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Regular paper

Androgen receptor and c-Myc transcription factors as putative partners in the *in vivo* cross-talk between androgen receptor-mediated and c-Met-mediated signalling pathways

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Cross-talk between two signal transduction pathways leads to a negative regulation of androgen-induced ornithine decarboxylase (ODC) gene expression in the mouse kidney. One pathway is triggered by testosterone *via* the intracellular androgen receptor, AR, and the other is induced by antifolate CB 3717 or folate *via* hepatocyte growth factor and its cell membrane receptor c-Met. Here we report the studies of the expression of AR and c-Myc transcription factors involved in ODC transactivation. Administration of CB 3717 or folate decreased the expression of AR. In contrast, testosterone did not modify AR mRNA content but augmented the AR protein. Furthermore, we demonstrate that administration of folate, but not testosterone, increases c-Myc transcript and protein level. We also document that activation of both examined pathways does not decrease the testosterone-induced AR protein level, but markedly increases c-Myc protein which is nearly 2-fold up-regulated compared to its level evoked solely by testosterone. We suspect that this pronounced increase of c-Myc protein might have functional consequences mirrored by down-regulated expression of AR target genes, among them ODC.

Keywords: androgen receptor, HGF/c-Met; c-Myc, antifolate/folate-injured kidney, cross-talk

INTRODUCTION

It is widely recognized that diverse signalling pathways do not act independently but are interconnected, forming a cellular communication network of rapidly increasing complexity. The cross-talk between different cellular signalling systems enables the cell to integrate the multitude of signals from its environment. Nuclear receptors, forming a superfamily of ligand-activated transcription factors, undergo fine tuning of their response to the incoming signals. The precise regulation of their transcriptional activity depends not only on their response to hormonal ligands but also on the numerous signalling pathways activated by a large variety of external stimuli. Post-translational modification of the receptor itself as well as its distinct complexes of coregulatory proteins, *via* combinatorial control, modulate transactivation of the nuclear receptor (McKenna & O'Malley, 2002; Perrisi & Rosenfeld, 2005).

Previously, when studying renal polyamine biosynthesis *in vivo*, we reported the induction of ODC, a key enzyme limiting biosynthesis of polyamines, in testosterone-induced hypertrophic and antifolate CB 3717-induced hyperplastic mouse kidney (Manteuffel-Cymborowska *et al.*, 1993). We showed that activated signalling pathways mediated by AR and c-Met receptors, respectively, were intercon-

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Abbreviations: AR, androgen receptor; HGF, hepatocyte growth factor; ODC, ornithine decarboxylase; PTEN, phosphatase and tensin homolog deleted on chromosome 10.

nected, and their antagonistic cross-talk resulted in a negative regulation of testosterone-induced ODC and CB 3717/folate-induced c-Met expression (Dudkowska *et al.*, 2001). Thus, the testosterone-induced ODC expression becomes drastically decreased under conditions of subsequent activation of HGF/c-Met signalling by CB 3717 or folate. In contrast, a synergistic interaction has been found between the signalling pathways activated *via* cell membrane catecholamine receptors and AR as well as c-Met (Manteuffel-Cymborowska *et al.*, 1997; Dudkowska *et al.*, 1999).

Two different transcription factors — AR and c-Myc — have been postulated to be involved in the induction of the renal *odc* gene under conditions of activated testosterone/AR and HGF/c-Met signalling, respectively (Dudkowska *et al.*, 2001). It is noteworthy that ODC is one of the first identified c-Myc target genes (Law *et al.*, 1995; Tobias *et al.*, 1995).

The antagonism between these two pathways could be connected with, among other factors, a decreased level of AR and/or c-Myc. It is well established that the c-Myc transcription factor, a key regulator of cell proliferation, can both activate and repress transcription (Murphy *et al.*, 2005; Adhikary & Eilers, 2005). It is induced as a primary response gene by numerous signal transduction pathways, including growth factor/tyrosine kinase receptor pathways (e.g. Pelengaris & Khan, 2003). Several functional links between the AR and c-Myc transcription factors are known. AR transcription is not only subject to autoregulation (Lee & Chang, 2003) but it is also regulated by c-Myc (Grad *et al.*, 1999), while the *c-myc* gene is regulated by AR (Bièche *et al.*, 2001). Furthermore, both AR and c-Myc expression can be regulated by Akt kinase (Lin *et al.*, 2001; Gregory *et al.*, 2003). This serine-threonine kinase regulates multiple cellular processes, including cell proliferation and survival (Song *et al.*, 2005; Taneja *et al.*, 2005). Here, we present results on the expression of AR and c-Myc transcription factors that appear especially important in view of our working hypothesis concerning the AR/c-Myc interaction and the possibility of a negative regulation of AR transactivation by the HGF/c-Met signalling pathway (Dudkowska *et al.*, 2001).

MATERIAL AND METHODS

Animals. Female Swiss mice (2.5–3 months old) were injected i.p. 24 h prior to killing with a quinazoline antifolate, CB 3717 (N^{10}-propargyl-5,8-dideazafolic acid) or folate (300 mg/kg or 250 mg/kg, respectively), dissolved in phosphate-buffered saline (PBS) adjusted to pH 9–9.5. Mice were also treated with testosterone alone (5 days prior to killing, 125 mg/kg, s.c.), in combination with antiandrogen casodex (40 mg/kg, s.c.), injected 1 h before testosterone, both dissolved in soybean oil, or with testosterone and either CB 3717 or folate. Controls received an equivalent volume of vehicle. Mice were killed by cervical dislocation, the kidneys removed and stored at –70°C until further processing for RNA and protein content.

Northern blot analysis. RNA was isolated from kidney tissue, subjected to agarose gel electrophoresis and blotted onto nylon membranes then the levels of chosen mRNAs were estimated as described previously (Manteuffel-Cymborowska *et al.*, 1997). The probes used were: *Eco*RI/*Xho*I insert of pcDNA3 plasmid carrying a 350 bp fragment of human AR cDNA, and 4.8 kb *Xho*I/*Bam*HI insert of pSVc-Myc plasmid containing the second and third exons of mouse *c-myc* gene. AR and c-Myc mRNA levels were quantified by densitometric scanning of autoradiograms using the Ingenius System with Gene Tools software (Syngene, UK) and corrected for total RNA loaded into the gels as determined by ethidium bromide staining of 28S rRNA.

Western blot. Kidney tissue used for AR protein analysis was homogenized in RIPA lysis buffer containing 1% NP40, 150 mM NaCl, 1 mM sodium orthovanadate, 1 mM NaF, 50 mM Tris/HCl (pH 7.4), 2 mM DTT, 1 mM phenylmethanesulfonyl fluoride (PMSF) and protease inhibitor cocktail, 10 μl/ml. The homogenate was incubated at 4°C for 1 h, then centrifuged at $40000 \times g$ for 30 min. Kidney tissue used for c-Myc protein analysis was homogenized in PBS containing 1 mM PMSF and protease inhibitor cocktail, 10 μl/ml, then centrifuged at $50000 \times g$ for 10 min. An aliquot of 100 μg of protein was separated by SDS/PAGE and electrotransferred onto nitrocellulose or PVDF membranes. After blocking with 5% milk, the membranes were incubated at 4°C overnight with primary antibody, followed by 1 h incubation with appropriate secondary antibody conjugated with HRP (horseradish peroxidase). The signals were visualized by ECL (Enhanced Chemiluminescence System, Amersham) and quantified by densitometric scanning.

Chemicals and antibodies. All chemicals purchased from commercial sources were of analytical grade. Testosterone was obtained from Jelfa (Poland), protease inhibitor cocktail (Sigma, USA), Rediprime, Hybond-N, Hyperfilm-MP, [α-^{32}P]dCTP (110 TBq/mmol), Hybond-ECL, Hyperfilm ECL, ECL Western Blotting Detection Reagents from Amersham (UK) and Immun-Blot PVDF and nitrocellulose membranes from BioRad. CB 3717 and casodex were provided by Zeneca Pharmaceuticals (UK). The following primary antibodies were used: anti-c-Myc (N-262) (Santa Cruz, USA) and anti-AR (PG-21) (Upstate, USA) rabbit polyclonal antibodies, and anti-ac-

tin (Ab-1) mouse monoclonal antibody (Calbiochem, USA). Goat anti-rabbit IgG (Pierce, USA) and goat anti-mouse IgM (Calbiochem, USA) were applied as secondary antibodies.

Statistical analysis. Data were evaluated using the Mann–Whitney test.

RESULTS AND DISCUSSION

Renal expression of AR mRNA and AR protein is differentially modulated by testosterone and down-regulated by CB 3717 or folate

It is well known that the action of androgens in target tissues is mediated by the AR and the regulation of the androgen-AR signalling pathway can be linked, among others, to AR protein expression. In the mouse kidney, testosterone substantially increased the expression of ODC and c-Met (Dudkowska *et al.*, 2001), however, as shown in the present study, it did not affect AR mRNA content (Fig. 1A). Similarly, injection of the antiandrogen casodex prior to testosterone did not modify the expression of AR mRNA (Fig. 2A). The mode of regulation of AR mRNA expression by androgens is complex, being controlled by transcriptional (Wiren *et al.*, 1997) and/or post-transcriptional events, in particular the stability of AR mRNA (Yeap *et al.*, 2004). Androgen-induced modification of AR mRNA content, known to be tissue-specific and differentiated (Lee & Chang, 2003), can vary from down-regulation (Wolf *et al.*, 1993; Wiren *et al.*, 1997), through no response (Wolf *et al.*, 1993; this paper), to up-regulation (Wiren *et al.*, 1997). The lack of androgen- or antiandrogen-induced effect on AR mRNA (Figs. 1A and 2A) contrasts markedly with the significant up-regulation of AR protein content by these compounds (Figs. 1B and 2B). An equivalent increase of AR protein content was found after testosterone administration and when injection of casodex preceded testosterone treatment.

Unlike several nuclear receptors, AR protein is not degraded in the presence of its ligand *via* the ubiquitin-26S proteasome pathway (Lee & Chang, 2003). On the contrary, androgens are known to increase the AR protein level in various cell contexts (Furutani *et al.*, 2002; Lee & Chang, 2003) due to its stabilization and/or increased translation of AR mRNA (Furutani *et al.*, 2002). This may provide an explanation for our finding that testosterone did not change the AR mRNA level but significantly induced the AR protein content. This suggests that testosterone evokes a post-transcriptional positive regulation of AR expression in the mouse kidney.

Activation of HGF/c-Met signalling in CB 3717/folate-injured kidney significantly decreased, by nearly 40%, the expression of AR mRNA (Fig. 1A). The down-regulation of AR protein (Fig. 1B), which gradually decreased with time by 10%, 22% and 42% after 1, 3 and 24 h of antifolate treatment, respectively, is shown in Fig. 3. The decrease of both bands of AR, which represent probably its differentially phosphorylated isoforms (Wong *et al.*, 2004), was visible. The parallel decrease of AR transcript and protein following activation of the HGF-signalling pathway supports the suggestion that the repression of AR

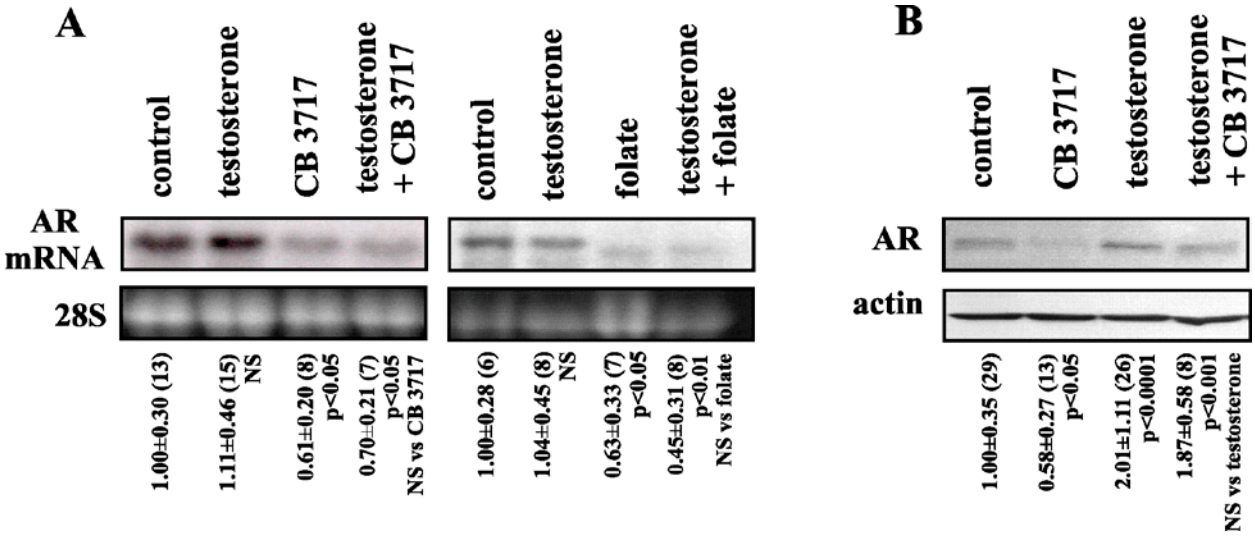

Figure 1. Differential effect of testosterone and/or CB 3717/folate on AR mRNA (A) and AR protein (B).
Testosterone was injected 5 days and CB 3717 or folate 1 day prior to killing. Mice pretreated with testosterone for 4 days were injected with CB 3717 or folate for a further 1 day. Each lane represents RNA or protein from an individual mouse. The level of 28S rRNA (A) and actin (B) was used as a loading control. Results are expressed as means ±S.D.; the number of mice in each experimental group (in parentheses) and *P* values (compared with control or as indicated) are shown beneath the appropriate lanes.

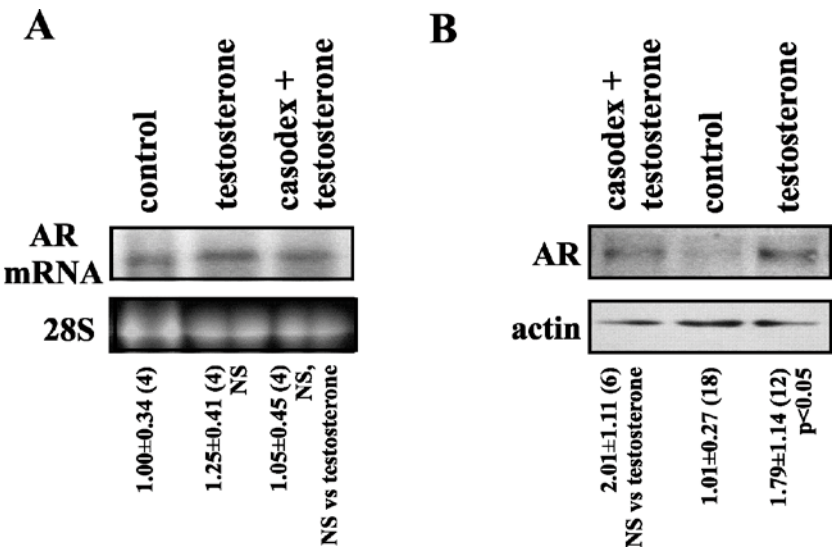

Figure 2. Casodex does not affect AR mRNA (A), but similarly to testosterone up-regulates AR protein (B).
Casodex was given 1 h before testosterone which was injected 5 days prior to killing. Each lane represents RNA or protein from an individual mouse. The level of 28S rRNA (A) and actin (B) was used as a loading control. Results are expressed as means ±S.D.; the number of mice in each experimental group (in parentheses) and *P* values (compared with control or as indicated) are shown beneath the appropriate lanes.

expression under these conditions occurs primarily at the level of transcription or mRNA stability (Mizokami *et al.*, 1992).

It also cannot be excluded that activation of the HGF/c-Met pathway might also affect AR transcription through activated Akt kinase (Dudkowska *et al.*, 2006) that regulates FOXO3a and NFκB, the transcription factors for the *AR* gene. FOXO3a has recently been documented to be a positive regulator of the *AR* gene (Yang *et al.*, 2005). Thus, activated Akt, known to inhibit FOXO3a transcriptional activity (Accili & Arden, 2004), might result in down-regulation of AR mRNA level. In contrast to FOXO3a, NFκB is activated by Akt (Kane *et al.*, 1999), but as a repressor of the *AR* gene (Supakar *et al.*, 1995) it might down-regulate AR transcription.

As a plausible mechanism explaining the decrease of renal AR protein after antifolate or folate treatment one can also consider the effect of the tumor suppressor PTEN, known to regulate AR protein degradation and AR signalling in prostate cancer cells due to its direct interaction with this transcription factor (Lin *et al.*, 2004). Studies of the expression of phosphorylated and unphosphorylated PTEN after activation of HGF/c-Met signalling are under way.

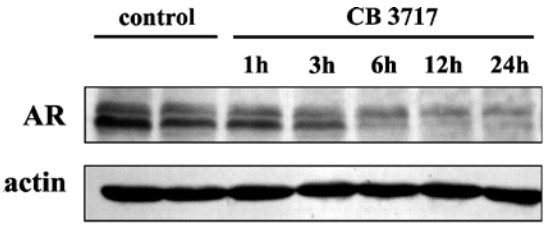

Figure 3. Time course of the decrease of AR protein level after CB 3717 administration.
CB 3717 was injected for time indicated. Each lane represents protein from an individual mouse, the level of actin was used as a loading control. A representative experiment is shown.

Cross-talk between testosterone-activated and antifolate/folate-activated signalling pathways results in differential regulation of renal AR expression

AR mRNA content unaffected by testosterone exposure decreased significantly by 30% or 55% when androgen treatment was followed by the injection of antifolate or by folate, respectively (Fig. 1A). The changes in AR mRNA content following activation of both AR- and c-Met-signalling pathways were statistically indistinguishable from the c-Met-induced activation alone. In contrast to AR message, the AR protein content after testosterone and CB 3717 treatment was 1.9-fold up-regulated, similarly to the testosterone-induced AR protein (Fig. 1B). These results show that AR mRNA and AR protein undergo differential regulation under conditions of activation of both examined signalling pathways. It appears, therefore, that HGF/c-Met signalling, when activated sequentially with the androgen/AR pathway, does not antagonize AR function by down-regulation of the level of this transcription factor. However, it should be stressed that the transcriptional activity of AR depends not only on its level but also

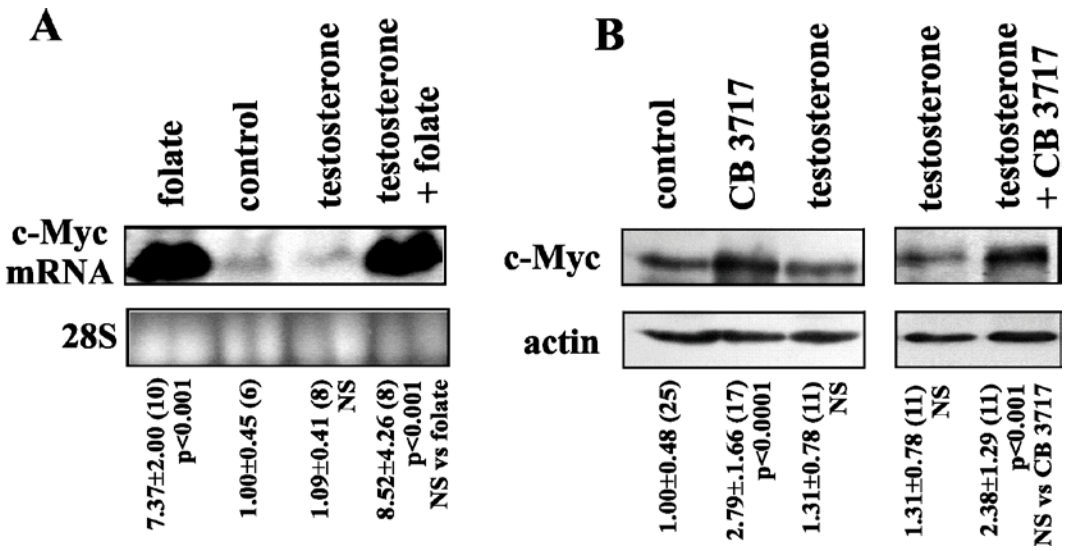

Figure 4. Effect of testosterone and/or CB 3717/folate on c-Myc mRNA (A) and c-Myc protein (B).
Testosterone was injected 5 days, and CB 3717 or folate 1 day before killing. Mice pretreated with testosterone for 4 days were injected with CB 3717 or folate for a further 1 day. Each lane represents RNA or protein from an individual mouse. The level of 28S RNA (A) and actin (B) was used as a loading control. Results are expressed as means ±S.D.; the number of mice in each experimental group (in parentheses) and *P* values (compared with control or as indicated) are shown beneath the appropriate lanes.

on its phosphorylation status. Therefore, it is highly probable that phosphorylation of renal AR and/or its coregulators by, e.g., Akt kinase, the down-stream effector of HGF/c-Met signalling activated in CB 3717-injured kidney (Dudkowska *et al.*, 2006), can have profound effects on AR transcriptional activity, and in consequence on the expression of its target genes, including ODC. This is consistent with the view that Akt kinase may represent a link between growth factors, acting *via* cell membrane receptors, and AR transcriptional activity. However, under limitations of *in vivo* studies, this hypothesis cannot be proved conclusively.

CB 3717/folate but not testosterone up-regulates renal c-Myc expression

The expression of c-Myc, a transcriptional regulator of *odc*, was examined following activation of HGF- and AR-mediated signalling pathways in the mouse kidney. As shown in Fig. 4A and 4B, testosterone did not modify the c-Myc mRNA level and had a negligible effect on c-Myc protein content. Thus, although in some cell types androgens have been shown to exert a cell-specific effect on c-Myc expression (Wolf *et al.*, 1993; Lim *et al.*, 1994, Silva *et al.*, 2001), in our study testosterone did not modify c-Myc at the transcriptional or post-transcriptional level in the mouse kidney.

In contrast to the lack of androgen effect on c-Myc expression, in kidneys injured with folate we found a highly significant up-regulation of c-Myc mRNA (Fig. 4A), comparable to that induced by CB 3717 (Stachurska *et al.*, 2004). This is consistent with our previous studies showing that both drugs, CB 3717 and folate, evoke kidney damage and to the same extent induce ODC expression as well a c-Met mRNA (Manteuffel-Cymborowska *et al.*, 1991; Dudkowska *et al.*, 2001). An antifolate insult also induced a very distinct augmentation of c-Myc protein that remained, nevertheless, significantly lower than the increase of c-Myc transcript (Fig. 4B). The documented up-regulation of c-Myc expression indicates that transcription factor is a putative down-stream target of HGF/c-Met signalling in our experimental model of drug-injured kidney. The regulation of c-Myc can proceed *via* the PI3K/Akt pathway *via* β-catenin/TCF/LEF (He *et al.*, 1998) and/or NFκB (Grumont *et al.*, 2002). It is known that c-Myc is a transcriptional target of TCF-4 and its coactivator, β-catenin (He *et al.*, 1998; Kikuchi, 2000). Translocation of β-catenin to the nucleus depends on its cytoplasmic pool, which is tightly regulated by several proteins, including GSK-3β (Kikuchi, 2000; Bienz, 2005), a substrate of Akt kinase (Song *et al.*, 2005), a down-stream effector of HGF/c-Met in the injured kidney. After sequential administration of testosterone and antifolate/folate the c-Myc mRNA and protein level is statistically indistinguishable from the c-Myc expression induced by folate or antifolate alone, but it is significantly higher than after androgen treatment. In the case of c-Myc protein this difference is nearly 2-fold (Figs. 4A, B).

What might be the consequences, if any, of the substantial up-regulation of c-Myc protein? The mechanism of cross-modulation of the AR-medi-

ated signalling pathway involves, among others, the interaction of AR with diverse proteins, including transcription factors, as an important means of positive or negative regulation of gene expression and cell fate (e.g. Matsuda *et al.*, 2001). Therefore, the present results support our working hypothesis that the cross-talk between the androgen- and HGF-activated signalling pathways might be regarded as an interaction between AR and c-Myc transcription factors for *odc* gene or their competition for common coregulators (Dudkowska *et al.*, 2001). Validation of this hypothesis will require further studies.

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