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EDITED BY  
Beatrice Aramini,  
University of Bologna, Italy

REVIEWED BY  
Sandra Donnini,  
University of Siena, Italy  
Collene Jeter,  
University of Texas MD Anderson  
Cancer Center, United States

\*CORRESPONDENCE  
Siyuan Xia  
xiasy@sustech.edu.cn  
Baotong Zhang  
zhangbt@sustech.edu.cn

†These authors have contributed  
equally to this work

SPECIALTY SECTION  
This article was submitted to  
Cancer Molecular Targets  
and Therapeutics,  
a section of the journal  
Frontiers in Oncology

RECEIVED 24 August 2022  
ACCEPTED 26 September 2022  
PUBLISHED 10 October 2022

CITATION  
Ma M, He W, Zhao K, Xue L, Xia S and  
Zhang B (2022) Targeting aldehyde  
dehydrogenase for prostate  
cancer therapies.  
*Front. Oncol.* 12:1006340.  
doi: 10.3389/fonc.2022.1006340

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# Targeting aldehyde dehydrogenase for prostate cancer therapies

Miao Ma<sup>†</sup>, Wenyu He<sup>†</sup>, Keyu Zhao<sup>†</sup>, Linyuan Xue<sup>†</sup>,  
Siyuan Xia\* and Baotong Zhang\*

Department of Human Cell Biology and Genetics, School of Medicine, Southern University of Science and Technology, Shenzhen, China

Prostate cancer (PCa) is the most common cancer in men in the United States. About 10 – 20% of PCa progress to castration-resistant PCa (CRPC), which is accompanied by metastasis and therapeutic resistance. Aldehyde dehydrogenase (ALDH) is famous as a marker of cancer stem-like cells in different cancer types, including PCa. Generally, ALDHs catalyze aldehyde oxidation into less toxic carboxylic acids and give cancers a survival advantage by reducing oxidative stress caused by aldehyde accumulation. In PCa, the expression of ALDHs is associated with a higher tumor stage and more lymph node metastasis. Functionally, increased ALDH activity makes PCa cells gain more capabilities in self-renewal and metastasis and reduces the sensitivity to castration and radiotherapy. Therefore, it is promising to target ALDH or ALDH<sup>high</sup> cells to eradicate PCa. However, challenges remain in moving the ALDH inhibitors to PCa therapy, potentially due to the toxicity of pan-ALDH inhibitors, the redundancy of ALDH isoforms, and the lack of explicit understanding of the metabolic signaling transduction details. For targeting PCa stem-like cells (PCSCs), different regulators have been revealed in ALDH<sup>high</sup> cells to control cell proliferation and tumorigenicity. ALDH rewires essential signaling transduction in PCa cells. It has been shown that ALDHs produce retinoic acid (RA), bind with androgen, and modulate diverse signaling. This review summarizes and discusses the pathways directly modulated by ALDHs, the crucial regulators that control the activities of ALDH<sup>high</sup> PCSCs, and the recent progress of ALDH targeted therapies in PCa. These efforts will provide insight into improving ALDH-targeted treatment.

## KEYWORDS

prostate cancer, aldehyde dehydrogenase, targeted therapy, drug resistance, cancer stem-like cells (CSCs), signaling transduction

## Introduction

Human prostate cancer (PCa) is the most common cancer and the second leading cause of death in men in the United States. There will be 268,490 new cases and 34,500 deaths from PCa in the United States in 2022, with PCa alone accounting for 27% of all cancer diagnoses (1). Although many new advances in research on PCa, the underlying molecular mechanism is not fully understood. Generally, localized PCa can be removed by radiation therapy or radical prostatectomy. Androgen deprivation therapy is effective as androgen receptor signaling is a dominant pathway that fuels PCa progression (2–4). About 10 – 20% PCa progresses to its advanced stage, castration-resistant prostate cancer (CRPC) (5–7). Most CRPC typically gains capabilities in metastasis and resistance to systematic therapeutics and thus is lethal to the patients (8, 9). Currently, PARP inhibitors are the only FDA-approved targeted therapy for PCa, and other effective drug targets are under development.

Heterogeneity is crucial to the sensitivity of treatment for PCa, and emerging evidence has shown that there are subsets of PCa cells with stem cell properties in the tumor microenvironment (TME) (10). These prostate cancer stem cells (PCSCs) are responsible for PCa initiation, progression, therapy resistance, and metastasis (11–16). In addition, PCSCs have the characteristics of self-renewal and resistance to radiation or chemotherapy (13, 14, 16, 17), and thus are effective targets for PCa treatment potentially (11, 16, 18). For instance, retinoic acid was used in clinical trials to drive the differentiation of PCSCs<sup>80</sup>.

Aldehyde dehydrogenase (ALDH) is famous as a marker of cancer stem cells in different cancer types, including PCa (19). Generally, the ALDHs are a superfamily with 19 different isoforms in humans and catalyze aldehyde oxidation into less toxic carboxylic acids (18). The expression of ALDH is elevated in PCSCs. It has been shown that ALDH<sup>high</sup>CD44<sup>+</sup> PCa cells and the corresponding ALDH<sup>low</sup>CD44<sup>-</sup> PCa cells manifest as PCSCs and non-PCSCs (20). A recent review by Dr. Jakob Püschel et al. summarized the roles of different members in ALDH superfamily in PCSCs detailly (18). Among them, ALDH1A1 and ALDH3A1 are the most reported because they play a critical role in maintaining PCSC stemness (18, 21, 22). On the other hand, Dr. Saketh S. Dinavahi et al. give us a detailed review of the latest progress on ALDH inhibitors in cancer therapy (23). Several efforts have been made to understand particular signaling transduction and metabolic pathways in ALDH<sup>high</sup> cells. Moreover, ALDH is more than a marker of cancer stem-like cells, it also directly regulates diverse signaling pathways. This review will focus on the ALDH directly involved signaling pathways, the regulators of ALDH<sup>high</sup> PCSCs, and the potential strategies to overcome the limitations of ALDH-targeted therapy in PCa.

## ALDH-associated metabolism and convergence on signaling pathways

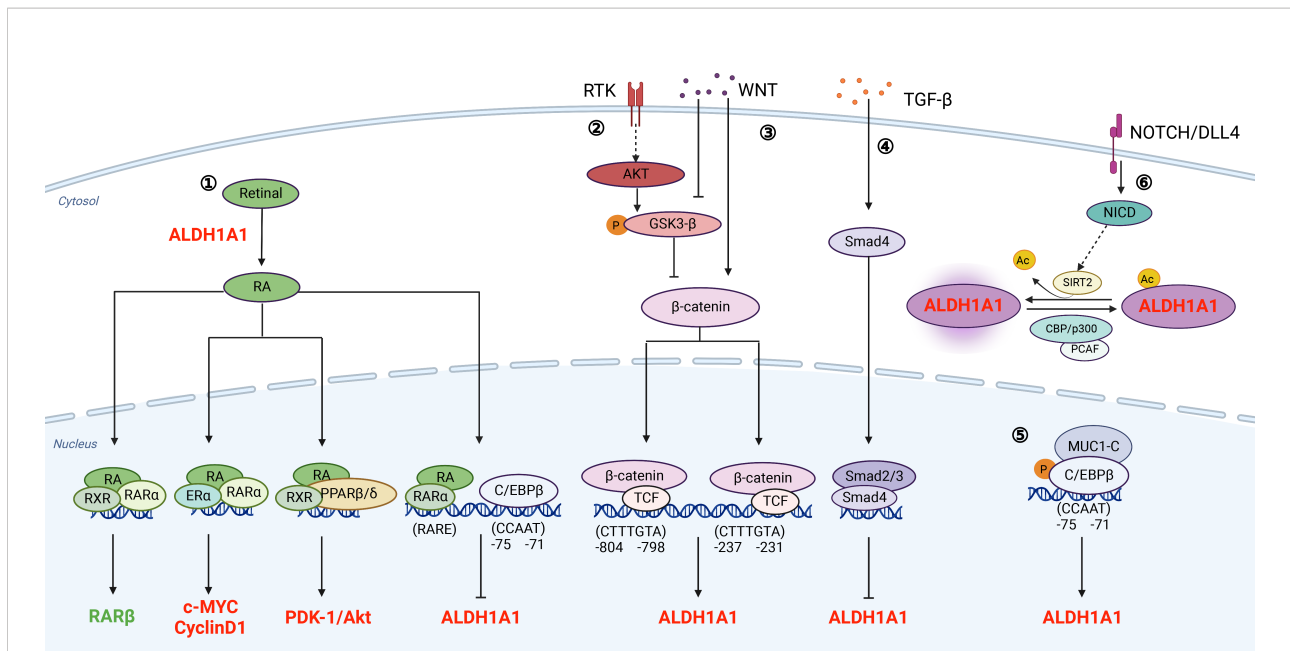
ALDHs typically catalyze aldehyde oxidation into less toxic carboxylic acids (18). Nevertheless, ALDHs are not only biomarkers of cancer stem-like cells but also directly participate into signaling transduction which regulates biological activities of cancer cells. Herein, we summarize the well-recognized pathways involving ALDHs directly (Figure 1).

### Retinoic acid (RA)

Retinol (vitamin A) absorbed by cells is oxidized to retinal, which is further oxidized to RA in a reaction catalyzed mainly by ALDH1A1, ALDH1A2, and ALDH1A3 (24, 25). The metabolized RA product includes all-trans RA (ATRA), 9-cis RA, and 13-cis RA. Among these three forms, ALDH1 has higher affinity for ATRA and 9-cis RA, especially ALDH1A1 (19, 26). Canonically, RA suppresses tumor progression by binding to its nuclear receptors (RAR $\alpha$  or RXR) and causes loss of stem cell markers, differentiation, cell cycle arrest, and morphology change (27). As a feedback loop, RA binds to RAR $\alpha$  to inhibit ALDH1A1 through decreasing C/EBP $\beta$  (28, 29). On the other hand, RA has non-canonical pathways to promote tumor growth. RARs and RXRs form heterodimers with other receptors, such as estrogen receptor- $\alpha$  (ER $\alpha$ ) and peroxisome proliferator-activated receptors (PPAR $\beta/\delta$ ) (30, 31). The heterodimers of RXRs and ER $\alpha$  induce c-myc and cyclin D1, which promote tumor growth and inhibits apoptosis (22, 32). In addition, RXRs and PPAR $\beta/\delta$  form a dimer to upregulate pro-survival genes, including PDK1/Akt (19, 30, 33, 34). Thus, ALDH-mediated conversion of retinol to RA metabolites indirectly promotes prostate tumorigenesis and disease progression by converging on survival and tumor-promoting proliferative signaling pathways, such as Myc and PDK1/Akt1.

### WNT/ $\beta$ -catenin

ALDH1 was reported to be regulated by Wnt/ $\beta$ -catenin signaling in breast cancer (35), ovarian cancer (36), and PCa (37, 38). Typically,  $\beta$ -catenin degradation, induced by tankyrase inhibitor XAV939 or its siRNAs, decreases ALDH1A1 expression. Further biochemical analyses reveal that  $\beta$ -catenin/TCF transcriptional complex binds to the ALDH1A1 promoter *via* two consensus  $\beta$ -catenin/TCF recognition sites (37, 38). Therefore, inhibition of WNT signaling diminishes ALDH<sup>high</sup> population and induces radiosensitization in PCa cells (39).



**FIGURE 1**  
 Signaling pathways that associate with ALDHs directly. ① RA signaling pathway: ALDHs oxidize retinal to generate RA. Meanwhile, the transcription of ALDH is also regulated by RA. As a feedback loop, increased levels of ALDH promote the synthesis of RA; ② and ③ PI3K/AKT pathway and WNT signaling pathway regulate the transcription of ALDH through β-catenin; ④ TGF-β signaling pathway: TGF-β inhibits the transcription of ALDH through Smad4; ⑤ MUC1-C pathway: The protein complex of MUC1-C and C/EBPβ binds to the promoter of ALDH and promotes its transcription; ⑥ NOTCH/DLL4 pathway: Notch signaling promotes ALDH activity by inducing SIRT2 and triggering ALDH1A1 deacetylation. The regulators in red refer to those promoting PCSCs, and the regulators in green refer to those inhibiting PCSCs. This figure is generated by BioRender with an agreement number of QR24HA6NER.

## TGF-β/Smad4

TGF-β/Smad4 pathway suppresses early tumor growth and promotes chemoresistance and bone metastasis in PCa (40–42). Furthermore, silencing of SMAD4 upregulates the expression of ALDH1A1. Mechanistically, Dr. Hoshino et al. reveal that TGF-β regulates ALDH1A1 mRNA transcription through binding of Smad4 to its regulatory sequence (43). Thus, TGF-β/Smad4 pathway inhibits CSCs by transcriptional suppression of ALDH1A1.

## MUC1

Mucin 1 (MUC1) is a transmembrane protein aberrantly overexpressed in PCa (44). An increase in MUC1 gene copy number was observed in 35% of CRPCs (45). Dr. Alam et al. indicate that MUC1 induces ERK activation and thereby phosphorylates C/EBPβ. Furthermore, MUC1 and C/EBPβ form a transcriptional complex on the *ALDH1A1* gene promoter and activate *ALDH1A1* gene transcription (46). Collectively, MUC1 activates ERK and C/EBPβ pathways to increase ALDH<sup>high</sup> CSCs.

## NOTCH

NOTCH controls cell differentiation in normal prostate gland and increased NOTCH signaling promotes PCa progression (47–50). It has been shown that NOTCH signaling regulates ALDH1A1 acetylation, which is negatively associated with ALDH activities. Dr. Zhao et al. indicate that p300/CBP-associated factor and deacetylase sirtuin 2 (SIRT2) are the enzymes responsible for the acetylation and deacetylation of ALDH1A1 K353. NOTCH activation results in SIRT2 induction, which deacetylates and activates ALDH1A1 (51). Therefore, NOTCH induces ALDH1A1 deacetylation to promote CSCs.

## Androgen receptor (AR)

AR signaling is a cornerstone of PCa progression and AR-targeted therapy is one of the most successful targeted therapies in cancer treatment (52, 53). In PCa cell line LNCaP, androgen dihydrotestosterone (DHT) induces ALDH1A3, but not ALDH1A1 and ALDH1A2. Mechanistically, the regulation of DHT on ALDH1A3 is likely due to the typical AR nuclear-translocation cascade (54). ALDH1A3 correlates with AR

signaling pathway and localizes at luminal layers (55). Knockout of ALDH1A3 gradually acquired resistance to androgen deprivation therapy (56), although whether and how PCSCs are involved in this process remains unknown.

## Crucial regulators that maintain ALDH<sup>high</sup> prostate CSCs

ALDH is a marker of cancer stem-like cells in different cancers, including PCa. Cancer stem-like cells are considered as a reservoir of cancer cells that can initiate tumor growth, survive after therapies, reestablish heterogeneous tumors, and thus cause drug resistance and recurrence (57). In addition to the signaling pathways that directly modulate ALDHs, accumulating efforts have been made to disclose prominent regulators in ALDH<sup>high</sup> PCSCs. Here, we will endeavor to review recent findings regarding the pathways that regulate the maintenance of ALDH<sup>high</sup> CSCs in PCa. Furthermore, applying the ALDH inhibitors for PCa therapies is potentially limited by the toxicity of pan-ALDH inhibitors and the redundancy of ALDH isoforms. Understanding crucial pathways that control the stemness of ALDH<sup>high</sup> PCa cells would provide a valuable choice for developing novel therapeutic strategies for targeting PCSCs. We therefore summarize recent findings below and itemize key regulators in Table 1.

### WNT/ $\beta$ -catenin

Activation of the WNT/ $\beta$ -catenin pathway enhances ALDH transcription, and disruption of WNT signaling diminishes

ALDH<sup>high</sup> PCSCs (39). Furthermore, Period circadian regulator 3 (PER3), a circadian rhythm gene, suppresses the WNT/ $\beta$ -catenin pathway *via* decreasing BMAL1 expression. Therefore, PER3 overexpression in ALDH<sup>high</sup> cells significantly suppresses sphere formation and tumorigenicity (20). GSK3 $\beta$  phosphorylates  $\beta$ -catenin to reduce its nuclear localization. AR79, an inhibitor of GSK3 $\beta$ , increases the proportion of ALDH<sup>high</sup> CD133+ cancer stem cell-like in PCa cell lines, promoting tumor growth and tumor-induced bone remodeling (58). Salinomycin, an antibiotic that selectively kills cancer stem-like cells, is also found to suppress WNT/ $\beta$ -catenin pathway and trigger more apoptosis in ALDH<sup>high</sup> cells in PCa (59).

### BRCA1 and EZH2

BRCA1 negatively regulates PRC2-dependent H3K27 methylation, which involves multiple cellular processes, including DNA repair, transcriptional regulation, and DNA damage responses (66). EZH2, a core member of PRC2, promotes cancer progression by histone methylation-driven dedifferentiation (67). Silence of EZH2 and BRCA1 leads to a significant increase in the ALDH<sup>high</sup> cell population, and knockdown of both genes has a cumulative effect on ALDH activity, suggesting that BRCA1 and EZH2 cooperate in the regulation of PCSCs phenotype (60).

### Glutaminase (GLS)

PCSCs are radioresistant and have a high glutamine demand. GLS-driven glutamine catabolism provides energy

TABLE 1 Crucial signaling pathways that regulate ALDH+ cells in prostate cancer.

Involved signaling pathways	ALDH+ cells	Key genes	Gene functions in PCSC stemness	Findings in PCa research	References
WNT/ $\beta$ -Catenin	PC-3; DU 145	PER3	Suppress	Expression decreased in PCa	(20)
WNT/ $\beta$ -Catenin	C4-2B; DU 145	GSK3 $\beta$	Suppress	Suppress PCa growth in soft tissue and bone	(58)
WNT/ $\beta$ -Catenin	PC-3	$\beta$ -Catenin	Enhance	Suppress apoptosis in ALDH+ cells	(59)
EZH2/BRCA1	DU 145-RR; LNCaP-RR	BRCA1; EZH2	Suppress	Genetic silencing of EZH2 and BRCA1 enhances ALDH1A1 and ALDH1A3 activity	(60)
Glutamine/ $\alpha$ -KG-	DU 145-RR; LNCaP-RR	Glutaminase	Enhance	Maintenance of the redox state, and enhanced radioresistance	(61)
SLUG/ TWIST1/SOX2	PC-3	TMPRSS4	Enhance	Promote cancer stem-like properties	(16)
PI3K/AKT	DU 145; LNCaP	HOXB9	Enhance	Alter the expression of a panel of CSC growth- and invasion/bone metastasis-related genes <i>via</i> TGF- $\beta$ signaling	(62)
$\alpha_v$ and $\alpha_6$ -integrins	PC-3M-Pro4Luc2; C4-2B	miR-25	Suppress	Expression in PCSCs is low/absent	(63)
Steroids/MMP9	PC-3M	cyclin A1/ Aromatase	Enhance	Provide a suitable micro environment for PCSCs to establish bone metastatic growth	(64)
IL-6/STAT3	DU 145; LNCaP	STAT3	Enhance	Maintain the proportion of PCSCs and the expression of ALDH1A1	(65)

and maintains the redox state in cancer cells. Glutamine catabolism contributes to the maintenance of PCSCs by a  $\alpha$ -KG dependent chromatin-modifying dioxygenase. Therefore, lack of glutamine decreases ALDH<sup>high</sup> PCSCs and suppresses tumor formation in the xenograft mouse model (61).

## TMPRSS4

Transmembrane serine protease 4 (TMPRSS4) is a cell surface anchored serine protease that promotes resistance to anoikis, tumor sphere formation, and therapeutic resistance of PCa cells. TMPRSS4-induced invasive and metastatic phenotypes are accompanied by the upregulation of stemness factors, including SOX2, BMI1, and CD133. Importantly, TMPRSS4 increases ALDH<sup>high</sup> PCSCs. Mechanistically, TMPRSS4 upregulates SLUG and TWIST1, which in turn increases the expression level of SOX2, a crucial stemness factor maintaining PCSCs (16).

## Human homeobox B9 (HOXB9)

HOXB9 is a transcription factor that is upregulated in PCa and found to be essential for PCa metastasis (68). HOXB9 alters cancer stem cell markers, such as CD44, and affects chemosensitivity and metastatic ability of ALDH<sup>high</sup>/CD44+/CXCR4+/CD24+ PCSCs (62). Mechanistically, silencing of HOXB9 inhibits PCa cell proliferation and migration by suppressing PI3K/AKT pathways (68).

## miR-25

miR-25 expression is low or absent in PCSCs and increases during their differentiation into cells with a luminal epithelial phenotype. Furthermore, overexpression of miR-25 suppresses the migration and metastasis of ALDH<sup>high</sup> cells by affecting the invasive cytoskeleton *via* directly targeting  $\alpha_v$ - and  $\alpha_6$  integrins (63).

## Cyclin A1

Cyclin A1 is an important cell cycle regulator that is elevated in PCa (69). Interestingly, the expression of cyclin A1 is higher in metastatic lesions, such as lymph nodes, lung, and bone. Overexpression of cyclin A1 in ALDH<sup>high</sup> PCa cells enhances bone metastatic growth and their self-renewal capability, suggesting that cyclin A1 is a key regulator of ALDH<sup>high</sup> PCSCs. Furthermore, the expression of cyclin A1 is correlated with aromatase CYP19A1, which regulates androgen to estrogen

metabolism. Estrogen and MMP9 facilitate the growth of ALDH<sup>high</sup> PCSCs (64).

## Candidate ALDH targeted therapies in PCa

The crucial roles of ALDH validate that it is promising to target ALDH or ALDH<sup>high</sup> cells to eradicate PCa. Recent years, multiple ALDH inhibitors have been developed for cancer therapy. Dr. Dinavahi et al. have made an elaborated review of ALDH inhibitors for cancer therapy (23). Herein, we focus on the ALDH inhibitors in PCa for their recent progress (Supplementary Table 1).

### 4-(Diethylamino)benzaldehyde (DEAB)

DEAB is a non-isoform-specific inhibitor commonly used for ALDH inhibitor in aldefluor assays (70). DEAB is a competitive inhibitor of ALDH1A1, 1A3, 1B1, and 5A1. Additionally, DEAB has been unraveled to irreversibly inactivates ALDH7A1 (71) and ALDH1A2 through forming a stable covalent adduct (72). In PCa, DEAB inhibits ALDH activity and ALDH<sup>high</sup> population and decreases sphere-forming capability (73). However, the efficacy of DEAB was impeded by variations in ALDH expression. In addition, the lack of evidence in animal experiments also limits DEAB use for PCa treatment (74).

### DIMATE

DIMATE is an irreversible and competitive inhibitor of ALDH 1 and 3, suppressing ALDH activity and promoting apoptosis. In addition, the inhibition is reversibly for normal prostate cells but irreversible for PCa cells (75). Therefore, further animal and clinical trials are worth taking.

### Imidazo[1,2-a] pyridine derivatives

Imidazo[1,2-a] pyridine derivatives 3b and 6-(4-fluorophenyl)-2-phenylimidazo [1,2-a] pyridine inhibit ALDH1A1 and ALDH1A3 expression and suppress cell proliferation in different PCa cell lines. Derivative 3d more selectively inhibits colony formation of PC-3 PCa cells than PNT2-C2 or BPH-1 normal prostate epithelial cells (76, 77).

### Retinoic acid (RA)

A few evidence has proved RA as a potential therapy for PCa. Early in 2005, RA was found to reduce the activity of



ALDH1A1 and ALDH3A1 and cause cytotoxicity (78). In addition, ALDH1A2, the enzyme responsible for RA synthesis, is reduced in PCa and associated with a shorter relapse-free survival (79). Furthermore, RA inhibits the proliferation and neuroendocrine phenotype of PCa cells and promote apoptosis in TRAMP model (80). However, a phase II trial of all trans retinoic acid (ATRA, a form of RA as we mentioned above) in hormone refractory PCa showed that patients did not respond to ATRA. This failure may be due to the low efficiency of drug delivery to tumor tissue or the rapid degradation of ATRA (81, 82). Accordingly, optimizing the delivery strategy of RA, such as the use of solid lipid nanoparticles, improves the efficiency of RA in tumor tissue (83). Moreover, RA affects multiple cellular pathways, which brings great challenges for RA use in clinical treatment. Currently, combined ATRA with 5-azacitidine (5-AZA) leads to an ongoing phase II clinical trial in PCa with PSA-only recurrence after local treatment (NCT03572387).

## Disulfiram (DSF)

DSF is well established as an alcohol abstinence drug by inhibiting acetaldehyde dehydrogenase (84). In addition, DSF also inhibits DNA topoisomerases (85) and DNA methylation (86), thus alleviating the proliferation of PCa cells. Strikingly, DSF selectively inhibits the growth of PCa cells at nanomolar concentrations compared to normal PrECs. However, DSF failed to completely block tumor growth of VCaP xenografts (86, 87) and change per-cell PSA level in a clinical trial (NCT01118741). Fortunately, the antiproliferation capability of DSF can be enhanced by copper or zinc in breast cancer and melanoma (88, 89). Accordingly, DSF/copper has been widely used to treat various cancers, including PCa. A phase Ib study with intravenous copper administration and oral DSF was performed in metastatic castration-resistant PCa. This clinical trial was terminated because oral administration of DSF showed poor stability and fast metabolism (NCT02963051) (90).

## Discussion

Accumulating studies have shown that ALDH is a promising stem cell marker for various CSCs, including PCa (91, 92). ALDH<sup>high</sup> PCa cells have higher capabilities in self-renewal, clonogenicity and metastasis (12). ALDHs decrease oxidative stress for self-protection (93) and associate with less sensibility of tumor cells to chemotherapy and radiotherapy (94, 95). Especially, a high ALDH1A1 expression and ALDH3A1 is positively associated with a poor prognosis of PCa (21, 96). ALDH expression is regulated at the transcriptional level by RA signaling, WNT/ $\beta$ -catenin, and TGF- $\beta$ . In addition, ALDH activity is modulated by NOTCH signaling *via* ALDH1A1

acetylation at K353 (Figure 1). Moreover, ALDHs are markers of cancer stem-like cells and regulate signaling transduction, such as canonical RA signaling, c-MYC, cyclinD1 and PDK1/AKT (Figure 1).

Compounds targeting ALDHs directly are still limited for PCa therapy (Supplementary Table 1). Collectively, potential reasons include: (1) toxicity of pan-ALDH inhibitors (23, 97, 98); (2) redundancy of ALDH isoforms (23, 99, 100); (3) Ineffective delivery method (81, 82, 101); (4) the complexity of RA signaling (102). As we summarized in Figure 1, RA has canonical and noncanonical pathways to suppress or promote tumor growth. Different concentrations of RA would have opposite functions in tumor progression (103). Therefore, targeting indispensable regulators in ALDH<sup>high</sup> population instead would provide valuable options for eradicating PCSCs. We thus summarize crucial genes that control the bioactivities of ALDH<sup>high</sup> PCa cells in Table 1. Some studies have tested some compounds focusing on WNT/ $\beta$ -catenin and STAT3 pathways, two prominent pathways that are essential for ALDH<sup>high</sup> PCSCs (Supplementary Table 1). Galiellalactone (GL) inhibits the binding of activated STAT3 to DNA, reduces ALDH<sup>high</sup> PCa population, downregulates ALDH1A1, and sensitizes chemotherapy (65, 104). Stattic binds to the SH2 domain of STAT3, inhibits its phosphorylation at Y705 (105), and reduces ALDH<sup>high</sup> population in PC3M-1E8 and clinical PCa samples. Silibinin inhibits PCa cell proliferation and invasion by targeting STAT3 and WNT signaling (106). A clinical trial of Silibinin was performed, although no formal PSA response was detected and little silybin was found in PCa tissues (101). XAV-939, an effective tankyrase inhibitor antagonizing Wnt/ $\beta$ -catenin signaling (107), significantly reduces ALDH<sup>high</sup> population, suppresses colonization and migration capacity of PCa cells, and sensitizes PCa cells to radiotherapy (95).

Given CRPC is the lethal stage in PCa development, we ask if targeting ALDH could be effective for CRPC. Strikingly, STAT3 inhibitor Galiellalactone selectively promotes apoptosis in androgen-insensitive DU145 and PC-3 cells, but not in androgen-sensitive LNCaP cells, providing a potential approach for CRPC treatment (108). Therefore, targeting crucial regulators to disrupt the activity of ALDH<sup>high</sup> population would provide promising strategy for CRPC treatment.

## Author contributions

MM summarized the regulators of ALDH+ prostate cancer cells; WH recapitulated the application and limitations for ALDH targeted therapies. KZ listed the signaling pathways regulated by ALDH. LX collected the expression levels of ALDHs in PCa. BZ and SX designed the overall frame, provided guidance, and revised and finalized the manuscript.

All authors contributed to the article and approved the submitted version.

## Funding

This work was supported by grants 2021A1515110051 and 2021A1515110144 from GuangDong Basic and Applied Basic Research Foundation.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.1006340/full#supplementary-material>

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