Characterization of Proteins Binding to E-box/Ku86 Sites and Function of Ku86 in Transcriptional Regulation of the Human Xanthine Oxidoreductase Gene*

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We reported previously that E-box and TATA-like elements repress human xanthine oxidoreductase gene (hXOR) expression. In the present investigation, we determined the means by which the E-box site functions in this basal repression. DNA affinity purification demonstrated that at least five proteins are involved in the nuclear protein complex binding to the E-box and adjacent Ku86-binding sites. Amino acid sequence analysis demonstrated that three proteins, DNA-PK catalytic subunit, Ku86, and Ku70 are components of DNA-dependent protein kinase (DNA-PK). By electrophoretic mobility shift assays, gel-shift, and site-directed mutagenesis, we confirmed Ku86 binding to the Ku86 site. Studies indicated that the other two proteins of the complex are AREB6-like proteins binding to the E-box. Pull-down and immunoprecipitation analyses demonstrated the binding of Ku86 to AREB6-like proteins. The functional loss of Ku86 increases hXOR promoter activity and transcript expression. Based on the findings, we propose that DNA-PK/AREB6-like proteins play a central role in repression of basal hXOR activity. AREB6-like proteins specifically bind to the E-box, whereas Ku86 binds an adjacent site and recruits DNA-PK catalytic subunit and Ku70 proteins. A working model is presented to account for the role of DNA-PK and AREB6-like proteins in regulating hXOR activity.

Xanthine oxidoreductase (XOR)1 (EC 1.1.3.22), a member of molybdoflavoprotein hydroxylases, is a homodimer with each subunit of about 150 kDa containing four redox active centers: iron-sulfur, one FAD, and one molybdenopterin (1–3). In mammals, XOR exists in two interconvertible forms, xanthine dehydrogenase and xanthine oxidase (XO). Xanthine dehydrogenase transfers the reducing equivalents generated by the oxidation of substrates to NAD+, whereas XO transfers them to oxygen, with the resultant production of superoxide anion and hydrogen peroxide. As the rate-limiting enzyme in nucleic acid degradation, XOR catalyzes the final two reactions of purine catabolism, with the resultant production of urate.

More than just a rate-limiting enzyme in purine degradation, XOR plays important roles in physiological and pathological conditions as a producer of both urate and reactive oxygen species (ROS). Urate, which scavenges hydroxyl radical, singlet oxygen, hypochlorous acid, oxymethoxides, and hydroperoxyl radicals and is a potent iron chelator (4–7), has been proposed as a major antioxidant in plasma (4, 5, 8) and epithelial secretions (9). Blood urate concentrations are ~10-fold higher in humans and most primates than in other mammals because of the evolutionary loss of uricase. Urate functioning as an antioxidant has been cited as a possible basis for the relative increase in life span and the decrease in cancer rates of humans compared with other species (4). The high concentrations, however, predispose to crystalline deposition, the histopathologic hallmark of gout, the “king of diseases.” In Western industrialized countries, ~5% of the population has hyperuricaemia (10).

In contrast to the role of urate as a protective antioxidant, XOR-derived superoxide anion and hydrogen peroxide lead to oxidative tissue injury in a variety of animal models that simulate several clinical disorders, including renal failure, endotoxin-induced mucosal injury, viral pneumonia, ischemia-reperfusion injury, and cutaneous photosensitivity to hematoporphyrins (11–18). In animal models, XOR activity and gene expression have been shown to be up-regulated by cytokines and hypoxia in a profile consistent with an acute-phase response and during ischemia/reperfusion (19–22). In addition, the XOR-derived ROS may contribute to the regulation of physiological functions as inducers of signal transduction and gene transcription (23–26).

It has been demonstrated that XOR enzyme activity is 100 times lower in humans than that in nonprimate species, including rats and mice (27–29), suggesting that the results obtained from the nonprimate species cannot be simply extrapolated to humans. To understand the physiological and pathophysiological role of XOR in humans, it is important to study the mechanisms underlying the regulation of its expression. To date, little is known regarding the regulation of human XOR, although post-translational mechanisms seem to partially explain the low activity (30, 31). Recently, we cloned human XOR (hXOR) and characterized its chromosomal location, genomic organization, and basal transcriptional regulation (32–35). We demonstrated that the basal expression of hXOR is restricted by a repressive mechanism involving E-box and TATA-like elements (35). We also identified a conjunct consensus GTTTC located 19-bp upstream of the E-box that, in the human 70-kDa heat-shock gene promoter, is required for repressive function of the E-box (36). In addition, there is a Ku86 binding site (GAGAAA) immediately upstream of the E-box. The Ku86 pro-

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*The abbreviations used are: XOR, xanthine oxidoreductase; hXOR, human xanthine oxidoreductase gene; DNA-PK, DNA-dependent protein kinase; EMSA, electrophoretic mobility shift assay; ROS, reactive oxygen species.

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tein is an important component of DNA-dependent protein kinase (DNA-PK) that participates in repair of damaged DNA and phosphorylation of transcription factors (37, 38). In the current study, we investigated the basis for the E-box/Ku86 repression of hXOR.

MATERIALS AND METHODS

Cell Culture—PF5K-1 cells, a neural cell line obtained from American Type Culture Collection (ATCC), were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum, 2.0 mM l-glutamine, and penicillin/streptomycin. V79–4 and XR-V15B cells were cultured according to ATCC recommendations. V79–4 cells are a fibroblast cell line derived from Chinese hamster lung fibroblasts. XR-V15B cells are Ku86-deficient. V79–4 cells resulting from the internal in-frame deletion of 46 amino acids generated by ethynitrosourea-mutagenesis (39, 40). Nuclear extracts were prepared from cultured cells as described previously (35, 41). Protein concentrations of the extracts were determined spectrophotometrically using Bio-Rad protein reagents.

Electrophoretic Mobility Shift Assays (EMSA)—EMSA were employed to study the binding of nuclear or AREB6 proteins to DNA probes (34, 35, 42). In EMSA, DNA probes EG (wild-type), 3× EG (three repeats of EG), EGm (mutant GTTTC), and EmGm (combined mutant E-box and GTTTC) were used as binding probes, whereas EG (specific), EmG (mutant E-box), Kum1 and Kum2 (mutants of the Ku86 binding sites) were used as competitors, as illustrated in Fig. IA. For gel-shift assays using nuclear extracts, 15–30 fmol of labeled binding probes were incubated for 30 min at room temperature with 5–10 μg of nuclear proteins in a 50-μl reaction mixture containing 4% glycerol, 10 mM Tris, pH 7.5, 10 mM NaCl, 0.5 mM dithiothreitol, 1 mM MgCl2, 0.5 mM EDTA, 0.05% Nonidet P-40, and 25 μg of bovine serum albumin plus 3 μg of poly(dI-dC) or poly(dI-dT) to reduce nonspecific binding. For competition studies, the samples were pre-incubated with unlabeled competitors for 10 min at room temperature prior to the addition of the labeled binding probes. For gel-shift analysis, incubation of EMSA reaction mixtures for 15 min at room temperature was followed by the addition of the specific or irrelevant antibodies and incubation for an additional 30 min at room temperature. AREB6 antisera was generated and purified using an affinity column as described below. Ku70, Ku86, and DNA-PKcs antibodies were purchased from Santa Cruz Biotechnology. The reaction samples were electrophoresed and then transferred to nylon membranes by electroblotting. The oligonucleotides were fixed onto the membranes by baking at 100 °C for 30 min. The chemiluminescent signals were detected following the DIG gel shift kit (Roche Applied Science) protocol.

Purification of Nuclear Proteins Binding to the Probe EG—For DNA affinity purification, biotin-labeled DNA probe 3× EG (three repeats of probe EG, 47 bp for each repeat that contains the E-box, conjugate GTTTC, and Ku86 site) was generated by PCR amplification (43). The labeled probe was chemically conjugated to Dynal streptavidin magnetic beads (44). The nuclear extracts were purified by anion exchange purification using a Hi-Trap column following the recommended protocol (Dynal). The nucleoprotein complexes were analyzed by immunoblotting with AREB6 antiserum (1:3000) and irrelevant antibodies (pre-immune serum and sulfite oxidase antiserum, 1:3000) were used as primary antibodies. For GST pull-down, AREB6-C, AREB6-H, and AREB6-N proteins were conjugated to glutathione-Sepharose beads (Amersham Biosciences). The conjugated beads were incubated with nuclear extracts at 4 °C for 2 h in a total volume of 400 μl of binding buffer (25 mM Hepes, pH 7.5, 10% glycerol, 150 mM NaCl, and 0.2 mM EDTA) containing 0.05% Triton X-100. After extensive washing with binding buffer, the beads were suspended in sample buffer for SDS-PAGE. Ku86 antibodies (1:3000) were used as primary antibodies to detect the signals. The immunoprecipitation of nuclear extracts was performed using Ku86 or irrelevant (Vimentin, Santa Cruz Biotechnol- ogy) antibodies described in Ref. 44. The precipitates were analyzed by immunoblotting with AREB6 antisera (1:3000) as primary antibodies, as described above.

RESULTS

Nuclear Proteins Bind to the E-box and Ku86 Sites—We demonstrated previously that an E-box restricts basal hXOR promoter activity (35). Further sequence analysis indicated that a Ku86 binding site is located 2 bp upstream of the E-box, as shown in Fig. IA. To determine mechanisms by which the E-box/Ku86 region regulates hXOR promoter activity, we examined the nuclear proteins binding to the E-box and Ku86 sites. Probe EG containing E-box and Ku86 sites was used as the binding probe and specific competitor in the experiments. The DNA probes used in the experiments are illustrated in Fig. IA. As shown in Fig. 1B, binding of nuclear proteins to the probe EG caused multiple shifted bands. One of the bands was competed for specifically by the probes (Kum1, Kum2, and specific competitor) containing the E-box (lanes 3, 4, and 5) but not the probe containing the mutant E-box (probe EmG, lane 6), as indicated by an arrow and labeled E-box binding. The results demonstrate specific binding of nuclear protein to the E-box. Besides the E-box binding band, Fig. 1B demonstrated that two nuclear proteins binding to probe EG were specifically competed for by the specific competitor (lane 5) and the probe containing the mutant E-box (probe EmG, lane 6), but not by the probes containing a mutant Ku86 site (probe Kum1 and Kum2, lanes 3 and 4), indicating that specific nuclear proteins bind to the Ku86 site. Meanwhile, the probe with a mutant E-box (probe EmG) was able to compete for the Ku86 binding but not with the E-box binding, suggesting no interference between E-box and Ku86 sites in the binding of nuclear proteins.

Magnetic DNA Affinity Purification and Sequence Analysis of Nuclear Proteins Binding to the Probe EG—To further characterize the nuclear proteins binding to the E-box/Ku86 site,
DNA probes containing three repeats of probe EG (probe 3× EG) were conjugated to the Dynal magnetic beads. As shown in Fig. 2A, the binding pattern of nuclear proteins to probe 3× EG was similar in comparison with that to probe EG (Fig. 1B). Of particular note, the competition pattern of the binding by various competitors was similar in both experiments, indicating that the proteins binding to probe 3× EG are likely the same as those binding to probe EG. Five proteins were eluted from probe 3× EG-conjugated Dynal beads (Fig. 2B). The three major proteins were ~350, 86, and 70 kDa. Sequence analysis identified these proteins as DNA-PKcs (350 kDa), Ku86 (86 kDa), and Ku70 (70 kDa). The other two proteins with sizes of around 200 and 100 kDa could not be sequenced because of inadequate amounts.

Ku86 Antibodies Block the Nuclear Protein Binding to Probe EG—DNA-PKcs, Ku86, and Ku70 are all subunits of DNA-PK complex (37, 38). To further characterize binding of the DNA-PK complex, by using gel-shift assays we examined the effect of DNA-PKcs, Ku86, and Ku70 antibodies on the binding of nuclear proteins to the EG probe. As shown in Fig. 3, the Ku86 antibody, but not the other two, specifically blocked binding of nuclear proteins. Combining with the results in Figs. 1 and 2, it appears that Ku86 binds to the EG probe.

Immunoreactivities to AREB6 Antiserum of the Nuclear Extracts and the Eluted Proteins from Probe 3×-conjugated Dynal Beads—As already indicated, sequence analysis identified a conjunct consensus GTTTC 19 bp upstream of the E-box in the hXOR promoter (35). To date, AREB6 is the only E-box binding protein shown to require the consensus for its repressive function (36). To test whether the other proteins eluted from the probe 3× EG-conjugated Dynal beads, in addition to the DNA-PK complex, were AREB6-like proteins, Western blot analysis with AREB6 antiserum was performed. As demonstrated in Fig. 4A, proteins immunoreactive to AREB6 antiserum were present in nuclear extracts. The sizes of the major AREB6-immunoreactive proteins were ~200, 160, 100, and 75 kDa. Similar results were obtained in Western blot analysis of proteins eluted from probe 3× EG-conjugated Dynal beads (Fig. 4B). The bands ~100 and 75 kDa are likely nonspecific because of the cross-immunoreactivity to pre-immune and sulfite oxidase antiserum. A protein of 200 kDa was also observed in Fig. 2B as discussed above. It appears that the protein ~200 kDa is AREB6-like. The protein ~160 kDa may be a partially degraded or distinct AREB6-like protein.
The Eluted Proteins Contain Specific Binding Activity to the E-box; AREB6 Antiserum Blocks the Binding of Crude Nuclear Proteins to the Probe EG—We assumed that if the eluted proteins contain AREB6-like proteins, then they will have E-box binding activity. To test this hypothesis, the binding to the E-box of proteins eluted from probe 3× EG-conjugated Dynal beads was analyzed. As demonstrated in Fig. 5A, one binding band was competed for by the specific but not by mutant E-box or nonspecific probes. The same competition pattern in the experiments with eluted (Fig. 5A) and crude (Fig. 1B) nuclear proteins indicates the same E-box binding in both preparations. The results demonstrate E-box binding activity in the eluted proteins that is similar to that in crude nuclear proteins. To determine whether the native AREB6 immunoreactive nuclear proteins bind to the probe EG, the binding of native AREB6-like proteins in nuclear extracts was analyzed using gel-shift assays with AREB6 antiserum. As demonstrated in Fig. 5B, the AREB6 antiserum specifically blocked the binding, indicating that native nuclear proteins with AREB6 immunoreactivity bind to the E-box.

Recombinant AREB6-C Binds the E-box—To examine further whether AREB6-like proteins are able to bind to the E-box of the hXOR promoter, we generated a recombinant C-terminal fragment of human AREB6 (AREB6-C) that contains a C-terminal zinc-finger domain with the binding activity to the E-box (36). In these experiments, probes EG, EGm (mutant GTTTC), and EmGm (combined mutant E-box and GTTTC) were used. As shown in Fig. 6A, AREB6-C proteins bound to probe EG. AREB6 antiserum blocked the binding. Fig. 6B
shows that mutation of GTTTC (probe EGm, lane 2) slightly reduced the binding of AREB6-C, whereas the mutations of both E-box and GTTTC (probe EmGm, lane 4) significantly reduced the binding. The results indicate that AREB6 proteins bind to the E-box of the hXOR promoter.

**AREB6 Proteins Interact with Ku86 Proteins**—To determine whether AREB6-like proteins interact with Ku86 proteins, we examined the ability of recombinant AREB6 to interact with Ku86 proteins present in the nuclear extracts. Fig. 7A shows that Ku86 proteins were pulled-down from nuclear extracts by AREB6-C and AREB6-N fusion proteins. The absence of interaction between AREB6-H and Ku86, as an endogenous negative control, indicates that the interaction is specific. To examine the interaction in the opposite direction and with native nuclear proteins, we used Ku86 antibodies to immunoprecipitate proteins from nuclear extracts, using vimentin antibodies as a negative control. Fig. 7B shows that proteins around 200 and 160 kDa identified by AREB6 antiserum were present in immunoprecipitates using Ku86 but not vimentin antibodies. The results indicate interactions between native AREB6-like and Ku86 proteins.

**The Loss of Ku86 Function Enhances the Repressed hXOR Promoter Activity and Increases XOR mRNA Expression**—We next determined whether the loss of Ku86 protein binding altered hXOR promoter activity. In these experiments, hXOR promoter activity in V79–4 cells (wild type) was compared with that in XR-V15B cells (the mutant of Ku86 proteins). To avoid problems caused by variation of transfection efficiencies between the two cell lines, co-transfections with pSV-β-gal plasmid DNA were performed. The luciferase activity was normalized to β-galactosidase activity and protein concentrations. As shown in Fig. 8A, hXOR promoter activity in XR-V15B cells was substantially higher than that in V79–4 cells. These results indicate functional involvement of Ku86 proteins in regulation of basal hXOR promoter activity.

To investigate further whether Ku86 proteins regulate XOR expression, we determined XOR mRNA levels in V79–4 cells
and XR-V15B cells. These results, presented in Fig. 8B, reveal that the expression of XOR mRNA was significantly higher in XR-V15B cells than in V79–4 cells, indicating that Ku86 proteins regulate the expression of XOR in vivo.

DISCUSSION

DNA-PK and AREB6-like Proteins Binding to the E-box/Ku86 Site—We demonstrated previously that XOR uses repressive transcriptional mechanisms to regulate its basal expression in humans (35). Mutational analysis suggested that an E-box was important in this repressive activity. In the present investigation, we sought to identify the nuclear proteins binding to the E-box and the adjacent Ku86 binding site, and to determine the functions of Ku86 proteins in regulation of hXOR transcription.

DNA affinity purification identified at least five proteins (350, 200, 100, 86, and 70 kDa) involved in binding to the region containing the E-box/Ku86 site. Sequence analysis demonstrated that three of the proteins (350, 86, and 70 kDa) are DNA-PKcs, Ku86, and Ku70, respectively, all components of DNA-PK complex. DNA-PK is a nuclear serine/threonine protein kinase complex that is composed of a large catalytic subunit termed DNA-PKcs and a regulatory factor termed Ku (a dimer of Ku86 and Ku70). DNA-PK functions as a key component in DNA double-strand break repair and in the V(D)J recombination apparatus (37, 45, 46). In interactions between DNA-PK and DNA strands, Ku and DNA-PKcs function interdependently, in that DNA-PKcs is recruited to DNA by Ku and activated by interactions with DNA. In addition to the above functions, DNA-PK phosphorylates transcription factors, and contributes to signaling DNA-damage and telomere maintenance (37). Ku proteins function as the DNA-targeting component non-specifically binding to DNA-ends in DNA double-strand break repair or as nuclear proteins specifically binding to DNA with a consensus of GAGAAA. This consensus is immediately upstream of the E-box in the hXOR promoter (35). In the present study, EMSA, combined with mutational analysis of the Ku86 site and gel-shift analysis, demonstrated that Ku86-immunoreactive proteins bind specifically to the Ku86 site. In view of the interdependence of Ku and DNA-PKcs, it is likely that Ku86 proteins bind directly to the site and recruit DNA-PKcs and Ku70 through protein-protein interaction. This suggestion is supported by the findings presented in Fig. 1B showing that two shifted bands are associated with the Ku86 binding site, indicating the interaction of Ku86 with other proteins.

EMSA combined with mutational analysis of the E-box demonstrated specific binding of proteins to the E-box. The two proteins (200 and 100 kDa) obtained by DNA affinity purification are candidates for binding to the E-box. Considering the presence of a conjunct consensus GTTTC 19 bp upstream of the E-box in the hXOR promoter (35), which is required for the E-box binding protein AREB6 to repressively regulate gene transcription (36), we hypothesized that AREB6-like proteins are the best candidates for binding to the E-box in hXOR. This hypothesis is supported by experiments demonstrating that: (i) proteins around 200 kDa are immunoreactive to AREB6 antiserum, and are present in the nuclear extract and proteins eluted from probe 3× EG-conjugated Dynal beads; (ii) the eluted proteins are able to bind to the E-box; and (iii) the AREB6 antisera specifically blocks binding of nuclear proteins to the E-box. In addition, AREB6-C binds to the E-box. The estimated molecular mass of AREB6 is ~120 kDa, based on the deduced amino acid residues from the cDNA sequence. To date, AREB6, a zinc-finger-homeodomain transcription factor (47), is the only E-box binding protein requiring the consensus GTTTC for its repressive function. Three transcription factors homologous to AREB6 have been reported. One, ZEP, is a 1164-amino acid residue protein that has 40 extra amino acid residues at the N-terminal compared with AREB6. ZEP regulates lymphocyte and smooth muscle cell differentiation (48). A second, Nil-2-α, a negative regulator of the interleukin-2 gene, is a 734-amino acid residue protein that is similar to AREB6 but lacks the N-terminal (49). The third, BZP, is a homologue of AREB6 in hamsters and functions as a serum-responsive transcriptional repressor (50). None of these proteins has a mass around 200 kDa. Based on Western blot analysis, the proteins around 100 kDa are likely non-specific. Therefore, the protein around 200 kDa may represent a new member of AREB6 group or post-translationally modified form of AREB6. In addition, a protein around 160 kDa and immunoreactive to AREB6 antisera was observed in nuclear extracts and purified nuclear proteins. The biochemical property of the protein is unknown and may be a partially degraded or distinct AREB6-like protein. Direct sequence analysis will be required to further characterize these proteins.

Function of Ku86 in Regulation of hXOR—In the present study, we showed that loss of function of Ku86 causes enhanced hXOR promoter activity and transcript expression. These results indicate that, besides AREB6-like proteins that bind to the E-box, Ku86 proteins also contribute to the repressive regulation of hXOR. Compared with our previous study showing that mutation of the Ku86 binding site did not significantly release the repressed promoter activity (35), the use of Ku86-deficient cells in the present study clearly demonstrates that Ku86 proteins regulate hXOR expression. The basis for this disparity is not known but may be a result of residual binding to the mutated Ku86 in the former study. Using animals and cells deficient in DNA-PKcs or Ku, it has been demonstrated that DNA-PK is important in DNA repair and V(D)J recomb-
The characterization of the E-box/Ku86-bound nuclear proteins provides a basis for further addressing the function of E-box/Ku86 site in the regulation of the hXOR promoter. In view of the close relationship between the E-box and Ku86 sites, DNA-PK and AREB6-like proteins could be organized in a cluster with other proteins in the binding region. DNA-PK, besides its function in DNA repair, has been demonstrated to regulate gene transcription by phosphorylation of transcription factors (46). In the cluster, ABRE6-like proteins could be regulated by DNA-PKcs through phosphorylation (51). This regulation is important in various physiologic and pathologic conditions. Fig. 9 illustrates a working model based on our results. In this model, hXOR transcription is regulated by means of alteration of phosphorylation status of transcription factors. In the model, the transcription factors include DNA-PK, AREB6-like proteins, co-repressors, TFIIID, and other unknown proteins. Future studies will be directed at further assessing the importance of phosphorylation of transcription factors in regulating hXOR activity.

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