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ORIGINAL ARTICLE

# FGF-2 and HGF reverse abiraterone's effect on intracellular levels of DHT in androgen-dependent and androgen independent prostate cancer cell lines

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## Summary

***Purpose:*** *Growth factors such as fibroblast growth factor 2 (FGF-2) and hepatocyte growth factor (HGF) appear at high levels in prostate cancer (PC). Abiraterone is an androgen biosynthesis inhibitor which is currently in use as a standard treatment in clinics to impair tumor growth. Development of resistance to anticancer therapies is unfortunately a very common feature of cancer cells that threatens the patient lives. This study aimed to investigate whether FGF-2 and HGF act as a possible resistant mechanism to the abiraterone activity on the androgen synthesis pathway in PC.*

***Methods:*** *The intracellular levels of 17-OH progesterone and dihydrotestosterone (DHT) were determined by enzyme immunoassays in cell lysates of LNCaP and PC3 PC cells upon co-treatment of cells with abiraterone and FGF-2 or HGF.*

***Results:*** *Abiraterone treatment resulted in significant reduction in the intracellular levels of 17-OH progesterone and DHT in both LnCap and PC3 cells. FGF-2 and HGF were found to decrease the intracellular levels of 17-OH progesterone in both cell lines, whereas HGF alone was found to increase the intracellular levels of DHT only in PC3 cells. However, the simultaneous exposure of cells to abiraterone and FGF-2 or HGF was found to result in an increase in the intracellular levels of DHT, while it did not result in changes in the intracellular levels of 17-OH progesterone.*

***Conclusion:*** *These findings suggest that FGF-2 and HGF may act as an escape mechanism, aiding the development of resistance to abiraterone by restoring intra-tumoral androgen synthesis that may contribute to disease progression.*

***Key words:*** *abiraterone, DHT, FGF-2, HGF, prostate cancer, 17-OH progesterone*

## Introduction

Prostate cancer (PC) is an increasingly important health issue globally, being the most common primary cancer (29% of new estimated cases in the U.S.) and the second most common cause of cancer-related deaths (9%) among males [1]. At the time of initial diagnosis, PC is hormone-sensitive but becomes hormone-refractory during progression. One of the standards of care for patients with PC is androgen deprivation therapy. However, all patients eventually develop castration-resistant prostate cancer (CRPC), with less than 20% of men surviving beyond 3 years [2]. Abiraterone, a derivative of pregnenolone, is an approved steroidogenesis inhibitor of the androgen synthesis pathway. Abiraterone functions by blocking CYP17A1 activity (17α- Hydroxylase and C17,20 -lyase), thus preventing the conversion of pregnenolone to dihydrotestosterone (DHT) [3,4]. This action of abiraterone is

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expected to inhibit the production of androgens in peripheral tissues as well as the production of precursors needed for intra-tumoral androgen synthesis. However, one-third of patients display a primary resistance to abiraterone treatment and many of the patients who initially responded to abiraterone treatment are characterized by progression to metastatic CRPC (mCRPC), which has not been fully elucidated [5].

In many studies, protein tyrosine kinases are shown to have a key role in tumor and microenvironment functions. Fibroblast growth factor (FGF) and hepatocyte growth factor (HGF) are expressed in a wide range of tissues and associated with a number of normal and pathological conditions. Interestingly, both factors have been linked to the initiation and progression of PC and other malignancies [6]. Previous studies have demonstrated that FGF-2 is present at higher concentrations in cancerous prostate tissue (almost 2.5-fold), as compared to normal prostate tissue [7]. On the other hand, HGF signaling through its tyrosine kinase receptor (TKR), c-MET, has been shown to be overactivated in cancer cells and is highly associated with cancer cell growth, matrix invasion, and cell motility [8,9]. c-MET has been found to be overexpressed in primary PC as well as in subsequent bone metastasis and to be associated with the development of CRPC. An increasing number of basic, translational, and clinical studies suggests the implication of the HGF signaling in the progression of PC [10].

Taking into account the expressions of these growth factors in PC and the fact that several pathways that may play a role in the development of abiraterone resistance involve re-activation of androgen synthesis, we investigated whether FGF-2 and/or HGF may alter the action of abiraterone on the androgen synthesis pathway. We thus used LNCaP and PC3 cell lines as *in vitro* models of androgen-dependent (AD) and androgen-independent (AI) PC, respectively, and investigated the changes in the intracellular levels of 17-OH progesterone and DHT upon co-treatment of cells with abiraterone and FGF-2 or HGF.

## Methods

*Cell lines and culture*

Human LNCaP and PC3 PCa cell lines were purchased from the European Collection of Animal Cell Cultures (ECACC, Health Protection Agency, Salisbury, UK). Both cell lines were cultured in RPMI 1640 (Gibco, Thermo Fischer Scientific, Waltham, MA, USA). The medium was supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco, Thermo Fischer Scientific, Waltham, MA, USA), 1% L-glutamine (Gibco, Thermo Fischer Scientific, Waltham, MA, USA), and 1% penicillin/streptomycin solution (Gibco, Thermo Fischer Scientific, Waltham, MA, USA). All cultures were maintained in a humidified 5% $CO_2$ incubator at 37°C. For all experiments, Neprilysin Activity Assay (NEP) specific activity was measured [11] and low-passage LNCaP cells were used. Cells were incubated in serum-free media for 24 h before each experiment. All other incubation protocols were stated in figure legends.

*Reagents*

Abiraterone acetate was provided by Janssen-Cilag (Belgium) that also funded this study. A stock solution (5.7 mM) of abiraterone was prepared in dimethylsulphoxide (DMSO) stored at -80°C until further use. Stock solution was appropriately diluted in culture medium (see Cell line and culture above). Cell cultures receiving only the corresponding amount of DMSO were used as negative controls. FGF-2 and HGF were purchased from Biorbyt, UK and diluted in normal saline and then again stored until further use.

*Quantification of DHT and 17-OH Progesterone*

LNCaP and PC3 cells were plated in flasks and incubated with the indicated chemicals. Total lysates were prepared using a buffer containing 10 mM Tris-HCl, 50 mM EDTA, 150 mM NaCl, 1% Triton-X, and 10% Glycerol for ELISA purposes. 17-OH progesterone and DHT were determined in cell lysates using ELISA kits (IBL International, Hamburg, Germany) according to manufacturer's instructions. Intra-assay coefficients of variation for the measurement of 17-OH progesterone and DHT levels were 2.8-4.9% and 4.75-6.25% respectively; inter-assay coefficients of variation were 5.8-9.2% and 6.79-7.47%, respectively. The lowest detection limits of the assays for 17-OH progesterone and DHT were 0.03 ng/ml and 6 pg/ml, respectively.

**Table 1.** The intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cells treated with FGF-2 or HGF

| | *LNCaP cells* | | | *PC3 cells* | | |
|---|---|---|---|---|---|---|
| | *CTL* | *FGF-2* | *HGF* | *CTL* | *FGF-2* | *HGF* |
| 17-OH progesterone (ng/mg) | 0.462±0.022 | 0.342±0.011** | 0.387±0.02** | 0.32±0.025 | 0.245±0..016** | 0.267±0.033** |
| DHT (pg/mg) | 15.75±0.478 | 18.13±0.965ns | 13.81±0.484* | 11.48±0.815 | 12,1±0.695ns | 14±0.627** |

Values are expressed as ng/mg of total protein for 17-OH progesterone and pg/mg for DHT and represent the mean±SEM of four independent experiments (*p<0.05, **p<0.01, – compared to control (CTL)

*Statistics*

Statistical differences between the two groups of data were assessed using the unpaired t-test in the GraphPad Prism version 5.04 software. P<0.05 was deemed statistically significant (*p<0.05; **p<0.01; ***p<0.001).

## Results

*Effect of FGF-2 and HGF on the intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cells*

Exposure of LNCaP and PC3 cells to 10 ng/ml of FGF-2 for 24 h resulted in a statistically significant reduction in the intracellular levels of 17-OH progesterone, approximately 26% for LNCaP (p<0.01) and 23% for PC3 cells (p<0.01) (Table 1, Figure 1A). On the other hand, FGF-2 had no significant effect on the intracellular levels of DHT in both cell lines (Table 1, Figure 1B). Treatment of cells with HGF (33 ng/ml) for 24 h also caused a statistically significant decrease in the intracellular levels 17-OH progesterone in LNCaP and PC3 cells, approximately 16% for LNCaP (p<0.01) and 17.5% for PC3 cells (p<0.01) (Table 1, Figure 1A). Additionally, the intracellular levels of DHT in LNCaP cells treated with HGF were slightly decreased, but in PC3 cells treated with HGF were significantly increased compared to the control (Table 1, Figure 1B).

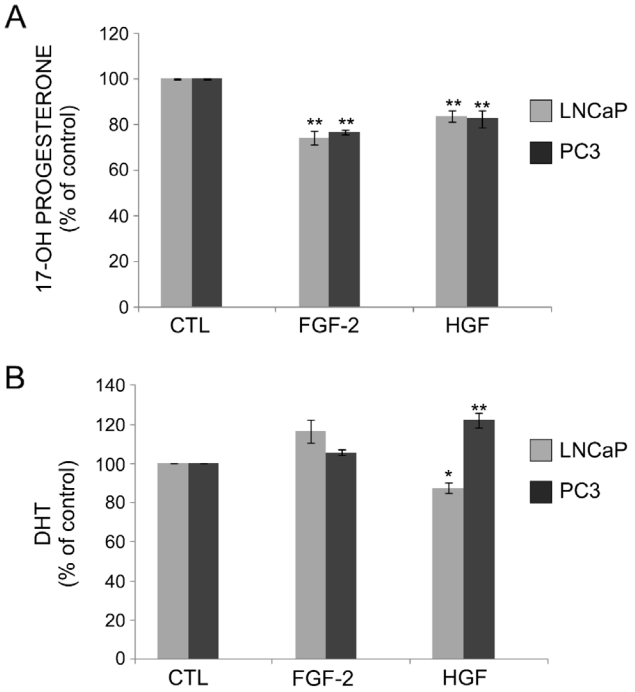


**Figure 1.** Effect of FGF-2 and HGF on the intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cells. Cells were treated with FGF-2 (10 ng/ml) or HGF (33 ng/ml) for 24 h and the intracellular levels of **(A)** 17-OH progesterone and **(B)** DHT were measured in cell lysates. Results are shown as percent of 17-OH progesterone or DHT levels in relation to control and represent the means of four independent experiments performed in duplicate (±s.e.m) (*p<0.05, **p<0.01 – compared to control (CTL).

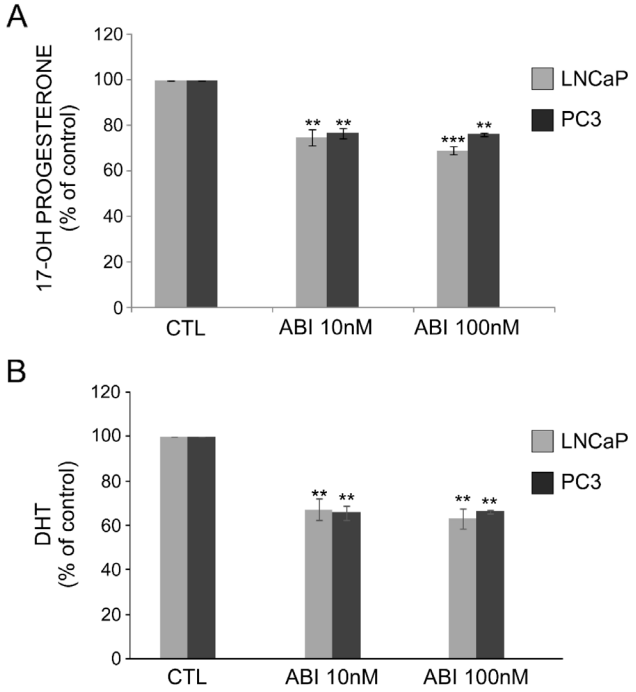


**Figure 2.** Effect of abiraterone on intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cells. Cells were treated with abiraterone for 24 hours and the intracellular levels of **(A)** 17-OH progesterone and **(B)** DHT were measured in cell lysates. Results are shown as percent of 17-OH progesterone or DHT levels in relation to control and represent the means of four independent experiments performed in duplicate (± s.e.m) (**p<0.01, ***p< 0.001 – compared to control (CTL).

**Table 2.** The intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cells treated with abiraterone

| | *LNCaP cells* | | | PC3 cells | | |
|---|---|---|---|---|---|---|
| | *CTL* | *ABI 10nM* | *ABI 100nM* | *CTL* | *ABI 10nM* | *ABI 100nM* |
| 17-OH progesterone (ng/mg) | 0.462±0.022 | 0.347±0.026** | 0.32±0.021*** | 0.32±0.025 | 0.245±0.015** | 0,245±0,017** |
| DHT (pg/mg) | 15.75±0.478 | 10.63±0.688** | 10±0.912** | 11.48 ± 0.815 | 7.5±0.288** | 7,705±0,554** |

Values are expressed as ng/mg of total protein for 17-OH progesterone and pg/mg for DHT and represent the mean±SEM. of four independent experiments (**p<0.01, ***p< 0.001 – compared to control (CTL)

*Effect of abiraterone on the intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cells*

Using the same experimental approach, LNCaP and PC3 cells were exposed to 10 nM and 100 nM of abiraterone for 24 h in serum-free media. Both concentrations of abiraterone caused statistically significant reduction in the intracellular levels of 17-OH progesterone and DHT compared to the controls (Table 2). More specifically, exposure of cells to 10 nM of abiraterone triggered a decrease in the intracellular levels of 17-OH progesterone by 25% ($p<0.01$) in LNCaP cells and 24% ($p<0.01$) in PC3 cells compared to the corresponding controls (Figure 2A). Same results were observed when cells were exposed to 100 nM of abiraterone (Figure 2A). In addition, exposure of cells to 10 nM of abiraterone resulted in a more marked decrease in the intracellular levels of DHT, i.e. 33% reduction in LNCaP cells ($p<0.01$) and 35% in PC3 cells compared to the controls ($p<0.01$), as shown in Figure 2B. Again, the effect was same when cells were treated with 100nM of abiraterone. In this case, DHT levels were again reduced by 37% in LNCaP cells ($p<0.01$) and 33% in PC3 cells compared to the control ($p<0.01$) (Figure 2B). As both concentrations of the abiraterone (10 nM and 100 nM) had same effect on the intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cell lines, we used only 10 nM abiraterone in the next experiments.

*Effect of co-treatment with abiraterone and FGF-2 or HGF on the intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cells*

In order to investigate whether FGF-2 and/or HGF may alter the action of abiraterone on intracellular levels of 17-OH progesterone and DHT, cells were exposed to FGF-2 (10 ng/ml) or HGF (33 ng/ml) with 10 nM of abiraterone for 24 h. The co-exposure of cells to abiraterone and FGF-2 resulted in a statistically significant increase only in the intracellular levels of DHT (Figure 4), while no changes in the intracellular levels of 17-OH

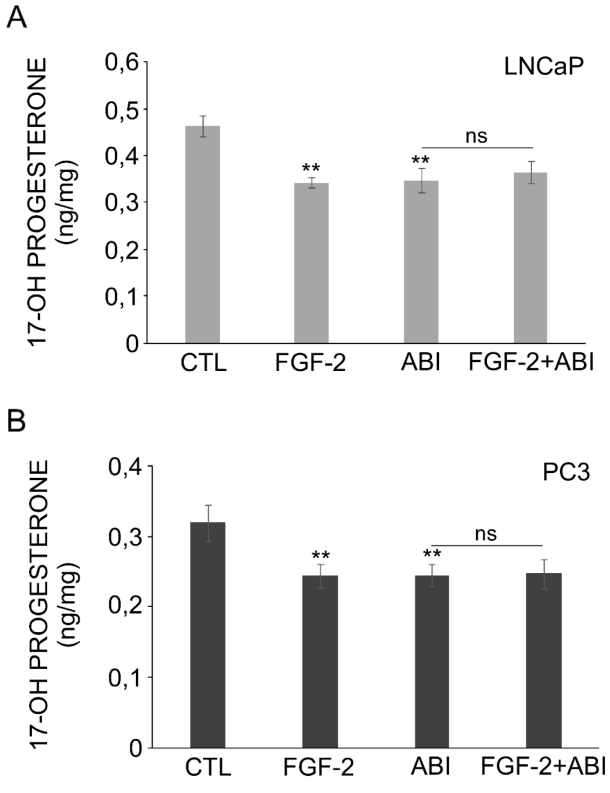


**Figure 3.** Effect of co-exposure of FGF-2 and abiraterone on intracellular levels of 17-OH progesterone in LNCaP and PC3 cells. Cells were exposed to FGF-2 (10 ng/ml) and abiraterone (10 nM) for 24 h and the intracellular levels of 17-OH progesterone were measured in **(A)** LNCaP and **(B)** PC3 cell lysates. Values are expressed as ng/mg of total protein and represent the mean±s.e.m. of four independent experiments performed in duplicate (**$p<0.01$ – compared to control (CTL), ns: not statistically significant abiraterone versus co-exposure abiraterone + FGF-2).

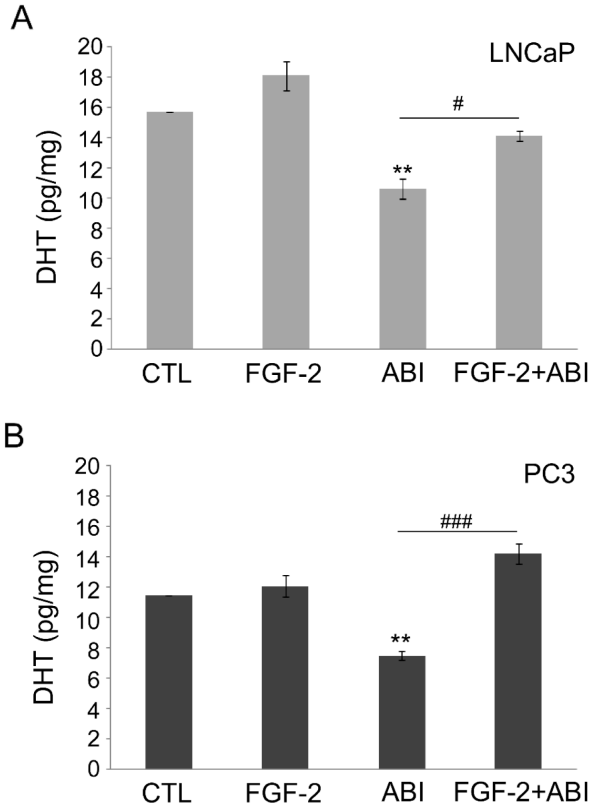


**Figure 4.** Effect of co-exposure of FGF-2 and abiraterone on intracellular levels of DHT in LNCaP and PC3 cells. Cells were exposed to FGF-2 (10 ng/ml) and abiraterone (10 nM) for 24 h and the intracellular levels of DHT were measured in **(A)** LNCaP and **(B)** PC3 cell lysates. Values are expressed as pg/mg of total protein and represent the mean±s.e.m. of four independent experiments performed in duplicate (**$p<0.01$ – compared to control (CTL), $^{\#}p<0.05$, $^{\#\#\#}p<0.001$: abiraterone versus co-exposure abiraterone + FGF-2).

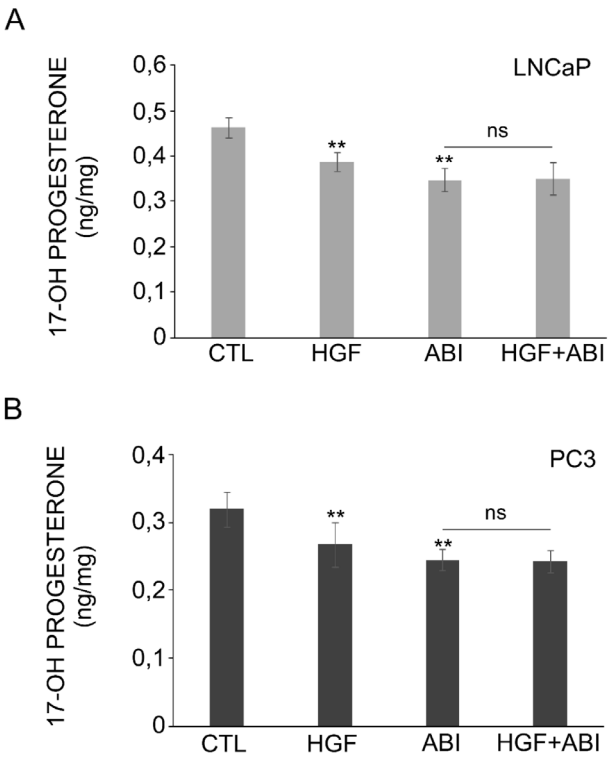


**Figure 5.** Effect of co-exposure of HGF and abiraterone on intracellular levels of 17-OH progesterone in LNCaP and PC3 cells. Cells were exposed to HGF (33 ng/ml) and abiraterone (10 nM) for 24 h and the intracellular levels of 17-OH progesterone were measured in **(A)** LNCaP and **(B)** PC3 cell lysates. Values are expressed as ng/mg of total protein and represent the mean±s.e.m. of four independent experiments performed in duplicate (**p<0.01– compared to control (CTL), ns: not statistically significant abiraterone versus co-exposure abiraterone + HGF).

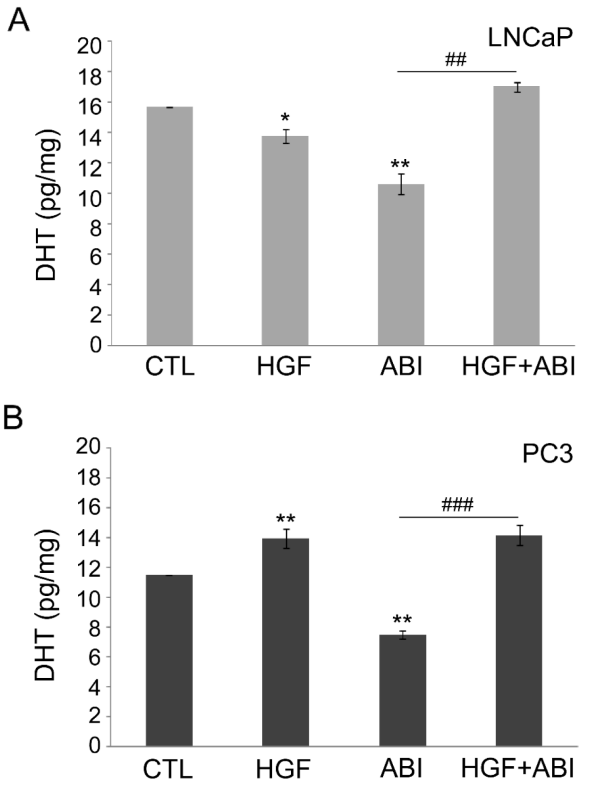


**Figure 6.** Effect of co-exposure of HGF and abiraterone on intracellular levels of DHT in LNCaP and PC3 cells. Cells were exposed to HGF (33 ng/ml) and abiraterone (10 nM) for 24 h and the intracellular levels of DHT were measured in **(A)** LNCaP and **(B)** PC3 cell lysates. Values are expressed as pg/mg of total protein and represent the mean±s.e.m. of four independent experiments performed in duplicate (*p<0.05, **p<0.01 – compared to control (CTL), ##p<0.01, ###p<0.001: abiraterone versus co-exposure abiraterone + HGF).

progesterone (Figure 3) were observed in both cell lines compared to the cells exposed to abiraterone alone. More specifically in LNCaP cells, the co-treatment with FGF-2 and abiraterone triggered an increase in DHT levels up to 23% (p<0.05), while a more marked increase (up to 60%) was observed in PC3 cells compared to cells exposed to abiraterone alone (Figure 4A and B, respectively).

DHT intracellular levels were further determined under co-treatment of cells with 10 nM of abiraterone and HGF. Similar to the action of FGF-2, the co-exposure of cells to abiraterone and HGF did not alter the intracellular levels of 17-OH progesterone compared to the cells exposed to abiraterone alone (Figure 5A,B). However, in LNCaP cells, abiraterone and HGF co-treatment caused a statistically significant increase in the intracellular levels of DHT up to 41% (p<0.01) compared to that of abiraterone alone (Figure 6A). In PC3 cells, the addition of HGF in abiraterone-exposed cells led to a rise by 57% in DHT levels compared to that of abiraterone alone (p<0.001) (Figure 6B).

Thus, our results demonstrated that FGF-2 and HGF may reverse the effect of abiraterone on the intracellular levels of DHT.

## Discussion

Abiraterone acetate (AA) was approved for the treatment of mCRPC in 2011 and for the treatment of metastatic high-risk castration-sensitive PC in 2018 [12]. Unfortunately, considerable evidence from both experimental and clinical studies suggests that mCRPC patients develop resistance to abiraterone therapy. Our results suggest that FGF-2 and HGF have the ability to change the intracellular levels of 17-OH progesterone and DHT in AD- and AI-PC cell lines, thereby altering the abiraterone-mediated inhibition on the two above-steroid hormones, more typically the late-phase steroid hormone (DHT).

Abiraterone is designed to suppress tumor growth by inhibiting CYP17A1 which is the key enzyme required for androgen synthesis from cholesterol. By blocking CYP17A1 activity, abiraterone

prevents the conversion of pregnenolone or progesterone to DHT via 17-OH progesterone [13]. In our findings, both concentrations of the abiraterone (10 nM and 100 nM) resulted in a decrease in the intracellular levels of 17-OH progesterone and DHT in LNCaP and PC3 cell lines. The effect was not concentration-dependent, although the two concentrations were one log different, suggesting that, at least, under the experimental conditions tested the activity of AA plateaus at 10 nM.

Studies have identified biologically relevant levels of FGF-2 in normal prostate mesenchyme, whereas FGFRs are expressed in prostatic epithelium [6]. Dysregulated expression of FGF-2 and FGF receptors leads to constitutive activation of multiple downstream pathways and induce many mechanisms in PC progression, including survival, mitogenesis, differentiation, motility/invasiveness, and angiogenesis [14,15]. On the other hand, HGF is primarily expressed in cells of mesenchymal origin and bone metastatic PC cells, whereas c-MET is expressed in epithelial and endothelial cells [16,17]. Dysregulation of HGF and/or c-MET expression has been observed in PC and is often correlated with poor prognosis [18,19]. Patients with mCRPC present with higher serum HGF levels and have poorer outcomes compared to patients with localized tumors or other benign lesions [20-22]. However, in the literature there is limited evidence regarding the effect of FGF-2 and HGF on androgen synthesis in PC. Our data show that FGF-2 and HGF alter intracellular levels of 17-OH progesterone and DHT in both AD- (LNCaP) and AI- (PC3) PC cell lines. More specifically, FGF-2 was found to decrease 17-OH progesterone, but it had no significant effect on DHT in both cell lines. On the other hand, HGF reduced 17-OH progesterone in both cell lines as well as reducing DHT in LNCaP cell line; however, unexpectedly, HGF increased DHT in the PC3 cell line. Thus, for the first time, we show that FGF-2 and HGF are implicated in the processes of the androgen regulation and downregulate 17-OH progesterone. Previous study has shown that HGF may be capable of stimulating the proliferation of human granulosa cell line and suppressing progesterone synthesis via mitogen-activated protein kinase (MAPK) pathway. More specifically, authors demonstrated that HGF suppressed the expression of forskolin-induced steroidogenic acute regulatory protein (StAR), which is a key regulator in steroidogenesis and androgen synthesis and this effect may also interpret to our observations [23].

These effects of the two growth factors in steroidogenesis prompted us to further examine whether they may affect androgen deprivation caused by abiraterone. Our findings suggest for the first time that FGF-2 and HGF raise intracellular levels of DHT compared to those in the cells exposed to abiraterone alone, suggesting that FGF-2 and HGF promote the intracellular synthesis of DHT, without affecting 17-OH progesterone synthesis despite the presence of abiraterone. These results are in accordance with a study supporting that IGF-2 play an important role in increasing *de novo* steroidogenesis in PC cells [24]. Also, several studies have shown that there are alternative pathways that can promote androgen synthesis in CRPC and can play an important role in disease progression. Chang et al reported that the dominant pathway to DHT synthesis in CRPC follow an alternative route that bypasses testosterone [25]. In addition, another previous study has shown that androgen deprivation promotes intra-tumoral synthesis of DHT from androgen metabolites in PC [26]. Accordingly, this underlines the possibility that the increase in DHT in the presence of FGF-2 or HGF, despite the anti-androgenic synthesis of abiraterone in our PC cell lines, may be due to the acceleration of the back conversion of DHT from androgen derivates.

Previous clinical studies have shown that c-MET expression is deregulated in different kinds of cancers and that the evaluation of c-MET expression could be helpful for prognostic or therapeutic stratification of late-stage PC, although not yet in clinical practice [27]. c-MET and VEGFR2, which are targets for cabozantinib, have been associated with development of castration resistance in patients. Clinical trials that evaluate the combination of abiraterone (with prednisone) and cabozantinib are ongoing and some data regarding these trials have been released [28]. Consequently, our findings are in accordance with the literature as the high levels of HGF in PC act as a resistant mechanism to the action of abiraterone. In addition to cabozantinib, dovitinib, an oral multitargeted receptor tyrosine kinase (RTK) inhibitor, is also under evaluation in patients with CRPC [29].

In conclusion, our findings suggest that FGF-2 and HGF may affect androgen synthesis and contribute to the appearance of resistance in androgen-deprived prostate cancer. Further *in vitro* and *in vivo* studies on FGF or HGF inhibitors with abiraterone aiming to shed more light on the potential role of abiraterone in advanced prostate cancer are obviously required.

## Funding

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## Conflict of interests

The authors declare no conflict of interests.

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