c-Jun Potentiates the Functional Interaction between the Amino and Carboxyl Termini of the Androgen Receptor*

Received for publication, August 1, 2001, and in revised form, September 13, 2001 Published, JBC Papers in Press, September 27, 2001, DOI 10.1074/jbc.M107346200

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The transactivation functions of the human androgen receptor (hAR) are regulated by several accessory factors that can be either positive or negative. One factor that has been previously shown to mediate hAR transactivation is the proto-oncoprotein c-Jun. The positive effect is a primary one, can be exerted by both endogenous and exogenous c-Jun, and requires multiple regions of c-Jun. However, the exact mechanism by which c-Jun exerts its enhancing function is unknown. In this study, we have used a mammalian two-hybrid system to ask if c-Jun influences the ligand-dependent amino- to carboxyl-terminal (N-to-C) interaction of hAR, which is thought to be responsible for the homodimerization of this receptor. Our results show that c-Jun enhances both hAR N-to-C terminal interaction and DNA binding in vitro. We have also tested a panel of c-Jun and c-Fos mutants for their activities on the N-to-C interaction, and the data demonstrate that the activities of these mutants parallel their activities on hAR transactivation. A mutation in the hAR activation function-2 (AF-2) abrogates N-to-C interaction, DNA binding, and transactivation, and these activities are not rescued by exogenous c-Jun. Interestingly, the p160 coactivator TIF2 can stimulate hAR N-to-C interaction, providing consistent with the effect on hAR transactivation. These data strongly suggest that the hAR N-to-C interaction is the target of c-Jun action, and this activity requires a functional receptor AF-2.

Transcriptional activation is an important step at which gene expression can be regulated. The nuclear receptors form the only family of transcriptional activators whose activity is ligand-dependent (reviewed in Refs. 1–5). Upon binding lipophilic ligands, nuclear receptors are activated to turn on (and sometimes turn off) the transcription of specific responsive genes, thereby regulating gene expression. In this way, these small hydrophobic ligands, which include steroid and thyroid hormones and vitamins A and D, exert their effects on many biological processes, including development, differentiation, and homeostasis. The receptors that mediate these effects include the retinoic acid receptor (RAR), retinoid X receptor, thyroid hormone receptor, vitamin D receptor, the subfamily of steroid receptors (including the glucocorticoid receptor, progesterone receptor, androgen receptor, and estrogen receptors), and numerous “orphan” receptors, ligands for which remain unidentified (6).

AR is the nuclear receptor that mediates the biological actions of androgens. Androgens are found in two physiologically active forms, testosterone and dihydrotestosterone (DHT), and are involved in male sexual differentiation and development (7–9). As a member of the nuclear receptor superfamily, AR consists of multiple functionally distinct domains, including domains involved in DNA or ligand binding, dimerization, and transcriptional activation specifically found in activation functions-1 (AF-1) and -2 (AF-2) (10). Perhaps unique among the nuclear receptors, AR and other steroid receptors require ligand binding for homodimerization, which itself is necessary for subsequent DNA binding and transcriptional activation (reviewed in Ref. 1). This sequential order of events is responsible for androgen signaling within a cell, and disruption of any one step interferes with the signaling pathway. AR homodimerization has been reported by several laboratories to result from an intra- or inter-molecular interaction between the amino and carboxyl termini of the receptor (11–13). This interaction was demonstrated using a mammalian two-hybrid system and provided evidence to Langley et al. (12) suggesting that AR binds to DNA as an anti-parallel dimer. Subsequent studies further characterized the amino- to carboxyl-terminal (N-to-C) interaction and showed that naturally occurring mutations in the ligand-binding domain (LBD) found in androgen insensitivity syndromes do not affect ligand binding but disrupt the N-to-C interaction (11). It has been suggested that the N-to-C interaction may also facilitate ligand retention by the AR (14). Mutational analysis of the AR amino and carboxyl termini has identified amino acids 3–36 and the activation function-2 (AF-2) core as being required for the N-to-C interaction (13, 15). Further dissection of AR regions involved in the N-to-C interaction has led to the identification of two sequences similar to but distinct from LXXLL core sequence that are known to directly interact with the nuclear receptor AF-2. These AR sequences are FQNLF (amino acids 23–27) and WHTLF (amino acids 433–437), which were shown to bind to the receptor’s
AF-2 and a region outside AF-2, respectively (16). The AR AF-2 is not only the target of these amino-terminal regions but also provides a site of interaction for LXXLL-containing coactivators, including CREB-binding protein (CBP) (17, 18) and the p160 coactivators steroid receptor coactivator-1 (SRC-1) (19) and transcription intermediary factor-2 (TIF2) (20). Interestingly, these same coactivators have been reported to facilitate the N-to-C interaction of AR and suggested in this way to mediate the transcriptional activity of this steroid receptor (15, 20, 21).

Although SRC-1, TIF2, and CBP target both the amino terminus and AF-2 of AR (15, 17–21), c-Jun, the dimerization partner of c-Fos (reviewed in Ref. 22) appears to function as an AR coactivator by acting only on the amino terminus (23). Indeed, the AR amino acids 503–555, which harbor an autonomous transcription function, are both necessary and sufficient for the c-Jun-positive response (23). Earlier studies on the c-Jun enhancement of AR transactivation had shown that (i) the activity is independent of promoter- or cell-specific factors (24, 25), (ii) both exogenous and endogenous c-Jun can carry the activity is independent of promoter- or cell-specific factors (24, 25), (iii) the c-Jun effect is primary (24), (iv) c-Jun dimerization with c-Jun blocks the latter activity (26), and (v) c-Jun enhancement of AR transactivation had shown that (i) the AR AF-2 is essential for the activity of c-Jun and p160 coactivators, because it is required for the N-to-C interaction.

EXPERIMENTAL PROCEDURES

Plasmids—Human forms of AR and c-Jun were all expressed from the mammalian expression plasmid pSG5 (28), as previously described (24). To generate hAR(Δ504–555), complementary oligos 5′-CTTGGGCACTTGCACAGAGATGATGGGTGCCATCATTTC-3′ and 5′-AGCTTTCATCTCCACAGATCAGGCAGGTCTTGTCGCGACTCTGGTACGCAGC-3′ and the downstream oligo 5′-GATCGATCTCCAGAAGATGGAATTCTCGAGTCTCTGTGGAGATGA-3′. This PCR fragment was digested with Sacl and BgelII and inserted into hAR(AB)pTL1, which was digested with the same enzymes. This new construct was subsequently digested with BamlII and HindIII and inserted into hARI, digested with the same enzymes. hAR(AB)pTL1 was constructed by digesting hAR with BamlII and XhoI and inserting the restriction fragment into pTL1, digested with the same enzymes.

To generate hAR(Δ504–555), hAR amino acids were PCR-amplified using the upstream oligo 5′-GATCGAGATCTCCAGAAGATGGAATTCTCGAGTCTCTGTGGAGATGA-3′ and the downstream oligo 5′-GATCGATCTCAAGCTTGGCTGCACAGCAGATCAGGCAGGTCTTGTCGCGACTCTGGTACGCAGC-3′, which were annealed, creating a 5′-KpnI site and a 3′-HindIII site. This annealed fragment was inserted into hAR, which was digested with the same two enzymes.

To make hAR(Δ358–555), hAR amino acids were PCR-amplified using the upstream oligo 5′-GATCGAGATCTCCAGAAGATGGAATTCTCGAGTCTCTGTGGAGATGA-3′ and the downstream oligo 5′-GATCGATCTCAAGCTTGGCTGCACAGCAGATCAGGCAGGTCTTGTCGCGACTCTGGTACGCAGC-3′. This PCR fragment was digested with Sacl and BgelII and inserted into hAR(AB)pTL1, which was digested with the same enzymes. This new construct was subsequently digested with BamlII and HindIII and inserted into hAR, digested with the same enzymes. hAR(AB)pTL1 was constructed by digesting hAR with BamlII and XhoI and inserting the restriction fragment into pTL1, digested with the same enzymes.

To generate hAR(Δ358–555), hAR amino acids were PCR-amplified using the upstream oligo 5′-GATCGAGATCTCAAGCTTGGCTGCACAGCAGATCAGGCAGGTCTTGTCGCGACTCTGGTACGCAGC-3′ and the downstream oligo 5′-GATCGATCTCAAGCTTGGCTGCACAGCAGATCAGGCAGGTCTTGTCGCGACTCTGGTACGCAGC-3′. This PCR fragment was digested with Sacl and BgelII and inserted into hAR(AB)pTL1, which was digested with the same enzymes. This new construct was subsequently digested with BamlII and HindIII and inserted into hAR, digested with the same enzymes. hAR(AB)pTL1 was constructed by digesting hAR with BamlII and XhoI and inserting the restriction fragment into pTL1, digested with the same enzymes.

To make hAR(E896P), hAR amino acids 556–918 were PCR-amplified using the upstream oligo 5′-GATCGAGATCTCAAGCTTGGCTGCACAGCAGATCAGGCAGGTCTTGTCGCGACTCTGGTACGCAGC-3′ and the downstream oligo 5′-GATCGATCTCAAGCTTGGCTGCACAGCAGATCAGGCAGGTCTTGTCGCGACTCTGGTACGCAGC-3′, which were annealed, creating a 5′-KpnI site and a 3′-HindIII site. This annealed fragment was inserted into hAR, which was digested with the same two enzymes.

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**RESULTS**

The c-Jun-positive Activity on hAR Requires the Carboxyl Terminus of the Receptor but Not a Complete AB Region—As a member of the receptor superfamily, hAR is a modular protein, consisting of an amino-terminal AB region, which contains AF-1, and a carboxy-terminal E region, which harbors both the LBD and AF-2 (Fig. 1). The AF-1 has been further divided into the functions AF-1a (amino acids 169–182) and AF-1b (amino acids 293–357) (31). We have previously shown that the hAR AB region and, specifically, amino acids 503–555 within this region are essential and sufficient for c-Jun enhancement of GAL-hAR(AB) transcriptional activity (23). To study the importance of these amino acids in the full-length receptor, hAR proteins lacking different parts of the AB region were generated and studied in transient transfection experiments in COS cells using the androgen-responsive reporter MMTV-CAT and the internal control pCH110 (24) (Fig. 1).

When hARΔ504–555 was compared with wild-type hAR, the two proteins exhibited the same transcriptional activity. Surprisingly, the mutant protein also responded to cotransfected c-Jun as strongly as the wild-type counterpart, clearly demonstrating that, in the context of full-length protein, amino acids 504–555 are dispensable for c-Jun enhancement of hAR transactivation (Fig. 1A). A larger deletion of the AB region, encompassing amino acids 358–555, which eliminates part of the AF-1b, greatly compromised hAR transcriptional activity, demonstrating the importance of the AF-1 (Fig. 1). However, this mutated hAR, hARΔ358–555, responded strongly to transfected c-Jun, further arguing that the carboxyl terminus of the hAR AB region is not required for c-Jun activity (Fig. 1A). In contrast, truncation of amino acids 804–918 completely blocked hAR transactivation in either the absence or presence of c-Jun, suggesting that the carboxyl terminus of the full-length hAR is required for c-Jun activity (Fig. 1A). Note that the absence of activity in hARΔ804–918 is due to the absence of protein expression (Fig. 1B). Together, these data show that c-Jun requires the carboxyl terminus of the full-length hAR, but not a complete AB region, for its positive activity.

A Functional AF-2 Is Necessary for the Positive Effect on hAR by Either c-Jun or TIF2—Because amino acids 804–918 contain the hAR AF-2 (32), it is possible that hARΔ804–918 is unable to activate transcription due to the absence of the AF-2.
To directly test this hypothesis, we generated a mutant of hAR with a single amino acid change in the AF-2 (E896P) (Fig. 2A) that has previously been demonstrated to disrupt AF-2 function in RAR (32). hAR(E896P) was transcriptionally silent, either in the absence or presence of transfected c-Jun, whereas wild-type hAR exhibited the expected strong activity (Fig. 2C). As a control for this mutant’s activity, we used TIF2, a coactivator that has previously been shown to require a functional AF-2 (15, 20). As expected, hAR(E896P) was unable to respond to transfected c-Jun. 100 nM DHT was used as indicated. C, the activities of c-Jun mutants in hAR N-to-C interaction closely parallel their activities in hAR transactivation. COS cells were transfected with 1 μg of MMTV-CAT reporter, 1 μg of hAR, and 1 μg of c-Jun plasmid (for transactivation) or 1 μg of 17M-tk-CAT, 5 μg of GAL-hAR(+/−), 3 μg of VP16-hAR(AB), and 1 μg of c-Jun plasmid (for N-to-C interaction). The various c-Jun proteins were expressed from three different promoters (SV40, Rous sarcoma virus (RSV), and cytomegalovirus (CMV)). The RSV promoter drives the expression of mutants M5, M9, M14, Ala63/73, Δ194–223, Δ146–221, and v-Jun, whereas the CMV promoter does the same for mutants A265–D In265, Δ287–331, Δ1–245, JunB, and JunD. 100 nM DHT was used in all cases. Note that, for both transactivation and N-to-C interaction, CAT activity is represented relative to activity of the first condition, which was activity without transfected c-Jun, and this was set to 1.

FIG. 3. c-Jun Potentiates hAR N-to-C Interaction. A, schematic diagram of hAR fusion proteins used in mammalian two-hybrid system to measure the hAR N-to-C interaction. Note that the hAR(+/−) is encoded by amino acids 624–918 and hAR(AB) by amino acids 1–655. B, c-Jun potentiates the hAR N-to-C interaction. COS cells were transfected with 1 μg of 17M-tk-CAT reporter plasmid and 5 μg of GAL-hAR(+/−), with or without 3 μg of VP16-hAR(AB) and 1 μg of c-Jun, as indicated. Note that gray bars are without and black bars with transfected c-Jun. 100 nM DHT was used as indicated. C, the activities of c-Jun mutants in hAR N-to-C interaction closely parallel their activities in hAR transactivation. COS cells were transfected with 1 μg of MMTV-CAT reporter, 1 μg of hAR, and 1 μg of c-Jun plasmid for (transactivation) or 1 μg of 17M-tk-CAT, 5 μg of GAL-hAR(+/−), 3 μg of VP16-hAR(AB), and 1 μg of c-Jun plasmid (for N-to-C interaction). The various c-Jun proteins were expressed from three different promoters (SV40, Rous sarcoma virus (RSV), and cytomegalovirus (CMV)). The RSV promoter drives the expression of mutants M5, M9, M14, Ala63/73, Δ194–223, Δ146–221, and v-Jun, whereas the CMV promoter does the same for mutants A265–D In265, Δ287–331, Δ1–245, JunB, and JunD. 100 nM DHT was used in all cases. Note that, for both transactivation and N-to-C interaction, CAT activity is represented relative to activity of the first condition, which was activity without transfected c-Jun, and this was set to 1.

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Fig. 4. The c-Jun-positive effect on hAR N-to-C interaction requires a functional AF-2. A, schematic diagram of the AF-2 point mutant GAL-hAR(DE/E896P). B, c-Jun is unable to act on the dimerization-deficient mutant GAL-hAR(DE/E896P). COS cells were transfected with 1 μg of 17M-tk-CAT reporter, 5 μg of GAL-hAR(DE), or GAL-hAR(DE/E896P), with or without 3 μg of VP16-hAR(AB) and 1 μg of c-Jun, as indicated. 100 nM DHT was used in all cases. Note that CAT activity is represented relative to activity of GAL-hAR(DE) and VP16-hAR(AB) with DHT, and this was set to 1.

Discussion

Fusion of AR regions to the DBD of the yeast transcription factor GAL4 (35) has been used to identify and delineate the AFs of this receptor and to determine that AF-1 contains significantly more inherent transcriptional activity than AF-2 (31, 36–38). In an earlier study, we used the same approach with the AB and E regions of hAR and determined that the c-Jun-positive effect on hAR is targeted to the AB region (23). Transactivation analysis of the hAR AB region led to the identification of amino acids 503–555 as necessary for the c-Jun activity and harboring an autonomous and c-Jun-responsive transcriptional activation function (23). In this report, we studied the importance of these amino acids in the full-length receptor. Deletion of amino acids 504–555 was found to have no effect on hAR transactivation either in the absence or presence of transfected c-Jun. Although this result is seemingly surprising, it is consistent with published data (31, 38) showing that the size and location of the amino-terminal AFs in hAR are variable, depending on whether the LBD is present or not. Another interesting aspect to come out of this present study is that, although deletion of amino acids 503–555 completely abolishes hAR transactivation, significant activity is recovered when c-Jun is cotransfected. These data suggest that hAR amino acids 1–357 are sufficient for c-Jun potentiation of hAR transactivation when the LBD is present. In contrast, deletion of only amino acids 503–555 is sufficient for eliminating the c-Jun effect on the AB region when the LBD is absent (23). All these results taken together demonstrate that the transcriptional activity of the AR AB region is complex and argue that the AR has the capacity to use different parts of this AB region for transacti-

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hancement of both hAR activities and those lacking this region having no effect. These results with c-Jun and c-Fos mutants strongly argue that c-Jun enhances hAR transactivation by mediating receptor dimerization and that c-Fos can interfere with this c-Jun activity.

Homodimerization of AR and other steroid receptors is required for these transcription factors to bind DNA in a sequence-specific manner (reviewed in Ref. 1). Therefore, a factor that mediates this dimerization would be expected to enhance DNA binding. Our data with c-Jun support this, because this proto-oncoprotein is able to significantly enhance hAR DNA binding when it is cotransfected with the receptor. The hAR N-to-C interaction is dependent on a functional AF-2, which appears to be directly involved in associating with the amino terminus. As others have shown previously (11) and we show here, mutations that disrupt AF-2 function interfere with the N-to-C interaction. However, in this study we go a step further to provide a direct link between hAR N-to-C interaction and DNA binding, because the AF-2 mutation E896P disrupts both N-to-C interaction and in vitro DNA binding. Moreover, hAR (E896P) is completely inactive in transcription, even with an androgen concentration (100 nM) above the physiological range. This differs from an earlier study in which other mutations in the AR LBD were determined to also disrupt both hAR N-to-C interaction and transactivation, but the effect on transactivation could be overcome with 100 nM DHT (11). It appears that that residue E896, which is highly conserved among nuclear receptors (32), is critical for hAR transactivation because of its possible role in the N-to-C interaction. In view of this and the c-Jun enhancement of hAR N-to-C interaction, it was not surprising to discover that c-Jun was unable to up-regulate DNA binding, N-to-C interaction, or transactivation by the E896P mutant.

The AR N-to-C interaction is mediated not only by c-Jun but also by several nuclear receptor coactivators, including SRC-1, TIF2, and CBP (15, 20, 21). All three coactivators have been shown to interact with the AR AF-2, and SRC-1 was recently reported to also interact with the AF-1 (41). Because our data suggest that c-Jun is acting via the AB region (23), it is possible that c-Jun- and AF-2-interacting coactivators function together by targeting different regions of the receptor. Our previous data with c-Jun and TIF2 support this hypothesis, because these two proteins have additive effects in hAR transactivation (23). The role of SRC-1 or CBP has yet to be fully examined, although it is interesting to note that both of these proteins have been shown to interact with and mediate the transcriptional properties of c-Jun on AP-1-responsive promoters (42, 43). Preliminary data suggest that neither CBP nor the related
protein p300 significantly affect the c-Jun coactivation functions on hAR.  

How could c-Jun mediate the hAR N-to-C interaction? c-Jun may be acting as a bridging factor between the hAR amino and carboxyl termini, as it has been suggested for p160 coactivators (19). Support for this mechanism of c-Jun action comes from Sato et al. (44), who have reported that c-Jun can physically associate with hAR. Using a similar immunoprecipitation approach in transient transfection studies, we have preliminary data to support this finding. However, this possible c-Jun-hAR complex appears to be very weak, because only a small fraction of c-Jun is found to interact with hAR. Furthermore, our finding in this report that c-Jun can increase the intensity of the hAR-DNA complex without affecting its mobility in in vitro DNA binding studies demonstrates that c-Jun is not found in hAR when this receptor is bound to DNA. With respect to other AR coactivators, even those shown to physically interact with AR, there is no evidence reported to suggest that the interaction occurs on DNA (17–21, 45–50). Thus, it is likely that proteins that enhance hAR N-to-C interaction, and therefore are presumed to potentiate DNA binding, perform this activity by engaging in short-lived protein-protein interactions with the receptor. Irrespective of what the precise mechanism of c-Jun action is, it is clear from all of the data accumulated thus far that the AR N-to-C interaction is a target of several different kinds of proteins that mediate hAR transactivation. Interestingly, this interaction is also affected by proteins that inhibit hAR activity. In this study, we provide evidence that c-Fos represses hAR activity by blocking the c-Jun potentiation of hAR N-to-C interaction. We have also obtained data to suggest that p53 exerts its negative effect on the expression of prostate-specific antigen by inhibiting hAR N-to-C interaction and DNA binding (51). All these data are consistent with the hypothesis that accessory factors can up- or down-regulate AR transcriptional activity by influencing the N-to-C interaction, which directly controls the transcriptional properties of this receptor.

Acknowledgments—We thank M. Rothkegel for providing the anti-Birch prophilin antibody and N. Hernandez for critical reading of the manuscript.

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J. Biol. Chem. 2001, 276:44704-44711.
doi: 10.1074/jbc.M107346200 originally published online September 27, 2001

Access the most updated version of this article at doi: 10.1074/jbc.M107346200

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