Editorial

Targeting the glucocorticoid receptor for a combinatory treatment strategy for castration resistant prostate cancer?

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Comment on: Puhr M, Hoefer J, Eigentler A, *et al.* The Glucocorticoid Receptor Is a Key Player for Prostate Cancer Cell Survival and a Target for Improved Antiandrogen Therapy. Clin Cancer Res 2018;24:927-38.

Received: 02 February 2018; Accepted: 08 March 2018; Published: 21 March 2018.

doi: 10.21037/amj.2018.03.07

View this article at: http://dx.doi.org/10.21037/amj.2018.03.07

Castration resistant prostate cancer (CRPCa)

Prostate cancer (PCa) ranks the most frequently diagnosed male cancer in the Western world (1). It develops first as an androgen-dependent tumor in which androgens promote the growth of the PCa cells. Eventually, it develops into a castration resistant stage that no longer depends on androgens. Nevertheless, these PCa cells express the androgen receptor (AR) and the tumor proliferation remains dependent on the AR-signaling (2), but the AR-signaling exhibits some adaptive responses to the therapy (3). Since AR plays a leading role in PCa progression, targeting the AR-signaling by androgen deprivation therapy (ADT) and treatment with AR-antagonists, such as enzalutamide or androgen synthesis inhibitor (abiraterone), are generally applied to patients with CRPCa (4). Despite the initial benefits, these therapeutic options will eventually reach the limitation due to a rapid development of drug resistance of CRPCa and adaptive responses of the AR-signaling (3,5-8), suggesting that identifying pathways that mediate resistance are important for developing novel, back up or combinatorial strategies for PCa therapy.

The glucocorticoid receptor (GR) in PCa

In addition to ADT in combination with anti-androgens, treatment with glucocorticoids (i.e., prednisone, hydrocortisone or dexamethasone) is used for metastatic PCa patients for decades, due to the benefit in inhibition of the adrenal androgen production (9-11). However, whether the long-term treatment of glucocorticoids is really beneficial for PCa patients emerges as controversial. According to the recent analyses of therapy resistance of PCa, it is emphasized that glucocorticoids and the GR mediate therapy resistance to PCa and are key players to bypass AR-blockade (12-14).

GR and AR are closely related both structurally and at amino acid sequence level. Both receptors act as hormone-activated transcription factors and belong to the steroid receptor subfamily of the nuclear hormone receptor superfamily. Unlike AR, the GR is expressed in nearly all cell types in the human body and regulates a wide range of biological processes including metabolism, immune responses, reproduction, and cell fate decisions. Importantly, the GR can control programs regulating cell proliferation, differentiation, and apoptosis independently of the AR (15). However, based on their functional similarities, it would be interesting to know how much the AR-signaling overlaps with the GR-signaling, importantly which AR-functions can be substituted by the GR in CRPCa, and what would be the consequences for PCa patients.

Both GR- and AR-actions are induced by binding of their cognate ligands, which induces a conformational change of the receptors, leading to release of the receptors from the heat shock factors. The ligand-bound receptors then translocate into the nucleus where they bind to similar response elements of their target genes and mediate transcriptional activation or repression. Similar to AR, the GR regulates the transcription of target genes up to 10–20% of the human genome (16). Therefore, it is not

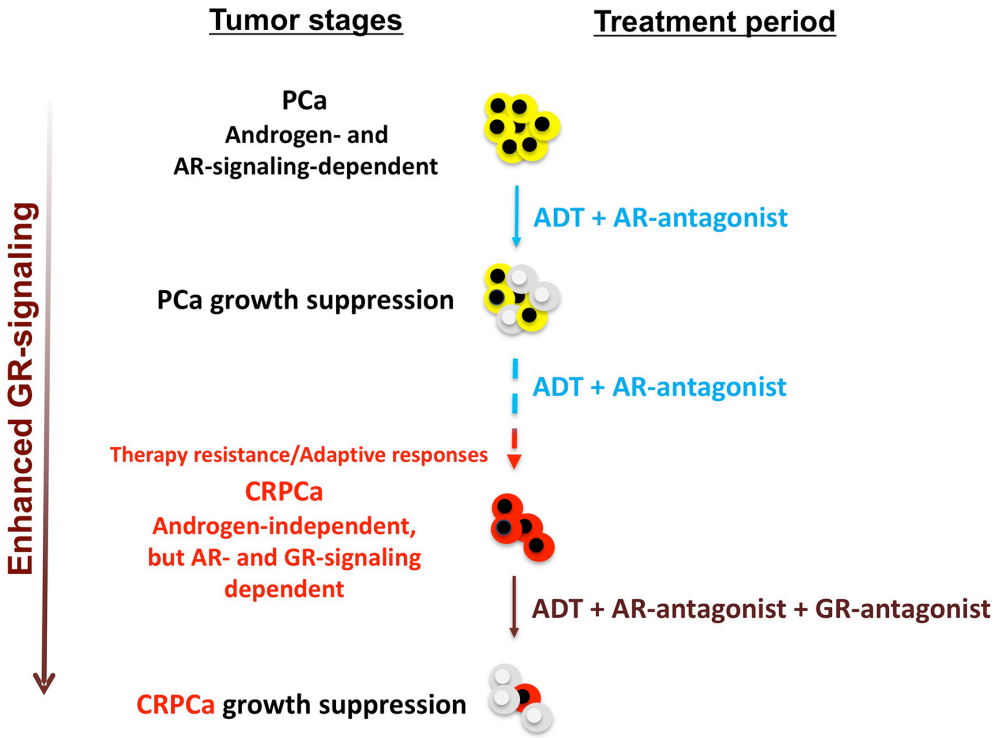

Figure 1 Model of tumor development and adaptation of the AR-signaling along with increasing GR-activity towards therapy resistance. Tumor evolution by selection and adaptive responses of AR-signaling renders the initial androgen-dependent PCa to CRPCa. Similarly, therapy resistance towards second generation AR-antagonists and/or abiraterone occurs despite the presence of the AR. Coincidently, the expression and activity of the GR are increased. Inhibition of both signaling pathways of AR and GR, such as by specific antagonists is suggested to have a beneficial role combating CRPCa therapy resistance. CRPCa, castration resistant prostate cancer.

surprising that GR and AR share a significant overlap in their transcriptomes and also protein interactomes (12,17), thus, affecting similar downstream cellular signaling pathways. These strengthen the possibility that GR may be able to compensate the AR-signaling in PCa when AR is inhibited by ADT and anti-androgens, or even in the absence of the AR.

Adaptive response and anti-androgen therapy resistance through the GR

The current publication in *Clinical Cancer Research* by Puhr *et al.* describes the correlation between GR expression and relapse of patients' progression-free survival (18). These authors showed that those patients with intermediate-high GR expression had a significantly reduced progression-free survival compared to patients with low GR expression. Furthermore, the GR immunoreactivity suggests that GR expression is reduced in primary PCa compared to benign tissues and is restored in metastases PCa. The results are consistent with earlier published studies revealing that the expression of GR is decreased in PCa tissues compared to normal prostate tissues, but up-regulated in CRPCa (12,19). These observations provide a hint that GR-signaling activities are also enhanced from androgen-dependent PCa towards the CRPCa stage (*Figure 1*).

Consistently, Puhr *et al.* has observed an interesting inverse expression of GR and AR in benign and PCa cell models (18), indicating a cross-talk in the expression levels between these two receptors and may suggest a compensatory mechanism (20). It is suggested that in therapy resistant PCa, the increased expression of GR seems to be an adaptive response of PCa cells to overcome the pharmacological inhibition of AR (*Figure 1*). In this context, those cells may evade the AR-controlled proliferation blockade by enhancing GR-signaling pathways as selection-

based tumor evolution.

Targeting the GR in PCa cells

Mechanistically, Puhr *et al.* revealed that the GR is a key player for PCa cells survival (18). Knockdown of GR in various human PCa cell lines resulted in significantly reduced cell proliferation and impaired the ability to form 3D-spheroids. Moreover, pharmacological inhibition of GR with the GR-antagonist, RU-486, also decreased the PCa cell proliferation and 3D-spheroid formation, despite the fact that RU-486 is also an anti-progestin. The specificity of the GR-antagonist is due to the fact that the progesterone receptor is not expressed in the employed PCa cell line models. Surprisingly, these authors observed the reduction of both the GR and AR protein levels upon inhibition of GR by RU-486.

In addition to previous studies which described increased GR levels as one of the key factors to bypass the AR blockade (12-14). The result of Puhr *et al.* suggests that the elevated GR expression is a general consequence of an adaptive response by both ADT and anti-androgen treatment (18). Authors generated many therapy resistant human PCa cell lines by long-term treatment with either abiraterone or enzalutamide (7,18). Under this selection force, both the GR mRNA and protein levels increase in the resistant cells. Furthermore, a step-wise increase of GR expression at different passages of long-term abiraterone treated cells was observed by the authors. It is therefore suggested that GR induction is a frequent survival mechanism for PCa cells under endocrine-therapy. Importantly, the overexpressed GR in resistant cells is functionally active, since the significant increase of GR target gene expression was observed after GR-agonist treatment (18). These evidences support the notion that long-term treatment of glucocorticoids during anti-androgen therapy could be critical for patient, especially under ADT and with the combination of anti-androgen treatment.

Inhibition of both GR- and AR-signaling as a combinatory treatment option for therapy resistant PCa

In the current discussed study, Puhr *et al.* revealed that GR is an interesting target for improving anti-androgen therapy (18). Inhibition of GR expression or activity in addition to inhibition of AR-signaling might be useful for PCa treatment. A previous study demonstrated that enzalutamide resistance is conferred by treatment with the GR-agonist, dexamethasone, whereas a GR antagonist restored the enzalutamide sensitivity (12). In line with this, Puhr *et al.* revealed that the combined treatment of RU-468 and abiraterone reduces cell number and significantly diminished 3D-spheroid growth in both androgen-dependent and independent PCa cells. Please note that abiraterone binds and inhibits CYP17, thus, reducing androgen production, but it can also directly bind to the AR and acts as an AR-antagonist with a potency similar to enzalutamide (21,22). Surprisingly, even single treatment with the GR-antagonist, RU-486, massively reduced the cell proliferation, cell number and viability as well as impaired 3D-spheroid formation in abiraterone- or enzalutamide-resistant PCa cells. Moreover, authors described that the combination of RU-486 and abiraterone was even more effective than abiraterone alone (18), indicating that GR inhibition enhances the anti-tumor effects of abiraterone.

However, which type of GR-inhibitor or antagonist is favorable to apply to patients must be carefully evaluated, including a preferable high GR-specificity, knowledge about optimal dosage and side-effects. Ideally, the identification of a PCa-specific GR-antagonist would be very beneficial (*Figure 1*). As an example, the current discussed study conducted by Puhr *et al.* with the treatment of RU-486 in *in vitro* revealed an impressive beneficial effect (18). However, RU-486 has already been tested in clinical trials and showed limited activity in CRPCa patients (23). The patients treated with RU-486 interestingly showed marked increase in adrenal androgens, testosterone, and dihydrotestosterone.

Concerning GR-specific antagonist, it has been reported that two novel non-steroidal selective GR-modulators, CORT118335 and CORT108297, have the ability to block the GR activity in PCa and slow CRPCa progression (24). In contrast to RU-486, both CORT118335 and CORT108297 potentially inhibit GR activity and slow the progression of PCa without affecting AR signaling by inhibiting only the GR transcriptional activity. Moreover, these compounds decrease GR-mediated tumor cell survival after AR blockade. Importantly, in *in vivo* mouse model system, CORT118335 and CORT108297 significantly inhibit CRPCa progression in high GR-expressing xenograft models, demonstrating the therapeutic potential of these compounds for further evaluation trials, thus, providing us more therapeutic options and possibilities to

apply for PCa patients.

Conclusions

Taken together, the results of Puhr *et al.* provide novel insights into the adaptive response of ADT and anti-androgen therapy. GR levels as a key player for resistance to current PCa hormone therapy are induced. Also, treatment with anti-androgens induces the GR expression in PCa cells. The high expression of GR is correlated with the reduction of relapse patients' progression-free survival. Yet, the treatment with a GR-antagonist significantly inhibits the anti-androgen resistant PCa cells progression, thus, supporting the idea that inhibition of the GR pathway, in addition to the AR-signaling, is a potential backup strategy for PCa therapy. However, the GR-specificity, the PCa-tissue-specificity, dosage and side-effects of the candidate GR-modulators in medications must be carefully evaluated for further development of efficient CRPCa therapy.

Acknowledgements

Funding: This work was supported by the German Academic Exchange Service (DAAD) to TP.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xiao Li (Department of Urologic Surgery, The Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.03.07). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2018.03.07
Cite this article as: Pungsrinont T, Baniahmad A. Targeting the glucocorticoid receptor for a combinatory treatment strategy for castration resistant prostate cancer? AME Med J 2018;3:41.

