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REVIEW

Molecular panorama of therapy resistance in prostate cancer: a pre-clinical and bioinformatics analysis for clinical translation

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Abstract

Prostate cancer (PCa) is a malignant disorder of prostate gland being asymptomatic in early stages and high metastatic potential in advanced stages. The chemotherapy and surgical resection have provided favourable prognosis of PCa patients, but advanced and aggressive forms of PCa including CRPC and AVPC lack response to therapy properly, and therefore, prognosis of patients is deteriorated. At the advanced stages, PCa cells do not respond to chemotherapy and radiotherapy in a satisfactory level, and therefore, therapy resistance is emerged. Molecular profile analysis of PCa cells reveals the apoptosis suppression, pro-survival autophagy induction, and EMT induction as factors in escalating malignant of cancer cells and development of therapy resistance. The dysregulation in molecular profile of PCa including upregulation of STAT3 and PI3K/Akt, downregulation of STAT3, and aberrant expression of non-coding RNAs are determining factor for response of cancer cells to chemotherapy. Because of prevalence of drug resistance in PCa, combination therapy including co-utilization of anti-cancer drugs and nanotherapeutic approaches has been suggested in PCa therapy. As a result of increase in DNA damage repair, PCa cells induce radioresistance and RelB overexpression prevents irradiation-mediated cell death. Similar to chemotherapy, nanomaterials are promising for promoting radiosensitivity through delivery of cargo, improving accumulation in PCa cells, and targeting survival-related pathways. In respect to emergence of immunotherapy as a new tool in PCa suppression, tumour cells are able to increase PD-L1 expression and inactivate NK cells in mediating immune evasion. The bioinformatics analysis for evaluation of drug resistance-related genes has been performed.

Keywords Prostate cancer · Chemoresistance · Radioresistance · Immune evasion · Bioinformatics

Highlights
- The drug resistance development in prostate cancer (PCa) has resulted in therapy failure in patients.
- Abnormal biological mechanisms including apoptosis, autophagy, and EMT mediate chemoresistance.
- Dysregulation of molecular pathways induces both chemoresistance and radioresistance in PCa.
- Pharmacological compounds and nanostructures increase therapy sensitivity.
- Immune evasion compromises function of immunotherapy in PCa suppression.

1 Introduction

A significant health concern in the world results from development of prostate cancer (PCa) in males that in 2020, this malignancy caused approximately 400,000 deaths in patients that is in warning stage [1]. Due to malignant transformation of cells present in the prostate gland, the development

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of PCa occurs, and when disease is at first and localized stage, the tumour cells only proliferate in the tissue, while conditions are different at advanced stages with metastasis into surrounding tissue and disseminate in the body [2]. The prognosis of PCa appears to be promising and desirable at early stages with intervention of chemotherapy and surgical resection [3]. However, the prognosis is deteriorated; when PCa cells begin their spread in the body and after dissemination, the ability of aforementioned therapeutic approaches is diminished significantly. Among various factors, the survival and proliferation of malignant PCa cells depend on androgen signalling, and therefore, androgen-deprivation therapy (ADT) has been rationally developed for therapy of PCa [4]. In spite of bringing hope in the treatment of cancer patients, after PCa therapy with ADT for 2–3 years, castration-resistant prostate cancer (CRPC) is emerged that compromises the efficacy of ADT and results in resistance to this strategy [4, 5]. The CRPC is defined as a condition in which androgen signalling is stimulated in spite of androgen deprivation [6]. However, CRPC is not the end of PCa progression, and after abnormal progression of CRPC, it is developed into a new form that is known as aggressive variant prostate cancer (AVPC) that its most prominent characteristic is high metastatic potential [7]. The AVPC is also known as neuroendocrine prostate cancer (NEPC), since neuroendocrine markers display high expression in this subtype [7]. The treatment of AVPC is more difficult than CRPC, since CRPC still requires androgen receptor (AR) signalling for malignant progression, while alternative survival and proliferative pathways are stimulated in AVPC, and therefore, current ADT-based interventions are not applicable for AVPC, and therefore, it is completely lethal with average survival of less than 1 year [8]. Figure 1 depicts the stages of PCa with short description of PCa pathogenesis.

One of the prominent feature of PCa cells is the chromatin remodelling and the dysregulation of related pathways. Along with progression of PCa stem cells, the MUC1-C plays a significant role in process of tumourigenesis. MUC1-C increases E2F1 expression to upregulate PBAF, BRG1, and esBAF. Then, overexpression of ARID1A and PBRM1 occurs to mediate progression of CSCs. Therefore, the stimulation of chromatin remodelling complex PBAF by MUC1-C can accelerate tumourigenesis [11]. Furthermore, the chromatin remodelling pathways can determine the immune reactions in PCa. The upregulation of MUC1-C can promote BAF, PBAF, and NuRD levels. FBXW7 is suppressed by NuRD to upregulate IFNGR1, while BAF directly increases IFNGR1 expression. Then, upregulation of STAT1 occurs to promote IRF1 levels, mediating immunosuppression [12]. The proteins related to the chromatin remodelling can also enhance the progression and metastasis of PCa. BRG1 as a chromatin remodelling protein has ability of ELOVL3 transactivation in enhancing the invasion and migration of PCa [13]. Interestingly, overexpression of CHD6 in PCa can increase the detachment of nucleosomes from the promoters to stimulate the tumour-promoting factors in PCa [14]. The changes in expression levels of chromatin remodelling ATPase BRG1 and PTEN can affect tumourigenesis and clinical outcome. The upregulation of BRG1 and downregulation of PTEN can cause the poor prognosis in PCa [15].

The accumulation of mutations in PCa progression from early stages that symptoms are not specific to advanced and metastatic stages with clinically detectable symptoms results in changes in biological behaviour of tumour cells. The genomic background of PCa appears to be unstable [16], and most commonly studied germline mutations are *BRCA1* and *BRCA2* genes as tumour-suppressor factor [17–20]. However, molecular profile of PCa is not ended to dysregulation of *BRCA1* and *BRCA2*, thanks to advances in field of biology that has made it possible to highlight the molecular profile of PCa. An integrative analysis has revealed that changes in levels of ASCL1, FOXA2, NKX2-2, POU3F2, and SOX2 can occur in NEPC [21]. More importantly, FOXA1 and Ku70/Ku80 are considered as potential therapeutic targets of ivermectin through integrated analysis for treatment of PCa [22]. Such alterations in genomic landscape of PCa can result in heterogeneous nature and plasticity of tumour cells [23]. More importantly, AR mutations and changes can be observed in 75% of metastatic CRPC patients [24], confirming its function as potential carcinogenic factor. The multi-omics analysis of NSUN2 highlights its upregulation in PCa and its function in unfavourable prognosis of patients [25]. Even the immune system function in PCa and the infiltration of immune cells in the tumour microenvironment (TME) are changed by the molecular landscape [26, 27]. However, the story is beyond simple function of genes in control of PCa progression and epigenetic factors [28] and epigenetic silencing of genes [29] play a vital role of in tumourigenesis process. It is widely accepted that increase in malignancy of tumour cells mediated by genetic and epigenetic factors can result in chemoresistance. Therefore, current review aims to provide a detailed discussion on the function of molecular networks in progression-related chemoresistance in PCa, the interaction of signalling pathways, and the molecular mechanisms regulating drug resistance. This molecular landscape is evaluated for determining response of PCa cells to chemotherapy, radiotherapy, and immunotherapy. Moreover, a bioinformatics analysis is provided to shed more light on the genes involved in therapy resistance in PCa. The current therapeutic approaches including application of combination therapy and nanostructures for impairing tumourigenesis in PCa are discussed.

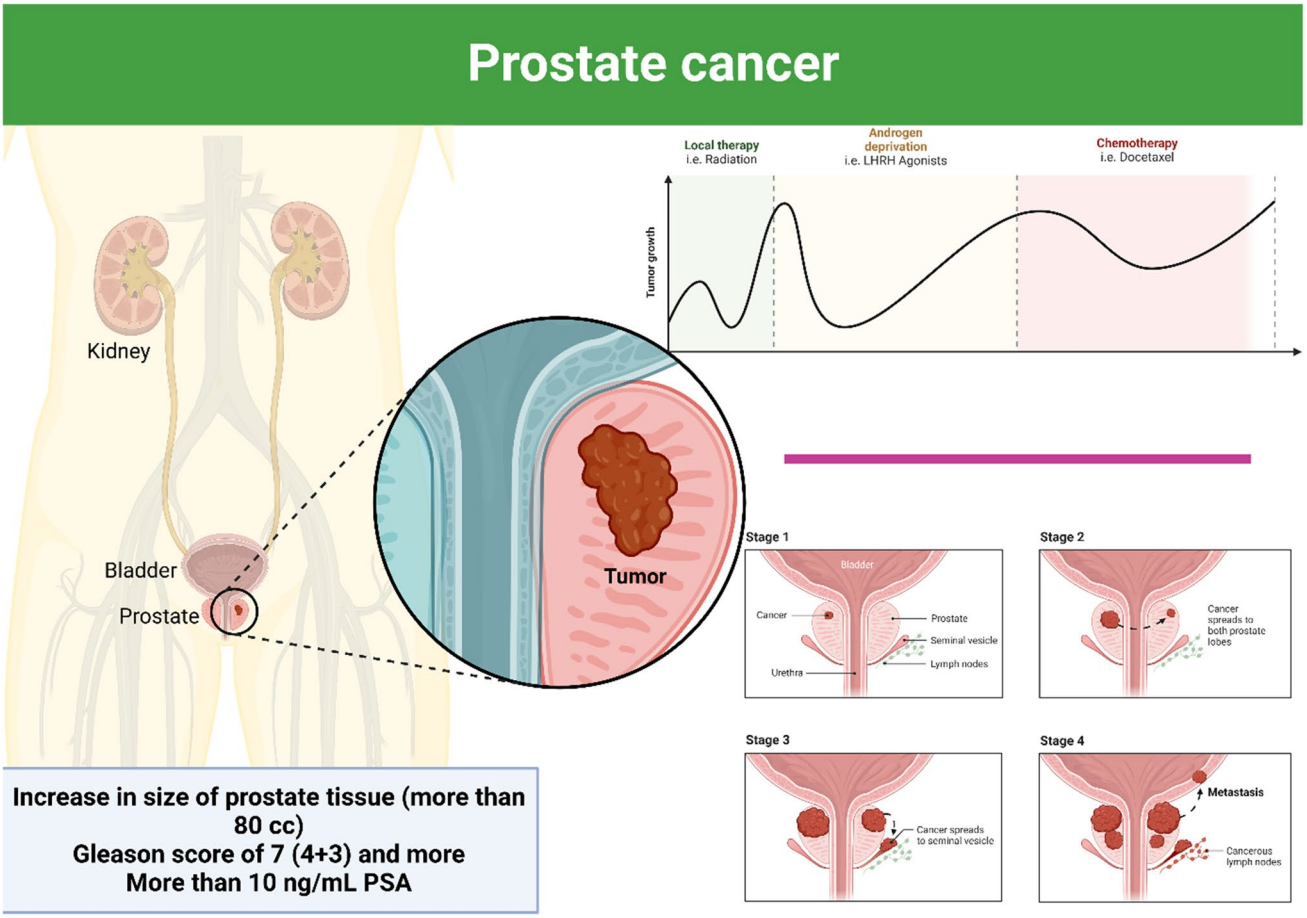


Fig. 1 The prostate gland has been located in the retroperitoneal space of body, and this male-specific gland responds to hormones. The prostate gland has a physical connection with urethra and bladder tissue, and in terms of anatomical view, it is divided into four categories and zones including peripheral zone, central zone, transitional zone, and periurethral zone. In view of histological analysis, prostate gland has a basal layer of epithelial cells that are covered by columnar secretory cells and fibromuscular stroma separates the cells. The growth and viability of cells present in the prostate tissue are controlled by androgens, and prostate atrophy occurs as a result of androgen removal. Three pathological events can occur in prostate tissue including inflammation, hyperplasia, and malignant tumour transformation [9]. After the development of PCa, a number of characteristics are found including increase in size of prostate tissue to more than 80 cc, enhanced level of PSA to more than 10 ng/mL, and Gleason score of 7 (4 + 3) [10]. Radiation is used as a local therapy, and then, it is followed by application of hormone therapy and chemotherapy with docetaxel. Four stages for metastasis of PCa are considered that in stage I, the tumour is localized, and in stage II, cancer cells disseminate in both lobes of tumour tissue. Then, spread of cancer cells to seminal vesicles in stage III occurs and followed by dissemination to surrounding tissues in stage IV

2 Search strategy

The data and studies for the current review were selected from the major databases including PubMed, Google Scholar, and ScienceDirect using the keywords including "prostate cancer," "cancer drug resistance," "prostate cancer + drug resistance," "prostate cancer + radioresistance," "immune evasion + prostate cancer," "hormone resistance + prostate cancer," "pharmacological intervention," and "nanoparticles + prostate cancer." Moreover, the bioinformatics analysis was performed by the GEO database and using the RStudio software.

3 The mechanisms of drug resistance: a biological standpoint

3.1 Cancer mass and growth factors

The curability of a certain cancer mainly depends on its size [30, 31], and the size of tumour is used to determine the prognosis of patients. The risk of metastasis and invasion to surrounding tissues could be escalated with enhancement in size of tumours [32]. Although the correlation between tumour size, curability, and chemotherapy response has not been fully predicted, it is quite obvious that application of

various classes of anti-cancer drugs that individually suppress distinct pathways and cells in the TME can result in full eradication of cancer that has been approved by early mathematical methods including "log kill" hypothesis [33]. This has been shown to be correct for a number of cancers including lymphomas and germ cell cancers, but it is not valid for all cancer types. For better understanding, other kinds of models and hypotheses including Goldie–Coldman hypothesis were published that was informed by seminal microbiology experiments [34, 35] and it is responsible for understanding the relationship between tumour burden and therapy resistance risk. This hypothesis brings into attention that tumour size and mutation rates are two critical factors in determining resistance [34]. Therefore, if a same mutation rate is considered, tumour size can determine resistance to chemotherapy. As a result, this notion has been developed that if therapy regimens with non-cross-resistant probabilities are used, the chance of resistance is lower than when all the treatment strategies are utilized at once. However, such hypothesis has not been applied in clinic, showing that there are still complications and complexities to be revealed [36].

3.2 Heterogeneous nature of cancers

The easiest understanding of the chemoresistance in human cancers is role of tumour heterogeneity [37]. Throughout their progression, genomic changes accumulate in cancer cells that form a spatial and temporal genetic diversity and promote cancer heterogeneity [38]. The evolutionary speed of such heterogeneity is unique, and it can be slow such as mutations related to age, and it can be frequent occurring by APOBEC enzymes. Moreover, such changes can be rapid and quick, similar to what happens by genomic instability [39], chromothripsis [40], and chromosomal instability [41].

3.3 Physical barriers

The distinct feature of TME of cancers is hypoxia that is defined by low oxygenation. The spatial gradients are generated in the tumours that can prevent the normal blood flow in TME, and therefore, a hypoxic condition with tumourigenesis function is created, and moreover, less anti-cancer drugs are reached to tumour site. It may be a question that anti-angiogenic strategies have been applied in cancer therapy and reducing blood flow to cancer site is a therapeutic approach. However, this is not the complete story and there are evidences showing that anti-angiogenic therapies may result in normalization of vascular structure and function [42]. Therefore, chemotherapy drugs and targeted therapy are delivered to tumour site in an appropriate way [43]. That is why tyrosine kinase inhibitors with anti-angiogenic function have been used along with anti-PD-1/PD-L1 therapies in synergistic tumour suppression [44, 45]. Moreover, blood–brain barrier (BBB) is considered as another impediment towards effective cancer chemotherapy that by reducing chemical exposure of brain tumours, the risk of resistance enhances, urging to develop targeted systems for crossing over BBB [46].

3.4 Drug efflux transporters

The drug efflux transporters presence on the surface of cancer cells are connected to the phenomenon of chemoresistance that enhance efflux of chemotherapy drugs from cancer cells. ATP-binding cassette (ABC) transporters have been localized across cell membrane with different structures and have been related to cancer drug resistance [47, 48]. Although there are 49 members of this protein family, only three of them have been under attention and widely analysed including MDR1 (also known as P-glycoprotein (P-gp) or ABCB1), MRP1 (ABCC1), and BCRP (ABCG2) [49]. The first drug transporter that was identified is MDR1, and the glycoprotein is bounded to cell membrane and is low expressed in approximately all tissues with higher expression and activity in epithelial cells with excretory functions including those lining colon, intestine, pancreatic tubules, and bile ducts [50, 51]. The upregulation of MDR1 is found on various tumours, and interestingly, chemotherapy drugs have ability of increasing its expression [52]. As a result, its inhibitors including zosuquidar and tariquidar have been introduced and developed, but their clinical efficacy is comprised. For instance, co-application of tariquidar with anthracycline or taxanes has restricted potential in females with breast cancer at stages III–IV [53].

3.5 Activation and inactivation of chemotherapy drug

Owing to specific changes occurring in drugs, they may be inactivated or their activation is suppressed that is observed in platinum compounds after inactivation by thiol glutathione [54]. Moreover, when there is absence of cellular enzymes, the transformation of 5-flourouracil (5-FU) and methotrexate (MTX) to their active form does not occur [55, 56]. The conversion of capacitabine to 5-FU occurs by function of phosphorylase [57]. Therefore, capacitabine resistance occurs when methylation of gene encoding thymidine phosphorylase occurs [58]. The inactivation of irinotecan is observed by function of UGT1A1, and when DNA methylation of UTG1A1 promoter occurs, it can escalate activity of irinotecan [59, 60].

3.6 Decrease in drug uptake

Although main focus is on the role of dug efflux transporters, there are also evidences showing that decrease in drug

uptake can result in development of chemoresistance in cancers [61]. However, the mechanism of action is similar to drug efflux to decrease accumulation of chemotherapy drug in cancer cells and restrict its potential. A number of anti-cancer drugs including 5-FU, cisplatin (CP), and 8-azaguanine use solute carriers for cancer cell internalization and their cellular uptake may be diminished [62]. In order to solve such problem, it is suggested to use active transport pathways or focus on passive permeability of anti-cancer drug.

3.7 Changes in drug targets

The mutations and abnormal changes in the target of drugs have been considered as another way in the development of resistance to anti-cancer drugs [63]. The Cancer Genome Atlas (TCGA) has detected the mutations of genes in 12 cancer classes [64], and a number of tumour-promoting factors including EGFR, RAS, RAF, and PI3K are considered as most common mutations in tumours. Furthermore, the mutations and changes can result in downregulating or silencing factors including PTEN, Rb, and p16INK4a that are common in human cancers [65]. In addition to changes, mutations and amplifications of genes, such changes in amino acids, can also mediate resistance of tumours to chemotherapy.

3.8 Apoptotic machinery

The aberrant proliferation of tumour cells along with apoptosis suppression can result in development of a condition in which promote tumourigenesis [66]. The alterations in molecular factors such as MYC that participate in regulation of proliferation can also modulate apoptosis. Apoptosis is the final aim of anti-cancer drugs in reducing tumourigenesis, and alterations in apoptotic machinery can lead to development of resistance [67]. Drug resistance has been considered as a result of such defects and abnormal changes in apoptotic machinery, and hence, effective removal of cancer cells depends on caspase-dependent and -independent mechanisms [68]. The anti-apoptotic factors such as Bcl-2 (upregulation) and pro-apoptotic factors such as Bax (downregulation) can be controlled in development of chemoresistance in human cancers [69].

3.9 DNA damage repair

Another major mechanism in the development of chemoresistance is DNA damage repair. In addition to apoptosis, anti-cancer drugs plan in triggering damage into DNA of tumour cells in mediating cell death. However, the stimulation of DNA damage repair mechanisms can induce chemoresistance in human cancers [70]. The anti-cancer drugs stimulate double-strand break (DSB) in tumour cells, and when DNA repair pathways and homologous recombination are stimulated, such activity is reduced or suppressed [71]. The role of DNA damage repair is not certain to a single type of cancer, and it can result in chemoresistance in various tumours including breast tumour [72], hepatocellular carcinoma [73], and ovarian cancer [74]. BMAL1 has been suggested to collaborate with CLOCK in enhancing DNA damage repair and the development of drug resistance [75]. The function of copper is related to increased DNA damage repair through ATOX1 in cancer drug resistance [76].

3.10 Cancer stem cells and drug resistance

Cancer stem cells (CSCs) are a rare population in the tumour colonies that are correlated with the malignant biological features of cancers including drug resistance, radioresistance, cancer recurrence, and capacity of G0 phase arrest in the development of new tumours [77, 78]. The first characterization of CSCs was performed in 1990s in which they were recognized in leukaemia and their isolation occurred through $CD34^+$ and $CD38^-$ surface marker expression [79, 80]. Then, the CSCs were detected in the different solid and haematological tumours and they express a number of surface makers including CD133, nestin, and CD44 [81, 82]. The CSCs have self-renewal capacity and ability of differentiation into several cellular subtypes [83]. The function of CSCs can be modulated by a number of intracellular and extracellular factors, providing new insights and promising targets in cancer therapy [84]. The process of carcinogenesis can be regulated by CSCs in the different tumour classes. The CSC-like properties can be increased in ovarian tumour through function of actin-like protein 6A, and this stimulates unfavourable prognosis [85]. The suppression of AKT/GSK3β/β-catenin axis by MASM can impair the CSC-like features in $EpCAM^+$ cells [86]. Furthermore, the proanthocyanidins have ability of suppressing Wnt/β-catenin axis to impair the CSC features in colorectal tumour [87]. The extracellular vesicles can be derived from CSCs and possess the ability of targeting MHC-II-macrophages and PD^{1+} T cells [88], showing the ability of CSCs in the tumour microenvironment remodelling. The several molecular pathways have ability of regulating CSCs including Notch, Hedgehog, PI3K/Akt, Wnt, MAPK, and JAK/STAT. These related pathways of CSCs can be targeted by the natural products for cancer therapy and impairing tumourigenesis and therapy resistance [89].

3.11 Pro-survival autophagy

A programmed cell death (PCD) mechanism with potential functions in the regulation of cancer drug resistance is known as autophagy. The aberrant activation of autophagy

has been well-documented in human cancer [90], and it is considered as a potent regulator of drug resistance [91], capable of decreasing/increasing cancer progression, and therapy resistance based on its dual function. Adaptor SH3BGRL elevates stability of ATG12 and increases translation of PIK3C3 to mediate autophagy in the development of drug resistance [92]. The sequestration of miR-488-3p by circPOFUT1 results in stimulation of PLAG1/ATG12 axis in autophagy induction and enhancing chemoresistance [93]. SMC4 is another factor in the development of autophagy to mediate drug resistance [94]. Other types of autophagy also play a significant role of drug resistance such as mitophagy in cancer drug resistance [95]. Figure 2 displays the role of factors in development of drug resistance in human cancers. Table 1 represents the mechanisms causing drug resistance in PCa.

4 The molecular landscape of drug resistance in prostate cancer

4.1 microRNAs

The small RNA molecules lacking ability in protein translation are known as microRNAs (miRNAs) that their length is less than 24 nts and their aberrant expression

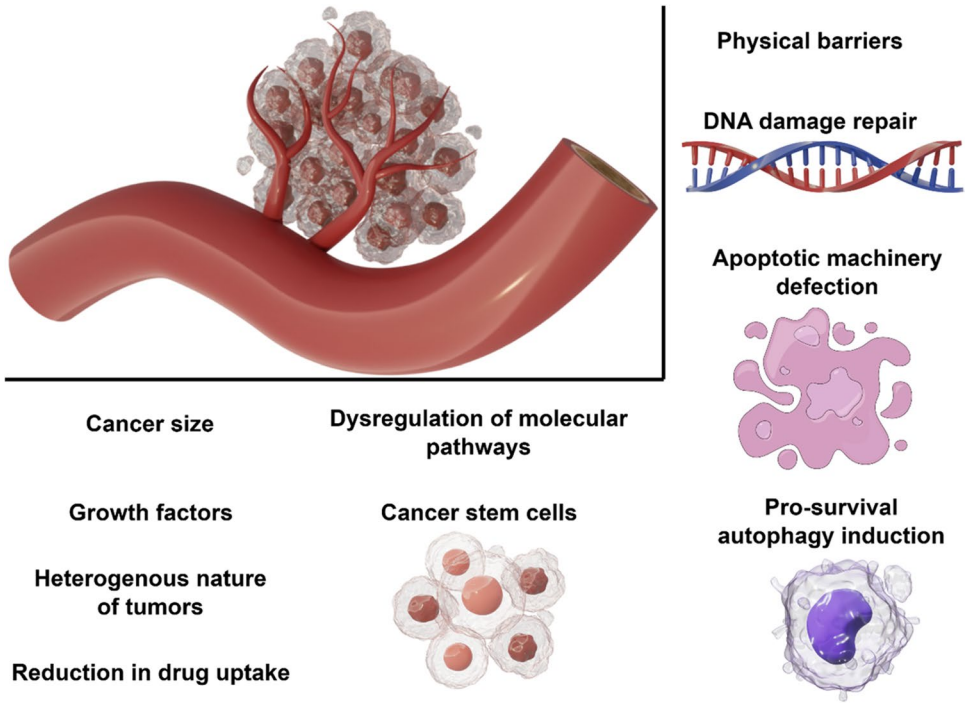


Fig. 2 The role of molecular mechanisms in the development of chemoresistance. The process of drug resistance in human cancers is complicated in which various types of mechanisms participate in its development that is started from physical barriers with increase in DNA damage repair and preventing apoptosis. Moreover, there is an association between tumour size and the development of chemoresistance. The drug efflux transporters reduce the accumulation of cytotoxic drugs in cancer cells to mediate chemoresistance and dysregulation in molecular pathways causes development of drug resistance. The angiogenesis induction and the elevation in stemness are other factors causing chemoresistance

Table 1 An overview of drug resistance mechanisms in PCa

Molecular profile	Highlights	Ref
CircFoxo3	CircFoxo3 impairs EMT and reduces proliferation and survival of tumour cells in increasing docetaxel sensitivity	[96]
WDR5	WDR5 upregulates PD-L1 expression and stimulates drug resistance	[97]
DRD2	Bromocriptine promotes DRD2 expression and reverses drug resistance	[98]
BMP	The downregulation of BMP enhances drug sensitivity	[99]
Akt	The downregulation of Akt isoforms, especially Akt1 and Akt2 significantly suppress chemoresistance	[100]
ZEB1	ZEB1 increases MRP4 levels to induce drug resistance	[101]
E-cadherin	E-cadherin downregulation causes Notch upregulation to mediate chemoresistance	[102]
EED/EZH2	The non-canonical EED-EZH2 axis suppression by pharmacological compounds impairs drug resistance	[103]
NPRL2	NPRL2 impairs mTOR axis to induce autophagy and inhibit apoptosis, causing drug resistance	[104]
NOTCH1	NOTCH1 increases ABCC1 expression in causing drug resistance	[105]
IGFBP2	Hyperglycaemia increases IGFBP2 expression to mediate drug resistance	[106]
ETS1	ETS1 increases MDR1 and MMP0 levels in causing drug resistance and increasing cancer metastasis	[107]

has been confirmed in various diseases, especially cancer [108]. The recent studies have emphasized on the potential role of miRNAs in regulation of apoptosis [109], metastasis [110], and other biological behaviours. The miR-375 has been suggested to involve in the development of DTX resistance in PCa. SEC23A and YAP1 play a significant role in development of chemosensitivity. However, miR-375 reduces levels of YAP1 and SEC23A to diminish response of PCa cells to DTX chemotherapy [111]. On the other hand, miR-34a enhances chemosensitivity through stimulation of apoptosis and cell cycle arrest by decreasing SIRT1 expression [112]. miR-99b-5p suppression and mTOR enhancement can jointly participate in the development of chemoresistance in African American PCa [113]. Interestingly, miRNAs can be enriched in exosomes as small extracellular vesicles to regulate tumourigenesis and exosomes function as cell–cell communication tools [114]. The enrichment of miR-27a in exosomes is observed in PCa that by reducing p53 expression, they participate in the drug resistance development in tumour cells [115]. However, a few studies have focused on this potential of exosomal miRNAs in the regulation of chemoresistance and more studies should be conducted in this case. According to the studies, miRNAs can participate in both reducing and increasing response of PCa cells to chemotherapy. For instance, miR-21 participates in the development of chemoresistance in PCa through downregulation of PDCD4, and therefore, manipulating expression level of miR-21 can contribute to modulation of tumourigenesis and therapy response in PCa [116]. In order to increase potential in increasing drug sensitivity, studies have focused on regulating more than one factor. The upregulation of miR-145 and downregulation ofTR4 can result in DTX sensitivity of PCa cells [117]. miR-17–92 cluster has been considered as a factor involved in drug resistance that stimulates Akt axis in promoting ERK1/2 expression [118]. miR-199a is a critical player in regulating tumourigenesis and miR-199a-5p inhibition results in upregulation of HIF-1α to increase tumourigenesis in PCa [119]. ROR2 reduces expression level of miR-199a-5p to suppress metastasis of PCa cells [120]. Hence, miR-199a disrupts pathogenesis and tumourigenesis of PCa; miR-199a diminishesYES1 expression to enhance DTX sensitivity [121]. miR-34a is able to increase drug sensitivity; miR-34a diminishes JAG1/Notch1axis to increase paclitaxel (PTX) sensitivity [122]. On the other hand, miR-129-5p stimulates DTX resistance through downregulation of CAMK2N1 to trigger DTX resistance [123]. Hence, regulating expression level of miRNAs, especially silencing miRNAs can enhance drug sensitivity. miR-193a-5p diminishes Bach2 expression to stimulate DTX resistance, and therefore, silencing miR-193a-5p can increase drug sensitivity [124].

4.2 LncRNAs

The long non-coding RNAs (lncRNAs) are other factors with significant contribution in regulating PCa tumourigenesis. The function of lncRNAs in PCa is versatile, and they are promising modulators of tumourigenesis that at cellular and molecular level; they can control a number of pathways and mechanisms including proliferation, metastasis, apoptosis, autophagy, cell cycle arrest, and related molecular pathways [125]. The recent studies have revealed function of lncRNAs in the regulation of chemoresistance in PCa. The function of chemotherapy drugs in reducing tumourigenesis is attributed to the potential in preventing cell death. The ferroptosis is an iron-dependent cell death that its regulation in PCa is mediated by a number of molecular pathways. CEMIP is capable of preventing ferroptosis to promote viability of PCa cells [126]. Moreover, SGK2 escalates expression level of GPX4 to suppress ferroptosis in increasing invasion of PCa cells [127]. The expression level of lncRNA PCAT1 can be increased by function of TFAP2C that subsequently enhances stability of c-Myc. Moreover, PCAT1 increases SLC7A11 expression through miR-25-3p suppression in decreasing iron accumulation and avoiding ferroptosis in cancer cells [128]. The function of lncRNAs in drug resistance regulation in PCa is more than simple control of molecular mechanisms such as ferroptosis. LncRNA HOTTIP has been involved in the development of cisplatin resistance in PCa; to this end, HOTTIP stimulates Wnt/β-catenin axis to trigger cisplatin resistance [129]. Silencing such lncRNAs can contribute to increased toxicity of anticancer drugs. Silencing SNHG6 leads to the suppression of growth and metastasis of PCa cells and increases PCa sensitivity to PTX chemotherapy [130]. Moreover, knock-out of LINC01963 results in DTX sensitivity in PCa cells through promoting expression level of its target miR-216b-5p and suppressing carcinogenesis and lung invasion [131]. The function of lncRNAs in the regulation of drug sensitivity in PCa has been widely evaluated in regard to regulation of miRNAs including miR-183 [132], miR-24-3p [133], miR-149-5p [134], miR-497-5p [135], and miR-33b-5p [136]. However, function of lncRNAs in the modulation of drug resistance in PCa can be distinct from miRNA sponging like function of HOXD-AS1 that recruits WDR5 for drug resistance development [137].

4.3 CircRNAs

The circular RNAs (circRNAs) are similar to lncRNAs and miRNA from the standpoint that none of them are able to encode proteins and their functions in cells is regulatory. The circRNAs have a covalently closed loop structure, and they are promising candidates in the regulation of tumourigenesis in PCa, mainly through sponging and controlling

miRNAs [138–141]. However, there are studies showing that circRNA function in PCa can be mediated in a miRNA-independent manner such as circ-0006156 that prevents ubiquitination of S100A9 in reducing PCa invasion [142]. A few experiments have evaluated the potential of circRNAs in the modulation of drug resistance in PCa; circ-0004087 is at class of oncogenic circRNAs that a result of its interaction with SND1 is to escalate mitotic error in promoting DTX resistance [143]. However, the role of circRNAs in the regulation of chemoresistance has been mainly evaluated in terms of regulation of miRNAs. miR-7 has ability of increasing DTX sensitivity in PCa; however, circ-0000735 reduces miR-7 expression to escalate DTX resistance [144]. Hence, circRNA-miRNA circuit regulates response of PCa cells to chemotherapy [145]. Recently, circRNAs enriched in exosomes have obtained much attention in field of tumour diagnosis and acting as biomarker [146]. The function of exosomal circRNAs in human cancers is versatile, and they are potent regulators of proliferation, invasion, and metabolism [147]. The exosomal circ-SFMBT2 has been considered as a regulator of tumourigenesis in PCa and response to DTX chemotherapy. Exosomal circ-SFMBT2 positively regulates TRIB1 expression through miR-136-5psponging to escalate tumourigenesis for DTX resistance development [148]. Figure 3 depicts the role of non-coding RNAs in regulation of chemotherapy response in PCa cells.

4.4 PI3K/Akt

The PI3K/Akt axis is another factor in the development of chemoresistance in PCa. Increasing evidence has shown potential of this axis in enhancing carcinogenesis. The upregulation of PI3K/Akt enhances tumourigenesis, induces EMT, and stimulates DTX resistance. The function of INPP4B is against tumourigenesis in PCa, and INPP4B reduces PI3K/Akt expression to suppress EMT and DTX resistance [149]. In fact, PI3K/Akt participates in both increasing invasions of PCa cells and reducing the response to chemotherapy. The progression and malignancy of PCa cells enhance by the function of EpCAM, and it stimulates PI3K/Akt/mTOR axis in triggering resistance to chemotherapy and radiotherapy [150]. The role of PI3K/Akt in the development of chemoresistance in human cancers is related to preventing apoptosis. In fact,

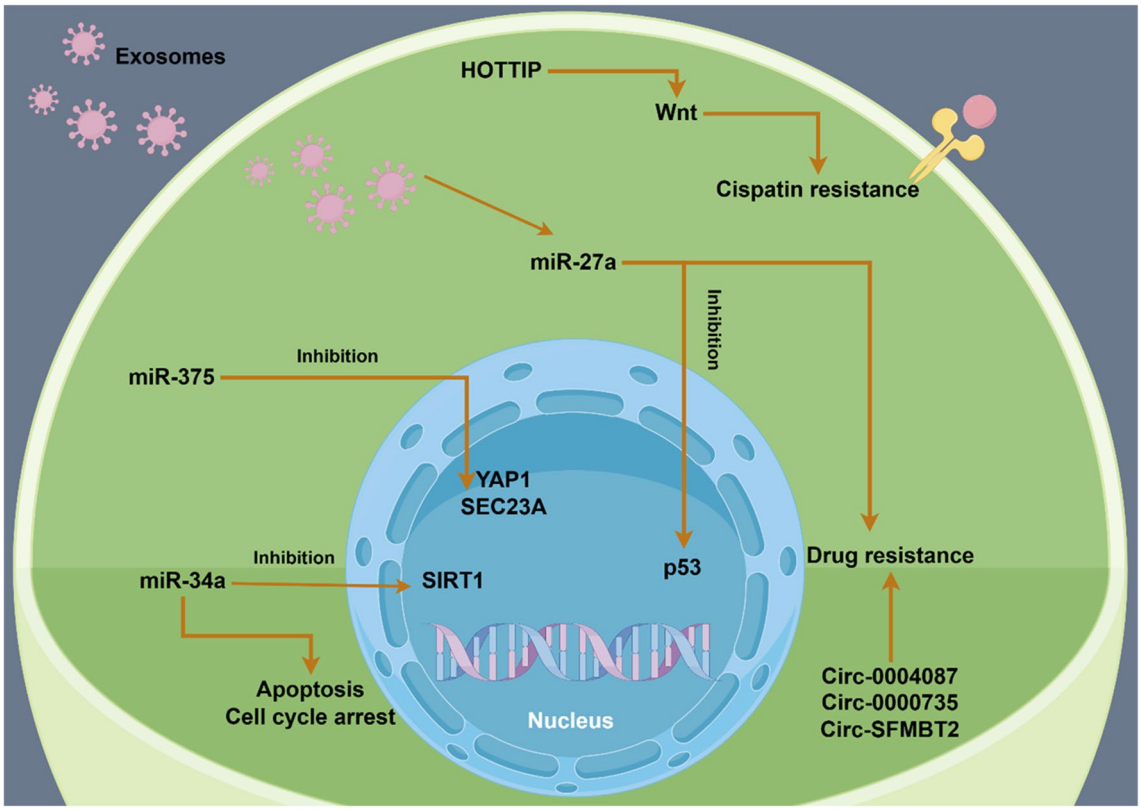


Fig. 3 The non-coding RNA-mediated regulation of chemotherapy response. In case of circRNAs, only oncogenic circRNAs with ability of inducing drug resistance have been described including circ-0004087, circ-0000735, and circ-SFMBT2. Moreover, miRNAs and their exosomal forms can suppress apoptosis and induce chemoresistance through regulation of p53, SIRT1, and YAP1, among others. In terms of lncRNAs, they can sponge miRNAs for ferroptosis inhibition. Moreover, HOTTIP stimulates Wnt axis to mediate cisplatin resistance

CCR9 stimulates PI3K/Akt axis to enhance and evoke anti-apoptotic signal in decreasing response of PCa cells to etoposide chemotherapy [151]. In addition to apoptosis, the expression level of MRP-1 as a potential factor involved in the chemoresistance is affected by PI3K. The upregulation of MRP-1 by PI3K results in reduction in response of PCa cells to chemotherapy [152]. Moreover, the drug efflux transporters including MDR1 can be stimulated by EGFR through upregulation of AKt to induce DTX resistance [153]. However, PI3K/Akt is not the only pathway and an oncogenic factor can regulate different downstream targets. CD44v6 increases lymph node metastasis of PCa cells and increases sphere formation. Interestingly, CD44v6 enhances expression level of PI3K/Akt/mTOR, EMT, and Wnt/β-catenin in the development of chemoresistance and radioresistance in PCa cells [154]. As a result of silencing such carcinogenic factors in cancers, the drug sensitivity enhances. The interesting point is the involvement of endothelial cells in development of DTX resistance in PCa cells through stimulation of Akt/mTOR axis [155].

4.4.1 PTEN

The previous section focused on the role of PI3K/Akt axis in the development of drug resistance in PCa cells. The function of PI3K/Akt in PCa is oncogenic, and it mediates chemoresistance. However, PTEN is upstream mediator of PI3K/Akt and suppresses its activation. The PTEN deficiency escalates the progression of PCa cells, and when loss of PTEN occurs, it causes degradation of FBP1 to induce Warburg impact in increasing tumourigenesis [156]. Furthermore, loss of PTEN mediates the poor prognosis of PCa patients [157]. The therapy response of Pca cells is regulated by PTEN signalling. BRD4 escalates expression level of KDM5C through transcriptional level to suppress PTEN expression in enhancing tumourigenesis and escalating cancer growth [158]. When expression level of PTEN enhances, it promotes potential of drugs in apoptosis induction and enhances sensitivity of Pca cells to DR-induced cell death [159]. Furthermore, PTEN reduces expression level of Bcl-2 as an anti-apoptotic protein in increasing drug sensitivity [160]. The activity of drug transporters is regulated by PTEN. Low expression level of miR-21 results in PTEN overexpression to downregulate P-gp in increasing drug sensitivity in Pca [161]. Notably, low expression of PTEN can result in the development of resistance to more than one anticancer drug. TUBB3 reduces PTEN expression, and when TUBB3 silencing is performed, it causes PTEN upregulation and sensitivity to DTX and cabazitaxel promotes [162]. A clinical study has revealed that upregulation of TUBB3 and downregulation of PTEN result in poor prognosis [163].

4.4.2 STAT3

STAT3 is considered as another factor involved in tumourigenesis in PCa. Increasing evidence highlights the function of STAT3 in favour of tumourigenesis in PCa and its downregulation by Pinus mugo essential oil leads to apoptosis and oxidative damage in tumour cells [164]. The upregulation of JAK/STAT3 by HSPB8 leads to increase in PCa progression [165] and STAT3 downregulation mediates apoptosis [166]. Interestingly, the strategy of drug repurposing has focused on regulation of STAT3 in cancer therapy [167]. The dysregulation and abnormal alterations in gut microbiota mediate the DTX resistance in PCa that is due to stimulation of NF-κB axis that promotes IL-6 levels in STAT3 induction [168]. Therefore, IL-6 can function as upstream mediator of STAT3 in cancer drug resistance. Interestingly, cancer-associated fibroblasts are able to secrete IL-6 in stimulation of JAK/STAT3 axis to stimulate doxorubicin resistance in PCa [169]. The suppression of STAT3 promotes enzalutamide sensitivity of PCa cells [170]

5 Molecular mechanisms of drug resistance in prostate cancer

5.1 Apoptosis

Apoptosis was mentioned before as a factor in cancer chemotherapy that defects in this system can result in the development of drug resistance. The stimuli including ROS overgeneration and endoplasmic reticulum stress can result in apoptosis. Several caspases participate in process of apoptosis and finally, irreversible alterations occur in cells. The cell shrinkage, chromatin condensation, blebbing, and generation of apoptotic bodies are morphological characteristics of apoptosis [171]. The lack of response of PCa cells to apoptosis can pave the way in development of chemoresistance. The molecular interactions that prevent apoptosis in Pca play a critical role in drug resistance development. Calcitonin has ability of increasing expression level of Akt to induce survivin expression. Then, apoptosis resistance is observed against the anti-cancer drugs in Pca [172]. The apoptotic rate and proliferation of Pca cells have close interaction. The exposure of Pca cells to chemotherapy results in apoptosis induction and reduction in proliferation rate. Such association has been evaluated in the function of WD repeat domain 5 (WDR5) in which regulates apoptosis and proliferation of Pca cells. Moreover, apoptosis and DNA damage repair can be regulated together in determining the response of Pca cells to the therapy. The apoptosis inhibition and DNA damage repair can be mediated by WDR5 in triggering cisplatin resistance in PCa, and a number of factors such as AURKA, CCNB1, E2F1, PLK1, BIRC5, XRCC2,

and PD-L1 are modulated [97]. The DTX is another chemotherapy drug in PCa suppression that is potential is based on modulating depolymarization of microtubules. The DTX-mediated apoptosis can be suppressed by molecular interactions; miR-204 upregulation results in ZEB1 downregulation to stimulate apoptosis and prevent drug resistance [173]. Furthermore, there is correlation between drug efflux transporters and apoptosis in PCa cells [174]. Cofilin-1 is considered as a factor relating drug efflux and apoptosis. Exosomal transfer RPS3 results in stimulation of PI3K/Akt axis to enhance cofilin-1 levels in drug resistance development [175]. The phosphorylation of cofilin-1 can be stimulated by ERK1/2 and phatycodin D can suppress drug resistance by suppressing cofilin-1 [176]. The cofilin-1 increases levels of p38 MAPK to upregulate activity of MDR1 to prevent apoptosis in drug resistance development [174].

CXCR4 increases HMGA2 expression to induce chemoresistance [177] and HMGA2 escalates FOXL2 expression to stimulate EMT in increasing drug resistance [178]. HMGA2 is able to increase expression level of Wnt in promoting 5-FU resistance [122]. Upregulation of HMGA2 prevents apoptosis in PCa [179], and this may result in chemoresistance in tumour cells in the future. USP9x reduces apoptosis in PCa cells and can develop drug resistance. Reduction USP9x can lead to the degradation to PBX1 to trigger apoptosis and reverse drug resistance [180]. The high expression level of Notch-1 PCa can decrease potential of DTX in cancer therapy. Therefore, silencing Notch-1 participates in apoptosis induction and mediating mitotic arrest mediated by DTX [181]. The cleavage of PARP1 is vital for triggering apoptosis in PCa cells. Interestingly, cisplatin stimulates DNA damage and promotes PARP1 claevage to induce apoptosis. Moreover, NRF2 downregulation leads to ROS overgeneration and sensitivity of PCa cells to cisplatin [182]. The regulation of anti- and pro-apoptotic proteins can control apoptosis in PCa cells. The TLR4 upregulation prevents apoptosis to induce DTX resistance in PCa, while silencing TLR4 promotes Bax expression and reduces Bcl-2 levels in apoptosis induction and reversing DTX insensitivity [183]. However, the regulation of apoptosis is more than simple regulation of apoptotic proteins. PDIA-4 is able to induce phosphorylation of Akt in apoptosis inhibition and mediating DTX resistance [184]. Therefore, apoptosis is a determining factor of therapy response in PCa cells.

5.2 Autophagy

Autophagy is considered as a regulated cell death similar to apoptosis in which degrades toxic macromolecules and aged organelles in cell homeostasis, while its function is transformed in tumour cells and it can reduce/increase carcinogenesis. The autophagy is a highly regulated mechanism in which autophagy-related genes (ATGs), ULK1, Beclin-1, and AMPK stimulate autophagy, while mTOR suppresses autophagy. Autophagy function in PCa has been fully investigated showing that proliferation and metastasis of PCa cells can be dually induced/suppressed by autophagy. This mechanism can regulate apoptosis in PCa cells and therefore, understanding its function in therapy response of PCa cells is of importance that is aim of current section.

The role of autophagy in chemotherapy response of PCa cells can be protective that upon upregulation of autophagy by Ambra1 in PCa cells, apoptosis is reduced and therefore, sensitivity of tumour cells to chemotherapy diminishes [185]. STAT3 is a regulator of tumourigenesis in human cancers and evaluation of its function in PCa displays that STAT3 controls the biological behaviour of PCa cells and its phosphorylation escalates tumourigenesis [186]. The miR-125a upregulation by curcumol results in STAT3 suppression to impair carcinogenesis in PCa [187]. Furthermore, the expression level of JAK2/STAT3 in PCa is regulated by SOCS3 [188]. In CRPC, the tumour cells lack response to DTX chemotherapy that is attributed to pro-survival autophagy stimulation. Notably, STAT3 overexpression is vital for autophagy induction and lack of response of PCa cells to DTX chemotherapy [189]. Interestingly, regulation of autophagy can sensitize tumour cells to apoptosis and improve chemosensitivity. NPRL2 has been suggested to reduce expression level of mTOR in autophagy induction, while silencing NPRL2 suppresses autophagy and escalates apoptosis in mediating DTX sensitivity [104].

The NEPC is a malignant and progressive type of PCa that IL-6 is critical for NEPC. Interestingly, autophagy is a pre-requisite for IL-6-medaited NEPC and stimulates drug resistance. IL-6 increases AMPK phosphorylation and reduces mTOR expression in triggering drug resistance and advancing progression into NEPC. Autophagy suppression promotes apoptosis in PCa cells [190]. Furthermore, AMPK/mTOR axis is vital for regulation of ATG4B expression in PCa. The methylation of miR-34a results in downregulation of this miRNA, and then, AMPK upregulation occurs. Then, mTOR expression reduce to increase ATG4B expression in autophagy induction and accelerating drug resistance [191]. Owing to this critical function of autophagy in cancer drug resistance, its suppression can lead to reduction in resistance. However, function of autophagy is lethal in PCa sometimes, and in this case, autophagy suppression induces chemoresistance. It has been reported that PrLZ is an oncogenic factor in PCa that reduces LKB1 expression to suppress AMPK/autophagy axis in triggering DTX resistance [192]. The AMPK/mTOR axis is not the only factor regulating autophagy in PCa and upregulation of Beclin-1 results in autophagy stimulation to induce drug resistance [193]. After the downregulation and inhibition of PLIN3, autophagy intensification occurs that mediates DTX resistance in PCa

and such drug resistance is suppressed by chloroquine as inhibitor of autophagy [194].

Cisplatin resistance also commonly occurs in PCa; the glycolysis dysfunction can be induced by RSL3 in accelerating potential of cisplatin in PCa suppression [195]. DUSP1 upregulation can be provided by resveratrol in apoptosis induction and increasing cisplatin sensitivity of PCa [196]. However, stimulation of pro-survival autophagy can mediate cisplatin resistance in PCa. Silencing CFTR promotes cisplatin sensitivity of PCa cells through autophagy inhibition [197]. At the time that autophagy exerts protective role, its inhibition enhances apoptosis and reverses drug resistance [198]. In case that autophagy stimulates drug resistance, the autophagy-related proteins can be directly targeted. For instance, FOXM1 stimulates AMPK/mTOR axis in autophagy induction and mediating DTX resistance. Silencing ATG7, Beclin-1, or application of chloroquine can suppress DTX resistance [199]. Furthermore, enhanced autophagy through NPRL2 stimulates Everolimus resistance in PCa [200]. Interestingly, the progression of PCa can be provided by HMGB1 through AR upregulation [201]. HMGB1 stimulates Akt axis in increasing carcinogenesis in PCa [202], and it is a regulator of NF-κB in enhancing cancer metastasis [203]. The gemcitabine resistance can be facilitated through HMGB1-induced autophagy [204]. Therefore, autophagy plays a critical role in regulating chemotherapy response of PCa cells [205–209].

5.3 Cancer stem cells in prostate cancer and therapy resistance

The regulation of CSC features and phenotype in PCa occurs through different molecular mechanisms. SFRP1 has ability of elevating the CSC features and phenotype in prostate cancer through upregulation of Wnt/β-catenin axis and increasing levels of SOX2, NANOG, and OCT4 [210]. Both SFRP1 and GSK-3β can be regulated by miR-1301-3p. SFRP1 and GSK-3β are suppressed by miR-1301-3p that are Wnt inhibitor, causing upregulation of OCT4, SOX2, NANOG, CD44, KLF4, c-MYC, and MMP2 and improving CSC features in PCa [211]. The upregulation of ZEB1 accelerates the CSC features in PCa, and downregulation of ZEB1 reduces levels of CD44, CD133, and SOX2 as markers of stemness [212]. The stimulation of Jagged1/Notch1 axis by bone marrow mesenchymal stem cells can enhance the stemness of PCa [213]. The increasing evidences have shown that stemness and CSCs participate in the development of therapy resistance in PCa. The CSCs appear to be resistant into radiotherapy and a combination of fractionated irradiation and B7-H3 can significantly suppress the growth of PCa [214]. An interesting part is the relationship of CSCs and EMT in the regulation of cancer metastasis. The upregulation of CSC markers in PCa including SOX2, NANOG, KIF4, OCT3/4, and c-Myc can accelerate the invasion and metastasis through overexpression of Slug, ZEB1, and Twist1 [215]. The increase in CSC features and cancer invasion can cause the development of castration resistance [216]. The proliferation of CSCs occurs slowly, and they stimulate DNA damage repair, and upregulation of γH2AX is another factor in the reduced anti-cancer activity of etoposide against PCa [217]. The overexpression of NANOG promotes levels of CXCR4, CD133, ALDH1, and IGFBP5 in the expansion of CSCs and the development of androgen deprivation resistance [218]. Therefore, it can be perceived that CSCs contribute to the development of therapy resistance in PCa.

5.4 Epithelial-mesenchymal transition

The epithelial-mesenchymal transition (EMT) has been suggested to be one of the leaders in the regulation of cancer metastasis with growing contribution to low therapy response of tumour cells. With improvement in understanding the molecular and structural changes of EMT, it is now obvious that morphological aspect of EMT is mesenchymal transformation of epithelial cells, and at molecular level, E-cadherin as epithelial marker is suppressed, and then, N-cadherin and vimentin are escalated. The increasing evidence highlights the function of EMT in the development of resistance to various chemotherapy drugs [219, 220]. The recent experiments have highlighted the fact that EMT plays a significant role in the progression of PCa cells [221]. The loss of vitamin D results in EMT stimulation in escalating cancer metastasis [222], and EMT suppression by atractylenolide I increases anti-cancer function of cabozantinib [223]. The increase in progression of PCa cells can be accompanied with the development of chemoresistance. The EMT and drug resistance occur simultaneously in PCa. SPP1 is able to stimulate PI3K/Akt and ERK1/2 pathways in mediating EMT and development of enzalutamide resistance [224]. CNTN-1 stimulates PI3K/Akt axis and induces EMT in evoking DTX resistance [225]. The wealth evidence displays that EMT induction by oncogenic factors can mediate chemoresistance in PCa cells. The EMT mechanism can participate in the chemoresistance in Pca through both intrinsic and extrinsic pathways. In intrinsic mechanism, EGFR promotes Rad51 expression to stimulate EMT and increase DNA damage repair in intrinsic resistance [226]. Furthermore, the ability of CRPC cells in developing resistance to enzalutamide is based on progression acceleration that is mediated by function of ISL1 in inducing EMT [227]. There is essential association between metastasis of Pca cells to bone and their ability of developing resistance to DTX chemotherapy. TGF-β escalates acetylation of KLF5 in promoting bone metastasis of Pca cells, and acetylated form of KLF5 promotes osteoclastogenesis and increases bone metastatic lesions through stimulation of CXCR4. Moreover,

acetylated KLF-5 has been associated with enhancement in carcinogenesis and increasing DTX resistance (Fig. 4) [228].

6 Combination therapies in prostate cancer: application of small molecule inhibitors and natural products

Both natural compounds and synthetic small molecules have been introduced in regulating the therapy response of PCa cells regarding molecular view. Each of these compounds have ability of affecting a certain molecular pathway in increasing chemosensitivity of PCa cells. There are differences about using natural products or small molecules in the treatment of PCa that their efficacy is various. For instance, small molecules are designed for a specific target in PCa therapy, while natural compounds are able to affect various pathways. Furthermore, phytochemicals are more available compared to small molecules, they are affordable, and their biocompatibility is higher compared to small molecules. The quercetin is a natural compound commonly utilized in the treatment of PCa; quercetin is capable of escalating radiosensitivity of PCa cells [229], and by increasing ER stress and ROS generation, it promotes paclitaxel sensitivity of PCa cells [230]. The upregulation of c-met can induce doxorubicin resistance in PCa cells; quercetin decreases c-met expression to suppress PI3K/Akt axis in enhancing doxorubicin sensitivity of PCa cells [231]. Moreover, the response of PCa cells to docetaxel can be improved. Quercetin is able to suppress AR and PI3K/Akt pathways and increase apoptosis to promote docetaxel sensitivity of PCa cells [232]. The important molecular pathways regulating tumourigenesis in PCa are affected by natural compounds. For instance, eupatilin is able to suppress NF-κB axis and elevate PTEN expression in disrupting growth and metastasis of PCa cells [233]. The combination of natural compounds in exerting more inhibitory impact on PCa cells than monotherapy is suggested. A combination of green tea and quercetin can be utilized for downregulation of PI3K/Akt to escalate DTX sensitivity of PCa cells [234]. Owing to multi-targeting feature of green sources, they are capable of regulating more than one molecular pathway in PCa removal. The β-elemonic acid is capable of stimulating apoptosis in PCa cells, and for this purpose, it diminishes expression level of JAK2/STAT3 to downregulate MCL-1, and it suppresses NF-κB axis in impairing tumourigenesis [235]. Moreover, natural products are beneficial in disrupting tumourigenesis in drug resistant-tumour cells. Acetyl-11-keto-β-boswellic acid has been shown to downregulate Akt and STAT3 pathways and inhibits stem-like features in PCa to impair tumourigenesis [236]. Even components of tumour microenvironment can be regulated in affecting chemoresistance in PCa cells. Qi Ling is capable of suppressing IL-6/STAT3 axis, and it reduces M2 polarization of macrophages in elevating PTX sensitivity of PCa cells [237]. STAT3/AR downregulation by galiellalactone can disrupt enzalutamide insensitivity in PCa [238]. Notably, reduction in metastatic potential of PCa cells can participate in chemosensitivity; metformin has been suggested to suppress EMT through STAT3 downregulation in escalating enzalutamide

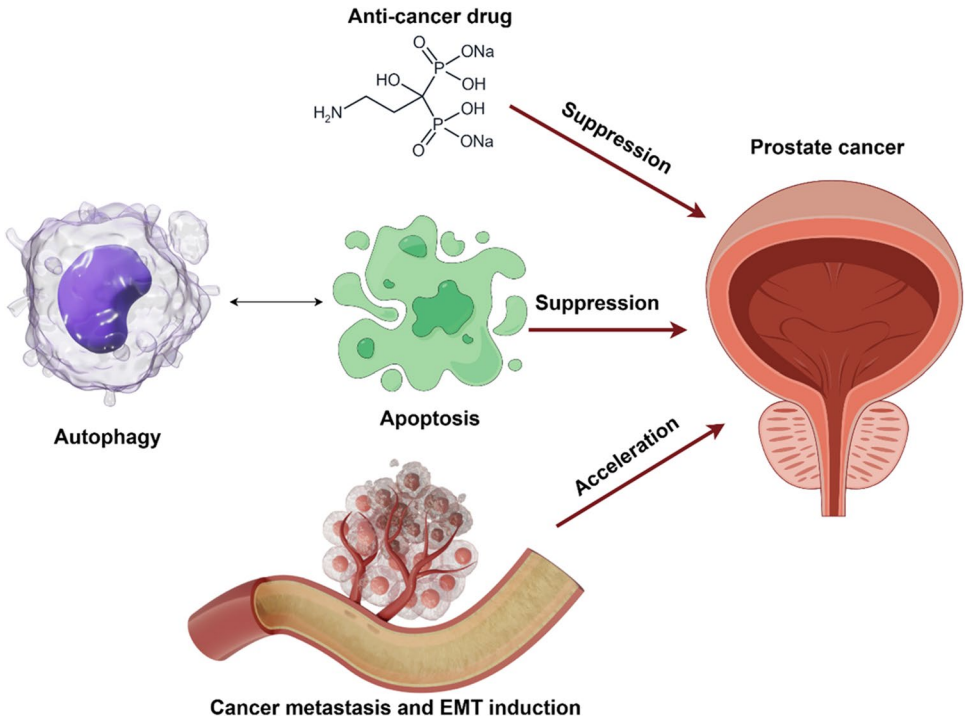


Fig. 4 The role of biological mechanisms in development of chemoresistance. In the development of drug resistance, several biological mechanisms demonstrate interactions with each other in which protective autophagy inhibits apoptosis, while lethal autophagy stimulates apoptosis to increase drug sensitivity in prostate cancer. Moreover, the increase in the EMT can accelerate drug resistance. The association of autophagy and EMT in prostate cancer drug resistance requires more investigation

sensitivity [239]. When a molecular pathways such as Akt is suppressed by phytochemicals, it causes reduction in the proliferation of PCa cells and promotes their chemosensitivity [240]. Hence, phytochemicals are promising candidates in the regulation of drug sensitivity in PCa [241, 242].

In addition to natural products, the small molecules have been widely utilized in regulating response of PCa cells to chemotherapy. GBP730 is a small molecule inhibitor of STAT3 that has ability of increasing sensitivity of PCa cells to enzalutamide chemotherapy [243]. The suppression of STAT33/AR axis by niclosamide results in reduction in metastasis of PCa cells to reverse enzalutamide resistance [244]. Upon regulation of molecular pathways, a plan is provided for regulating apoptosis and drug efflux transporters in PCa cells. BKM1972 is considered as a small molecule in which reduces survivin expression and downregulates P-gp activity in enhancing DTX sensitivity in PCa cells [245]. Rapamycin is a regulator of autophagy that diminishes expression level of cyclin D1 in increasing potential of cisplatin in PCa suppression [246]. Therefore, combination therapy can bring new hopes in the treatment of PCa and the reason is regulation of underlying molecular pathways in suppressing tumourigenesis. Everolimus (RAD001) can be utilized for reducing levels of HIF-1α and sphingosine kinase 1 to increase DTX sensitivity of PCa cells [247]. Accordingly, both drugs, small molecules and phytochemicals, are promising candidates in regulation of drug sensitivity in PCa.

7 Radioresistance in prostate cancer

7.1 Molecular interactions

Although the main focus of the studies is on evaluation the underlying molecular pathways regulating chemoresistance, there are evidences showing that molecular interactions can also regulate response of PCa cells to radiotherapy. The complicated networks among pathways can regulate radioresistance in PCa. HIF-1α is able to escalate nuclear transfer of β-catenin in apoptosis inhibition, increasing growth and metastasis, and promoting DNA repair to mediate radioresistance [248]. Interestingly, chemoresistance and radioresistance in PCa can occur simultaneously. Keap1 deficiency leads to stimulation of chemoresistance and radioresistance in PCa cells. This is due to the fact that loss of Keap1 results in upregulation of Nrf2 to mediate therapy resistance [249]. The factors regulating radioresistance have been shown to induce therapy resistance in both in vitro and in vivo. EHMT2 is an inducer of radioresistance in PCa that decreases ERP29 expression in mediating resistance in both in vitro and in vivo [250]. Similar to chemoresistance, non-coding RNAs have been considered as factors regulating radioresistance. As it was mentioned in introduction section, enhancement in DNA damage repair can cause development of radioresistance in PCa. The miR-205 is able to escalate radiosensitivity in PCa cells, and to this end, miR-205 diminishes expression levels of ZEB1 and PKCε to preventing DNA damage repair and enhancing radiosensitivity [251]. Hence, regulation of DNA damage repair can lead to changes in radiosensitivity of PCa cells. Downregulation of cyclin D1 is vital for disrupting DNA break repair [252].

The progression of PCa cells is highly dependent on the hypoxia in TME that is due to insufficient oxygenation of cancer cells. The stimulation of HIF-1α/Notch1 can occur in PCa to increase stem cell phenotype [253], and hypoxia is capable of triggering radioresistance [254]. The expression level of miRNAs is regulated by hypoxia. The hypoxic TME reduces expression levels of miR-124 and miR-144 as a way to upregulate PIM1 to evoke autophagy in development of radioresistance [255]. Similar to chemotherapy, function of autophagy in radiotherapy can be oncogenic or onco-suppressor. Downregulation of PC1/PrLZ results in reduction in DNA damage repair and stimulation of autophagic cell death in enhancing radiosensitivity [256]. Interestingly, plasticity is a determining factor for radiotherapy response of PCa cells. Upon irradiation, the number of ALDH + cells exceeds ALDH- to mediate radioresistance [257]. The increase in antioxidant defense system can lead to development of radioresistance, while miR-17-3p has ability of impairing antioxidant defense in PCa cells to enhance radiosensitivity [258]. Hence, radiotherapy response of PCa cells is regulated by a number of underlying molecular interactions and mechanisms including apoptosis, autophagy, and DNA damage repair participate in this condition.

7.2 Therapeutic approaches

The therapeutic approaches have been displayed to be beneficial in enhancing radiosensitivity in PCa cells. The application of PARP1 inhibitor along with irradiation can result in increase in radiosensitivity of PCa cells [259]. For overcoming radioresistance, intermittent radiotherapy has been suggested. However, fractionated irradiation can lead to neuroendocrine differentiation of PCa cells. Therefore, JNJ-64619178 has been utilized as a factor to avoid DNA damage repair and increase radiosensitivity of PCa cells [260]. Both in vitro and in vivo experiments have revealed that combination therapy can elevate drug sensitivity of PCa cells. Atorvastatin is able to enhance response of PCa cells and mice to radiotherapy, and for this purpose, it stimulates interaction of Bcl-2 and MSH2 in accelerating potential of irradiation in PCa removal [261]. Besides, the DNA damage repair can be regulated by therapeutic compounds. Silibinin as anti-cancer

agent is able to diminish DNA damage repair in PCa cells, and this is beneficial for increasing radiosensitivity [262].

Recently, resveratrol has been suggested as a new therapy for PCa. The TRAF6/PTCH/SMO axis can be suppressed by resveratrol in impairing PCa progression [263]. The liposomes for co-delivery of resveratrol and docetaxel have been fabricated to suppress PCa malignancy [264]. Moreover, vasculogenic mimicry in PCa can be inhibited by function of resveratrol through downregulation of Akt [265]. Interestingly, resveratrol is beneficial in increasing radiosensitivity of PCa cells. Administration of resveratrol escalates apoptosis and cell senescence in PCa and disrupt growth through increasing p15, p21, and mutant p53; reducing cyclin B, cyclin D, and cdk2; and enhancing Fas and TRAILR1 to accelerate radiation-mediated PCa removal [266]. The control of DNA-PKcs is another factor in regulation of irradiation response of PCa cells. Interestingly, metformin is able to reduce levels of EGFR/PI3K/Akt to prevent phosphorylation of DNA-PKcs in elevating radiosensitivity [267]. The reason of using complementary therapies with PCa is that when tumour cells are exposed to radiation, they may develop relapse and metastasis in next steps. Therefore, application of BEZ235 as suppressor of PI3K and mTOR is suggested to impair tumourigenesis and mediate cell cycle arrest at G2/M phase in enhancing radiosensitivity [268]. In fact, the anti-cancer drugs and small molecules are able to disrupt to barriers towards effective radiotherapy of PCa cells. HZ08 has shown potential in increasing ROS production, decreasing mitochondrial respiration, reducing level of MnSOD as antioxidant enzymes, suppressing PI3K/Akt/IKKα, and impairing nuclear transfer of RelB that all of these impacts result in impairment in PCa progression and increased radiosensitivity [269]. The high expression level of both PI3K/Akt and MAPK can result in radioresistance in PCa that antrocin has ability of downregulating MAPK and PI3K/Akt in enhancing radiosensitivity [270]. Table 2 and Fig. 5 summary the radioresistance mechanism in PCa cells.

8 Immune evasion in prostate cancer

Immunotherapy has been emerged as a new tool in treatment of PCa that its potential is based on stimulation of immune cells, increasing their infiltration in TME and preventing the activation of immunosuppressive pathways including PD-1/PD-L1 axis. Upregulation of PD-L1 results in immune evasion of PCa cells. Interestingly, there is close association between immune evasion and chemoresistance in PCa cells. The endocrine therapy results in low expression level of FLII to suppress YBX1/PD-L1 axis in immune evasion. However, FLII has ability of suppressing enzalutamide resistance through regulating PD-L1-mediated immune evasion [286]. Moreover, there is association between metastasis and immune evasion of PCa cells. N-cadherin is a regulator of EMT and its upregulation stimulates EMT. The overexpression of N-cadherin mediates immune evasion in PCa cells through reducing CD8 + T cells and enhancing number of CD4 + /DOXP3 + cells [287]. Regarding the function of PD-L1 in immune evasion, its related molecular interactions in PCa cells have been understood. The lncRNA

Table 2 The underlying mechanisms involved in radioresistance of PCa cells

Molecular network	Remark	Ref
GAS5/miR-320a/RAB21	GAS5 reduces miR-320a expression to promote RAB21 levels in mediating radiosensitivity	[271]
RelB	RelB upregulation prevents apoptosis	[272]
JMJD1A	Increase in DNA damage repair	[273]
-	The PI3K/Akt/mTOR inhibitors reduce radioresistance	[274]
LPAR3/miR-513b-5p/JPT1	CircRNA LPAR3 increases JPT1 expression through miR-513b-5p suppression in glycolysis induction and increasing radioresistance	[275]
miR-106a	miR-106a reduces LITAF expression in increasing tumourigenesis	[276]
Glucocorticoid receptor	Overexpression of GR induces radioresistance	[277]
Circ-ABCC4/miR-1253/SOX4	Circ-ABCC4 escalates SOX4 expression through miR-1253 sponging in radioresistance development	[141]
miR-301a/b/NDRG2	The miR-301a/b upregulation by hypoxia occurs to reduce NDRG2 expression in radioresistance development	[278]
AP-1	AP-1 increases proliferation and radioresistance	[279]
Circ-ZNF609/miR-501-3p/HK2	Circ-ZNF609 modulates miR-501-3p/HK2 axis to enhance glycolysis in radioresistance development	[280]
αvβ3 Integrin/survivin	αvβ3 Integrin escalates survivin expression to induce radioresistance	[281]
MEK5	Downregulation of MEK5 impairs NHEJ mechanism and increases DNA damage	[282]
PAFR/Beclin-1	PAFR reduces Beclin-1 expression in autophagy inhibition and enhancing radiosensitivity	[283]
MEK/ERK/c-Myc	Suppressing MEK/ERK/c-Myc axis increases radiosensitivity	[284]
IL-6	IL-6 increases activity of DNA repair factors to induce radioresistance	[285]

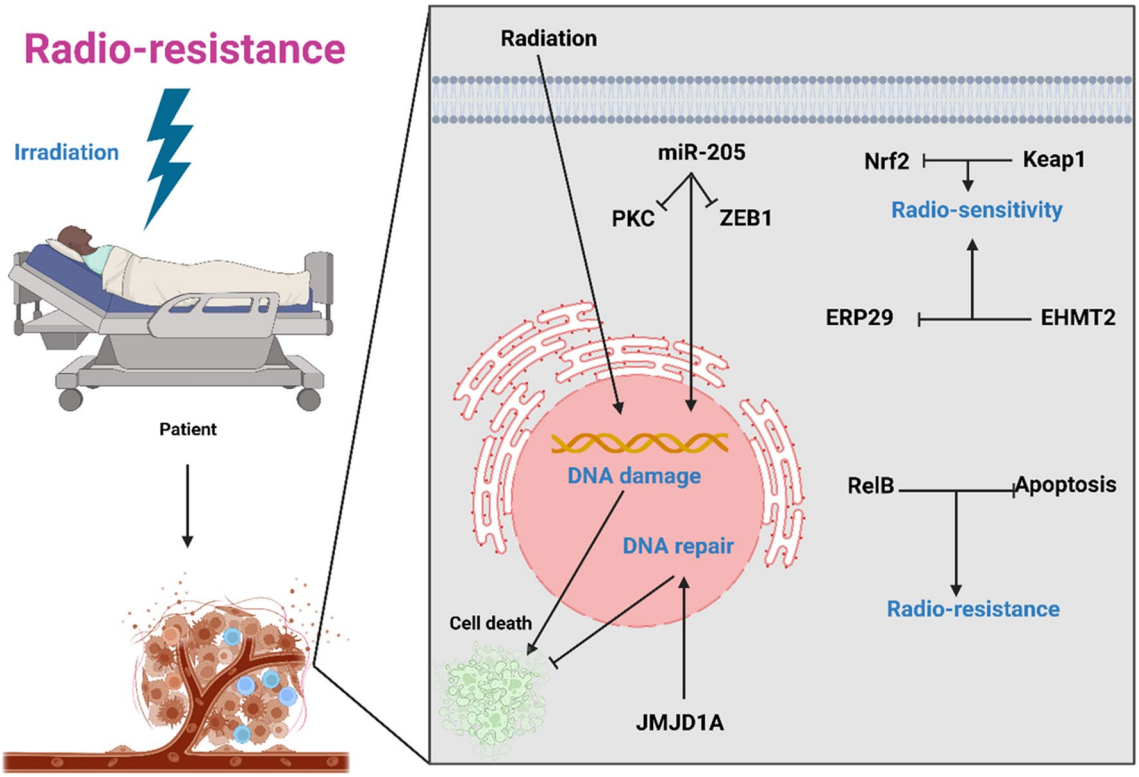


Fig. 5 The radioresistance development in PCa cells. The application of irradiation is mainly related to the DNA damage induction, while JMJD1A causes DNA damage repair to increase tumourigenesis and prevent cell death, causing radioresistance. Moreover, apoptosis inhibition by RelB stimulates radioresistance. The upregulation of Nrf2 as redox regulator mediates radioresistance

KCNQ1OT1 has ability of sponging miR-15a as a mechanism to increase PD-L1 expression for facilitating immune evasion in PCa [288]. In PCa patients, there is loss of JUN and ATF3 that can cause immune evasion. Interestingly, application of lipid nanostructures for delivery of JUN and ATF3 results in increase in immune surveillance for improving immunotherapy potential in PCa suppression [289].

Inflammation is considered as a factor involved in PCa pathogenesis and nitric oxide stimulates inflammation by affecting macrophages to escalate tumourigenesis [290]. The pro-inflammatory cytokines have been identified as factors involved in immune evasion. Upregulation of TLR9 and LIF secretion by PCa cells can upregulate STAT3 to increase infiltration of PMN-MDSCs in TME and mediating immunosuppression [291]. The inflammation and immune evasion have association in PCa; *Porphyromonas gingivalis* can cause chronic inflammation, and this is vital for promoting PD-L1 expression in triggering immune evasion in PCa [292]. The pathway in which inflammation causes immune evasion is that inflammation can promote IKKβ activation for purpose of ARID1A phosphorylation. Then, downregulation of ARID1A occurs to stimulate NF-κB axis in providing myeloid-derived suppressor cell chemotaxis [293]. Due to important function of PD-L1 in immune evasion, multiple regulators including C5a receptor [294] and RelB [295] have ability of enhancing PD-L1 expression in tumour cells. More importantly, upregulation of Dickkopf-1 in PCa can prevent activation of natural killer cells in mediating immune evasion [296]. Notably, PRC1 participates in providing stemness, immune evasion, and neoangiogenesis in increasing metastasis of PCa cells [297]. Furthermore, APOE has ability of increasing TREM2 expression to increase senescence of neutrophils [298].

9 Hormone, castration, and ADT resistance in prostate cancer

Although main focus is on radio- and chemo-resistance in PCa, there are studies evaluating ability of PCa cells in development of resistance to hormone therapy and other strategies. In CRPC, HSP90 chaperone function is related to hormone resistance; HSP90 has ability of interaction with AR-FL/AR-V7 to develop hormone resistance, while bruceantin targets HSP90 in suppressing hormone resistance [299]. In addition, Hsp60 has been considered as a factor in enhancing lymph node metastasis and development of hormone resistance in PCa [300]. Even under the androgen

deprivation, the PCa cells have ability of developing hormone resistance. There is close association between lipid synthesis and hormone resistance. Notably, caveolin-1 is considered as a factor in enhancing ACC1/FASIN expression and elevates lipid synthesis in development of hormone resistance [301]. On the other hand, decrease in EBP1 expression results in enhancement in carcinogenesis and mediates hormone resistance [302]. Moreover, the upregulation of Bcl-xL is observed in hormone-resistant PCa cells [303]. Even PCa cells can develop resistance to intensive hormone therapy due to loss of chromosome 10q and alterations to TP53 [304]. The interesting point is that the presence of castration-resistant PCa-like cells can cause development of hormone resistance [305]. Another challenge is castration resistance that can be caused by dysregulation of PI3K/Akt/mTOR axis [306] and interference in Hippo/YAP axis by MYBL2 [307].

The castration resistance has been a challenge into the treatment of PCa. In the advanced stages of mCRPC, there are mutations in RB1, TP53, and AR and such genomic alterations can be utilized for the diagnosis and prediction of castration resistance [308]. GREM1 has been considered as a factor causing castration resistance in PCa causing linear plasticity and mediating castration resistance. Furthermore, AR suppresses GREM1 transcription, while it is activated during ADT. Moreover, GREM1 stimulates MAPK axis through interaction with FGFR1 [309]. OBP2A is considered as a small extracellular protein that participates in transporting small and volatile molecules or the odorants via the nasal mucus to olfactory receptors. Moreover, OBP2A may function as a scavenger of toxic odours [310]. Recently, the function of OBP2A in the regulation castration resistance in PCa has been mentioned. The application of ADT causes the release of OBP2A from the tumour cells to upregulate the expression level of CXCL15/IL-8 as pro-survival factors and promoting the MDSC infiltration into the tumour microenvironment, accelerating the castration resistance in PCa [311]. A number of factors demonstrate high expression during the progression of PCa and the development of castration resistance. The AR-V7 expression is poor in primary PCa, while in almost 75% of cases, the expression of AR-V7 enhances after AD therapy and upon the exposure to abiraterone acetate or enzalutamide, its expression remarkably promotes and can be considered as a factor in the stimulation of castration resistance [312]. The stability of AR-V7 enhances due to its interaction with USP14 and USP22. However, application of nobiletin can prevent the interaction of AR-V7 with USP14 and USP22 to enhance the proteasomal degradation of AR-V7 and overcoming castration resistance [313]. The overexpression of SLC12A5 during the progression of PCa can cause the castration resistance in which SLC12A5 interacts with YTHDC1 in the nucleus to enhance HOXB13 expression, increasing the proliferation and metastasis of cancer cells as well as triggering castration resistance [314]. Moreover, the CRISPR screening has recognized RNF19A as a new factor in the development of castration resistance in PCa. AR upregulates HIF1A to increase RNF19A expression, upregulating TRIP13 expression and mediating castration resistance in PCa [315].

10 Nanotherapeutic approaches in prostate cancer

The nanotechnological approaches have been shown to be promising in PCa therapy. The nanostructures can be utilized for gene and drug delivery, immunotherapy, bioimaging, and preventing chemoresistance in PCa cells. The application of nanoparticles for delivery of cargo can remarkably disrupt tumourigenesis. The cyclodextrin-based nanostructures can be functionalized with sialic acid to deliver CSF-1R siRNA. Such nano-scale delivery results in targeted delivery of cargo and switching M2 macrophages to M1 macrophages in improving cancer immunotherapy [316]. Even in PCa cells that are resistant to DTX chemotherapy, application of curcumin-loaded nanostructures can cause cytotoxicity against tumour cells [317]. Besides, the polymeric nanostructures developed from carboxymethylcellulose are able to deliver cabazitaxel in suppressing PCa cells resistant to DTX [318]. The efficacy of current therapeutics can be significantly improved using nanostructures. The GSH-responsive nanoarchitectures are capable of co-delivery of cisplatin and AZD7762 in improving potential in PCa removal [319]. Interestingly, the hybrid nanostructures developed from lipid and polymer can be utilized for co-delivery of DTX and curcumin in effective PCa elimination [320]. It was mentioned that PCa cells have ability of developing resistance to enzalutamide; however, targeted delivery of this drug by nanostructures increases PCa removal [321]. Such nanocarriers display high biocompatibility in treatment of PCa [322, 323] and the interesting point is their ability in co-delivery of drugs and genes in cancer therapy [324].

The wealth evidence has highlighted the fact that nanostructures can improve response of PCa cells to therapy. Although GSH can be exploited as a factor in development of smart and multifunctional nanocarriers, the high levels of GSH in the tumour cells stimulate chemoresistance. For overcoming such condition, small molecule–based nanodrugs loaded with carboplatin have been developed that have 48% drug loading and great plasma stability. Such nanocarriers are able to diminish GSH levels in the tumour cells, and therefore, the ability of platinum compounds as anti-cancer drugs in chelation with DNA increases, overcoming chemoresistance [325]. The drug resistance in PCa cells can be reversed as a result of using nanostructures for co-delivery of drugs and genes. The core–shell

nanostructures have been functionalized with aptamer to deliver PTX and siRNAs. After cytoplasmic delivery of cargo, they suppressed EMT and enhanced PTX sensitivity of cancer cells [326]. Moreover, epigenetic factors such as miR-205 can be loaded in nanostructures comprised of iron oxide core decorated with PEI/PEG layers to increase its cellular uptake, stimulate apoptosis and promote drug sensitivity [327]. More importantly, targeted delivery of two anti-cancer drugs including resveratrol and DTX can be provided by PBM nanostructures in overcoming chemoresistance [328]. More importantly, nanostructures have ability of being used for radiosensitivity of PCa cells [329]. High expression of AR results in radioresistance and delivery of AR-shRNA by nanostructures suppresses this condition. For improving targeting of PCa cells, the functionalization of nanoparticles with folate has been mediated [330]. More interestingly, chemotherapy drug (DTX)-loaded titanate nanotubes have ability of increasing PCa radiosensitivity [331]. Figure 6 highlights the application of nanomaterials in therapy sensitivity.

11 Bioinformatic analysis of molecular pathways-related to carcinogenesis

We analysed GSE46602 datasets (https://www.ncbi.nlm.nih.gov/geo/) [332] and identified 135 differentially expressed genes between prostate cancer tissues and normal specimens (Fig. 7A and B). Then, we performed GO assays and found that 135 differentially expressed genes were mainly enriched in cell junction assembly, cell-substrate junction assembly, cell-substrate junction organization, collagen-containing extracellular matrix, neuron projection terminus, presynaptic active zone membrane, receptor ligand activity, signalling receptor activator activity, and sulphur compound binding (Fig. 7C). The results of KEGG assays suggested that 135 differentially expressed genes were mainly related to glutathione metabolism, malaria, drug metabolism-cytochrome P450, and ECM-receptor interaction (Fig. 7D). In addition, DO analysis revealed that 135 differentially expressed genes were mainly associated with prostate cancer, male reproductive organ cancer, cell type benign neoplasm, urinary system cancer, renal carcinoma, and kidney cancer (Fig. 7E). Then,

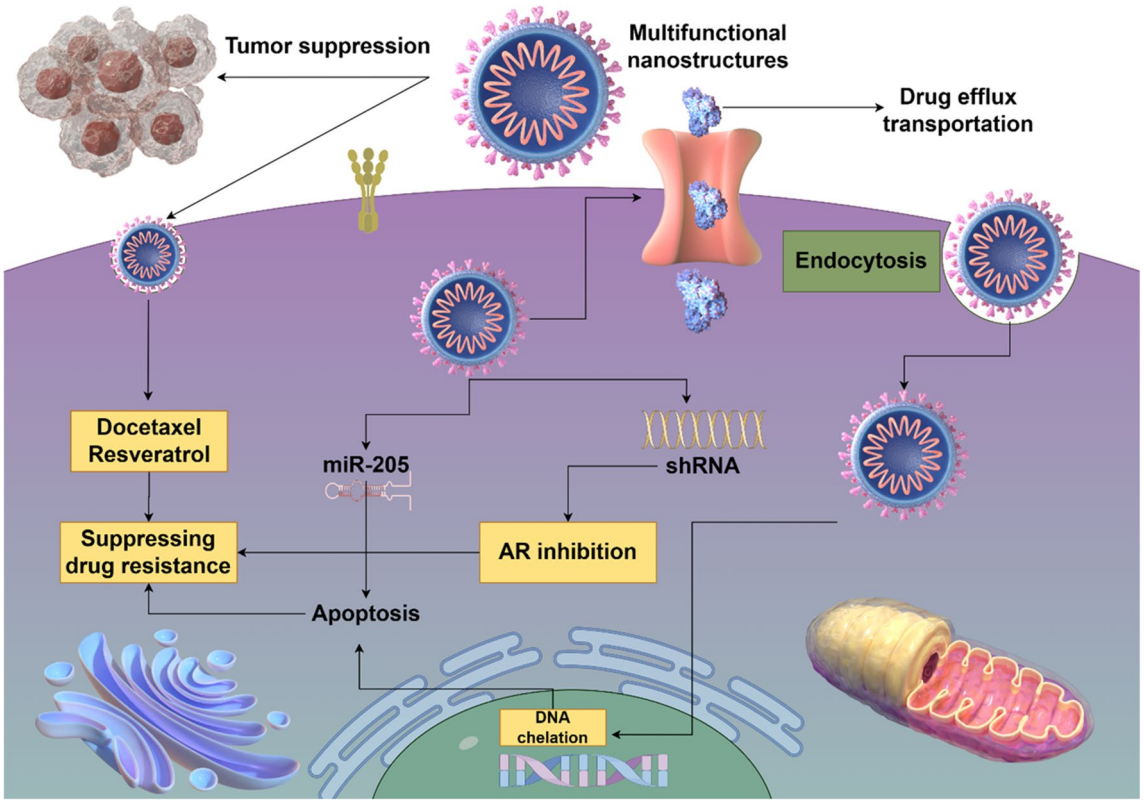
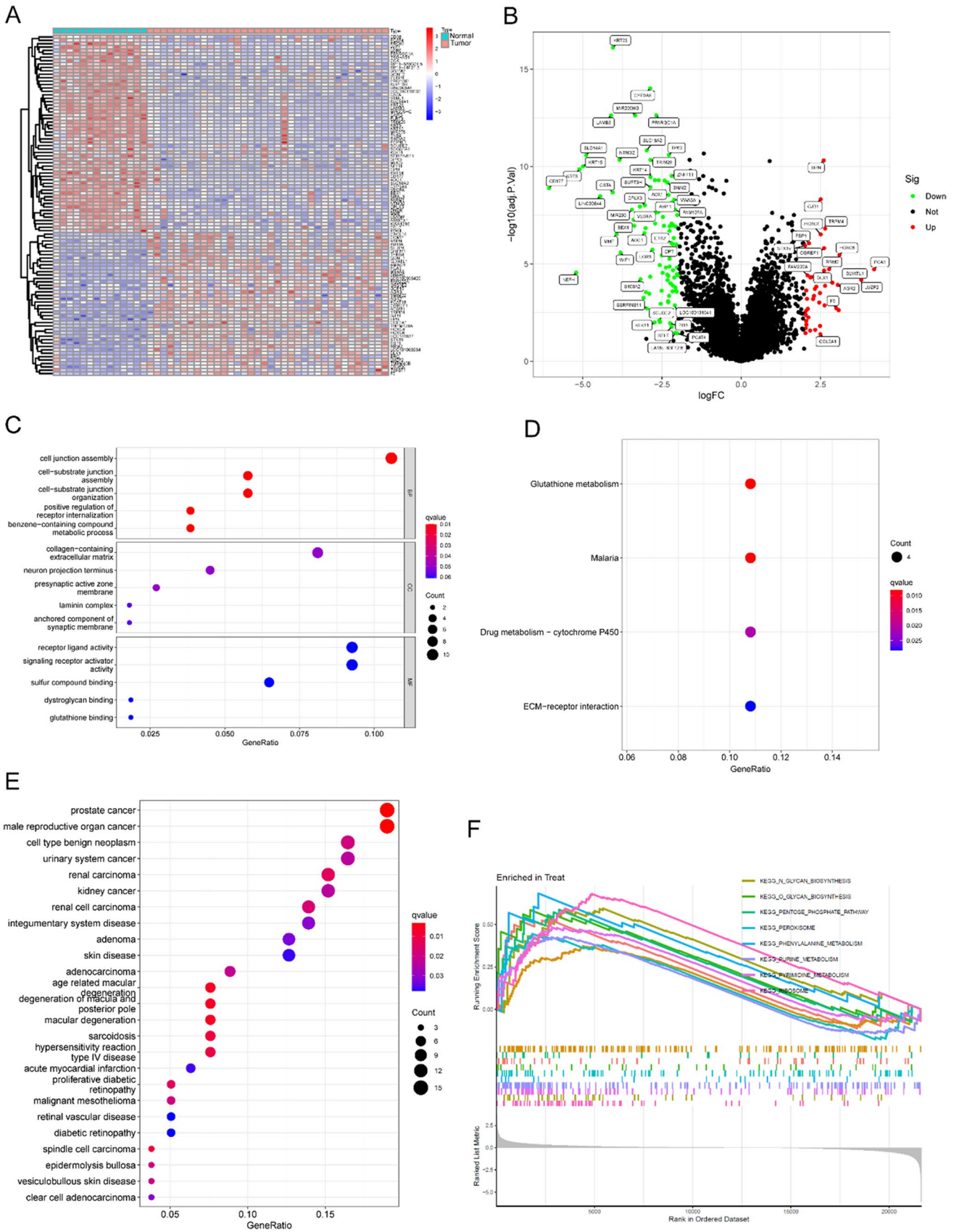


Fig. 6 The role of nanostructures for therapy sensitivity. The most important application of nanostructures is related to increasing the internalization of cargos (drugs and genes) in the tumour cells to improve potential in cancer suppression. The nanoparticles can mediate DNA chelation to cause cell death. Furthermore, the co-delivery of docetaxel and resveratrol by nanostructures can impair the chemoresistance. The miR-205 delivery by nanoparticles can induce apoptosis in enhancing chemosensitivity. Furthermore, the nanoparticles can bypass drug efflux transporters and reduce the export of the drugs out of cancer cells


A
Type
Normal
Tumor
B
−log10(adj.P.Val)
logFC
Sig
Down
Not
Up
C
cell junction assembly
cell−substrate junction assembly
cell−substrate junction organization
positive regulation of receptor internalization
benzene−containing compound metabolic process
collagen−containing extracellular matrix
neuron projection terminus
presynaptic active zone membrane
laminin complex
anchored component of synaptic membrane
receptor ligand activity
signaling receptor activator activity
sulfur compound binding
dystroglycan binding
glutathione binding
BP
CC
MF
qvalue
Count
GeneRatio
D
Glutathione metabolism
Malaria
Drug metabolism − cytochrome P450
ECM−receptor interaction
Count
qvalue
GeneRatio
E
prostate cancer
male reproductive organ cancer
cell type benign neoplasm
urinary system cancer
renal carcinoma
kidney cancer
renal cell carcinoma
integumentary system disease
adenoma
skin disease
adenocarcinoma
age related macular degeneration
degeneration of macula and posterior pole
macular degeneration
sarcoidosis
hypersensitivity reaction type IV disease
acute myocardial infarction
proliferative diabetic retinopathy
malignant mesothelioma
retinal vascular disease
diabetic retinopathy
spindle cell carcinoma
epidermolysis bullosa
vesiculobullous skin disease
clear cell adenocarcinoma
qvalue
Count
GeneRatio
F
Enriched in Treat
KEGG_N_GLYCAN_BIOSYNTHESIS
KEGG_O_GLYCAN_BIOSYNTHESIS
KEGG_PENTOSE_PHOSPHATE_PATHWAY
KEGG_PEROXISOME
KEGG_PHENYLALANINE_METABOLISM
KEGG_PURINE_METABOLISM
KEGG_PYRIMIDINE_METABOLISM
KEGG_RIBOSOME
Running Enrichment Score
Ranked List Metric
Rank in Ordered Dataset

◂**Fig. 7** Bioinformatics analysis of the datasets for GSE46602 with prostate cancer. **A** and **B** Differentially expressed genes between prostate cancer tissues and normal specimens, shown in Heat Map and volcano plot. **C** GO function assays of differentially expressed genes. **D** KEGG pathway assays of differentially expressed genes. **E** Disease assays of differentially expressed genes. **F** GSEA analysis for prostate cancer specimens

we performed GSEA analysis and found that the N_GLYCAN_BIOSYNTHESIS, O_GLYCAN_BIOSYNTHESIS, PENTOSE_PHOSPHATE_PATHWAY, PEROXISOME, PHENYLALANINE_METABOLISM, PURINE_METABOLISM, YRIMIDINE_METABOLISM, and RIBOSOME were significantly enriched in the tumour group (Fig. 7F). Importantly, several studies have confirmed that abnormalities in glutathione metabolism may be associated with tumour development, drug resistance, and treatment response. Tumour cells are often in a state of heightened oxidative stress and require increased antioxidant capacity to counteract free radicals and oxidative damage. Glutathione, as a major intracellular antioxidant, plays a crucial role in tumour cells. By protecting cells from oxidative stress damage, glutathione may influence the sensitivity of tumour cells to treatment. In addition, some enzymes in the glutathione metabolism pathway, such as glutathione S-transferase (GST), are involved in drug metabolism and detoxification processes. Elevated activity of GST in tumour cells may enhance the metabolism and clearance of anti-cancer drugs, thereby affecting drug efficacy. Moreover, certain genes related to glutathione metabolism play a significant role in tumour drug resistance. For instance, the expression levels of genes such as glutathione reductase and glutathione peroxidase may be associated with tumour resistance to chemotherapy drugs. On the other hand, cytochrome P450 is a class of enzymes involved in drug metabolism and plays a crucial role in the transformation and clearance of drugs. The association of differentially expressed genes with the drug metabolism-cytochrome P450 pathway suggests that changes may have occurred in drug metabolism and drug responsiveness in the study subjects. This could potentially have implications for drug efficacy, drug safety, and drug-drug interactions. Our findings suggested the 135 differentially expressed genes may influence drug resistance via regulating glutathione metabolism and drug metabolism-cytochrome P450.

12 Conclusion and remarks

The urological cancers are responsible for high death, even in developed countries, and among them, PCa is a threatening disease for men. The molecular profile of PC in terms of development of resistance to therapy is interesting and this resistance can occur to chemotherapy, radiotherapy, immunotherapy, and hormone therapy. The major focus of studies is on evaluating radioresistance and chemoresistance in PCa. However, underlying mechanisms involved in immune evasion and hormone resistance have been highlighted, showing that the genomic alterations can stimulate therapy failure. The changes in molecular interactions can affect a wide variety of mechanisms related to drug resistance including activity of drug transporters, DNA damage, apoptosis, and autophagy machinery. The molecular interactions are not specified to nucleus and due to changes in both cytoplasm and nucleus, and interactions at transcriptional, translational, and post-translational levels can affect chemoresistance. The major focus in radiotherapy is effect on the DNA damage in tumour cells, and when DNA damage repair occurs, the response to radiotherapy decreases. About hormonal therapy resistance, the interesting point is ability of castration-resistant PC cells in hormone resistance, showing that there are some crosslinkings between them. The bioinformatics analysis revealed some of the most dysregulated genes in therapy resistance in PC, and therefore, future studies can focus on such genes to improve ability in treatment of PCa at clinical level.

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Data availability Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no conflict of interest.

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