Journal of Cancer Biomoleculars and Therapeutics

ETERNO PRESS

Review

Apoptosis Dysregulation in Prostate Cancer: The BAX/BCL-2 Dynamics and Caspase Cascade Activation Networks

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Article history

Received: 4 April 2026
Revised: 10 July 2026
Accepted: 17 July 2026
Published online: 21 July 2026

Keywords

Prostate cancer
Apoptosis dysregulation
BAX/BCL-2 ratio
Caspase cascade
Androgen receptor signaling
Therapeutic targets

Abstract

Prostate cancer is one of the most diagnosed cancers in men and a leading cause of cancer-related deaths across the globe. Apoptotic disruption is a hallmark of prostate tumorigenesis that is highly regulated and ensures maintenance of cellular homeostasis. There has been growing evidence that the balance of the B-cell lymphoma 2 (BCL-2) family proteins, especially the ratio between pro-apoptotic BCL-2-associated X protein (BAX) and anti-apoptotic BCL-2, is a leading factor in the control of mitochondrial apoptosis and a contributing factor to prostate cancer progression and resistance to treatment. Under normal prostate conditions, the survival of epithelial cells via intricate stromal epithelial communications is coordinated by the androgen receptor (AR) signaling, and androgen deprivation leads to apoptotic regression of prostate epithelial cells. But at the advanced stage of disease progression, the tumors of the prostate gland often transform into androgen-independent or castration-resistant forms with high BCL-2 expression levels and low apoptosis susceptibility. The mechanisms of apoptosis dysregulation in prostate cancer are presented in this review through the BAX/BCL-2 control of apoptosis, and downstream regulation of the caspase cascade. It also discusses the role of changes in the major signaling pathways involving phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), signal transducer and activator of transcription 3 (STAT3), nuclear factor kappa light chain enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) in the regulation of the activity of BCL-2 and the survival of tumor cells. Besides this, developing regulatory networks between microRNAs and autophagy-related proteins (Beclin-1 and Autophagy/beclin-1 regulator 1 (AMBRA1)) and other regulators are also discussed in terms of their roles in controlling apoptosis and responsiveness to treatment. The existing therapeutic plans of BCL-2 and it signaling partners are also considered, where the potential and shortcomings of the existing inhibitors in the clinical context are outlined. Together, the knowledge of the complex regulation of the apoptotic pathways in prostate cancer offers some valuable information on the development of the disease and the means of resistance. Inhibiting the BAX/BCL-2 axis and caspase-driven apoptotic signaling can thus provide good prospects in the elaboration of more applicable treatment approaches to the treatment of advanced and castration-resistant prostate cancer (CRPC).

1. Introduction

The second most diagnosed male cancer and fifth most common cause of cancer-related mortality in the world is prostate cancer. According to the Global Cancer Observatory (GLOBOCAN 2022), prostate cancer remains one of the most frequently diagnosed malignancies among men worldwide, with approximately 1.47 million new cases and over 397,000 deaths reported in 2022 [1]. It is currently the second most commonly diagnosed cancer in men globally and continues to represent a substantial public health burden due to its increasing incidence, aging populations, and geographical disparities in disease occurrence and mortality. These updated epidemiological trends underscore the continued need for improved understanding of the molecular mechanisms underlying prostate cancer progression and the development of effective targeted therapeutic strategies. The global burden of prostate cancer has been increasing, although the incidence significantly differs among regions, and there is over 25-fold difference among nations [2]. Prostate cancer is a multifactorial disease influenced by genetic, environmental, and lifestyle-related factors. Established risk factors include advancing age, family history, inherited genetic mutations (particularly in *BRCA1*, *BRCA2*, and *HOXB13*), African ancestry, and hormonal influences. In addition, obesity, diets rich in

saturated fats and red meat, chronic inflammation, smoking, and physical inactivity have been associated with an increased risk of disease development and progression. Although several of these factors are well established, the contribution of modifiable lifestyle and environmental exposures continues to be investigated [3,4].

Prostate cancer treatment methods comprise androgen deprivation therapy (ADT), external beam radiotherapy, brachytherapy and cryotherapy. Numerous of these therapies rely fundamentally on the fact that normal prostate cells and early-stage tumors rely on androgen signaling to grow and survive [5]. But these strategies do not tend to be effective at advanced stages, especially with androgen-independent prostate cancers (AIPCs). The B-cell lymphoma 2 (BCL-2) protein family is also divided into 3 functional categories: BH3-only proteins, anti-apoptotic (pro-survival) and multi-domain pro-apoptotic proteins. BCL-2 itself also serves as a key controller of cell survival and has been closely linked to tumor development. There is growing evidence to suggest that BCL-2 signaling plays a role in carcinogenesis and the progression of chemoresistance in advanced prostate cancer, especially in AIPCs. High levels of BCL-2 have been detected in clinical and xenograft models after ablation or castration of the androgen receptor (AR). Various small-molecule BCL-2 inhibitors have been developed as clinical agents in cancer therapies of chronic lymphoid leukemia, treatment-resistant multiple myeloma, pancreatic carcinoma, and ovarian carcinoma. These include Navitoclax, Venetoclax, oblimersen sodium, AT-101, and GX15-070 (Obatoclax) [6,7]. Nevertheless, few studies exist regarding the use of BCL-2 inhibitors as their own treatment in prostate cancer and few studies examine combinations, including ABT-263 with abiraterone acetate and AT-101 with prednisone in metastatic castration-resistant PC. Furthermore, the exact functions of BCL-2 and its relevant signal pathways in androgen-dependent prostate cancer (ADPC) and AIPC are not well understood and somewhat controversial. However, the overexpression of BCL-2 is reported to provide resistance to tumor cells by avoiding apoptotic signaling. Thus, the review is concerned with the biomolecular processes of BCL-2 and their interactions with AR-dependent and independent pathways, such as microRNAs and other signaling entities that promote the progression of prostate cancer [8-10].

2. Apoptosis in Prostatic Epithelial Cells is Regulated by AR Signaling in the Stromal Compartment

2.1 Stromal and Luminal Microenvironments of the Prostate

The prostate gland in humans is made up of two large sections, epithelial and stromal. The epithelial compartment consists of basal and luminal epithelial cells, but the stromal compartment embraces and nourishes the epithelium. Luminal epithelial cells refer to polarized cellular structures comprising of columnar cells that make up a continuous layer covering the lumen of a gland [11]. The prostate has non-secretory basal epithelial cells which are concentrated along the basement membrane in the form of a barrier between the luminal and stromal compartments. These cells are defined as cells that are expressed with cytokeratin 5 and 14, p63, and GSTP1 with a comparatively low level of AR expression. Besides this, there are a few neuroendocrine cells in the basal layer; they are AR-negative cells that produce neuropeptides and growth factors controlling the activity of the luminal epithelial cells [12]. There are also rare neuroendocrine cells in the basal layer; these AR-deficient cells produce neuropeptides and mitogenic factors that control the activity of luminal epithelial cells. The compartment of stromal cells consists of fibroblasts that produce extracellular matrixes, smooth muscle cells that expel the prostate fluid, and other elements, e.g., blood vessels, nerves, and immune cells, that help form the tissue structure and intercellular communication [13-15].

2.2 Androgen Ablation Triggers Apoptosis

Androgen signaling through the AR is required to drive the normal prostate gland growth, differentiation, and function and the growth and progression of prostate cancer. The AR can be modulated by two androgens, testosterone and a stronger product of this hormone, dihydrotestosterone (DHT). In the prostate, DHT is produced by changing testosterone into the more potent androgen DHT with the help of 5α-reductase [16]. In the absence of androgen binding, the AR is maintained in the cytoplasm in an inactive form in association with heat shock proteins (HSPs) but is ready to become active through ligand interaction. On androgen binding, AR changes conformation and dissociates from HSPs and is activated. Active AR dimers translocate to the nucleus, where they bind to androgen-responsive elements (AREs) using the DNA-binding domain of the promoter regions of the target genes of the AR. Then, RNA polymerase II, complexes and coactivators are recruited, and the target gene transcription is either induced or repressed [17,18].

Early foundational investigations of prostate gland involution following bilateral orchidectomy in canine models were preceded by seminal experiments characterizing the structural patterns of active cell deletion in regression tissue [19]. In experimental rats, which revealed spectacular prostatic atrophic remodeling was revealed following testicular excision, with a significant reduction in organ weight on day 3 following testicular ablation, which persisted until days. Ultrastructural analyses have established important morphological characteristics of apoptosis in prostate tissue during androgen deprivation, including the formation of autophagic vacuoles, chromatin condensation, nuclear fragmentation, and macrophage and epithelial cell phagocytosis of apoptotic bodies. The temporal analysis indicates that the apoptotic activity is almost three times more intense on the second day after castration, the peak of the activity is on the third day after castration, and then the activity decreases slowly. The apoptotic cells are mostly seen in the epithelial layer, but aggregates can also be found in the glandular lumina. These results suggest that ventrally located prostate

involution in castrated animal models occurs mainly as a result of apoptosis. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) and mitotic index determinations made by quantitative measurements indicated that prostate involution was caused both by decreased cell proliferation and an increase in cellular apoptosis [20]. The evaluation of apoptosis via the TUNEL method of detecting DNA fragmentations and the evaluation of cellular proliferation by means of the tritiated thymidine labeling in vivo has shown that the involution of prostate correlates with reduced proliferation rate and increased apoptosis. It seems that apoptosis is the leading role in the process, and experimental models with prostate-specific expression of BCL-2 support it. BCL2 transgenic mice by the probasin promoter framework, displayed a distinct pattern of active cellular deletion following androgen deprivation. This classic apoptotic regression in the rodent ventral prostate is characterized by distinct morphological stages, including nuclear chromatin condensation, cytoplasmic fragmentation, and subsequent phagocytosis by neighboring cells [21]. Furthermore, early kinetic analyses of this process demonstrated that biochemical markers of cell death, such as DNA fragmentation, peak sharply around day 3 to 4 following castration [22]. In addition to BCL-2, other anti-apoptotic members of the BCL-2 family, particularly myeloid cell leukemia-1 (MCL-1) and B-cell lymphoma-extra-large (BCL-xL), play critical roles in regulating mitochondrial apoptosis and therapeutic resistance in advanced prostate cancer. Both proteins are frequently upregulated in castration-resistant prostate cancer (CRPC), where they inhibit BCL-2-associated X protein/BCL-2 antagonist/killer (BAX/BAK)-mediated mitochondrial outer membrane permeabilization, thereby promoting tumor cell survival despite androgen deprivation and systemic therapies. Emerging evidence further indicates that compensatory upregulation of anti-apoptotic proteins like MCL-1 and BCL-xL often drives resistance in advanced CRPC. To counteract this mechanism, recent therapeutic strategies have focused on dietary phytochemicals and natural compounds. For instance, the cruciferous vegetable-derived compound sulforaphane has been shown to downregulate these survival factors and induce apoptotic cascades in prostate cancer cells [23]. Similarly, secondary lichen metabolites such as physodic acid have demonstrated significant efficacy in modulating the BCL-2 family network, effectively tilting the cellular balance toward programmed cell death in resistant phenotypes [24].

2.3 AR–Dependent Stromal Modulation of Epithelial Apoptosis

In pre-clinical studies, experimental analysis has revealed that luminal epithelial cells undergo apoptosis after androgen deprivation and can be regenerated after androgen levels are restored [25]. Beyond classical apoptosis, modern paradigms highlight the importance of interconnected, inflammatory programmed cell death networks in halting advanced prostate cancer progression. Specifically, the activation of PANoptosis-a highly coordinated process integrating molecular features of pyroptosis, apoptosis, and necroptosis—has emerged as a vital regulatory mechanism to overcome conventional treatment resistance and stimulate anti-tumor immunity within the urological microenvironment [26]. Concurrently, natural product research has identified novel marine derivatives capable of inducing these very cascades. For instance, the ethanolic extract of the diatom *Chaetoceros socialis* has demonstrated selective in vitro cytotoxic and pro-apoptotic efficacy against human prostate cancer cell lines (such as LNCaP) by actively modulating downstream protein kinase B/phosphatase and tensin homolog (AKT/PTEN), mechanistic target of rapamycin (mTOR), and BAX/BCL-2 signaling pathways to tip the balance toward cellular destruction [27]. To further delineate the regulatory mechanisms controlling these pathways, investigators have explored highly conserved tumor suppressor genes that dictate mitochondrial integrity. The longevity assurance homolog 2 (LASS2) gene plays a critical role in inducing early apoptosis through a caspase-dependent mitochondrial pathway, decreasing anti-apoptotic BCL-2 expression while accelerating downstream caspase-9 and caspase-3 activation-a mechanism heavily evaluated across various aggressive carcinoma models [28]. Complementing these genetic frameworks, small-molecule interventions such as chalcone derivatives are increasingly utilized to trigger alternate, immunogenic death modalities. These natural compounds bypass standard apoptotic blockades by concurrently provoking mitochondria-mediated apoptosis and gasdermin-dependent pyroptosis, inducing membrane perforation and inflammatory cytokine release to effectively eradicate resistant prostate cancer cells and reshape the suppressive tumor microenvironment [29,30].

The dysregulation of mitochondrial dynamics and survival pathways is a hallmark of aggressive malignancies, prompting comparative studies across different therapeutic resistance models. For instance, investigations into the blood-brain barrier-permeable agents in glioblastoma have highlighted how modulating baseline chemosensitivity and cellular stress pathways can dictate overall treatment response [31]. Parallel to these findings in other hard-to-treat cancers, targeted interventions in prostate oncology are actively exploiting mitochondrial vulnerabilities. Specifically, combining the PARP inhibitor Rucaparib with agents targeting dynamin-related protein 1 (Drp1) has demonstrated a profound ability to disrupt mitochondrial fission and fusion kinetics. This synergistic approach effectively triggers massive mitochondrial dysfunction and downstream apoptotic cascades, providing a powerful strategy to overcome standard castration-resistant phenotypes [32]. Fibroblast growth factor/extracellular signal-regulated kinase (FGF/ERK) signaling pathway has also been found to be involved in developing resistance to ADT in prostate cancer cell lines. Besides epithelial apoptosis, it has also been reported that androgen deprivation is related to apoptosis of the endothelial cells in the prostate stroma [33]. Even though low blood flow and hypoxia were hypothesized at the beginning as possible factors, later researchers have not always supported the presence of hypoxia after castration.

A combination of tissue recombination experiments, prostate-specific transgenic models, and the analysis of single-cell RNA sequencing all provide evidence that even though the AR is highly expressed in prostate epithelial cells, it does not directly regulate prostate epithelial cell proliferation or survival [34]. In its place, growth and survival of the luminal epithelial cells in a paracrine manner are controlled by AR-dependent expression of growth and survival factors by the cells in the stromal compartment. Emerging data on the AR signaling controlling the indirect, paracrine control of prostate epithelial cells in stromal compartments challenge the traditional modality of non-selective androgen ablation therapy. This research highlights the importance of further specific therapeutic approaches that can specifically regulate AR activity in the tumor stroma [35,36]. Moreover, more advanced research that involves inducible transgenic models as well as single-cell genomic and proteomic research should be done to establish the most important paracrine mediators of apoptosis post androgen deprivation. There is also needed to clarify the apoptosis-controlling molecules, which are affected by these stromal-derived signals [10,37,38].

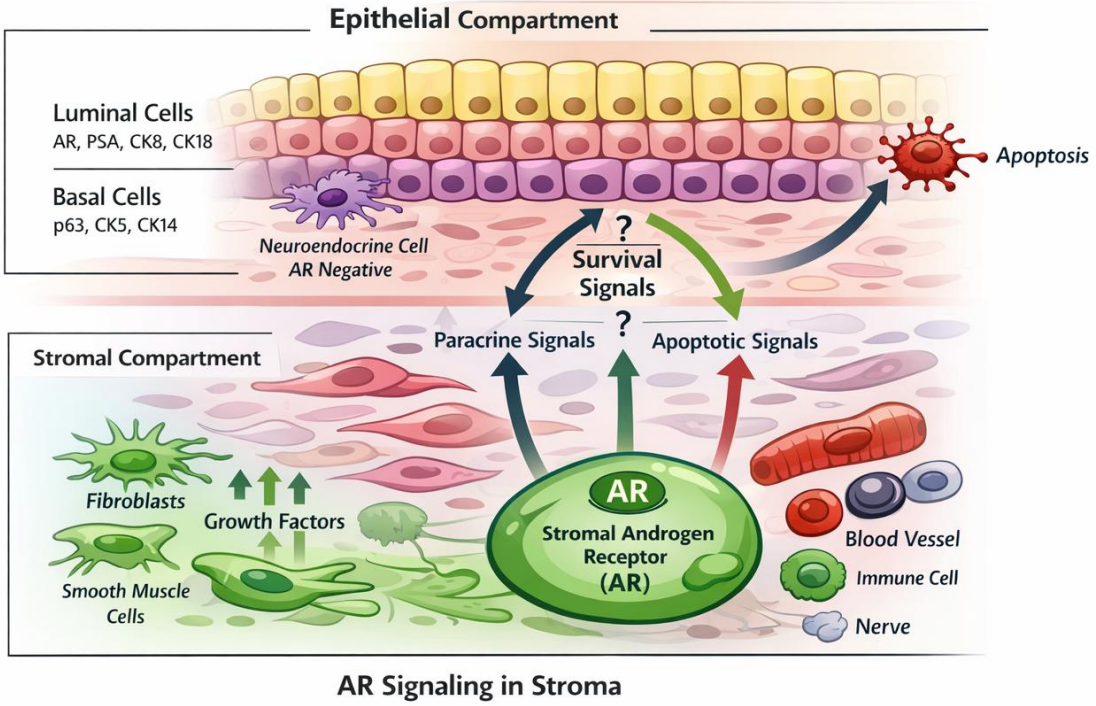

Figure 1. Stromal AR-mediated regulation of epithelial apoptosis in the prostate. Schematic representation of prostate gland organization showing epithelial (luminal, basal, and neuroendocrine cells) and stromal compartments. Activation of the androgen receptor (AR) in stromal cells induces paracrine growth factors that regulate the survival of luminal epithelial cells, whereas androgen deprivation reduces stromal AR signaling and triggers epithelial apoptosis (Source: Self-made by BioRender.com).

2.4 Intrinsic and Extrinsic Apoptotic Pathways in Prostate Cancer

In prostatic epithelial cells, apoptosis may be triggered either by intrinsic or extrinsic (death receptor-mediated) pathways. Activation of the extrinsic pathway occurs through death receptors of the tumor necrosis factor (TNF) receptor superfamily that consists of TNFRSF1A, FAS, and TRAIL receptors (TNFRSF10A: DR4), (TNFRSF25: DR3), and (TNFRSF21: DR6). When these receptors bind to the ligand, they assemble into a death-inducing signaling complex (DISC), which in turn stimulates initiator caspases 8 and 10. Subsequent effector caspases 3, 6, and 7 are then initiated by these initiator caspases, resulting in the proteolytic cleavage of cellular substrates, causing apoptosis to occur [39]. The protein CFLAR/FLIP can prevent the extrinsic apoptotic pathway. Mixed results have been obtained through experimental research on the role of death receptor signaling in involution of the prostate. While early research using FAS-defective *lpr* mice suggested that prostate involution after castration requires functional death receptor signaling, subsequent comparative studies revealed a more complex mechanism. Although FAS ligand (FASL) is significantly upregulated following castration, apoptotic indices do not show substantial differences between wild-type and *lpr* strains, indicating that standalone FAS deficiency is insufficient to halt structural regression. Subsequent comparative studies that employed knockout models showed that activated TNFR1 signaling inhibition and not FAS deficiency were linked to impaired prostate involution. These results indicate that stromal-derived TNF-alpha is an important mediator of prostate involution by TNFR1 signaling in luminal epithelial cells [40,41]. The rate of involution was, however, not always related to apoptotic indices and TNF-alpha alone was not enough to promote structural regression in intact mice, implying that androgen deprivation primes epithelial cells to TNF-alpha-mediated apoptosis [42,43].

The FLICE-like inhibitory protein (FLIP) is a possible gene under the AR regulation that helps in regulating death receptor-mediated apoptosis. FLIP is a downstream

mediator of the death receptor activation process, and as an inhibitor of DISC formation, has the potential to be a regulatory mediator in apoptosis signalling. Controlled expression of FLIP via AR pathway was shown by experiments with androgen deprived rats and in prostate cell lines that had sensitivity to apoptosis mediated by TRAIL determined by FLIP concentrations. More studies using inducible knockout models of individual death receptors as well as downstream signaling components are needed to further define the individual contribution of each pathway to prostate involution following androgen depletion [44,45]. BH3-only protein BID is a molecular bridge connecting extrinsic and intrinsic apoptotic pathways; the direct contribution to castration-induced apoptosis has not been completely clarified yet. Rather, the research has majorly concentrated on the mitochondrial apoptotic regulators like BAX and BCL-2. Both BAX and BCL-2 levels of expression have been found to increase as a result of castration of murine prostate tissue [46]. Apoptosis analysis of BAX-deficient (BAX- minus/minus) mice by TUNEL assays showed a very significant decrease in apoptosis after 5 days of post castration in comparison to the mice, but there is no substantial difference in apoptosis at other times. This and other data showing that BAX and BAK appear to be functionally redundant in other knockout systems imply that it may be crucial to delete both proteins at the same time to define the functions of both proteins in apoptosis [47,48]. Likewise, transgenic mice with BCL-2 overexpression in the prostate had lower indices of apoptosis after castration, but relative comprehensive data of prostate involution in transgenic mice has not been established. Prostate-specific overexpression of BCL-2 in the transgenic models under probasin promoters have shown a considerable decrease in apoptotic index, but their effects in prostate involution are not well understood. On the same note, other studies employing Bcl-2 transgenes that are driven by other promoters have failed to give conclusive information on the effect of castration on apoptosis or the regression of the prostate. It seems that AR inactivation of the prostate stroma causes more death receptor ligands and less survival factors that cause epithelial cell apoptosis. All in all, the outcome of transgenic mice indicates that the apoptotic regulatory proteins in regards to death receptor and mitochondrial pathways have a combined effect in regulating apoptosis caused by androgen ablation in the prostate gland [49-51].

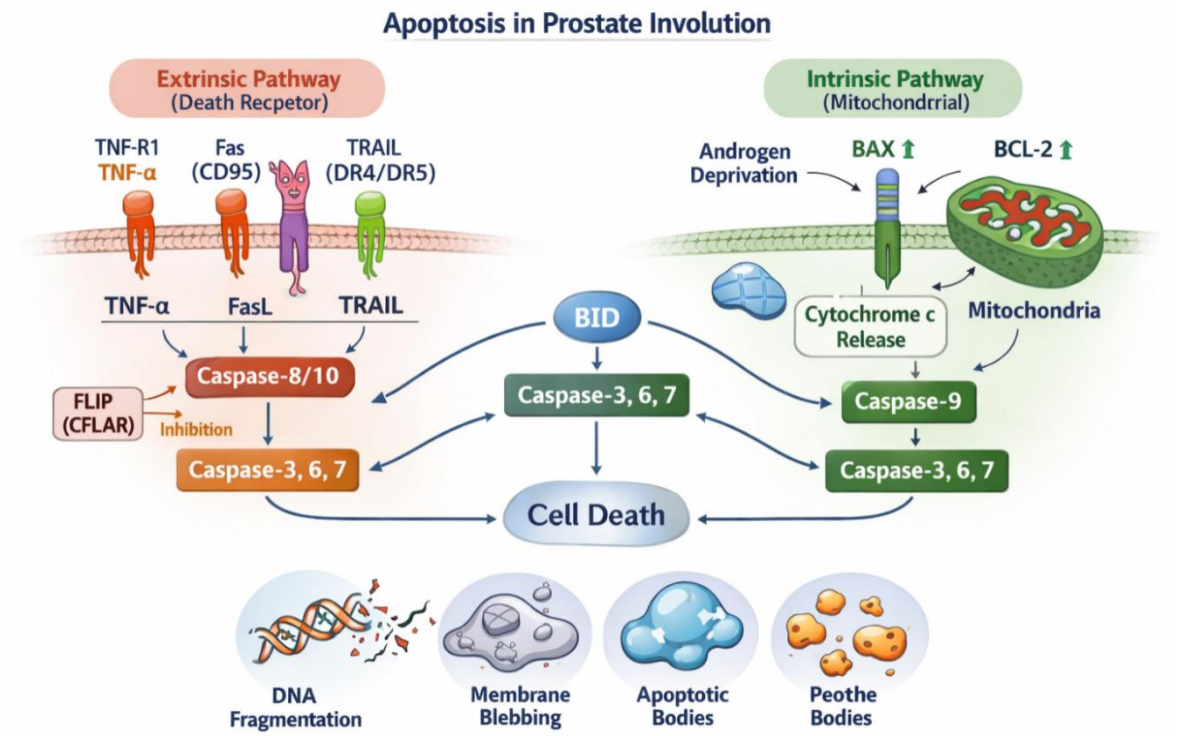

Figure 2. Diagrammatic representation of the mitochondrial and death receptor-mediated apoptotic mechanisms that took place in the prostate during involution due to androgen deprivation. It is emphasized in the diagram that the important signaling molecules involve TNF-alpha/TNFR1, FAS/FASL, TRAIL receptors, FLIP, BID, Bax/BCL-2, and caspase cascades that result in the apoptosis of epithelial cells. Both mechanisms lead to effector caspases (caspase-3, -6, -7), which result in the programmed cell death, which is marked by DNA fragmentation, membrane blebbing, and the formation of apoptotic bodies (Source: Self-made by BioRender.com).

3. BCL-2 Family and Androgen-Dependent or AIPCs

3.1 BCL-2 Family

BCL-2 plays a major role in anti-apoptotic protein by enhancing cell survival, cell proliferation and tumor formation. It is majorly localized at the outer mitochondrial membrane, endoplasmic reticulum, and nuclear envelope and it controls apoptotic signaling pathways. In these regions, there are anti-apoptotic proteins, including BCL-2 and MCL-1, BFL1/A1 BHL and BH2 domains and direct interactions between them and the pro-apoptotic proteins, such as BCL-2-like protein 11 (BIM), BID, BCL-2-associated agonist of cell death (BAD), p53 upregulated modulator of apoptosis (PUMA) and NOXA [40,52]. The post-translation

modification of the BCL-2 is paramount in the control of the BCL-2 functionality. Serine-70 phosphorylation is linked to anti-apoptotic activity and enhanced chemoresistance, whereas dephosphorylation of threonine-56, threonine-69, serine-70, threonine-74 and serine-87 increases the cellular susceptibility to anticancer agents [53,54]. BCL-2, in its mechanism of action, prevents apoptosis by heterodimerization with pro-apoptotic molecules, including BAX or p23 R-Ras. Hyperphosphorylation of BCL-2 on the contrary destabilizes these complexes hence promoting the apoptosis. Multi-domain pro-apoptotic members (e.g. BAX, BAK, and BOK) interact with BH3-only proteins to facilitate oligomeric pore formation in the mitochondrial membrane and release cytochrome c. The structural analysis has shown an anti-apoptotic protection of BCL-2 family members to start with the hydrophobic groove binding to the BH3 α-helical domain of pro-apoptotic proteins, thus deactivating them. [55,56].

3.2 Androgen Signaling in Prostate Cancer Progression

AR activation happens when it binds its ligands, testosterone or DHT, in cytoplasm and then translocates to nucleus and acts as a transcription factor [57,58]. The AR is the one that controls the prostate-specific antigen (PSA) expression, and it is the key player in several cellular activities, such as proliferation, differentiation, migration and invasion in prostate cancer. In ADPC, AR signaling plays a vital role in the early-stage prostate carcinogenesis, which is, in turn, largely dependent on androgens. Nonetheless, the onset of the disease to the advanced stages is mostly linked to resistance to therapy especially after hormonal therapy or castration. Such resistance is mediated by various processes, which are: AR gene amplification, splice variants, post-translational modifications, co-regulator changes, and point mutations [59,60]. In addition, experimental research has proved that upregulation of BCL-2 provides insensitivity to apoptosis in LNCaP prostate cancer cells. Engineered LNCaP cells that overexpress BCL-2 protein were resistant to apoptotic stimuli, e.g., serum deprivation or phorbol ester treatment. The in vivo research with nude mouse models demonstrated that tumor development in BCL-2- overexpressing cells did not differ significantly from the controls, though the androgen deprivation was still effective in suppressing tumor development by castration [61,62]. Therefore, BCL-2 targeting can be an excellent approach to the successful treatment of either AIPC or CRPC, despite the use of ADT or castration as an ADPC treatment methodology [63].

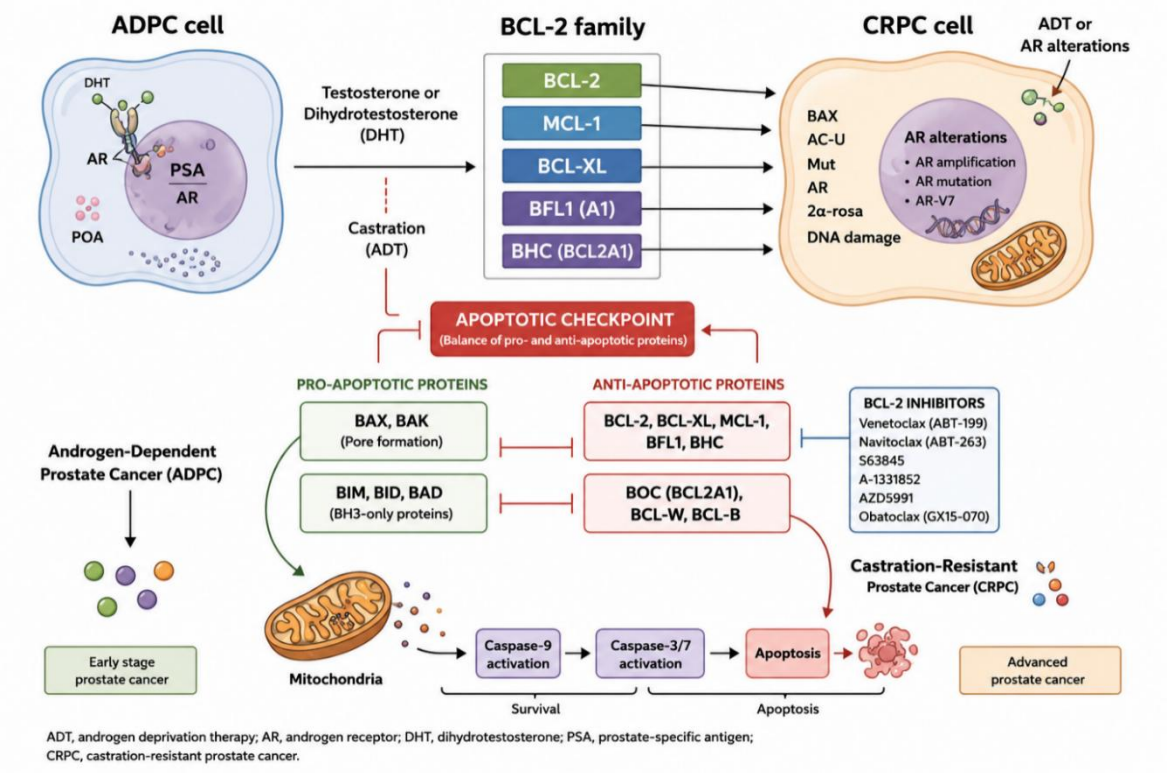

Figure 3. Schematic representation of BCL-2 family proteins and androgen receptor (AR) signaling in the progression from androgen-dependent to castration-resistant prostate cancer (CRPC). It highlights the balance between pro- and anti-apoptotic regulators and their role in apoptosis resistance and tumor progression (Source: Self-made by BioRender.com).

3.3 Development of AIPC

ADT is commonly used to treat hormone-sensitive prostate cancers but often results in additional progression into AIPCs, which are more aggressive and metastatic. Despite an initial favorable response, most patients receiving ADT eventually progress to CRPC, which typically develops within 2-3 years after the initiation of ADT, although the time to progression varies depending on disease burden, tumor biology, and therapeutic response. Sometimes, though not always, the level of serum PSA decreases at the beginning but often increases once again in patients with advanced or metastatic disease following treatment with first-generation anti-androgens (flutamide or bicalutamide). It is worth noting that AIPC has increased BCL-2

expression after androgen ablation, contrary to androgen-sensitive prostate cancer (ADPC) where BCL-2 expression and activity are relatively low. Five primary molecular mechanisms drive the progression of AIPC: the hypersensitive, promiscuous, outlaw, bypass, and stem cell pathways. These pathways collectively demonstrate that AIPC development can be triggered by heightened androgen sensitivity, AR gene amplification, or elevated intratumoral androgen synthesis, maintaining signaling even under castrate conditions [64]. Several adaptive mechanisms such as the amplification of the AR, amplification of ARs, amplification of the intratumoral androgen levels, and heightened sensitivity to androgens are found in the progression of androgen independent prostate cancer. Other pathways involve AR gene mutations, receptor tyrosine kinase activation, and AKT and mitogen-activated protein kinase (MAPK) downstream pathway signaling. Some of these bypass signalling are independent of AR signalling and play a role in disease progression.The bypass pathway is typically marked by an increase in BCL-2 expression and thus its importance in maintaining the survival of tumors that are independent of androgens [40,65]. Further, events involving the skeleton (SREs), such as pathological fractures, compression of the spinal cord, orthopedic surgery, and palliative radiotherapy, often occur in metastatic CRPC and can have serious consequences in patient outcomes. It has been shown that BCL-XL plays a role in bone metastasis in CRPC, especially by interplaying with MDM2, Nuclear factor kappa light chain enhancer of activated B cells (NF-κB), and other oncogenic signaling pathways, and is frequently associated with increased serum levels of alkaline phosphatase [66]. Even though Src kinase inhibition has been suggested as a possible treatment approach to inhibit androgen-independent proliferation and bone metastasis, the mechanisms by which Src signaling relates to BCL-2 is poorly comprehended in CRPC [67].

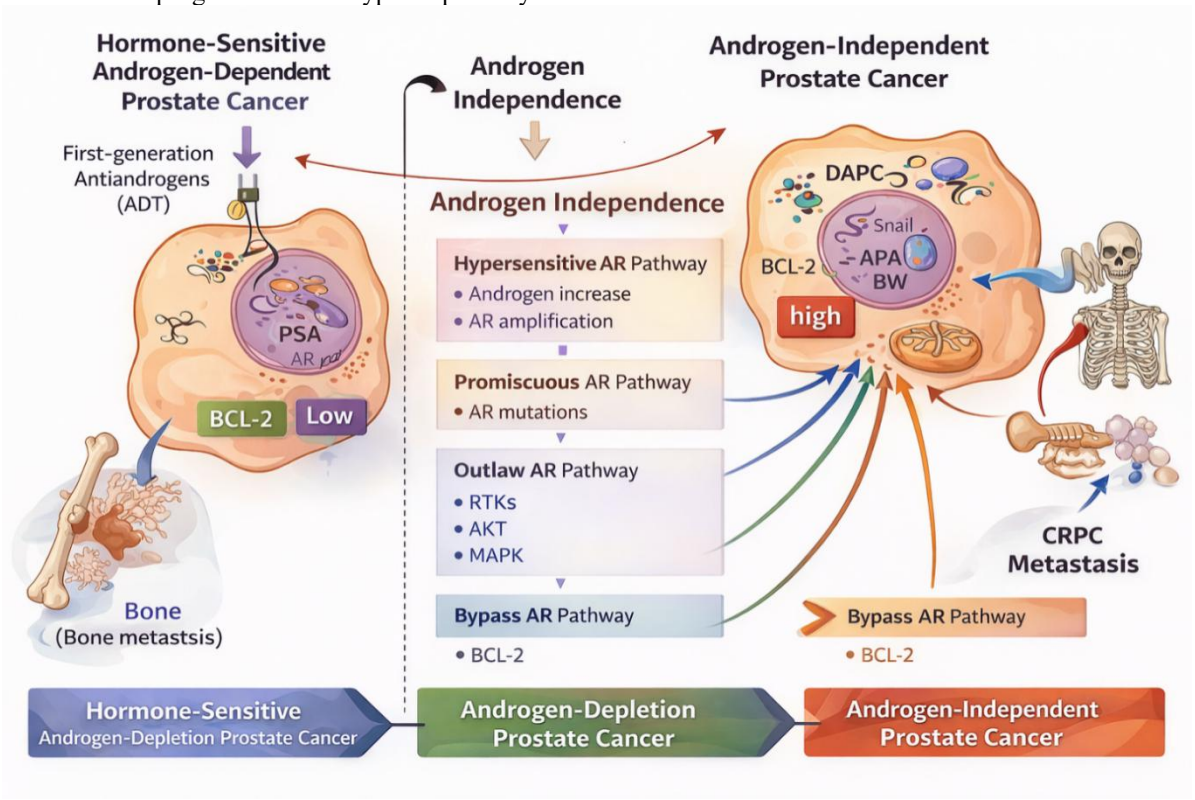

Figure 4. Schematic representation of the transition from androgen-dependent prostate cancer (ADPC) to androgen-independent prostate cancer (AIPC) following androgen deprivation therapy (ADT), highlighting key androgen receptor (AR) signaling alterations and BCL-2 upregulation. Multiple pathways, including hypersensitive, promiscuous, outlaw, and bypass AR signaling, contribute to therapy resistance and metastatic progression in CRPC (Source: Self-made by Canva).

4. Regulatory Interactions of BCL-2 within Cellular Signaling Networks

4.1 Upregulation of BCL-2 Induced by PTEN and p53 Loss of Function.

One of the key tumor suppressors is PTEN, a 10q23 gene on chromosome 10q23. It is an essential tumor suppressor because it negatively regulates the phosphoinositide 3-kinase (PI3K) signaling pathway. Loss of PTEN, which is commonly found in progressive prostate cancer, results in increased cell proliferation, cell survival and poor prognosis [68,69]. Beyond localized cellular signaling, the systemic tracking of treatment failure and disease progression has become a major clinical priority. Genetic alterations-such as PTEN depletion coupled with BCL-2 overexpression fundamentally reshape the tumor's secretory profile, leading to the release of distinct epigenetic molecules into the peripheral circulation. Consequently, circulating microRNAs have emerged as invaluable, non-invasive liquid biopsy biomarkers. Characterizing these specific serum and plasma microRNA signatures allows clinicians to dynamically monitor real-time shifts in

downstream apoptotic pathways, offering early detection of emergence of aggressive, resistant prostate cancer phenotypes [70]. Besides, it was reported that attenuation of BCL-2 with siRNA can sensitize the PTEN-mutant cells to apoptosis triggered by taxanes or nutrient deprivation and that BCL-2 overexpression is involved in radio resistance in prostate cancer cells. There is also a correlation between PTEN mutations and other regulatory molecules such as KLF6, p21 (WAF1/ CIP1), Rb and p53. Notably, the interaction of p53 and BCL-2 also regulates the process of apoptosis by altering the ratio between BCL-2 and the molecular interaction of BAX with the unstructured loop region of Bcl-2 [71]. The p53 mutations commonly occur in progressive prostate cancer. MicroRNA-340 has been shown to cause stabilization of p53, and elevation of p21 and down-regulation of BCL-2 in prostate cancer cells. These molecules in combination with PTEN form diagnostic and therapeutic biomarkers in progressive and androgen-resistant prostate carcinoma [62,72,73].

4.2 Regulatory Association of BCL-2 with AKT, Signal Transducer and Activator of Transcription 3 (STAT3), and NF-κB Pathways

Signal transduction and transcriptional regulator protein STAT3 exists in an inactive form in resting cell, which transmits several extracellular cytokine and growth factor signals via cell surface phosphorylation of Janus kinase (JAK), receptor tyrosine kinases (RTK) and PIK3. Various signaling cascades regulated by RTKs involve RAS/RAF/MEK/ERK pathway, which interacts with BCL-2 and facilitates NF-κB signaling, thereby enhancing progression of prostatic carcinoma. BCL-2 inhibition has been linked with compensatory increase of AKT1 and STAT3, as well as AR, Interleukin-6 (IL-6), and cyclin D1, in cured LNCaP cells [74,75]. Moreover, it has been shown that the androgen-inducible prostate-specific PrLZ/PC-1 gene helps prostate cancer cells to avoid phenoptosis caused by androgen withdrawal through the stimulation of AKT/BCL-2 pathway. On the other hand, BCL-2 is suppressed by the suppression of STAT3, which demonstrates a close functional correlation of these molecules [76]. STAT3 is also involved in autophagy regulation by transcriptionally regulating the expression of BECN1, PIK3C3, BNIP3 and microRNAs associated with them. In addition, STAT3 increases cell survival by increasing the level of anti-apoptotic proteins, BCL-2 and BCL-XL, in prostate cancer. Simultaneously, the NF-κB signal systems, including molecules like NIK, TRAF-6, interleukins, etc. play a role in inflammation, growth, and malignancy. NF-kB activation has been reported to activate AR signaling in prostate cancer cells. It is worth noting that BCL-2 is increased by TNF-alpha and is repressed by NF-kB inhibitors [60,77,78].

4.3 Modulation of BCL-2 Activity via MAPK-Dependent Pathways

BCL-2 is functionally associated with RAF1 because of its interaction at the mitochondrial membrane with a significant regulator of the MAPK signaling pathway, RAF1, and the phosphorylation of the pro-apoptotic protein BAD. It is also reported that the RAF1/MAPK pathway can cause cell cycle arrest in prostate cancer cells and may be used as a therapeutic target. Phosphorylation of BCL-2 via p38 MAPK has also been indicated to control the apoptotic signaling by modulating the cytochrome c release and caspase activation. These apoptotic processes are inhibited by the inhibition of p38 signaling [36,79]. BCL-2 phosphorylation is an important factor in apoptosis regulation. As an example, BCL-2 phosphorylation at Ser70 catalyzed by p38 MAPK and associated with tetrandrine-mediated apoptotic response in PC3 and DU145 cells. There is also analogous effect when docetaxel and ERK inhibitor PD98059 are used in combination to increase apoptosis, in part by elevating phosphorylation-mediated inactivation of BCL-2 and activation of BAX. ERK1 or 2 and BCL-2 or BCL-xL signaling inhibition with BH3 mimetics like ABT-737 induces mitochondrial apoptosis by inducing transcription of pro-apoptotic proteins, including BIM. The ERK1/2 and protein kinase C phosphorylation of BCL-2 at Thr69, Ser70, and Ser89 additionally indicates that MAPK signaling is important in regulating BCL-2 activity. Such results indicate that modulation of BCL-2 through MAPK pathways could be a relevant approach to therapy in prostate cancer [16,80,81].

4.4 BCL-2 Involvement in Autophagy via Beclin1/AMBRA1 Complex Formation

Autophagy refers to a cellular destruction mechanism that is triggered when cells are stressed (e.g. when they are deprived of nutrients or infected). It entails sealing of the cytoplasmic materials in the vesicles with membranes referred to as autophagosomes. The BH3 domain protein Beclin 1 triggers autophagy through destabilization of BCL-2 family proteins complexes. BCL-2 is an important factor in the control of autophagy by interacting with Beclin-1 (BECN1) to prevent the formation of autophagosomes [67,82]. Balance between apoptosis and autophagy is dependent on the level of expression of BCL-2. Indicatively, the natural BH3 mimetic gossypol causes autophagy in BCL-2-expressing AIPC cells but has minimal effect in BCL-2-lower cells. Gossypol destabilizes the BCL-2-Beclin-1 at the endoplasmic reticulum, where Beclin-1 is released to trigger autophagy. On the same note, the drugs like 3-AWA trigger autophagic cell death by inhibiting BCL-2 and promoting pro-apoptotic proteins, including PAWR [37,62]. Also, BCL-2 interacts with other autophagy regulators such as AMBRA1 which harbors a BH3 domain necessary to interact with BCL-2. These two authors also verified that the AMBRA1-BCL-2 complex has dual effects: the mitochondrial pool of BCL2 suppressed AMBRA1-dependent autophagy, whereas caspases break down AMBRA1, which interferes with the pro-survival effect of BCL-2, and induces apoptosis. AMBRA1 and SQSTM1/p62 increased expression and LC3-II level of accumulation has been reported in the tissues of prostate cancer, which supports the notion that autophagy is activated during prostate cancer progression and may facilitate tumor cell survival under conditions of therapeutic and metabolic stress [83-85]. In the context

of prostate cancer, autophagy exhibits a dual and highly context-dependent role. Although excessive or sustained autophagy may contribute to autophagy-associated cell death under certain experimental conditions, current evidence suggests that Beclin-1- and AMBRA1-mediated autophagy predominantly functions as a cytoprotective mechanism in advanced and CRPC. By facilitating the recycling of intracellular components and maintaining cellular homeostasis during androgen deprivation, hypoxia, nutrient deprivation, and therapeutic stress, autophagy promotes tumor cell survival and contributes to resistance against AR-targeted therapies and chemotherapy. Therefore, the functional outcome of autophagy depends on the disease stage, tumor microenvironment, and therapeutic context, highlighting its complex role in prostate cancer progression and treatment response [86,87].

4.5 BCL-2 and miRNAs

MicroRNAs (miRNAs) are short (20-24 bases), non-coding RNA molecules that control gene expression by degrading mRNAs, or repressing translation. MiR-34a is among them and it was demonstrated to suppress the proliferation and metastasis of prostate cancer stem cells by acting on the CD44 promoter. It also increases PC-3 cell paclitaxel sensitivity by inhibiting the expression of BCL-2, HuR, and SIRT1. On the same note, miR-34 suppresses the BCL-2 and Notch signaling by activating the tumor suppressor, p53, in pancreatic cancer models [88,89]. Also, research has shown that the cell proliferation, self-renewal, and motility processes under the control of miR-34 are impaired in models lacking miR-34 and p53, and that miR-34 and p53 act functionally together. The p53-mutant prostate cancers have also been found to be silenced by the epigenetic repression of miR-34a and miR-34b/c, which further confirms them to be regulated by miR-34a. In addition to miR-34 family members, the tumor-suppressive miR-15a/miR-16-1 cluster represents one of the best-characterized regulators of BCL-2 expression. These microRNAs directly bind to the 3′-untranslated region (3′-UTR) of BCL-2 mRNA, resulting in reduced BCL-2 expression, enhanced apoptosis, and suppression of prostate cancer cell proliferation. Loss or downregulation of miR-15a and miR-16-1 has been associated with increased BCL-2 expression, impaired apoptotic signaling, and disease progression, highlighting their important role in regulating apoptosis and therapeutic response in prostate cancer. To map the global molecular shifts responsible for driving this refractory behavior, advanced high-throughput screening methodologies have been deployed. Utilizing SWATH-based quantitative proteomic profiling has allowed researchers to map the entire proteomic landscape of resistant prostate cancer cells, uncovering key clusters of up-regulated chaperone and anti-apoptotic proteins that shield the tumor from therapeutic stress [25,90]. Furthermore, miR-204 has been identified to prevent prostate cancer cell growth and to sensitize prostate cancer cells to AR-based targeted therapy. MicroRNAs also control BCL-2 level and determine therapeutic respons [91,92]. As an illustration, miR-195 and miR-204 amplify chemosensitivity of gastric carcinoma cells to 5-fluorouracil and oxaliplatin via BCL-2 mRNA. On the other hand, miR-205 and miR-31 downregulation have been related to heightened resistance to chemotherapy in metastatic prostate cancer. Besides miRNAs, long non-coding RNAs are also important in the regulation of cell proliferation, apoptosis, and migration. As an example, the maternally expressed gene 3 (MEG3) inhibits tumor growth by downregulating BCL-2 expression, which in turn facilitates the stimulation of BAX and the apoptotic caspase-3 in DU145 and PC3 prostate cancer cells [86]. Armed with these precise proteomic targets, investigators have successfully utilized targeted genetic knockdown strategies to exploit these vulnerabilities. Among these, antisense BCL-2 oligodeoxynucleotides (such as OGX-011) have proven highly effective in preclinical models; by specifically hybridizing with BCL-2 mRNA, these antisense constructs significantly lower systemic tumor burden and markedly enhance the therapeutic efficacy of standard docetaxel chemotherapy in athymic mice bearing human prostate cancer xenografts [93,94].

4.6 BCL-2 and FKBP38/ NR4A1/GAL3

BCL-2 is an immune suppressor and a new mTOR regulator, which has the anti-caspase-dependent degradation of FK506 binding protein 38, a protein in the immunophilin family [93]. In line with this, FKBP38 siRNA depletion led to BCL-2 downregulation, and FKBP38 overexpression inhibited apoptosis. NUR77 is an orphan member of the nuclear receptor superfamily, which also has anti-apoptotic and pro-apoptotic roles. NUR77 is a dual regulator, which is an oncogenic survival factor in the nucleus and facilitates apoptosis in the mitochondria. It causes cytochrome c leakage through interaction with BCL-2 which changes it into a pro-apoptotic molecule instead of the anti-apoptotic one [88,94]. Conversely, the susceptibility of PC-3 prostate cancer cells to inhibition of the resistance to docetaxel by chromatin-modifying agents has been revealed as NUR77. Galectin-3 (Gal-3) is another regulator of significance; it is a 2 -galactoside-binding protein that is structurally similar to BCL-2 with the presence of the conserved NWGR motif. Gal-3 has anti-apoptotic effects and participates in several cellular events and functions such as growth, angiogenesis, adhesion, and apoptosis. There is even evidence that Gal-3-targeting can improve the treatment efficacy of BCL-2-targeting drugs, especially due to the low level of success in anti-BCL-2 drug trials in the last ten years [89,95].

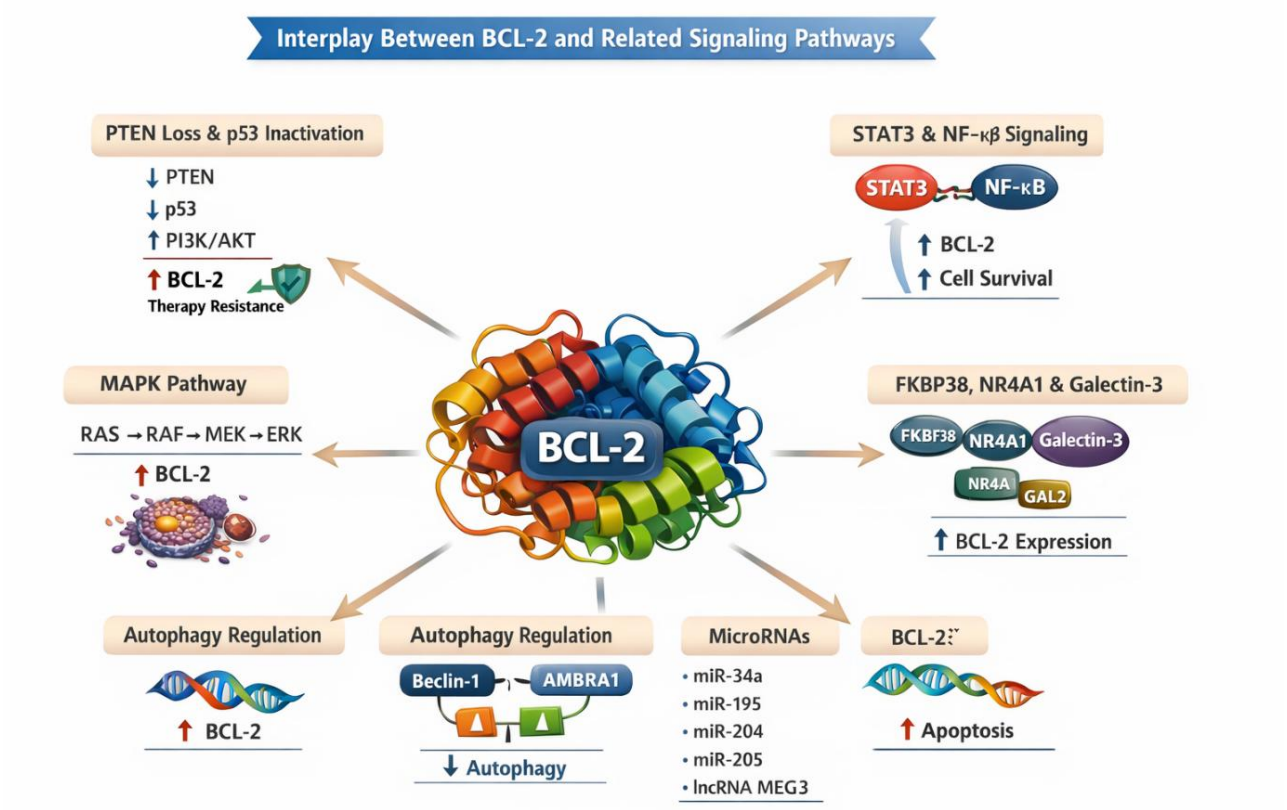

Figure 5. Interplay between BCL-2 and related cell signaling pathways. Schematic overview detailing the cross-talk between the BCL-2 family of proteins and major intracellular cascades including signal transducer and activator of transcription 3 (STAT3), Nuclear factor kappa light chain enhancer of activated B cells (NF-κB), and mitogen-activated protein kinase (MAPK) signaling during prostate cancer progression (Source: Self-made by BioRender.com).

5. Clinical Studies on BCL-2 Antagonists

BCL-2 has been widely studied about its use as a therapeutic target in prostate cancer. Gleave et al. established that antisense BCL-2 oligodeoxynucleotides had a significant impact on lowering the growth and the serum PSA levels in castrated athymic mice that had LNCaP tumors [90]. Although BCL-2 inhibitors have been studied widely, their clinical efficacy is not very high. As an example, AT-101 has not shown any enhancement in the overall survival of patients with metastatic CRPC about use alongside conventional chemotherapeutic treatments [67]. In a similar vein, there was no significant difference in the effectiveness of the combination of obatoclax and topotecan in contrast to the use of topotecan in relapsed small-cell lung cancer. However, unlike ABT-737, BCL-2, BCL-XL and BCL-W are multiple anti-apoptotic proteins targeted by ABT-737 that appear to increase its antitumor activity when used with other chemotherapeutic agents, particularly in acute lymphoblastic leukemia. The clinical use of the same, however, is restricted by drug delivery obstacles as well as resistance mediated by Mcl-1 [27,91,92]. Combination solutions are now under investigation, including abiraterone acetate with ABT-263, with or without hydroxychloroquine, in metastatic CRPC. These methods indicate that BCL-2 and other related signaling pathways should be targeted, as this could offer a more viable treatment plan. Due to a complicated interplay of BCL-2 with various regulatory circuits, more mechanistic investigations and clinical trials are needed [96-98]. In this case, it can be assumed that multiple targets, such as BCL2 and signaling associated with it may be an effective approach to treating prostate cancer because BCL-2 and the connected molecules and signaling are closely interconnected, and BCL-2 is indeed the center of further development of AIPC through mechanistic investigation in vivo and in vitro; more experimental studies are necessary.

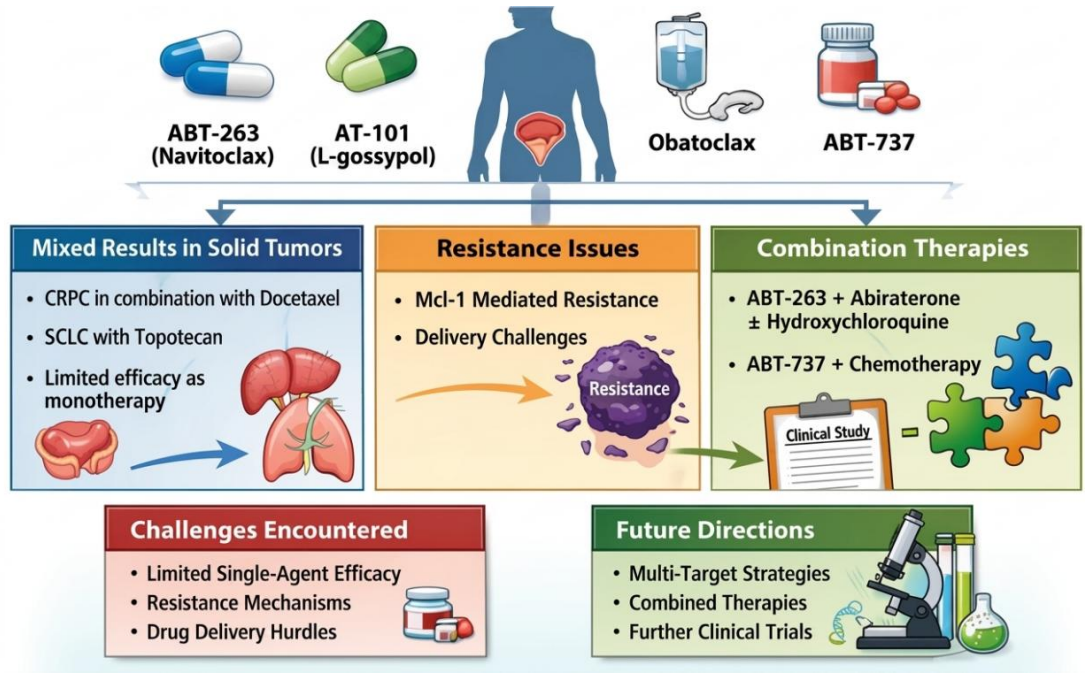

Figure 6. Clinical applications, challenges, and future directions of BCL-2 inhibitors. Overview of key therapeutic agents including Navitoclax (ABT-263), AT-101, Obatoclax, and ABT-737 highlighting Mcl-1-mediated resistance, combination regimens in CRPC, and future multi-target strategic designs (Source: Self-made by BioRender.com).

6. Conclusion

AIPC is a characteristic of this cancer type that is associated with the overexpression of BCL-2, specifically in the advanced stages and metastasis after androgen deprivation. Androgen signaling, conversely, inhibits BCL-2 in ADPC. The BCL-2 also plays a role in tumor progression by preventing apoptosis by interacting with the various molecular pathways such as PTEN loss, inactivation of p53, activation of PI3K/AKT, and the RTK/STAT3/NF-kB and Ras/Raf/MEK/ERK pathways. Also, other non-coding RNAs, such as miR-24, miR-31, miR-34, miR-195, and lncRNA MEG3 are also involved in the regulation of BCL-2 expression and activity. Although great progress has been made in the understanding of these mechanisms, there is still much to be done in terms of identifying new therapeutic selective targets and in demystifying the intricate interactions between BCL-2 and its effective management of AIPC. Also, some BCL-2 inhibitors like L-gossypol, ABT-737, or ABT-263 could be used beneficially in AIPC patients. Still, further preclinical studies and clinical trials are suggested to utilize it in clinical practice effectively. Overall, targeting apoptosis-related signaling pathways, including members of the BCL-2 family and the caspase cascade, represents a promising therapeutic direction for prostate cancer. However, the successful clinical implementation of these strategies requires further mechanistic investigations, rigorous clinical validation, and the identification of reliable predictive biomarkers to overcome translational challenges and facilitate precision medicine approaches.

7. Limitations and Future Directions

Despite the considerable progress in elucidating the molecular mechanisms governing apoptosis dysregulation in prostate cancer, several limitations should be acknowledged. Much of the current evidence regarding BCL-2 family proteins, caspase signaling, and apoptosis-targeted therapeutic strategies is derived from in vitro experiments, animal models, or extrapolation from other malignancies, which may not fully recapitulate the biological complexity and heterogeneity of human prostate cancer. Moreover, the substantial functional redundancy and compensatory interactions among BCL-2 family members may reduce the effectiveness of therapies targeting a single anti-apoptotic protein and contribute to the emergence of therapeutic resistance. Another major challenge is the limited translation of promising preclinical findings into successful clinical outcomes, highlighting the need for well-designed clinical trials to establish efficacy and safety in patients. Furthermore, reliable predictive biomarkers capable of stratifying patients according to apoptosis-related molecular profiles remain insufficiently developed, limiting the implementation of personalized therapeutic approaches. Future investigations should focus on validating apoptosis-associated biomarkers, integrating multi-omics technologies for patient stratification, and evaluating rational combination therapies that simultaneously target multiple apoptotic pathways to improve clinical outcomes in prostate cancer.

Abbreviations

ADPC: Androgen-dependent prostate cancer

ADT: Androgen deprivation therapy

AIPC: Androgen-independent prostate cancer

AKT: Protein kinase B

AMBRA1: Autophagy/beclin-1 regulator 1

AR: Androgen receptor

ARE: Androgen-responsive element

BAD: BCL-2-associated agonist of cell death

BAK: BCL-2 antagonist/killer

BAX: BCL-2-associated X protein

BCL-2: B-cell lymphoma 2

BCL-xL: B-cell lymphoma-extra-large

BECN1: Beclin-1

BID: BH3-interacting domain death agonist

BIM: BCL-2-like protein 11

BRCA1/2: Breast cancer gene 1/2

CRPC: Castration-resistant prostate cancer

DHT: Dihydrotestosterone

ERK: Extracellular signal-regulated kinase

FGF: Fibroblast growth factor

HOXB13: Homeobox B13

HSP: Heat shock protein

IL-6: Interleukin-6

JAK: Janus kinase

MAPK: Mitogen-activated protein kinase

MCL-1: Myeloid cell leukemia-1

mTOR: Mechanistic target of rapamycin

NF-κB: Nuclear factor kappa light chain enhancer of activated B cells

NOXA: Phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1)

PI3K: Phosphoinositide 3-kinase

PSA: Prostate-specific antigen

PTEN: Phosphatase and tensin homolog

PUMA: p53 upregulated modulator of apoptosis

RTK: Receptor tyrosine kinases

STAT3: Signal transducer and activator of transcription 3

TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling

Autor's Contribution

AHA and EN[2] conceived and designed the project. AHA, EN[2], and CO contributed to the literature search and drafting of the manuscript. EN[2], CO, and EN[4] assisted in organizing content and editing. AHA supervised the work and provided critical revisions.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgement and Funding

This review article did not get any financial support from any agency/institution.

Data Availability

All the data collected is included in the article.

Ethics Statement

No study was conducted on live animals/humans; thus, it did not require any ethical approval.

Generative AI Statement

The authors declare that no generative artificial intelligence technologies were used when preparing this manuscript.

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