accordance with 18 U.S.C. Section 1734 solely to indicate this fact. The p75TNFR is expressed at physiologically relevant levels, induction of NFκB is capable of mediating these effects when expressed fluoscine isothiocyanate; EPR, exhaustive photon reassignment; polymerase chain reaction; PBS, phosphate-buffered solution; FITC, responses that can be attributed exclusively to signaling via similarity, they share activities like NFκB via the receptor subtype (13, 14). Although the intracellular receptor domains show only little

In our report we describe the identification of a novel p75TNF isoform, termed icp75TNFR, generated by the use of an additional transcriptional start site. The elucidated open reading frame of icp75TNFR revealed that the leader sequence in exon 1 of p75TNFR is replaced by an alternative exon. Immunohistochemical staining indicated intracellular expression of the icp75TNFR protein. We further present evidence that expression of icp75TNFR induces NFκB activation in TNF-stimulated cells, thus providing an example for intracellular cytokine receptor activation.

EXPERIMENTAL PROCEDURES

Reagents, Cell Lines—The rat anti-human p75TNFR antibody had been purchased from Genzyme (Genzyme, Cambridge, MA). The polyclonal antiseraum M80 as well as the monoclonal antibodies (mAbs) 80M2, 80A5, and MR2–1 had been kindly provided by M. Grell (Stuttgart, Germany). Mouse L929 cells (fibrosarcoma cells) and the human cell lines HEK 293, HepG2, KMY-1, THP1, U937, and HeLa (ATCC, American Type Culture Collection, Manassas, VA) were maintained in RPMI 1640 medium (Sigma) supplemented with 10% heat-inactivated fetal calf serum (Life Technologies Inc.) and 0.05 mg/ml gentamicin (PAA Laboratories Linz, Austria). HUVECs and HMEC were kindly provided by G. Eiser (Regensburg, Germany).

Primer Extension Analysis—Total RNA was isolated from THP-1 cells, and primer extension analysis was performed as described previously (15) using the following primers: Primer 1, 5′-GGCGCTTTTATAGGCACAGGCCACACTGCTCG-3′; Primer 2, 5′-GGGACCCGCCCATTGCGGCGGGCAGG-3′. PCR amplification was performed using sense and antisense primers for icp75TNFR (5′-GGGAAGCTTGAACATGCGGAAACCCCACAT-3′ and 5′-GGGCTAGGTAGATTACGCTGACCCAGATGCGG-3′). p75TNFR expression plasmids (p75TNFR, icp75TNFR, icp75TNFR ΔTRAF, and icp75TNFR ΔTNFR) were constructed by inserting the corresponding cDNAs into pcDNA 3.1Hygro (Invitrogen, Groningen, The Netherlands). All expression constructs have been verified by sequencing.

Protein Expression and Western Blot Analysis—Twenty-four h after transfection, cells were lysed in 1 ml of lysis buffer (1% Nonidet P-40, 0.1% Triton X-100, 0.1% SDS, 150 mM NaCl, 50 mM Tris-HCl, pH 8.0, 1 μg/ml aproteinin, 1 μg/ml leupeptin, and 1 μM phenylmethylsulfonyl fluoride) for 30 min on ice. Supernatants were incubated overnight at 4 °C with 50 μl of NTA-agarose (Qiagen), washed twice with 1 ml of wash buffer (8 M urea, 0.1% SDS, 1 M Tris, pH 6.8). Eluted proteins were subjected to SDS polyacrylamide electrophoresis and blotted. Immunoblot analysis was performed with a horseradish peroxidase coupled-anti-V5 epitope antibody (Invitrogen) using the Enhanced Chemiluminescence (ECL) Western Blot Detection System (Energene, Regensburg, Germany).

Immunofluorescence Microscopy—HeLa cells seeded on glass slides were transfected with expression plasmids using LipofectAMINE (Life Technologies Inc.) according to the manufacturer’s instructions. Nuclei of cells were stained with Hoechst 33342 (Molecular Probes, Leiden, The Netherlands) was added for 1 h at room temperature.

Colocalization of the Myc-tagged icp75TNFR protein with mitochondria was studied with the exhaustive photon reassignment (EPR) method. To examine TNF binding of cells overexpressing p75TNFR or
icp75TNFR, HeLa cells were seeded on glass slides and transfected with the corresponding expression plasmids as described above. Twenty-four h later, cells were washed with PBS and incubated with biotinylated TNF (100 ng/ml in PBS; R&D Systems, Wiesbaden, Germany) for 2 h on ice and then washed again with PBS and incubated at 37 °C under standard culture conditions. After 2 h, cells were fixed, permeabilized, and blocked as described before. Primary anti-Myc antibody (2 μg/ml (Invitrogen) in PBS containing 2% bovine serum albumin) was added, and cells were incubated at 4 °C overnight. The following day, cells were incubated with FITC-conjugated rabbit anti-mouse IgG (Dako) and Cy3-conjugated streptavidin (Dako) for 1 h at room temperature.

**Transient Transfection and Reporter Assays**—Murine L929 cells stably expressing p75TNFR (L929 p75TNFR), icp75TNFR (L929 icp75TNFR), p75TNFR ΔTNF (L929 p75TNFR ΔTNF) or mock-transfected cells (L929 pcDNA3.1) were seeded at a density of 1 × 10⁵. Cells were transiently transfected with an NFκB-dependent luciferase reporter plasmid or cotransfected with the NFκB reporter plasmid and the expression plasmids encoding icp75TNFR ΔTRAF or icp75TNFR ΔTNF deletion mutants using DOTAP (Roche Diagnostics) according to the manufacturer’s instructions. Sixteen h after transfection cells were incubated with medium with or without 20 ng/ml mouse TNF for 6 h, and luciferase activity was assayed using the Luciferase Assay System (Promega) according to the manufacturer’s directions. Each transfection was done in triplicate and repeated at least three times.

**RESULTS**

While studying the transcriptional regulation of the human p75TNFR it was realized that this promoter sequence lacks a consensus TATA element within the first few hundred base pairs proximal to the translational start site ATG, whereas several TATA elements are located further upstream of the translational start site. To determine whether these TATA elements are active transcriptional initiation sites we performed primer extension analysis using RNA derived from THP-1 cells. Two oligonucleotides complementary to the nucleotides +16 to −19 in the cDNA and 5′-UTR (primer 2) and complementary to the nucleotides −795 to −835 in the 5′-flanking region (primer 1) were used as primers (Fig. 1, bottom). The primer extension analysis identified two transcriptional start sites within the 5′-flanking region of the p75TNFR gene. One of them is located at position −47 (TSI) relative to the translational start site, whereas a second transcriptional start site can be localized at position −870 (TSH) relative to the translational start site (Fig. 1, top). We previously reported about two functional major start sites of transcription in the promoter of the mouse p75TNFR gene (15).

To identify the corresponding cDNA complementary to the mRNA originating from TSH we performed RT-PCR using a 5′-primer located at position −858 to −826 and a 3′-primer located at the 3′-end of the p75TNFR cDNA (Fig. 2A). Three independent cDNA clones were isolated and revealed sequence identity. Primary sequence analysis indicated that transcriptional initiation at TSH within the 5′-flanking region of the p75TNFR gene results in a novel p75TNFR cDNA. Comparison of the two p75TNFR cDNAs indicated sequence identity in the extracellular (ED), transmembrane (TM) and intracellular domain (ID). In contrast, the new p75TNFR cDNA isoform lacks the 5′-UTR and the first exon of p75TNFR (Fig. 2A). Alignment with the genomic sequence further shows that the mRNA transcript initiated at TSH generates a splice donor site at position −600, which fuses the newly transcribed exon 1a to the splice acceptor site at the 5′-end of exon 2 of the p75TNFR transcript. The fusion of this new exon 1a generates an open reading frame (ORF 1a) by positioning the ATG at −681 in frame with exon 2 of the p75TNFR transcript as a potential translational initiation codon (Fig. 2B). Thus, the ORF 1a of the new p75TNFR transcript generates a cDNA that encodes for a mature p75TNFR preceded by a stretch of 27 amino acids encoded by exon 1a (Fig. 2C). To address the question whether exon 1a encodes a putative signal sequence, we compared the predicted amino acid sequences of the p75TNFR cDNA (amino acids 1–26) and the new p75TNFR cDNA (amino acids 1–27) using two different signal peptide prediction methods (SignalP V1.1 and PSORT II, data not shown). Although the first 26 amino acids of p75TNFR were identified as a signal peptide capable of directing a nascent protein to the cell surface, no similarity to any known targeting sequence can be found within the first 27 amino acids of the new p75TNFR.

To determine the expression pattern of icp75TNFR mRNA, we performed RT-PCR analysis using a primer specific for the 5′-end of icp75TNFR cDNA and a 3′-primer annealing in the second exon of the icp75TNFR cDNA resulting in a 360-base pair PCR product. From various cell lines cDNA was prepared and the PCR products were verified by hybridization with a probe specific for the 5′-untranslated region of the icp75TNFR cDNA. Whereas no icp75TNFR mRNA could be detected in HEK 293 and HepG2 cells, HeLa, Kym-1, THP-1, as well as HMEC cells expressed the icp75TNFR mRNA (Fig. 2D). Furthermore, stimulation of HUVEC and U937 cells with lipopolysaccharide resulted in an up-regulation of icp75TNFR mRNA suggesting that the icp75TNFR expression is regulated by proinflammatory stimuli (Fig. 2E).

Transient expression of the icp75TNFR cDNA with a C-terminal V5 His-tag in HeLa cells followed by purification and Western blot analysis using an antibody to V5 resulted in detection of a single protein band with an apparent molecular mass of ~50 kDa (Fig. 3A, lane 2), whereas no protein expression was detected in wild-type HeLa cells (Fig. 3A, lane 1). Thus,
the identified ORF 1a generated by the use of TSII and subsequent alternative splicing of the p75TNFR mRNA resulted in the icp75TNFR protein with an expected molecular mass. The elucidated molecular mass of icp75TNFR is very close to the calculated value of 48.5 kDa. In contrast, it has been shown in previous studies that the expression of the p75TNFR cDNA results in a protein signal; 75 kDa using Western blot analysis.

HeLa cells were transiently transfected with Myc-tagged icp75TNFR cDNA and incubated with biotinylated human TNF followed by simultaneous staining with FITC-coupled anti-Myc antibody and Cy3-coupled streptavidin (Fig. 3B). In contrast to the staining of TNF bound to endogenous TNFRs in wild-type HeLa cells, which is visible as clustering in close proximity to the nucleus, the staining pattern of HeLa cells overexpressing icp75TNFR protein was characterized by a dispersed intracellular receptor staining that was colocalized with biotinylated TNF. This result indicates that the icp75TNFR protein is capable of binding TNF.

To further characterize the icp75TNFR protein, immunohistochemical staining of transiently transfected mouse L929 cells was performed using different mAbs as well as a polyclonal antiserum raised against the human p75TNFR protein. We observed positive staining in L929 cells transfected with either the p75TNFR or icp75TNFR cDNA indicating that the icp75TNFR is indistinguishable from p75TNFR by the use of a polyclonal anti-human p75TNFR serum and by all mAbs we have tested so far (Fig. 3C). No difference was observed in fluorescence-activated cell sorter staining experiments when U937 cells were either nontreated for staining of membrane

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p75TNFR or when the cell membrane was perforated for intracellular staining (data not shown). In both cases the staining of the p75TNFR protein was clearly enhanced after lipopolysaccharide stimulation.

To investigate the subcellular localization of the icp75TNFR protein we performed immunohistochemical staining of transiently transfected HeLa cells expressing either of the two p75TNFR cDNA isoforms fused to a C-terminal Myc-tag. Staining with an anti-Myc antibody revealed that the expression of p75TNFR can easily be recognized on the cell surface of the transiently transfected HeLa cells (Fig. 4A). In contrast, the expression of icp75TNFR was localized predominantly in the intracellular compartment (Fig. 4B), whereas no specific staining was detected in cells transfected with expression plasmid alone (Fig. 4C).

The result of an EPR analysis, which provides a computer-based digital-confocal imaging, confirmed intracellular expression of the icp75TNFR protein characterized by a diffuse intracellular staining (Fig. 4D). Colocalization of icp75TNFR with a mitochondrial marker was recognized only to a small extent.

Because there have been several reports in the past correlating the expression level of p75TNFR with NFκB activation (16) we asked whether the expression of icp75TNFR would influence the TNF-induced activation of NFκB in L929 cells. L929 cells stably transfected with the cDNA of p75TNFR or icp75TNFR were tested for their ability to activate a NFκB-dependent reporter gene. Although expression of the p75TNFR protein in L929 cells resulted in only marginal activation of NFκB after treatment with TNF compared with a control transfection, a significant increase in NFκB activation was detected in L929 cells transfected with the cDNA for the icp75TNFR (Fig. 5A). In contrast L929 cells expressing icp75TNFR protein lacking the TNF binding domain are no longer capable of inducing NFκB after TNF treatment (Fig. 5B). This result indicates that ligand binding by the icp75TNFR protein is necessary for signal transduction and NFκB activation.

It has been shown by mutational analysis within the cytoplasmic domain of p75TNFR that a C-terminal region responsible for the binding of TNF receptor-associated factor 2 (TRAF2) is indispensable for signal transduction and NFκB activation. Coexpression of a p75TNFR mutant, which lacks the TRAF2 domain, resulted in a dominant-negative effect implicating that this domain is essential for the response (17). Accordingly, we tested whether the TRAF2 domain of icp75TNFR is also involved in signal transduction of the icp75TNFR. In fact, coexpression of icp75TNFR lacking the TRAF2 binding domain in the corresponding stably transfected L929 cells resulted in inhibition of TNF-induced NFκB activation (Fig. 5C). This observation suggests that, also for the intracellularly expressed form of icp75TNFR, the TRAF2 domain is critical for signal transduction. In contrast, coexpress-
plasmids encoding Myc-tagged icp75TNFR. HeLa cells were transiently transfected with expression plasmids coding for p75TNFR (A), icp75TNFR (B), or the empty expression plasmid (C). Twenty-four h after transfection, cells were stained with anti-Myc antibody and a FITC-conjugated secondary antibody. Magnification factor of the left and middle panels is 1000-fold. HeLa cells transfected with p75TNFR demonstrate a cell membrane staining, whereas cells transfected with icp75TNFR show a diffuse intracellular staining. D, EPR analysis of the subcellular distribution of icp75TNFR. HeLa cells were transiently transfected with the Myc-tagged icp75TNFR expression plasmid. Cells were incubated with the mitochondria marker MitoTracker Red CMXRos for 30 min. Myc-tagged icp75TNFR was detected with a FITC-conjugated antibody as described above. A diffuse intracellular staining of icp75TNFR was confirmed using the EPR method as described under “Experimental Procedures.” Colocalization of icp75TNFR (green) with the mitochondrial marker (red) can be seen only to a small extent using combined immunofluorescence (yellow).

FIG. 4. Different subcellular localization of p75TNFR and icp75TNFR. HeLa cells were transiently transfected with expression plasmids encoding Myc-tagged p75TNFR (A), icp75TNFR (B), or the empty expression plasmid (C). Twenty-four h after transfection, cells were stained with anti-Myc antibody and a FITC-conjugated secondary antibody. Magnification factor of the left and middle panels is 1000-fold. HeLa cells transfected with p75TNFR demonstrate a cell membrane staining, whereas cells transfected with icp75TNFR show a diffuse intracellular staining. D, EPR analysis of the subcellular distribution of icp75TNFR. HeLa cells were transiently transfected with the Myc-tagged icp75TNFR expression plasmid. Cells were incubated with the mitochondria marker MitoTracker Red CMXRos for 30 min. Myc-tagged icp75TNFR was detected with a FITC-conjugated antibody as described above. A diffuse intracellular staining of icp75TNFR was confirmed using the EPR method as described under “Experimental Procedures.” Colocalization of icp75TNFR (green) with the mitochondrial marker (red) can be seen only to a small extent using combined immunofluorescence (yellow).

FIG. 5. TNF-mediated NFκB activation in L929 cells expressing different p75TNFR variants. A, enhanced NFκB activation in L929 expressing icp75TNFR. L929 cells were stably transfected with expression plasmids coding for p75TNFR or icp75TNFR, respectively, or were mock-transfected. Stable transfectants were assayed for NFκB activation by transient transfection of a NFκB reporter plasmid. Sixteen h after transfection, cells were stimulated with 20 ng/ml mouse TNF (hatched bars) or cultured in TNF-free medium for another 6 h (white bars). Luciferase activity was determined as described under “Experimental Procedures.” B, impaired NFκB activation in L929 cells expressing an icp75TNFR deletion mutant lacking the TNF binding domain. Stable transfectants were assayed as described above in A. C, different effects on NFκB activation by overexpression of icp75TNFR deletion mutants lacking the TRAF2 binding domain or the TNF binding domain. L929 cells stably expressing icp75TNFR were cotransfected with a NFκB reporter plasmid and the expression plasmids for the icp75TNFR proteins without the TRAF2 binding domain (icp75 ΔTRAF2) or without the TNF binding domain (icp75 ΔTNF). Sixteen h later, cells were stimulated with 20 ng/ml mouse TNF or cultured in TNF-free medium for another 6 h. Luciferase activity was determined as described under “Experimental Procedures.”
evidence for intracellular expression of icp75TNFR was given by the observation that the expressed protein is detected with an apparent molecular mass of ~50 kDa, which is close to the calculated value of the primary amino acid sequence (48.5 kDa). This suggests that no posttranslational modifications, e.g. glycosylation, occur by which the transmembrane form of the p75TNFR is characterized. Interestingly, Ledgerwood et al. (20) described a 60-kDa protein localized in the inner mitochondrial membrane of umbilical vein endothelial cells, which was recognized by a specific mAb against human p75TNFR and was also capable of binding TNF. Our data show that the icp75TNFR protein was recognized by all mAbs raised against human p75TNFR that we have tested so far including the one used by Ledgerwood et al. EPR analysis showed that in addition to diffuse intracellular staining a small amount of icp75TNFR protein possibly was colocalized with a mitochondrial marker. The difference in the staining pattern may be due to overexpression of icp75TNFR in our experiments. Specific staining of endogenous icp75TNFR protein by cytochemistry or fluorescence-activated cell sorter analysis was not possible so far because no reagents are available that can distinguish between the membrane form of the p75TNFR and the icp75TNFR. More detailed localization studies have to be done to dissect the expression pattern of two p75TNFR isoforms.

Overexpression of icp75TNFR induced significant NFκB activation in L929 cells after TNF stimulation suggesting that this receptor subtype is capable of triggering signaling events in a TNF-dependent manner. L929 cells stably transfected with the p75TNFR cDNA encoding the transmembrane receptor subtype as confirmed by immunocytochemical staining and RT-PCR analysis show only a marginal TNF-induced increase in NFκB-dependent reporter gene activation compared with the control cells. It has been shown previously that p75TNFR is capable of inducing NFκB activation and that for this signal transduction the TRAF2 binding domain is indispensable (17). This also seems to be the case for NFκB activation by the icp75TNFR protein arguing for a direct involvement in TNF-mediated signaling. It remains to be analyzed whether TNF has to be internalized by the transmembrane receptors as described earlier (19), by a suggested TNFR-independent mechanism (20), and/or whether endogenously produced TNF is responsible for activation of icp75TNFR followed by intracellular signaling. In addition, the functional consequences of such intracellular TNF signaling via the icp75TNFR is currently under investigation.

Acknowledgments—We thank Dr. Matthias Grell for the anti-p75TNFR antibodies and helpful discussions.

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A Novel p75TNF Receptor Isoform Mediating NFκB Activation
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J. Biol. Chem. 2001, 276:19390-19395.
doi: 10.1074/jbc.M101336200 originally published online March 1, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M101336200

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