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Immune-Prostate Axis: The Role of Oxidative Stress and Inflammatory Mediators in the Pathogenesis of Benign Prostate Hyperplasia (BPH)

Kibibi Wairimu H.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

Benign prostatic hyperplasia (BPH) is a highly prevalent condition in aging men, historically attributed to androgenic and hormonal imbalances. However, mounting evidence supports a central role for the immune–prostate axis in its development. Chronic inflammation, immune-cell infiltration (e.g., T cells, macrophages), and sustained cytokine release contribute to a pro-proliferative microenvironment in the prostate. At the same time, oxidative stress (OS)-driven by excessive reactive oxygen species (ROS) from immune cells and metabolic dysregulation fosters tissue damage, DNA instability, and stromal-epithelial proliferation. The synergy of inflammation and OS disrupts apoptosis, enhances proliferation via MAPK, NF- κB, and STAT3 pathways, and triggers fibrotic remodeling. Emerging studies implicate deregulated antioxidant defense (e.g., diminished Nrf2 activity), autophagy/ferroptosis imbalance, and immune-mediated signaling in the stromal expansion characteristic of BPH. This review synthesizes current mechanistic knowledge of the immune–prostate axis in BPH pathogenesis, highlights key molecular mediators, and discusses potential therapeutic strategies targeting inflammation and oxidative stress to complement conventional treatments.

Keywords: benign prostatic hyperplasia, inflammation, oxidative stress, immune cells, Nrf2

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prevalent urological condition, affecting a substantial proportion of men over 50 years of age and representing a major contributor to lower urinary tract symptoms (LUTS), including urinary frequency, nocturia, hesitancy, and weak stream. Traditionally, BPH has been conceptualized as an age-related and androgen-driven disease, with dihydrotestosterone (DHT) and other sex steroids promoting stromal and epithelial proliferation[1]. However, these classical factors alone fail to account for the considerable variability in disease onset, severity, and progression observed across individuals. Notably, some men with similar androgenic profiles or age exhibit marked differences in prostate volume and symptom burden, indicating that additional mechanisms underlie hyperplastic growth[2]. Recent research has highlighted the critical role of the immune–prostate axis in BPH pathogenesis. Histological and molecular studies of hyperplastic prostate tissue consistently reveal infiltration by immune cells, particularly T lymphocytes, macrophages, and, to a lesser extent, neutrophils and plasma cells[3]. These cells produce a spectrum of proinflammatory cytokines and growth factors-including interleukin- 6 (IL-6), interleukin- 8 (IL-8), tumor necrosis factor-α (TNF-α), and transforming growth factor- β (TGF-β)-which collectively promote stromal expansion, epithelial proliferation, and angiogenesis[4]. Chronic inflammation thus creates a microenvironment that actively supports hyperplasia rather than serving as a passive response to tissue enlargement or damage. Concurrently, oxidative stress (OS) emerges as a central mediator linking inflammation to cellular proliferation and tissue remodeling[5]. Reactive oxygen species (ROS), generated by infiltrating immune cells and metabolically stressed stromal or epithelial cells, overwhelm intrinsic antioxidant defenses in the prostate. Excess ROS induces lipid peroxidation, protein oxidation, and DNA damage, while also activating pro-survival signaling pathways such as NF- κB, MAPK, and PI3K/AKT[6]. These effects not only enhance cell proliferation and resistance to apoptosis but also perpetuate immune cell recruitment and inflammatory cytokine production, establishing a self-reinforcing loop that drives BPH progression. Understanding the complex interplay between immune dysregulation and oxidative stress is

therefore critical for advancing mechanistic models of BPH and developing more effective, targeted therapeutic strategies[7]. Integrating insights from immunology, redox biology, and endocrine regulation may allow for precision interventions that modulate inflammation, restore antioxidant capacity, and limit hyperplastic growth, ultimately improving clinical outcomes for men suffering from this highly prevalent condition[8].

2. Immune Infiltration and Inflammatory Mediators in BPH

2.1 Immune Cell Profiles in BPH

Histopathological studies of benign prostatic hyperplasia consistently reveal significant immune cell infiltration within both stromal and glandular compartments[9]. The infiltrates are predominantly composed of T lymphocytes, with CD8+ T cells concentrated in periglandular regions and CD4+ T cells more abundant in the stromal matrix[10]. Macrophages form another substantial component of this infiltrate, contributing to local cytokine production and reactive oxygen species generation. Less frequently, neutrophils and plasma cells are observed, often in regions exhibiting epithelial disruption or microtrauma[11]. The density and composition of these immune cells have been correlated with prostate volume and severity of lower urinary tract symptoms, suggesting that inflammation is not merely a secondary phenomenon but actively contributes to tissue remodeling and hyperplastic growth[12]. In addition, immune cell infiltration can vary based on patient age, comorbidities, and prior exposure to urinary tract infections, highlighting the multifactorial triggers of immune activation in the prostate.

2.2 Cytokines and Growth Factors Driving Hyperplasia

The infiltrating immune cells secrete a variety of cytokines and growth factors that establish a pro-proliferative and anti-apoptotic microenvironment[13]. Key mediators include interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and transforming growth factor-β (TGF-β). IL-8, produced both by stromal and epithelial cells, functions in autocrine and paracrine modes to stimulate cellular proliferation and angiogenesis[14]. TNF-α and IL-6 further potentiate inflammatory signaling via NF-κB and STAT3 pathways, enhancing stromal expansion and epithelial hyperplasia. Chronic inflammation may be initiated or exacerbated by subclinical bacterial infections, urinary reflux, mechanical microtrauma, or autoimmune reactions against exposed self-antigens[15]. Over time, sustained cytokine production promotes extracellular matrix deposition, angiogenesis, and nodular formation, characteristic features of BPH progression.

3. Oxidative Stress in the Prostate: Sources and Consequences

3.1 Origins of ROS in Prostatic Tissue

Reactive oxygen species (ROS) in the prostate are produced from multiple converging sources[16]. Activated macrophages and neutrophils generate superoxide, nitric oxide, and other free radicals as part of the inflammatory response. Aging prostate cells also contribute via mitochondrial dysfunction, where electron transport chain inefficiencies lead to superoxide leakage[17]. NADPH oxidases, particularly NOX4, are upregulated in hyperplastic tissue and further enhance ROS production under inflammatory stimulation. Experimental models demonstrate that NOX4 overexpression correlates with increased oxidative DNA damage, stromal cell proliferation, and enlarged prostate volume[18].

3.2 Oxidative Damage and Proliferative Signaling

Excess ROS damages cellular macromolecules, including lipids, proteins, and nucleic acids[19]. Oxidative DNA lesions, such as 8-hydroxy-2′-deoxyguanosine, are elevated in BPH tissue and correlate with both histological severity and prostate size[20]. ROS simultaneously act as signaling molecules, activating MAPK (ERK), PI3K/AKT, and NF-κB pathways, which promote cell survival, proliferation, and resistance to apoptosis[21]. This dual role of ROS—as both damaging agents and intracellular messengers-creates a microenvironment that favors hyperplastic growth while perpetuating immune activation.

3.3 Impaired Antioxidant Defenses

In BPH, antioxidant defense systems are compromised[22]. Key enzymes, including superoxide dismutase, glutathione peroxidase, and catalase, exhibit diminished activity in hyperplastic tissue. Chronic inflammation suppresses nuclear factor erythroid 2–related factor 2 (Nrf2), a master regulator of cellular antioxidant responses[23]. Reduced Nrf2 activity diminishes transcription of protective enzymes, weakening the prostate's capacity to neutralize ROS. This deficit establishes a vicious cycle in which oxidative stress amplifies inflammation, cytokine production, and stromal-epithelial proliferation, driving further hyperplasia[24].

4. Emerging Molecular Mediators: Nrf2, Autophagy, and Ferroptosis

4.1 Role of Nrf2 in Macrophage Regulation

Nuclear factor erythroid 2–related factor 2 (Nrf2) is increasingly recognized as a central regulator of oxidative stress and immune responses within the prostate[25]. In the context of BPH, Nrf2 activity in macrophages modulates their phenotype and functional output. Activation of Nrf2 promotes an anti-inflammatory, antioxidant-rich state, suppressing the production of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β, while upregulating genes involved in reactive oxygen species detoxification, including heme oxygenase-1 (HO-1),

glutathione peroxidase, and superoxide dismutase[26]. This dual action restrains stromal proliferation and mitigates epithelial hyperplasia. Conversely, loss or suppression of Nrf2 signaling-observed in aged or metabolically stressed prostate tissue-enhances macrophage proinflammatory polarization, increases ROS production, and perpetuates oxidative injury, contributing directly to the progression of BPH[27]. Nrf2 thus represents a critical checkpoint in the immune–prostate axis, linking redox regulation to tissue remodeling and hyperplastic growth.

4.2 Autophagy, Ferroptosis, and Cellular Homeostasis

Autophagy and ferroptosis are emerging as pivotal mechanisms governing cellular homeostasis and redox balance in BPH[28]. Autophagy, particularly mitophagy, facilitates the removal of damaged mitochondria and excess iron, reducing ROS accumulation and lipid peroxidation[29]. Dysregulation of autophagic pathways in hyperplastic prostate tissue results in the accumulation of damaged organelles and reactive intermediates, promoting cellular stress and pyroptotic death via NLRP3 inflammasome activation[30]. Elevated expression of mitochondrial antioxidant proteins, such as peroxiredoxin 3 (PRDX3), represents a compensatory response; however, persistent oxidative challenges can overwhelm these protective mechanisms[31]. Ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation, is similarly implicated. In BPH, abnormal ferroptotic signaling may drive selective stromal cell survival, exacerbate inflammation, and disrupt local immune responses, creating conditions that favor hyperplasia and nodular growth[32].

5. Metabolic and Systemic Contributors to the Immune-Prostate Axis

Metabolic disorders-including obesity, insulin resistance, and components of metabolic syndrome-intensify the immune–prostate axis and exacerbate BPH progression[33]. High-fat diet-induced BPH models demonstrate upregulation of STAT3 and NF-κB signaling, increased expression of COX-2 and inducible nitric oxide synthase (iNOS), and elevated proinflammatory cytokines, all of which amplify oxidative stress[34]. These systemic metabolic stressors not only enhance ROS generation within the prostate but also suppress Nrf2-mediated antioxidant defenses, reducing the tissue's ability to counteract oxidative damage. Consequently, a pro-proliferative, anti-apoptotic microenvironment is established, characterized by stromal expansion, epithelial hyperplasia, and extracellular matrix remodeling[35]. Moreover, metabolic dysregulation can exacerbate immune cell infiltration, cytokine release, and mitochondrial dysfunction, creating a feed-forward loop that integrates systemic metabolic stress with local immune–oxidative signaling. Together, these pathways underscore the multifactorial nature of BPH pathogenesis, highlighting the interplay between systemic metabolism, local inflammation, and redox imbalance in driving prostate enlargement and lower urinary tract symptoms[36].

CONCLUSION

Benign prostatic hyperplasia should no longer be viewed solely as a hormone-driven disease. The immune–prostate axis-mediated by chronic inflammation, immune cell infiltration, oxidative stress, and dysregulated redox signaling-plays a defining role in its pathogenesis. Immune-derived ROS, cytokines, and growth factors converge to create a microenvironment that promotes hyperplasia, fibrosis, and resistance to cell death. Dysregulation of antioxidant defenses, including Nrf2 suppression and impaired autophagy, amplifies this process. Recognizing the centrality of immune–oxidative interactions opens new avenues for therapy, including antioxidant and anti-inflammatory strategies tailored to the aging, metabolically challenged prostate. Bridging basic mechanistic research with translational clinical studies will be key to unlocking these opportunities and improving outcomes for men with BPH.

REFERENCES

1. Xiang J, Zheng Y, Chen D, Zeng Y, Zhang J, Chang D, Chang C. The pathogenesis of benign prostatic hyperplasia and the roles of Prdx3, oxidative stress, pyroptosis and autophagy:a review. Front Oncol. 2025 Aug 5;15:1579539. doi: 10.3389/fonc.2025.1579539.
2. Tufail, T., Uti, D.E., Aja, P.M., Offor, C.E., Ibiam, U.A., Ukaidi, C.U.A. Utilizing Indigenous Flora in East Africa for Breast Cancer Treatment: An Overview. Anticancer Agents Med Chem. 2024 Sep 18. doi: 10.2174/0118715206338557240909081833.
3. Uroko Robert Ikechukwu, Fatima Amin Adamude, Egba Simeon Ikechukwu, Chinedu Paulinus Nwuke, Chidinma Lilian Asadu and Peter Anyaorah. Effect of combined ethanol extract of Funtumia Africana and Abutilon mauritanium leaves on prostate biomarkers and serum mineral levels in prostatic hyperplasia induced in rats. J. Renal Endocrinol 2021; 7:e06
4. Obeagu, E.I., Alum, E.U., Obeagu, G.U. and Ugwu, O. P. C. Prostate Cancer: Review on Risk Factors. Eurasian Experiment Journal of Public Health (EEJPH). 2023; 4(1): 4-7. https://www.eejournals.org/public/uploads/1688032824-872978821ba373725554.pdf
5. Stojanovic B, Milivojcevic Bevc I, Dimitrijevic Stojanovic M, Stojanovic BS, Lazarevic T, Spasic M, Petrovic M, Stefanovic I, Markovic M, Nesic J, Jovanovic D, Peulic M, Azanjac Arsic A, Lukovic A, Mirkovic N, Eric S, Zornic N. Oxidative Stress, Inflammation, and Cellular Senescence in Neuropathic Pain: Mechanistic Crosstalk. Antioxidants (Basel). 2025 Sep 25;14(10):1166. doi:

10.3390/antiox14101166.

6. Ogbonna OA., Egba, SI., Uhuo EN., Omeoga HC., Obeagu EI. Toxic outcomes of ciprofloxacin and gentamicin co-administration and possible ameliorating role for antioxidant vitamins C and E in Wistar Rats. Elite Journal of Medicine, 2024; 2(3): 1-14.
7. Ibiam, U. A., Uti, D. E., Ejeogo, C. C., Orji, O. U., Aja, P. M., Ezeaani, N. N., Chukwu, C., AlokeC., Chinedum, K. E., Agu, P. and Nwobodo, V.In Vivo and in Silico Assessment of Ameliorative Effects of Xylopiaaethiopica on Testosterone Propionate-Induced Benign Prostatic Hyperplasia. *Pharmaceut Fronts.* 2023;5: e64–e76.DOI:10.1055/s-0043-1768477
8. Ugwu, CE., Sure, SM., Dike, CC., Okpoga, NA and Egba, SI. Phytochemical and *in vitro* antioxidant activities of methanol leave extract of *Alternanthera basiliana*. Journal of Pharmacy Research, 2018; 12(6): 835-839
9. Ibiam U. A.,Uti, D. E., Ejeogo, C.C., Orji, O. U. Aja, P. M., Ezeani, N. N., Alum, E. U., Chukwu, C., Aloke, C., Itodo, M. O., Agada, S. A., Umoru, G. U., Obeten, U. N., Nwobodo, V. O. G., Nwadum, S. K., Udoudoh, M. P. Xylopiaaethiopica Attenuates Oxidative Stress and Hepatorenal Damage in Testosterone Propionate-Induced Benign Prostatic Hyperplasia in Rats. Journal of Health and Allied Sciences. 2024, 01: 1-148. https://doi.org/10.1055/s-0043-1777836.
10. Hiraoka K, Miyamoto M, Cho Y, Suzuoki M, Oshikiri T, Nakakubo Y, Itoh T, Ohbuchi T, Kondo S, Katoh H. Concurrent infiltration by CD8+ T cells and CD4+ T cells is a favourable prognostic factor in non-small-cell lung carcinoma. Br J Cancer. 2006 Jan 30;94(2):275-80. doi: 10.1038/sj.bjc.6602934.
11. Kovtun A, Messerer DAC, Scharffetter-Kochanek K, Huber-Lang M, Ignatius A. Neutrophils in Tissue Trauma of the Skin, Bone, and Lung: Two Sides of the Same Coin. J Immunol Res. 2018 Apr 23;2018:8173983. doi: 10.1155/2018/8173983.
12. Renò F, Pagano CA, Bignotto M, Sabbatini M. Neutrophil Heterogeneity in Wound Healing. Biomedicines. 2025; 13(3):694. https://doi.org/10.3390/biomedicines13030694
13. Emmanuel Ifeanyi Obeagu, Getrude Uzoma Obeagu, Simeon Ikechukwu Egba and Obioma Raluchukwu Emeka Obi. Combatting Anaemia in Paediatric Malaria: Effective management strategies Int. J. Curr. Res. Med. Sci. 2023. 9(11): 1-7
14. Nishida A, Andoh A. The Role of Inflammation in Cancer: Mechanisms of Tumor Initiation, Progression, and Metastasis. Cells. 2025; 14(7):488. https://doi.org/10.3390/cells14070488
15. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017 Dec 14;9(6):7204-7218. doi: 10.18632/oncotarget.23208.
16. Alum EU, Uti DE, Obeagu EI, Ugwu OPC, Alum BN. Cancer's Psychosocial Aspects: Impact on Patient Outcomes. Elite Journal of Medicine, 2024; 2(6): 32-42.
17. Liou G-Y, C'lay-Pettis R, Kavuri S. Involvement of Reactive Oxygen Species in Prostate Cancer and Its Disparity in African Descendants. International Journal of Molecular Sciences. 2024; 25(12):6665. https://doi.org/10.3390/ijms25126665
18. Jin BR, Kim HJ, Na JH, Lee WK, An HJ. Targeting benign prostate hyperplasia treatments: AR/TGF-β/NOX4 inhibition by apocynin suppresses inflammation and proliferation. J Adv Res. 2024 Mar;57:135-147. doi: 10.1016/j.jare.2023.04.006.
19. Uhuo E N, Egba S I, Nwuke P C, Obike C A and Kelechi G K. Antioxidative properties of Adansonia digitata L. (baobab) leaf extractexert protective effect on doxorubicin induced cardiac toxicity in Wistar rats. Clinical Nutrition Open Science 2022; 45:3-16
20. Hong Y, Boiti A, Vallone D, Foulkes NS. Reactive Oxygen Species Signaling and Oxidative Stress: Transcriptional Regulation and Evolution. Antioxidants. 2024; 13(3):312. https://doi.org/10.3390/antiox13030312
21. Brandl N, Seitz R, Sendtner N, Müller M, Gülow K. Living on the Edge: ROS Homeostasis in Cancer Cells and Its Potential as a Therapeutic Target. Antioxidants (Basel). 2025 Aug 16;14(8):1002. doi: 10.3390/antiox14081002.
22. Edyedu I, Ugwu OP, Ugwu CN, Alum EU, Eze VHU, Basajja M, Ugwu JN, Ogenyi FC, Ejemot-Nwadiaro RI, Okon MB, Egba SI, Uti DE, Aja PM. The role of pharmacological interventions in managing urological complications during pregnancy and childbirth: A review. Medicine (Baltimore). 2025 Feb 14;104(7):e41381. doi: 10.1097/MD.0000000000041381. PMID: 39960970; PMCID: PMC11835077.
23. Uhuo EN, Egba SI, Obike CA, Anyiam PN, Alaebo PO, Okeke PM, et al. Combined extracts of Syzygium aromaticum (Clove) and Xylopia aethiopica (Negro pepper) seeds inhibit testosterone propionate-induced benign prostatic hyperplasia in Wistar rats. All Life [Internet]. 2024 Dec 5;17(1). Available from:https://www.tandfonline.com/doi/epdf/10.1080/26895293.2024.2435277

24. Vomund S, Schäfer A, Parnham MJ, Brüne B, Von Knethen A. Nrf2, the Master Regulator of Anti-Oxidative Responses. International Journal of Molecular Sciences. 2017; 18(12):2772. https://doi.org/10.3390/ijms1812277225. Buttari B, Arese M, Oberley-Deegan RE, Saso L, Chatterjee A. NRF2: A crucial regulator for mitochondrial metabolic shift and prostate cancer progression. Front Physiol. 2022 Sep 23;13:989793. doi: 10.3389/fphys.2022.989793.
25. Hasan SK, Jayakumar S, Espina Barroso E, Jha A, Catalano G, Sandur SK, Noguera NI. Molecular Targets of Oxidative Stress: Focus on Nuclear Factor Erythroid 2–Related Factor 2 Function in Leukemia and Other Cancers. Cells. 2025; 14(10):713. https://doi.org/10.3390/cells14100713
26. Kaltsas A, Giannakas T, Stavropoulos M, Kratiras Z, Chrisofos M. Oxidative Stress in Benign Prostatic Hyperplasia: Mechanisms, Clinical Relevance and Therapeutic Perspectives. Diseases. 2025; 13(2):53. https://doi.org/10.3390/diseases13020053
27. Uhuo EN, Egba SI, Obike CA, Anyiam PN, Alaebo PO, Okeke PM, et al. Combined extracts of Syzygium aromaticum (Clove) and Xylopia aethiopica (Negro pepper) seeds inhibit testosterone propionate-induced benign prostatic hyperplasia in Wistar rats. All Life [Internet]. 2024 Dec 5;17(1). Available from:https://www.tandfonline.com/doi/epdf/10.1080/26895293.2024.2435277
28. Yang Y, Lin X. Potential relationship between autophagy and ferroptosis in myocardial ischemia/reperfusion injury. Genes Dis. 2022 Mar 29;10(6):2285-2295. doi: 10.1016/j.gendis.2022.02.012.
29. Zhou XZ, Huang P, Wu YK, Yu JB, Sun J. Autophagy in benign prostatic hyperplasia: insights and therapeutic potential. BMC Urol. 2024 Sep 12;24(1):198. doi: 10.1186/s12894-024-01585-7.
30. Lv S, Liu H, Wang H. The Interplay between Autophagy and NLRP3 Inflammasome in Ischemia/Reperfusion Injury. International Journal of Molecular Sciences. 2021; 22(16):8773. https://doi.org/10.3390/ijms22168773
31. Alum, E.U., Akwari, A.A., Okoroh, P.N., Aniokete, U.C., Abba, J.N., Uti, D.E. Phytochemicals as modulators of ferroptosis: a novel therapeutic avenue in cancer and neurodegeneration. *Mol Biol Rep* **52**, 636 (2025). https://doi.org/10.1007/s11033-025-10752-4
32. Ngai HY, Yuen KS, Ng CM, Cheng CH, Chu SP. Metabolic syndrome and benign prostatic hyperplasia: An update. Asian J Urol. 2017 Jul;4(3):164-173. doi: 10.1016/j.ajur.2017.05.001.
33. Shankar E, Bhaskaran N, MacLennan GT, Liu G, Daneshgari F, Gupta S. Inflammatory Signaling Involved in High-Fat Diet Induced Prostate Diseases. J Urol Res. 2015 Jan 1;2(1):1018.
34. Li Y, Shi B, Dong F, Zhu X, Liu B, Liu Y. Effects of inflammatory responses, apoptosis, and STAT3/NF-κB- and Nrf2-mediated oxidative stress on benign prostatic hyperplasia induced by a high-fat diet. Aging (Albany NY). 2019 Aug 14;11(15):5570-5578. doi: 10.18632/aging.102138.
35. Lee CL, Kuo HC. Pathophysiology of benign prostate enlargement and lower urinary tract symptoms: Current concepts. Tzu Chi Med J. 2017 Apr-Jun;29(2):79-83. doi: 10.4103/tcmj.tcmj_20_17.

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