DJ-1 Positively Regulates the Androgen Receptor by Impairing the Binding of PIASxα to the Receptor*

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DJ-1 was first identified by our group as a novel candidate of the oncogene product that transformed mouse NIH3T3 cells in cooperation with an activated ras. Later DJ-1 was also found to be an infertility-related protein that was reduced in rat sperm treated with sperm toxicants that cause infertility in rats. To determine the functions of DJ-1, cDNAs encoding DJ-1-binding proteins were screened by the yeast two-hybrid method. Of several proteins identified, PIASxα/ARIIP3, a modulator of androgen receptor (AR), was first characterized as the DJ-1-binding protein in this study. DJ-1 directly bound to the AR-binding region of PIASxα by an in vitro coimmunoprecipitation assay and also bound to PIASxα in human 293T cells. Both proteins were co-localized in the nuclei. PIASxα impaired the AR transcription activity in a dose-dependent manner in cotransfected monkey CV1 cells with an androgen responsive element-luciferase reporter. Introduction of DJ-1 into CV1 cells in a state of inhibition of AR activity by PIASxα restored AR transcription activity by absorbing PIASxα from the AR-PIASxα complex, while a DJ-1 mutant harboring an amino acid substitution at number 130 from lysine to arginine did not restore it. These results indicate that DJ-1 is a positive regulator of the androgen receptor.

DJ-1 was first identified by our group as a novel candidate of the oncogene product that transformed mouse NIH3T3 cells in cooperation with activated ras (1). Both human and mouse DJ-1 genomic DNAs comprise seven exons, and exons 2–7 code for DJ-1 proteins (2). The human DJ-1 gene is mapped at chromosome 1p36.2–36.3, where a hot spot of chromosome abnormalities has been reported in several tumors (2). DJ-1 is preferentially expressed in the testis and moderately in other tissues, and it is translocated from the cytoplasm to nuclei during the cell cycle after mitogen stimulation, suggesting that DJ-1 has a growth-related function (1). However, the mechanism by which cells are transformed has not been clarified. Another group has also identified RS, another name for human DJ-1, as a regulatory component of an RNA-binding protein complex (3). Furthermore, CAP-1 or SP22, a rat homolog of human DJ-1, has been identified by other laboratories as a key protein related to the infertility of male rats exposed to sperm toxicants such as ornidazole and epichlorohydrin in which DJ-1 in the sperm and epididymis decreased in parallel with the following infertility of rat (4–7). It was shown that DJ-1/CAP-1/SP22 is a first protein clearly related to male infertility (4, 5, 7). In addition to its expression in spermatocytes and spermatids, DJ-1 is also expressed in the sperm head and is translocated to the cytoplasmic side of sperm after the sperm toxicant treatment in infertile rats, suggesting that DJ-1 plays a role in fertilization (7–9). The exact roles of DJ-1 in spermatogenesis and fertilization, however, have not been determined.

The androgen receptor (AR)1 bound by androgen activates the genes essential for development and maintenance of male reproductive function, including spermatogenesis (10–12). AR belongs to the family of nuclear receptor proteins that act as ligand-dependent transcription factors that bind to respective DNA elements (13–18). The nuclear receptor is composed of at least three domains, a ligand-independent transcription activation (AF1) domain, a DNA-binding domain, and a ligand-dependent transactivation (AF2) domain, and the molecular mechanisms underlying the transactivation functions of nuclear receptors, especially the estrogen receptor, have been extensively studied. The N-terminal domains along with DNA-binding domains of AR (19–22), estrogen receptor (23, 24), progesterone receptor (25), and PPARγ (26) interact with the ligand-bound C-terminal domain of AF2. The fragment containing the N-terminal domains along with the DNA-binding domain of AR is constitutively active in transcription without a ligand, whereas that of AF2 along with the DNA-binding domain lacks transcription activation activity in either the absence or presence of androgen (22, 27). Nuclear receptors bind DNA elements as homo- or heterodimers, and AR homodimerization is stimulated by the presence of an androgen-responsive element (ARE).

Activation of the transcription of genes targeted by the nuclear receptors is modulated by the interaction between the nuclear receptors and their coactivators that bridge the general transcription machinery, and several coactivators that modulate the activity of nuclear receptors have been identified (28–33). These include CBP/p300, the p160 family, pCAF/GCN5, and TRAP/DIP (34, 35). A number of AR-associated proteins, such as ARA24 (36), ARA54 (37), ARA55 (38), ARA70 (39), ARA160 (40) FHL2/DRAL (41), and cyclin E (42), have also been reported to modulate AR transcription activity. Transcription repression of the nuclear receptor-specific genes is relieved through receptor binding of cofactors, including histone acetyltransferase, and other chromatin remodeling factors that increase the accessibility of nucleosome DNA to transcription complex (43, 44). HB01, a protein first identified as a

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1 The abbreviations used are: AR, androgen receptor; ARE, androgen responsive element; PIAS, protein inhibitor of activated STAT (signal transducers and activators of transcription); HA, hemagglutinin.
protein that binds to an origin-recognition complex (45), has been shown to have a putative histone acetyltransferase activity and to repress AR transcription activity (46).

ARIP3/PIASxα belongs to the family of PIAS (protein inhibitor of activated STAT) proteins, which includes PIAS1/GBP, PIAS3, PIASγ, and PIASβ/ARIP3. PIAS1 and PIAS3 have been suggested to inhibit cytokine signaling (47, 48). ARIP3/PIASxα was found to modulate AR transcription activity in a manner dependent on cells or the target genes; ARIP3/PIASxα first activates and then represses ARE-E1b promoter (minimal promoter) activity while it represses the probasin promoter, a natural target promoter of AR, in a dose-dependent manner in monkey CosI cells (49, 50). Recent studies have shown that PIAS1 and PIASβ possess inherited transcription activity, whereas PIASxα and PIAS3 lack such activity (50). It has also been reported that PIAS1 stimulated AR promoter activity (51), whereas PIAS3 inhibited it (52).

To try to determine the molecular mechanism of DJ-1 function, we screened cDNAs encoding DJ-1-binding proteins by the yeast two-hybrid method using a human testis cDNA library, and we identified PIASxα as a DJ-1-binding protein. PIASxα inhibited the AR minimal promoter activity in monkey CV1 cells, and DJ-1 antagonized the repression activity of PIASxα by AR by absorbing PIASxα from the AR–PIASxα complex.

EXPERIMENTAL PROCEDURES

Cells—Mouse 3T3, mouse HEPG2, mouse TM4, monkey CosI, and monkey CV1 cells were cultured in Dulbecco’s modified Eagle’s medium with 10% calf serum.

Plasmids—pSG5αAR, a expression vector for rat AR, and pARE2-TATA-Luc, a reporter plasmid for testing AR transcription activity, were provided from J.J. Palvimo, cDNAs of human PIASβ and mouse PIAS3 were provided from K. Shuai and H. Yokosawa, respectively. An expressed sequence tag clone, ID no. 2228314 corresponding to human PIASγ cDNA, was purchased from Incyte Genomics. pGlex-DJ-1-D1 DJ-1 cDNA starting first ATG was inserted in frame into the EcoRI–Xhol site of pGlex, a modified version of the LexA-derived bait vector for yeast two-hybrid screening (53). pcDNA3–F-DJ-1 and pcDNA3–F-AR-DJ-1 cDNA and AR cDNA starting first ATG were inserted into the EcoRI–Xhol sites of pCMV-F, a pcDNA3 containing FLAG-tag (50). pEP-PIASxα-HA-PIASxα cDNA was inserted into the EcoRI–NotI sites of pEF-HA (53).

Cloning of DJ-1-binding Proteins by a Two-hybrid System—Saccharomyces cerevisiae L40 cells containing the lacZ gene driven by the GAL1 promoter were transformed first with pGlex-DJ-1, which did not activate lacZ transcription by itself. The transformant cells were subsequently co-transformed with human testis MATCHMAKER cDNA (CLONTECH), a cDNA library expressing the GAL4 activation domain (GALAD) fused to the cDNAs from human testis cells. Approximately 1.5 × 10⁵ colonies were screened for lacZ expression, which indicated the association of a GALAD-fused protein with the LexABD-fused DJ-1. The plasmid DNAs in the lacZ-positive cells were extracted by the procedure described in the protocols from CLONTECH. Nucleotide sequences of the plasmids derived from positive colonies were determined by using an ABI377 or Li-Cor Long Reader 4200 autosequencer.

In Vitro Binding Assay—35S-labeled FLAG-tagged DJ-1 and PIASxα were synthesized in vitro using the reticulocyte lysate of the TnT transcription-translation-coupled system (Promega). Labeled proteins were mixed at 4°C for 120 min and then immunoprecipitated with a mouse anti-FLAG antibody (M2, Sigma) or with nonspecific mouse IgG in a buffer containing 150 mM NaCl, 5 mM EDTA, 50 mM Tris (pH 7.5), 1 mg/ml bovine serum albumin, and 1% Nonidet P-40. After washing with the same buffer, the precipitates were separated in a 12.5% of polyacrylamide gel containing SDS and visualized by fluorography.

In Vivo Binding Assay—Ten μg of pcDNA3–F-DJ-1 together with 10 μg of pEP-PIASxα-HA was transfected to human 293T cells (Fig. 1A). Neither the N-terminal fragment spanning amino acids 1–334 nor the C-terminal fragment spanning amino acids 494–572 of PIASxα bound to DJ-1. All other fragments including the original clones isolated (335–572, 340–572, and 433–572) bound to DJ-1 more strongly than the full-size PIASxα did. These results indicate that DJ-1 binds to the C-terminal region of PIASxα spanning amino acids 433–493 that includes the AR-interacting domain. The binding activity of DJ-1 to AR was...
then examined by the two-hybrid method. DJ-1 fused to the LexA DNA-binding domain was not able to bind to AR fused to GALAD (Fig. 1B).

Then, the interaction of DJ-1 with other PIAS family proteins, including PIAS1, PIAS3, PIASxβ, and PIASy, was tested by the yeast two-hybrid method, where DJ-1 and PIAS family were fused to LexA DNA-binding domain and GAL4 activation domain, respectively (Fig. 1C). Of the PIAS family proteins, DJ-1 strongly bound to PIAS3 and PIASxα, weakly bound to PIASy, and did not bind to PIAS1. We therefore concentrated on PIASxα in this study.

Interaction of DJ-1 with PIASxα in Vitro and in Vivo—An in vitro binding assay was then performed by using 35S-labeled FLAG-tagged DJ-1 and PIASxα synthesized in vitro. Both labeled proteins were mixed together, and the proteins were immunoprecipitated with an anti-FLAG antibody or nonspecific IgG. Then the precipitate(s) was separated on the gel and visualized by fluorography (Fig. 2A). First, it was confirmed that the anti-FLAG antibody alone did not precipitate labeled PIASxα without DJ-1 (data not shown). PIASxα was coimmunoprecipitated with DJ-1 by the anti-FLAG antibody but not by IgG (Fig. 2A, lanes 1 and 2, respectively), suggesting that there was a direct interaction between DJ-1 and PIASxα.

To observe the complex formation of PIASxα with DJ-1 in vivo, expression vectors for FLAG-tagged DJ-1 and HA-tagged PIASxα together were transfected to human 293T cells. Forty-eight h after transfection, the cell extract was prepared, and the proteins in the extract were first immunoprecipitated with an anti-FLAG mouse monoclonal antibody or nonspecific IgG, and the precipitates were separated in polyacrylamide gel. In lane 3, 1/100 amount of the labeled PIASxα and FLAG-DJ-1 used for the reactions (input) was run in parallel. B, HeLa cells were transfected with expression vectors for FLAG-DJ-1 and PIASxα-HA by the calcium phosphate precipitation technique, and the cell extract was prepared 48 h after transfection. Proteins in the extract were first precipitated with an anti-FLAG mouse monoclonal antibody or nonspecific IgG, and the precipitates were immunoblotted with an anti-HA rabbit polyclonal antibody (Y-11, Santa Cruz). In lane 1, 1/100 amount of the labeled PIASxα and FLAG-DJ-1 used for the reactions (input) was run in parallel.
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The anti-FLAG antibody did precipitate FLAG-DJ-1 (data not shown). PIASα/HA, on the other hand, was detected in the immunoprecipitate with the anti-HA antibody but not with IgG (Fig. 2B, lanes 3 and 2, respectively), indicating that PIASα was associated with DJ-1 in ectopic-expressed 293T cells.

Co-localization of DJ-1 with PIASα in Cells—Previous studies have shown that DJ-1 was localized both in the cytoplasm and nucleus in DJ-1-transfected human HeLa cells and translocated from the cytoplasm to nuclei during the S-phase of the cell cycle upon induction by mitogen (1) and that PIASα/ARIP3 was located in nucleus (49). To determine the cellular localization of PIASα and DJ-1, expression vectors for FLAG-tagged DJ-1 and HA-tagged PIASα were transfected into monkey CosI cells. Two days after transfection, the cells were stained with anti-FLAG and anti-HA antibodies, and the proteins were detected by fluorescein isothiocyanate-conjugated anti-mouse IgG and a rhodamine-conjugated anti-rabbit IgG, respectively. The two figures have been merged.

The results of the Western blotting showed that DJ-1 was conjugated with SUMO-1, a small ubiquitin-like modifier, at lysine of amino acid number 130, and that this modification is necessary for DJ-1 to manifest full activities for cell transformation in collaboration with activated ras and stimulation of cell growth. DJ-1-K130RX is a point mutant where lysine at amino acid number 130 was changed to arginine and three amino acids at amino acid numbers 57, 96, and 126 were also changed from serine, glutamic acid, and histidine to arginine, glycine, and tyrosine, respectively. Because this mutant was found to lose full activities of DJ-1 and also binding activity to PIASα (see Fig. 5C), we used K130RX3 as a negative control of wild-type DJ-1 in this study.

It has been reported that PIASα/ARIP3 modulates AR transcription activity in a cell type or promoter-dependent manner (49, 50). PIASα/ARIP3 first stimulates and then decreases AR activity with a dose of PIASα/ARIP3 introduced into the ARE-E1b promoter (minimal promoter), but it represses the activity of probasin promoter, a natural target of AR, in monkey CosI cells (50). Moreover, PIASα/ARIP3 lacks the inherent transcription activation function, whereas other PIAS family proteins, PIAS1/GBP and PIASβ/Miz1, possess this function (50). To confirm this observation, we first cotransfected the expression vector for AR, PIASα or DJ-1 together with the ARE minimal promoter-luciferase reporter (pARE2-TATA-Luc) into monkey CV1 cells in the presence or absence of testosterone, and then we measured the luciferase activity two days after transfection. In the absence of testosterone, a low level of transcription activity was observed without the AR expression vector (see Fig. 6), and this value was therefore set at 1 in all the transcription analyses. In the presence of testosterone, the luciferase activity was stimulated by the expression vector for AR in a dose-dependent manner, while the expression vector for PIASα and DJ-1 did not stimulate the luciferase activity (Fig. 4A). When the expression vector for PIASα was added to the point where AR activity was almost at maximal level (0.5 µg of pSG5rAR, an AR expression vector), PIASα repressed AR activity to 40% of the original level in a dose-dependent manner, whereas DJ-1 (pcDNA3-F-DJ-1) or its point mutant, pcDNA3-F-DJ-1-K130RX, did not (Fig. 4B). Constant amounts of AR or a dose-dependent increase in the amount of PIASα in the transfected cell extracts were confirmed by Western blotting (Fig. 4C). Even small amounts (0.01, 0.05, and 0.1 µg) of the expression vector for PIASα also repressed AR activity in CV1 cells, and a marginal stimulation of AR activity was observed with small amounts (0.01 and 0.05 µg), but not with amounts above 0.1 µg, of the expression vector for PIASα in CosI cells (data not shown). These results suggest that PIASα modulates AR transcription activity in a cell type-specific manner but that the priority function of PIASα is repression of AR activity.

Because DJ-1 binds to the AR-interacting domain of PIASα, it is thought that DJ-1 abrogates the binding of PIASα to AR. To address this issue, HA-tagged DJ-1 was cotransfected into CV1 cells with constant amounts of FLAG-tagged AR and HA-tagged PIASα. Two days after transfection, the proteins in the cell extract were precipitated with an anti-FLAG antibody, and the precipitates were immunoblotted with the anti-FLAG antibody to detect the precipitated FLAG-AR and an anti-HA antibody to detect the immunoprecipitated PIASα (Fig. 5A). The results of the Western blotting showed that DJ-1 was expressed in the cells in a dose-dependent manner. While the amounts of the precipitated AR were almost constant over the ranges used, AR-bound PIASα was reversibly decreased with the amounts of DJ-1. When the same experiment was carried out using HA-tagged DJ-1-K130RX instead of wild-type DJ-1, the relatively constant binding activity of PIASα to AR was observed (Fig. 5B). The ratio of the amount of AR-bound PIASα to that of the precipitated AR was changed little over the ranges of DJ-1-K130RX. The DJ-1-K130RX was found not to bind to PIASα by the yeast two-hybrid assay (Fig. 5C). Because DJ-1 does not bind to AR, this result suggests that DJ-1 but not DJ-1-K130RX absorbs PIASα from the PIASα-AR complex.

Abrogation of PIASα-suppressed AR Transcription Activity by DJ-1—To observe the effect of DJ-1 on the AR-transcription activity suppressed by PIASα, DJ-1 and its mutant K130RX3 were introduced into CV1 cells in a combination of AR and PIASα. As reported previously, ARE-minimal promoter activ-
Fig. 4. Effect of PIASxα on the transcriptional activity of AR. A, CV1 cells were transfected with the expression vector for AR, PIASxα-HA, or FLAG-DJ-1 together with pARE2-TATA-Luc, a reporter plasmid for AR transcription activity. Two days after transfection, cell extracts were prepared, and the luciferase activity of each effector DNA was measured as described under "Experimental Procedures." B, CV1 cells were transfected with various doses of the expression vector for FLAG-DJ-1, FLAG-K130RX mutant of DJ-1 (F-DJ-1-K130RX) or PIASxα-HA together with pARE2-TATA-Luc and 0.5 μg of pSG5rAR, an expression vector for AR. Two days after transfection, the luciferase activities were measured as in A. C, proteins in an aliquot of the extract used in B were separated in 10% polyacrylamide gel and blotted with an anti-AR antibody (N-20, Santa Cruz), an anti-HA monoclonal antibody (12CA5, Roche Molecular Biochemicals), or an anti-actin antibody (C4, Roche Molecular Biochemicals).

Fig. 5. Abrogation of AR-PIASxα complex by DJ-1. 293T cells were transfected with various combinations of expression vectors for FLAG-AR, PIASxα-HA, DJ-1-HA (A) and DJ-1-K130RX-HA (B). Two days after transfection, cell extracts were prepared, and the proteins in the extracts were first immunoprecipitated with an anti-FLAG monoclonal antibody. The precipitates were immunoblotted with an anti-HA polyclonal antibody (AR-bound PIASxα) or the anti-FLAG monoclonal antibody (AR). Aliquots of the extracts were also immunoblotted with the anti-HA monoclonal antibody (DJ-1 and DJ-1-K130RX) or the anti-PIASxα-HA monoclonal antibody (PIASxα). C, DNA binding assay with DJ-1. DJ-1-K130RX and PIASxα was carried out as in Fig. 1A. PIASxα fused to the GAL4 activation domain was used.
FIG. 6. Restoration of AR-suppressed transcription activity by DJ-1. A, CV1 cells were transfected with various doses of the expression vector for FLAG-DJ-1, FLAG-K130RX mutant of DJ-1 (F-DJ-1-K130RX), or PIASx-HA together with pARE2-TATA-Luc and 0.5 μg of pSG5xAR, an expression vector for AR. Two days after transfection, the luciferase activities were measured as described in Fig. 4. A, B, proteins in an aliquot of the extract used in A were separated in 10% polyacrylamide gel and blotted with an anti-AR antibody (N-20, Santa Cruz), an anti-HA monoclonal antibody (12CA5, Roche Molecular Biochemicals), or an anti-actin antibody (C4, Roche Molecular Biochemicals). C, nuclear extracts were prepared from an aliquot of the transfected cells and used for a bandshift assay with a labeled oligonucleotide corresponding to the AR-responsive element as described under “Experimental Procedures.” Free and AR complex indicate the positions of the free probe and AR-DNA complex, respectively.

DISCUSSION

We found that DJ-1 acts as a positive regulator of AR by preventing PIASx from binding to AR. DJ-1 bound to the AR-binding region of PIASx, thereby interfering with the binding of PIASx to AR. PIASx is a member of the PIAS family proteins that were first identified as inhibitors of STAT, a transcription factor employing cytokine signaling (4, 8). The proteins belonging to the PIAS family are PIAS1/GBP, PIAS3, PIASy, PIASx/ARIP3, and PIASx/Miz1. As described in the Introduction, there seems to be two separate groups: proteins possessing inherit transcription activation activity and those lacking this activity. The former group includes PIAS1/GBP and PIASy, and the latter group includes PIAS3 and PIASx/ARIP3 (50). DJ-1 was found to bind to the latter group of PIAS family proteins possessing inherit transcription suppression activity. DJ-1 also bound to PIASy, which has been recently reported to repress AR transcription activity in LNCaP prostate cancer cells (58). Although the transcription activities of these proteins toward AR appeared to reflect their intrinsic activities, discrepant results, depending on the cells or promoters used in the experiments, have been reported (50). In the CV1 cells in this study, we always observed inhibitory activities of PIASx to AR, as shown in Figs. 4 and 6, even when only amounts of PIASx had been transfected into the cells. In the HepG2 cells, we also observed the stimulating activity of PIASx to AR transcription as described previously (50), and DJ-1 had no effect on AR transcription activity stimulated by PIASx. DJ-1 alone does not directly bind to AR and therefore

promoter context alter the effect of PIAS family proteins on AR-dependent transcription, the effect of DJ-1 on AR transcription activity was examined in human HepG2 and mouse TM4 cells in addition to monkey CV1 cells. In HepG2 hepatoma cells, ARIP3/PIASxα has been reported to potentate ARE-dependent transcription of AR (50). TM4 is an established Sertoli cell line in which AR is expressed (57). Expression vectors for AR, PIASxα, DJ-1, or DJ-1-K130RX were transfected together with ARE-reporter into these cells, and their luciferase activities were measured two days after transfection (Fig. 7). In TM4 cells like CV1 cells, PIASxα inhibited AR transcription activity in a dose-dependent manner and DJ-1 reversibly antagonized AR activity suppressed by PIASxα in a dose-dependent manner, whereas the K130RX mutant of DJ-1 did not (Fig. 7B). In HepG2 cells, on the other hand, PIASxα stimulated AR transcription activity in a dose-dependent manner as described previously (50), and DJ-1 had little effect of AR activity stimulated by PIASxα, whereas the K130RX mutant of DJ-1 rather inhibited it in a dose-dependent manner (Fig. 7A). These results suggest that cell background alters the effect of PIAS family proteins on AR-dependent transcription, and DJ-1 responds to suppressed AR activity.

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does not respond to an AR-responsive element as shown in Fig. 4A. What then is the mechanism by which PIASxα inhibits the activity of AR? Because PIASxα bound to the DNA-binding region of AR as previously reported (49) and the results of bandshift analysis in this study using an AR-responsive element as a probe showed that PIASxα and DJ-1 were not able to form a tight complex with AR on DNA, PIASxα is thought to mask the DNA-binding region of AR and DJ-1 is thought to relieve its masked state.

Our recent results have shown that a lysine residue at amino acid number 130 of DJ-1 is conjugated with SUMO-1 and that the sumoylated state of DJ-1 may be necessary to show the full activity of DJ-1 in terms of cell transformation and cell growth stimulation2. We used two substitution mutants of DJ-1, K130R, in which the lysine at amino acid number 130 was changed to arginine, and K130RX3, in which three amino acids, in addition to the lysine at amino acid number 130, were changed, to determine the effects on PIASxα and AR. Because K130RX3 was found to have the similar characters to those of K130R and to lose binding activity to PIASxα, we therefore used K130RX3 as a mutant to wild-type DJ-1 in this study. K130RX3 did not antagonize the function of PIASxα to AR due to no binding activity to PIASxα, confirming that DJ-1 is a positive regulator of AR. Although the K130R mutant of DJ-1 bound to PIASxα to the same extent as that of wild-type DJ-1, the antagonized transcriptional function of DJ-1 against PIASxα was hampered (data not shown). Although the molecular reason of this difference in the activities of wild-type and K130R DJ-1 is not clear at present, other factors associated with DJ-1 but not with K130R DJ-1 may be responsible for these different phenomena. These factors may determine the location of DJ-1 in cells where DJ-1 is active or, alternatively, may keep the proper conformation of the active form of DJ-1.

As described in the Introduction, a number of AR-specific or nuclear receptor-binding proteins have been reported. We are now screening these proteins, including the cofactors stated in the Introduction, to determine which distinctly bind to wild-type DJ-1 and K130R mutant DJ-1.

The finding that DJ-1 is a positive regulator of AR in somatic cells may explain the relationship between the reduced amount of DJ-1 and infertility in rats in which the AR inactivated by PIASxα does not activate the genes essential for spermatogenesis.
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DJ-1 Positively Regulates the Androgen Receptor by Impairing the Binding of PIASx α to the Receptor
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