Isolation of a Novel Interleukin-1-inducible Nuclear Protein Bearing Ankyrin-repeat Motifs*

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We isolated a novel gene termed interleukin (IL)-1-inducible nuclear ankyrin-repeat protein (INAP), of which expression was specifically induced by IL-1 in OP9 stromal cells. The INAP has ankyrin-repeat motifs and shares weak amino acid sequence homology with Bcl-3 and other IκB family members. The human genomic INAP gene found in the NCBI database is located at chromosome 3q3.1. Northern blot analyses revealed that INAP was not expressed in any examined tissues without stimulation, but INAP expression was rapidly and transiently induced by IL-1 although not by tumor necrosis factor α nor by phorbol 12-myristate 13-acetate in OP9 cells. Immunoblots with anti-INAP-specific antibody demonstrated that INAP was rapidly and specifically produced by IL-1 stimulation and was predominantly localized in the nucleus. Immunofluorescence stainings showed that the INAP newly synthesized by IL-1 stimulation was clearly localized in the nucleus. The possible interaction of INAP with RelA/p65, NF-κB2/p52, C/EBPβ, and retinoid X receptor was examined, but we could detect none of these interactions in the nuclear extracts of IL-1-stimulated cells. Unlike Bcl-3 and other IκB family members, INAP may play a unique role in IL-1-induced specific gene expression and/or signal transduction in the nucleus.

NF-κB is a transcription factor that is known to play an important role in regulating immune and inflammatory responses (1–3). There are presently five members of the mammalian NF-κB/Rel family, NF-κB1/p50, NF-κB2/p52, c-Rel, RelA/p65, and RelB (1–3). The classic form of NF-κB, the heterodimer of the NF-κB1/p50 and RelA/p65, is normally retained in the cytoplasm through interactions with inhibitor protein IκB. The IκB family of proteins includes IκBa, IκBβ, IκBε, Bcl-3, NF-κB1/p105, and NF-κB2/p100, all of which possess 5–7 ankyrin-repeat motifs (1–3), which form a functional unit able to interact with the Rel homology domain of NF-κB. The cytoplasmic retention of the classic form of NF-κB is primarily carried out by IκBa and IκBβ (4–7). Inductive stimuli, such as tumor necrosis factor α (TNFα), interleukin-1 (IL-1), and bacterial endotoxin, lead to the phosphorylation and degradation of IκBa, allowing NF-κB to translocate into the nucleus and regulate specific gene expression (1–3).

IκBa is degraded in response to the NF-κB inducers TNFα, IL-1, lipopolysaccharide (LPS), phorbol 12-myristate 13-acetate (PMA), and double-stranded RNA. In contrast, IκBβ is degraded only when cells are stimulated with IL-1 or LPS, both of which cause persistent long term activation of NF-κB (4–7). Following degradation of the initial pool of IκBβ in response to IL-1 or LPS, newly synthesized IκBβ accumulates as an unphosphorylated protein that forms a stable complex with NF-κB and prevents it from binding to newly synthesized IκBa (4–7), resulting in the prolonged activation of NF-κB (4, 8). This unphosphorylated IκBβ cannot block the nuclear localization signal of NF-κB, thus this NF-κB/IκBβ complex translocates into the nucleus. The function of this complex in the nucleus is yet to be elucidated, and the mechanism by which only IL-1 and LPS can degrade IκBβ remains to be resolved.

Unlike the other IκB family members, Bcl-3 is a nuclear protein (9–11). It does not bind to RelA/p65 but specifically binds to NF-κB1/p50 or NF-κB2/p52 homodimers (10, 12–14) and takes them into the nucleus where it exhibits transactivating activity (11, 15). The formation of Bcl-3/NF-κB1/p50, NF-κB complex or Bcl-3/NF-κB2/p52 NF-κB complex is regulated by the phosphorylation status of Bcl-3 (14, 16). Bcl-3 also interacts with retinoid X receptor (RXR) or activating protein-1 (AP-1) and functions as their transcription coactivator (17, 18). However, the detailed characters of this unique IκB family member remain mysterious.

Here we identified a novel IκB family member, termed IL-1-inducible nuclear ankyrin-repeat protein (INAP), of which expression is specifically induced by IL-1. INAP was found to be weakly homologous to Bcl-3 and localized in the nucleus like Bcl-3. We discuss here the possible function of this novel IκB family member.

EXPERIMENTAL PROCEDURES

Isolation of INAP cDNA—OP9 cells were cultured in α-minimum Eagle’s medium supplemented with 20% fetal calf serum (FCS) with or without 10 ng/ml of mouse IL-1α (Genzyme/Techne) in the presence of 10 μg/ml of cycloheximide for 1 h, and total mRNA was isolated. The PCR-Select cDNA subtraction kit (CLONTECH) was used for cDNA synthesis and suppressive subtractive hybridization, according to the manufacturer’s instructions. The cDNA from OP9 cells incubated with IL-1α was used as the tester sample, and that from untreated cells was used as the driver sample. The 5’ end of INAP cDNA was confirmed by the rapid amplification of the cDNA ends (5’ RACE) method.

Northern Blot Analysis—Total mRNAs from OP9 cells stimulated

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The nucleotide sequence(s) reported in this paper has been submitted to the DDBJ/GenBank™/EBI Data Bank with accession number(s) AB928351.

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1 The abbreviations used are: TNFα, tumor necrosis factor α; IL-1, interleukin-1; PMA, phorbol 12-myristate 13-acetate; DAPI, 4,6-diamidino-2-phenylindole; LPS, lipopolysaccharide; RXR, retinoid X receptor; GST, glutathione S-transferase; PAGE, polyacrylamide gel electrophoresis; PBS, phosphate-buffered saline; AP-1, activating protein-1; INAP, IL-1-inducible nuclear ankyrin-repeat protein; FCS, fetal calf serum; DIG, digoxigenin; ECL, enhanced chemiluminescence; bp, base pair; CIP, calf intestine alkaline phosphatase; HA, hemagglutinin.

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IL-1-inducible Nuclear Protein with Ankyrin Repeats

RESULTS

Isolation and Structure of INAP—We attempted to isolate the genes of which transcriptions were induced by IL-1 in mouse stromal OP9 cells. Subtraction of mRNAs of OP9 cells with 10 ng/ml of mouse IL-1α, 20 ng/ml of mouse TNFα (Genzyme/Techne), or 100 ng/ml of PMA (Sigma) for the indicated period of time were isolated. Total mRNA (20 μg/lane) was resolved on a 1% agarose gel and transferred to a Hybond-N+ membrane. The filters were hybridized with the digoxigenin (DIG)-labeled INAP cDNA probe (nucleotides 338–1368) at 42 °C for 16 h in DIG Easy Hyb solution (Roche Diagnostics). After washing at 68 °C for 30 min in 1 × SSC containing 0.2% SDS, the hybridized bands were detected by chemiluminescent detection using CDP-StarTM substrate (Roche Diagnostics).

Preparation of Glutathione S-Transferase (GST)-INAP and Anti-INAP Antibody—The INAP cDNA (amino acids 108 to 403) was ligated into pGEX2T and expressed in Escherichia coli BL21(DE3) pLysS cells. Rabbit antiserum was raised against GST-INAP, and the polyclonal antibody was purified by GST-INAP affinity chromatography.

Indirect Immunofluorescence Staining of OP9 Cells—Cells on coverslips were fixed with 3% formaldehyde and 0.2% Triton X-100 for 15 min. The cells were blocked with 5% FCS in PBS and incubated with purified anti-INAP-specific rabbit antibody. The cells were then reacted with Cy3-conjugated F(ab’)2 fragment donkey anti-rabbit antibody (Jackson ImmunoResearch Laboratories) and 1 mg/ml 4,6-diamidino-2-phenylindole (DAPI). The coverslips were mounted in PBS containing 90% glycerol and 0.1% 1,4-para-phenylene diamine and were observed with a fluorescence microscope (Olympus BX60–34-FLBD1).

Immunoblot Analysis—Cells were sonicated in 20 mM Hepes, pH 7.4, 1 mM EDTA, 0.1 mM EGTA, 2 mM MglCl, 1 mM NaVO4, 20 mM NaF, 150 mM NaCl, 5% glycerol, 0.2% Nonidet P-40, 1 μg/ml pepstatin A, 1 μg/ml aprotinin, 5 μg/ml leupeptin, and 5 μg/ml Pefabloc SC. Samples were fractionated by 10% SDS-PAGE and electrotransferred to an ECL membrane. The membrane was blocked with 5% milk in 20 mM Tris-HCl, pH 7.5, 150 mM NaCl, and 0.5% Tween 20, incubated with anti-INAP-specific rabbit antibody for 2 h, and then incubated with horseradish peroxidase-conjugated F(ab’)2 fragment donkey anti-rabbit antibody. The antibody complexes were visualized by an ECL system (Amersham Pharmacia Biotech).

INAP Expression Is Rapidly and Specifically Induced by IL-1 Stimulation—Expression of INAP in various mouse tissues was examined by Northern blot analyses, but no INAP mRNA was detectable in any tissues examined because of its sparse expression (data not shown). Therefore, we examined INAP expression in OP9 cells at various time points after IL-1α before and after IL-1 stimulation to led to the isolation of a number of cDNA fragments encoding factors related to the IL-1 response. Among them, we focused on a novel gene, termed INAP. The isolated mouse full-length INAP cDNA (2339 bp) contained an open reading frame, which encoded a polypeptide of 728 amino acids with a calculated molecular mass of 79,007 daltons and a predicted pl of 6.45. A search in the NCBI database using the BLAST program revealed that a human genomic sequence (map element NT_022504) of chromosome 3 contained the human INAP gene, which consists of 12 exons and is located at chromosome 3q13.11. Human INAP constituted of 718 amino acids has a predicted molecular mass of 78,061 daltons. Human INAP has 82% amino acid identity and 85% similarity with mouse INAP and has a 10-amino acid deletion at amino acid 301–310 compared with mouse sequences.

Fig. 1A shows the schematic drawings of the isolated mouse INAP cDNA and of the human genomic INAP gene found in the NCBI data base. Mouse and human INAP were found to be weakly homologous to the IκB family and the Rel family. The most striking feature of mouse and human INAP is that both INAP contain five highly conserved ankyrin-repeat motifs in carboxyl-terminal regions. Using PESTFIND software, it was also found that both INAP have PEST (P, E, D, S, and T residue-rich)-like sequences, which are implicated in the rapid turnover of proteins (19). Although IκBα and IκBβ have PEST sequences in carboxyl-terminal ends, both mouse and human INAP have them at amino-terminal regions (amino acids 11–84 and 185–203 in mouse and 184–204 in human). A serine-rich region was also found in amino-terminal regions (amino acids 53–77 in mouse and 51–86 in human), and a glycine-rich region was found in the middle regions (amino acids 245–308 in mouse and 247–299 in human). However, the glycine-rich region, Rel homology domain, or obvious nuclear localization signal, which commonly exist in the Rel family, was not found in INAP. Reinhardt’s method (20) for cytoplasmic or nuclear discrimination predicted that there is a 94% possibility that INAP is localized in the nucleus.

To examine the relationship of INAP to other members of the IκB and Rel families, a phylogenetic tree was constructed using the amino acid sequences of all known mammalian IκB and Rel family (Fig. 1B). The closest protein of INAP turned out to be Bcl-3, and the second closest was IκBε. Mouse INAP has 30–33% identity and 36–38% similarity with human Bcl-3 and mouse Bcl-3. Mouse INAP has 26–29% identity and 33–36% similarity with those of the other IκB family members and has 22–35% identity and 22–41% similarity with those of Rel family members.

INAP Expression Is Rapidly and Specifically Induced by IL-1 Stimulation—Expression of INAP in various mouse tissues was examined by Northern blot analyses, but no INAP mRNA was detectable in any tissues examined because of its sparse expression (data not shown). Therefore, we examined INAP expression in OP9 cells at various time points after IL-1α stimulation.

FIG. 1. Structure of INAP. A, schematic drawings of mouse full-length INAP cDNA (mINAP) and of the human genomic INAP gene (hINAP). The locations of the serine-rich region, glutamine-rich region, PEST-like sequences, and ankyrin-repeat motifs are indicated. B, phylogenetic tree of INAP and its related proteins. The phylogenetic tree was constructed by the neighbor-joining method using ClustalX 1.8 based on the alignment and visualized with the Treeview program 1.6.1. Species abbreviations are as follows: h, Homo sapiens; m, Mus musculus; r, Rattus norvegicus; b, Bos taurus; and s, Sus scrofa.

FIG. 2. INAP transcripts were specifically induced by IL-1. Northern blot analysis of INAP mRNA expression in OP9 cells is shown. OP9 cells were treated with TNFα (left panel), PMA (middle panel), or IL-1α (right panel) for the indicated time period, and total mRNA (20 μg/lane) blotted on the filters was hybridized with DIG-labeled INAP cDNA probe.
specifically produced by IL-1 stimulation. OP9 cells were treated with INAP rabbit antibody. The blotted proteins were reacted with anti-phosphatase (CIP), separated by SDS-PAGE, and immunoblotted with anti-INAP antibody. Arrows indicate double bands of INAP. Location and size (in kDa) of protein standards are shown at the left. B, INAP was not phosphorylated and was localized in the nucleus. OP9 cells were treated with (+) or without (−) IL-1, and nuclear extracts and cytosolic extracts were prepared. The INAP was immunoprecipitated with purified anti-INAP-specific rabbit antibody, treated (+) or untreated (−) with CIP, and separated by SDS-PAGE. The blotted proteins were reacted with anti-INAP rabbit antibody. Arrows indicate double bands of INAP.

stimulation (Fig. 2, right panel). Although no INAP mRNA was detected in unstimulated OP9 cells (Fig. 2, right panel, lane 1), a single hybridized band was weakly detected 15 min after IL-1α stimulation (lane 2). The level of INAP mRNA increased and reached the maximum at 1 h after IL-1α stimulation (lane 4) and then decreased thereafter (lanes 5, 6), indicating that the INAP gene was rapidly and transiently transcribed after IL-1α stimulation in OP9 cells. IL-1β also exhibited the same effect on INAP expression (data not shown). Similarly, INAP expression after TNFα or PMA stimulation was examined, but no transcript was detected (Fig. 2, left and middle panels) although OP9 cells are responsive to TNFα and PMA, indicating that INAP transcription was specifically induced by IL-1 stimulation.

The expression of mouse INAP in the protein level was examined by immunoblot analyses with a purified anti-INAP-specific rabbit antibody. As shown in Fig. 3A, mouse INAP of 79 and 82 kDa were clearly detected in IL-1α (right panel)- but not TNFα (left panel)- or PMA (middle panel)-stimulated OP9 cells, confirming that INAP expression was specifically induced by IL-1α. The double bands were clearly detected within 30 min after IL-1α stimulation (Fig. 3A, right panel, lane 2), although they were not seen in the cells without stimulation (lane 1). Although INAP transcripts were transiently expressed, the protein level increased until 1 h after IL-1α stimulation and retained its level even 24 h after stimulation (lanes 3–5), suggesting that the newly synthesized INAP is relatively stable and accumulates in the cells. We also detected human INAP in IL-1α-stimulated HeLa cell extracts by the same antibody (data not shown).

The double bands were clearly recognized by anti-INAP antibody, and thus we speculated that the upper band might be the phosphorylated form of the lower band. The INAP was therefore immunoprecipitated with its specific antibody from the nuclear extracts, as well as the cytosolic extracts, which were prepared from OP9 cells treated with or without IL-1α. The immunoprecipitates were treated with calf intestine alkaline phosphatase (CIP), separated by SDS-PAGE, and immunoblotted with anti-INAP antibody. The results demonstrated that INAP was predominantly detected in the nuclear extracts and that the double bands were not affected by phosphatase treatment (Fig. 3B), indicating that INAP was not phosphorylated and that subcellular localization of INAP was not affected by its phosphorylation status. We therefore concluded that the upper band was not the phosphorylated form of the lower band.

We further noticed that the INAP has a second Met codon at amino acid 26, and thus the lower band may be the protein product translated from this second Met codon.

INAP Is Rapidly Translocated into the Nucleus—Subcellular localization of INAP in OP9 cells with or without IL-1α stimulation for 1 h was examined by indirect immunofluorescence microscopic analysis, and the fluorescent images were overlaid on difference interference contrast images (Fig. 4A). The INAP stained with purified anti-INAP-specific antibody in red were predominantly detected in the nuclei of OP9 cells treated with IL-1α for 1 h (Fig. 4A, left lower panel), whereas it was rarely seen in the cells prior to IL-1α stimulation (left upper panel). The chromosomes stained with DAPI in blue (right lower panel) were completely overlapped with INAP stained in red (left lower panel). These results clearly demonstrated that newly synthesized INAP was promptly translocated into the nucleus by IL-1α stimulation in OP9 cells. Furthermore, we found that IL-1 stimulated the production of INAP in various mouse organs including spleen, small intestine, lung, liver, heart, and kidney and that INAP was always localized in nucleus in these IL-1-stimulated tissues (data not shown). Thus, IL-1-specific INAP expression and its nuclear localization are not specific events observed only in OP9 cells.

To confirm these findings, FLAG-tagged INAP and HA-tagged INAP were transiently expressed in mouse fibroblast NIH/3T3 cells. Fig. 4B shows that FLAG-tagged INAP was
clearly detected only in the nucleus of the transfected cells by anti-FLAG antibody (stained in green; left panel). The chromo-
somes stained with DAPI in blue (right panel) were completely
overlapped with INAP stained in green (left panel) in transfe-
tants. Similarly, HA-tagged INAP was also localized in the
nucleus (data not shown). Taken together, these results clearly
indicate that INAP was promptly translocated into the nucleus
after INAP protein synthesis was induced by IL-1 stimulation.

DISCUSSION

We isolated a novel IL-1-inducible nuclear factor, INAP,
which is related to the IκB family and the Rel family. It is well
known that IκB family members bind to the RelA/p65-NF-κB1/
p50 complex and prevents the complex from activating and
translocating into the nucleus. Therefore, possible interaction
of INAP with the RelA/p65-NF-κB1/p50 complex was examined
by immunoprecipitation followed by immunoblot analysis.
However, we failed to detect the direct and/or indirect binding
of INAP to RelA/p65 (data not shown). Furthermore, one of
the most important factors induced by IL-1 stimulation is IL6, of
which gene expression is regulated by C/EBPβ (NF-IL6), AP-1,
and NF-κB (21, 22). Therefore, we also examined the possible
interactions of INAP with C/EBPβ and c-Fos/c-Jun in nuclear
extracts prepared from IL-1α-stimulated OP9 cells. Once
again, we could not detect the interactions of INAP with
C/EBPβ or with c-Fos/c-Jun (data not shown). Moreover, the
fact that Bcl-3, the protein most closely related to INAP, asso-
ciates NF-κB1/p50 or NF-κB2/p52 homodimers and modulates
their transactivation activities (11, 16) motivated us to exam-
ine whether INAP associates with NF-κB1/p50 or NF-κB2/p52
in IL-1-stimulated nucleus. None of these interactions, how-
ever, was detected by immunoprecipitation followed by immu-
noblot analysis (data not shown). It has also been reported that
Bcl-3 binds to RXR (17) or to AP-1 (18) and regulate specific
actions of INAP with RXR or with AP-1 but failed to detect the
binding of INAP, but it does exist in the nucleus. Furthermore, INAP was
found to be a novel nuclear factor related to the Rel family and is clearly distinct even from the most closely
related IκB family member, Bcl-3. To determine the biological
function of INAP on IL-1 signalings it is very important to
identify the INAP-binding proteins in the IL-1-stimulated nu-
cleus by other means such as yeast two-hybrid screening, pull-
down experiments, and far-Western screening.

INAP was found to be a novel nuclear factor related to the
IκB family, but by IL-1 stimulation INAP was newly produced
and accumulated in the nucleus, rather than being degraded as
were other IκB family members. From a gene expression point
of view, INAP is quite a distinct protein from these family
members. There exists no obvious nuclear localization signal
in INAP, but it does exist in the nucleus. Furthermore, INAP was
not phosphorylated no matter whether it was localized in the
cytoplasm or nucleus, indicating that the phosphorylation sta-
thus of INAP does not affect its subcellular localization.

A few potential NF-κB binding sites were found around −340
bp upstream from the initiation codon in human INAP gene
promoter regions. However, we demonstrated that INAP gene
expression was rapidly induced by IL-1 but not by TNFα nor by
PMA, all of which are known to activate the NF-κB signaling
pathway. Thus, INAP gene expression is not simply regulated
by NF-κB signaling. IL-1- and LPS-specific persistent activa-
tion of NF-κB has been reported (4, 5), but rapid IL-1- (and
LPS-) specific INAP gene expression cannot be explained by
this mechanism. The mechanism is thus obscure at this mo-
tim, and further analyses are required.

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