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Review

Mechanisms of Immune Evasion in PTEN Loss Prostate Cancer

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Abstract: *PTEN* (phosphatase and tensin homolog) is a frequently lost tumor suppressor gene in prostate cancer, leading to aggressive tumor behavior and poor clinical outcomes. *PTEN* loss results in aberrant activation of the PI3K/AKT/mTOR pathway, promoting oncogenesis. These alterations also lead to an immunosuppressive tumor microenvironment with altered immune cell infiltration, cytokine profiles, and immune checkpoint regulation. This review aims to provide a comprehensive overview of the mechanisms underlying *PTEN* loss in prostate cancer and the consequent immune alterations observed in this subtype, thus underscoring the importance of understanding *PTEN*-mediated immune modulation for the development of effective therapeutic interventions in prostate cancer.

Keywords: prostate cancer; *PTEN* loss; immune evasion; immunotherapy

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1. Introduction

Prostate cancer (PCa) represents the second most frequently diagnosed neoplasm in males, although mortality rates are lower [1]. Prostate cancer is usually diagnosed in localized stages; however, a relevant percentage of patients will progress to metastatic stage. Androgen receptor (AR) plays a key role in the pathogenesis of PCa and androgen deprivation therapy (ADT) in combination with androgen receptor signaling inhibitors (ARSI) with or without chemotherapy is the standard of care for metastatic hormone-sensitive prostate cancer (HSPC). However, tumors will eventually develop resistance to treatment and cancer cells will be able to sustain growth independently from androgen signaling becoming castration-resistant prostate cancer (CRPC). Acquired mutations of the AR pathway to bypass signaling inhibition is one of the most important mechanisms of resistance to treatment. Amplification or gain-of-function mutations, increased transcription of AR, increased AR signaling, or AR transcript splice variants that constitutively activate AR, such as AR-V7, are some of these resistance mechanisms. CRPC is also associated with dysregulation of additional genes implicated in growth control and genetic stability [2]. One of the most important is the inactivation of the phosphatase and tensin homolog (*PTEN*) gene on chromosome 10, which is the most commonly lost tumor suppressor gene in primary disease [3]. Preclinical evidence supports the role of *PTEN* inactivation as a driver in the progression of the disease, from pre-malignant neoplasms to CRPC. Interplay between the AR and phosphatidylinositol-4,5 biphosphate 3-kinase (PI3K) pathway in patients with or without *PTEN* loss has been extensively characterized [4]. PCa has also been linked

to chronic inflammation of the prostate caused by dietary factors, unknown pathogenic infections, hormonal changes, or chronic trauma [5]. However, growing evidence supports the role of *PTEN* alterations in modulating the immune microenvironment in PCa. The aim of this review is to provide an overview of the mechanisms underlying *PTEN* loss in PCa.

2. *PTEN* Molecular Pathway

2.1. PTEN. Overview and Biological Functions

The *PTEN* is a critical tumor suppressor gene that plays an important role in regulating cell growth, survival, and proliferation [3]. Since its discovery in 1997, *PTEN* has been extensively studied for its involvement in human cancer development, particularly in prostate cancer [6].

PTEN is a dual-specificity phosphatase that converts phosphatidylinositol 3,4,5-trisphosphate (PIP3) into phosphatidylinositol 4,5-bisphosphate (PIP2), acting as a direct antagonist of PI3K activity and negatively regulating the AKT and mTOR signaling pathways [3]. Loss or mutation of *PTEN* leads to uncontrolled PI3K activation, accumulation of PIP3 on the cell membrane, and subsequent activation of multiple proteins such as PDK1 and its substrate AKT, enhancing cellular proliferation, survival, and motility [7].

Besides its role as a lipid phosphatase, PTEN also has protein phosphatase activity that regulates different processes, like cell adhesion (via FAK and SRC activation), and influences nuclear functions such as cell cycle regulation [8,9]. It is also worth noting that PTEN is involved in DNA repair, probably mediating the expression of RAD-51 protein. Mutations in its protein phosphatase domain of PTEN can lead to centromere instability and spontaneous DNA-double strand breaks, a triggering factor for a genomic instability scenario [10,11].

2.2. PTEN Loss in Prostate Cancer

PTEN is the most commonly lost tumor suppressor gene in primary prostate cancer, being observed in approximately 40–50% of the cases [3,12]. Most prostate tumors inactivate *PTEN* through genomic deletions. They are highly associated with aggressive phenotypes, which include more advanced tumor stages, higher Gleason scores, increased metastasis rates, and worse overall prognosis. *PTEN* loss results in unopposed activation of the PI3K/AKT/mTOR pathway, which enhances cell survival, proliferation, and resistance to apoptosis, leading to cancer progression.

However, the previously reported frequency of *PTEN* deletions varies depending on the cohort studied and the methods used to assess *PTEN* status. In early studies performing microsatellite analysis, the reported loss of heterozygosity (LOH) at the *PTEN* locus varies from 10 to 55% of primary and advanced tumors. In contrast, fluorescence in situ hybridization (FISH) studies have shown *PTEN* deletions in up to 68% of primary tumors [13,14]. More recent studies report *PTEN* deletion in about 15–20% of surgically treated cases, with higher rates observed in metastatic prostate cancer, where *PTEN* loss is seen in approximately 40% of cases [4].

In CRPC, *PTEN* loss is more significant than in earlier stages, with approximately 30% of patients exhibiting deep and likely homozygous deletions, all accompanied by additional mutations and gene fusions in another 10%. These genetic alterations contribute to the aggressive nature of CRPC and its resistance to conventional therapies [15].

2.3. Mechanisms of PTEN Inactivation

The most common cause of functional *PTEN* loss in prostate cancer is genomic biallelic deletion. However, other mechanisms may also contribute at a lower frequency, including genomic rearrangements, mutations, methylation, and post-transcriptional regulation [16–21]. *PTEN* inactivation by mutation or promoter methylation is uncommon, affecting only less than 10% of cases [22]. Post-translational modifications such as phosphorylation, ubiquitylation, oxidation, and acetylation have been described as potential

regulators of *PTEN*'s stability and activity, further complicating its role in cancer biology [23].

Moreover, *PTEN* loss is often heterogeneous within primary prostate tumors, indicating that it typically occurs after other genetic changes, such as TMPRSS2–ERG rearrangements [24]. This heterogeneity presents challenges for accurately detecting *PTEN* status in diagnostic biopsies. However, it is clearly known that *PTEN* inactivation generally occurs in primary tumors before progression to metastatic diseases, with identical *PTEN* deletion patterns often observed in both primary tumors and their corresponding metastases [25]. These findings suggest that *PTEN* inactivation could be a key event in the development of metastatic disease.

2.4. Treatment Strategies for PTEN Loss Prostate Cancer

As previously mentioned, *PTEN* loss is a significant factor in the progression of aggressive prostate cancer, particularly in castration-resistant prostate cancer, a disease known to be resistant to treatments and the primary cause of death in prostate cancer. Given the important role that PTEN plays in regulating the PI3K/AKT/mTOR signaling pathway, new therapeutic strategies have been specifically designed to control the activation of this pathway, both directly addressing the PTEN deficiency and also targeting other proteins in this axis [26]. Herein, we discuss current and evolving treatment strategies in the landscape of *PTEN* deficient prostate cancer considering the most recent advances in the area.

2.4.1. PI3K/AKT/mTOR Inhibition

The direct inhibition of the PI3K/AKT/mTOR axis has been one of the major priorities of therapeutic intervention for *PTEN* loss. Despite the promising data observed in preclinical in vitro studies, dose-limiting toxicities, along with insufficient on-target efficacy in early clinical testing, pose significant difficulties in the development of the first therapies targeting this axis [27]. Nonetheless, recent advancements in these inhibitors have been promising.

Early direct PI3K inhibitors like LY294002 showed potential in preclinical models but were too toxic for clinical use [28]. Newer agents such as buparlisib and copanlisib have shown better tolerability and efficacy [29,30]. Particularly buparlisib, has demonstrated the ability to inhibit AKT activity in prostate cancer models, although its impact on tumor cell death remains limited [31]. A phase II trial combining buparlisib plus enzalutamide did not show significant activity in men with mCRPC [32]. Ongoing trials are exploring the combination of PI3K inhibitors with other treatments like PARP inhibitors to enhance therapeutic outcomes [33,34].

AKT is a key downstream effector of the PI3K pathway, making it an attractive target in *PTEN*-deficient prostate cancers [35]. AKT inhibitors such as capivasertib and ipatasertib have shown strong anti-tumor effects in preclinical models and have been tested in combination with antiandrogenic therapies like enzalutamide or abiraterone [36,37]. These combinations aim to overcome the resistance often seen in *PTEN*-deficient CRPC, with early clinical data showing promise in improving patient outcomes.

mTORC1 and mTORC2 are crucial components of the PI3K/AKT pathway, and their inhibition is a strategic approach in *PTEN*-deficient cancers [38]. While mTORC1 inhibitors like rapamycin showed initial promise, their clinical application has been limited by resistance mechanisms, leading to the development of dual mTORC1/2 inhibitors [39–41]. Agents such as vistusertib and sapanisertib have shown efficacy in preclinical models, although their clinical use has been hampered by toxicity and limited therapeutic responses [42,43].

2.4.2. Restoring PTEN Function

Another innovative approach to treating *PTEN*-deficient prostate cancer is the direct restoration of PTEN function. This strategy includes delivering functional PTEN to tumor cells or targeting the regulatory mechanisms that suppress *PTEN* expression. PTEN is

delivered directly in the oncogene-depleted environment, through a nanoparticle-assisted delivery, to prostate cancer cells [44,45]. This can decrease cell viability, as indicated by preclinical studies utilizing the alternative translation *PTEN*-deficient cancer models. Additionally, the translation variant *PTEN*-Long uses its secretion and uptake by the surrounding cells to restore tumor-suppressive functions, therefore offering a new therapeutic opportunity [46].

2.4.3. Targeting PTEN Regulators

Another approach involves overcoming the post-transcriptional repression of PTEN by targeting negative regulators, such as miRNAs that downregulate PTEN expression [47]. For example, the inhibition of oncomiRs like miR-21 using antisense oligonucleotides has shown the potential to restore *PTEN* function in cancer models [48]. Additionally, CRISPR/Cas9 technology is being explored to reactivate *PTEN* transcription in tumors where *PTEN* is suppressed but not deleted [49].

3. Immune Alterations in PTEN Loss Prostate Cancer

3.1. Role of Immune Infiltration in PCa

Immune infiltration in the tumor microenvironment (TME) is generally composed of different cell populations with diverse origins, such as B and T lymphocytes, monocytes, tumor-associated macrophages (TAMs), mast cells, myeloid-derived suppressor cells (MDSC), other cell types, and immunomodulatory cytokines [5]. A higher tumor immune infiltration has been correlated in other tumor types with better prognosis [50], but, in PCa, this observation has led to mixed results. A study found a relationship between high intratumoral $CD8^+$ infiltration and improved survival after radical prostatectomy [51], while others have found an inverse correlation between high intratumoral $CD8^+$ lymphocyte infiltration and worse biochemical recurrence-free survival (bRFS) or progression in node-positive PCa [52,53]. Another study found that a higher immune infiltration was correlated with poor diverse outcomes such as bRFS, distant-metastases free survival (DMFS), and overall survival (OS), supporting the notion that inflammation may be detrimental in PCa. Interestingly, there was also an association between individual immune cell types with DMFS. A high ratio of activated mast cells and NK cells dendritic cells was associated with a better DMFS while a high ratio of M1+M2 vs. M0 macrophages and total T cells was associated with worse DMFS [54]. In another report, in silico data from The Cancer Genome Atlas (TCGA) and data from a cohort of PCa patients treated in the Memorial Sloan Kettering Cancer Center (MSKCC) further reinforces this notion, as tumors from patients with *PTEN* loss were enriched in FoxP3+ regulatory T cells (Tregs). Further validation of these data in an independent cohort showed that this enrichment in Tregs correlated with higher Indoleamine 2,3-dioxygenase (IDO1) expression, which has been related to impaired antitumor immune-cell response [55,56]. Immune infiltration has also been shown to be related to pathogenic mutations present in the primary tumor. Differences in TME composition and spatial disposition of lymphocytes have been found in patients with and without germline mutations of Homologous Recombination Repair (HRR) genes. Samples from patients with germline HRR mutations had a more T-cell-inflamed TME. Surprisingly, although T-cell density and composition were similar between patients with and without HRR mutations, distinct spatial profiles were found. Patients with HRR mutations had significantly more free T cells infiltrating the tumor compared with sporadic (without HRR mutations) tumors. Spearman correlation between the ratio of free and clustered $CD8^+$ lymphocytes and gene expression of the sampled allowed authors to create a gene expression profile composed of five genes (*IRF7*, *CEACAM1*, *ITGAM*, *LILRA1*, and BAX). This gene expression correlated with lower Gleason grade and longer DMFS. These findings suggest that mutations in the primary tumor may modulate the spatial distribution of immune infiltration of the tumor and patient outcome [57].

3.2. Immune Alterations in PTEN Loss PCa During Tumor Initiation

High-grade prostatic intraepithelial neoplasia (HG-PIN) has been proposed as a precursor of PCa. PIN develops from the luminal epithelial cell layer, which expresses AR and also shows molecular alterations as TMPRSS2 fusions and *PTEN* deletions [58,59]. Mouse models with conditional deletion of *PTEN* limited to the prostatic epithelial layer ($PTEN^{-/-}$:Pb-Cre4) are extensively used to study PCa evolution from PIN to invasive adenocarcinoma [60]. In this model, significant immune infiltration in PIN and invasive carcinoma has been found compared to *PTEN* wild-type samples, correlating with the degree of tumor invasion [61]. Diverse cellular subpopulations have been characterized in tumors and microenvironments. In the tumoral compartment, there are populations of proliferative and senescent cancer cells. In the TME of *PTEN* loss mouse models, there is a particular increase in $Gr1^+$. and $CD11b^+$ MDSCs and a decrease in dendritic cells (DCs) and macrophages. In parallel with tumor invasiveness, there is an expansion of MDSC in the TME that is inversely correlated with the populations of CD8+ cells and DC [61]. Analysis of gene expression demonstrated an upregulation of inflammatory response genes in *PTEN* loss epithelial cells, such as *CSF1*, interleukin (IL)-1β and their receptors, and CXCL2. CXCL2 secretion may be responsible for the spatial distribution of $Gr\text{-}1^+$ MDSCs in TME, in close proximity with the proliferative tumor compartment. CSF1 and IL-1β are cytokines that have been implicated in the migration and expansion of MDSCs. IL-1β has also been correlated with MDSC-mediated inhibition of T cells by induction of Arginase 1 (*Arg1)* and inducible nitric oxide synthase (*iNOS)* [62–64]. Interestingly, only $CD11b^+$ cells isolated from prostate tissue showed increased expression of *Arg1* and *iNOS* compared to $CD11b^+$ cells isolated from bone marrow or spleen. Conversely, $Gr\text{-}1^+$ MDSCs release IL-R1A in the TME. IL-R1A is an antagonist of IL-1α and impairs senescence in vitro [61,65]. Taken together, this evidence suggests the existence of an autocrine and paracrine loop in the primary tumor that promotes its development in the early stages.

Gene expression patterns have shown that the transcription factors AR, NF-κB, HIF-1α, as well as other immunological mediators such as interferon-γ, toll-like receptors 7–8 and prostaglandin receptors may be upregulated in *PTEN* loss prostate cancer models [66]. Some molecular pathways have been described. Chromatin regulator CHD1 is rarely deleted in *PTEN* loss PCa due to its important role in the pathogenesis of these tumors. *PTEN* loss inhibits the degradation of CDH1, which in turn alters AR binding to lineage-specific enhancers [67]. Increased levels of CHD1 lead to activation of *NF-κB* target genes. CHD1 is also able to bind directly to the *Il6* gene promoter, thus promoting IL-6 expression. IL-6 has been proposed as a mediator in MDSC recruitment to a PCa microenvironment as IL-6 depletion and IL-6R blockade led to a decrease in MDSC infiltration in PCa models. This finding was replicated with *CHD1* deletion [68]. The JAK2/STAT3 pathway is also activated in PTEN-null tumors, particularly in the senescent compartment of the tumor. Conditional knockout models of *Stat3* had decreased secretion of several immune-suppressive chemokines including CXCL2, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, macrophage colony-stimulating factor, C5a, IL10, and IL13 while maintaining chemoattractants for B and T cells such as MCP-1 and CXCL10. This depletion of immune-suppressive chemokines leads to a decrease in MDSC infiltration and, interestingly, an increase in $CD8^+$ T, plasmatic, and NK cell infiltration with markers of increased activation. These changes were reflected in the impaired development of invasive tumors [69].

Also, changes in miRNA expression have been found, with overexpression of miR-155, miR-21, miR-132, miR-223, and miR-150 and downregulation of miR-1 and miR-133 [66]. Overexpressed miRNAs are related to mammalian inflammatory responses, apoptotic resistance, and proliferation of endothelial cells and have been shown to correlate with tumor recurrence and metastases [70–72].

Taken together, evidence suggests that *PTEN* loss in PCa cells triggers changes in gene and microRNA expression, leading to a localized inflammatory state supported by

autocrine and paracrine loops. This inflammatory state and secondary infiltration of diverse immune cells may be detrimental and have a significant effect on *PTEN* loss PCa.

3.3. Immune Alterations of PTEN Loss PCa During Tumor Progression

PCa aggressivity is often determined by diverse mutations. Some of these mutations may be present in the primary tumor and are associated with a worse prognosis, as *TP53*, *RB1*, *MYC*, and mutations in the DNA damage response (DDR) genes, while other mutations may arise as resistance mechanisms to treatment. This last group is mainly represented by mutations in the AR, although other mechanisms of resistance and progression have been described [73,74]. *TP53* mutations are representative of tumors with an aggressive biology, as they are present in approximately 8% of patients with localized PCa, but are present in 25% and 50% of metastatic HSPC and CRPC patients, respectively [75]. Knockout of *TP53* and *PTEN* in mouse models and in human PCa cell lines lead to more aggressive tumors [76]. Specifically, primary tumors from murine prostate tumor models, show differences in tumor cell infiltrates. In $Pten^{pc-/-}$ models, and even more so in $Pten^{pc-/-}$ and $Trp53^{pc-/-}$ models, an increased number of Gr-1+CD11b+ MDSCs have been observed compared to control mice. Tumor-associated Gr-1+CD11b+ cells exhibited a tumor-promoting phenotype in $Pten^{pc-/-}$ and $Trp53^{pc-/-}$ models, with this effect linked to Treg-mediated antitumor immunosuppression. This effect is mediated in part by expression of *Arg1* and *iNOS* as described earlier. Notably, at later stages, tumors are primarily infiltrated by polymorphonuclear leukocyte cells and macrophages, which may derive from MO-MDSCs. In $Pten^{pc-/-}$ and $Trp53^{pc-/-}$ models also exists an upregulation of CXCL17, a cytokine known as an attractant for monocytic cells [77] Another important factor that may alter TME composition in *TP53*- and *PTEN*-defective PCa is a distinctive profile of immune checkpoint expression. B7-H3 overexpression by tumor cells is related to a poor prognosis in PCa [78]. In prostate tumors with defects in *PTEN* and *TP53*, B7-H3 is the most significantly overexpressed immune checkpoint. This effect was not found in tumors with only *PTEN* deletion [79]. This modulation by TP53 defects is thought to be mediated by transcription factor SP1. P53 and Sp1 have antagonistic roles on the expression of target genes, but PI3K signaling can activate Sp1 in cancer cells [80]. B7-H3 depletion in mouse models suppressed the growth on PTEN/p53-deficient tumors by an increase in tumor-infiltrating T cells, enhancement of $CD8^+$ and NK cells, and depletion of MDSCs. To further emphasize the relevant role of immune cells in progression in this model, this effect was not seen in immunosuppressed mice [79].

PTEN-null mouse models with additional mutations in the TGFβ/BMP–SMAD4 axis are characterized by rapid PCa progression and development of metastases and SMAD4-downregulation has been found in human PCa metastases [81,82]. In this model, concurrent deletion of *SMAD4* and *PTEN* further increased immune infiltration in the primary tumor, with $CD11b^+$ MDSC representing a significant population. T-cell proliferation was profoundly impaired due to reactive oxygen species (ROS) production by MDSCs. Compared with $PTEN^{pc/-/-}$ tumors, $PTEN^{pc-/-}SMAD4^{pc-/-}$ showed an hyperactivated Hippo-YAP pathway. This hyperactivation led to *Cxcl5* overexpression which acts as a main MDSC recruiter. Knockdown of Yap1 or pharmacological inhibition of Cxcl5 caused an important reduction of infiltration of MDSCs in prostate tumors, which in turn caused a significant decrease in tumor burden [83]. Interestingly, YAP1 has been found to be overexpressed in some human prostate cancers [84]. Using TCGA RNA-seq data and using a 39 gene signature of MDSC-related genes, investigators were able to categorize some TCGA primary prostate tumors into three categories: MDSC-high, MDSC-medium, and MDSC-low. YAP1 signature genes were significantly overexpressed in MDSC-high samples. Strikingly, CXCL6, the human homologue of murine Cxcl5, was overexpressed in MDSC-high samples compared to MDSC-low, suggesting that a subset of human PCa may share the pathogenic role of MDSC as seen in mouse models [83]. Interestingly, when *SMAD4* was deleted in TP53- and *PTEN*-deficient models, no effect on B7-H3 expression was found, further highlighting the role of different mutations in the interrelationship between the tumor and

the microenvironment and how different molecular mechanisms may lead by different pathways to an immunosuppressive TME [79].

Metabolic reprogramming caused by *PTEN* defects in PCa may also be responsible for tumor progression. *PTEN* loss enhances metabolic reprogramming in cancer cells, driving aerobic glycolysis (the Warburg effect). Glucose uptake and consumption in cells with alterations in the PI3K pathway are increased due to a greater expression of GLUT-1/4 transporters on the plasma membrane and activation of hexokinase-2, respectively. This ultimately leads to an increase in lactate production [85,86]. Histone lactylation due to lactate accumulation and secondary changes in gene expression may be responsible for of M2-TAM polarization. In these macrophages, lactate upregulates the citric acid cycle and enhances *Arg1* and *iNos* expression, which leads to detrimental effects in T-cell function and favors immune evasion as described above [87,88].

Other changes in TME in *PTEN* loss patients may be related to the metastatic niche. Metastatic lesions have been found to be further enriched in Tregs, with lower abundance of plasma and NK cells. Interestingly there may be differences between metastatic organs, as this infiltration of Tregs was shown to be higher in metastatic liver lesions than in bone. However, the molecular mechanism behind this observation is not yet fully understood [55].

Figure 1 summarizes the main relevant alterations described in *PTEN* loss PCa to date.

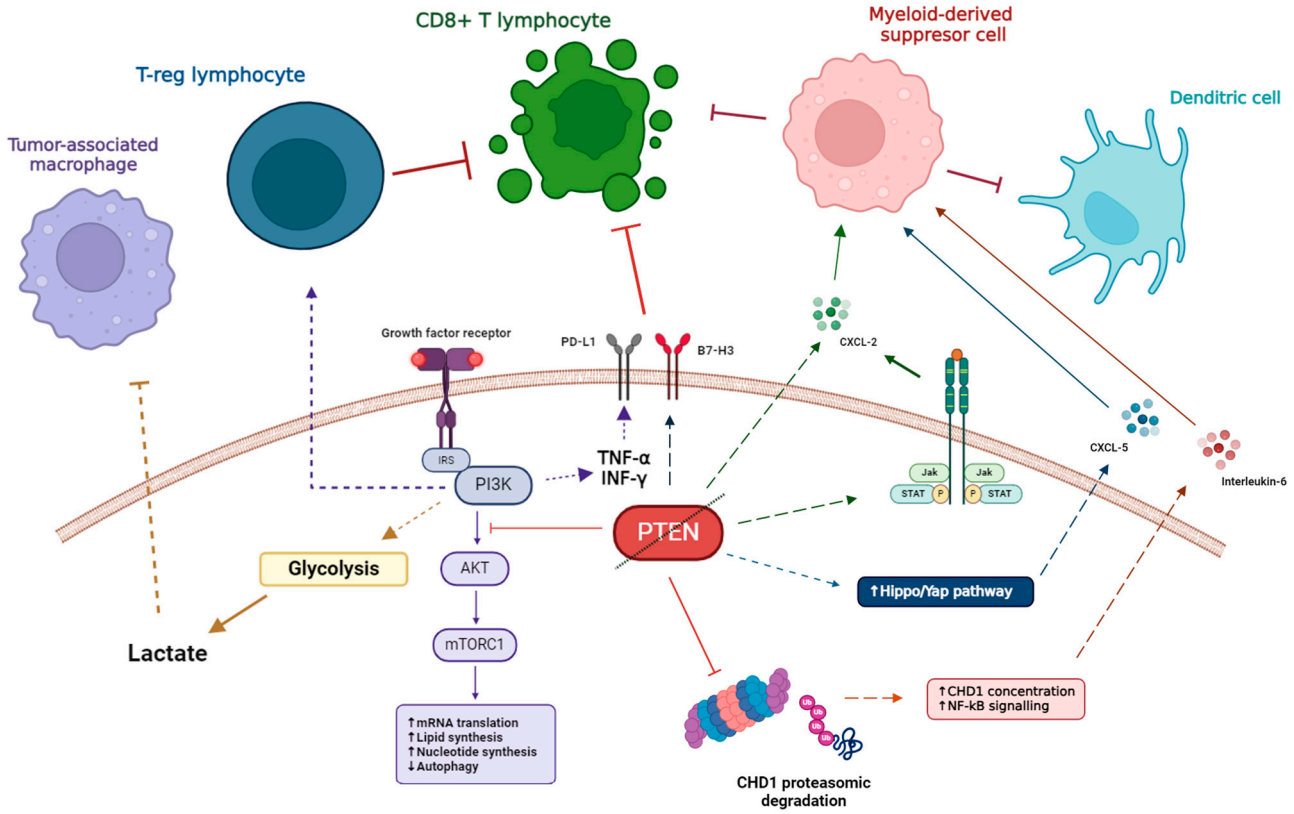

Figure 1. Main alterations in immune system caused by *PTEN* loss in PCa. *PTEN*-null tumors are characterized by an immunosuppressive TME caused by a paracrine loop between cancer cells and MDSCs due to increased secretion of chemokines regulated by *NF-κB*, Hippo/Yap or JAK/STAT signalling. MDSCs are also able to maintain tumor growth and collaborate to promote tumor growth and castration resistance231. Hyperactivation of PI3K pathway also increases checkpoint inhibitor expression on membrane collaborating to create an immunosuppressive environment. Increased glycolysis leads to histone lactylation and reduced macrophagic activity.

4. Strategies to Overcome Treatment Resistance in *PTEN* Loss PCa and Future Directions

4.1. Resistance to Androgen Receptor Signaling Inhibitors and Taxane Chemotherapy

Taxane chemotherapy in combination with ARSIs and ADT are currently the cornerstone of treatment in metastatic HSPC. However, patients will eventually develop resistance to treatment and become CRPC. As mentioned before, acquired mutations of the AR to bypass signaling inhibition is one of the most important mechanisms of resistance to treatment. However, there is growing evidence that not only factors of the cancer cell are responsible for the development of resistance to treatment but also TME may have a role. During the development of castration resistance in *PTEN*-null mice, numbers of MDSCs were found to be the most increased immune-subset during the development of CRPC. MDSCs were able to sustain the proliferation of cancer cells and increase transcription of AR-related genes even in a culture medium with the absence of androgens by secretion of IL-23. IL-23 is able to activate the pSTAT3/RORγ axis to drive the transcription of AR independently of androgens [89]. Blocking migration of MDSCs by antagonizing CXCR2 delayed tumor progression and castration resistance. Furthermore, overexpression of IL-23 by MDSCs was also found in human CRPC compared to HSPC samples, highlighting the translational relevance of these findings. Interestingly, IL-23 concentrations were also increased in the plasma of CRPC patients, but the prognostic role of circulating IL-23 was not assessed in this study [90].

There are diverse resistance mechanisms to taxane therapy in cancer cells, such as alterations of microtubules, upregulation of the drug-efflux transporter, or activation or apoptosis escape. Preclinical evidence shows that *PTEN* loss PCa cells may be resistant to docetaxel treatment [69,91]. However, clinical studies have suggested similar outcomes in patients with or without *PTEN* loss [92]. *PTEN* loss, through activation of the mTOR pathway, not only promotes cellular proliferation but may also contribute to taxane resistance, potentially mediated by alterations in microtubule dynamics and cell cycle regulation [41]. TME may support treatment resistance by secretion of growth factors and hypoxic response by activation of hypoxia-inducible factor 1 (HIF-1α) [93]. MDSCs may also have a role in docetaxel resistance in these models. As described earlier, *PTEN*-null tumors are characterized by an immunosuppressive TME caused by a paracrine loop between cancer cells and MDSCs. Docetaxel treatment in *PTEN*-null mouse models caused an enhancement of senescence in tumors but without significant reductions in tumor volume. Pharmacological treatment is directed to alter this immunosuppressive TME by inhibition of the JAK/STAT3 pathway or by directly impairing MDSC recruitment by blocking CXCR2 synergized with docetaxel causing dramatic reductions in tumor volume [65,69].

4.2. Resistance to Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (ICI) have provided disappointing results in PCa [94–96]. However, there are some predictive biomarkers of response that are currently under investigation. Mismatch Repair Deficiency (dMMR) is present in 2–4% of patients with PCa and retrospective data show an increased response rate compared to unselected populations [97,98]. Other predictive biomarkers under investigation are mutations in the polymerase genes *POLE* and *POLD1* and bi-allelic inactivation of cyclin-dependent kinase 12 (*CDK12*) [99,100].

Animal and human cellular models have shown that *PTEN* loss PCa is unresponsive to ICI treatment due to the immunosuppressive TME, but post hoc analyses of a phase III trial of atezolizumab + enzalutamide suggested that patients with *PTEN* loss may benefit from treatment, although molecular mechanisms remain unclear [101]. However, this molecular alteration may provide some therapeutic opportunities as *PTEN* loss has shown to be a crucial factor in the formation of this "cold" TME. *PTEN* loss promotes an immunosuppressive tumor microenvironment by affecting the infiltration of immune cells such as regulatory T cells (Tregs) and NK cells. Recent studies have shown that the activation of PI3K-δ, specifically in *PTEN* deficient tumors, inhibits T-cell function and contributes to immune evasion, suggesting a mechanism of resistance to immunotherapy [102]. Di-

rect inhibition of PI3K by PI3Kα/β/δ inhibitors can delay growth in cancer cells but also PI3Kδ inhibition can inhibit Tregs allowing $CD8^+$ T cells to activate and clonally proliferate. Interestingly, experiments show that dose and schedule might be important to enhance these activating effects. Intermittent PI3K blockades showed an increased CD8/Treg ratio compared to daily treatment, with clonal expansion of infiltrating $CD8^+$ T cells contributing to an inflamed TME. Secondary activation of IFNα and IFNγ pathways in cancer cells led to an upregulation in PD-L1 expression. Therefore, maximum cytotoxic effects were achieved with a sequential combination of intermittent PI3K inhibition followed by anti-PD1 blockades in mice [103]. Androgen deprivation in PTEN/p53-deficient mouse models can also increase phagocytic activity of TAMs, but only the major histocompatibility complex (MHC)-II^{hi}/PD^{lo} population. The addition of copanlisib, a PI3K inhibitor, can increase activation of TAMs by diminishing lactate production by cancer cells, as described earlier. Further addition of an anti-PD1 was able to increase the phagocytic activity of a previously inactive subset of TAMs, the MHC-II^{hi}/PD^{hi} population, leading to treatment responses in mice [104]. But it is also important to note that the population of MHC-II^{lo}/PD^{lo} or PD^{hi} was not activated with any of the treatments described above. This subpopulation of cells was characterized by Wnt/b-catenin pathway activation, which has been shown to have a higher CD47 expression [105]. Treatment with anti-CD47 might lead to responses in this population but this has not been investigated.

Another relevant immune checkpoint in this population is B7-H3, as described above. Inhibition of this receptor and inhibition of the AR with enzalutamide synergized in CRPC cells with anti-PD1 and anti-CTLA4 agents. Interestingly, enzalutamide in combination with anti-PD-1/PD-L1 agents showed little CD8 infiltration and activation. Treatment with anti-B7-H3 or anti-CTLA-4 showed a greater degree of CD8 infiltration while the greatest effect was found in the anti-B7-H3/anti-CTLA-4 combination. CTLA-4 agent showed an important decrease in Tregs and this might be responsible for the effect mentioned earlier [79]. This might prove important in the future as drugs targeting B7-H3 are currently being tested in clinical trials and might be combined with ICI in the future. Targeting other interleukins responsible for MDSC recruitment might also prove useful, as shown by combinations of IL-6 inhibition with anti-PD1 or anti-CTLA-4 agents [68].

5. Discussion

Apart from specific subpopulations of patients, immunotherapy with ICI in PCa has shown only modest outcomes, although there are new immunotherapy drugs that have shown promising results that should be confirmed in phase II and III trials [106,107]. *PTEN* loss PCa patients, which represent roughly half of the patients in the CRPC phase, represent an important unmet clinical need as these patients will have worse outcomes with the currently available treatments. There is a paucity of data from patients with *PTEN* loss treated with immunotherapy and we will obtain more data as ongoing clinical trials publish results (Table 1). Published datas so far have been centered on tolerability and early signs of activity without addressing the specific contribution of the addition of a PI3K pathway in the activity of immunotherapy [108,109].

When investigating *PTEN* loss in PCa in human patients, we must acknowledge several limitations. The high frequency of *PTEN* loss heterogeneity adds difficulties to assess the status of the gene [110]. Also, although great efforts have been made to validate FISH and immunohistochemistry (IHC) assays in PCa, there is no standardized *PTEN* loss detection technique and cut-off. IHC has been accepted as an efficient technique to implement in clinical care and is commercially available [111], but clinical trials and observational studies to date have used different thresholds for this positivity [37,111–117]. Ipatential-150 trial showed a modest increase in radiographic progression-free survival (rPFS) with the addition of Ipatasertib, an AKT inhibitor, to abiraterone in patients with *PTEN* loss mCRPC (18.5 months vs. 16.5; $p = 0.0034$). *PTEN* status was centrally determined and defined as 50% or more of the specimen tumor area having no detectable *PTEN* staining [37]. However, a different cut-off and antibody were used in a previous phase II

trial with the same combination. In this trial, cut-off was defined by a complete absence of PTEN staining or weak intensity staining compared with internal control in no more than 10% of cancer cells [114]. Interestingly, in Ipatential-150 authors assessed differences in subgroups based on genetic alterations identified by NGS (FoundationOne CDx) and found that differences in rPFS were more prominent (19.1 vs. 14.2 months) in patients with *PTEN* loss detected with this technique but, additionally, that patients with alterations in PI3KCA/AKT1/PTEN also may benefit more from treatment (19.3 vs. 14.1 months). This underscores the importance of defining the most adequate diagnostic technique to characterize the population that may benefit the most from PI3K pathway inhibition.

Table 1. Ongoing clinical trials testing combinations of immunotherapy and PI3K pathway inhibitors.

Trial Number	Drug	Phase
NCT04317105	Copanlisib Nivolumab +/− Ipilimumab	I/II
NCT03673787	Ipatasertib Atezolizumab	I
NCT03842228	Copanlisib Olaparib +/− Durvalumab	I
NCT04975958	Buparlisib Atezolizumab AN2025/AN2005	I
NCT03772561	Capivasertib Olaparib Atezolizumab	I
NCT02637531	Eganelisib Nivolumab	I

Pharmacological inhibition of the PI3K pathway in *PTEN* loss PCa is also complex. Firstly, the reciprocal feedback between the AR and PI3K pathway requires that simultaneous antagonism of the AR is required for optimal outcomes. Several clinical trials have tested different inhibitors for critical components of the PI3K pathway such as mTOR, pan-PI3K, dual PI3K/mTOR, PI3K isoform-specific, and AKT inhibitors, with modest outcomes in the majority of published trials [118]. Additionally, data regarding how inhibition of different points of the pathway may lead to different outcomes in immune system modulation is scarce. Concerns about therapeutic efficacy arise as mTOR1 inhibitors may cause a paradoxical AKT activation and PI3K inhibitors may relieve feedback inhibition of IGF1R and other receptors, leading to reciprocal activation of the pathway [119]. There is preclinical evidence that PI3K/mTOR inhibition may be superior compared to inhibition of PI3KCA alone when combined with ICI in breast cancer models [120]. Additionally, isoforms α/β are ubiquitously expressed, adding toxicity to the treatment, while δ/γ are commonly restricted to leukocytes and essential for immune surveillance and possibly causing detrimental effects to a hypothetical immunotherapy treatment [121]. Intermittent dosing or inhibitors with short half-life may represent a potential way to enhance anti-tumor immunity, therapeutic index, and overcome therapeutic resistance [103,122,123].

6. Conclusions

Evidence suggests that loss of *PTEN* in prostate cancer significantly contributes to immune evasion. The activation of the PI3K/AKT pathway, resulting from *PTEN* loss, alters the tumor microenvironment mainly by recruiting immune-suppressive cell populations to the TME. Understanding these immune evasion strategies is critical for the development of targeted therapies aimed at restoring effective immune surveillance in patients with *PTEN* deficient prostate cancer.

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Glossary

ADT	Androgen deprivation therapy
AR	Androgen receptor
ARSI	Androgen receptor signaling inhibitors
bRFS	Biochemical-failure free recurrence free survival
CDK12	Cyclin-dependent kinase 12
CRPC	Castration-resistant prostate cancer
DC	Dendritic cells
DMFS	Distant-metastases free survival
FISH	Fluorescent in situ hybridization
HG-PIN	High-grade prostatic intraepithelial neoplasia
HSPC	Hormone-sensitive prostate cancer
ICI	Immune checkpoint inhibitors
IDO	Indoleamine 2,3-dioxygenase
IHC	Immunohistochemistry
IL	Interleukin
LOH	Loss of heterozygosity
MDSC	Myeloid-derived suppressor cells
MHC	Major histocompatibility complex
MMR	Mismatch-repair
NGS	Next-generation sequencing
OS	Overall survival
PCa	Prostate cancer
PI3K	phosphatydilinositol-4,5 biphosphate 3-kinase
PIP2	phosphatidylinositol 4,5-bisphosphate
PIP3	phosphatidylinositol 3,4,5-trisphosphate
PTEN	Phosphatase and tensin homolog
ROS	Reactive oxygen species
rPFS	Radiographic progression-free survival
TAM	Tumor-associated macrophage
TCGA	The Cancer Genome Atlas.
TME	Tumor microenvironment

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