https://doi.org/10.48047/AFJBS.6.15.2024.5587-5603

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

The Analysis Study of Role of Glucocorticoids in Treatment of Prostate Cancer : A Comprehensive Systematic Review

[1] Muhammad Ridwan Musa, [2] Muhammad Yatsrib Semme

[1] Arifin Nu'mang Rappang Regional General Hospital, Sidenreng Rappang Regency, South Sulawesi, Indonesia
[2] Wisata Universitas Indonesia Timur General Hospital, Makassar City, South Sulawesi, Indonesia

Correspponding Author : Muhammad Ridwan Musa., MD. Arifin Nu'mang Rappang Regional General Hospital, Ahmad Yani Street No.01. Panca Rijang.Sidenreng Rappang Regency, South Sulawesi, Indonesia. Email: muhammadridwanmusa@gmail.com

Volume 6, Issue 15, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 05 Sep 2024

doi: 10.48047/AFJBS.6.15.2024.5587-5603

ABSTRACT

Background: Glucocorticoids are essential for maintaining homeostasis and regulating physiological functions, including metabolism, cardiovascular health, and immune responses. They are commonly used in treatment for prostate cancer, but their mechanisms underlying castration-resistant prostate cancer (CRPC) remain unclear. Glucocorticoids can stimulate cell death and decrease inflammation, but their effects on prostate cancer cells remain unclear. **Methods:** Following PRISMA 2020 guidelines, this systematic review focused exclusively on full-text articles published in English between 2014 and 2024. To ensure the inclusion of high-quality sources, editorial pieces and review articles were excluded unless they were accompanied by a DOI. The literature search was conducted using several reputable databases, including ScienceDirect, PubMed, and SagePub, to comprehensively gather relevant studies. **Result:** The study conducted a comprehensive review of over 1,000 publications sourced from reputable databases, including ScienceDirect, SagePub, and PubMed. Following an initial screening, eight publications were identified as warranting more in-depth analysis. Consequently, a thorough review of these selected studies was performed to ensure a detailed and rigorous evaluation. **Conclusion:** Glucocorticoid receptors play a crucial role in the treatment of prostate cancer, affecting normal cell proliferation and accelerating tumor growth. Elevated expression of these receptors can induce drug insensitivity, leading to potential adverse effects. Clinical studies are needed to explore the feasibility of reducing GC use during chemotherapy and abiraterone treatment.

Keyword: Glucocorticoid, prostate cancer, chemotherapy

INTRODUCTION

Glucocorticoids, secreted by the adrenal glands, are crucial for maintaining homeostasis and regulating various physiological functions, including metabolism, cardiovascular health, immune responses, and mood.[1] Due to their potent anti-inflammatory and immunosuppressive properties, synthetic glucocorticoids are extensively prescribed for treating inflammatory and autoimmune conditions such as asthma, allergies, sepsis, rheumatoid arthritis, ulcerative colitis, and multiple sclerosis. They also prevent organ transplant rejection and manage lymphoid malignancies, including leukemias, lymphomas, and myelomas.[2,3] However, long-term use of synthetic glucocorticoids can lead to significant adverse effects, including osteoporosis, diabetes, obesity, glaucoma, growth retardation in children, and hypertension.[4]

Globally, prostate cancer ranks among the top 10 most prevalent malignancies and presents a significant risk to human well-being. Among men, it is the most commonly detected malignancy in 112 countries in 2018.[5] Systemic androgen deprivation therapy is a fundamental treatment for individuals with advanced prostate cancer and serves as the foundation for innovative combination therapy. Nevertheless, even with a median treatment duration of 18-24 months, the majority of patients will develop castration-resistant prostate cancer (CRPC).[6] The mechanisms underlying the development of CRPC are intricate. Most investigations have concentrated on mechanisms that rely on androgen receptors (ARs).[7]

Glucocorticoids are commonly used in cancer treatment for lymphoid malignancies to stimulate cell death and as a co-medication with chemotherapy for solid tumors to decrease inflammation and cytotoxic effects. They can alleviate symptoms associated with chemotherapy or cancer in some solid tumors.[8] However, glucocorticoids can also increase the likelihood of chemotherapy failure. Recent studies suggest that glucocorticoids may play a role in the ineffectiveness of chemotherapy and the advancement of solid tumors, such as triple-negative breast cancer (TNBC) and CRPC.[9,10] They decelerate cell growth in estrogen receptor-positive breast cancer, suppress chemotherapy-induced cytotoxicity in

TNBC, inhibit tumor cell growth in androgen-dependent prostate cancer, and promote tumor advancement in CRPC.[11,12]

Researchers have discovered that glucocorticoid receptors (GRs) may contribute to developing CRPC, a type of cancer. Glucocorticoids are widely used in prostate cancer therapies to arrest tumor growth and slow proliferation, as well as alleviate symptoms.[11,13] However, their mechanisms on prostate cancer cells remain unclear. GR activation promotes cell proliferation by inhibiting apoptosis, potentially conferring resistance to anti-androgens.[14,15] This article summarizes published data and new ideas on the effectiveness of glucocorticoid therapy in prostate cancer over the past ten years.

METHODS

Protocol

The study was executed with precise adherence to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards, demonstrating a high level of compliance with established methodological protocols. This adherence underscores a dedication to improving transparency, reproducibility, and methodological rigor throughout the review process. The approach involved systematic and thorough strategies for literature searching, data extraction, and synthesis of results, all aimed at minimizing bias and reinforcing the reliability of the conclusions drawn.

Criteria for Eligibility

This study offers a comprehensive evaluation of the literature from the past decade on glucocorticoid therapy in prostate cancer patients. By systematically reviewing and synthesizing data from various studies, the research seeks to identify key patterns and enhance patient care strategies for this co-morbid group.

The primary aim is to highlight significant themes from a wide range of academic sources, thus contributing to a deeper understanding of the relationship between glucocorticoids and prostate cancer. To ensure rigorous analysis, strict inclusion and exclusion criteria were enforced: only peer-reviewed studies published in English between 2014 and 2024, and those with a DOI, were

considered. Non-research documents such as reviews, editorials, and duplicate entries were excluded to preserve the focus and integrity of the dataset.

This rigorous approach guarantees that the data analyzed is both pertinent and reliable, laying a solid foundation for drawing significant conclusions and advancing clinical practices.

Search Strategy

We used "prostate cancer OR ca prostate OR glucocorticoids." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Table 1. Search Strategy

Database	**Search Strategy**	***Hits***
Pubmed	*("prostate cancer" OR "ca prostate" AND "glucocorticoids")*	1046
Science Direct	*("prostate cancer" OR "ca prostate" AND "glucocorticoids")*	10
Sagepub	*("prostate cancer" AND "glucocorticoids")*	361

Data retrieval

The authors performed a thorough preliminary review of each article by examining abstracts and titles to assess their relevance before advancing to a more detailed investigation. Only studies that aligned with the study's objectives and satisfied the predefined inclusion criteria were considered for further analysis. This method allowed for the identification of clear and consistent patterns across the research.

Full-text articles were limited to those published in English to maintain uniformity in the study's language. A stringent screening process was applied to select content directly relevant to the study's focus, ensuring adherence to all inclusion criteria. Studies that did not meet these criteria were systematically excluded from in-depth analysis and were not included in the final evaluation.

The evaluation covered a wide array of data, including study characteristics, titles, authors, publication dates, research locations, and methodologies. This comprehensive approach ensured that only the most relevant and high-quality content was included in the analysis, thereby strengthening the reliability of the study's conclusions.

Quality Assessment and Data Synthesis

The authors undertook a detailed review of abstracts and titles to determine which articles merited further examination. Documents that passed this preliminary screening were then subjected to an extensive and thorough evaluation. The results of this initial assessment informed the selection of review papers, ensuring that only those of significant relevance proceeded to detailed analysis. This rigorous approach optimized the selection process, facilitating a more comprehensive and nuanced analysis of existing research and its evaluative context.

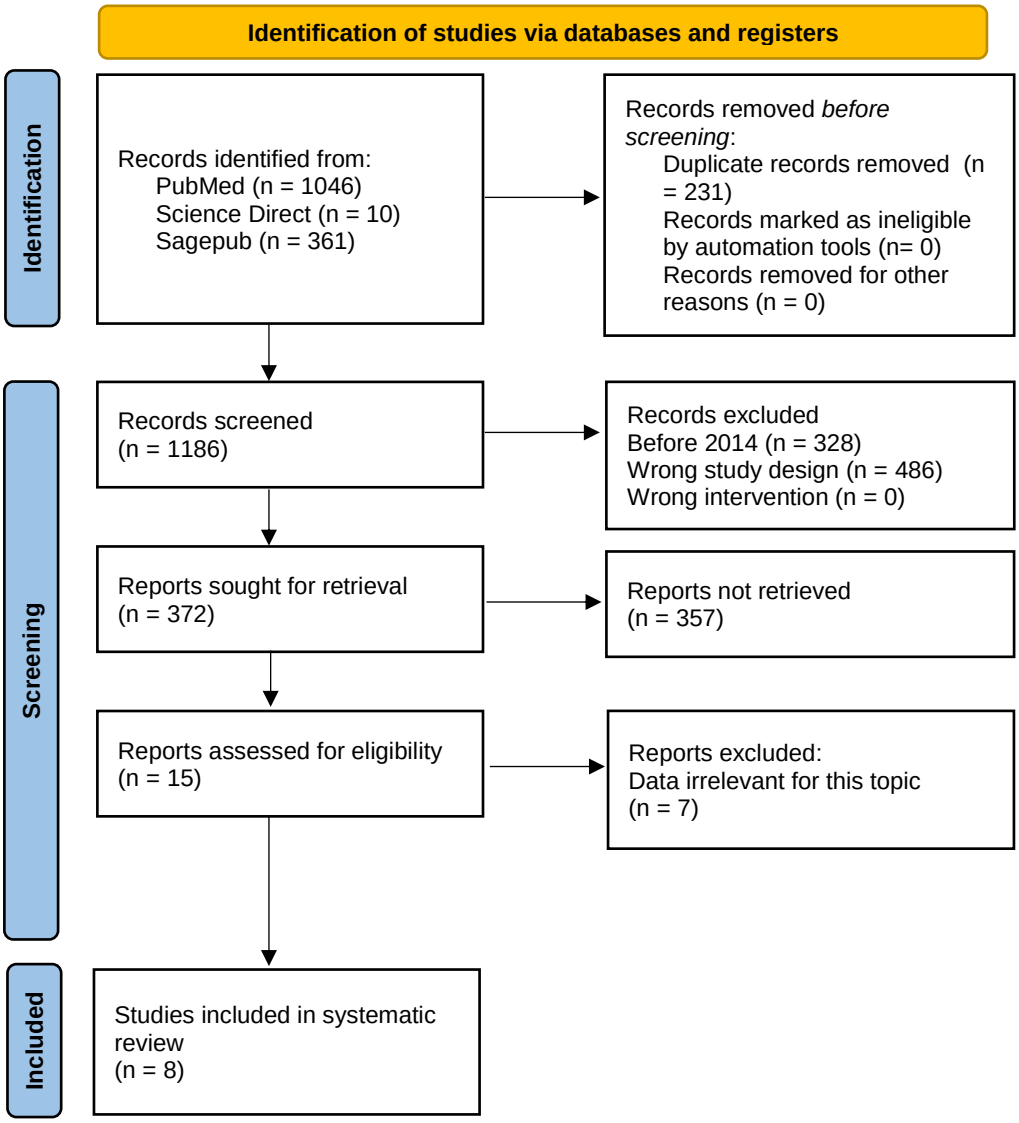

Figure 1. Article search flow chart

Table 2. Critical appraisal of Study

Parameters	(Montgomery et al., 2014)	(Narayan et al., 2015)	(Ndibe., 2015)	(Hu & Chen., 2016)	(Kumar, Raj., 2020)	(Sakellakis & Flores., 2022)	(Zhou et al., 2022)	(Eigentler et al., 2024)
1. Bias related to temporal precedence Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation Was there a control group?	No	No	No	No	No	No	No	No
3. Bias related to confounding factors Were participants included in any comparisons similar?	No	No	No	No	No	No	No	No
4. Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No.	No.	No.	No.	No.	No.	No.	No.
5. Bias related to assessment, detection, and measurement of the outcome Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	No	No	No	No	No	No	No	No
Were outcomes measured in a reliable way?	No	No	No	No	No	No	No	No
6. Bias related to participant retention Was follow-up	No	No	No	No	No	No	No	No

complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?								
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	No	No	No	No	No	No	No	No

RESULT

We initiated the investigation by systematically gathering a significant assortment of papers from reputable sources such as Science Direct, PubMed, and SagePub. After a thorough three-stage screening process, we selected eight papers that were considered very pertinent to our ongoing systematic inquiry. Subsequently, we selected certain topics for further examination and meticulously evaluated each report. In order to expedite our study, we have included a concise summary of the evaluated information in Table 3.

Table 3. The literature included in this study

Author	Origin	Method	Sample	Result
Montgomery et al.[11] (2014)	USA	Review	-	Glucocorticoids are a treatment option for prostate cancer, used to slow disease progression, improve pain control, and offset side effects of chemo- and hormonal therapy. However, they may also drive prostate cancer growth via mutated androgen receptors or glucocorticoid receptors. This review examines their historical and contemporary use, potential mechanisms, and their contribution to prostate cancer biology.
Narayan et al.[16] (2016)	USA	Review	-	The treatment of castration-resistant prostate cancer (CRPC) has improved patient outcomes with new antiandrogens

				and androgen synthesis inhibitors. The role of glucocorticoids in the treatment, management, and progression of CRPC is crucial. However, unexpected glucocorticoid-related mechanisms have emerged, potentially contributing to drug resistance and disease progression despite optimal androgen deprivation therapy. Understanding the biological role of glucocorticoids in prostate cancer patients is essential for new and evolving therapies.
Ndibe et al.[17] (2015)	USA	Review	-	Corticosteroids are used in prostate cancer management for over 30 years, providing palliative benefits. They are associated with objective responses, circulating tumor cell declines, and osteoporosis. However, long-term use can be complicated by toxicities and immunosuppression.
Hu & Chen.[15] (2016)	China	Review	-	Glucocorticoids are adjuvant drugs used to treat castration-resistant prostate cancer (CRPC) by ameliorating toxic side effects and inhibiting adrenal androgen production. However, their effects on prostate cancer cells are poorly defined. Glucocorticoids' effects depend on glucocorticoid receptor isoforms, with studies finding GR conferring resistance to androgen deprivation therapy.
Kumar, Raj.[18] (2020)	USA	Review	-	Glucocorticoids, used in chemotherapy, may

				contribute to CRPC tumor progression. The glucocorticoid signaling pathway is a therapeutic target, with selective modulators being developed to block the GR mechanism, potentially improving therapeutic options.
Sakellakis & Flores.[19] (2022)	USA	Review	-	Glucocorticoids act on the glucocorticoid receptor (GR) to target and inhibit prostate cancer growth. Despite their potential to inhibit AR activation, GR is crucial for cell survival and can undermine antiandrogen treatment, chemotherapy, and radiotherapy.
Zhou et al.[7] (2022)	China	Review	-	Over the past 60 years, research on GR isoforms has shown potential involvement in CRPC development. Clinical trials in the past 5 years have focused on drug efficacy in CRPC treatments. Prednisone and dexamethasone are the most widely used steroid hormones, with similar efficacy in PSA response rate and median time to progression.
Eigentler et al.[20] (2024)	Austria	Review	-	GR signaling plays a crucial role in the treatment of metastatic prostate cancer (PCa), with glucocorticoids (GCs) being used as concomitant medications. Elevated GR signaling affects CAF secretome and ECM architecture, influencing

				epithelial tumor cell growth.

DISCUSSION

Glucocorticoid (GC) treatment significantly alters the morphology of cancer-associated fibroblasts (CAFs), corroborating previous studies. Ribeiro et al. observed similar effects in Wistar rats, noting fibroblast activation and atrophy of smooth muscle cells. Despite these morphological changes, normal cell proliferation was not adversely affected. RNA sequencing of GC-treated CAFs revealed substantial alterations in gene expression, particularly affecting cellular adhesion and extracellular matrix (ECM) organization. Notably, expressions of FN1 and ITGA10 were elevated.[20,21] FN1 facilitates cancer cell adhesion, migration, invasion, and formation of metastatic niches, while ITGA10 influences cell-ECM adhesion and can be targeted by anti-ITGA10 antibodies.[22] Increased ITGA10 mRNA expression was associated with poorer progression-free survival in prostate cancer (PCa) patients. Functional assays demonstrated that GC treatment enhanced the adhesion capabilities of both normal and cancer-associated fibroblasts, impacting the attachment of epithelial PCa cells.[20,23]

Elevated expression and activity of epithelial glucocorticoid receptors (GRs) significantly affect the epithelial compartment, accelerating tumor growth, therapy resistance, and decreasing overall survival in PCa. However, stromal GR expression and the direct effects of GC on GR signaling within the prostate tumor microenvironment (TME) are less understood.[24,25] This study expanded on previous findings, revealing distinct GR mRNA expression profiles in various stromal cell populations, including immortalized fibroblasts, smooth muscle cells, and primary isolated normal and cancer-associated fibroblasts. Neither GR knockdown nor pharmacological GR inhibition, whether used alone or in combination, had a significant impact on CAF viability or apoptosis.[26] Nevertheless, CAFs cannot be directly targeted by androgen receptor pathway inhibitors (ARPIs). Post-GC treatment, a modified stroma-specific chemokine expression profile at both the mRNA and protein levels significantly affected the epithelial compartment. The increase in PCa cell proliferation was attributed to a broadly altered CAF secretome rather than changes in specific soluble factors.[20]

In metastatic PCa management, glucocorticoids (GCs) are commonly used adjunctively due to their anti-inflammatory and antiemetic properties. However, their independent impact on survival remains unclear, and they are linked to accelerated PCa progression and chemotherapy resistance.[27] GC administration has been shown to induce drug insensitivity in 89% of 157 examined cell lines and patient-derived xenograft models. Analysis of the Phase III AFFIRM trial, which evaluated enzalutamide in castration-resistant prostate cancer (CRPC), revealed that baseline GC use correlates with reduced radiographic progression-free survival, time to PSA progression, and overall survival.[28] This suggests that GC use and elevated epithelial and stromal GR signaling may promote cancer progression and resistance to therapy. Clinical studies are needed to explore the feasibility of reducing or discontinuing GC use during chemotherapy and abiraterone treatment, given the potential adverse effects of antineoplastic treatments.[20]

In CRPC patients, corticosteroid use may lead to enzalutamide resistance due to the upregulation of glucocorticoid receptors, allowing tumor cells to bypass androgen receptor blockade. Enzalutamide induces glucocorticoid receptor expression, promoting tumor growth and resistance. When GCs bind to their receptors in an androgen-depleted environment, the activated glucocorticoid receptor complex induces the expression of genes and transcription factors that overlap with those promoted by androgen receptor signaling. This interaction facilitates tumor growth and resistance.[29,30] Preclinical data suggest that ligand-occupied glucocorticoid receptors may partially mimic antiandrogen activity by attenuating the androgen receptor-dependent transcription program, highlighting the potential role of corticosteroids in advancing prostate cancer growth and resistance.[29]

CONCLUSION

Glucocorticoid (GC) therapy markedly influences the morphology and gene expression of cancer-associated fibroblasts (CAFs), with notable effects on cellular adhesion. Elevated levels of epithelial glucocorticoid receptors (GRs) are associated with accelerated tumor progression, increased resistance to therapy, and reduced overall survival in prostate cancer (PCa). Although GCs are frequently

administered as adjunctive treatments for their anti-inflammatory and antiemetic effects, their independent impact on patient survival remains poorly defined. Additionally, the upregulation of glucocorticoid receptors may contribute to enzalutamide resistance by promoting tumor growth and enhancing resistance mechanisms.

REFERENCES

1. 1. Kumar, R., & Thompson, E. B. (2005). Gene regulation by the glucocorticoid receptor: structure:function relationship. The Journal of steroid biochemistry and molecular biology, 94(5), 383–394. https://doi.org/10.1016/j.jsbmb.2004.12.046
2. Oakley, R. H., & Cidlowski, J. A. (2013). The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. The Journal of allergy and clinical immunology, 132(5), 1033–1044. https://doi.org/10.1016/j.jaci.2013.09.007
3. Wang, L., Heckmann, B. L., Yang, X., & Long, H. (2019). Osteoblast autophagy in glucocorticoid-induced osteoporosis. Journal of cellular physiology, 234(4), 3207–3215. https://doi.org/10.1002/jcp.27335
4. Radhakutty, A., & Burt, M. G. (2018). MANAGEMENT OF ENDOCRINE DISEASE: Critical review of the evidence underlying management of glucocorticoid-induced hyperglycaemia. European journal of endocrinology, 179(4), R207–R218. https://doi.org/10.1530/EJE-18-0315
5. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians, 71(3), 209–249. https://doi.org/10.3322/caac.21660
6. Bishr, M., Lattouf, J. B., Gannon, P. O., & Saad, F. (2011). Updates on therapeutic targets and agents in castration-resistant prostate cancer. Minerva urologica e nefrologica = The Italian journal of urology and nephrology, 63(2), 131–143.

7. Zhou F, Shi Y, Zhao G, Aufderklamm S, Murray KS, Jin B. A narrative review of the role of glucocorticoid receptors in prostate cancer: developments in last 5 years. Transl Androl Urol. 2022 Aug;11(8):1189-1199. doi: 10.21037/tau-22-501. PMID: 36092840; PMCID: PMC9459548.
8. Schmidt, S., Rainer, J., Ploner, C., Presul, E., Riml, S., & Kofler, R. (2004). Glucocorticoid-induced apoptosis and glucocorticoid resistance: molecular mechanisms and clinical relevance. Cell death and differentiation, 11 Suppl 1, S45–S55. https://doi.org/10.1038/sj.cdd.4401456
9. Skor, M. N., Wonder, E. L., Kocherginsky, M., Goyal, A., Hall, B. A., Cai, Y., & Conzen, S. D. (2013). Glucocorticoid receptor antagonism as a novel therapy for triple-negative breast cancer. Clinical cancer research : an official journal of the American Association for Cancer Research, 19(22), 6163–6172. https://doi.org/10.1158/1078-0432.CCR-12-3826
10. Chen, Z., Lan, X., Wu, D., Sunkel, B., Ye, Z., Huang, J., Liu, Z., Clinton, S. K., Jin, V. X., & Wang, Q. (2015). Ligand-dependent genomic function of glucocorticoid receptor in triple-negative breast cancer. Nature communications, 6, 8323. https://doi.org/10.1038/ncomms9323
11. Montgomery, B., Cheng, H. H., Drechsler, J., & Mostaghel, E. A. (2014). Glucocorticoids and prostate cancer treatment: friend or foe?. Asian journal of andrology, 16(3), 354–358. https://doi.org/10.4103/1008-682X.125392
12. Huang, Y., Jiang, X., Liang, X., & Jiang, G. (2018). Molecular and cellular mechanisms of castration resistant prostate cancer. Oncology letters, 15(5), 6063–6076. https://doi.org/10.3892/ol.2018.8123
13. Yemelyanov, A., Czwornog, J., Chebotaev, D., Karseladze, A., Kulevitch, E., Yang, X., & Budunova, I. (2007). Tumor suppressor activity of glucocorticoid receptor in the prostate. Oncogene, 26(13), 1885–1896. https://doi.org/10.1038/sj.onc.1209991
14. Isikbay, M., Otto, K., Kregel, S., Kach, J., Cai, Y., Vander Griend, D. J., Conzen, S. D., & Szmulewitz, R. Z. (2014). Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate

cancer. Hormones & cancer, 5(2), 72–89. https://doi.org/10.1007/s12672-014-0173-2

15. Hu, J., & Chen, Q. (2017). The role of glucocorticoid receptor in prostate cancer progression: from bench to bedside. International urology and nephrology, 49(3), 369–380. https://doi.org/10.1007/s11255-016-1476-8.
16. Narayanan S, Srinivas S, Feldman D. Androgen-glucocorticoid interactions in the era of novel prostate cancer therapy. Nat Rev Urol. 2016 Jan;13(1):47-60. doi: 10.1038/nrurol.2015.254. Epub 2015 Dec 8. PMID: 26643568.
17. Ndibe C, Wang CG, Sonpavde G. Corticosteroids in the management of prostate cancer: a critical review. Curr Treat Options Oncol. 2015 Feb;16(2):6. doi: 10.1007/s11864-014-0320-6. PMID: 25762121.
18. Kumar R. (2020). Emerging role of glucocorticoid receptor in castration resistant prostate cancer: A potential therapeutic target. Journal of Cancer, 11(3), 696–701. https://doi.org/10.7150/jca.32497
19. Sakellakis M, Flores LJ. Is the glucocorticoid receptor a key player in prostate cancer?: A literature review. Medicine (Baltimore). 2022 Jul 22;101(29):e29716. doi: 10.1097/MD.0000000000029716. PMID: 35866830; PMCID: PMC9302310.
20. Eigentler A, Handle F, Schanung S, Degen A, Hackl H, Erb HHH, Fotakis G, Hoefer J, Ploner C, Jöhrer K, Heidegger I, Pircher A, Klotz W, Herold M, Schäfer G, Culig Z, Puhr M. Glucocorticoid treatment influences prostate cancer cell growth and the tumor microenvironment via altered glucocorticoid receptor signaling in prostate fibroblasts. Oncogene. 2024 Jan;43(4):235-247. doi: 10.1038/s41388-023-02901-5. Epub 2023 Nov 29. PMID: 38017134; PMCID: PMC10798901.
21. Ribeiro, D. L., Rafacho, A., Bosqueiro, J. R., Taboga, S. R., & Góes, R. M. (2008). Cellular changes in the prostatic stroma of glucocorticoid-treated rats. Cell and tissue research, 332(3), 499–508. https://doi.org/10.1007/s00441-008-0581-0

22. Albrecht, M., Janssen, M., Konrad, L., Renneberg, H., & Aumüller, G. (2002). Effects of dexamethasone on proliferation of and fibronectin synthesis by human primary prostatic stromal cells in vitro. Andrologia, 34(1), 11–21. https://doi.org/10.1046/j.1439-0272.2002.00455.x

23. Okada, T., Lee, A. Y., Qin, L. X., Agaram, N., Mimae, T., Shen, Y., O'Connor, R., López-Lago, M. A., Craig, A., Miller, M. L., Agius, P., Molinelli, E., Socci, N. D., Crago, A. M., Shima, F., Sander, C., & Singer, S. (2016). Integrin-α10 Dependency Identifies RAC and RICTOR as Therapeutic Targets in High-Grade Myxofibrosarcoma. Cancer discovery, 6(10), 1148–1165. https://doi.org/10.1158/2159-8290.CD-15-1481

24. Mohler, J. L., Chen, Y., Hamil, K., Hall, S. H., Cidlowski, J. A., Wilson, E. M., French, F. S., & Sar, M. (1996). Androgen and glucocorticoid receptors in the stroma and epithelium of prostatic hyperplasia and carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research, 2(5), 889–895.

25. Hidalgo, A. A., Montecinos, V. P., Paredes, R., Godoy, A. S., McNerney, E. M., Tovar, H., Pantoja, D., Johnson, C., Trump, D., & Onate, S. A. (2011). Biochemical characterization of nuclear receptors for vitamin D3 and glucocorticoids in prostate stroma cell microenvironment. Biochemical and biophysical research communications, 412(1), 13–19. https://doi.org/10.1016/j.bbrc.2011.06.181

26. Nagarsheth, N., Wicha, M. S., & Zou, W. (2017). Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nature reviews. Immunology, 17(9), 559–572. https://doi.org/10.1038/nri.2017.49

27. Zhang, C., Wenger, T., Mattern, J., Ilea, S., Frey, C., Gutwein, P., Altevogt, P., Bodenmüller, W., Gassler, N., Schnabel, P. A., Dienemann, H., Marmé, A., Hohenfellner, M., Haferkamp, A., Pfitzenmaier, J., Gröne, H. J., Kolb, A., Büchler, P., Büchler, M., Friess, H., … Herr, I. (2007). Clinical and mechanistic aspects of glucocorticoid-induced chemotherapy resistance in the majority of solid tumors. Cancer biology & therapy, 6(2), 278–287. https://doi.org/10.4161/cbt.6.2.3652

28. Zhao, J. L., Fizazi, K., Saad, F., Chi, K. N., Taplin, M. E., Sternberg, C. N., Armstrong, A. J., de Bono, J. S., Duggan, W. T., & Scher, H. I. (2022). The Effect of Corticosteroids on Prostate Cancer Outcome Following Treatment with Enzalutamide: A Multivariate Analysis of the Phase III AFFIRM Trial. Clinical cancer research : an official journal of the American Association for Cancer Research, 28(5), 860–869. https://doi.org/10.1158/1078-0432.CCR-21-1090

29. Sahu, B., Laakso, M., Pihlajamaa, P., Ovaska, K., Sinielnikov, I., Hautaniemi, S., & Jänne, O. A. (2013). FoxA1 specifies unique androgen and glucocorticoid receptor binding events in prostate cancer cells. Cancer research, 73(5), 1570–1580. https://doi.org/10.1158/0008-5472.CAN-12-2350

30. Sharifi N. (2014). Steroid receptors aplenty in prostate cancer. The New England journal of medicine, 370(10), 970–971. https://doi.org/10.1056/NEJMcibr1315706.