Gut microbiota and its metabolites: Key factors of drug resistance in the treatment of advanced prostate cancer (Review)

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Abstract. Prostate cancer (PCa) is a leading cause of cancer-related deaths among men, and its incidence is increasing worldwide. Current treatments include androgen deprivation therapy, surgery, radiotherapy, chemotherapy and immunotherapy, among others. Surgical treatment has a less effective therapeutic effect in patients with advanced PCa. However, drug-based treatments often lead to the development of drug resistance, highlighting the need to adopt new treatment strategies. The present review summarizes the role of gut microbiota and its metabolites in the treatment resistance of advanced PCa, potential microbiome-targeted therapies and future research directions, for developing novel therapeutic approaches to overcome drug resistance and improve prognosis.

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1. Introduction

Prostate cancer (PCa) is a significant global health concern, with an estimated 1.4 million new cases and >375,000 associated mortalities annually in 2020 (1). In the United States, PCa is the most commonly diagnosed cancer among men, with ~290,000 new cases and 35,000 mortalities reported

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Abbreviations: ABCB1, ATP-binding cassette subfamily B member 1 (P-glycoprotein); ADT, androgen deprivation therapy; AhR, aryl hydrocarbon receptor; AKT, protein kinase B; AR, androgen receptor; ARV7, androgen receptor splicing variant 7; ATM, ataxia telangiectasia-mutated gene; ATR, ataxia telangiectasia and Rad3-related protein; BCL2, B-cell lymphoma 2; BRCA2, breast cancer susceptibility gene 2; CAFs, cancer-associated fibroblasts; CB2, cannabinoid receptor 2; CCL20, C-C motif chemokine ligand 20; CRPC, castration-resistant prostate cancer; mCRPC, metastatic CRPC; DIM, 3,3'-diindolylmethane; EMT, epithelial-mesenchymal transition; FMT, fecal microbiota transplantation; FOS, fructooligosaccharides; FXR, farnesoid X receptor; GOS, galactooligosaccharides; HDAC, histone deacetylase; HDC, histidine decarboxylase; HIF-1α, hypoxia-inducible factor-1α; HMOX1, heme oxygenase-1; I3C, indole-3-carbinol; JAK2, Janus kinase 2; LPC, lysophosphatidylcholine; LPCAT1, lysophosphatidylcholine acyltransferase 1; MALDI-TOF/MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MAPK, mitogen-activated protein kinase; MDSCs, myeloid-derived suppressor cells; MIF, macrophage migration inhibitory factor; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NK, natural killer; NOTCH1, neurogenic locus notch homolog protein 1; PAG, phenylacetylglutamine; PC, phosphatidylcholine; PCa, prostate cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; SCFAs, short-chain fatty acids; STAT3, signal transducer and activator of transcription 3; TGR5, Takeda G protein-coupled receptor 5; TMAO, trimethylamine N-oxide; Tregs, regulatory T cells

Key words: gut microbiota, PCa, ADT, chemotherapy, immunotherapy, treatment resistance

annually (2). The incidence of PCa has also been increasing in Asia, reflecting the growing global burden of this disease (1). This increasing trend underscores the importance of understanding the mechanisms driving PCa progression and treatment resistance to improve patient outcomes.

The treatment landscape for PCa has evolved significantly, with androgen deprivation therapy (ADT) remaining the cornerstone of treatment for advanced disease (3,4). While ADT initially elicits favorable clinical responses, most patients eventually progress to castration-resistant prostate cancer (CRPC) within 3 years (2). Some patients develop highly aggressive small-cell neuroendocrine carcinoma, which is often characterized by resistance to ADT, a relative lack of clinical treatment strategies and a high mortality rate (5-year survival rate is only ~10%) (5-7).

The gut microbiota, a complex microbial community in the gastrointestinal tract, plays a crucial role in human health and disease. Research has shown that the gut microbiota can influence cancer development, progression and treatment response through multiple mechanisms, including drug metabolism, immune modulation and metabolite production, thereby affecting tumor biology (8-10). For instance, the gut microbiota can directly metabolize anticancer drugs, thereby altering their efficacy and contributing to treatment resistance (8,11-14). Specifically, in PCa, the gut microbiota may influence disease progression and treatment resistance through androgen metabolism and the production of procarcinogenic metabolites (8,15,16).

Gut microbiota-derived metabolites constitute a critical but underappreciated axis in the development of treatment resistance in advanced PCa, acting through convergent pathways involving androgen receptor (AR) signaling, immune modulation and metabolic adaptation. The present review summarizes the current status of treatment resistance in PCa and examines the effects of gut microbiota on treatment resistance in PCa through direct and indirect pathways. The aim of the current study is to integrate existing knowledge and explore novel approaches (for example, probiotics, prebiotics, fecal microbiota transplantation) in order to improve the understanding of the impact of gut microbiota on treatment resistance in PCa, paving the way for improved treatment strategies.

2. Gut microbiota and treatment resistance

The gut microbiota, a complex and dynamic community of microorganisms residing in the gastrointestinal tract, has emerged as a critical determinant of the efficacy and resistance to cancer treatments across various malignancies. Accumulating evidence suggests that the composition and function of the gut microbiota can modulate host immune responses, drug metabolism and tumor microenvironments, thereby playing a pivotal role in determining the success of therapeutic interventions. In this context, understanding the intricate interplay between gut microbiota and cancer treatments is essential for developing novel strategies to overcome resistance and improve patient outcomes.

Butyric acid produced by *Clostridium butyricum* can reverse the anti-programmed cell death protein 1 (PD-1) resistance in patients with non-small cell lung cancer caused via the use of proton pump inhibitors by upregulating the expression of perforin and granzyme B in $CD8^+$ T cells (17). Similarly, study on pan-cancer have revealed that the effect of indole-3-carboxaldehyde derived from *Lactobacillus* is bidirectional. By activating the aryl hydrocarbon receptor (AhR), indole-3-carboxaldehyde can maintain the stem cell-like phenotype of T cells and enhance the efficacy of immune checkpoint inhibitors in breast cancer and melanoma. However, indole-3-carboxaldehyde can also upregulate the expression of ATP-binding cassette subfamily B member 1 (P-glycoprotein) (ABCB1) in tumor cells through AhR activation, promoting cross-resistance of breast cancer to taxane drugs (18). In addition, dysbiosis caused by a high-fat diet leads to excessive production of leucine derived from the *Clostridium* genus in the intestine, activating mammalian target of rapamycin (mTOR) signaling in myeloid-derived suppressor cells (MDSCs) (19). This weakens the efficacy of cyclin-dependent kinases 4 and 6 inhibitors in breast cancer and promotes immune escape of estrogen receptor-positive tumors (19). In liver cancer, *Fusobacterium nucleatum* binds to E-cadherin in tumor cells through its surface *Fusobacterium* adhesin A, thereby activating β-catenin signaling pathway to upregulate multidrug resistance protein 1 transcription and promote acquired resistance to sorafenib (20). *Bacteroides fragilis* directly binds to the neurogenic locus notch homolog protein 1 (NOTCH1) receptor on tumor cells via its surface proteins, activating the NOTCH1 signaling pathway and inducing epithelial-mesenchymal transition (EMT) and a stem cell-like phenotype, thereby promoting resistance to 5-fluorouracil and oxaliplatin in colorectal cancer (21). In PCa, the decreased abundance of *Akkermansia muciniphila* is associated with enzalutamide resistance (22). Based on the cross-cancer hypothesis-the concept that molecular mechanisms or resistance pathways observed in one cancer type may be universally present and functionally relevant across histologically distinct malignancies-the mechanism of enzalutamide resistance may be related to reducing the production of short-chain fatty acids (SCFAs) (especially butyrate) and relieving regulatory T cell (Treg)-mediated immunosuppression (23). However, the transferability of mechanisms between different cancer types remains controversial, and direct evidence in PCa is lacking.

Multiple recent systematic reviews and meta-analyses have provided important evidence-based insights into the role of the microbiome in PCa. A meta-analysis by Huang *et al* (24) encompassing seven studies (including 250 PCa patients and 192 controls), demonstrated that the α-diversity of the gut microbiota was notably lower in patients with PCa compared with healthy controls. Regarding microbial abundance, patients with PCa exhibited markedly higher relative abundances of Proteobacteria, the class Bacteroidia, the class Clostridia, as well as the genera *Prevotella*, *Escherichia-Shigella* and *Faecalibacterium* (24). Conversely, the abundances of Actinobacteria, Firmicutes and the genus *Veillonella* were notably reduced (24). Another systematic review, covering 42 studies, further elucidated the multifaceted role of the microbiome in PCa diagnosis, prognosis and treatment response (25). The urinary microbiota demonstrated potential diagnostic value (sensitivity 58-82%). Enrichment of the class *Betaproteobacteria* in the gut was associated with earlier progression to CRPC, with a median time to progression shortened by 5.2 months (hazard ratio, 1.8; 95%

confidence interval, 1.3-2.5) (25). Furthermore, ADT-induced dysbiosis (for example, overgrowth of *Klebsiella* species) was associated with a 2.1-fold increased risk of resistance, while responders to immunotherapy exhibited enrichment of *Akkermansia muciniphila* (25). This body of cross-cancer and PCa-specific evidence indicates that the gut microbiota can influence cancer detection, progression and therapeutic efficacy through both direct and indirect mechanisms, thereby laying a theoretical foundation for the development of microbiota-targeted intervention strategies.

3. Current status of PCa treatment resistance

ADT is the cornerstone treatment for metastatic PCa, but resistance is a major challenge, with most patients progressing to CRPC within 18-24 months (26). In North America and Europe, 10-20% of patients develop CRPC within 5 years of starting ADT, while in Asia, the progression rate is similar, but overall survival outcomes are worse due to differences in healthcare infrastructure and treatment availability (27). Chemotherapy, particularly with docetaxel, is the mainstay treatment for metastatic CRPC (mCRPC); however, resistance is common (26). In North America, 30-40% of patients with mCRPC do not respond to initial docetaxel treatment, and in Asia, up to 45% of patients may not benefit from docetaxel-based therapy (27). Immunotherapy, including immune checkpoint inhibitors, has shown promise in treating advanced PCa; however, resistance remains a significant issue (26). In North America, the response rate to immune checkpoint inhibitors is 15-20%, whereas in Asia, the response rate is slightly lower, at 10-15% (26,27).

The landscape of PCa treatment has evolved significantly, yet the emergence of treatment resistance remains a formidable barrier to achieving durable therapeutic success. Previous investigations have unveiled the multifaceted mechanisms underlying resistance to ADT, immunotherapy and chemotherapy (Table I; Fig. 1). Elucidating these mechanisms is essential for devising more effective and targeted therapeutic strategies. This section provides an in-depth overview of the current status of treatment resistance in PCa, with a focus on the biological, genetic and microenvironmental factors that contribute to therapeutic failure.

ADT resistance. ADT, which targets the AR signaling pathway, has long been the cornerstone of treatment for advanced PCa. However, the development of ADT resistance, which leads to CRPC, is a key concern. Understanding the mechanisms underlying this resistance is critical for developing effective treatment strategies.

Alterations in the AR. AR gene amplification and subsequent upregulation are common resistance mechanisms. Studies have shown that AR amplification occurs in an important proportion of patients with CRPC, allowing cancer cells to maintain AR signaling despite low androgen levels (28,29). Mutations in the AR gene can lead to receptor activation by non-androgenic ligands or antagonists. For example, mutations such as T877A and H874Y have been identified, which enable the receptor to be activated by alternative ligands (30). This alteration highlights the adaptability of PCa cells to maintain AR signaling and disease progression under conditions of ADT.

Intratumoral androgen synthesis. PCa cells can develop the ability to synthesize androgens intratumorally, thereby bypassing the need for circulating androgens. This is achieved through upregulation of enzymes involved in androgen biosynthesis, such as cytochrome P450 family 17 subfamily A member 1, aldo-keto reductase family 1 member C3 and hydroxysteroid 3β-dehydrogenase type 1. These enzymes convert precursor molecules into active androgens within the tumor microenvironment, sustaining AR activation (31,32).

Other mechanisms. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mTOR pathway can be activated by PIK3CA mutation, loss of phosphatase and tensin homolog (PTEN), or other mechanisms (e.g., PIK3CB mutation, PIK3CB mutation, AKT1 mutation, TSC1/TSC2 inactivating mutation, MTOR mutation) to promote PCa cell survival and proliferation independent of AR signaling (33). ADT drives metabolic reprogramming of adenomatosis polyposis coli downregulated 1-positive cancer-associated fibroblasts (CAFs) via activation of the PI3K/AKT/hypoxia-inducible factor-1α (HIF-1α) signaling cascade. Lactate is then exported to the microenvironment and transported into cancer cells, where it induces the lactylation of small nuclear ribonucleoprotein polypeptide A, thereby regulating splicing of AR and generating AR splicing variant 7 (ARV7) (34). Although ADT can induce androgen-sensitive PCa cells to enter the senescent state, a previous study has shown that the continuous increase of active ARV7 is associated with the escape of PCa from cell senescence (35). ARV7 can directly bind to the SKP2 promoter and activate its transcription, promoting the proteasomal degradation of p27 protein and subsequent G_1/S transition, thereby achieving aging escape (36). Li *et al* (37) revealed that ADT, by inhibiting AR signaling, leads to the upregulation of macrophage migration inhibitory factor (MIF) expression, which in turn promotes PCa cell proliferation by upregulating AMP deaminase 2 expression. Although AR negatively regulates MIF expression, its splice variant ARV7 does not (37). A study has found that B-cell lymphoma 2 (BCL2) is almost universally upregulated in ADT treatment castration-sensitive PCa cells, and BCL2 in turn mediates bidirectional signaling between AR-BCL2 and PI3K pathway through non-classical functions, driving the transformation of hormone sensitive to castration resistant phenotype (38). Neuroendocrine differentiation is another mechanism, where PCa cells transition to a neuroendocrine phenotype, which is less dependent on androgen signaling (39).

Immunotherapy resistance. Immunotherapy, including immune checkpoint inhibitors, has shown promise in the treatment of advanced PCa, but its efficacy is limited by factors such as drug resistance (40). Further research is needed to identify novel biomarkers and therapeutic strategies to enhance the efficacy of immune checkpoint inhibitors in castration-resistant PCa.

Tumor microenvironment and immunosuppression. Immunosuppressive cells such as Tregs, MDSCs and tumor-associated macrophages are often enriched in the tumor microenvironment, creating an immunosuppressive niche that hinders the efficacy of immune checkpoint inhibitors (41-43). Novysedlak *et al* (41) highlighted the role of MDSCs in promoting an immunosuppressive environment in PCa, which can limit the effectiveness of immune checkpoint inhibitors.

Table I. Mechanisms of therapeutic resistance in PCa.

A, ADT

Resistance mechanism category	Specific resistance mechanism	(Refs.)
Alterations in AR	AR gene amplification and overexpression, allowing cancer cells to maintain AR signaling despite low androgen levels. AR gene mutations lead to receptor activation by non-androgenic ligands or antagonists (T877A and H874Y mutations).	(27-29)
Intratumoral androgen synthesis	PCa cells synthesize androgens intratumorally via upregulation of enzymes such as CYP17A1, AKR1C3 and HSD3B1, bypassing the need for circulating androgens.	(30,31)
Other mechanisms	The aberrant activation of the PI3K/AKT pathway bypasses AR signaling; ADT-induced metabolic reprogramming generates the AR-V7 splice variant; AR-V7 drives senescence escape; upregulation of MIF and bidirectional signaling of BCL2 promote proliferation; along with neuroendocrine differentiation, collectively drive castration resistance.	(32-38)

B, Immunotherapy

Resistance mechanism category	Specific resistance mechanism	(Refs.)
Tumor microenvironment and immunosuppression	Immunosuppressive cells (Tregs, MDSCs, TAMs) create an immunosuppressive niche in the tumor microenvironment, hindering the efficacy of immune checkpoint inhibitors.	(40-42)
Genetic and epigenetic alterations	Mutations in DNA repair genes (BRCA2, ATM) lead to genomic instability; epigenetic changes alter the expression of immune-related genes, contributing to resistance.	(43-45)
Immune checkpoint inhibitors and resistance mechanisms	Low tumor mutational burden and lack of PD-L1 expression in patients with PCa; immunosuppressive cytokines (TGF-β, IL-10) inhibit the antitumor immune response.	(46-48)

C, Chemotherapy

Resistance mechanism category	Specific resistance mechanism	(Refs.)
Docetaxel resistance	Overexpression of ABC transporters (ABCB1) effluxes cytotoxic drugs, reducing intracellular drug concentration; alterations in microtubule dynamics and upregulation of survival pathways to (PI3K/AKT/mTOR) promote cell survival. Activation of the AKT pathway stabilizes anti-apoptotic protein MCL-1, inhibiting apoptosis induced by docetaxel; heat shock proteins protect cancer cells from docetaxel-induced stress.	(49-53)
Cabazitaxel resistance	Overexpression of ABC transporters and activation of survival pathways; AR gene mutations lead to constitutive receptor activation independent of androgen levels. Upregulation of the Wnt/β-catenin signaling pathway enhances cell survival and promotes an EMT phenotype, associated with increased metastatic potential and drug resistance.	(54-56)
Cisplatin resistance	Increased DNA repair capacity (upregulation of ERCC1 and BRCA1/2), reduces drug uptake and activation of survival pathways (NF-κB pathway). Expression of multidrug resistance-associated protein 2 reduces intracellular cisplatin levels by mediating drug efflux.	(57-59)
Mitoxantrone resistance	Overexpression of ABC transporters (ABCB1) increases drug efflux, reducing intracellular drug concentration; defects in the DNA damage response (mutations in BRCA2) enhance repair of mitoxantrone-induced DNA damage.	(60,61)

Table I. Continued.

C, Chemotherapy		
Resistance mechanism category	Specific resistance mechanism	(Refs.)
Epirubicin resistance	Overexpression of multidrug resistance proteins and breast cancer resistance protein reduces intracellular epirubicin levels; alterations in topoisomerase II impair the drug ability to induce DNA strand breaks.	(62,63)
Vinblastine resistance	Changes in tubulin dynamics (mutations or overexpression of β-tubulin isotypes) reduce vinblastine ability to inhibit microtubule polymerization; activation of prosurvival pathways (MAPK pathway) promotes cell survival.	(64,65)
Tumor microenvironment	Cancer-associated fibroblasts secrete cytokines and growth factors (IL-6) that activate survival pathways (for example, JAK2/STAT3) in cancer cells, promoting resistance. Hypoxic microenvironment induces HIF-1α expression, promoting EMT and activating survival pathways, contributing to chemotherapy resistance.	(66,67)

ADT, androgen deprivation therapy; AKR1C3, aldo-keto reductase family 1 member C3; AKT, protein kinase B; BCL2, B-cell lymphoma 2; BRCA1, breast cancer susceptibility gene 1; BRCA2, breast cancer susceptibility gene 2; CYP17A1, cytochrome P450 family 17 subfamily A member 1; EMT, epithelial-mesenchymal transition; ERCC1, excision repair cross-complementation group 1; HIF-1α, hypoxia-inducible factor 1-α; HSD3B1, hydroxysteroid 3β-dehydrogenase type 1; JAK2, Janus kinase 2; MAPK, mitogen-activated protein kinase; MCL-1, myeloid cell leukemia 1; MDSCs, myeloid-derived suppressor cells; MIF, macrophage migration inhibitory factor; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PCa, prostate cancer; PD-L1, programmed death-ligand 1; PI3K, phosphatidylinositol 3-kinase; STAT3, signal transducer and activator of transcription 3; TAMS, tumor-associated macrophages; TGF-β, transforming growth factor-β; Tregs, regulatory T cells; ABC, ATP-binding cassette; ABCB1, ATP-binding cassette subfamily B member 1 (P-glycoprotein).

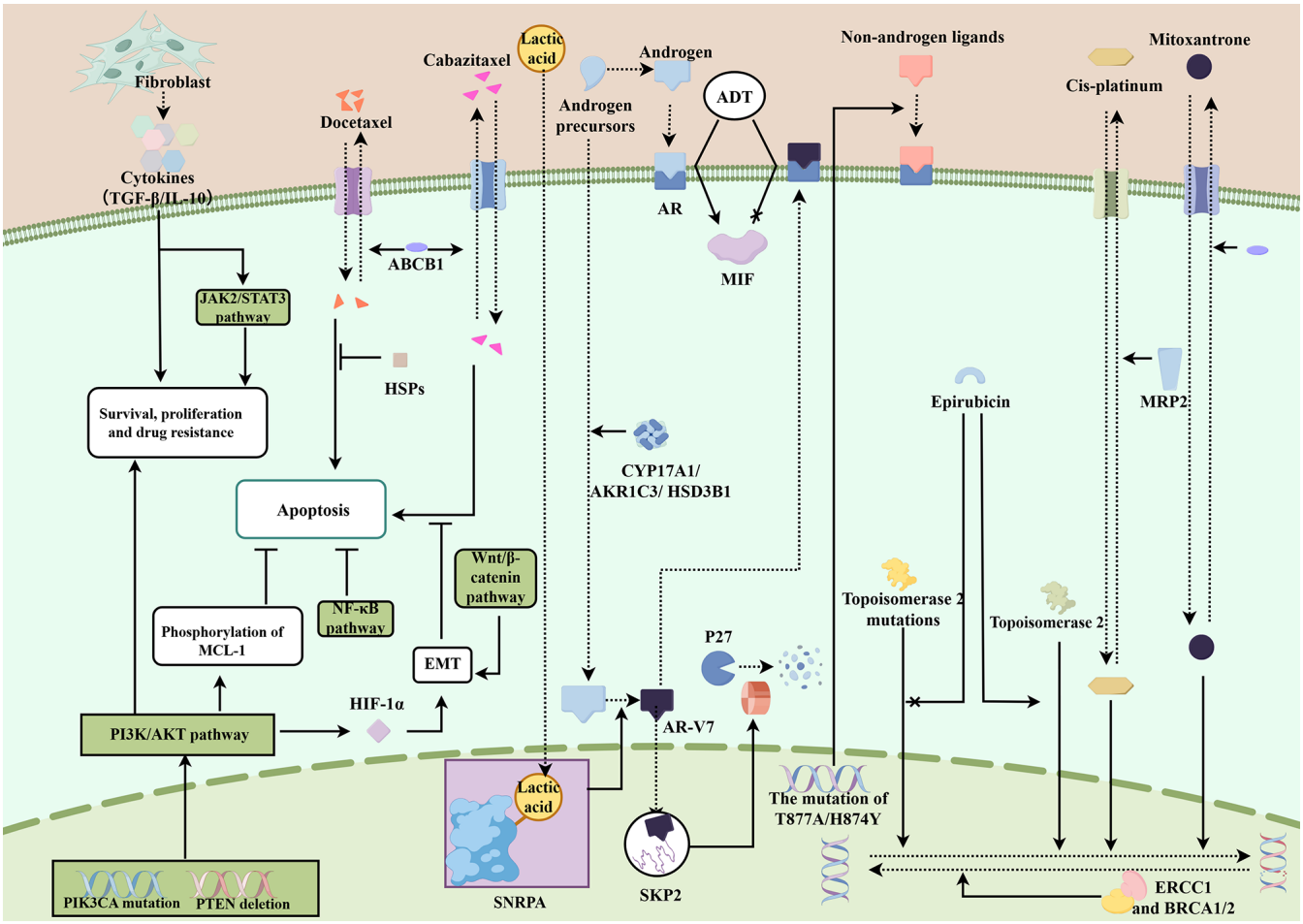

Figure 1. Current resistance mechanisms of ADT, chemotherapy and immunotherapy in PCa. This figure elucidates the resistance mechanisms of PCa to ADT, immunotherapy and chemotherapy (Figdraw; www.figdraw.com; ID, UPPYYb6b66). It summarizes key mechanisms underlying treatment resistance, including AR alterations, intratumoral androgen synthesis, activation of survival pathways (PI3K/AKT, NF-κB), and tumor microenvironment contributions. Specific resistance mechanisms for chemotherapeutic agents (such as docetaxel, cisplatin and mitoxantrone) are also depicted. ABCB1, atp-binding cassette subfamily b member 1 (p-glycoprotein); ADT, androgen deprivation therapy; AKR1C3, aldo-keto reductase family 1 member c3; AR, androgen receptor; AR-V7, androgen receptor splicing variant 7; BRCA1/2, breast cancer susceptibility gene 1/2; CYP17A1, cytochrome p450 family 17 subfamily a member 1; EMT, epithelial-mesenchymal transition; ERCC1, excision repair cross-complementation group 1; H874Y, androgen receptor mutation at position 874 (histidine to tyrosine); HIF-1α, hypoxia-inducible factor 1α; HSD3B1, hydroxysteroid 3β-dehydrogenase type 1; HSPs, heat shock proteins; IL-10, interleukin-10; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; MIF, macrophage migration inhibitory factor; MRP2, multidrug resistance-associated protein 2; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; P27, cyclin-dependent kinase inhibitor 1b; PI3K/AKT, phosphoinositide 3-kinase/protein kinase b; PI3KCA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; PTEN, phosphatase and tensin homolog; SKP2, S-phase kinase-associated protein 2; SNRPA, small nuclear ribonucleoprotein polypeptide a; T877A, androgen receptor mutation at position 877 (threonine to alanine); TGF-β, transforming growth factor-β; Wnt, wingless-related integration site.

Genetic and epigenetic alterations. Genetic mutations and epigenetic modifications can drive resistance to immunotherapy. For instance, mutations in DNA repair genes, such as breast cancer susceptibility gene (BRCA) 2 and ataxia telangiectasia-mutated gene (ATM), can lead to genomic instability, which may influence the immune landscape of prostate tumor (44-46).

Immune checkpoint inhibitors and resistance mechanisms. PD-1/programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors have shown promise in a variety of cancers; however, their efficacy has been limited in PCa. PCa resistance mechanisms include low tumor mutational burden and lack of PD-1 expression, which are often observed in patients (47,48). In addition, the presence of immunosuppressive cytokines, such as transforming growth factor-β (TGF-β) and IL-10, contribute to the resistance of prostate cancer to immune checkpoint inhibitors by constructing an immunosuppressive tumor microenvironment and inhibiting the function of effector T cells (49).

Resistance to chemotherapy. Chemotherapy remains a cornerstone in the management of advanced PCa; however, resistance to chemotherapeutic agents is a significant challenge that hampers treatment efficacy. This section delves into the mechanisms underlying chemotherapy resistance in PCa, with a focus on specific drugs and associated signaling pathways.

Docetaxel resistance. Docetaxel is the first-line chemotherapeutic agent for mCRPC. However, resistance to docetaxel is common and driven by multiple mechanisms. One key factor is the overexpression of ATP-binding cassette (ABC) transporters, such as ABCB1 (P-glycoprotein), which efflux cytotoxic drugs from cancer cells, thereby

reducing intracellular drug concentration and efficacy (50). Alterations in microtubule dynamics and upregulation of survival pathways, such as the PI3K/AKT/mTOR pathway, contribute to docetaxel resistance by promoting cell survival and proliferation (51). A study has shown that activation of the AKT pathway can phosphorylate and stabilize myeloid cell leukemia 1, an anti-apoptotic protein, thereby inhibiting apoptosis induced by docetaxel (52). Furthermore, the expression of heat shock proteins can stabilize oncogenic proteins and protect cancer cells from docetaxel-induced stress (53). Chemotherapy-induced neurotoxicity remains a major clinical issue, with increasing evidence pointing to the role of cellular stress and survival pathways in mediating resistance (54). These findings suggest that strategies targeting these pathways may provide new therapeutic opportunities to overcome chemotherapy resistance in PCa.

Cabazitaxel resistance. Cabazitaxel is used as second-line therapy for patients who have progressed to docetaxel. Resistance to cabazitaxel can arise through mechanisms similar to docetaxel resistance, including overexpression of ABC transporters and activation of survival pathways (55). Additionally, genetic alterations in the AR pathway contribute to cabazitaxel resistance. For example, mutations in the AR gene can lead to constitutive activation of the receptor, promoting cell survival and proliferation independently of androgen levels (56). Moreover, upregulation of the Wnt/β-catenin signaling pathway has been implicated in cabazitaxel resistance by enhancing cell survival and promoting an EMT phenotype, which is associated with increased metastatic potential and drug resistance (57).

Cisplatin resistance. Cisplatin is used in combination regimens for aggressive PCa variants. Resistance to cisplatin can be attributed to several mechanisms, including increased DNA repair capacity, reduced drug uptake and the activation of survival pathways. Specifically, upregulation of DNA repair proteins, such as excision repair cross-complementation group 1 and BRCA 1/2, can enhance the repair of cisplatin-induced DNA damage, thereby reducing the cytotoxic effects of the drug (58). Additionally, activation of the nuclear factor kappa-B (NF-κB) pathway can promote cell survival by upregulating anti-apoptotic genes, thereby contributing to cisplatin resistance (59). Similarly, the expression of multidrug resistance-associated protein 2 can reduce intracellular cisplatin levels by effluxing the drug, thereby diminishing its efficacy (60).

Mitoxantrone resistance. Mitoxantrone is an anthracycline derivative widely used in the treatment of mCRPC. Resistance to mitoxantrone has been linked to alterations in the drug efflux and DNA repair pathways. Specifically, upregulation of ABC transporters, such as ABCB1 (P-glycoprotein), can lead to increased drug efflux, reducing intracellular drug concentration and efficacy (61). Additionally, mitoxantrone resistance may be associated with defects in DNA damage response. For instance, mutations or overexpression of genes involved in the DNA repair machinery, such as BRCA2, can promote resistance by enhancing the repair of mitoxantrone-induced DNA damage (62).

Epirubicin resistance. Epirubicin, another anthracycline antibiotic, is used in combination regimens for PCa treatment. Resistance to epirubicin often involves mechanisms similar to those of mitoxantrone. Overexpression of multidrug resistance proteins and breast cancer resistance protein notably reduces intracellular epirubicin levels (63). Moreover, alterations in topoisomerase II, which is the primary target of epirubicin, can lead to resistance. Mutations or downregulation of topoisomerase II can impair the ability of the drug to induce DNA strand breaks, thereby reducing its cytotoxic effects (64).

Vinblastine resistance. Vinblastine, a vinca alkaloid, is used in various chemotherapy regimens for PCa treatment. Vinblastine resistance is often associated with changes in tubulin dynamics. Specifically, mutations or overexpression of β-tubulin isotypes can affect the binding affinity of vinblastine for tubulin, thereby reducing its ability to inhibit microtubule polymerization (65). Additionally, similar to docetaxel, the activation of pro-survival pathways such as the mitogen-activated protein kinase (MAPK) pathway can contribute to resistance by promoting cell survival and proliferation (66).

Mechanisms involving tumor microenvironment. The tumor microenvironment also plays a crucial role in resistance to chemotherapy. The presence of CAFs can promote resistance by secreting cytokines and growth factors that activate the survival pathways in cancer cells. For example, CAFs secrete IL-6, which activates the Janus kinase 2 (JAK2) signal transducer and activator of transcription 3 (STAT3) pathway, leading to increased cell survival and resistance to chemotherapy (67). Additionally, the hypoxic microenvironment within tumors can induce the expression of HIF-1α, which promotes EMT and activates survival pathways, thereby contributing to chemotherapy resistance (68).

4. Mechanisms of gut microbiota in PCa treatment resistance

Gut microbiota has emerged as a critical player in the modulation of treatment resistance in PCa. Accumulating evidence suggests that specific metabolites produced by gut microbiota can influence the efficacy of ADT, chemotherapy and immunotherapy, thereby contributing to treatment resistance (Table II; Fig. 2). This section will delve into the detailed mechanisms by which key metabolites from the gut microbiota impact treatment resistance in PCa, with a particular focus on distinguishing between ADT, chemotherapy and immunotherapy resistance mechanisms.

SCFAs. SCFAs, including acetate, propionic acid and butyric acid, are produced by gut microbiota such as Firmicutes and Bacteroidetes by fermenting dietary fiber (69). These metabolites regulate cellular metabolism and signaling pathways, thereby influencing PCa progression and treatment response. Recent studies on metabolic reprogramming have shown that tumor cells often rewire their metabolism to resist immune responses, similar to findings observed in lung cancer (70). In PCa, SCFAs may influence disease progression and treatment resistance through androgen metabolism and the production of procarcinogenic metabolites.

ADT is the cornerstone therapy for treating advanced PCa. However, a number of patients eventually develop resistance to ADT, leading to the progression of CRPC. An *in vitro* study revealed that treatment with butyrate and acetate markedly upregulated both the protein and mRNA levels of the AR and

Table II. Mechanisms of gut microbiota metabolites in PCa treatment resistance.

A, Short chain fatty acids

Impact on treatment	Pathway involved	Outcome	(Refs.)
Promotes ADT resistance	1. HDAC inhibition leads to histone hyperacetylation at AR gene promoter, which leads to upregulation of AR and ARV7. 2. Upregulates 17β-HSD and 3β-HSD in intestinal epithelial cells and hepatocytes.	1. Drives CRPC progression under low-androgen conditions. 2. Increases peripheral androgen synthesis.	(69-71)
Counteracts ADT resistance	Inhibits the JAK2/STAT3/Nrf2/Glo1 pathway, thereby increasing methylglyoxal production.	Induces mitochondrial damage and apoptosis in PCa cells (concentration-dependent).	(72)
Promotes chemotherapy resistance	1. Activates ATM/ATR-mediated DNA damage repair pathway. 2. Upregulates acetyl-CoA synthetase 2, which enhances acetyl-CoA production and promotes neuroendocrine differentiation.	Reduces docetaxel-induced apoptosis; enhances tolerance to chemotherapeutic agents.	(73,74)
Promotes immunotherapy resistance	1. Induces protective autophagy in PCa cells. 2. Activates Toll-like receptor 3/NF-κB/MAPK pathway, which upregulates CCL20 and recruits $CCR6^+$ macrophages, thereby suppressing $CD8^+$ T cell function.	Establishes immunosuppressive microenvironment; reduces efficacy of immune checkpoint inhibitors.	(69)

B, Trimethylamine N-oxide

Impact on treatment	Pathway involved	Outcome	(Refs.)
Promotes ADT resistance	Upregulates p38/HMOX1 pathway, which increases AR and prostate-specific antigen expression.	Enhances antioxidant adaptation under androgen deficiency; promotes cell proliferation.	(76,77)
Promotes chemotherapy resistance	Reduces apoptotic response of PCa cells to chemotherapeutic agents.	Decreases chemosensitivity.	(76)

C, I3C

Impact on treatment	Pathway involved	Outcome	(Refs.)
Anti-tumor (via DIM)	1. Acts as CB2 receptor agonist. 2. Inhibits PI3K/AKT and NF-κB pathways. 3. Reprograms glycolysis, TCA cycle and lipid metabolism in prostate tissue.	1. Modulates tumor immune microenvironment; inhibits proliferation. 2. Induces apoptosis; suppresses invasion. 3. Inhibits PCa cell energy metabolism and biosynthesis.	(82-85)

Table II. Continued.

D, LPC			
Impact on treatment	Pathway involved	Outcome	(Refs.)
Promotes ADT resistance	Upregulates LPCAT1 expression.	Enhances DNA repair pathways; promotes survival under low-androgen conditions.	(93)

E, Phenylacetylglutamine			
Impact on treatment	Pathway involved	Outcome	(Refs.)
Potential to enhance treatment sensitivity	Inhibits Wnt/β-catenin signaling pathway by upregulating CCNG2 expression.	Reduces expression of downstream target genes, such as c-Myc and cyclin D1.	(94)

F, Bile acids			
Impact on treatment	Pathway involved	Outcome	(Refs.)
Associated with PCa treatment	Mechanism remains to be determined.	May modulate immune microenvironment and lipid metabolism; role in treatment resistance unclear.	(109-111)

G, Histamine			
Impact on treatment	Pathway involved	Outcome	(Refs.)
Promotes PCa progression	Activates H1 receptor.	Promotes tumor growth under high-fat diet conditions.	(113)
Potential anti-PCa activity	Long-term H2 receptor antagonist use associated with reduced PCa risk.	Mechanism remains to be determined.	(117)

ADT, androgen deprivation therapy; AKT, protein kinase B; ARV7, androgen receptor splicing variant 7; ATM, ataxia telangiectasia-mutated gene; ATR, ataxia telangiectasia and Rad3-related protein; CB2, cannabinoid receptor 2; CCL20, C-C motif chemokine ligand 20; CCR6, C-C chemokine receptor type 6; CRPC, castration-resistant prostate cancer; DIM, 3,3'-diindolylmethane; Glo1, glyoxalase 1; HDAC, histone deacetylase; HMOX1, heme oxygenase-1; I3C, Indole-3-Carbinol; JAK2, Janus kinase 2; LPC, lysophosphatidylcholine; LPCAT1, lysophosphatidylcholine acyltransferase 1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2-related factor 2; PCa, prostate cancer; STAT3, signal transducer and activator of transcription 3.

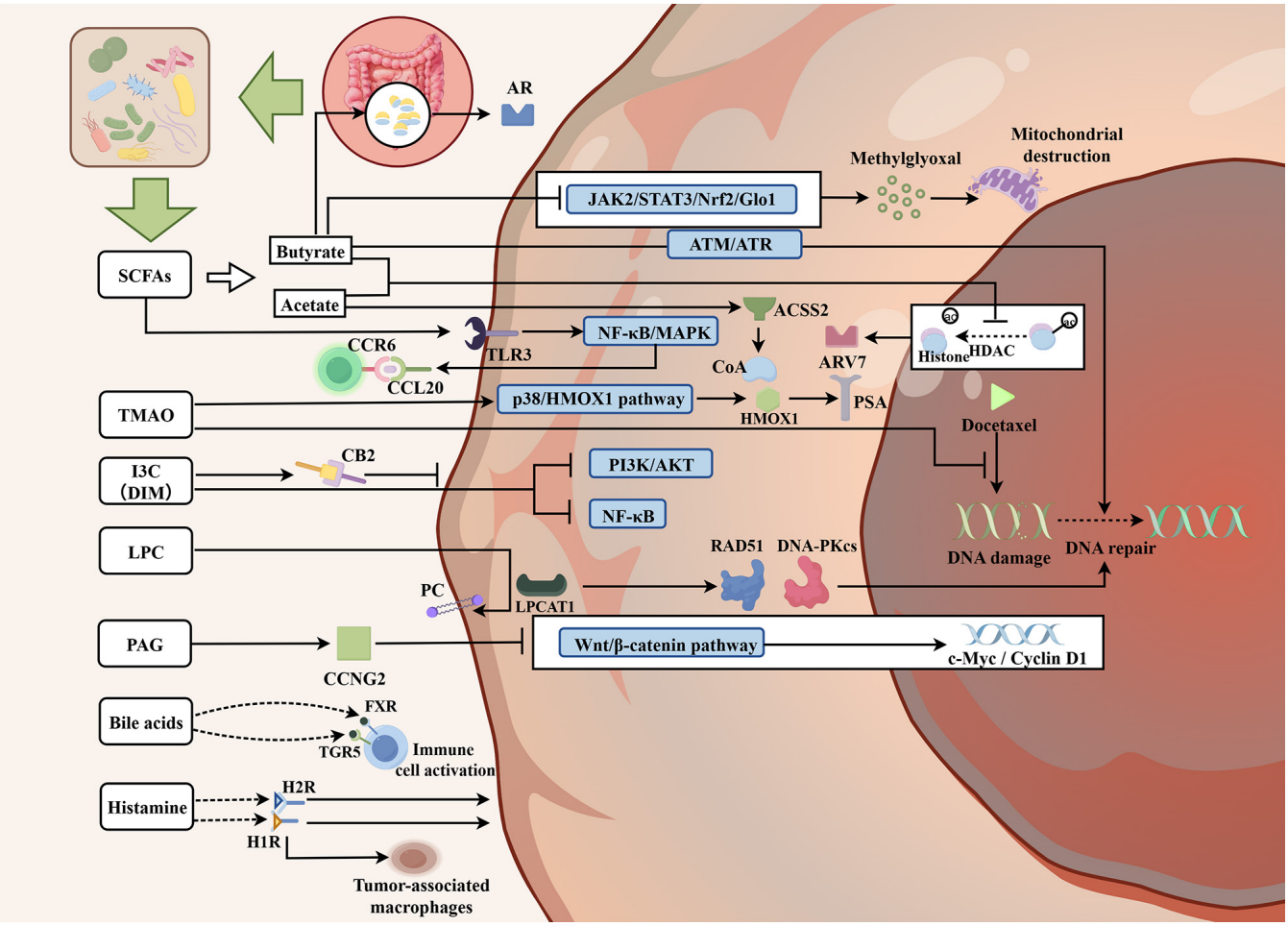

Figure 2. Mechanism of gut microbiota metabolites in PCa treatment resistance. This diagram illustrates the role of gut microbiota metabolites in modulating PCa treatment resistance (Figdraw; www.figdraw.com; ID, PISAAda91d). It illustrates how gut microbiota-derived metabolites (SCFAs, TMAO, I3C, LPC, PAG, bile acids and histamine) modulate resistance to ADT, chemotherapy and immunotherapy through AR signaling, DNA repair, immune cell function, and key pathways including Wnt/β-catenin, PI3K/AKT and p38/HMOX1. ACSS2, acetyl-coa synthetase 2; AR, androgen receptor; ARV7, androgen receptor splicing variant 7; ATM/ATR, ataxia telangiectasia-mutated/ataxia telangiectasia and rad3-related protein; CCL20, c-c motif chemokine ligand 20; CCR6, c-c chemokine receptor type 6; CB2, cannabinoid receptor 2; CCNG2, cyclin g2; CoA, coenzyme a; c-Myc, myc proto-oncogene; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; FXR, farnesoid x receptor; Glo1, glyoxalase 1; H1/2R, histamine h1 receptor/h2 receptor; HDAC, histone deacetylase; HMOX1, heme oxygenase-1; I3C (DIM), indole-3-carbinol (3,3'-diindolylmethane); JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; Nrf2, nuclear factor erythroid 2-related factor 2; Glo1, glyoxalase 1; LPC, lysophosphatidylcholine; LPCAT1, lysophosphatidylcholine acyltransferase 1; NF-κB, nuclear factor κB; MAPK, mitogen-activated protein kinase; HMOX1, heme oxygenase-1; PAG, phenylacetylglutamine; PC, phosphatidylcholine; PI3K, phosphoinositide 3-kinase; PSA, prostate-specific antigen; RAD51, DNA repair protein RAD51 homolog 1; SCFAs, short-chain fatty acids; TGR5, g protein-coupled bile acid receptor 1; TLR3, toll-like receptor 3; TMAO, trimethylamine n-oxide; Wnt, wingless-related integration site.

its splice variant ARV7 in PCa cells, suggesting that SCFAs may directly regulate AR gene transcription (69). Subsequent histone deacetylase (HDAC) activity assays and chromatin immunoprecipitation analyses further confirmed that butyrate and acetate function as HDAC inhibitors, inducing histone hyperacetylation at the AR gene promoter region and thereby directly enhancing the expression of AR and its splice variants (69). Furthermore, Bui *et al* (71) demonstrated that treatment of intestinal epithelial cells or hepatocytes with SCFAs, particularly butyrate, notably upregulated the expression and activity of 17β-hydroxysteroid dehydrogenase and 3β-hydroxysteroid dehydrogenase. These two enzymes are the key rate-limiting enzymes responsible for converting precursors into active androgens. Subsequent animal experiments further confirmed that SCFAs, particularly butyrate, contributes to peripheral androgen synthesis, thereby promoting ADT resistance in PCa (71). By contrast, Hsia *et al* (72) demonstrated that butyrate (2 to 4 mM) increases methylglyoxal production by inhibiting the JAK2/STAT3/nuclear factor erythroid 2-related factor 2/glyoxalase 1 pathway, thereby inducing mitochondrial damage and subsequent apoptosis in PCa cells. This inhibitory effect on PCa was concentration-dependent, and no pro-proliferative effect was observed at lower concentrations. This finding contrasts with previous reports (69,71) revealing the bidirectional role of SCFAs, particularly butyrate, in PCa therapy. We hypothesize that the absence of a pro-proliferative effect at low concentrations may be attributed to a lower threshold for this functional switch. Future studies aimed at identifying the molecular switch that precisely regulates this threshold hold promise for transforming butyrate into a manipulable and precise therapeutic tool.

Chemotherapy is another important treatment modality for PCa, particularly in patients with metastatic disease. However, resistance to chemotherapy is a major challenge

limiting the effectiveness of this treatment. SCFAs have been shown to influence the sensitivity of PCa cells to chemotherapeutic agents through various mechanisms. Zhong *et al* (73) demonstrated that butyrate pretreatment markedly reduced docetaxel-induced apoptosis in PCa cells, concomitant with activation of the ATM/ataxia telangiectasia and Rad3-related protein (ATR) pathway. Notably, the research team experimentally showed that pharmacological inhibition of the ATM/ATR signaling axis markedly reversed butyrate-induced docetaxel resistance (73). These findings indicate that butyrate confers docetaxel resistance in PCa cells by activating the ATM/ATR-mediated DNA damage repair pathway. As demonstrated by Gao *et al* (74) through both *in vitro* cell models and *in vivo* experiments, acetate treatment notably promotes neuroendocrine differentiation in PCa cells, a critical phenotype associated with acquired therapeutic resistance (74). The study further revealed that acetate upregulates the expression of acetyl-CoA synthetase 2, thereby enhancing acetyl-coenzyme A production and subsequently activating transcriptional programs linked to neuroendocrine differentiation. This cascade ultimately leads to enhanced tumor tolerance to chemotherapeutic agents such as docetaxel (74). SCFAs promote the formation of chemotherapy resistance in PCa through multiple independent yet complementary signaling pathways. Rather than acting through a single mechanism, SCFAs establish a multifaceted defense system that synergistically enhances tumor cell tolerance to chemotherapeutic agents such as docetaxel.

Immunotherapy, including immune checkpoint inhibitors, has shown promise for the treatment of advanced PCa. However, the response rate to immunotherapy remains low and many patients develop resistance (2). SCFAs have emerged as important modulators of the immune system, particularly in PCa immunotherapy. A study utilizing co-culture systems and a PCa mouse model systematically investigated the effects of SCFAs on the tumor immune microenvironment (69). The findings demonstrated that SCFAs not only directly induced protective autophagy in PCa cells, thereby shielding them from immune attack, but also, more importantly, stimulated the expression and secretion of C-C motif chemokine ligand 20 (CCL20) in PCa cells via the Toll-like receptor 3/NF-κB/MAPK signaling pathway. The secreted CCL20 subsequently recruited C-C chemokine receptor type 6-expressing macrophages into the tumor microenvironment (69). These polarized macrophages further suppress the infiltration and cytotoxic function of $CD8^+$ T cells through the secretion of inhibitory cytokines, thereby establishing an immunosuppressive microenvironment. This mechanism is speculated to be a key factor contributing to the poor response of PCa to immune checkpoint inhibitors such as PD-1/PD-L1 antibodies (69). Based on bioinformatical analyses, Matsushita *et al* (75) hypothesized that gut microbiota-derived butyrate may promote the progression of high-risk PCa by facilitating Tregs differentiation and subsequently suppressing antitumor immune responses. However, the conclusions drawn from the bioinformatics analysis still require further experimental research to clarify the specific pathways and effects.

SCFAs exert a bidirectional regulatory role in PCa. On one hand, they contribute to therapeutic resistance through multiple mechanisms, including enhancing AR signaling, promoting androgen synthesis, activating DNA damage repair pathways and inducing immunosuppression, thereby compromising the efficacy of endocrine therapy, chemotherapy and immunotherapy. On the other hand, specific SCFAs such as butyrate, at appropriate concentrations, can induce apoptosis in PCa cells, exerting antitumor effects. Future research should focus on elucidating the molecular switch governing this functional duality, with the goal of transitioning SCFAs from risk factors to precise therapeutic tools.

Trimethylamine N-oxide (TMAO). TMAO is produced by *Escherichia coli, Enterobacter* aerogenes and other gut microbiota by metabolizing dietary choline and carnitine (73). This metabolite can influence cellular stress responses and inflammation, thereby promoting resistance to treatment.

Zhou *et al* (76) treated PCa cell lines with varying concentrations of TMAO and observed that cell proliferation markedly increased in a concentration-dependent manner. Through mechanistic investigation using molecular biology techniques, the study revealed that TMAO treatment upregulated the p38/heme oxygenase-1 (HMOX1) pathway and increased the expression of AR and its downstream target genes, such as prostate-specific antigen (76). Activation of HMOX1 confers antioxidant adaptation in cells under androgen deficiency conditions and enhances the resistance of PCa cells to ADT treatment (77). Furthermore, the study examined the impact of TMAO pretreatment on chemosensitivity, demonstrating that higher concentrations of TMAO (≥200 μM) notably reduced the apoptotic response of PCa cells to chemotherapeutic agents, including docetaxel (76).

Studies on other cancer types have shown that TMAO can affect cellular metabolism and signaling pathways associated with drug resistance. For example, TMAO has been shown to affect mitochondrial function and reactive oxygen species levels, which are key determinants of sensitivity (69). Given the metabolic changes associated with TMAO, this metabolite may affect therapeutic efficacy in PCa in a similar manner by modulating the cellular redox status and survival pathways. TMAO can promote the polarization of macrophages to the M2 phenotype, leading to an immunosuppressive tumor microenvironment, thereby reducing the efficacy of immunotherapy (78). Simultaneously, TMAO impairs the function of dendritic cells, reducing their ability to present antigens and activate T cells, leading to a weakened adaptive immune response (79). Since immune cells are key players in the treatment of PCa, we hypothesize that the effects of TMAO on immune cells may play the same role in the treatment of PCa. However, further studies are needed to confirm whether these effects play a role in PCa.

Although direct clinical investigations into the role of TMAO in promoting resistance are still in their preliminary stages, existing evidence from population-based studies and multi-omics analyses suggests a potential link. A prospective analysis of the PLCO cancer screening trial cohort by Reichard *et al* (80) demonstrated that elevated circulating TMAO levels were markedly associated with an increased risk of lethal PCa, suggesting that TMAO may actively participate in disease progression and lethal transformation.

Indole-3-carbinol (I3C). I3C, derived from cruciferous vegetables and produced by *Bacteroides fragilis* and *Clostridium* sporogenes, affects the expression of genes involved in cell cycle regulation and apoptosis (81). The *in vivo* activity of I3C is largely attributed to its dimeric derivative, 3,3'-diindolylmethane (DIM). To the best of our knowledge, Tucci *et al* (82) were the first to report that DIM acts as a cannabinoid receptor 2 (CB2) agonist in both androgen-dependent and androgen-independent PCa cell models. The experiment revealed that activation of the CB2 receptor can modulate the tumor immune microenvironment and inhibit tumor cell proliferation, suggesting that DIM exerts its anti-PCa effects through the CB2 signaling axis (82).

DIM has been shown to inhibit multiple oncogenic pathways, including PI3K/AKT and NF-κB, thereby inducing apoptosis and suppressing invasion (83,84). Although various carcinogenic pathways have been identified in PCa, it remains to be further investigated whether the multiple carcinogenic pathway inhibition mediated by DIM can be effective in PCa. An animal study has revealed that dietary supplementation with I3C notably alters the metabolic profile of mouse prostate tissue, involving reprogramming of intermediates related to glycolysis, the tricarboxylic acid cycle and lipid metabolism (85). Such metabolic modulation may impact the energy metabolism and biosynthesis of PCa cells, thereby inhibiting tumor growth. In addition, I3C has been demonstrated to upregulate PTEN expression (86) and inhibit the Wnt/β-catenin pathway (87) in other tumor types (for example, colorectal and esophageal cancers). Among the multiple oncogenic pathways inhibited by I3C, mechanistic pathways, including the PI3K/AKT, NF-κB and Wnt/β-catenin pathways, were also activated in PCa. Among the multiple oncogenic pathways inhibited by I3C, mechanistic pathways including PI3K/AKT, NF-κB and Wnt/β-catenin pathways were also activated in PCa. The present study hypothesizes that I3C may enhance the efficacy of existing therapies through multiple pathways.

As naturally occurring dietary compounds, I3C and its derivatives offer favorable safety profiles and accessibility. Future research should systematically evaluate the antitumor activity of I3C/DIM in CRPC and different molecular subtypes of PCa models, elucidate their interplay with AR signaling, lipid metabolism and the immune microenvironment, and explore their synergistic effects and potential to overcome resistance when combined with ADT, novel endocrine agents and immunotherapy.

Lysophosphatidylcholine (LPC). Bacteria such as *Escherichia*, *Bilophila*, *Enterorhabdus* and *Gordonibacter* may produce LPC by secreting phospholipases (for example, phospholipase D or phospholipase A2), which catalyze the hydrolysis of dietary or host-derived phosphatidylcholine (PC) as a substrate (88). Buszewska-Forajta *et al* (89) reviewed the application of lipidomics in PCa diagnosis and highlighted the potential of LPC as a diagnostic biomarker. Subsequently, the same group utilized matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) to analyze urinary metabolites from patients with PCa and established a diagnostic model based on LPC and other lipid metabolites, demonstrating favorable discriminatory performance (90). Similarly, Li *et al* (91) employed the acidified Bligh-Dyer method to extract lipids from urine samples, followed by detection and analysis using MALDI-TOF/MS. Their results demonstrated that the urinary PCs/LPC ratio was significantly higher in patients with PCa than in those with benign prostatic hyperplasia in both the discovery and validation cohorts ($P<0.001$) (91). These findings reveal that urinary LPC and its ratio to PC (PC/LPC) may serve as potential non-invasive biomarkers for the diagnosis and metabolic stratification of PCa.

Lysophosphatidylcholine acyltransferase 1 (LPCAT1) catalyzes the conversion of LPC to PC and serves as a key enzyme in maintaining the homeostasis of membrane phospholipids (92). Using fecal microbiota transplantation (FMT), Liu *et al* (93) demonstrated that transferring fecal microbiota from patients with mCRPC into mice led to an increased abundance of intestinal *Ruminococcus*, marked upregulation of LPCAT1 expression in prostate tissues, and elevated levels of the DNA repair proteins (DNA repair protein RAD51 homolog 1 and DNA-dependent protein kinase catalytic subunit). Lipidomic analysis further revealed markedly increased fecal levels of LPC and PC following CRPC microbiota transplantation, suggesting that gut microbiota dysbiosis may induce reprogramming of intestinal lipid metabolism (93). This study provides preliminary evidence for the involvement of the 'gut microbiota-LPCAT1-DNA repair axis' in PCa resistance; however, the precise molecular mechanisms through which LPCAT1 regulates DNA repair, as well as the role of its substrate LPC in this process, warrant further investigation.

Collectively, these findings position LPC and its metabolic regulator LPCAT1 at the intersection of microbial ecology, lipid remodeling and DNA repair in PCa. While LPC-related biomarkers show promise for non-invasive stratification, the functional role of LPC within the tumor microenvironment, particularly whether it actively modulates treatment response, remains unclear. Future studies integrating spatial metabolomics with microbiota targeted interventions are warranted to determine if LPC represents not only a diagnostic tool but also a potential therapeutic target.

Phenylacetylglutamine (PAG). PAG is an end product of phenylalanine metabolism dependent on gut microbiota. It is generated by intestinal microorganisms converting dietary phenylalanine to phenylacetic acid, which combines with glutamine in the liver to form PAG and is released into the circulation (94). In the field of cardiovascular diseases, PAG activates adrenergic receptors, promoting high platelet reactivity and inflammatory responses, notably increasing the risks of complications such as myocardial infarction, stroke and heart failure (95-98).

In the field of oncology, the role of PAG presents a different aspect. The latest research has revealed that it exerts a protective effect in PCa. Lv *et al* (94) demonstrated through *in vitro* cell experiments and *in vivo* animal models that the gut microbiota-derived metabolite PAG inhibits PCa progression by upregulating cyclin G2 expression, thereby suppressing the Wnt/β-catenin signaling pathway and its downstream target genes, including c-Myc and cyclin D1 (94). The abnormal activation of the Wnt/β-catenin pathway has been confirmed to be involved in the formation of castration-resistant PCa, and is closely related to the resistance to various treatments

(such as AR signal inhibitors and chemotherapy) (99,100). Therefore, the inhibition of the Wnt pathway mediated by PAG may enhance the sensitivity of existing treatment methods by weakening the characteristics of tumor stem cells and reversing EMT, thereby delaying the occurrence of drug resistance.

In recent years, the role of PAG in tumor biology has gradually attracted attention. However, the expression level of PAG in PCa tissues and its association with patient prognosis remain to be clarified. Future studies need to further elucidate the receptor targets of PAG in the PCa microenvironment, evaluate the correlation between its serum or tumor local levels and the patient treatment response and drug resistance time, and explore the feasibility of modulating the intestinal microbiota or supplementing PAG to enhance existing treatments while preventing the risk of cardiovascular diseases.

Bile acids. Bile acids are amphipathic steroidal compounds synthesized from cholesterol in the liver. The gut microbiota enzymatically converts primary bile acids into secondary bile acids through deconjugation via bile salt hydrolases and subsequent 7α-dehydroxylation. Beyond their role in lipid metabolism, these secondary bile acids function as signaling molecules that activate the farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5), thereby participating in the regulation of host metabolism, immunity and inflammation (101-103).

In colorectal cancer, the abnormal bile acid metabolism mediated by the gut microbiota can also inhibit the Wnt/β-catenin pathway (104). This is similar to the role of PAG, but it is still unknown whether it can inhibit the treatment resistance of PCa. Furthermore, bile acids and their metabolites also play a significant role. For instance, 3-oxolithocholic acid inhibits colorectal cancer progression by modulating T cell differentiation (105); microbiota-derived bile acids activate TGR5 to induce the infiltration of MDSCs into the liver, thereby promoting colorectal cancer liver metastasis (106); conjugated bile acids impair $CD8^+$ T cells function in hepatocellular carcinoma (107); aldo-keto reductase family 1 member D1-mediated bile acid metabolism enhances natural killer (NK) cell cytotoxicity and suppresses hepatocellular carcinoma progression (108). Therefore, bile acids have shown a significant impact on immune cells in gastrointestinal tumors. The immune microenvironment is a crucial aspect in cancer treatment. Bile acids are expected to become an important factor in regulating the immune microenvironment of PCa. However, further research is still needed to explore its effects on the immune cells in PCa tissues.

Previous studies have emphasized the significance of bile acids as signaling molecules in the treatment of PCa (109,110). The study by Kure *et al* (111) indicates that ADT treatment markedly alters the abundance of bacteria involved in bile acid metabolism in the gut microbiota. This discovery provides indirect evidence that bile acids are involved in the efficacy and drug resistance formation of ADT.

We hypothesize that, on one hand, bile acids may modulate lipid metabolism and inflammatory responses through nuclear receptors such as FXR or TGR5, as well as other pathways, with lipid metabolic reprogramming being a characteristic feature of PCa progression and castration resistance. On the other hand, the immunomodulatory effects of bile acids on immune cells, including T cells and MDSCs, may reshape the immunosuppressive tumor microenvironment in PCa. However, their role in PCa therapy remains to be elucidated. Moving forward, it is essential to systematically characterize the bile acid profiles of patients with PCa and integrate functional experiments to clarify the specific mechanisms by which they modulate AR signaling. It is expected to become a key factor in the treatment of PCa.

Histamine. Histamine is a multifunctional bioactive amine synthesized from histidine via catalysis by histidine decarboxylase (HDC), and exerts a broad spectrum of physiological and pathological effects through four G protein-coupled receptors (H1-H4 receptors) (112).

Matsushita *et al* (113) demonstrated that high-fat diet feeding notably increased histamine levels in mouse prostate tissues, and that histamine promotes PCa cell proliferation and tumor growth through activation of the H1 receptor. Notably, administration of the H1 receptor antagonist loratadine or genetic ablation of HDC markedly suppressed high-fat diet-induced tumor promotion. The study links histamine signaling to lipid metabolic reprogramming and diet-associated tumor progression, suggesting that histamine serves as a key node connecting environmental factors with the biological behavior of PCa (113). Furthermore, a case-control study by Wang *et al* (114) suggested that long-term use of H2 receptor antagonists is associated with a reduced risk of PCa. This raises the possibility that antihistamines may possess potential anti-PCa activity, although whether the underlying mechanism depends on histamine receptor blockade remains to be determined.

In recent years, numerous researchers have studied the role of histamine receptors in oncology. However, whether they can have an impact on the treatment of PCa requires further experimental verification. Lauretta *et al* (115) reviewed the therapeutic potential of the H3 receptor in oncology, noting that it may influence the tumor microenvironment by modulating neurotransmitter release and immune cell function. Li *et al* (116) revealed that the allergic mediator histamine induces PD-L1 expression and T helper 2 cell-type inflammation via activation of the H1 receptor on tumor-associated macrophages, thereby conferring resistance to cancer immunotherapy. These findings suggest that the functions of histamine receptors are subtype-specific.

Research on the role of histamine signaling in PCa therapy is still in its infancy. Future efforts should systematically characterize the expression and function of each histamine receptor subtype in PCa cells and the tumor microenvironment, and elucidate their crosstalk with AR signaling and lipid metabolism. Concurrently, leveraging the safety and accessibility of existing antihistamines, it is worthwhile exploring their clinical translational potential in combination with ADT, novel endocrine agents or immunotherapy to enhance sensitivity and overcome resistance.

5. Potential therapeutic strategies

Due to the possible role of the gut microbiota in PCa treatment resistance, an increasing number of potential therapeutic measures related to the gut microbiota have become the focus of research.

Probiotics. Several probiotic strains have been identified for their potential benefits in modulating gut microbiota and influencing PCa treatment outcomes.

Lactobacillus acidophilus. This strain produces lactic acid, which lowers the pH of the gut and inhibits the growth of harmful bacteria. It also enhances the production of SCFAs such as butyrate, which have anti-inflammatory and anticancer properties (24,79).

Lactobacillus rhamnosus. This strain has been shown to improve gut barrier function and reduce the translocation of harmful bacteria and their metabolites into systemic circulation. It also enhances the activity of NK cells and Tregs, which play crucial roles in immune surveillance and cancer cell elimination (117).

Bifidobacterium bifidum. This strain produces antimicrobial substances that inhibit the growth of pathogenic bacteria. It also modulates the immune system by promoting the production of cytokines that enhance the function of the immune cells (118).

Bifidobacterium longum. This strain has been shown to produce SCFAs and other metabolites that influence the tumor microenvironment and reduce inflammation, thereby potentially improving PCa outcomes (119).

Streptococcus thermophilus. This strain is commonly used in combination with other probiotics (for example, *Bifidobacterium* and *Bacteroides dorei*) (120). It enhances the production of lactic acid and SCFAs, which can inhibit the growth of harmful bacteria and promote healthy gut microbiota balance (121).

Future research should focus on identifying specific probiotic strains and combinations. Personalized probiotic therapies based on the characteristics of an individual's gut microbiota may be a promising approach. In conclusion, probiotics offer a novel and promising therapeutic strategy for regulating the gut microbiota of patients with PCa by combining probiotics with other treatments, such as immunotherapy or ADT, which may enhance their therapeutic benefit in patients with PCa. Probiotics have the potential to improve prognosis and reduce PCa treatment resistance by enhancing immune function, reducing inflammation and improving treatment effectiveness.

Prebiotics. Modulating the gut microbiota using prebiotics is a promising therapeutic strategy to mitigate this resistance. Prebiotics are non-digestible food components that selectively stimulate the growth and activity of beneficial gut bacteria, thereby improving the health of the host. This section explores the potential mechanisms and therapeutic applications of specific prebiotics in the context of resistance to PCa treatment.

Inulin is a fructan that selectively promotes the growth of beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*. These bacteria produce SCFAs such as butyrate, which have anti-inflammatory and anticancer properties (122). Inulin has been shown to reduce the levels of pro-inflammatory cytokines in patients with PCa, potentially lowering the risk of disease progression (79).

Fructooligosaccharides (FOS) selectively stimulate the growth of beneficial bacteria, leading to the increased production of SCFAs and enhanced gut barrier function. This reduces the translocation of harmful bacteria and their metabolites into systemic circulation (116). FOS enhance the function of Tregs and NK cells, which play crucial roles in immune surveillance and cancer cell elimination (118).

Galactooligosaccharides (GOS) promote the growth of beneficial bacteria, particularly *Bifidobacterium* species, which produce SCFAs and other metabolites that modulate the immune system (24). GOS improve gut barrier function and reduce systemic inflammation, potentially enhancing the efficacy of other treatments such as ADT and immunotherapy (79).

Future research should focus on identifying specific prebiotic formulations and doses that most effectively regulate the gut microbiota and improve PCa prognosis. Personalized prebiotic therapy is also very important, according to the different selection of different prebiotics in the patient's gut flora, which may achieve a good effect. Similarly, combining prebiotics with other treatments such as immunotherapy or ADT may enhance their therapeutic effects.

FMT. FMT has emerged as a promising therapeutic strategy for modulating the gut microbiota to overcome treatment resistance in PCa. Previous studies have highlighted the critical role of the gut microbiota in influencing the immune response and tumor progression, suggesting that altering the microbial composition could enhance the efficacy of existing treatments and mitigate resistance mechanisms.

Preclinical studies have begun to elucidate the mechanisms by which FMT may exert antitumor effects. Pernigoni *et al* (15) demonstrated, through metagenomic sequencing, a marked enrichment of bacterial strains (for example, certain *Ruminococcaceae* species) capable of encoding enzymes involved in androgen biosynthesis, such as androstenedione, in the fecal microbiota of men with CRPC. Transplantation of this 'resistance-associated microbiota' into murine models enabled tumors to proliferate despite castration levels of androgens (15). Conversely, antibiotic-mediated microbiota depletion or intervention with specific probiotics restored tumor sensitivity to ADT (15). This provides direct evidence supporting the rationale for using FMT to replace a 'resistant' microbiota. Further research indicates that combinations of specific compounds, such as icaritin and curcumol, can inhibit PCa progression by modulating the gut microbiota-enriching beneficial taxa, which in turn suppresses DNA methyltransferase 1 expression and activates $CD8^+$ T cell-mediated antitumor immunity (123). This suggests that FMT may exert synergistic effects through epigenetic modulation and immune remodeling. FMT offers a comprehensive and direct approach to microbiota modulation compared with other interventions targeting the gut microbiota. Probiotics introduce specific beneficial bacteria, but may not address overall dysbiosis as effectively as FMT (124). Additionally, FMT has the potential to influence a broader range of microbial species and their interactions, which are essential for restoring a balanced microbiota ecosystem. By contrast, dietary interventions, although effective in some cases, may take longer to achieve notable changes in microbiota composition (79).

Despite the potential of FMT, its clinical translation remains hindered by multiple obstacles. The foremost challenge lies in inter-individual variability and the consequent lack of reproducibility. Host dietary habits and genetic background may influence the colonization efficacy of

FMT, leading to divergent therapeutic outcomes even when the same donor microbiota is transplanted into different recipients. Second, safety concerns cannot be overlooked. If donor screening for FMT is not rigorous, transplantation of microbiota containing an overabundance of SCFAs-producing bacteria or harboring pro-tumorigenic functional genes could paradoxically exacerbate disease progression. Furthermore, FMT in cancer patients carries the inherent risk of introducing opportunistic pathogens, particularly in immunocompromised individuals with advanced disease. Finally, regulatory and standardization barriers impede clinical implementation. Currently, the application of FMT in oncology lacks unified criteria for donor selection, standardized protocols for fecal material preparation, and consensus on administration routes and dosages (125). Moreover, regulatory policies vary considerably across countries and remain ambiguous, hindering the conduct of large-scale clinical studies (126).

An ongoing FMT clinical trial (NCT05273255) being conducted at the University Hospital Zurich (Zurich, Switzerland), encompassing multiple solid tumors including PCa, aims to restore treatment sensitivity in recipients by altering their gut microbiota, thereby identifying specific microbial strains that could be utilized for future personalized therapies.

In summary, FMT, as a gut microbiota-targeted intervention strategy, holds promise for reversing treatment resistance in PCa. Future research should prioritize: i) Validating its efficacy and safety through multicenter clinical trials; ii) integrating metagenomic and metabolomic approaches to develop functionally defined synthetic microbial consortia as alternatives to whole fecal transplantation, thereby enhancing therapeutic reproducibility; and iii) elucidating the complex microbiota-host-tumor interplay to establish a foundation for precision FMT-based therapies.

6. Challenges and future perspectives

Despite growing evidence highlighting the critical role of gut microbiota in PCa treatment resistance, several challenges remain in translating these findings into clinical practice. Addressing these challenges and exploring innovative strategies are essential for advancing our understanding and improving patient outcomes.

Complexity of the gut microbiota. Gut microbiota is an incredibly complex ecosystem, with thousands of microbial species and their metabolites interacting in ways that are not yet fully understood. This complexity makes it difficult to pinpoint the specific microbial signatures or pathways that drive treatment resistance in PCa. While studies have identified certain bacterial taxa associated with resistance to ADT and immunotherapy, the mechanisms by which these bacteria exert their effects remain unclear. Future research should focus on high-resolution microbiome analyses, integrating metagenomics, metatranscriptomics and metabolomics, to unravel the intricate interactions between the gut microbiota and PCa.

Clinical translation. Translating microbiome research from the laboratory to the clinic has several challenges. One major issue is the lack of standardized protocols for microbiome analysis and intervention. The preparation and administration of FMT have not yet been standardized, and rigorous clinical trials are needed to establish its safety and efficacy in PCa. Additionally, regulatory hurdles and ethical considerations regarding the use of live microbial therapies must be addressed. Collaborative efforts among researchers, clinicians and regulatory bodies are essential to develop guidelines and frameworks for the safe and effective use of microbiome-based therapies.

Immune and metabolic interactions. Gut microbiota influences PCa through multiple pathways, including immune modulation and metabolic alterations. However, the precise mechanisms by which these pathways interact to drive treatment resistance remain unclear. For example, while certain gut bacteria can enhance the efficacy of immune checkpoint inhibitors by promoting T cell infiltration, others may produce metabolites that suppress antitumor immunity. Understanding these complex interactions will require interdisciplinary research combining immunology, microbiology and bioinformatics. Developing combination therapies that target both the microbiota and the tumor microenvironment may offer a more effective approach to overcoming resistance.

Longitudinal studies and biomarker development. Most current studies on gut microbiota and PCa are cross-sectional, providing snapshots of the microbiota at a single time point. Longitudinal studies are needed to track changes in microbiota over time and to correlate these changes with treatment response and disease progression. Additionally, robust biomarkers that can predict treatment resistance and monitor therapeutic efficacy are needed. Metabolomic and proteomic approaches may help identify biomarkers that can guide clinical decision making and improve patient outcomes.

Novel therapeutic approaches. Emerging therapeutic strategies, such as probiotics, prebiotics and synthetic microbiota, hold promise for modulating gut microbiota to overcome treatment resistance. Further research is required to identify the most effective strains and formulations. Although certain probiotic strains have shown potential benefits in modulating the immune system and reducing inflammation, their long-term effects and interactions with other treatments remain unclear. Similarly, prebiotics and synthetic microbiota offer innovative approaches; however, their mechanisms of action and optimal dosing need to be further researched.

7. Conclusion

Gut microbiota and their metabolites represent a hidden but critical factor driving the formation of treatment resistance in advanced PCa. Metabolites such as SCFAs, TMAO and LPC are deeply involved in the evolution of resistance to ADT, chemotherapy and immunotherapy through the regulation of AR signaling, drug efflux and immune evasion. Future research must shift from ‘descriptive association’ to ‘mechanistic intervention’, aiming to target the gut microbiota-metabolite network and thereby establish a new therapeutic paradigm that improves upon the traditional tumor-centric view.

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Availability of data and materials

Not applicable.

Authors' contributions

JS, YX, HS and ZZ were responsible for the conception of this study. JS, YX, ZZ and HS were responsible for literature retrieval, screening and evaluation. JS, HC, PY, YuL, GZ, YaL, AT and JC were involved in the creation of the images and the language editing of this article. JS, HC and PY were mainly responsible for the writing of the article. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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