World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Signaling pathways in prostate cancer progression

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World Journal of Biology Pharmacy and Health Sciences, 2025, 22(03), 146-156

Publication history: Received on 28 April 2025; revised on 01 June 2025; accepted on 04 June 2025

Article DOI: https://doi.org/10.30574/wjbphs.2025.22.3.0534

Abstract

This review article explores the intricate signaling pathways involved in the development and progression of prostate cancer, a leading malignancy among men. The primary focus is on the androgen receptor signaling pathway, which is crucial for the growth of androgen-dependent tumors, and the mechanisms by which tumors develop resistance to androgen deprivation therapy. Additionally, the review examines the roles of the phosphatidylinositol 3-kinase/Akt/mTOR pathway, the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, and receptor tyrosine kinases in promoting tumor survival and proliferation. Notably, the cross-talk between these pathways contributes to treatment resistance, complicating therapeutic strategies. The review highlights emerging research on novel therapeutic targets and personalized medicine approaches, emphasizing the need for combination therapies to enhance treatment efficacy. By elucidating the molecular mechanisms underlying prostate cancer progression, this review aims to provide insights that could inform future therapeutic developments and improve patient outcomes in advanced and treatment-resistant cases.

Keywords: Prostate Cancer; Signaling Pathway; Tumor; Cross-Talk; Therapeutic Target

1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed non-cutaneous malignancy in men, with over 890,000 new cases and more than 258,000 deaths reported annually worldwide (1).The epidemiology of prostate cancer reveals significant variations in incidence and mortality rates across different demographics, including age, race, and geographical location.

1.1. Epidemiology of Prostate Cancer

Age: Prostate cancer is predominantly a disease of older men, with the risk of developing the disease increasing significantly with age. It is rare in men under 40 years of age, but the incidence rises sharply after the age of 50. Approximately 60% of cases are diagnosed in men aged 65 or older, and the median age at diagnosis is around 66 years (2).Race: There are notable racial disparities in prostate cancer incidence and outcomes. African American men have

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the highest incidence rates of prostate cancer, nearly 1.7 times higher than that of Caucasian men. They are also more likely to be diagnosed at an advanced stage and have a higher mortality rate. In contrast, Asian American men have the lowest incidence rates, which may be attributed to genetic, environmental, and lifestyle factors (3).

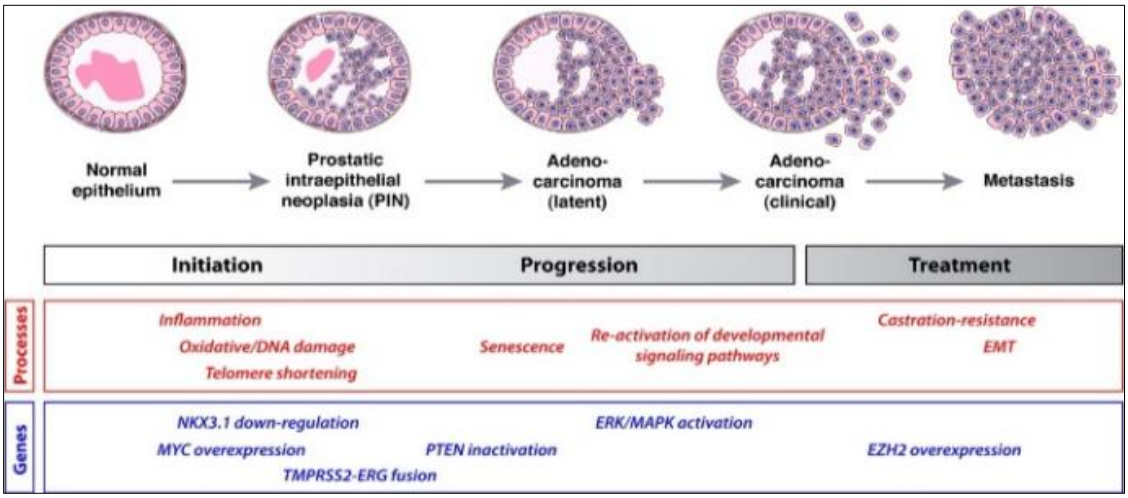
Geographical Location: The incidence of prostate cancer varies significantly by geographical region. In North America and Northern Europe, the rates are among the highest globally, while lower rates are observed in Asia and Africa. This variation may be influenced by factors such as access to healthcare, screening practices, dietary habits, and genetic predispositions. For instance, countries with widespread screening programs tend to report higher incidence rates due to early detection(4).

1.2. Biology of Prostate Cancer

The biology of prostate cancer is complex, involving a series of molecular and cellular changes that lead to tumor initiation and progression. The disease typically begins with benign prostatic hyperplasia (BPH), a non-cancerous enlargement of the prostate gland, which is common in older men. While BPH itself is not cancerous, it can create an environment conducive to the development of prostate cancer.

1.2.1. Stages of Progression

- Prostatic Intraepithelial Neoplasia (PIN): This is often considered a precursor to prostate cancer. PIN is characterized by abnormal changes in the prostate gland's epithelial cells. High-grade PIN is associated with a higher risk of developing prostate cancer and is often detected during biopsies.
- Localized Prostate Cancer: At this stage, cancer cells are confined to the prostate gland. Localized prostate cancer may be asymptomatic and is often detected through screening methods such as prostate-specific antigen (PSA) testing or digital rectal examinations. Treatment options include active surveillance, surgery, or radiation therapy, depending on the cancer's aggressiveness and the patient's overall health.
- Locally Advanced Prostate Cancer: This stage occurs when cancer has spread beyond the prostate capsule but remains within the surrounding tissues. Patients may experience symptoms such as urinary difficulties or pelvic pain. Treatment typically involves a combination of hormone therapy and radiation, as well as potential surgical intervention.
- Castration-Resistant Prostate Cancer (CRPC): This advanced stage occurs when prostate cancer continues to progress despite androgen deprivation therapy. CRPC is characterized by the emergence of androgen-independent cancer cells, which can proliferate in low androgen environments. Patients with CRPC often face a poor prognosis, and treatment options may include chemotherapy, second-line hormone therapies, and novel agents targeting specific molecular pathways.
- Metastatic Prostate Cancer: At this stage, cancer cells have spread to distant sites, commonly affecting bones, lymph nodes, and other organs. Metastatic prostate cancer is associated with significant morbidity and mortality. Treatment focuses on systemic therapies, including chemotherapy, immunotherapy, and targeted therapies, aimed at controlling disease progression and alleviating symptoms.



Source: Adapted from Abate-Shen and Shen (5)

Figure 1 Progression pathway for human cancer. Stages of progression are shown, together with molecular processes and genes/pathways that are likely to be significant at each stage

Understanding the epidemiology and biology of prostate cancer is crucial for developing effective prevention, early detection, and treatment strategies. Continued research into the molecular mechanisms underlying prostate cancer progression will enhance our ability to identify novel therapeutic targets and improve patient outcomes.

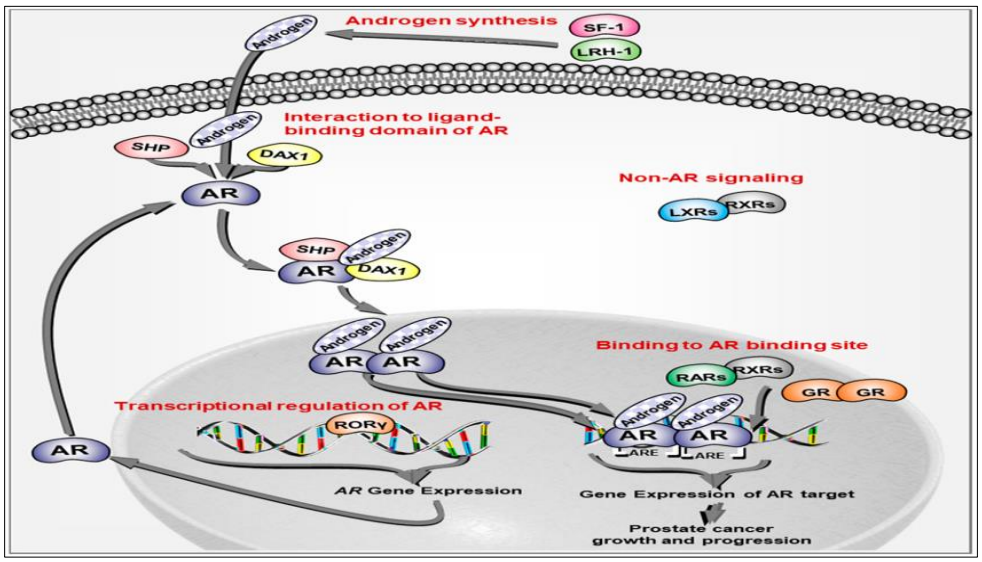
2. Common signaling pathways in prostate cancer

2.1. Androgen Receptor (AR) Signaling Pathway

2.1.1. Overview of AR Signaling Pathway

The androgen receptor (AR) signaling pathway is a critical regulator of prostate cancer (PCa) development and progression. In normal prostate cells, androgens, primarily testosterone and its more potent derivative dihydrotestosterone (DHT), bind to the AR, leading to a cascade of cellular events that promote cell growth, differentiation, and survival. The AR is a member of the nuclear receptor superfamily and functions as a transcription factor that regulates the expression of genes involved in various biological processes.

In the context of prostate cancer, the AR pathway becomes dysregulated. Mutations, amplifications, or overexpression of the AR can lead to androgen-independent activation, allowing cancer cells to proliferate even in low androgen environments, a hallmark of castration-resistant prostate cancer (CRPC) (6).



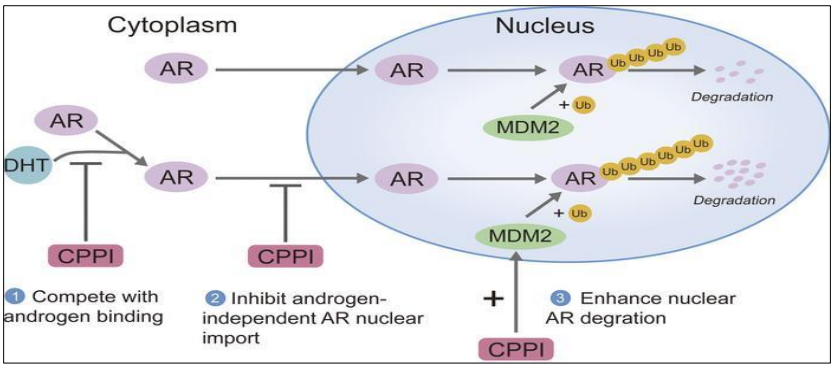
Source: Adapted From Cronin et al.(7)

Figure 2 Diagram illustrating the AR signaling pathway, including ligand binding, nuclear translocation, and gene regulation

2.2. Molecular Mechanisms of AR Signalin

2.2.1. Ligand Binding and Activation

In the absence of androgens, the AR resides in the cytoplasm in an inactive form, bound to heat shock proteins (HSPs) that maintain its stability. Upon androgen binding, the AR undergoes a conformational change, leading to its dissociation from HSPs and subsequent translocation to the nucleus. –



Source: Adapted From Lv et al.(8)

Figure 3 Diagram illustrating the binding of androgens to the AR and the subsequent translocation to the nucleus

2.2.2. Nuclear Translocation and Gene Regulation

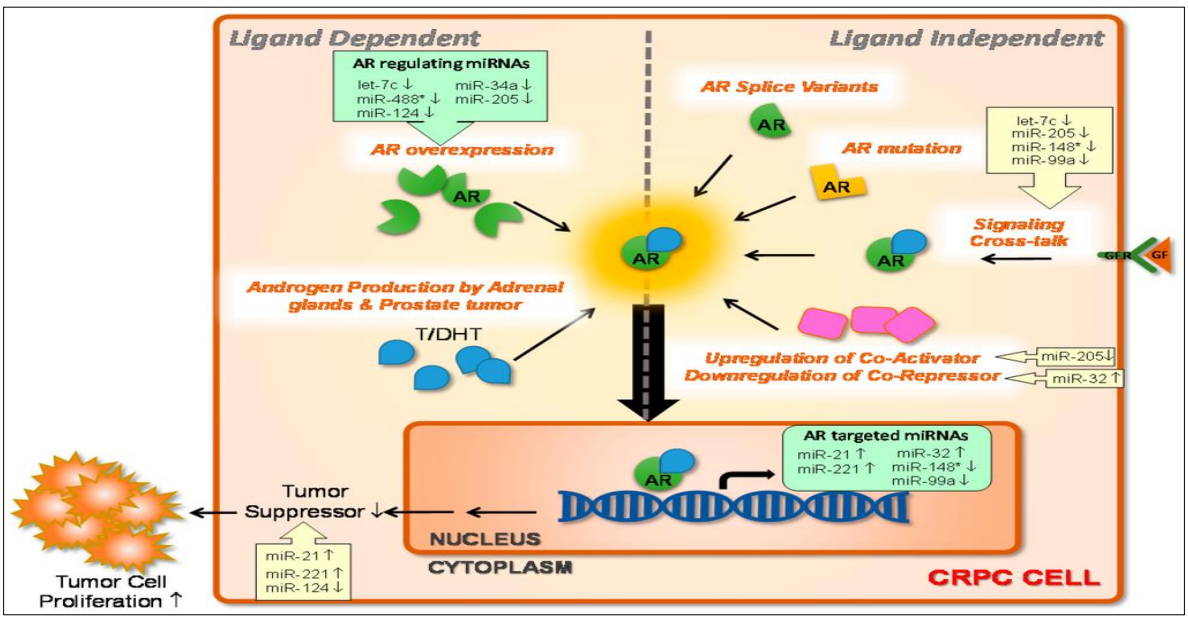
Once in the nucleus, the AR binds to androgen response elements (AREs) located in the promoter regions of target genes. This binding recruits coactivators and other transcription factors, leading to the transcription of genes that promote cell survival and proliferation, such as prostate-specific antigen (PSA) and transmembrane protease, serine 2 (TMPRSS2) (9).

Feedback Mechanisms: The AR signaling pathway is subject to feedback regulation. For instance, the expression of certain target genes can lead to the upregulation of AR itself or its coactivators, enhancing the pathway's activity.

2.2.3. Cross-Talk with Other Signaling Pathways

The AR signaling pathway interacts with several other pathways, including the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway. This cross-talk can enhance cell survival and contribute to therapeutic resistance. For example, activation of the PI3K/Akt pathway can lead to the phosphorylation of AR, enhancing its transcriptional activity even in low androgen conditions. Conversely, AR can modulate the expression of components in the PI3K/Akt pathway, creating a feedback loop that promotes tumor growth.

2.2.4. Castration-Resistant Prostate Cancer (CRPC)



Source: Adapted From Shih et al. (10)

Figure 4 Diagram showing the mechanisms of resistance in CRPC, including AR mutations and alternative pathway activation

In CRPC, the AR remains active despite androgen deprivation therapy (ADT). Mechanisms of resistance include AR mutations that allow for ligand-independent activation, the expression of AR splice variants (e.g., AR-V7) that lack the ligand-binding domain, and the activation of alternative signaling pathways that bypass AR signaling.

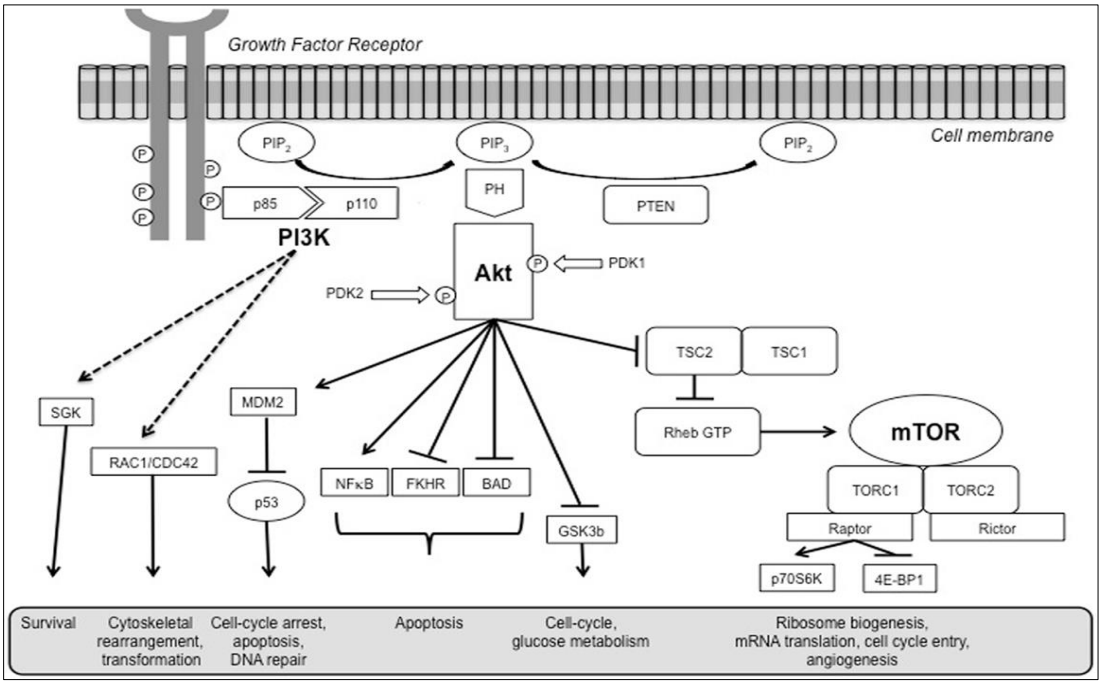
2.3. PI3K/AKT/MTOR PATHWAY

2.3.1. Overview

The PI3K/Akt/mTOR pathway is a critical signaling cascade that regulates cell growth, survival, and metabolism. It is frequently activated in various cancers, including prostate cancer, often due to mutations in upstream regulators like PTEN.

2.3.2. Molecular Mechanisms of PI3K/AKT/MTOR Pathway

- Activation: The pathway is activated by receptor tyrosine kinases (RTKs) or G protein-coupled receptors (GPCRs), leading to the recruitment of PI3K to the plasma membrane.
- Phosphorylation: PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3), which recruits Akt to the membrane.
- Akt Activation: Akt is phosphorylated by PDK1 and mTORC2, leading to its activation. Activated Akt promotes cell survival by inhibiting pro-apoptotic factors and enhancing cell cycle progression.
- mTOR Activation: Akt activates mTORC1, which regulates protein synthesis and cell growth by phosphorylating downstream targets like S6K and 4E-BP1.
- Feedback and Cross-Talk: The pathway exhibits feedback regulation, where mTORC1 can inhibit upstream signaling, and it interacts with other pathways, such as the AR pathway, to promote resistance to therapies.



Source: Adapted From Porta et al.(11)

Figure 5 Diagram depicting the PI3K/Akt/mTOR pathway, highlighting key activation steps and downstream effects

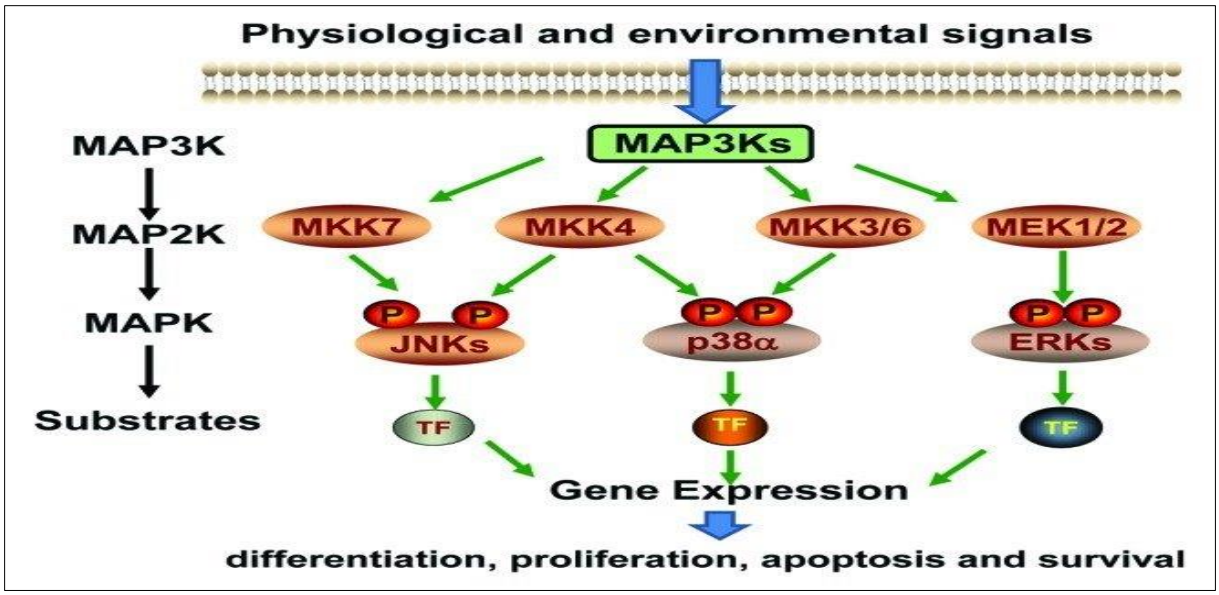
2.4. MAPK/ERK PATHWAY

2.4.1. Overview

The MAPK/ERK pathway is essential for regulating cell proliferation, differentiation, and survival. It is often dysregulated in cancer, leading to enhanced tumor growth and metastasis.

2.4.2. Molecular Mechanisms of MAPK/ERK Pathway

- ctivation: The pathway is activated by various stimuli, including growth factors binding to receptor tyrosine kinases (RTKs), leading to the activation of Ras.
- Ras Activation: Activated Ras recruits and activates Raf, a MAPK kinase kinase (MAP3K), initiating a phosphorylation cascade.
- MAPK Cascade: Raf phosphorylates MEK (MAPK kinase), which in turn phosphorylates ERK (extracellular signal-regulated kinase).
- ERK Activation: Activated ERK translocate to the nucleus, where it regulates gene expression by phosphorylating transcription factors such as Elk-1 and c-Fos.
- Feedback Mechanisms: The pathway is subject to negative feedback regulation, where ERK can phosphorylate and inhibit upstream components, and it interacts with other pathways, including the PI3K/Akt pathway, to promote cell survival.



Source : Adapted from Wang and Xia (12)

Figure 6 Diagram of the MAPK/ERK pathway, illustrating the phosphorylation cascade and gene regulation

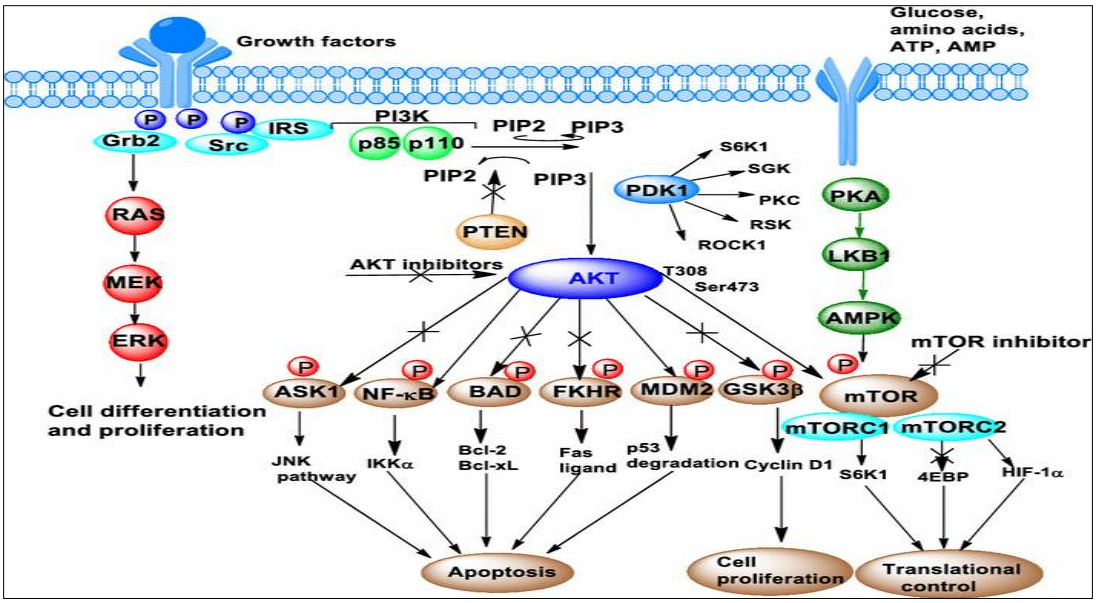
2.5. Receptor tyrosine kinase (RTK) pathway

2.5.1. Overview

Receptor tyrosine kinases are a family of cell surface receptors that play critical roles in regulating cellular processes such as growth, differentiation, and metabolism. Dysregulation of RTK signaling is implicated in various cancers.

2.5.2. Molecular Mechanisms of Receptor Tyrosine Kinase (RTK) Pathway

- ligand Binding: Binding of a dimeric ligand to RTKs induces receptor dimerization and autophosphorylation of tyrosine residues in the cytoplasmic domain.
- Signal Transduction: Autophosphorylation creates docking sites for downstream signaling proteins, activating pathways such as MAPK/ERK and PI3K/Akt.
- Downstream Effects: These pathways promote cell proliferation, survival, and migration. For example, the MAPK pathway enhances gene expression related to cell growth, while the PI3K pathway promotes cell survival.
- Negative Feedback: The activity of RTKs is regulated by negative feedback mechanisms, including the recruitment of protein tyrosine phosphatases that dephosphorylate active receptors.
- Cross-Talk: RTK signaling interacts with other pathways, such as the NF-κB pathway, to modulate inflammatory responses and tumor progression.



Source: Adapted From Gill et al. (13)

Figure 7 Diagram showing the RTK pathway, including ligand binding, signal transduction, and downstream effects

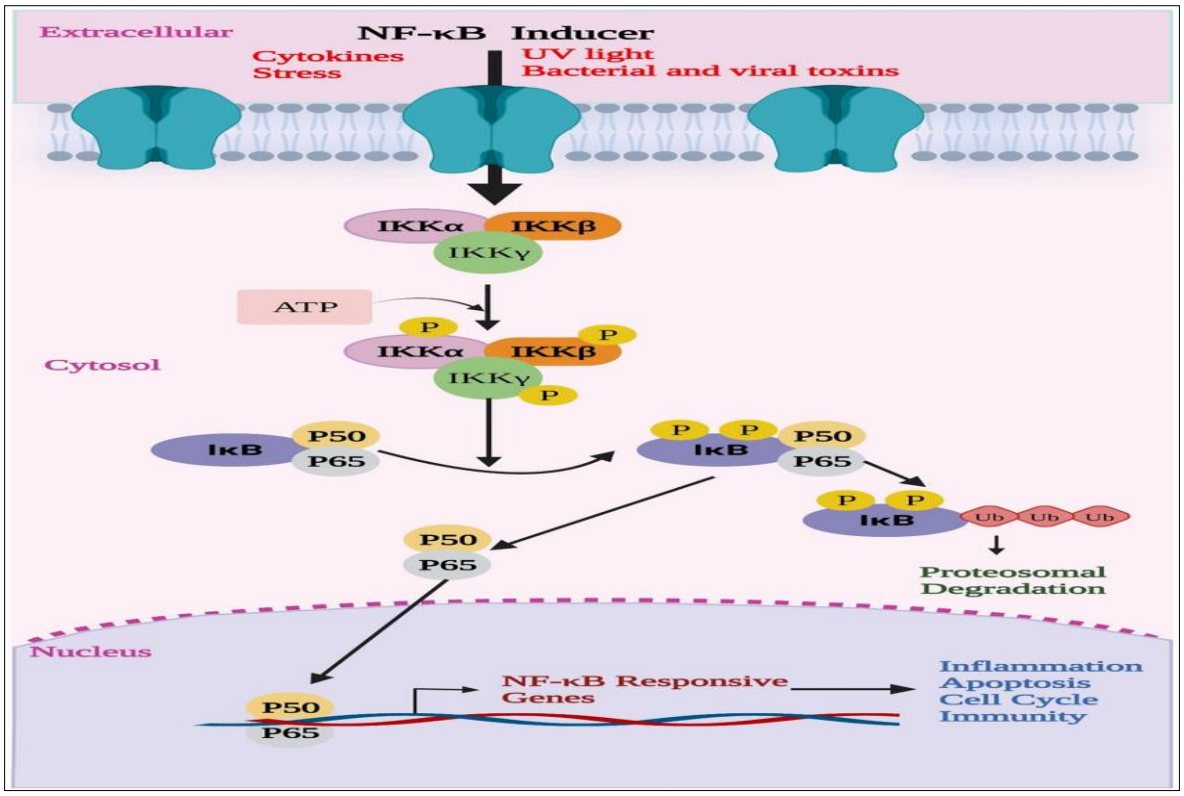
2.6. NF-KB PATHWAY

2.6.1. Overview

The NF-κB pathway is a key regulator of inflammation and immune responses. It is often activated in cancer, promoting cell survival and proliferation.

2.6.2. Molecular Mechanisms

- Activation: The pathway can be activated by various stimuli, including pro-inflammatory cytokines (e.g., TNF-α) and microbial products, leading to the phosphorylation and degradation of IκB proteins.
- NF-κB Release: Degradation of IκB releases NF-κB dimers (e.g., p65/RelA and p50) that translocate to the nucleus.
- Gene Regulation: In the nucleus, NF-κB binds to specific DNA sequences, regulating the expression of genes involved in inflammation, cell survival, and proliferation.
- Feedback Mechanisms: The pathway is subject to feedback regulation, where NF-κB can induce the expression of IκB proteins, which inhibit its own activity.
- Cross-Talk: NF-κB interacts with other signaling pathways, including the JAK/STAT pathway, to modulate immune responses and promote tumor progression.



Source: Adapted From Alharbi et al.(14)

Figure 8 Diagram of the NF-κB pathway, illustrating activation mechanisms and gene regulation

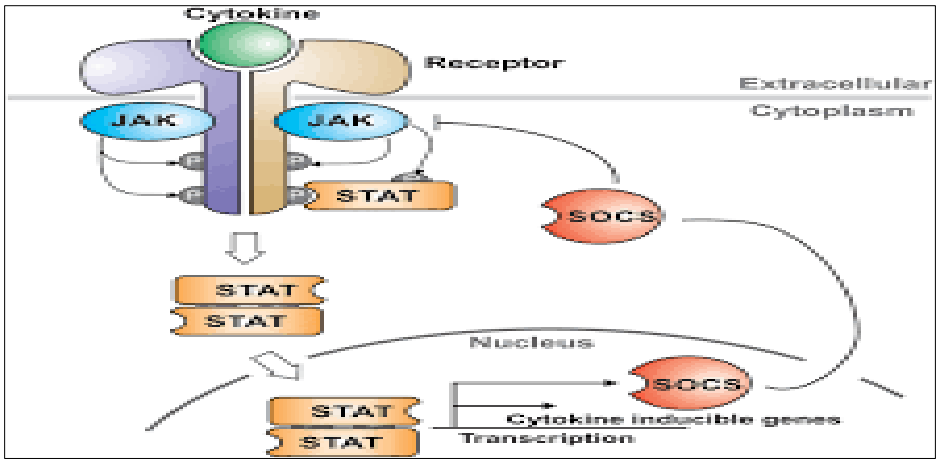
2.7. JAK/stat pathway

2.7.1. Overview

The JAK/STAT pathway is critical for mediating responses to cytokines and growth factors. It plays a significant role in immune signaling and has been implicated in cancer progression.

2.7.2. Molecular Mechanisms of JAK/STAT Pathway

- Cytokine Binding: Binding of cytokines (e.g., IL-6) to their receptors activates associated Janus kinases (JAKs), leading to their phosphorylation.
- TAT Activation: Phosphorylated JAKs then phosphorylate signal transducer and activator of transcription (STAT) proteins, which dimerize and translocate to the nucleus.
- Gene Regulation: In the nucleus, STAT dimers bind to specific DNA sequences, regulating the expression of genes involved in cell proliferation and survival.
- Feedback Mechanisms: The pathway exhibits feedback regulation, where activated STATs can induce the expression of suppressors of cytokine signaling (SOCS), which inhibit JAK activity.
- Cross-Talk: The JAK/STAT pathway interacts with other pathways, such as the NF-κB pathway, to modulate immune responses and contribute to tumorigenesis.
- In conclusion, each of these signaling pathways plays a pivotal role in the development and progression of prostate cancer. Understanding the intricate molecular mechanisms, feedback loops, and interactions between these pathways is essential for developing targeted therapies and improving patient outcomes. Further research into these pathways will enhance our ability to identify novel therapeutic targets and devise effective treatment strategies for advanced prostate cancer.



Source: Adapted From Morris et al.(15)

Figure 9 Diagram of the JAK/STAT pathway, highlighting cytokine binding, JAK activation, and STAT signaling

3. Clinical implications

The intricate signaling pathways involved in prostate cancer (PCa) development and progression have significant clinical implications, particularly in the context of treatment resistance, ongoing research, and the role of biomarkers in predicting treatment response and disease progression.

3.1. Current Clinical Trials and Ongoing Research

Numerous clinical trials are currently investigating novel therapeutic strategies targeting the key signaling pathways implicated in prostate cancer. For instance, trials are exploring the efficacy of inhibitors that target the androgen receptor (AR) signaling pathway, such as enzalutamide and abiraterone, in combination with other agents that inhibit the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway. These combination therapies aim to overcome resistance mechanisms that arise when tumors adapt to single-agent therapies.

Combination Therapies: Clinical trials are examining the effectiveness of combining AR inhibitors with PI3K inhibitors, such as BYL719, or mTOR inhibitors, like everolimus. These studies are designed to evaluate whether dual targeting can enhance therapeutic efficacy and delay the onset of castration-resistant prostate cancer (CRPC).

Targeting DNA Damage Repair: Emerging research has highlighted the importance of DNA damage repair defects in prostate cancer. Clinical trials are underway to assess the efficacy of PARP inhibitors, such as olaparib, in patients with BRCA mutations or other homologous recombination repair deficiencies. These trials aim to determine whether targeting DNA repair pathways can improve outcomes in specific patient populations.

Hippo Signaling Pathway: The Hippo signaling pathway, which regulates cell growth and organ size, has been implicated in prostate cancer progression. Ongoing research is investigating the potential of targeting components of this pathway to inhibit tumor growth and metastasis.

3.2. Implications of Pathways in Treatment Resistance

- The dysregulation of key signaling pathways in prostate cancer contributes to treatment resistance, a major challenge in managing the disease. Understanding these resistance mechanisms is crucial for developing effective treatment strategies.
- Androgen Receptor Pathway Resistance: In CRPC, tumors often develop resistance to androgen deprivation therapy (ADT) through mechanisms such as AR mutations, splice variants, and activation of alternative signaling pathways. This resistance necessitates the exploration of combination therapies that can target both the AR and alternative pathways, such as PI3K/Akt or MAPK/ERK, to enhance treatment efficacy.
- PI3K/Akt/mTOR Pathway Activation: The activation of the PI3K/Akt/mTOR pathway is frequently observed in advanced prostate cancer and is associated with resistance to AR-targeted therapies. Understanding the interplay between these pathways can inform the design of clinical trials that evaluate the effectiveness of dual inhibition strategies.

- Cross-Talk Between Pathways: The interaction between different signaling pathways can create a complex network that promotes tumor survival and growth. For example, the cross-talk between the AR and NF-κB pathways can enhance the aggressive phenotype of prostate cancer cells. Targeting these interactions may provide new avenues for overcoming resistance.

4. Conclusion

Each of these signaling pathways plays a pivotal role in the development and progression of prostate cancer. Understanding the intricate molecular mechanisms, feedback loops, and interactions between these pathways is essential for developing targeted therapies and improving patient outcomes. Ongoing research continues to explore novel therapeutic strategies and the potential of personalized medicine, paving the way for more effective treatments in prostate cancer management.

Compliance with ethical standards

Acknowledgment

The authors of this manuscript are thankful to Babcock University for the support provided to accomplish this review article.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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