The role of protein post-translational modifications in prostate cancer (#98082)

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- Are sources adequately cited? Quoted or paraphrased as appropriate?
- Is the review organized logically into coherent paragraphs/subsections?

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- Conclusions are well stated, linked to original research question & limited to
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3

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The role of protein post-translational modifications in prostate cancer

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Through the covalent attachment of functional groups or proteins, proteolytic cleavage of regulatory subunits, or destruction of complete proteins, protein translational modifications (PTMs) broaden the functional diversity of the proteome. These alterations, which include phosphorylation, glycosylation, ubiquitination, methylation, acetylation, lipidation, and lactation, have an impact on nearly normal biological cell function, are significant biological events in the development of cancer, and play vital roles in numerous biological processes. The processes behind essential functions, the screening of clinical illness signs, and the identification of therapeutic targets all depend heavily on further research into the PTMs. This page outlines the effects of several PTM types on prostate cancer (PCa) diagnosis, therapy, and prognosis in an effort to shed fresh light on the molecular causes and progression of the disease.

The role of protein post-translational modifications in prostate cancer

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Abstract

Through the covalent attachment of functional groups or proteins, proteolytic cleavage of regulatory subunits, or destruction of complete proteins, protein translational modifications (PTMs) broaden the functional diversity of the proteome. These alterations, which include phosphorylation, glycosylation, ubiquitination, methylation, acetylation, lipidation, and lactation, have an impact on nearly normal biological cell function, are significant biological events in the development of cancer, and play vital roles in numerous biological processes. The processes behind essential functions, the screening of clinical illness signs, and the identification of therapeutic targets all depend heavily on further research into the PTMs. This page outlines the effects of several PTM types on prostate cancer (PCa) diagnosis, therapy, and prognosis in an effort to shed fresh light on the molecular causes and progression of the disease.

Keywords: protein post-translational modification, prostate cancer, diagnosis, treatment, prognosis

Introduction

Only transcription and translation allow genes to become proteins, and practically all proteins undergo PTMs such phosphorylation, methylation, acetylation, glycosylation, and ubiquitination. Multiple PTMs can act in concert, or compete for the same sites to drive opposite outputs [1, 2].

As a result, different PTMs combinations influence the charge, conformation, and stability of proteins, which in turn affects numerous biological processes (Supplementary Materials, Table 1) and is linked to a number of human disorders [3]. Therefore, this article examines the impact of PTMs such as protein phosphorylation, glycosylation, ubiquitination, acetylation, methylation, succinylation, and lipidation on the diagnosis, treatment, and prognosis of PCa, to provide a new understanding of the molecular mechanism of its formation and development of prostate cancer.

Survey Methodology

PubMed database was used for related literature search using the keyword "prostate cancer," "cancer," "protein phosphorylation," "protein glycosylation," "protein ubiquitination," "protein acetylation," "protein methylation," "protein succinylation," and "protein lipidation."

RATIONALE

This study explores the influence of post-translational proteins on the diagnosis, treatment and prognosis of prostate cancer, hoping to provide a new perspective for the study of the molecular mechanism of the occurrence and development of prostate cancer, provide new targets and screening methods for drug research and development, and promote the discovery and development of new drugs.

AUDIENCE

This review describes the post-translational modifications of proteins related to prostate cancer in recent years, which is conducive to readers' understanding of the development mechanism, treatment and prognosis of prostate cancer, and also opens up ideas for the treatment of prostate cancer. Therefore, it is considered appropriate for the journal's diverse readership.

Classification and clinical application of the PTMs types in prostate cancer

1 Phosphorylation

Phosphorylation modulates and controls the activity and function of many proteins as one of the most common PTMs [4]. Tyrosine kinases and cyclin-dependent kinases, for instance, promote the course of malignant illness by phosphorylation or participation in the phosphorylation pathway, and the targeted phosphorylation pathway represents one of the prospective routes for the creation of anticancer drugs [5]. PI3K/Akt/mTOR and Ras/MAPK are two important signaling pathways implicated in PCa development (Figure 1). For instance, eukaryotic translation initiation factor 4E (eIF4E) is phosphorylated by Mnk1/2 in response to rapamycin (mTOR), and phosphorylation of eIF4E increases oncogene translation rates and promotes drug resistance in prostate cancer [6]. Phosphorylation of the leukemia inhibitory factor receptor (LIFR) under the action of extracellular signal-regulated kinase 2 (ERK2) contributes to the subsequent activation of the protein kinase B signaling pathway (AKT) and induces the expression of genes associated with proliferation and metastasis [7]. The COP9 complex subunit (COPS3) is highly expressed in PCa tissues and promotes epithelial-mesenchymal (EMT) transformation of PCa by increasing the phosphorylation level of P38 MAPK [8]. Phosphatase and tensin homolog (PTEN) can negatively regulate the P13K/Akt pathway. When miR-92a is highly expressed in PCa, it can

promote the proliferation, invasion, and migration of PCa cells through the activation of the PTEN/Akt signaling pathway, thereby accelerating the development of PCa [9]. In the presence of dehydroepiandrosterone (DHEA), bone marrow kinase on the X chromosome (BMX) is activated and phosphorylates 3β-hydroxysteroid dehydrogenase type 1 (3βHSD1) to form an active dimer that promotes the conversion of DHEA to dihydrotestosterone (DHT) [10]. Tousled-like kinase mediates the phosphorylation of NEK1, an amitotic gene A-associated kinase 1, leading to DNA damage and promoting the development of CRPC [11]. ErbB-2 is phosphorylated by Src kinase and phosphorylated by AKT, which promotes PCa cell proliferation and migration through PI3K/AKT [12]. In PCa, loss of nuclear FOXP3 is usually accompanied by low expression of TSC1, which induces c-Myc transcription and protein phosphorylation to synergistically increase c-MYC expression and activate mTOR signaling[13].

Figure 1. Schematic diagram of PI3K/Akt/mTOR signaling pathway

Note: PTEN, phosphatidylinositol 3-kinase (PI3K) and phosphatidylinositol 4,5-diphosphate (PIP2) work together to produce phosphatidylinositol triphosphate (PIP3). PIP3 recruits PDK1, a protein with pleckstrin homology domain, phosphorylates and disrupts tuberculosis complex 1/2 (TSC1-TSC2) through Akt, and phosphorylates mTOR through RHEB. The two complexes that mTOR proteins are involved in are mTOR protein complex 1 (mTORC1) and mTOR protein complex 2 (mTORC2). mTORC1 increases protein translation by phosphorylation of its two direct targets and P70S6K.

Therefore, targeting these phosphorylation targets and pathways can be developed for clinical applications in prostate cancer. Phosphorylation controls the androgen receptor (AR) and the PTEN/PI3K/AKT/mTOR axis [14]. Cyclin-dependent kinase 1 (CDK1) and AKT phosphorylate Ser81 and Ser213 of AR, respectively, while phenethyl caffeic acid (CAPE) reduces the protein levels and activity of CDK1 and AKT and inhibits the phosphorylation of Ser81 and Ser213 on AR, thereby regulating the stability of AR [15]. Under hypoxic conditions, the proviral integration site for Moloney murine leukemia virus-1 (PIM1) promotes prostate cancer invasion by directly phosphorylating ABI interactant 2 (ABI2). However, the use of PIM inhibitors can reduce prostate cancer metastasis [16, 17]. DHT will interact with AR to promote PCa to CRPC, the BMX inhibitor zanubrutinib can effectively block androgen biosynthesis [18], so this is also a treatment for CRPC. ErbB-2 can be used as a biomarker for invasive PCa when hyperphosphorylated [19] Antiandrogen inhibits ErbB-2, which is rarely overexpressed in patients with advanced PCa, so trastuzumab clinical trials in men with advanced PCa have shown little efficacy. However, when castration or antiandrogen is combined with trastuzumab or the mTOR inhibitor everolimus, the risk of recurrence of PCa xenografted tumors was significantly reduced [20]. Therefore, using ErbB-2 as the target, combining various methods to treat PCa is worthy of further study. LQB-118 is a sandalquinone with antitumor activity on prostate cancer cells [21], which regulates the proliferation, death and migration/invasion of PCa cells via a negative regulator of the Akt/GSK3 signaling pathway and is used to treat metastatic PCa in LQB can -118 is used alone or in combination with another chemotherapy drug [22]. Serine/threonine protein phosphatase 5

(PPP5C) is highly expressed in PCa tissues, and knockdown of PPP5C can inhibit the proliferation of PCa cells and promote the phosphorylation of JNK and ERK. Therefore, PPP5C may become a new diagnostic biomarker and therapeutic target for PCa [23]. Combined administration of c-MYC and mTOR inhibitors (Torin1) can overcome the resistance to mTOR inhibition that is common in prostate cancer cells, creating a new therapeutic target for prostate cancer patients with both signaling defects [13]. For a summary of studies on the impact of protein phosphorylation on the diagnosis, treatment, and prognosis of PCa, please refer to the Supplementary Materials Table 2.

2 Glycosylation

The modification of glycosylation is mainly catalyzed and regulated by various glycosyltransferases and glycosidases [24], which play an important role in the origin and development of malignant tumors. Most tumor markers used in clinical applications are glycoproteins [25]. Studies on the influence of glycosylation modification on the occurrence and development of prostate cancer mainly include 2,6-sialylation, nuclear fucosylation, branched N-sugar, and Lacdinac glycosylation [26]. The structures and types of these glycosylation modifications are illustrated in Figure 2.

Figure 2. Some types and structures of glycosylation.

St6-galactoside-2,6-sialtransferase 1 (ST6GAL1) is an enzyme that catalyzes the addition of 2,6-linked sialic acids to terminal N-linked sugars. Its upregulation in prostate cancer has been found to promote tumor growth and metastasis [27, 28]. Another protein, growth differentiation factor 15 (GDF15), is associated with low survival rate in prostate cancer patients. Its N-glycosylation at the N70 site activates the epidermal growth factor receptor (EGFR) signaling pathway, which provides a potential target for the development of selective GDF15 glycosylation-based inhibitors for the treatment of CRPC [29]. α (1,6) Fucosylaminotransferase (FUT8), an enzyme involved in N-glucosylfucosylation, has been implicated in tumor metastasis and immune escape [30]. FUT8 mediates glycosylation of several proteins including EGFR, TGF-beta receptor (TGFBR), E-cadherin, PD1/PD-L1, and β1-integrin, and plays an important role in promoting the malignant phenotype of tumor cells[30].

These studies suggest that further research into protein glycosylation may lead to the development of new biomarkers or drugs for the diagnosis and treatment of prostate cancer. The level of cofucosylated diantennacan in the serum of prostate cancer patients is significantly increased, and cofucosylated prostate-specific antigen (PSA) shows potential as a diagnostic biomarker for distinguishing prostate cancer from other prostate diseases, such as BPH [31, 32]. Serum prostate-specific antigen (sPSA) could not distinguish between poorly differentiated, moderately differentiated, and highly differentiated PCa. The integration of N-glycosylation profiles and prostate volume changes into a single urinary glycosylation profile marker (UGM) capable of distinguishing between BPH, PCa and prostatitis has high potential as a PCa

biomarker[33, 34]. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) has been employed to detect changes in O-glycans in prostate cancer cells, including increased O-glycan levels, decreased complex O-glycans, and increased salivary flow of O-glycans [35]. The polypeptide N-acetylgalactosaminyltransferase 7 (GALNT7) is a polypeptide that can alter the O-glycosylation of membrane and secreted proteins. It has been found that the levels of GALNT7 in urine and blood of patients with CRPC are higher than normal, and its diagnostic value exceeds that of PSA alone [36]. AC5GalNTGc is a small molecule inhibitor of O-linked glycosylation, and can effectively inhibit O-glycan biosynthesis. Furthermore, it has been shown to exhibit anti-inflammatory properties [37]. Treatment with Myc inhibitors (10074-G5 or 10058-F4) induces the IRE-α-XBP1s pathway to trigger fructose-6-phosphoamidotransferase-1 (GFAT1) and increased protein glycosylation. When Myc inhibitors are used in combination with GFAT-1 inhibitors (DON), there is a synergistic effect in inhibiting prostate cancer cell proliferation and migration, suggesting that targeting Myc and GFAT-1 is a novel approach that may represent a strategy for the treatment of prostate cancer [38].

3 Ubiquitination and deubiquitination

Ubiquitination is the process of attaching ubiquitin to a target protein, involving three enzymes: ubiquitin-activating enzyme E1, ubiquitin-conjugating enzyme E2, and ubiquitin ligase E3. Proteins can undergo either monoubiquitination or multiubiquitination. Multiubiquitination occurs when one of the seven lysine residues of ubiquitin is linked to another ubiquitin [39]. The process of ubiquitination is a reversible ATP-dependent reaction, with the removal of ubiquitin from the target protein referred to as deubiquitination [24]. The biological processes of ubiquitination and deubiquitination are shown in Figure 3.

Figure 3. Biological processes of protein ubiquitination and deubiquitination.

Note: Under the action of ATP energy supply, ubiquitin molecules combine with Cys of E1 to activate ubiquitin. E1 transfers ubiquitin to E2 and then transfers ubiquitin to the target protein under the action of E3, resulting in the target protein ubiquitin. The target protein can carry one or more ubiquitin molecules and the target protein with ubiquitin molecules is degraded on the one hand under the action of the proteasome. On the other hand, ubiquitin molecules are removed from the target protein under the action of deubiquitination enzymes, and ubiquitin molecules enter the next ubiquitination process.

Spot-type POZ protein (SPOP), the most commonly mutated tumor suppressor gene in human primary prostate cancer[40], is an E3 ubiquitin ligase that inhibits tumor growth by breaking down cancer-promoting substrates. WT-SPOP induces the expression of caprin1,3-phosphoinositol-dependent protein kinase-1 (PDK1) [41]. SPOP can hinder tumor growth by inhibiting the activity of AKT kinase [42]. Additionally, it can facilitate the degradation of HnRNPK by promoting its ubiquitination, thereby inhibiting the proliferation of prostate cancer cells [43]. The SPOP/CUL3/RBX1 complex inhibits PCa progression through ubiquitination of cyclin E1 [44]. However, mutant SPOP has different effects. It promotes the degradation of transcription factor

2 (ATF2), leading to the proliferation and migration of prostate cancer cells[45]. Additionally, mutant SPOP can increase androgen production, AR activation, and the growth of PCa cells [46]. The ubiquitin-binding enzyme E2S (UBE2S) regulates the stability of p16 and β-catenin through K11-linked ubiquitination, thereby promoting the migration and invasion of PCa cells [47]. The ubiquitination process requires ATP and hexokinase (HK) is the first rate-limiting enzyme in glycolysis [48]. Docetaxel can activate the expression of hypoxia-inducing factor 1 (HIF-1) and thereby increase the expression of SUMO-specific protease 1 (SENP1), which mediates HK2 desumoylation and promotes HK2 binding to mitochondria [49]. Melatonin reduces the expression of SENP1, which mediates the desumoylation of HDAC1, a key factor in AR transcription activity[50]. Furthermore, F-box and WD repeat domain containing 2 (FBXW2) can target EGFR for ubiquitination and degradation, thereby inhibiting the proliferation and metastasis of PCa cells [51]. USP16 and USP33, as the deubiquitinating enzymes of c-Myc, regulate the proliferation of PCa cells by deubiquitinating and stabilizing the expression of c-Myc. By down-regulating the expression of USP16 and USP33, the growth of PCa cells in vitro was significantly inhibited in vivo [52, 53]. Ovarian tumor deubiquitinase 6A (OTUD6A) is highly expressed in prostate cancer tissues, and OTUD6A stabilizes Brg1 and AR expression by removing FBXW7-mediated multiubiquitination of the K27 junction of Brg1 and the SPOP-mediated K11 junction of AR [54]. Brca1-associated protein 1 (BAP1) is a deubiquitinating enzyme that can inhibit prostate cancer progression by stabilizing the expression of PTEN and downregulating the PI3K-Akt pathway [55].

Nobiletin, a compound, has the ability to specifically promote the degradation of AR-V7 through the K48 ubiquitination form of the AR splice variant 7. It achieves this by preventing the interaction of the deubiquitinating enzymes USP14 and USP22 with AR-V7. In addition, Nobiletin also enhances the sensitivity of CRPC to enzalutamide, effectively inhibiting the growth of CRPC[56]. UBC9 mediates the SUMOylation of transcriptional activator 4 (STAT4). Inhibiting UBC9 with 2-D08 can promote the activation of tumor-associated macrophage (TAM) and CD8 T cells, preventing the progression of PCa [57]. USP14 is one of the related proteins of driver protein family member 15 (KIF15) and acts as a deubiquitination enzyme, preventing AR and AR-V7 degradation, thereby increasing prostate cancer resistance to enzalutamide [58]. At the same time, lncRNA PCBP1 antisense RNA 1 (PCBP1-AS1) can also stabilize USP22-AR/AR-V7 complex formation, enhance AR and AR-V7 deubiquitination, and promote CRPC progression and resistance to enzalutamide [59]. The ubiquitin-specific peptidase 1 (USP1) functions functionally as the deubiquitin enzyme, while SNS-032 functions as a kinase inhibitor, inducing apoptosis and downregulating USP1 expression, thereby inhibiting PCa proliferation[60]. In addition, overexpression of USP7, USP10 and USP12 in PCa cells is associated with poor prognosis in PCa patients and may be used as prognostic markers in PCa patients[61]. In addition, one of the induced degradation techniques developed for target proteins is PROTAC (Proteolytic Targeted Chimera) technology by forming ternary complexes that link the target proteins with E3 ligases [62]. AR degraders developed using PROTAC technology, such as ARD-61, ARV-110, ARD-2128, and ARD-266, have shown significant inhibitory effects on

cancer cell proliferation and have the potential to overcome drug resistance [63, 64]. Most prostate cancer patients treated with docetaxel develop resistance to docetaxel, and nuclear protein 1 (NUPR1) confers docetaxel resistance to prostate cancer cells, suggesting that NUPR1 plays a role in docetaxel resistance [65]. Additionally, some RNAs are involved in the ubiquitination process. For instance, circ_0006156 regulates S100A9 protein expression via the ubiquitination process, thereby inhibiting R transfer in PCa cells [66]. Detailed studies on the impact of protein ubiquitination on prostate cancer diagnosis, treatment, and prognosis can be found in the Supplementary Materials Table 3.

4 Acetylation and deacetylation

The acetylation of proteins is the transfer of the acetyl group to the protein by the acetyl donor (e.g., acetyl-coA) under the catalysis of acetyltransferase. The reverse process is called deacetylation [24].

Tumor protein D52 (TPD52) can be acetylated by lysine acetyltransferase 2B (KAT2B), creating antagonism with histone deacetylase 2 (HDAC2) and preventing the interaction between TPD52 and the HSPA8 member, resulting in tumor growth impairment. This represents a target for PCa treatment [67]. Lysine acetyltransferase 2A (KAT2A) acetylates AR and induces AR translocation from the cytoplasm to the nucleus, resulting in increased transcription activity of the AR target gene PSA, thereby increasing resistance to abiraterone [68]. CBP/P300 mediates the acetylation of HOXB13, AR, JMJD1A, SKP2 and other proteins and promotes the emergence and development of PCa, making it the key point of antiandrogen resistance of CRPC[69-72]. CBP/P300-related factors can promote the degradation of β-catenin through acetylation and thus inhibit prostate cancer progression [73]. Furthermore, in CRPC, carnitine palmitoyltransferase 1A (CPT1A) provides acetyl groups for histones to promote tumor growth and anti-androgen resistance (e.g., enzalutamide) [74]. In patients with advanced PCa, the degree of acetylation of the H3 in their tissues is significantly increased [75]. Furthermore, N-acetyltransferase 10 (NAA10) has been found to promote the proliferation and migration of prostate cancer cells, as well as induce autophagy [76]. On the other hand, acetylase acetyl-CoA acetyltransferase 1 (ACAT1), known as a protumor factor in prostate cancer, has been shown to promote the occurrence and development of the disease by inhibiting autophagy and eliminating reactive oxygen species [77]. SIRT5 inhibits PI3K and mediates PI3K/AKT/NF-B signaling to suppress prostate cancer metastasis [78]. Moreover, SIRT5 promotes the activity of the MAPK signaling pathway through ACAT1, enhancing the proliferative, migratory, and invasive abilities of prostate cancer cells [79].

Docetaxel, a semisynthetic taxane, has exhibited significant single-agent activity against prostatic tumors [80]. However, drug resistance and toxicity often occur during treatment [81]. It is therefore clear that acetylation and deacetylation of proteins affect the sensitivity of prostate cancer to drugs. Transforming growth factor-β (TGF-β) can induce a process known as acetylation of Kruppel-like factor 5 (KLF5) (Ac-KLF5), which promotes bone metastasis in PCa by activating the C-X-C chemokine receptor type 4 (CXCR4). The use of the CXCR4 inhibitor AMD3100 has been shown to increase tumor sensitivity to docetaxel and inhibit bone metastasis

in PCa [82]. Ac-KLF5 also plays a role in regulating prostate development [83]. Nitazoxanide which is an anti-parasitic drug with potent antiviral activity as an inhibitor can suppress Ac-KLF5-induced bone metastasis in PCa by regulating KLF5 function [84]. SIRT3 is involved in regulating the acetylation level of various proteins (such as HSD17B4, ACO2, etc.) to affect protein stability, and it can serve as a diagnostic marker for predicting PCa progression [85]. Notably, the activity of ACO2 is significantly increased in prostate cancer tissues. AR can regulate the expression of SIRT3 by binding to steroid receptor coactivator 2 (SRC-2). In the absence of SRC-2, the expression of SIRT3 is enhanced, and the acetylation of ACO2 is reduced. Increased expression of SRC-2 and decreased expression of SIRT3 serve as genetic markers for the accumulation of prostate cancer metastases [86]. Phosphoenolpyruvate carboxykinase subtype 2 (PCK2) reduces acetyl-CoA levels by shortening the TCA cycle, thereby promoting tumourigenesis. PCK2 is therefore a potential therapeutic target for aggressive prostate tumours [87].

5 Methylation

Protein methylation is an important epigenetic modification [88]. Studies have shown that some key genes in prostate cancer cells are altered by methylation modification, such that a change in the activity of the genes leads to the development of prostate cancer [89].

SET domain protein 2 (SETD2) mediates the expression of Zeste homolog 2 (EZH2) and promotes EZH2 degradation, which prevents PCa metastasis. However, metastasis is promoted when SETD2 is absent [90]. As a methyltransferase, EZH2 mediates the methylation of ERG and enhances its transcriptional and carcinogenic activity [91]. The administration of the EZH2 inhibitor GSK343 inhibits ERG methylation and tumor growth in PCa mouse models [92]. DNA methyltransferase 1 (DNMT1) promotes the emergence and metastasis of PCa by inhibiting the transcription of tumor necrosis factor receptor-associated factor 6 (TRAF6), which mediates EZH2 ubiquitination [88].

Histone methyltransferase has become an important therapeutic target in oncology. Telomere silencing 1-like disruptor (DOT1L) is overexpressed as a histone methyltransferase in PCa tissues and is associated with a poor prognosis [93]. It impairs the mobility of PCa cells and organoids. When DOT1L is knocked out or the inhibitors EPZ004777 or EPZ5676 are used, the expression of MYC decreases and the expression of HECTECT domain E3 ubiquitin protein ligase 4 (HECTD4) and MYCBP2 is regulated, ultimately promoting the degradation of AR and MYC [93]. Methylated H3 blocks antiandrogen resistance [93].

6 Succinylation

Succinylation b*y* transferring a succinyl group to a residue of the target protein in an enzymic or non-enzymic manner [94]. Therefore, the level of succinylation is mainly regulated by succinyl donor, succinyltransferase, and desuccinylase [95]. Succinylation alters rates of enzymes and pathways, especially mitochondrial metabolic pathways [96], thus linking metabolic

reprogramming with various pathological disorders including cancers [94]. However, little has been reported on the role and value of succinylation modification of the lysine site in prostate cancer.

The level of succinylation in PCa tissues was significantly increased and the level of succinylation correlated with the Gleason score and PDL1 expression level [97]. C-terminal binding protein 1 (CTBP1) is a corepressor in gene transcription regulation and is highly expressed in prostate cancer tissues. CTBP1 promotes migration of prostate cancer cells. E-cadherin (CDH1), a transmembrane glycoprotein that connects epithelial cells at adherent junctions, exerts its tumour suppressing role mainly by sequestering β-catenin from its binding to LEF (Lymphoid enhancer factor)/TCF (T cell factor)[98]. CDH1 functions as a substrate of CTBP1. KAT2A mediates succinylation of CTBP1 and inhibits the transcription activity of CTBP1 on CDH1 and thus play a role in cancer promotion [99]. In addition, desuccinylation also plays an important role in prostate cancer. For example, SIRT5, a nicotinamide adenine dinucleotide (NAD)-dependent desuccinylase, significantly reduced expression levels of SIRT5 and significantly increased succinylation at lactate dehydrogenase A (LDHA) lysine 118 (K118su) in aggressive PCa cells. As a substrate of SIRT5, LDHA-K118su significantly increased migration and invasion of PCa cells [100].

Fish oil (FO) composed of omega-3 polyunsaturated fatty acids (omega-3 PUFA) affects the succinylation of glutamate-oxaloacetic aminotransferase 2 (GOT2), which may inhibit PCa progression by interfering with aspartate synthesis and nucleotide production. This provides the basis for further investigation of succinylation and GOT2 as potential drug targets for future PCa treatment [101].

7 Lipidization

Protein lipid modification mainly includes cysteine palmitoylation, n-terminal glycine myristoylation, and cysteine isoprene [24]. The common protein lipidization modifications in prostate cancer mainly include the dysregulated expression of fatty acid synthase (FASN) and activated protein kinase (AMPK) [102] (Figure 4). FASN catalyzes the synthesis of malonyl coenzyme A (MCoA) and acetyl coenzyme A (ACoA) from procondensation and stores the palmitate by converting excess carbon uptake into fatty acids. It is responsible for the acylation of key regulatory switches in most signal transduction energy pathways and plays a central role in energy homeostasis [103].

Figure 4. Main metabolic pathways of FASN and AMPK in PCa cells.

Note: The condensation of MCoA and ACoA produces FASN, which plays a central role in energy homeostasis by converting excess carbon uptake into fatty acids for storage. Activation of AMPK can inhibit these pathways by direct phosphorylation of key lipoblast and key kinases (such as ACC or TSC1/TSC2) or by regulating SREBP1c transcription.

The elevated expression of FASN is associated with a poor prognosis of PCa, and the 5-reductase inhibitor (dutasteride) can inhibit the expression of FASN in prostate cancer cells [103].

Caveolin-1 promotes androgen resistance by upregulating acetyl-CoA carboxylase-1 (ACC1) and FASN expression and lipid synthesis and promotes the proliferation and metastasis of PCa cells [104]. FASN inhibitor (IPI-9119) and demonstrated that selective FASN inhibition antagonises CRPC growth through metabolic reprogramming and leads to decreased protein expression and transcriptional activity of full-length AR (AR-FL) and AR-V7 [105]. Overexpression of miR-107 alters key invasive characteristics of PCa cells and regulates the expression of lipid metabolism. Therefore, miR-107 may represent a novel and useful biomarker for personalised diagnosis and prognosis [106]. AMPK plays an on-off role in glucose and lipid metabolism. Therefore, drugs that induce AMPK activation have potential benefits in the prevention and treatment of prostate cancer [107]. For example, when AMPK is activated by 5-aminoimidazole-4-formamide riboside (AICAR) or thiazolidinedione rosiglitazone, AICAR inhibits mTOR and p70S6 expression, as well as ACC and FASN expression in LNCaP cells, thereby inhibiting cell growth [108].

8 Lactation

Lactic acid is an abundant metabolite in the tumor microenvironment, is secreted by cancer-related fibroblasts, and can be absorbed by cancer cells to maintain mitochondrial metabolism [109]. However, lactate modification is a novel protein modification that was only reported in 2019[110], so there are relatively few studies. HIF1 introduces lactic acid into PCa cells via monocarboxylate transporter 1 (MCT1), and HIF1 lactation enhances transcription of KIAA1199 and promotes prostate cancer angiogenesis [111]. In addition, regulation of histone lactation is also a potential PCa therapy target [112]. For example, tumor cells treated with PI3K inhibitors or anti-PD-1 antibodies (aPD-1) reduce lactate production and inhibit lactation of histone proteins within tumor-associated macrophages (tams), resulting in phagocytic activation [113]. Absence of the Numb/Parkin pathway in prostate cancer leads to metabolic reprogramming, a significant increase in lactic acid production and subsequent upregulation of histone lactation and neuroendocrine-associated gene transcription, a promising therapeutic target for cancer cell plasticity modulation of histone lactation [112].

9 Interaction of various PTMs

There are many forms of mutual regulation of PTMs between proteins, such as the interaction between ubiquitination and phosphorylation, the interaction between acetylation and ubiquitination, and the interaction between phosphorylation and lipidation.

In PCa tissues, overexpression of prostatic leucine zipper (PrLZ) can promote cell growth and migration [114], and Cullin 3/SPOP can mediate ubiquitination and degradation of PrLZ, thereby regulating prostate cancer progression (il - 6th) Activation of ERK1/2 expression prevents SPOP-mediated degradation of PrLZ phosphorylation at Ser40 [115]. Protein acetylation is also associated with protein degradation. Early studies demonstrated that proteins with free α-amino groups can be degraded by ATP-dependent ubiquitin degradation, and that ubiquitin-mediated

protein degradation can be prevented when the N-terminal α-amino group is acetylated [116, 117]. Activated kinase 6 (PAK6) of P21 in the inner mitochondrial membrane promotes sirtuin protein 4 (SIRT4) ubiquitination degradation, while SIRT4 abolishes acetylation of adenine nucleotide translocase 2 (ANT2) to promote ANT2 ubiquitination degradation and activates P21 Kinase 6 (PAK6) directly phosphorylates ANT2 to inhibit prostate cancer cell apoptosis, and the phosphorylation and deacetylation modification of ANT2 are mutually regulated, thereby promoting PCa progression [118]. Both CDK4/6 and CDK2 can phosphorylate RB, and RB phosphorylation decreases the interaction between HDAC5 and RB [119]. CBP/p300 interacts with the Glu/ASP-rich C-terminal domain transactivator 2 (CITED2) and binds to polymer complexes (NCL, p300, PRMT5) to drive nucleolar protein (NCL) methylation and acetylation, thus inducing NCL regulate translocation. AKT is activated to drive the EMT and cell migration [120]. Phenethyl isolipoate (PEITC) regulates histone acetylation, activates the PI3K/AKT pathway, and phosphorylates PI3K to regulate prostate cancer cell development [121].SPOP regulates lipid metabolism by reducing FASN expression and FA synthesis, thereby inhibiting tumour progression [40].

EZH2 prevents FOXA1 ubiquitination by enhancing FOXA1 methylation and increasing FOXA1 stability [122]. Simultaneously, the deubiquitinating enzyme USP7 also interacts with FOXA1 to reduce the ubiquitination of FOXA1, and the use of EZH2 and USP7 inhibitors (GSK-126 and EPZ-6438) inhibits the growth of PCa [123]. Acetylation of LIFR K620 is dependent on AKT production and promotes PCa progression through phosphorylation of LIFR S1044, which activates the AKT pathway and recruitment of 3-phosphoinositol-dependent protein kinase 1 (PDPK1) and PTEN loss connected is. This represents a biomarker to monitor the progression of PCa [118]. The retinoblastoma protein (RB) binds to HDAC, and when HDAC5 is absent, it increases prostate cancer cell resistance to the CDK4/6 inhibitor palbocinb. Baicalein can regulate fatty acid metabolism and induce cell apoptosis by activating the AKT-SREBP1-FASN signalling network in human PCa cells, showing potent anti-tumour effects. Therefore, it may be a promising candidate for anticancer drug development [124]. Eriobotrya japonica (EJCE) blocks SREBP-1/FASN-driven metabolism [125]. Targeting FASN or in combination with AR pathway inhibitors (SCD1 and AR) is likely to be a combined drug strategy [126]. The combination of orlistat (a FASN inhibitor) and radiotherapy significantly reduced NF-κB activity and associated downstream proteins in both prostate cancer cells, and the combination therapy showed the best tumour suppression [127]. By restricting histone lactation and HIF1A expression in PCa cells, Evodiine blocks lactate-induced angiogenesis and further enhances Sema3A transcription while inhibiting PD-L1 transcription. Evodiine is a promising agent for anti-angiogenesis therapy or immunotherapy of PCa [128].

Conclusion and perspective

In summary, post-translational modification of proteins plays an important role in cellular processes by regulating cell signalling, protein localisation and maintaining cellular function by altering protein structure and function. However, protein modifications such as protein

methylation, succinylation and lactation have been less studied in prostate cancer. At present, these studies only show that protein succinylation, lactation and methylation modifications can be used as promoting factors in prostate cancer, and do not conduct in-depth studies on the role these modifications play in prostate cancer and its treatment. Therefore, we can reasonably assume that the specific regulatory role of these modifications in prostate cancer may become a new direction of prostate cancer targeted therapy. In the future, it may be possible to use PROTAC technology to directly mediate protease degradation of target proteins for succinylation, lactation and methylation modification, or to mediate other types of modified enzymes to competitively target the sites of succinylation, lactation and methylation modification. and provide a new vision for gene therapy.

Now, with advances in biotechnology such as high-throughput sequencing, proteomics and metabolomics, these technologies can be used to screen for new biomarkers to reduce prostate cancer mortality[129]. High-throughput sequencing technologies have identified millions of genetic mutations in a wide range of human diseases. The combination of functional features such as PTMs with genetic mutations can distinguish disease-associated mutations and provide potential molecular targets for new therapeutic strategies[130]. Mass spectrometry can be used to detect and quantify proteins in prostate secretions, urine and blood to assess disease status[129]. For example, fucosylated [131]and n-glycosylated[132]N-glycans of the protein haptoglobin can be used as biomarkers for prostate cancer. Biomarkers for succinylation, lactation and methylation modifications can therefore be developed using these techniques. PTM regulators are an attractive and important target class for drug development. Kinase inhibitors, methyltransferase inhibitors, deacetyltransferase inhibitors and ubiquitin ligase inhibitors have achieved remarkable success in clinical use. Mass spectrometry-based proteomics is a powerful approach for system-wide characterisation of PTMs, helping to identify drug targets, elucidate drug mechanisms of action and personalise treatment[133].

In addition, the post-translational modification of proteins can provide new targets and screening methods for drug discovery and development. Irreversible post-translational modification of proteins that promote the migration and proliferation of tumour cells, such as the upcoming PROTAC technology mentioned above, so that they lose their biological function and can be used to treat disease. In addition, by comprehensively analysing different post-translational modification patterns, a new PTMI model was established that can accurately predict the clinical prognosis and treatment response of CRC patients[134]. New models can also be developed for prostate cancer, such as GlycoPAT, but only for glycosylation changes in prostate cancer[135]. Therefore, it may be possible in the future to develop a simulation platform for the computational assessment of methylation, succinylation and lactation in prostate cancer. A detailed study of post-translational protein modifications not only helps us to understand the mechanisms of prostate carcinogenesis, but also opens up new opportunities in the biopharmaceutical field. Therefore, it is hoped that by studying the aberrant changes in post-translational modifications of proteins, new markers associated with prostate cancer can be discovered and new diagnostic methods and treatment strategies can be developed.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contributions

YHH wrote the manuscript. JHH, WFL, CQG, JS, FMX, YZ, XYS, ZPH and YGL revised the manuscript. JHH provided the funding. All authors contributed to the article and approved the final manuscript.

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References

[1] VU L D, GEVAERT K, DE SMET I. Protein Language: Post-Translational Modifications Talking to Each Other [J]. Trends in plant science, 2018, 23(12): 1068-80.

[2] ANTFOLK D, ANTILA C, KEMPPAINEN K, et al. Decoding the PTM-switchboard of Notch [J]. Biochimica et biophysica acta Molecular cell research, 2019, 1866(12): 118507.

[3] LIU N, LING R, TANG X, et al. Post-Translational Modifications of BRD4: Therapeutic Targets for Tumor [J]. Front Oncol, 2022, 12: 847701.

[4] SINGH V, RAM M, KUMAR R, et al. Phosphorylation: Implications in Cancer [J]. The protein journal, 2017, 36(1): 1-6.

[5] LIU X, ZHANG Y, WANG Y, et al. Protein Phosphorylation in Cancer: Role of Nitric Oxide Signaling Pathway [J]. Biomolecules, 2021, 11(7).

[6] D'ABRONZO L S, GHOSH P M. eIF4E Phosphorylation in Prostate Cancer [J]. Neoplasia (New York, NY), 2018, 20(6): 563-73.

[7] SHAO J, ZHU W, DING Y, et al. Phosphorylation of LIFR promotes prostate cancer progression by activating the AKT pathway [J]. Cancer letters, 2019, 451: 110-21.

[8] ZHU Z, HONG Y, ZHANG F, et al. Knockdown of COPS3 inhibits the progress of prostate cancer through reducing phosphorylated p38 MAPK expression and impairs the epithelial-mesenchymal transition process [J]. The Prostate, 2019, 79(16): 1823-31.

[9] YANSHEN Z, LIFEN Y, XILIAN W, et al. miR-92a promotes proliferation and inhibits apoptosis of prostate cancer cells through the PTEN/Akt signaling pathway [J]. The Libyan journal of medicine, 2021, 16(1): 1971837.

[10] HETTEL D, SHARIFI N. HSD3B1 status as a biomarker of androgen deprivation resistance and implications for prostate cancer [J]. Nature reviews Urology, 2018, 15(3): 191-6.

[11] KHALIL M I, SINGH V, KING J, et al. TLK1-mediated MK5-S354 phosphorylation drives prostate cancer cell motility and may signify distinct pathologies [J]. Molecular oncology, 2022, 16(13): 2537-57.

[12] GAO S, YE H, GERRIN S, et al. ErbB2 Signaling Increases Androgen Receptor Expression in Abiraterone-Resistant Prostate Cancer [J]. Clinical cancer research : an official journal of the American Association for Cancer Research, 2016, 22(14): 3672-82.

[13] WU L, YI B, WEI S, et al. Loss of FOXP3 and TSC1 Accelerates Prostate Cancer Progression through Synergistic Transcriptional and Posttranslational Regulation of c-MYC [J]. Cancer research, 2019, 79(7): 1413-25.

[14] MCALLISTER M J, MCCALL P, DICKSON A, et al. Androgen receptor phosphorylation at serine 81 and serine 213 in castrate-resistant prostate cancer [J]. Prostate cancer and prostatic diseases, 2020, 23(4): 596-606.

[15] KUO Y Y, HUO C, LIN C Y, et al. Caffeic acid phenethyl ester suppresses androgen receptor signaling and stability via inhibition of phosphorylation on Ser81 and Ser213 [J]. Cell communication and signaling : CCS, 2019, 17(1): 100.

[16] CASILLAS A L, TOTH R K, SAINZ A G, et al. Hypoxia-Inducible PIM Kinase Expression Promotes Resistance to Antiangiogenic Agents [J]. Clinical cancer research : an official journal of the American Association for Cancer Research, 2018, 24(1): 169-80.

[17] JENSEN C C, CLEMENTS A N, LIOU H, et al. PIM1 phosphorylates ABI2 to enhance actin dynamics and promote tumor invasion [J]. The Journal of cell biology, 2023, 222(6).

[18] QIU Y. A phosphorylation switch controls androgen biosynthesis in prostate cancer [J]. J Clin Invest, 2023, 133(2).

[19] CHUANG T D, CHEN S J, LIN F F, et al. Human prostatic acid phosphatase, an authentic tyrosine phosphatase, dephosphorylates ErbB-2 and regulates prostate cancer cell growth [J]. The Journal of biological chemistry, 2010, 285(31): 23598-606.

[20] MILLER D R, INGERSOLL M A, LIN M F. ErbB-2 signaling in advanced prostate cancer progression and potential therapy [J]. Endocrine-related cancer, 2019, 26(4): R195-r209.

[21] MARTINO T, KUDROLLI T A, KUMAR B, et al. The orally active pterocarpanquinone LQB-118 exhibits cytotoxicity in prostate cancer cell and tumor models through cellular redox stress [J]. The Prostate, 2018, 78(2): 140-51.

[22] MARTINO T, GF D E B, SANTOS S V M, et al. LQB-118 Suppresses Migration and Invasion of Prostate Cancer Cells by Modulating the Akt/GSK3β Pathway and MMP-9/Reck Gene Expression [J]. Anticancer research, 2023, 43(1): 359-67.

[23] LV J M, CHEN L, GAO Y, et al. PPP5C promotes cell proliferation and survival in human prostate cancer by regulating of the JNK and ERK1/2 phosphorylation [J]. Onco Targets Ther, 2018, 11: 5797-809.

[24] SAMARŽIJA I. Post-Translational Modifications That Drive Prostate Cancer Progression [J]. Biomolecules, 2021, 11(2).

[25] BUTLER W, HUANG J. Glycosylation Changes in Prostate Cancer Progression [J]. Front Oncol, 2021, 11: 809170.

[26] KAŁUŻA A, SZCZYKUTOWICZ J, FERENS-SIECZKOWSKA M. Glycosylation: Rising Potential for Prostate Cancer Evaluation [J]. Cancers, 2021, 13(15).

[27] GARNHAM R, SCOTT E, LIVERMORE K E, et al. ST6GAL1: A key player in cancer [J]. Oncol Lett, 2019, 18(2): 983-9.

[28] GRATACóS-MULLERAS A, DURAN A, ASADI SHEHNI A, et al. Characterisation of the main PSA glycoforms in aggressive prostate cancer [J]. Sci Rep, 2020, 10(1): 18974.

[29] WANG R, WEN P, YANG G, et al. N-glycosylation of GDF15 abolishes its inhibitory effect on EGFR in AR inhibitor-resistant prostate cancer cells [J]. Cell death & disease, 2022, 13(7): 626.

[30] MAO C, LI J, FENG L, et al. Beyond antibody fucosylation: α-(1,6)-fucosyltransferase (Fut8) as a potential new therapeutic target for cancer immunotherapy [J]. Antibody therapeutics, 2023, 6(2): 87-96.

[31] LIAO C, AN J, YI S, et al. FUT8 and Protein Core Fucosylation in Tumours: From Diagnosis to Treatment [J]. J Cancer, 2021, 12(13): 4109-20.

[32] HöTI N, LIH T S, PAN J, et al. A Comprehensive Analysis of FUT8 Overexpressing Prostate Cancer Cells Reveals the Role of EGFR in Castration Resistance [J]. Cancers, 2020, 12(2).

[33] VERMASSEN T, VAN PRAET C, LUMEN N, et al. Urinary prostate protein glycosylation profiling as a diagnostic biomarker for prostate cancer [J]. The Prostate, 2015, 75(3): 314-22.

[34] VERMASSEN T, VAN PRAET C, POELAERT F, et al. Diagnostic accuracy of urinary prostate protein glycosylation profiling in prostatitis diagnosis [J]. Biochemia medica, 2015, 25(3): 439-49.

[35] BAI R, LUAN X, ZHANG Y, et al. The expression and functional analysis of the sialyl-T antigen in prostate cancer [J]. Glycoconjugate journal, 2020, 37(4): 423-33.

[36] SCOTT E, HODGSON K, CALLE B, et al. Upregulation of GALNT7 in prostate cancer modifies O-glycosylation and promotes tumour growth [J]. Oncogene, 2023, 42(12): 926-37.

[37] WANG S S, SOLAR V D, YU X, et al. Efficient inhibition of O-glycan biosynthesis using the hexosamine analog Ac(5)GalNTGc [J]. Cell chemical biology, 2021, 28(5): 699-710.e5.

[38] ZHANG Y, LI J, HUANG Y, et al. Improved antitumor activity against prostate cancer via synergistic targeting of Myc and GFAT-1 [J]. Theranostics, 2023, 13(2): 578-95.

[39] COCKRAM P E, KIST M, PRAKASH S, et al. Ubiquitination in the regulation of inflammatory cell death and cancer [J]. Cell death and differentiation, 2021, 28(2): 591-605.

[40] GANG X, XUAN L, ZHAO X, et al. Speckle-type POZ protein suppresses lipid accumulation and prostate cancer growth by stabilizing fatty acid synthase [J]. The Prostate, 2019, 79(8): 864-71.

[41] SHI Q, ZHU Y, MA J, et al. Prostate Cancer-associated SPOP mutations enhance cancer cell survival and docetaxel resistance by upregulating Caprin1-dependent stress granule assembly [J]. Molecular cancer, 2019, 18(1): 170.

[42] JIANG Q, ZHENG N, BU L, et al. SPOP-mediated ubiquitination and degradation of PDK1 suppresses AKT kinase activity and oncogenic functions [J]. Molecular cancer, 2021, 20(1): 100.

[43] WU H L, LI S M, HUANG Y C, et al. Transcriptional regulation and ubiquitination-dependent regulation of HnRNPK oncogenic function in prostate tumorigenesis [J]. Cancer cell international, 2021, 21(1): 641.

[44] JU L G, ZHU Y, LONG Q Y, et al. SPOP suppresses prostate cancer through regulation of CYCLIN E1 stability [J]. Cell death and differentiation, 2019, 26(6): 1156-68.

[45] MA J, CHANG K, PENG J, et al. SPOP promotes ATF2 ubiquitination and degradation to suppress prostate cancer progression [J]. Journal of experimental & clinical cancer research : CR, 2018, 37(1): 145.

[46] SHI L, YAN Y, HE Y, et al. Mutated SPOP E3 Ligase Promotes 17βHSD4 Protein Degradation to Drive Androgenesis and Prostate Cancer Progression [J]. Cancer research, 2021, 81(13): 3593-606.

[47] PENG S, CHEN X, HUANG C, et al. UBE2S as a novel ubiquitinated regulator of p16 and β-catenin to promote bone metastasis of prostate cancer [J]. International journal of biological sciences, 2022, 18(8): 3528-43.

[48] NOGUEIRA V, PATRA K C, HAY N. Selective eradication of cancer displaying hyperactive Akt by exploiting the metabolic consequences of Akt activation [J]. eLife, 2018, 7.

[49] SHANGGUAN X, HE J, MA Z, et al. SUMOylation controls the binding of hexokinase 2 to mitochondria and protects against prostate cancer tumorigenesis [J]. Nature communications, 2021, 12(1): 1812.

[50] HAO L, DONG Y, ZHANG J J, et al. Melatonin decreases androgen-sensitive prostate cancer growth by suppressing SENP1 expression [J]. Translational andrology and urology, 2022, 11(1): 91-103.

[51] ZHOU T, CHEN T, LAI B, et al. FBXW2 inhibits prostate cancer proliferation and metastasis via promoting EGFR ubiquitylation and degradation [J]. Cellular and molecular life sciences : CMLS, 2022, 79(5): 268.

[52] GE J, YU W, LI J, et al. USP16 regulates castration-resistant prostate cancer cell proliferation by deubiquitinating and stablizing c-Myc [J]. Journal of experimental & clinical cancer research : CR, 2021, 40(1): 59.

[53] DING T, ZHU Y, JIN H, et al. Circular RNA circ_0057558 Controls Prostate Cancer Cell Proliferation Through Regulating miR-206/USP33/c-Myc Axis [J]. Frontiers in cell and developmental biology, 2021, 9: 644397.

[54] FU X, ZHAO J, YU G, et al. OTUD6A promotes prostate tumorigenesis via deubiquitinating Brg1 and AR [J]. Communications biology, 2022, 5(1): 182.

[55] DENG R, GUO Y, LI L, et al. BAP1 suppresses prostate cancer progression by deubiquitinating and stabilizing PTEN [J]. Molecular oncology, 2021, 15(1): 279-98.

[56] LIU Y, YU C, SHAO Z, et al. Selective degradation of AR-V7 to overcome castration resistance of prostate cancer [J]. Cell death & disease, 2021, 12(10): 857.

[57] XIAO J, SUN F, WANG Y N, et al. UBC9 deficiency enhances immunostimulatory macrophage activation and subsequent antitumor T cell response in prostate cancer [J]. J Clin Invest, 2023, 133(4).

[58] GAO L, ZHANG W, ZHANG J, et al. KIF15-Mediated Stabilization of AR and AR-V7 Contributes to Enzalutamide Resistance in Prostate Cancer [J]. Cancer research, 2021, 81(4): 1026-39.

[59] ZHANG B, ZHANG M, SHEN C, et al. LncRNA PCBP1-AS1-mediated AR/AR-V7 deubiquitination enhances prostate cancer enzalutamide resistance [J]. Cell death & disease, 2021, 12(10): 856.

[60] LIAO Y, SUN W, SHAO Z, et al. A SIX1 degradation inducer blocks excessive proliferation of prostate cancer [J]. International journal of biological sciences, 2022, 18(6): 2439-51.

[61] GUO Y, CUI S, CHEN Y, et al. Ubiquitin specific peptidases and prostate cancer [J]. PeerJ, 2023, 11: e14799.

[62] QI S M, DONG J, XU Z Y, et al. PROTAC: An Effective Targeted Protein Degradation Strategy for Cancer Therapy [J]. Frontiers in pharmacology, 2021, 12: 692574.

[63] YEDLA P, BABALGHITH A O, ANDRA V V, et al. PROTACs in the Management of Prostate Cancer [J]. Molecules (Basel, Switzerland), 2023, 28(9).

[64] KARGBO R B. Potent PROTACs Targeting EGFR Mutants in Drug Discovery [J]. ACS medicinal chemistry letters, 2022, 13(12): 1835-6.

[65] SCHNEPP P M, SHELLEY G, DAI J, et al. Single-Cell Transcriptomics Analysis Identifies Nuclear Protein 1 as a Regulator of Docetaxel Resistance in Prostate Cancer Cells [J]. Molecular cancer research : MCR, 2020, 18(9): 1290-301.

[66] ZHANG Y, LIU F, FENG Y, et al. CircRNA circ_0006156 inhibits the metastasis of prostate cancer by blocking the ubiquitination of S100A9 [J]. Cancer gene therapy, 2022, 29(11): 1731-41.

[67] FAN Y, HOU T, GAO Y, et al. Acetylation-dependent regulation of TPD52 isoform 1 modulates chaperone-mediated autophagy in prostate cancer [J]. Autophagy, 2021, 17(12): 4386-400.

[68] LU D, SONG Y, YU Y, et al. KAT2A-mediated AR translocation into nucleus promotes abiraterone-resistance in castration-resistant prostate cancer [J]. Cell death & disease, 2021, 12(8): 787.

[69] WADDELL A R, HUANG H, LIAO D. CBP/p300: Critical Co-Activators for Nuclear Steroid Hormone Receptors and Emerging Therapeutic Targets in Prostate and Breast Cancers [J]. Cancers, 2021, 13(12).

[70] NGUYEN D T, YANG W, RENGANATHAN A, et al. Acetylated HOXB13 Regulated Super Enhancer Genes Define Therapeutic Vulnerabilities of Castration-Resistant Prostate Cancer [J]. Clinical cancer research : an official journal of the American Association for Cancer Research, 2022, 28(18): 4131-45.

[71] XU S, FAN L, JEON H Y, et al. p300-Mediated Acetylation of Histone Demethylase JMJD1A Prevents Its Degradation by Ubiquitin Ligase STUB1 and Enhances Its Activity in Prostate Cancer [J]. Cancer research, 2020, 80(15): 3074-87.

[72] REZAEIAN A H, PHAN L M, ZHOU X, et al. Pharmacological inhibition of the SKP2/p300 signaling axis restricts castration-resistant prostate cancer [J]. Neoplasia (New York, NY), 2023, 38: 100890.

[73] ZHOU R, YANG Y, PARK S Y, et al. p300/CBP-associated factor promotes autophagic degradation of δ-catenin through acetylation and decreases prostate cancer tumorigenicity [J]. Sci Rep, 2019, 9(1): 3351.

[74] JOSHI M, STOYKOVA G E, SALZMANN-SULLIVAN M, et al. CPT1A Supports Castration-Resistant Prostate Cancer in Androgen-Deprived Conditions [J]. Cells, 2019, 8(10).

[75] PUZYRENKO A, KUMAR S N, PANTAZIS C G, et al. Inverse co-expression of EZH2 and acetylated H3K27 in prostatic tissue [J]. Annals of diagnostic pathology, 2022, 59: 151956.

[76] KIM S M, HA E, KIM J, et al. NAA10 as a New Prognostic Marker for Cancer Progression [J]. Int J Mol Sci, 2020, 21(21).

[77] GUAN J, JIANG X, GUO Y, et al. Autophagy inhibition and reactive oxygen species elimination by acetyl-CoA acetyltransferase 1 through fused in sarcoma protein to promote prostate cancer [J]. BMC Cancer, 2022, 22(1): 1313.

[78] CHOI S Y, JEON J M, NA A Y, et al. SIRT5 Directly Inhibits the PI3K/AKT Pathway in Prostate Cancer Cell Lines [J]. Cancer genomics & proteomics, 2022, 19(1): 50-9.

[79] GUAN J, JIANG X, GAI J, et al. Sirtuin 5 regulates the proliferation, invasion and migration of prostate cancer cells through acetyl-CoA acetyltransferase 1 [J]. Journal of cellular and molecular medicine, 2020, 24(23): 14039-49.

[80] PIENTA K J. Preclinical mechanisms of action of docetaxel and docetaxel combinations in prostate cancer [J]. Seminars in oncology, 2001, 28(4 Suppl 15): 3-7.

[81] ARAGON-CHING J B, MADAN R A. The path forward in prostate cancer therapeutics [J]. Asian journal of andrology, 2018, 20(3): 213-4.

[82] ZHANG B, LI Y, WU Q, et al. Acetylation of KLF5 maintains EMT and tumorigenicity to cause chemoresistant bone metastasis in prostate cancer [J]. Nature communications, 2021, 12(1): 1714.

[83] ZHANG B, CI X, TAO R, et al. Klf5 acetylation regulates luminal differentiation of basal progenitors in prostate development and regeneration [J]. Nature communications, 2020, 11(1): 997.

[84] HUANG Q, LIU M, ZHANG D, et al. Nitazoxanide inhibits acetylated KLF5-induced bone metastasis by modulating KLF5 function in prostate cancer [J]. BMC medicine, 2023, 21(1): 68.

[85] HUANG H, LIU R, HUANG Y, et al. Acetylation-mediated degradation of HSD17B4 regulates the progression of prostate cancer [J]. Aging, 2020, 12(14): 14699-717.

[86] SAWANT DESSAI A, DOMINGUEZ M P, CHEN U I, et al. Transcriptional Repression of SIRT3 Potentiates Mitochondrial Aconitase Activation to Drive Aggressive Prostate Cancer to the Bone [J]. Cancer research, 2021, 81(1): 50-63.

[87] ZHAO J, LI J, FAN T W M, et al. Glycolytic reprogramming through PCK2 regulates tumor initiation of prostate cancer cells [J]. Oncotarget, 2017, 8(48): 83602-18.

[88] LI Z, LI B, YU H, et al. DNMT1-mediated epigenetic silencing of TRAF6 promotes prostate cancer tumorigenesis and metastasis by enhancing EZH2 stability [J]. Oncogene, 2022, 41(33): 3991-4002.

[89] ZHU A, HOPKINS K M, FRIEDMAN R A, et al. DNMT1 and DNMT3B regulate tumorigenicity of human prostate cancer cells by controlling RAD9 expression through targeted methylation [J]. Carcinogenesis, 2021, 42(2): 220-31.

[90] YUAN H, HAN Y, WANG X, et al. SETD2 Restricts Prostate Cancer Metastasis by Integrating EZH2 and AMPK Signaling Pathways [J]. Cancer cell, 2020, 38(3): 350-65.e7.

[91] SUGIURA M, SATO H, KANESAKA M, et al. Epigenetic modifications in prostate cancer [J]. International journal of urology : official journal of the Japanese Urological Association, 2021, 28(2): 140-9.

[92] ZOMA M, CURTI L, SHINDE D, et al. EZH2-induced lysine K362 methylation enhances TMPRSS2-ERG oncogenic activity in prostate cancer [J]. Nature communications, 2021, 12(1): 4147.

[93] BARATCHIAN M, TIWARI R, KHALIGHI S, et al. H3K9 methylation drives resistance to androgen receptor-antagonist therapy in prostate cancer [J]. Proceedings of the

National Academy of Sciences of the United States of America, 2022, 119(21): e2114324119.

[94] DAI X, ZHOU Y, HAN F, et al. Succinylation and redox status in cancer cells [J]. Front Oncol, 2022, 12: 1081712.

[95] LU K, HAN D. A review of the mechanism of succinylation in cancer [J]. Medicine (Baltimore), 2022, 101(45): e31493.

[96] YANG Y, GIBSON G E. Succinylation Links Metabolism to Protein Functions [J]. Neurochemical research, 2019, 44(10): 2346-59.

[97] ZHANG Z, CHEN Y, FANG L, et al. The involvement of high succinylation modification in the development of prostate cancer [J]. Front Oncol, 2022, 12: 1034605.

[98] WONG S H M, FANG C M, CHUAH L H, et al. E-cadherin: Its dysregulation in carcinogenesis and clinical implications [J]. Critical reviews in oncology/hematology, 2018, 121: 11-22.

[99] ZHOU J, YAN X, LIU Y, et al. Succinylation of CTBP1 mediated by KAT2A suppresses its inhibitory activity on the transcription of CDH1 to promote the progression of prostate cancer [J]. Biochemical and biophysical research communications, 2023, 650: 9-16.

[100] KWON O K, BANG I H, CHOI S Y, et al. SIRT5 Is the Desuccinylase of LDHA as Novel Cancer Metastatic Stimulator in Aggressive Prostate Cancer [J]. Genomics, proteomics & bioinformatics, 2022.

[101] JIANG Y, HE C, YE H, et al. Comprehensive analysis of the lysine succinylome in fish oil-treated prostate cancer cells [J]. Life science alliance, 2023, 6(11).

[102] FRITZ V, BENFODDA Z, HENRIQUET C, et al. Metabolic intervention on lipid synthesis converging pathways abrogates prostate cancer growth [J]. Oncogene, 2013, 32(42): 5101-10.

[103] SCHMIDT L J, BALLMAN K V, TINDALL D J. Inhibition of fatty acid synthase activity in prostate cancer cells by dutasteride [J]. The Prostate, 2007, 67(10): 1111-20.

[104] KARANTANOS T, KARANIKA S, WANG J, et al. Caveolin-1 regulates hormone resistance through lipid synthesis, creating novel therapeutic opportunities for castration-resistant prostate cancer [J]. Oncotarget, 2016, 7(29): 46321-34.

[105] ZADRA G, RIBEIRO C F, CHETTA P, et al. Inhibition of de novo lipogenesis targets androgen receptor signaling in castration-resistant prostate cancer [J]. Proceedings of the National Academy of Sciences of the United States of America, 2019, 116(2): 631-40.

[106] HERRERO-AGUAYO V, SáEZ-MARTíNEZ P, JIMéNEZ-VACAS J M, et al. Dysregulation of the miRNome unveils a crosstalk between obesity and prostate cancer: miR-107 asa personalized diagnostic and therapeutic tool [J]. Molecular therapy Nucleic acids, 2022, 27: 1164-78.

[107] FLAVIN R, ZADRA G, LODA M. Metabolic alterations and targeted therapies in prostate cancer [J]. The Journal of pathology, 2011, 223(2): 283-94.

[108] XIANG X, SAHA A K, WEN R, et al. AMP-activated protein kinase activators can inhibit the growth of prostate cancer cells by multiple mechanisms [J]. Biochemical and biophysical research communications, 2004, 321(1): 161-7.

[109] IPPOLITO L, COMITO G, PARRI M, et al. Lactate Rewires Lipid Metabolism and Sustains a Metabolic-Epigenetic Axis in Prostate Cancer [J]. Cancer research, 2022, 82(7): 1267-82.

[110] ZHANG D, TANG Z, HUANG H, et al. Metabolic regulation of gene expression by histone lactylation [J]. Nature, 2019, 574(7779): 575-80.

[111] LUO Y, YANG Z, YU Y, et al. HIF1α lactylation enhances KIAA1199 transcription to promote angiogenesis and vasculogenic mimicry in prostate cancer [J]. International journal of biological macromolecules, 2022, 222(Pt B): 2225-43.

[112] HE Y, JI Z, GONG Y, et al. Numb/Parkin-directed mitochondrial fitness governs cancer cell fate via metabolic regulation of histone lactylation [J]. Cell reports, 2023, 42(2): 112033.

[113] CHAUDAGAR K, HIEROMNIMON H M, KHURANA R, et al. Reversal of Lactate and PD-1-mediated Macrophage Immunosuppression Controls Growth of PTEN/p53-deficient Prostate Cancer [J]. Clinical cancer research : an official journal of the American Association for Cancer Research, 2023, 29(10): 1952-68.

[114] ZENG J, LIU W, FAN Y Z, et al. PrLZ increases prostate cancer docetaxel resistance by inhibiting LKB1/AMPK-mediated autophagy [J]. Theranostics, 2018, 8(1): 109-23.

[115] FAN Y, HOU T, DAN W, et al. ERK1/2 inhibits Cullin 3/SPOP-mediated PrLZ ubiquitination and degradation to modulate prostate cancer progression [J]. Cell death and differentiation, 2022, 29(8): 1611-24.

[116] XIA C, TAO Y, LI M, et al. Protein acetylation and deacetylation: An important regulatory modification in gene transcription (Review) [J]. Experimental and therapeutic medicine, 2020, 20(4): 2923-40.

[117] HWANG C S, SHEMORRY A, VARSHAVSKY A. N-terminal acetylation of cellular proteins creates specific degradation signals [J]. Science (New York, NY), 2010, 327(5968): 973-7.

[118] DING Y, CHI H, SHAO J, et al. Leukemia inhibitory factor receptor homodimerization mediated by acetylation of extracellular lysine promotes prostate cancer progression through the PDPK1/AKT/GCN5 axis [J]. Clinical and translational medicine, 2022, 12(2): e676.

[119] ZHOU Y, JIN X, MA J, et al. HDAC5 Loss Impairs RB Repression of Pro-Oncogenic Genes and Confers CDK4/6 Inhibitor Resistance in Cancer [J]. Cancer research, 2021, 81(6): 1486-99.

[120] SHIN S H, LEE G Y, LEE M, et al. Aberrant expression of CITED2 promotes prostate cancer metastasis by activating the nucleolin-AKT pathway [J]. Nature communications, 2018, 9(1): 4113.

[121] WU J, CANG S, LIU C, et al. Development of human prostate cancer stem cells involves epigenomic alteration and PI3K/AKT pathway activation [J]. Experimental hematology & oncology, 2020, 9: 12.

[122] PARK S H, FONG K W, KIM J, et al. Posttranslational regulation of FOXA1 by Polycomb and BUB3/USP7 deubiquitin complex in prostate cancer [J]. Science advances, 2021, 7(15).

[123] LI T, LI Y, LIU T, et al. Mitochondrial PAK6 inhibits prostate cancer cell apoptosis via the PAK6-SIRT4-ANT2 complex [J]. Theranostics, 2020, 10(6): 2571-86.

[124] SUN Y, GUO W, GUO Y, et al. Apoptosis induction in human prostate cancer cells related to the fatty acid metabolism by wogonin-mediated regulation of the AKT-SREBP1-FASN signaling network [J]. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association, 2022, 169: 113450.

[125] HSIEH P F, JIANG W P, BASAVARAJ P, et al. Cell suspension culture extract of Eriobotrya japonica attenuates growth and induces apoptosis in prostate cancer cells via targeting SREBP-1/FASN-driven metabolism and AR [J]. Phytomedicine : international journal of phytotherapy and phytopharmacology, 2021, 93: 153806.

[126] GALBRAITH L, LEUNG H Y, AHMAD I. Lipid pathway deregulation in advanced prostate cancer [J]. Pharmacological research, 2018, 131: 177-84.

[127] CHUANG H Y, LEE Y P, LIN W C, et al. Fatty Acid Inhibition Sensitizes Androgen-Dependent and -Independent Prostate Cancer to Radiotherapy via FASN/NF-κB Pathway [J]. Sci Rep, 2019, 9(1): 13284.

[128] YU Y, HUANG X, LIANG C, et al. Evodiamine impairs HIF1A histone lactylation to inhibit Sema3A-mediated angiogenesis and PD-L1 by inducing ferroptosis in prostate cancer [J]. European journal of pharmacology, 2023, 957: 176007.

[129] KHOO A, LIU L Y, NYALWIDHE J O, et al. Proteomic discovery of non-invasive biomarkers of localized prostate cancer using mass spectrometry [J]. Nature reviews Urology, 2021, 18(12): 707-24.

[130] PENG D, LI H, HU B, et al. PTMsnp: A Web Server for the Identification of Driver Mutations That Affect Protein Post-translational Modification [J]. Frontiers in cell and developmental biology, 2020, 8: 593661.

[131] TAKAHASHI S, SUGIYAMA T, SHIMOMURA M, et al. Site-specific and linkage analyses of fucosylated N-glycans on haptoglobin in sera of patients with various types of cancer: possible implication for the differential diagnosis of cancer [J]. Glycoconjugate journal, 2016, 33(3): 471-82.

[132] YANG X, LIU F, YAN Y, et al. Proteomic analysis of N-glycosylation of human seminal plasma [J]. Proteomics, 2015, 15(7): 1255-8.

[133] ZHAI L H, CHEN K F, HAO B B, et al. Proteomic characterization of post-translational modifications in drug discovery [J]. Acta pharmacologica Sinica, 2022, 43(12): 3112-29.

[134] LIU J, ZHU P. A Novel Gene Signature Associated with Protein Post-translational Modification to Predict Clinical Outcomes and Therapeutic Responses of Colorectal Cancer [J]. Molecular biotechnology, 2023.

[135] LIU G, CHENG K, LO C Y, et al. A Comprehensive, Open-source Platform for Mass Spectrometry-based Glycoproteomics Data Analysis [J]. Molecular & cellular proteomics : MCP, 2017, 16(11): 2032-47.

Figure 1

Schematic diagram of PI3K/Akt/mTOR signaling pathway

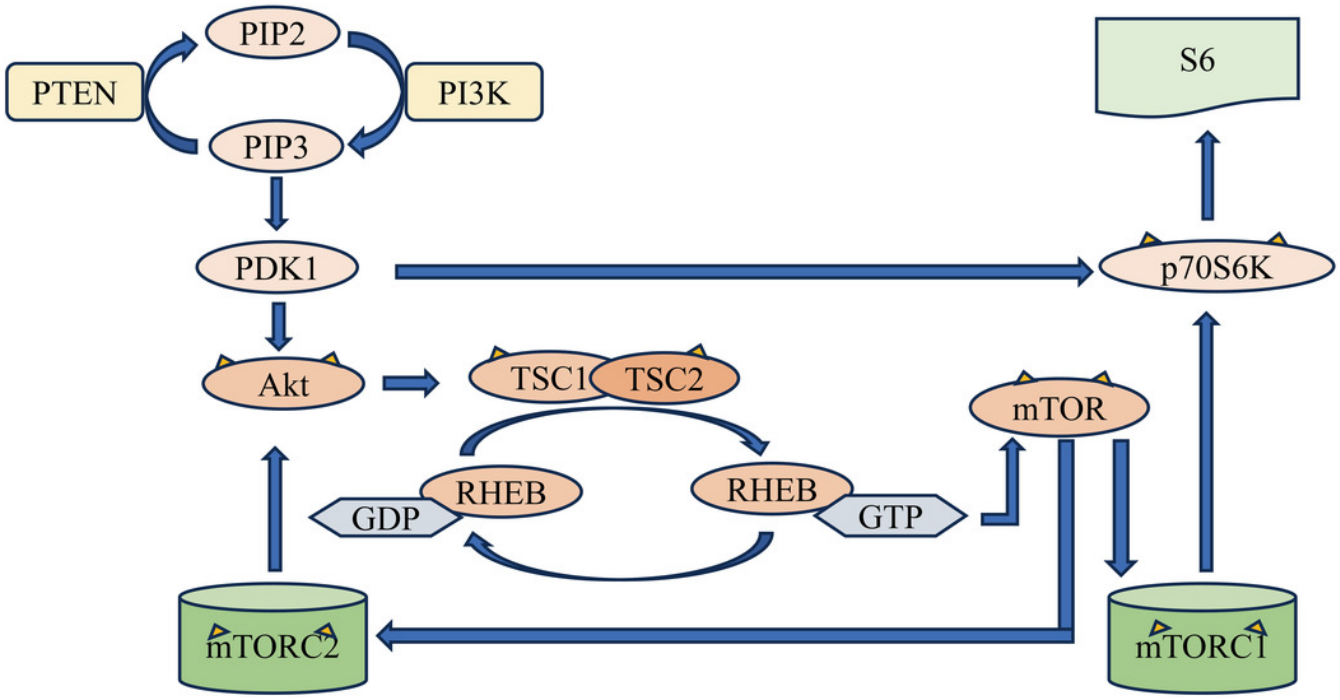

Figure 2

Some types and structures of glycosylation.

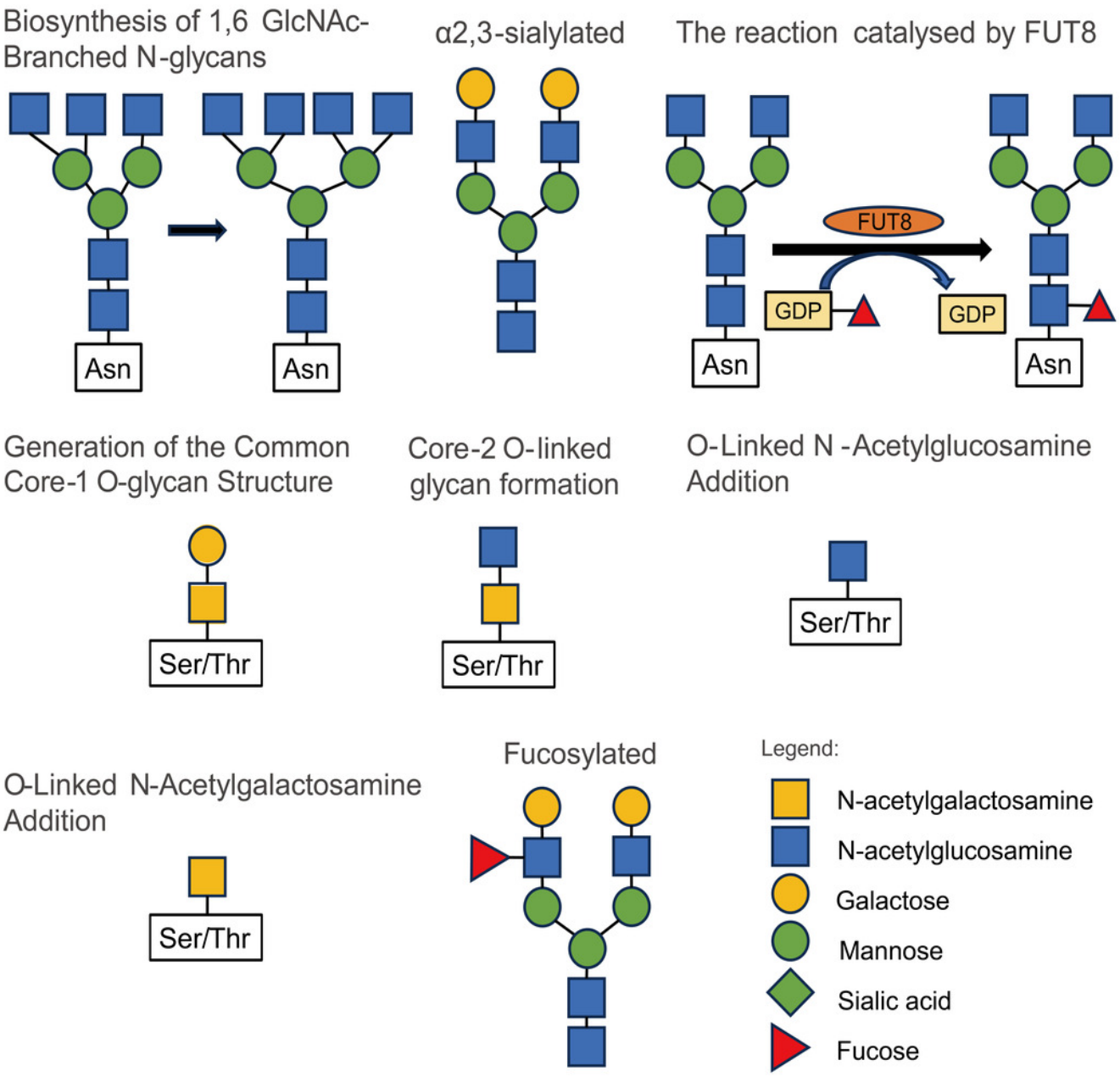

Figure 3

Main metabolic pathways of FASN and AMPK in PCa cells.

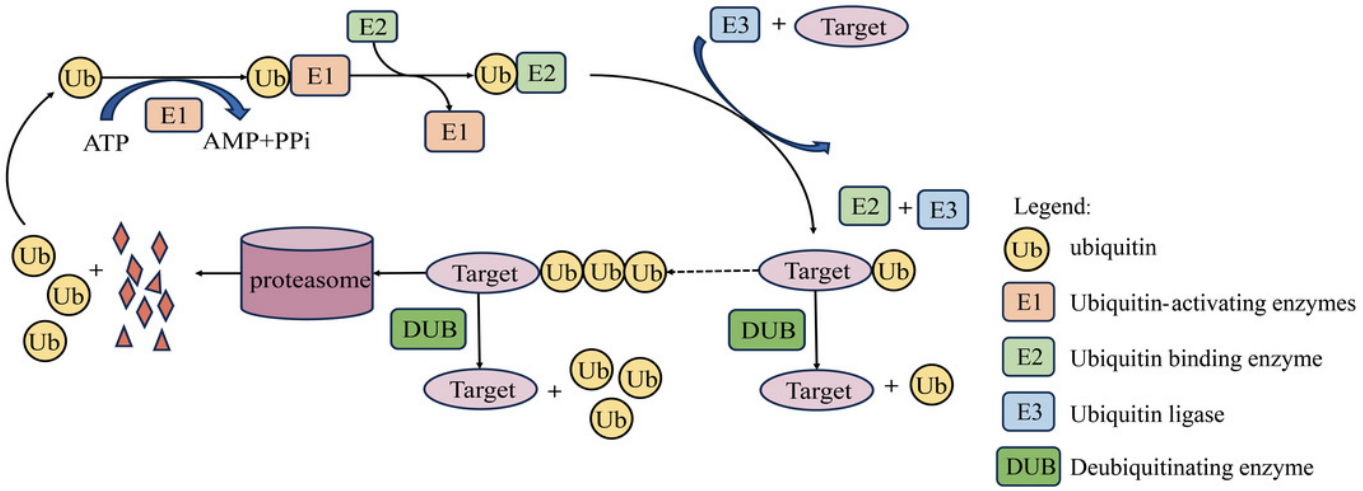

Figure 4

Biological processes of protein ubiquitination and deubiquitination.