Androgen Induction of the Androgen Receptor Coactivator Four and a Half LIM Domain Protein-2: Evidence for a Role for Serum Response Factor in Prostate Cancer

Hannelore V. Heemers, Kevin M. Regan, Scott M. Dehm, and Donald J. Tindall

Departments of Urology Research/Biochemistry and Molecular Biology, Mayo Clinic, Rochester, Minnesota

Abstract
Androgen receptor (AR) activity is critical for prostate cancer progression. Overexpression of several AR-associated coactivators has been shown to be essential for AR activation during disease progression. The stimuli and signaling pathways leading to overexpression of these coactivators, however, remain largely elusive. Here, we investigated whether androgen signaling, which demarcates critical transitions during prostate cancer disease progression, can affect coactivator expression. We found that expression of four and a half LIM domain protein-2 (FHL2), a key AR coactivator that is overexpressed in prostate cancer and associates with a poor prognosis, is induced strongly by androgens. Androgen induction of this coactivator established a feed-forward mechanism that robustly activated the AR. Stimulation of FHL2 after androgen exposure was time- and dose-dependent and relied on the presence of a functional AR. Androgen induction of FHL2 depended on active transcription of the FHL2 gene, mediated by action of serum response factor (SRF) on its proximal promoter. Loss of SRF, a transcription factor that preferentially regulates the expression of genes involved in mitogenic response and cytoskeletal organization, hampered prostate cancer cell proliferation. These results suggest a novel indirect mechanism of androgen action on FHL2 expression and provide evidence that SRF is an important determinant of AR action in prostate cancer cells. [Cancer Res 2007;67(21):10592–9]

Introduction
Androgen receptor (AR) activity is critical for prostate cancer cell proliferation throughout disease progression. In the androgen-stimulated locally advanced or metastatic stages of the disease, AR action is targeted by antiandrogen therapy (1). Moreover, despite their resistance to androgen ablation therapy, the AR is emerging as an attractive therapeutic target for the treatment of androgen depletion independent (ADI) prostate cancers (2–4). Aberrant activity of the AR in prostate cancer has, at least in part, been attributed to overexpression of several AR-associated coactivator proteins. Expression and activity of AR coregulators, as well as the AR itself, are currently under investigation as potential targets for therapeutic intervention (5, 6). The factors and signaling pathways responsible for overexpression of AR transcriptional regulators in prostate cancer cells, however, remain largely elusive. Resolving the cues that drive expression of these coregulators will be essential to fully understand the mechanism of AR activity in prostate cancer and to generate insights needed for novel therapeutic approaches. As androgen signaling demarcates critical transitions in prostate cancer progression (7), we investigated whether the androgenic milieu of prostate cancer cells could exert an effect on coactivator expression, using the key AR coactivator four and a half LIM (FHL) domain protein-2 (FHL2) as a candidate coactivator model (8).

FHL2 is a member of a subclass of LIM domain–only proteins that consist of FHLs. LIM domain–containing proteins typically fulfill roles in cytoskeleton organization and transcriptional control (9). FHL2 has been shown to bind to integrins and is found in focal adhesions (10). FHL2 also possesses an intrinsic transactivation domain, but displays no DNA-binding activity, and functions as a coregulator for several transcription factors, including the AR (8). Moreover, FHL2 interacts with several AR-associated coactivators (10–12). Expression of FHL2 is enriched in prostate epithelial cells, where FHL2 colocalizes with the AR. FHL2 expression is increased in prostate adenocarcinoma cells when compared with benign epithelial cells. Moreover, the nuclear content of FHL2 increases with prostate tumor dedifferentiation where it is predictive of prostate cancer recurrences (13, 14).

Here, we show that androgens substantially induce the expression of FHL2 in prostate cancer cells, establishing a feed-forward mechanism that results in robust AR activation. Investigation into the molecular machinery underlying androgen regulation of FHL2 led to the identification of a novel indirect mechanism of androgen action in which the effects of androgens on FHL2 are mediated by serum response factor (SRF). Our data are the first to indicate that SRF, a ubiquitously expressed transcription factor that regulates transcription of genes involved in cellular proliferation as well as cytoskeletal organization (15), plays an important role in prostate cancer cell survival.

Materials and Methods
Cell culture. LNCaP and C4-2 cells were purchased from the American Type Culture Collection and UroCor, respectively. LNCaP and C4-2 cells were cultured in phenol red–free RPMI 1640 (Invitrogen) containing 9% fetal bovine serum (FBS; Biosource), 100 units/ml streptomycin, and 0.25 μg/ml amphotericin B (fungizone; Invitrogen). The LNCaP subline LNCaP-Rf was generated and maintained as described (16). Cells were maintained at 37°C in a humidified atmosphere of 5% CO2 in air. LNCaP cells between passages 29 and 40 were used. In experiments assessing the effects of androgen treatment, cells were seeded in medium containing 9% charcoal-stripped serum (CSS), 100 units/ml streptomycin, and 0.25 μg/ml amphotericin B. For small interfering RNA (siRNA) transfection studies, antibiotics were left out of the culture medium.

Preparation of whole-cell lysates. Cells were washed with ice-cold PBS. Whole-cell lysis buffer [110 mmol/L SDS, 100 mmol/L DTT, 80 mmol/L

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

Requests for reprints: Donald J. Tindall, Departments of Urology Research/Biochemistry and Molecular Biology, Mayo Clinic, 200 1st Street Southwest, Rochester, MN 55905. Phone: 507-284-8139; Fax: 507-284-2384; E-mail: tindall.donald@mayo.edu.

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Tris-HCl (pH 6.9), 10% glycerol] was pipetted onto the culture dish. Cell lysates were boiled for 5 min and stored at −20°C until analysis.

Western blotting. Equal amounts of protein were loaded onto 10% Bis-Tris NuPAGE gels (Invitrogen) and electrophoresis was done according to the manufacturer's instructions. Proteins were blotted onto nitrocellulose membranes (Bio-Rad). Blots were reprobed with antibodies against β-actin to evaluate potential differences in protein loading.

siRNA transfection. LNcAP cells were seeded at a density of 1.6 × 10^6 in 100-mm culture dishes in phenol red–free RPMI 1640 supplemented with 9% FBS. The next day, cells were transfected with 500 pmol sGenome SMART pool directed against FHL2 or TK-Renilla were added to 2 mL serum-free medium containing 9% CSS, fresh CSS medium was added, and cells were treated with R1881 or vehicle. Two days later, cells were harvested and processed for real-time reverse transcription-PCR as described. Values represent relative fold induction of mRNA expression after R1881 treatment and correspond to the means and SE of triplicate samples of a representative experiment (first and second column). LNcAP cells were transfected with siRNAs targeting FHL2 or nonspecific control siRNAs (Control). Forty-two hours after transfection, cells were treated with 5 nmol/L R1881 or ethanol vehicle. Forty-eight hours later, FHL2, PSA, TMPRSS2, and KLK2 expression was evaluated by real-time reverse transcription-PCR as described. Values represent relative fold induction of mRNA expression after R1881 treatment and correspond to the means and SE of triplicate samples of a representative experiment (first and second column). LNcAP cells were transfected with an expression construct encoding FLAG-tagged FHL2 or a control vector. Forty-two hours after transfection, cells were treated with R1881 (5 nmol/L) or vehicle. After 48 h, cells were harvested and FHL2, PSA, TMPRSS2, and KLK2 expression was evaluated as described. Relative fold induction of mRNA expression was calculated and the values obtained from one representative experiment were used to adjust the values of control conditions shown in column 1 (column 3). Values represent relative fold induction of mRNA expression after R1881 treatment and correspond to the means and SE of triplicate samples of a representative experiment. D, evaluation of the expression of FHL2 in the two experiments shown in C. Western blotting and real-time reverse transcription-PCR was done as described above.

Figure 1. Androgens stimulate the expression of FHL2, resulting in a feed-forward mechanism that ensures robust AR activation. A, LNCaP cells were treated with 5 nmol/L of the synthetic androgen R1881 (black columns) or ethanol vehicle (gray columns) for 48 h. RNA was isolated and converted into cDNA. Real-time PCR was done using FHL2–specific primers. FHL2 mRNA levels were normalized with the values obtained from GAPDH expression. FHL2 mRNA levels are expressed as relative expression values, taking the value obtained from cells treated with vehicle as 1. Columns, mean values obtained from three independent experiments; bars, SE (top). Total protein extracts were prepared and Western blotting was done using an antibody directed against FHL2. To assess loading differences, the blot was stripped and reprobed with an antibody directed against β-actin (β-actin; bottom). B, model for the proposed feed-forward mechanism: Androgen induction of FHL2 ensures robust AR transcriptional activity. C, LNcAP cells were transfected with siRNAs targeting FHL2 or nonspecific control siRNAs (Control). Forty-two hours after transfection, cells were treated with 5 nmol/L R1881 or ethanol vehicle. Forty-eight hours later, FHL2, PSA, TMPRSS2, and KLK2 expression was evaluated by real-time reverse transcription-PCR as described. Values represent relative fold induction of mRNA expression after R1881 treatment and correspond to the means and SE of triplicate samples of a representative experiment (first and second column). LNcAP cells were transfected with an expression construct encoding FLAG-tagged FHL2 or a control vector. Forty-two hours after transfection, cells were treated with R1881 (5 nmol/L) or vehicle. After 48 h, cells were harvested and FHL2, PSA, TMPRSS2, and KLK2 expression was evaluated as described. Relative fold induction of mRNA expression was calculated and the values obtained from one representative experiment were used to adjust the values of control conditions shown in column 1 (column 3). Values represent relative fold induction of mRNA expression after R1881 treatment and correspond to the means and SE of triplicate samples of a representative experiment. D, evaluation of the expression of FHL2 in the two experiments shown in C. Western blotting and real-time reverse transcription-PCR was done as described above.
**Results**

Androgen treatment induces FHL2 expression, ensuring proper AR transcription. To explore whether changes in androgen concentrations affect FHL2 expression, androgen-responsive LNCaP prostate adenocarcinoma cells were seeded in androgen-depleted medium and cultured in the presence or absence of the synthetic androgen R1881 (methyltrienolone) for 2 days. Whole-cell lysates were prepared, and FHL2 protein and mRNA expression levels were evaluated by immunoblotting and real-time RT-PCR. As shown in Fig. 1A, androgen exposure led to a marked increase in FHL2 expression, both at the mRNA and protein levels. Because FHL2 functions as a coactivator for the AR, these results suggest the existence of a feed-forward mechanism in which androgens, through up-regulation of a positive regulator of their cognate receptor, ensure strong activation of androgen-responsive genes (Fig. 1B). To test this hypothesis, the effect of changes in FHL2 expression on full androgen induction of a set of endogenously expressed target genes containing well-characterized androgen response elements (ARE) in their promoter regions (Fig. 1C) was examined. To this end, LNCaP cells were transfected with siRNAs targeting FHL2 expression or non-targeting control siRNAs. Forty-two hours after transfection, when FHL2 levels had declined substantially in cells exposed to FHL2-specific siRNA, cells were treated with R1881 or vehicle. Forty-eight hours later, a 40% to 50% decline in androgen responsiveness of the genes encoding PSA, TMPRSS2, and KLK2 was noted in cells where FHL2 expression was targeted (Fig. 1C). In keeping with
these data, forced overexpression of FHL2 further increased the level of androgen induction of this set of androgen-regulated genes above that observed for control cells (Fig. 1C). The magnitude of this effect, however, was not as pronounced as the extent of the decrease observed after FHL2 knockdown. These data suggest that the increase in FHL2 expression induced by androgen stimulation is already sufficient to achieve full AR activity. The effect of the transfections on FHL2 expression levels is shown in Fig. 1D.

Androgen induction of FHL2 is mediated by an indirect mechanism that is dependent on SRF. To gain further insight into this phenomenon, the androgen-mediated induction of FHL2 expression was characterized in more detail. A time course was done in which LNCaP cells were treated with R1881 for up to 72 h. Androgen stimulation of FHL2 expression was first seen 16 h after treatment, became more pronounced after longer periods of treatment, and reached a maximum at 48 h (Fig. 2A). To further resolve the molecular mechanism(s) underlying androgen induction of FHL2 expression, the possibility that androgens affect transcription of the FHL2 gene was explored. To this end, LNCaP cells were pretreated for 30 min with the transcriptional inhibitor actinomycin D. Subsequently, R1881 or ethanol vehicle was added. Sixteen and 24 h later, cells were harvested, and FHL2 mRNA expression levels were evaluated. Treatment with actinomycin D decreased basal levels of FHL2 and completely prevented androgen induction of FHL2 expression at both time points (Fig. 3A), suggesting that active transcription might be involved. To further explore this hypothesis, an ~1.6-kb FHL2 promoter fragment flanking exon 1 (19) was cloned into the pGL3 basic vector. LNCaP cells transiently transfected with this promoter-reporter construct (FHL2-1570) were treated with R1881 or control vehicle for 48 h. Androgen treatment induced reporter gene activity ~12-fold (Fig. 3B), a magnitude of response similar to the fold induction of FHL2 mRNA levels after androgen stimulation (Figs. 1 and 2). To further delineate the androgen-responsive domain(s) within this DNA region, progressive 5′ deletions of ~200 bp were introduced in this fragment. Transient transfection studies with these deletion constructs revealed that full androgen responsiveness was maintained in a 145-bp proximal promoter fragment (Fig. 3B). Promoter-reporter constructs containing genomic fragments of intermediate size were equally androgen responsive, with basal reporter gene activity fluctuating moderately (data not shown). The use of transcription factor search algorithms (MatInspector and WebSignal Scan Program) and visual inspection failed to detect the presence of AREs within this 145-bp FHL2 promoter fragment. Thus, our cumulative data suggest that androgens regulate FHL2 expression through a mechanism that is different from that of an AR-ARE interaction on the FHL2 gene promoter.

A search for other candidate genomic regions that could potentially mediate the effects of androgens on FHL2 expression revealed the presence of a [CC(A/T)6GG] (CARG) box within the 145-bp sequence (Fig. 4A). CARG boxes are consensus binding sites for SRF, a widely expressed transcription factor with functions in cell proliferation and cytoarchitecture (15). Because FHL2 has been
identified as a SRF target gene (20), and reports from other laboratories suggest that some CArG-box–containing genes could be androgen responsive (21–23), the possibility that this CArG box could be involved in mediating the androgen induction of FHL2 was explored. To this end, a site-directed mutagenesis approach was used to introduce mutations in the CArG box sequence that would prevent binding of SRF (Fig. 4A). These mutations led to a decrease in basal levels of reporter gene activity and completely abolished androgen responsiveness of the 145-bp FHL2 promoter fragment. Similar results were obtained after mutation of the CArG box in the 1,570-bp FHL2 promoter reporter construct, and after cotransfection of wild-type and CArG box mutant FHL2 promoter-reporter constructs with an AR expression construct in AR-negative PC-3 prostate cancer cells (data not shown). To verify binding of SRF to this FHL2 proximal promoter region, ChIP experiments were done. LNCaP cells were seeded in androgen-depleted medium. After 2 days, the medium was replaced and cells were grown in the presence or absence of R1881. Sixteen hours later, cells were harvested and ChIP analysis was done using antibodies directed against SRF and AR or non-targeting antibodies. These experiments confirmed binding of SRF to the endogenous 145-bp FHL2 promoter fragment, both in the presence and absence of androgens (Fig. 4B). Consistent with our previous results, AR recruitment to this genomic region was not observed, whereas binding of AR to AREFIII (18) of the PSA gene was readily apparent. Control experiments done with non-specific antibodies or primer pairs amplifying non-relevant genomic sequences produced no signals (Fig. 4B). To corroborate the involvement of SRF in the androgen regulation of FHL2, the effect of loss of SRF expression on androgen induction of endogenous FHL2 expression was investigated. LNCaP cells were transfected with siRNAs targeting SRF expression or non-specific control siRNA. Forty-two hours later, cells were exposed to androgens or vehicle. Two days later, whole-cell lysates were prepared and analyzed by Western blotting. As shown in Fig. 4C, SRF-targeting siRNAs inhibited SRF expression. Suppression of SRF expression reduced the stimulatory effects of androgens on FHL2 expression, confirming its involvement in androgen regulation of the FHL2 gene. Moreover, rescue of SRF expression by a siRNA-resistant SRF expression construct (SRFsr#1; Supplementary Fig. S2) restored androgen induction of FHL2 expression. These effects were not due to changes in basal FHL2 levels upon loss of SRF expression, because knockdown of SRF did not affect mRNA levels of FHL2 under androgen-deprived conditions (Supplementary Fig. S3). Likewise, changes in SRF expression levels did not affect AR expression levels (data not shown). The androgen induction of the SRFsr#1 construct can be attributed to its transcription from the pSG5 vector. Importantly, loss of SRF expression also prevented full androgen induction of AR target genes. Whereas its effect on the androgen regulation of the TMPRSS2 gene was rather modest, decreased SRF expression severely compromised the androgen induction of the genes encoding PSA and KLK2 (Fig. 4D). Taken together, these data support the existence of a novel indirect mechanism of androgen action wherein the regulation of FHL2 is mediated by SRF.
SRF activity is critical for prostate cancer proliferation. To our knowledge, these data are the first to identify a role for SRF as a determinant of androgen action in prostate cancer. To further investigate the importance of SRF function in prostate cancer, the requirement of SRF for prostate cancer cell proliferation was examined. LNCaP cells seeded in serum-containing culture medium, which contains physiologic levels of androgens, were transfected with siRNAs targeting SRF or non-targeting control siRNAs (Fig. S4). This approach led to a successful knockdown of SRF and a concomitant decrease in FHL2 expression (Figs. 5A and 6B; data not shown). At the indicated time points after transfection, cell proliferation was evaluated by measuring metabolic activity with a 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay. Forty-eight hours post-transfection, cell proliferation had already decreased in cells transfected with SRF-targeting siRNA. MTS measurements 72 and 96 h after transfection showed a progressive impairment of cell growth (Fig. 5B). This decrease was not due to increased apoptosis because the cleavage pattern of the apoptotic marker poly(ADP-ribose)polymerase was not altered (data not shown). Instead, bromodeoxyuridine (BrdUrd) incorporation studies confirmed a decrease in cell proliferation upon loss of SRF expression. In line with the MTS data, this effect was observed 48 h post-transfection and increased with prolonged exposure of the cells to SRF-specific siRNA (Fig. 5C). Interestingly, similar effects on cell proliferation were observed when expression of FHL2 was targeted (Supplementary Fig. S4).

To explore the importance of FHL2 expression and its regulation by SRF in the progression of prostate cancer, experiments were done using the ADI LNCaP sublines C4-2 and LNCaP-Rf. The C4-2 cell line was derived from a second-generation LNCaP xenograft from castrated mice (24) and is grown in medium supplemented with FBS. LNCaP-Rf cells were generated in our laboratory by culturing LNCaP cells under androgen-deprived conditions (16). The LNCaP-Rf line is maintained in medium supplemented with CSS. First, FHL2 expression levels in these cell lines were assessed by real-time RT-PCR. As shown in Fig. 6A, FHL2 expression levels in C4-2 cells were comparable with those observed in the LNCaP line. In androgen-deprived LNCaP-Rf cells, FHL2 expression was ~30% lower than in the parental cells. To determine the involvement of SRF in FHL2 expression in these cell lines, cells were transfected with siRNAs targeting SRF or control siRNAs. Four days later, RNA was isolated from the cells and real-time RT-PCR was done. In line with the findings described above (Fig. 4; Supplementary Fig. S3), loss of SRF led to a decrease in FHL2 expression in androgen-supplemented LNCaP and C4-2 cells, but did not affect FHL2 expression in LNCaP-Rf cells (Fig. 6B). To evaluate the requirement of FHL2 and SRF for LNCaP-Rf cell proliferation, LNCaP-Rf cells were transfected with siRNAs targeting these genes or non-targeting control siRNAs. Cell proliferation was assessed by MTS assays. As shown in Fig. 6C, loss of FHL2 expression led to modest decreases in cell growth. This effect was first seen 48 h post-transfection. Importantly, targeting the expression of SRF severely hampered LNCaP-Rf cell proliferation (Fig. 6C). Taken together, these data indicate that FHL2 and SRF are critical for prostate cancer cell proliferation throughout disease progression and suggest the involvement of additional mechanisms that may be independent of the presence of androgens in the regulation of FHL2 expression.

Discussion

Tight regulation of transcription is critical for normal development, and deregulation of transcription by aberrant expression or activation of components of the transcriptional machinery contribute to pathologies (25–31). In the case of prostate cancer, overactivation of the AR results in disease progression and has been attributed at least in part to overexpression of several of its coactivators (5, 6). Both the AR and AR coregulators have been intensely studied as promising therapeutic targets for the treatment of this disease. Unraveling the signaling events responsible for overexpression of these cofactors as well as the cues triggering such signaling may suggest novel therapeutic avenues. Here, we investigated the regulation of FHL2, an AR coactivator that is overexpressed in prostate cancer and correlated with poor prognosis (8, 13, 14). We show that androgens induce FHL2 expression in a time- and dose-dependent manner. Because changes in FHL2 expression have a marked effect on the extent of androgen stimulation of several ARE-driven target genes, these observations enhance our understanding of the means by which androgen stimulation elicits robust activity of the AR in prostate cancer cells. It is tempting to speculate that such a feed-forward mechanism plays an important role in normal androgen-regulated physiology as well. For example, FHL2-deficient mice have been shown to suffer from osteopenia. Similarly, increased bone mass is seen in a transgenic mouse model where FHL2 is overexpressed in mature osteoblasts (32). Given that AR function is necessary to maintain bone mass and protect against osteoporosis (33), these observations suggest a similar FHL2-dependent regulation of AR activity in bone. Preliminary findings suggest that, although FHL2 might play a role in the regulation of its own basal gene expression, its presence is not required for androgen induction of FHL2 gene expression (Supplementary Fig. S5).

Mechanistic studies showed that androgens exert their effect on the FHL2 gene through a novel indirect mechanism of action mediated by SRF. By means of indirect mechanisms of action, androgens affect the expression of genes that do not contain AREs. Androgen modulation of the activity of a secondary transcription
factor is a prime example of an indirect mechanism of androgen action as this conveys androgen regulation to the expression of target genes of the affected transcription factor that lack AREs (34, 35). In the setting of prostate cancer, an overwhelming amount of data support a central role for the AR in the progression of the disease (5). However, target genes that are directly affected by AR signaling via AREs that mediate the effects of AR activity on cell proliferation and metastasis are only starting to emerge (36). Thus, identification of SRF, a transcription factor that preferentially controls the expression of genes involved in mitogenic responses and cytoskeletal organization (15, 37), as a determinant of androgen action is particularly interesting because this can have major implications for our understanding of prostate cancer cell proliferation and invasive potential. Supporting this possibility, our data show that loss of SRF hampers prostate cancer cell proliferation. Flow cytometry data assessing the effect of SRF silencing on cell cycle progression corroborated these findings.1 Thus far, the mechanism of SRF-dependent FHL2 expression has been observed in androgen-supplemented LNCaP cells, their ADI derivative C4-2 cell line, and following transfection of an expression construct encoding the AR into AR-negative ADI PC-3 cells (data not shown). In androgen-deprived ADI LNCaP-Rf and LNCaP cells, loss of SRF expression does not lead to a decrease in FHL2 expression. Nonetheless, both FHL2 and SRF remain important for LNCaP-Rf cell proliferation, suggesting that other means of action and of regulation of these proteins contribute to prostate cancer proliferation.

It will be important to ascertain if androgen regulation can be generalized to CArG-box–containing genes other than FHL2. Reports from other laboratories suggest that this is the case for the muscle lineage genes α-actin and γ-actin (21–23). Studies investigating the full extent of the overlap between genes making up the SRF target genes, the so-called CarGome (15), and genes subject to androgen regulation are ongoing in our laboratory. Another question that will be important to answer relates to the exact mechanism by which androgen and SRF signaling pathways intersect to regulate transcription of CArG box–containing genes. SRF constitutively binds as a dimer to CArG boxes in target genes. The activity of SRF and transcription of its target genes is controlled either by signaling pathways that converge on SRF and modulate its activity or by alterations in the composition of the cofactor complex it engages (15, 37, 38). Consistent with this method of action, our findings show that SRF is recruited to the FHL2 promoter even in the absence of androgens. Moreover, our data suggest that androgens do not affect SRF expression levels. A recent report using an in vitro assay system suggested that the AR could be recruited by SRF to a 20-bp DNA fragment harboring a CarG box and that, through this recruitment, SRF imparts androgen regulation to the skeletal α-actin gene in C2C12 myoblasts (23). As shown in Fig. 4B, the results of our ChIP experiments argue against recruitment of the AR as a cofactor for SRF at the FHL2 CarG box. These observations are consistent with ongoing ChIP-on-chip studies mapping genome-wide recruitment of the AR.2 In keeping with these findings, coimmunoprecipitation experiments in our laboratory have failed to detect interactions between endogenously expressed SRF and AR in LNCaP cells.1 The possibility that androgen-regulated cofactors that functionally and structurally interact with SRF (21, 39), or androgen-induced changes in signaling pathways that affect SRF-mediated transcription, could be responsible for androgen

1 Unpublished results.

2 M. Brown, personal communication.
regulation of SRF signaling is currently under investigation in our laboratory. In summary, we show that the expression of the AR coactivator FHL2 is stimulated in an AR- and androgen-dependent manner in prostate cancer cells. This finding provides insights into the regulation of FHL2 overexpression in prostate cancer and identifies a mechanism by which the AR is able to assure its aberrant activity in the progression of this disease. The identification of SRF as a mediator of androgen action on the FHL2 gene establishes the existence of a novel indirect mechanism of androgen action and provides the first indication that SRF action is important for prostate cancer survival.

References

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