REVIEW

Holistic anti-tumor resistance mechanism of YBX1 and its potential as a chemoresistance target in pancreatic ductal adenocarcinoma

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Abstract

The overall survival rate of pancreatic ductal adenocarcinoma (PDAC) is the worst among all cancers, which is mainly due to the fact that most patients are in the late tumor stage when diagnosed, lacking effective treatment options. Although targeted therapy has shown some prospects in PDAC, its efficacy is limited to patients with specific gene mutation or target gene expression. A large number of patients have no other treatment options except chemotherapy. However, the high drug resistance rate of chemotherapy for PDAC severely limits the improvement of curative effect. Therefore, determining the key factors that lead to drug resistance in PDAC is crucial to improve the prognosis of patients. Multifunctional oncoprotein Y-box binding protein 1 (YBX1) may be one of such potential targets. Studies have confirmed that YBX1 is associated with the inherent behavior of a variety of cancers, such as proliferation, invasion, metastasis, and cancer cell stemness. Herein, we integrated and analyzed the resistance mechanism of YBX1 in anti-tumor therapy, and discussed its potential as a therapeutic target to reverse the chemotherapy resistance of PDAC.

Keywords Pancreatic ductal adenocarcinoma, Y-box binding protein-1, Carcinogenesis, Antitumor resistance, Reverse drug resistance

1 The dilemma of pancreatic ductal adenocarcinoma treatment

Pancreatic ductal adenocarcinoma (PDAC) is the 12th most common malignant tumor in the world and the seventh leading cause of cancer death, with a 5-year survival rate of only 10% [1]. In the past 25 years, the global burden of PDAC has doubled, and it has ranked among the top 10 cancer deaths in more than 130 countries [2]. According to the latest data from the American Cancer Society, there will be about 60,430 new PDAC patients in 2021, including about 48,220 deaths. It is estimated that PDAC will become the second leading cause of cancer deaths in the United States in the next 20–30 years [1]. In European Union countries, PDAC is expected to surpass breast cancer and become the third leading cause of cancer related death [3]. In China, the 5-year survival rate of PDAC has not been significantly improved in the past decade, only 9.9%, almost the same as 30 years ago. With the growth of population, the acceleration of aging process and the popularization of westernized lifestyle, the incidence rate of PDAC is expected to rise in the next few years [4, 5].

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For populations with increased risk of PDAC, including those with family history, new diabetes or precancerous pancreatic cysts, early screening will be an important method to reduce the prevalence of PDAC and improve the prognosis. Genomics analyses of blood samples combined with clinical pathological examination from high-risk groups has been proved to be helpful to detect early PDAC and identify the types and stage of precancerous lesions. However, the current cognitive high-frequency classical gene mutations have limitations. For example, mutations in KRAS and / or GNAS genes are highly specific for mucous cysts such as intraductal papillary mucinous neoplasms, but it is impossible to predict the possibility and speed of patients' progression to malignant tumors. Besides, CDKN2A, TP53 and / or SMAD4 gene mutation are almost only seen in patients with advanced PDAC who have already become malignant. Therefore, although diagnosis at the early stage of PDAC can provide a better survival rate, most patients are still diagnosed as advanced diseases and lose the chance of surgery.

The heterogeneity of PDAC makes it difficult to find clinically relevant therapeutic targets. However, with the development of high-throughput sequencing technology, the detection flux has been improved to the level of whole exon / genome, which has made great progress in the research of PDAC in pathogenesis, molecular typing, and pharmacodynamics. For PDAC patients with NTRK fusion gene, larotinib or entropinib is the first choice for treatment. For patients with pathogenic germline BRCA1/2 gene or PALB2 gene mutation, platinum containing regimen is the first choice for first-line chemotherapy. If there is no progress ≥ 16 weeks after platinum treatment, it is recommended to use the PARP inhibitor olaparide for maintenance treatment [6]. A multicenter phase IIb clinical study (PCS07) in Germany used nitozumab combined with gemcitabine as a first-line scheme for locally advanced PDAC or metastatic PDAC patients with KRAS gene wild-type, which significantly improved the 1-year OS and PFS of the population [7]. Although, recent trials of immunotherapeutic strategies, such as the inhibitors pembrolizumab and nivolumab against the PD-1 checkpoint, have shown promise as first-line and second-line treatments for some PDAC. However, due to the lack of powerful biomarkers, the response to immunotherapy is unpredictable, thus it is still impossible to predict which patients will have a therapeutic response [8–11].

At present, the exploration of targeted and immunotherapy of PDAC only stays at the stage of single center and small sample clinical trials, and there is no dawn of clinical transformation. The current clinical practice guidelines for locally advanced or advanced PDAC still recommend gemcitabine chemotherapy combined with other drugs as the standard treatment strategy. Patients usually initially respond to gemcitabine-based chemotherapy, but inevitably develop into drug-resistant tumors [12]. One of the most important obstacles to anti-cancer treatment is the emergence of drug-resistant tumors. Developing powerful therapeutic drugs that can overcome drug resistance is a continuous challenge faced by cancer researchers.

2 Y-Box binding protein 1: a neglected multifunctional oncoprotein in PDAC

Due to the high drug resistance rate of PDAC, there is an urgent need to provide patients with treatment options to improve chemotherapy resistance. One such potential target is Y-Box binding protein 1 (YBX1). YBX1 was first found to be a transcription factor of major histocompatibility complex class II, which binds to the Y-box [13]. YBX1 is a part of a highly conserved cold shock protein superfamily, which contains a conserved nucleic acid binding region called the cold shock domain (CSD) [14, 15]. In addition to CSD, YBX1 is also composed of two other highly disordered domains, namely, alanine/proline rich variable N-terminal domain and C-terminal domain, each of which promotes different biological interactions. As a multifunctional protein, YBX1 exists in the nucleus and cytoplasm and plays different roles. As a transcriptional regulator in the nucleus, YBX1 regulates the expression of multiple genes by binding to the Y-box sequence located in the promoter that contributes to transcriptional regulation, and is also involved in the repair of DNA damage, and pre mRNA splicing [16–18]. In the cytoplasm, YBX1 is the main component of messenger ribonucleoprotein complex, and is closely related to mRNA stability and translation activation or inhibition of many genes [19, 20]. This functional diversity has shown the same extensive biological role in cancer, including participation in cell proliferation, tumorigenesis, invasion and metastasis, and drug resistance of cancer cells [21–23]. Intracellular localization is critical for YBX1 function, its nuclear localization or overexpression is closely related to the poor prognosis of more than 20 human tumors, and this translocation is induced by genotoxic stress induced by anticancer agent administration [24]. Accumulation of YBX1 in the nucleus induces the expression of many genes associated with cancer aggressiveness. Therefore, compounds that can inhibit anticancer drug-induced YBX1 nuclear translocation without cytotoxicity will be powerful tools in cancer chemotherapy. But until now, the molecular events governing YBX1 shuttling and subcellular localization have not been fully described. Raffetseder et al. describe that YBX1 nuclear localization is actively mediated by the splicing factor

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SRp30c/SRSF9 [25]. Furthermore, Stein et al. described heat shock-induced rapid nuclear accumulation of YBX1-induced multidrug resistance protein 1 (MDR1) transcription, which declined again within 4 h after heat shock [26]. Cytoplasmic-nuclear shuttling of YBX1 is a dynamic process controlled by a complex and underappreciated regulatory network and may be strongly dependent on the tumor cell microenvironment [27].

As a multifunctional oncoprotein, the role of YBX1 in PDAC seems to be ignored. Nevertheless, some studies suggest that YBX1 plays an important role in the occurrence, development, invasion and metastasis of PDAC. Studies have shown that the nuclear expression of YBX1 is related to the poor prognosis of PDAC, and its knockdown can inhibit tumor growth and metastasis in a mouse model [28]. Liu et al. found that overexpression of YBX1 can promote the growth of PDAC through GSK3B/cyclin D1/E1 pathway [29]. As a key reversible and heritable mechanism of transcriptional regulation, epigenetic modification plays a crucial role in tumorigenesis. Smoking can induce epigenetic modification to promote the development of PDAC. Chromobox homolog 3 (CBX3) is a key participant in tobacco induced PDAC. Cigarette smoke extract exposure promoted the overexpression of YBX1, which led to the up regulation of CBX3 in PDAC cells. Further study found that CBX3 may inhibit the expression of SMAD specific E3 ubiquitin protein ligase 2 (SMURF2) and activate TGF- β signal pathway to promotes the progress of PDAC. It indicates that YBX1/CBX3/SMURF2 signal axis may be a promising therapeutic target for smoking related PDAC [30]. YBX1 may also play a role in the invasion and metastasis of PDAC. Research shows that high YBX1 level is related to the invasion of peripheral nerves. Silencing YBX1 significantly reduces the ability of cell invasion [31].

3 Holistic analysis of anti-tumor resistance mechanism of YBX1

It was initially found that the expression of ATP binding cassette transporter gene ABCB1 and growth factor receptor genes EGFR and HER2/ErbB2 related to multiple drug resistance were transcriptionally activated by YBX1 in cancer cells. In addition, the expression of other drug resistance related genes MVP/LRP, TOP2A, CD44, CD49f, BCL2, MYC and androgen receptor are also activated by YBX1 transcription, which indicates that YBX1 may be at the center of resistance to anti-tumor treatment. Therefore, targeting YBX1 to overcome tumor resistance provides a new anti-cancer treatment strategy [32, 33]. In this article, we integrated and analyzed the anti-tumor treatment resistance mechanism of YBX1, and summarized the evidence supporting YBX1 to promote chemotherapy resistance (Table 1, Fig. 1), hormone therapy, targeted and immunotherapy resistance (Table 2, Fig. 2).

Table 1 Holistic anti-tumor resistance mechanism of YBX1 in chemotherapy resistance

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Platinum chemotherapy resistance	a. The proto-oncogene Twist1 regulates YBX1 gene and protein expression in bladder cancer cells, while YBX1 regulates Twist1 translation. Both Twist1 and YBX1 promote malignant potential, including tumor growth, invasion, and cisplatin anticancer resistance [34] b. NONO and RALY proteins are required for YBX1-induced resistance to oxaliplatin in colon adenocarcinoma cell line [35] c. YBX1 silencing sensitizes human neuroblastoma SH-SY5Y cells to cisplatin, and down-regulates MDR1 protein through the NF-κB signaling pathway to promote cisplatin-induced apoptosis [36] d. CircIPO7 promotes metastasis and cisplatin chemotherapy resistance in nasopharyngeal carcinoma by promoting nuclear translocation of YBX1 and activating transcription of FGFR1, TNC and NTRK1 [37]
Antimetabolic chemotherapy resistance	a. YBX1 is directly involved in the control of the basal promoter activity of drug resistance protein MVP and 5-FU-induced MVP promoter activity, thereby promoting 5-FU drug resistance in colon cancer [38] b. Abnormal TP53 gene in bladder cancer leads to p53 protein mutation, promotes YBX1 nuclear translocation, upregulates MDR1 transcription, and induces gemcitabine resistance in bladder cancer [39]
Alkaloid chemotherapy resistance	a. Increased nuclear localization of YBX1 was accompanied by upregulation of P-glycoprotein in paclitaxel-pretreated breast cancer. YBX1 may be responsible for paclitaxel resistance in some breast cancer patients [40] b. Taxanes activate RAF-1, which activates ERK, leading to the activation of ribosomal S6 kinase (RSK), which leads to the phosphorylation and activation of YBX1. Targeting RSK by siRNA or kinase inhibitors to indirectly downregulate YBX1 in taxane-resistant prostate cancer cells sensitizes cells to taxanes [41]
Anthracyclines chemotherapy resistance	a. Doxorubicin treatment of drug-sensitive MCF-7 breast cancer cells results in nuclear translocation of YBX1 with concomitant increase of MDR1 expression in P-glycoprotein and hence doxorubicin chemoresistance [42] b. In diffuse large B-cell lymphoma, overexpression of YBX1 increases the adhesion of DLBCL cells to fibronectin, which increases YBX1 phosphorylation at Ser102 and pYBX1 S102 nuclear translocation, conferring the cell adhesion-mediated resistance to mitoxantrone [43]
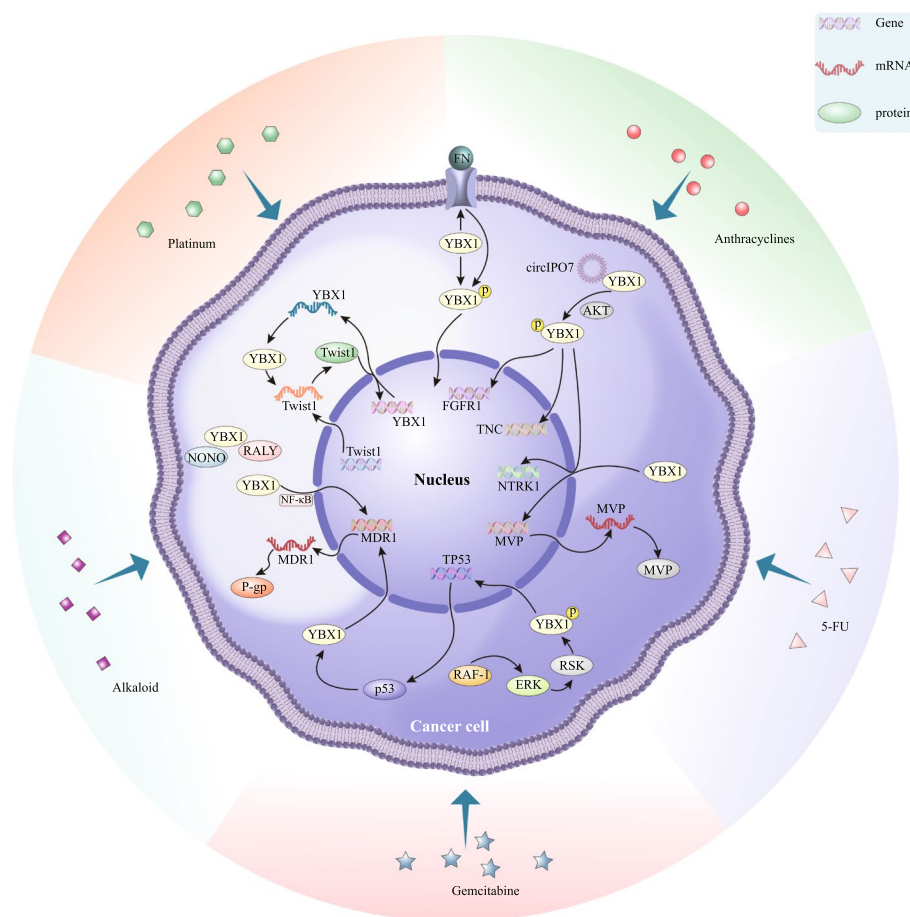
Fig. 1 Holistic anti-tumor resistance mechanism of YBX1 in chemotherapy resistance. The integration shows the molecules that may be involved in the process of YBX1 causing different types of chemotherapeutic drug resistance. Abbreviations: FN, fibronectin; MDR1, multidrug resistance protein 1; MVP, major vault protein; pYBX1, phosphorylated YBX1; P-gp, P-glycoprotein; RSK, ribosomal S6 kinase

Table 2 Holistic anti-tumor resistance mechanism of YBX1 in hormone therapy, targeted and immunotherapy resistance

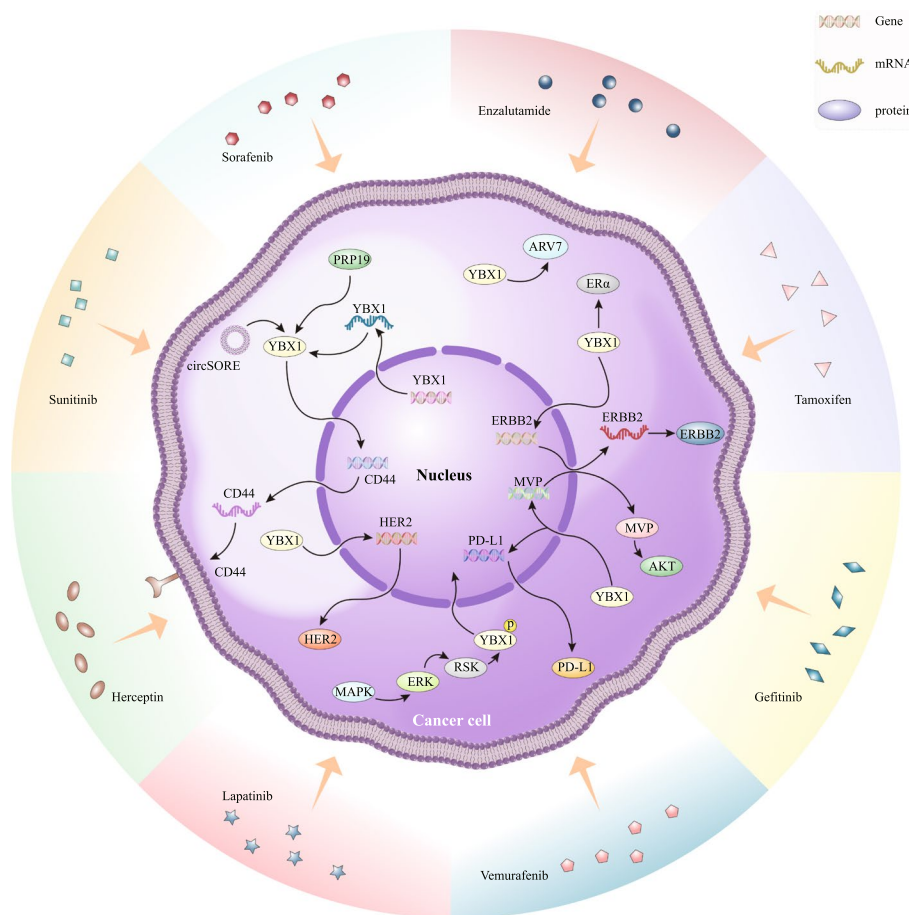|	
Endocrine therapy resistance	a. YBX1 specifically binds ER, causing it to accelerate the degradation of proteasome pathway and induce the transcriptional activation of ERBB2. At the same time, tamoxifen treatment also enhanced the binding of YBX1 to the ERBB2 promoter at the transcriptional level to induce the increase of ERBB2 expression. ER degradation and ERBB2 expression increase the resistance of breast cancer to estrogen [44] b. In castration resistant prostate cancer, YBX1 is also involved in drug resistance to non steroidal anti androgen enzalutamide by up regulating the expression of androgen receptor androgen variant 7. When YB1 is knocked down, the sensitivity of cells to enzalutamide increases [45]
Targeted treatment resistance	a. Herceptin resistant breast cancer cell lines have elevated levels of P-YBX1 S102 and its activated kinase P-RSK. Activated YBX1 mediates Herceptin resistance in breast cancer cells by increasing CD44 + cells, while inhibiting YBX1 can restore cell sensitivity to Herceptin [46] b. YBX1 can specifically control the expression of HER2, rather than EGFR and HER3, and affect the sensitivity of gastric cancer cells to HER2 targeted anticancer drug lapatinib [47] c. The resistance of malignant melanoma to vemurafenib is mediated by the upregulation of p90 ribosomal S6 kinase, which is a kinase downstream of the MAPK/ERK axis phosphorylating YBX1 S102 [48] d. YBX1 is critical in the development of acquired resistance to sunitinib in metastatic clear cell renal cell carcinoma [49] e. CircRNA-SORE mediates sorafenib resistance in hepatocellular carcinoma by stabilizing YBX1 [50] f. YBX1 promotes resistance to gefitinib in lung adenocarcinoma cells by targeting major vault protein to activate AKT signaling and epithelial-mesenchymal transition [51]
Immunotherapy resistance	a. In hepatocellular carcinoma, YBX1 expression was positively correlated with PD-L1, possibly through increased expression through binding to the PD-L1 promoter. Indicates that endogenous YBX1 plays a role in the development of chemoresistance associated with an induced tumor immunosuppressive microenvironment and immune evasion [52]

Fig. 2 Holistic anti-tumor resistance mechanism of YBX1 in hormone therapy, targeted and immunotherapy resistance. The integration shows the molecules that may be involved in different types of hormone therapy, targeted and immunotherapy resistance caused by YBX1. Abbreviations: ARV7, androgen receptor androgen variant 7; MVP, major vault protein

3.1 YBX1 in platinum chemotherapy resistance

Cisplatin is a representative cytotoxic anticancer drug. Studies have shown that enhanced YBX1 expression is usually associated with cisplatin resistance [53, 54]. Hideaki et al. found that YBX1 nuclear localization increased in acquired cisplatin resistant ovarian cancer [55]. When exposed to cisplatin, the expression of YBX1 will also increase in several breast cancer cell lines, and it is found that the overexpression of YBX1 is enough to endow breast cancer cell lines with cisplatin resistance [56, 57]. Many advanced bladder cancer are mainly treated with cisplatin based chemotherapy schemes, including methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), gemcitabine and cisplatin (GC). Twist1, a basic helix-loop-helix transcription factor, is a proto-oncogene [58]. Masaki et al. showed that Twist1 regulated the expression of YBX1 gene and protein in bladder cancer cells, while YBX1 regulated Twist1 translation. Twist1 and YBX1 both promote malignant potential, including tumor growth, invasion, and cisplatin resistance to cancer. This

study also shows that inhibition of Twist1 and YBX1 can improve the cytotoxicity of cisplatin [34].

Whether in adjuvant therapy or metastatic therapy, one of the most effective anti-colorectal cancer treatments is the combination of fluoropyrimidine and oxaliplatin. To determine how YBX1 mediates chemotherapy resistance, Tsofack et al. showed that YBX1 cDNA transfection confers oxaliplatin resistance on two colorectal cell lines SW480 and HT29. According to Oncomine microarray database, a list of 24 potential YBX1 interacting proteins was determined, followed by siRNA inhibition, to identify proteins that significantly affect oxaliplatin sensitivity after gene silencing. Only the down-regulation of NONO or RALY proteins made previously oxaliplatin resistant YBX1 overexpression cells sensitive. It shows that knockdown of NONO or RALY can significantly counteract oxaliplatin resistance in colorectal cancer overexpressing YBX1 protein [35].

Wang et al. established a neuroblastoma cell line with YBX1 silencing by using shRNA knockdown method to

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inhibit the expression of YBX1. YBX1 silenced neuroblastoma cell SH-SY5Y showed a significant decrease in cell proliferation and an increase in apoptosis rate in xenotransplantation tumor models in vitro and in vivo. At the molecular level, YBX1 silencing led to down-regulation of cyclin A, cyclin D1 and Bcl-2, and up-regulated levels of Bax, cleaved caspase-3 and cleaved PARP-1. In addition, xenograft tumors from neuroblastoma SH-SY5Y cell line were treated with YBX1 shRNA plasmid by intratumoral injection, effectively inhibiting tumor growth and inducing cell death [59]. A follow-up study found that YBX1 silencing made SH-SY5Y cells sensitive to cisplatin and passed through NF-κB signal pathway down regulates MDR1 and promotes cisplatin induced apoptosis. Therefore, targeted YBX1 is expected to be used in the treatment of neuroblastoma and overcome its cisplatin resistance when developing new therapeutic strategies for neuroblastoma [36].

Cisplatin based chemotherapy can effectively improve the distant metastasis of nasopharyngeal carcinoma, but about 30% of patients fail due to chemotherapy resistance. Hong et al. found that the novel circRNA circIPO7 was specifically overexpressed in patients with distant metastatic nasopharyngeal carcinoma through sequencing data. Knockout of circIPO7 in nasopharyngeal carcinoma cells can inhibit its metastasis and increase its sensitivity to cisplatin therapy in vitro and in vivo. In mechanism, circIPO7 binds to YBX1 in cytoplasm and promotes its phosphorylation at serine 102 (p-YBX1S102) through kinase AKT, thus further promoting YBX1 nuclear translocation and activating FGFR1, TNC and NTRK1 transcription, thus obtaining cisplatin resistance [37].

3.2 YBX1 in antimetabolic chemotherapy resistance
Vaults are thought to play a direct role in multidrug resistance (MDR) of anticancer drugs. Human major vault protein (MVP), also known as lung resistance-related protein (LRP), is a major component of Vaults and may be involved in defense against foreign organisms. MVP levels are high in some multidrug-resistant tumors, such as colon cancer [60–62]. Non-MDR-related drug 5-fluorouracil (5-FU) has been the main drug in colorectal cancer chemotherapy. Ulrike et al. confirmed in human colon cancer HCT116 cells that, in addition to MDR-related cytostatics, 5-FU can promote the binding activity of transcription factor YBX1 and human MVP gene promoter Y-box (CCAAT box) in a time-dependent manner and interaction, thereby inducing MVP mRNA and protein expression, while YBX1 cDNA transduction resulted in increased expression of endogenous MVP protein. Therefore, this study indicates that YBX1 is directly involved in the control of basal MVP promoter activity and 5-FU-induced MVP promoter activity, and that YBX1 is directly related to MVP-mediated drug resistance [38].

Approximately 80% of muscle-invasive bladder cancers are thought to be caused by the carcinoma in situ (CIS) pathway, which is associated with genetic abnormalities of the tumor suppressor genes TP53 and Rb, and the CIS pathway is thought to have a role in the development of anticancer drug resistance potential. The combination of gemcitabine and cisplatin has been accepted as the new standard of care for advanced bladder cancer because it has fewer adverse events than MVAC [63]. Despite reasonable response rates after initial chemotherapy, 60–70% of patients relapse within the first year probably due to resistance to gemcitabine. The tumor suppressor protein p53 is considered to be the key to the nuclear translocation of YBX1, and YBX1 plays an important role in the acquisition of drug resistance by up-regulating the expression of MDR-1 gene and its product P-glycoprotein (P-gp) through nuclear translocation. Yamashita found that the abnormality of TP53 gene in bladder cancer leads to mutation of p53 protein, coordinates the promotion of YBX1 nuclear translocation, up-regulates the transcription of MDR-1 gene, and induces gemcitabine resistance in bladder cancer. Thus, nuclear expression of YBX1 is important for resistance of TP53-mutant bladder cancer to chemotherapy including gemcitabine [39].

3.3 YBX1 in alkaloid chemotherapy resistance
Paclitaxel is an anticancer agent that is effective against a variety of human tumors, including non-small cell lung cancer, ovarian cancer, breast cancer, head and neck cancer, and melanoma, and has been widely used in locally advanced, metastatic, and recurrent breast cancer, and showed significant efficacy [64–68]. However, as is often observed with other chemotherapy agents, many patients who initially responded to paclitaxel later relapsed. Furthermore, some tumors have been shown to be completely resistant to paclitaxel even during initial treatment. YBX1 can regulate the expression of P-gp encoded by the MDR1 gene, and early studies have shown that paclitaxel is a substrate of P-gp [69]. However, little is known about the role of YBX1 in breast cancer treated with paclitaxel. Tomoyuki et al. found that paclitaxel pretreatment of breast cancer can increase the nuclear localization of YBX1, and paclitaxel may act as an external stress factor leading to YBX1 activation. Concurrently, increased binding of nuclear-translocated YBX1 to the Y-box of the MDR1 promoter upregulated the expression level of P-gp in breast tumors. The study shows that YBX1 may be involved in the occurrence of paclitaxel resistance in breast cancer [40].

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Androgen deprivation therapy (ADT) is currently the gold standard for treatment of recurrent or advanced prostate cancer. Although approximately 90% of prostate cancers are androgen-dependent for tumor growth and respond well to ADT, the majority of androgen-dependent prostate cancers eventually overcome low circulating androgen levels and relapse during ADT in a castration-resistant manner. Taxanes, including docetaxel and cabazitaxel, are currently the only chemotherapy agents that have been shown to confer a survival benefit in patients with castration-resistant prostate cancer (CRPC). However, they are not very efficient and they only prolong survival by a few months due to intrinsic and acquired resistance to taxanes [70, 71]. Masaki found that YBX1 was upregulated in CRPC, and docetaxel treatment further upregulated YBX1 and conferred taxane resistance through the TGF-β/Twist/YBX1 pathway, whereas knockdown of YBX1 sensitized prostate cancer cells to docetaxel [72]. Mechanistically, taxanes activate RAF-1, which activates ERK, leading to the activation of ribosomal S6 kinase (RSK), which leads to the phosphorylation and activation of YBX1, leading to taxane resistance. Targeting RSK by siRNA or kinase inhibitors to indirectly downregulate YBX1 in taxane-resistant prostate cancer cells sensitizes cells to taxanes [41].

3.4 YBX1 in anthracyclines chemotherapy resistance

The role of YBX1 in breast cancer was first observed by Bargou et al., who reported that treatment of drug-sensitive MCF-7 breast cancer cells with doxorubicin resulted in nuclear translocation of YBX1 and increased expression of MDR1 in P-gp, thus doxorubicin chemoresistance [42]. Miao found in human diffuse large B-cell lymphoma DLBCL cell line that YBX1 significantly increased cyclin D1 and cyclin E, accelerated G1/s transition and cell proliferation. Furthermore, overexpression of YBX1 increased the adhesion of DLBCL cells to fibronectin, which increased YBX1 phosphorylation at Ser102 and pYBX1 S102 nuclear translocation, conferring cell adhesion-mediated resistance to mitoxantrone, and silencing YBX1 expression sensitizes DLBCL cells to mitoxantrone and overcomes cell adhesion-mediated resistance phenotype in an AKT-dependent manner [43].

3.5 YBX1 in endocrine therapy resistance

Adjuvant endocrine therapy and chemotherapy have been widely used in the treatment of breast cancer [73]. However, the emergence of refractory tumors is a major complication in breast cancer patients receiving adjuvant endocrine therapy [74]. Targeting YBX1 may help overcome anti-estrogen resistance and malignant progression in breast cancer. YBX1 silencing induces significant downregulation of cell proliferation and cell cycle-related genes, such as HER2, FGFR2, and CDC6, and upregulation of ERα in human breast cancer cell lines, endowing breast cancer cells with enhanced responsiveness to endocrine therapy [44, 75–78]. Furthermore, YBX1 specifically binds ER, leading to its accelerated degradation by the proteasomal pathway, and induces transcriptional activation of ERBB2. Meanwhile, in a parallel manner, tamoxifen (a representative anti-estrogen drug) treatment also enhanced the binding of YBX1 to the ERBB2 promoter at the transcriptional level to induce increased ERBB2 expression. ER degradation and increased ERBB2 expression enhance breast cancer resistance to estrogen. The findings strongly suggest that YBX1 will serve as a target for the treatment of estrogen-resistant breast cancer [44]. In castration-resistant prostate cancer, YBX1 is also implicated in resistance to the nonsteroidal antiandrogen enzalutamide through upregulation of androgen receptor AR variant 7 (AR V7) expression. Sensitivity to enzalutamide increases when YBX1 is knocked down in castration-resistant prostate cancer cells [45].

3.6 YBX1 in targeted treatment resistance

Development of acquired trastuzumab resistance remains a common challenge in the treatment of patients with tumors expressing human epidermal growth factor 2 (HER2) [79, 80]. J Dhillon et al. found that breast cancer trastuzumab-resistant cell lines had elevated levels of P-YBX1 S102 and its activating kinase P-RSK. Expression of P-YBX1 S102 mediates trastuzumab resistance in breast cancer cells by increasing CD44 + cells, whereas inhibition of CD44 or YBX1 restores sensitivity to trastuzumab [23, 46]. The HER2-targeting antibody trastuzumab is an approved treatment modality for HER2-positive advanced gastric cancer. Tomohiro et al. found that nuclear YBX1 expression was significantly associated with HER-2 expression in gastric cancer patient tissues. YBX1 can specifically control the expression of HER2, but not EGFR and HER3, affecting the sensitivity of gastric cancer cells to the HER2-targeted anticancer drug lapatinib [47].

Small molecule inhibitors of mutated BRAF (BRAF V600E/K), such as vemurafenib (PLX4032) and dabrafenib (GSK2118436), have been shown to have significant antitumor activity in melanoma harboring such BRAF mutations, leading to long-term progression free and overall survival [81, 82]. However, initially impressive response rates are limited by the inevitable and often rapid emergence of resistance to targeted therapies [83]. Kosnopfel et al. found that in malignant melanoma cell lines, vemurafenib resistance is mediated by upregulation of p90 RSK, a downstream kinase of the MAPK/ERK axis that phosphorylates YBX1 S102. Inhibition of RSK using chemical inhibitors (BI-D1870 and LJH-685) significantly

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affected the viability of these cells [48]. Resistance to tyrosine kinase inhibitors (TKI) is a phenomenon of concern in patients with renal cell carcinoma (RCC). RCC is a highly vascular tumor, and sunitinib, the most commonly targeted anti-angiogenic drug, works by inhibiting receptor tyrosine kinases in endothelial cells. However, those who initially respond to treatment eventually resistant to TKI within 10–14 months, and YBX1 is found to be critical in the development of sunitinib-acquired resistance in metastatic RCC [49].

Sorafenib is a first-line chemotherapy drug for advanced hepatocellular carcinoma (HCC). However, drug resistance to sorafenib significantly limits its therapeutic effect, and the mechanism of drug resistance has not been fully elucidated. Xu reported a circular RNA circRNA-SORE upregulated in sorafenib-resistant HCC cells. circRNA-SORE binds to YBX1 in the cytoplasm, thereby preventing the nuclear interaction of YBX1 with the E3 ubiquitin ligase PRP19, thereby blocking the PRP19-mediated degradation of YBX1. In vitro and in vivo results showed that circRNA-SORE was transported by exosomes to propagate sorafenib resistance in HCC cells. This study suggests that targeting YBX1 is a potential strategy to overcome sorafenib resistance in HCC patients [50]. Lou et al. found that YBX1 was significantly upregulated in gefitinib-resistant lung adenocarcinoma cells compared with gefitinib-sensitive cells. YBX1 promotes resistance to gefitinib in lung adenocarcinoma cells by targeting MVP to activate AKT signaling and epithelial-mesenchymal transition. Therefore, targeting the YBX1/MVP axis may help overcome gefitinib resistance in lung adenocarcinoma patients [51].

3.7 YBX1 in immunotherapy resistance
Tumor cells can escape immune destruction in tumor chemoresistance, but the mechanisms underlying this phenomenon remain unclear. It has been shown that high YBX1 mRNA levels predict poor prognosis in luminal breast cancer, which is associated with M2 macrophage infiltration and T cell depletion in the tumor microenvironment. Combining classical therapy with immune checkpoint inhibitors and M1 polarizers may be an effective therapeutic strategy for YBX1-overexpressing luminal breast cancer [84]. In the process of resistance to endocrine therapy in prostate cancer, tumor cells can escape immune surveillance and immune killing. Studies have shown that Flightless I homologue (FLII) physically interacts with YBX1 to inhibit the nuclear localization of YBX1, thereby inhibiting the transcription of PD-L1 in enzalutamide-resistant tumors. Restoration of FLII expression reverses enzalutamide resistance by inhibiting the YBX1/PD-L1 pathway to activate T cell responses in the tumor microenvironment. The study also found

that reversal of endocrine therapy resistance and immune evasion was mediated by proliferation of effector CD8 + T cells and suppression of tumor infiltration by regulatory T cells and myeloid-derived suppressor cells. Taken together, these results demonstrate a functional and biological interplay between endocrine therapy resistance and immune evasion mediated through the FLII/YBX1/PD-L1 cascade [85]. Tao demonstrated that high expression of both YBX1 and PD-L1 was associated with a chemoresistant phenotype in HCC. Binding of YBX1 to the PD-L1 promoter enhances PD-L1 transcription. Knockdown of YBX1 in HCC chemoresistant cells resulted in decreased PD-L1 expression. YBX1 promotes PD-L1-associated CD8 + T cell apoptosis and regulates T cell cytokine secretion by upregulating PD-L1. These findings suggest that endogenous YBX1 plays a role in the development of chemoresistance associated with an induced tumor immunosuppressive microenvironment and immune evasion. Inhibition of PD-L1 by reducing endogenous YBX1 expression would improve the therapeutic index of chemotherapy-based tumor immunosuppressive microenvironment and immune evasion. Targeting the YBX1 signaling axis while reversing tumor immune evasion and multidrug resistance may improve antitumor responses [52].

4 Potential of YBX1 as a target of anti-chemoresistance in PDAC
Although there is evidence that YBX1 plays an important role in the development, invasion and metastasis of PDAC, it has rarely been reported in the study of PDAC chemotherapy resistance, and the latter is an important reason that seriously restricts the overall prognosis of PDAC. Long non-coding RNA HIF1A-AS1 can recruit phosphorylated YBX1 to HIF1α mRNA, thereby promoting the translation of HIF1α, enhancing glycolysis and promoting gemcitabine resistance in PDAC [86]. This study suggests that YBX1 plays a role in the process of gemcitabine resistance in PDAC, and targeting YBX1 may be a potential strategy to reverse PDAC chemoresistance. As mentioned before, Twist1 regulates the expression of YBX1 gene and protein in bladder cancer cells, and YBX1 regulates Twist1 translation, leading to cisplatin anticancer resistance [34]. In PDAC, Twist and growth differentiation factor 15 (GDF15) are involved in the tumor progression. Whereas Twist induces GDF15 expression through a p38 MAPK-dependent mechanism, thereby promoting PDAC cell invasion and cisplatin chemotherapy resistance [87]. These studies suggest that YBX1 may promote cisplatin chemotherapy resistance by regulating the expression of Twist1 in PDAC.

Previous explorations in other tumors also confirmed the potential of targeting YBX1 to reverse chemotherapy

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resistance.. Depletion of YBX1 expressed protein with antisense RNA directed against YBX1-specific mRNA resulted in increased sensitivity to cisplatin as reported by Ohga et al. [53, 88]. Similarly, Guay et al. found that shRNA-mediated silencing of the YBX1 gene enhanced cellular sensitivity to cisplatin, UV light, and camptothecin [57]. YBX1 silencing sensitizes neuroblastoma cells to cisplatin and promotes cisplatin-induced apoptosis by downregulating MDR1 through NF-κB signaling. Therefore, targeting YBX1 is promising for neuroblastoma therapy and to overcome its cisplatin resistance when developing new therapeutic strategies [36]. To date, only one small molecule, SU056, effectively inhibits YBX1. SU056 is an azopodophyllotoxin that biophysically binds YBX1 and has been shown to be potent in a syngeneic model of ovarian cancer. Further studies are needed to improve the specificity of SU056 for YBX1 and to identify other compounds specific for YBX1 [89]. However, we need to pay attention to the fact that the specific molecular mechanism of YBX1 leading to multi-drug resistance has not yet been elucidated. In future clinical practice, the side effects caused by targeting YBX1 also require our vigilance.

5 Conclusion and perspectives

Although there is strong evidence that YBX1 drives resistance to antitumor therapy in other cancers by upregulating a wide range of drug resistance-related genes, and studies have shown that YBX1 plays a role in the development of PDAC, the research on YBX1 in inducing chemoresistance in PDAC cells still in early stages. In conclusion, this review covers recent advances in cancer biology on YBX1-promoted resistance to antitumor therapy. Targeting YBX1 may be a potential strategy to reverse chemotherapy resistance in PDAC. Since YBX1 is a protein with pleiotropic functions, designing compounds that can specifically inhibit YBX1 chemoresistance activity or RNA-based drug delivery will be a challenging task.

Abbreviations

PDAC	Pancreatic ductal adenocarcinoma
YBX1	Y-box binding protein 1
CSD	Cold shock domain
MDR1	Multidrug resistance protein 1
CBX3	Chromobox homolog 3
SMURF2	SMAD specific E3 ubiquitin protein ligase 2
MVAC	Methotrexate, vinblastine, doxorubicin and cisplatin
GC	Gemcitabine and cisplatin
MVP	Major vault protein
LRP	Lung resistance-related protein
5-FU	5-Fluorouracil
CIS	Carcinoma in situ
P-gp	P-glycoprotein
ADT	Androgen deprivation therapy
CRPC	Castration-resistant prostate cancer
RSK	Ribosomal S6 kinase
AR V7	AR variant 7
TKI	Tyrosine kinase inhibitors
RCC	Renal cell carcinoma
HCC	Hepatocellular carcinoma
GDF15	Growth differentiation factor 15

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Yes, all the authors consent of publication.

Competing interests
All the authors have no conflicts of interest or financial ties to disclose.

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