KEYNOTE (GREEN)

Advances in understanding the role of P-gp in doxorubicin resistance: Molecular pathways, therapeutic strategies, and prospects

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P-glycoprotein (P-gp) is a drug efflux transporter that triggers doxorubicin (DOX) resistance. In this review, we highlight the molecular avenues regulating P-gp, such as Nrf2, HIF-1α, miRNAs, and long noncoding (lnc)RNAs, to reveal their participation in DOX resistance. These antitumor compounds and genetic tools synergistically reduce P-gp expression. Furthermore, ATP depletion impairs P-gp activity to enhance the antitumor activity of DOX. Nanoarchitectures, including

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liposomes, micelles, polymeric nanoparticles (NPs), and solid lipid nanocarriers, have been developed for the co-delivery of DOX with anticancer compounds and genes enhancing DOX cytotoxicity. Surface modification of nanocarriers, for instance with hyaluronic acid (HA), can promote selectivity toward cancer cells. We discuss these aspects with a focus on P-gp expression and activity.

Introduction

To date, a variety of strategies have been applied for cancer treatment. For more than half a century, chemotherapy has been a valuable tool in this arsenal.[1] However, subsets of patients who initially respond to chemotherapy will eventually develop resistance that significantly hampers their chances of survival.[2–5] Multidrug resistance (MDR) challenges the efficacy of chemotherapy and can drive the resistance of cancer cells to numerous chemotherapeutic agents that are structurally and mechanistically different.[6] Given the increasing incidence of cancers worldwide, significant efforts should be made to enhance the efficacy of chemotherapy.[7]

The underlying reasons for the emergence of MDR are unclear, but could include DNA repair, apoptosis inhibition, signaling pathway switching, detoxifying enzyme activation, metabolic alterations to cancer cells that enable survival under stress, evolutionary mechanisms, drug sequestration in organelles, or the intrinsic or adaptive overexpression of drug efflux proteins, among others.[8–15] Drug transporters present in the cell membrane can pump chemotherapeutic agents out of cancer cells to induce MDR.[16] The most well-known drug transporter is P-gp, also called MDR1 or ABCB1, a key ATP-binding cassette transporter.[17–20]

Previous reviews of mechanisms involved in mediating DOX resistance have focused on the role of molecular pathways, such as lncRNAs, other ncRNAs, and Nrf2, to show how these signaling networks lead to DOX resistance. There have also been efforts to reveal the role of antitumor compounds and nanoarchitectures in enhancing the potential of DOX in cancer therapy, preventing drug resistance and reducing its adverse impacts.[21–29] In the current review, we provide an introduction to P-gp, and its involvement in mediating chemoresistance. We then discuss DOX, its application in cancer therapy, and affiliated drug resistance mechanisms. Finally, we discuss the molecular pathways regulating P-gp in cancer cells, their relationships to alternative drug resistance pathways in cell metabolism, strategies to reverse DOX resistance by targeting P-gp, and prospects in the field.

Role of P-glycoprotein in chemoresistance: Beyond doxorubicin

The more than 100 members of the ABC family are vital transporters in organisms.[30–32] The efflux of toxic substances, nutrient uptake, ion and peptide transportation, and cell signaling are performed by ABC transporters.[33–35] In drug transportation, ABC transporters are involved in phase III of XXX by pumping drugs into fluids, including feces, urine, and bile.[35] However, ABC transporter mutations occur a variety of diseases, such as cystic fibrosis, Dubin–Johnson syndrome, Tangier disease, and cancer.[33,36–38]

P-gp was first discovered 40 years ago and is a potential target in reversing chemoresistance.[39] The expression level of P-gp differs across cancer cell lines, with 50% expression in melanoma and central nervous system cancers, and high expression levels in renal and colon carcinomas.[40–41] The enhanced expression and activity of P-gp are responsible for poor responses to chemotherapy, failure of chemotherapy, and cancer progression.[42] In terms of the involvement of P-gp in cancer resistance, experiments have focused on suppressing its expression in cancer cells.

Structurally, P-gp has two pseudo-symmetric halves. Each halve comprises a long transmembrane domain (TMD) and a cytosolic ABC or nucleotide-binding domain (NBD). The NBD domain is responsible for binding to ATP and its hydrolyzation.[43–49] Upon drug attachment to the binding site in P-gp, conformational alterations occur, in which drug is bound to one side and it is released at another side of P-gp.[50–51] These sites can be targeted by small molecules to inhibit P-gp activity. To date, a variety of P-gp inhibitors have been developed. The calcium channel blocker verapamil has binding affinity to P-gp as low as 10 mM, and is used in clinical studies.[52] Cyclosporine is another P-gp inhibitor with immunosuppressant activity and low affinity for P-gp.[53] However, here are issues related to these and other P-gp inhibitors. The first are adverse impacts on normal cells and tissues, which can be solved using targeted delivery. The second issue is the low specificity and potency of P-gp inhibitors. These issues should be considered when designing novel and efficient inhibitors of P-gp. Recently published studies revealed the role of P-gp in mediating chemoresistance in different cancers. For example, in patients with myeloid leukemia, P-gp upregulation in lymphocytes is associated with poor response to imatinib.[54] Antitumor agents capable of suppressing P-gp enhance the sensitivity of cancer cells to chemotherapy.[55–60]

Doxorubicin: Cancer therapy and resistance mechanisms

DOX is a potent chemotherapeutic agent that is used for treatment of various cancers, such as breast, lung, glioblastoma, glioma, and thyroid cancers.[61–64] However, cancer cells have developed resistance to conventional chemotherapy, including DOX. When used at an optimal dose, DOX efficiently suppresses cancer progression. However, following the frequent application of DOX, cancer cells switch among various molecular pathways to ensure their malignancy and prevent the antitumor activity of the drug. The strategy of increasing the DOX concentration is not recommended, because DOX can adversely affect other organs of the body, such as the heart. Cardiotoxicity and apoptotic cell death in these cells are a well-known adverse impact of DOX.[65–66] Therefore, efforts are required to develop novel strategies for suppressing DOX resistance. In exerting its antitu-

mor activity, DOX induces cell cycle arrest by binding to topoisomerases, inhibiting DNA replication, suppressing cancer cell proliferation, and directing cells toward death.[25] However, similar to other chemotherapeutic agents, each molecular pathway that is responsible for enhancing the proliferation and migration (i.e., malignant behavior) of cancer cells, is activated, reducing the chemosensitivity of cancer cells.[67–68] In addition, downregulation of tumor-suppressing factors is involved in the development of chemoresistance.[69–70]

To exert their antitumor effects, chemotherapeutic agents need to be taken up by cancer cells. Receptors on the cell membrane are responsible for regulating the entrance of agents into cells. P-gp is located on the membrane of cancer cells and increases in its expression are associated with preventing the entry into, or removing chemotherapeutic agents from, cancer cells.[71–72] Loading DOX on nanocarriers, such as HA-functionalized nanocarriers, promotes the penetration of this antitumor agent to cancer cells via receptor (CD44)-mediated endocytosis.[73] Thus, research has focused on developing smart nanostructures for DOX delivery.[74–75] Therefore, overcoming cell membrane receptors is vital for enhancing the chemotherapeutic efficacy of DOX. Here, we discuss the molecular pathways regulating P-gp and strategies used to suppress P-gp expression and activity to shed light on how to overcome DOX resistance.

Doxorubicin and P-glycoprotein

DOX is an activator of tumor-promoting molecular pathways in cancer progression. Exposing cancer cells to DOX stimulates P-gp expression, which further mediates chemoresistance. Molecular pathways promoting P-gp expression are important in this response. Protein kinase B (Akt) is part of the PI3K/Akt/mTOR signaling cascade and can promote the malignant behavior and proliferation of cancer cells. Its upregulation is associated with cancer cell chemoresistance.[76] There is a close relationship between P-gp and Akt in cancer cells, and chemosensitivity results by reducing P-gp expression via Akt inhibition.[77] By activating Akt signaling, DOX promotes P-gp expression to induce resistance. GRP78 activation is vital for Akt/P-gp signaling,[78] while reducing P-gp expression significantly enhances DOX sensitivity.[79] P-gp (C1236T) polymorphism affects the response of cancer cells to DOX and diminishes its intracellular accumulation, further confirming the role of P-gp in triggering DOX resistance.[80]

Glucose has an important role in DOX sensitivity. Exposing cancer cells to hyperglycemic culture conditions (HG) sensitizes cancer cells to DOX. By enhancing reactive oxygen species (ROS) levels, HG reduces P-gp expression to mediate DOX sensitivity. Reducing the expression of Dickkopf protein 4 (DKK4) increases glucose uptake, potentiating P-gp downregulation and enhancing DOX sensitivity.[81] In addition to HG, hypoxia can affect the response of cancer cells to chemotherapy. Hypoxia-inducible factor-1α (HIF-1α) is activated in hypoxic conditions to mediate adaptation to the new environment and to support cancer progression.[82–83] Furthermore, there are interactions between HIF-1α and P-gp in cancer cells.[84] Although most studies agree that cancer progresses in hypoxic condition via HIF-1α upregulation, results are controversial. For example, cancer cells in hypoxic conditions stimulate HIF-1α signaling that subsequently reduces P-gp expression, leading to enhanced DOX sensitivity.[85] Therefore, determining the molecular pathways regulating P-gp expression are vital for understanding DOX sensitivity.[86]

ncRNAs are key players in cancer chemotherapy. miRNAs are short ncRNAs that affect the response of cancer cells to DOX.[87–89] As transcription factors (TFs), miRNAs regulate the expression of downstream targets. As a tumor-suppressing miRNA, miRNA-34a reduces P-gp expression to augment DOX cytotoxicity against hepatocellular carcinoma cells (HepG2 cells), leading to cell cycle arrest (G1 phase).[90] Interest in elucidating the molecular pathways involved in DOX resistance stems from the fact that these signaling networks can be targeted to provide effective cancer chemotherapy. For instance, miRNA-222-3p functions as a double-edged sword in cancer. It can both suppress and induce cancer progression and is considered a reliable biomarker in patients with cancer.[91–93] miRNA-222-3p upregulation induces DOX chemoresistance, whereas its downregulation is associated with reduced expression of P-gp and activation of the caspase cascade, inducing apoptosis.[94] lncRNAs also have a significant role in chemoresistance/chemosensitivity.[95–96] They can regulate the expression of P-gp in cancer cells[97–98]. For example, in breast cancer cells, lncRNA cancer susceptibility candidate 9 (CASC9) binds to enhancer of zeste homolog 2 (EZH2) to promote its expression, leading to P-gp upregulation and DOX resistance.[99]

Pleiotrophin (PTN) is a neurotrophic growth factor with involvement in biological mechanisms, including proliferation, apoptosis, differentiation, and angiogenesis.[100] The potential role of PTN in carcinogenesis has been implicated in different cancers.[101–105] By increasing angiogenesis, PTN can induce vascular endothelial growth (VEGF) expression.[106] Furthermore, clinical studies have revealed the role of PTN as a diagnostic and prognostic factor in patients with cancer.[107–109] In addition, PTN is involved in DOX resistance. In osteosarcoma cells, downregulating PTN enhances sensitivity to DOX and inhibits colony formation by inducing apoptosis. Mechanistically, PTN stimulates anaplastic lymphoma kinase (ALK) expression to induce β-catenin, leading to P-gp upregulation and reduced the sensitive osteosarcoma cells to DOX.[110]

One of the pathways exploited by DOX to suppress cancer progression is the induction of cell death by enhancing ROS levels. Therefore, molecular pathways involved in reducing ROS levels can stimulate the DOX resistance of cancer cells. Nuclear factor erythroid 2-related factor 2 (Nrf2) is involved in the response of cells to oxidative stress. Upregulation of Nrf2 protects normal cells against cell death. However, increasing evidence demonstrates that Nrf2 overexpression is also associated with chemoresistance.[111–113] For example, DOX-resistant cancer cells demonstrate Nrf2 upregulation and investigation of molecular pathways revealed that P-gp undergoes upregulation in these malignant cells. Reducing Nrf2 expression is correlated with a decrease in P-gp expression and DOX sensitivity.[114] This clearly demonstrates the association of antioxidant factors with drug transporters and their collaboration in inducing DOX resis-

tance. It appears that DOX-mediated ROS overgeneration can induce DOX resistance. ROS overgeneration caused by DOX upregulates HIF-1α to enhance P-gp expression and activity, resulting in DOX resistance.[115] However, we are some way from determining the full role of signaling networks regulating P-gp in DOX resistance/sensitivity.[116–117] Here, we discuss strategies applied to target P-gp and its related molecular pathways that would improve the DOX sensitivity of cancer cells.[118]

Alternative metabolic pathways regulating multidrug resistance

Combining anticancer drugs is an emerging therapeutic strategy.[119–120] However, rational drug combinations and schedules that prevent the occurrence of resistance continue to be a challenge.[121–122] For example, scheduling DNA damage-inducing agents in specific sequence with inhibitors of the epidermal growth factor receptor (EGFR) kinase is vital to confer favorable outcomes *in vitro* and *in vivo*.[123] Recent evidence also suggests non-P-gp mechanisms can be targeted by timing the sequence of anticancer drugs against aggressive cancers, such as triple-negative breast cancer (TNBC).[124] Therefore, determining the molecular pathways that circumvent P-gp is important for the design of effective drug combinations and to drive durable responses in the clinic. An important molecular pathway that confers resistance via non-P-gp mechanisms is cancer cell metabolism.[125–127]

There is a close relationship between P-gp and cellular metabolism.[38] For example, TFs that regulate glucose homeostasis, such as HIF-1α, are directly correlated with expression of MDR-1 in aggressive gastrointestinal cancers.[128] Moreover, HIF-1α and related hypoxia protein expression are required for DOX resistance in breast cancer models.[129] Overexpression of HIF-1α signaling in osteosarcoma cells also prevents apoptosis via c-Myc upregulation to mediate DOX resistance. Here, the association between HIF-1α and P-gp is important. HIF-1α signaling enhances P-gp expression to trigger DOX resistance.[130] Hence, synthesizing antitumor agents suppressing HIF-1α signaling could reverse P-gp-mediated DOX resistance.[131]

PI3K/Akt and its downstream pathways, such as mammalian target of rapamycin (mTOR), have an important role in metabolism, drug resistance, and cancer progression.[132] There is also a significant link between the PI3K/Akt family of proteins and P-gp. However, circumventing P-gp via metabolic phenotypes is one way in which molecular pathways drive MDR mechanisms. For example, *in vitro*, *in vivo*, and human *ex vivo* studies show that resistance to taxane chemotherapy in aggressive breast cancer models results in an increase in PI3K/Akt/mTOR, feedback activation of HIF-1α, and recruitment of glycolytic phenotypes.[133] In addition, PI3K/Akt can regulate P-gp expression on its own. The overexpression of PI3K/Akt in breast tumor leads to P-gp upregulation and subsequent DOX resistance.[134] Disrupting the association between the metabolic pathway (PI3K/Akt) and P-gp expression using anticancer compounds, including ferulic acid and osthol, could prevent DOX resistance in tumors.[135–136] Studies have also focused on the role of tumor-suppressor metabolic pathways in regulating P-gp. PTEN signaling is tightly related to growth and glycolysis in tumors and its mutation, deletion, or downregulation leads to carcinogenesis. The overexpression of PTEN by miRNA-29a in colon tumor impairs metabolism and proliferation, and reduces P-gp expression by suppressing PI3K/Akt signaling, resulting in DOX sensitivity.[137]

The result of this metabolic cascade is cross-resistance to DOX, which shares an unrelated mechanism of action to taxanes. Using glucose-targeted and metabolic inhibitors in novel three-drug combinations, including novel inhibitors of glucose-6-phosphate dehydrogenase (G6PD), can reverse resistance development and improve response to treatment.[133] In other cancers, combining metformin [an activator of AMP kinase (AMPK) and modulator of glucose homeostasis[138–139]] with glucose analogs increased sensitivity to DOX in a P-gp-dependent manner.[140] Given the crucial role of AMPK in regulating the glycolysis, metabolism, and growth of tumors,[141] this pathway represent a good example of the association between the metabolic pathway and P-gp. The activation of AMPK signaling by berberine reduces the expression of both HIF-1α and P-gp, resulting in DOX sensitivity.[142] These findings present alternative pathways that either depend on P-gp or operate independently of P-gp to drive resistance mechanisms. Thus, novel drug schedules and sequences that exploit these properties could be used to improve response to DOX (Fig. 1).

In summary: (i) P-gp expression and activity are tightly regulated by upstream mediators that have tumor-suppressor or tumor-promoting activities; (ii) Akt, miRNA-222-3p, CACS9, β-catenin, Nrf2, HIF-1α, and PI3K/Akt are among the pathways enhancing P-gp expression and triggering DOX resistance; (iii) PTEN signaling and ROS overgeneration reduce P-gp expression, suppressing DOX resistance; and (iv) different metabolic pathways can regulate each other's expression. For example, AMPK and HIF-1α both modulate tumor cell metabolism, whereas AMPK stimulation suppresses HIF-1α to reduce P-gp expression and reverse DOX resistance,

Strategies to regulate P-glycoprotein expression and activity

Antitumor compounds

Monochemotherapy is rarely an effective cancer therapy, which is why studies have focused on polychemotherapy as a promising strategy to suppress the progression of cancer cells. P-gp requires energy to function as a drug transporter and, thus, agents reducing the energy levels of cancer cells are of relevance. For example, canagliflozin diminishes ATP levels to impair P-gp activity, resulting in DOX internalization in cancer cells, inhibiting their growth and viability (Fig. 2). Studies evaluating the role of canagliflozin *in vivo* in nude mice bearing HepG2 cells showed that canagliflozin significantly enhanced the efficacy of DOX in tumor eradication by reducing P-gp activity.[143] A variety of naturally occurring inhibitors of P-gp have been developed to promote the DOX sensitivity of cancer cells. For example, co-administration of piperine or capsaicin with DOX significantly elevated the tissue distribution of this chemotherapeutic agent in mice, increasing its tumor suppressor activity.[144–145] The regulation of P-gp is dose dependent manner; therefore, metformin administration decreases P-gp activity in a concentration-dependent manner by reducing ATP levels to induce the sensitiv-

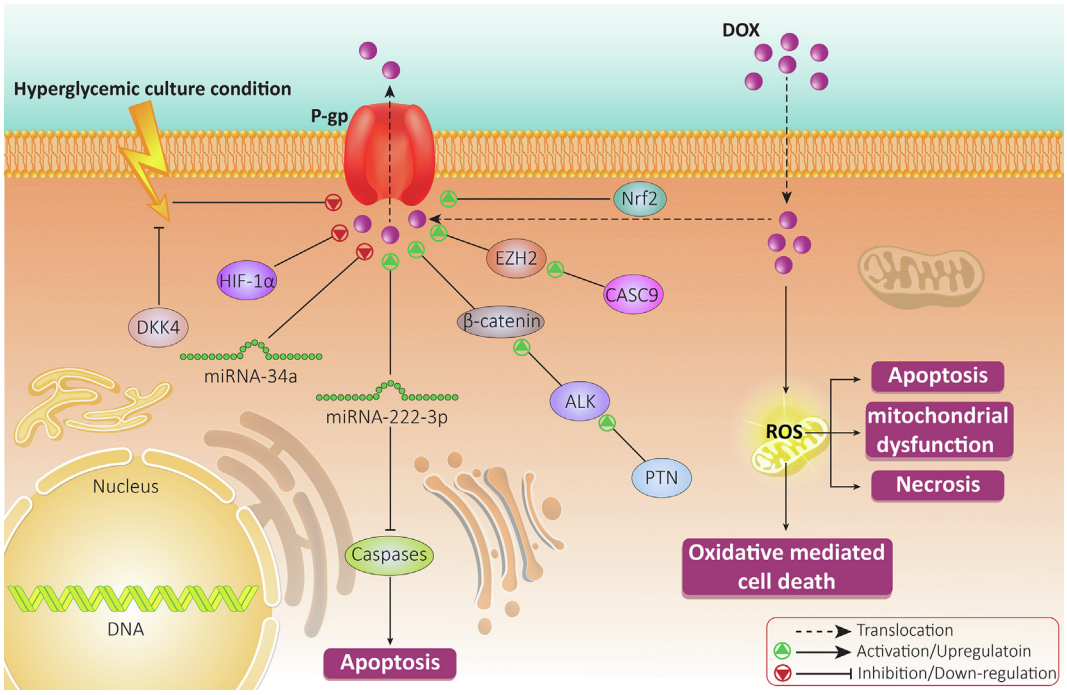

FIGURE 1

Molecular pathways regulating P-glycoprotein (P-gp) in doxorubicin (DOX) chemotherapy. By enhancing reactive oxygen species (ROS) levels in cancer cells, DOX can induce mechanisms of cell death, such as apoptosis and necrosis. Furthermore, ROS can impair the normal function of mitochondria, resulting in apoptotic cell death. Two major molecular pathways involving tumor-promoting and tumor-suppressing factors are involved in DOX resistance/sensitivity by activating and inhibiting the function and expression of P-gp. See main text for additional details.

ity of cancer cells to DOX chemotherapy.[146] In addition to affecting ATP levels, antitumor compounds can regulate the expression of P-gp. Curcumin administration (0.5–2 μM) diminished the expression of P-gp to promote the intracellular accumulation of DOX in leukemia cells, mediating their sensitivity.[147] Docking studies revealed that antitumor compounds with regulatory impacts on P-gp activity can bind to this drug transporter. For instance, the sesquiterpenes *β*-caryophyllene and *β*-caryophyllene oxide bind to the ATP-binding domain of P-gp to interfere with its activity, increasing DOX accumulation in cancer cells.[148]

Dihydroartemisinin (DHA) is another plant derived-natural compound with a primary role as an antimalarial agent.[149] It has demonstrated antitumor activity by inducing ferroptosis in cancer cells.[150] It is also considered as a potential chemosensitizer in that its administration promotes the sensitivity of cancer cells to chemotherapy-mediated cell death by inhibiting Hedgehog signaling and inducing cell cycle arrest.[151–152] In hepatocellular carcinoma cells, DHA downregulates p53 expression to inhibit the ERK1/2-NF-κB axis, resulting in P-gp downregulation and reducing efflux of DOX from cancer cells.[153] Such chemosensitizers can be developed from antitumor phytochemicals. For instance, derivatives of tetrahydroisoquinoline were prepared and their potential to enhance DOX sensitivity was evaluated. One derivative, compound 8b, reduced the expression level of P-gp to accelerate transportation of DOX through the gastrointestinal (GI) barrier, resulting in DOX sensitivity.[154]

Upstream mediators of P-gp can be targeted by antitumor compounds providing DOX sensitivity. Cyclooxygenase-2 (COX-2) and its association with P-gp is vital for hepatocellular carcinoma progression.[155–156] Furthermore, P-gp and COX-2 upregulation can mediate chemoresistance.[157] Therefore, elucidating their relationship is important for increasing DOX sensitivity. As an antitumor agent, guggulsterone decreases COX-2 expression to inhibit P-gp, leading to enhanced DOX sensitivity of cancer cells.[158] Exposing cancer cells to DOX is thought to mediate P-gp overexpression. Epigallocatechin-3-gallate suppresses both the PI3K/Akt and MEK/ERK signaling pathways to downregulate P-gp expression, leading to DOX sensitivity.[159] By decreasing P-gp expression, the antitumor activity of DOX was increased to 97.8%.[160] Therefore, both the expression and activity of P-gp can be negatively regulated by antitumor compounds to increase DOX sensitivity.[140,161–163]

To maximize antitumor activity against cancer cells, and prevent MDR, plant derived-natural compounds can be co-administered for synergistic impacts. A combination of capsaicin and piperine diminished the activity of P-gp to enhance DOX accumulation and promote its cytotoxicity.[164] *In vivo* experiments have revealed the role of P-gp and its expression in rats. Hepatocarcinoma was induced in rats with diethylnitrosamine and DOX was then intravenously administered. In these tumor-bearing rats, expression of P-gp was upregulated to affect pharmacokinetics (PK) of DOX.[165] However, this is not the only mechanism to use to affect DOX PK. The antitumor activity of

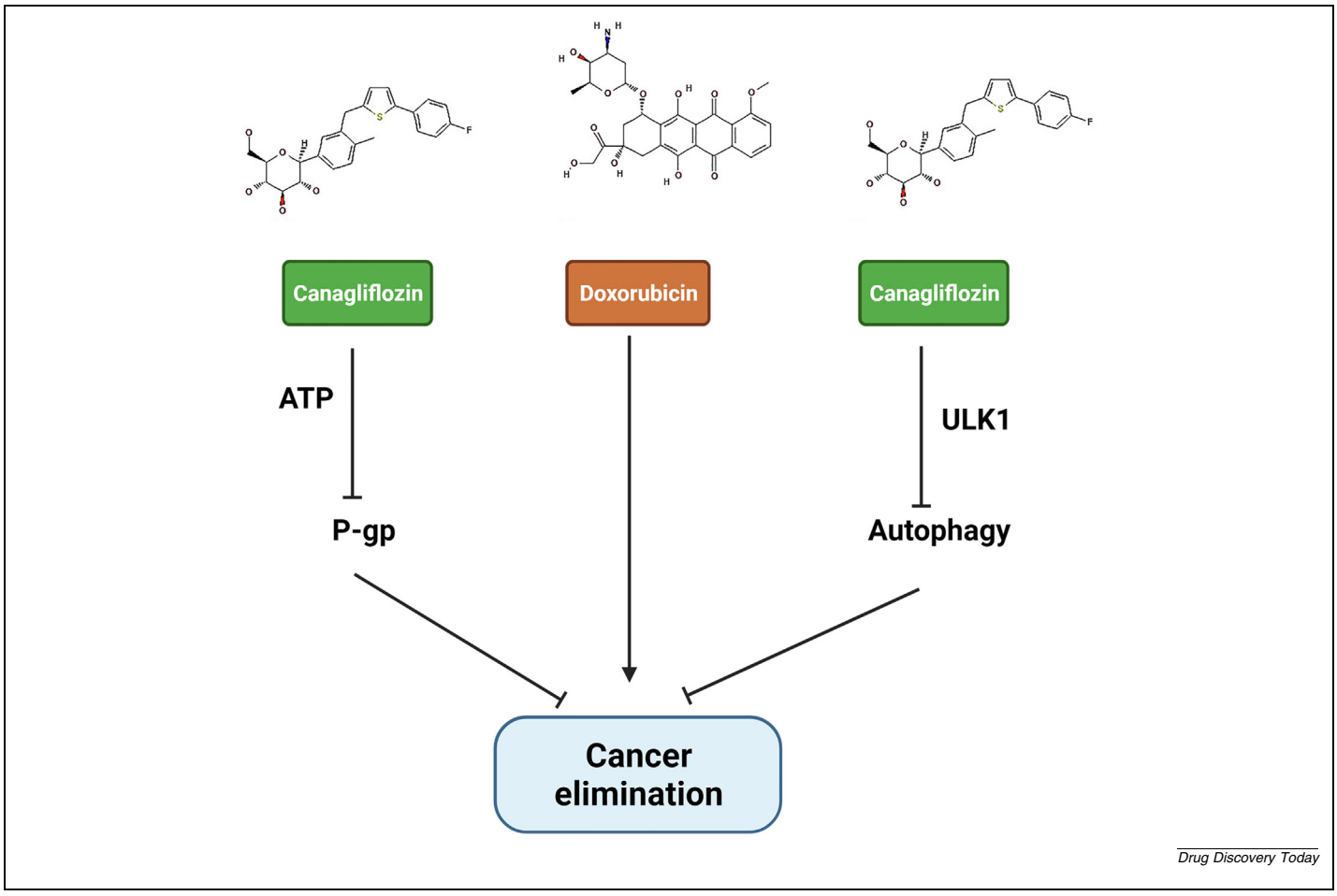

FIGURE 2
Summary of the enhanced effects and action mechanisms of canagliflozin on doxorubicin-treated tumor cells. Reproduced, with permission, from[143].

DOX and its intracellular accumulation can be increased by affecting P-gp expression and activity, as confirmed both *in vitro* and *in vivo*.[166–168]

An important aspect of P-gp is its correlation with ROS levels, which can be affected by antitumor agents. NAD^+ is vital for glycolysis and providing energy (ATP) to enhance the P-gp activity of cancer cells.[169] As an antitumor compound, ascorbate promotes ROS generation via the Haber–Weiss reaction and Fenton chemistry to stimulate DNA damage in cancer cells. PARP activation, as a DNA repair mechanism, requires NAD^+, leading to decreased NAD^+ levels and glycolysis inhibition in cancer cells.[170–172] In DOX-resistance breast cancer cells, ascorbate uses a similar strategy to enhance ROS generation, leading to P-gp downregulation via NAD+ depletion to elevate the antitumor activity of DOX.[173] However, further studies are required to select the appropriate agent for targeting P-gp in DOX-resistant cancer cells. For instance, exposing hepatocellular carcinoma cells to menthol increases P-gp expression to enhance the viability of cells exposed to DOX.[174]

Tanshinone IIA (Tan IIA) is derived from *Salvia miltiorrhiza* and is considered to be a potent chemosensitizer. Tan IIA can suppress ERK/Akt signaling to reverse the oxaliplatin resistance of colorectal cancer cells.[175] Tan IIA also promotes gefitinib sensitivity by downregulating Akt expression.[176] Furthermore, Tan IIA can exert synergistic effects with chemotherapeutic agents.[177] P-gp appears to be a target of Tan IIA in reversing DOX resistance. In breast cancer cells, Tan IIA diminishes P-gp expression to promote the intracellular accumulation of DOX, resulting in its cytotoxicity. Given that Tan IIA is a naturally occurring compound with antioxidant activity, it can simultaneously reduce adverse effects of DOX, such as nephrotoxicity and cardiotoxicity. *In vivo* studies in nude mouse demonstrated that Tan IIA not only diminishes the adverse effects of DOX, such as weight loss, myelosuppression, cardiotoxicity and nephrotoxicity, but also potentiates its antitumor activity in animal models.[178] Thus, research has focused on using phytochemicals to reverse DOX resistance. Algerian propolis can also increase DOX cytotoxicity against pancreatic cancer cells via P-gp inhibition.[179] Derivatives of a certain compound have different effects on DOX cytotoxicity against cancer cells. Enamino 3-benzazecine compounds were evaluated in terms of their chemosensitivity impacts. CO2Me derivates are more potent compared with acetyl derivatives and 10,11-dimethoxy compounds have the highest inhibitory impact against P-gp. These are considered as promising agents for reversing DOX resistance via P-gp inhibition (Fig. 3).[180] Table 1 summarizes the antitumor compounds applied to

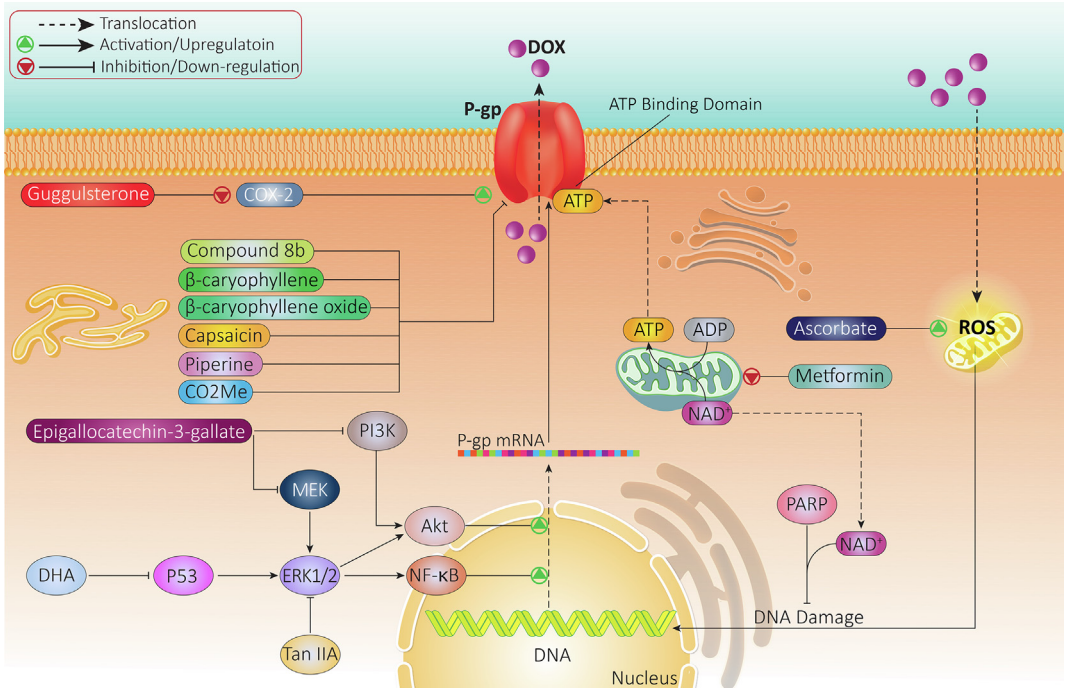

FIGURE 3

Antitumor agents suppressing P-glycoprotein (P-gp) expression and activity in doxorubicin (DOX) sensitivity. As a first step, antitumor compounds induce ATP depletion to prevent P-gp activity, leading to enhanced accumulation of DOX in cancer cells and triggering of its antitumor activity. As a result of DOX internalization, this chemotherapeutic agent, along with other antitumor compounds, enhances ROS levels to induce the death of, and DNA damage in, cancer cells. Finally, tumor-promoting molecular pathways, such as PI3K/Akt, NF-κB, and COX-2, are downregulated by antitumor compounds, potentiating the cytotoxicity of DOX against cancer cells. See main text for additional details.

enhance the sensitivity of cancer cells to DOX chemotherapy by modulating P-gp (Figs. 4–6).

In summary: (i) both synthetic and natural compounds can regulate P-gp expression and affect DOX resistance; (ii) most antitumor compounds regulating P-gp expression are phytochemical and can suppress DOX resistance; (iii) synthetic compounds can be derived from tetrahydroisoquinoline; (iv) based on the poor bioavailability of phytochemicals, the use of nanostructures to increasing their therapeutic potential and decreasing P-gp expression is suggested to reverse DOX resistance; and (v) one of the limitations of current work is that it has mainly been *in vitro* and few studies have examined the role of antitumor compounds in reducing P-gp expression and mediating DOX sensitivity *in vivo*, which should be a focus for future work.

Bioengineering strategies

Engineering in medicine is an evolving, crucial set of tools in the arsenal against cancer.[195] DOX delivery by nanocarriers can not only prevent the development of drug resistance, but also increase the potential of DOX as an antitumor agent. Studies have evaluated the role of nanostructures in DOX delivery and reducing P-gp expression to reverse DOX resistance. Osteosarcoma cells with high P-gp expression are resistant to DOX chemotherapy. Liposomes are nanostructures that can be used for drug and gene delivery with high efficacy. The surface modification of liposomes with ligands can promote their selectivity against cancer cells. HA is a naturally occurring polysaccharide that is used extensively for in the functionalization of NPs because of its interaction with CD44 receptors on the surface of cancer cells. HA modification of nanostructure enhances their entry into cancer cells because of CD44 receptor-mediated endocytosis.[196–197] Loading DOX on HA-based liposomes significantly enhanced the sensitivity of osteosarcoma cells to chemotherapy. After DOX is released inside osteosarcoma cells, it is internalized in endoplasmic reticulum (ER) to induce ER stress. Apoptosis induction then occurs via upregulation of C/EBP homologous protein (CHOP). As a result of DOX triggering ubiquitination and sulfhydration, the activity of P-gp reduces, sensitizing osteosarcoma cells to DOX chemotherapy.[198] However, one of the challenges to the use of DOX and other antitumor agents is their poor bioavailability, particularly of phytochemicals. Increasing evidence demonstrates that loading phytochemicals on NPs increases their antitumor activity.[199–200] Curcumin-loaded solid lipid NPs were applied to suppresses DOX resistance of TNBC cells. These curcumin-loaded nanocarriers were five-to-tenfold more efficient in increasing DOX sensitivity compared with curcumin alone, attributed to the enhanced bioavailability of curcumin through the use of NPs. By enhancing the intracellular accumulation of curcumin in breast cancer cells, curcumin promotes the generation of ROS to suppress Akt/IKKα-β/NF-κB, leading to transcription inhibition of P-gp and increased DOX sensitivity of TNBC cells.[201]

TABLE 1

DOX sensitivity using antitumor agents targeting P-gp.

Antitumor compound	Study design	Effect on P-gp	Effect on DOX chemotherapy	Molecular pathway	Remarks	Refs
Canagliflozin	HepG2 and MCF7 cells (up to 40 mM); nude mice (50 mg/kg)	Downregulation	Enhancement	–	Induced ATP depletion and reducing P-gp activity, resulting in enhanced DOX sensitivity of tumor cells; enhanced antitumor activity of DOX *in vivo* in nude mice	143
Pioglitazone	143B cells (150 μmol/l); orthotopic xenograft model (30 mg/kg)	Downregulation	Enhancement	–	Decreased P-gp expression at mRNA level in a concentration-dependent manner in 143B cells; retarded cancer growth *in vivo* because of synergistic impact of DOX and pioglitazone	167
Tanshinone IIA	MCF-7 cells; xenografts bearing MCF-7 cells (10 mg/kg)	Downregulation	Enhancement	–	Reduced P-gp expression level as a drug efflux transporter; Suppressed tumor growth *in vivo* and ameliorating side effects of DOX	178
Y6 (epigallocatechin gallate derivative)	HEK293 cells (0–100 μmol/l); nude mice (110 mg/kg)	Downregulation	Enhancement	–	Bind to transmembrane domain of ABCB1, reducing its expression and activity; sensitizes to DOX chemotherapy; intragastric administration of Y6 retards tumor growth and mediates DOX sensitivity	181
	BEL-7404 (hepatocellular carcinoma) cells; 0–100 μM DOX; 0–10 μM Y6	Downregulation	Enhancement	MDR1/P-gp	A combination of Y6 and DOX was more efficient in cancer chemotherapy compared with DOX alone by reversing P-gp expression	182
Alantolactone	A549 (lung cancer) cells; 30, 45, and 60 μM	Downregulation	Enhancement	–	Promotes apoptosis of cancer cells; suppresses cancer cell viability; enhances DOX internalization; reduces P-gp expression	183
Costunolide	K562 (myeloid leukemia) cells; 0–100 μM	Downregulation	Enhancement	–	Triggers antiproliferative activity; sensitizes cancer cells to apoptosis; decreases P-gp expression	184
Parthenolide	MDA-MB-231 (breast cancer) cells; 2 μM	Downregulation	Enhancement	–	Reduces Nrf2 expression to promote ROS generation and apoptosis, partially related to P-gp downregulation	185
Schisandrin A	MCF-7 (breast cancer) cells; 20 μM	Downregulation	Enhancement	–	Enhances intracellular accumulation of DOX via P-gp inhibition; enhances potential of DOX to upregulate caspase-9 and PARP	186
Schisandrin B	MCF-7 cells; 0–10 μM	Downregulation	Enhancement	–	Suppresses both expression and activity of P-gp; enhances DOX sensitivity	193
Celecoxib	Lymphoma	Downregulation	Enhancement	–	Potentiates antitumor activity of DOX via P-gp inhibition	187
Scabiosa atropurpurea	Caco-2 (colorectal cancer) cells	Downregulation	Enhancement	–	Induces chemosensitivity; enhances antitumor activity of DOX; reduces P-gp expression	188
SILA-409 and SILA-421	LoVo (colorectal cancer) cells; 0–50 μM	Downregulation	Enhancement	–	Inhibits P-gp activity; increases nuclear localization of DOX	189
Ascorbate	MCF-7 (breast cancer) cells; 0–30 μM DOX; 0–2000 μM ascorbate	Downregulation	Enhancement	–	Reduces activity of P-gp without affecting its expression at protein and mRNA level	173
Statins, phenotiazins	LoVo (colon cancer) cells	Downregulation	Enhancement	–	Decreases mRNA and protein levels of P-gp; mediates DOX sensitivity	190
Decursin	NCI/ADR-RES (ovarian cancer) cells; 0–50 μg/ml	Downregulation	Enhancement	–	Augments antitumor activity; stimulates apoptosis by triggering caspase cascade; suppresses P-gp activity	191
Curcumin	HT29 (colorectal cancer) cells; 0–10 μM	Downregulation	Enhancement	COX-2/P-gp	Overexpression of P-gp via COX-2; impairs COX-2/P-gp axis; promotes intracellular accumulation of DOX; triggers antitumor activity	192
Curcumin derivatives	K562 (leukemia) cells; 0–50 μM	Downregulation	Enhancement	–	Acts as P-gp blocker and promotes intracellular accumulation of DOX	194

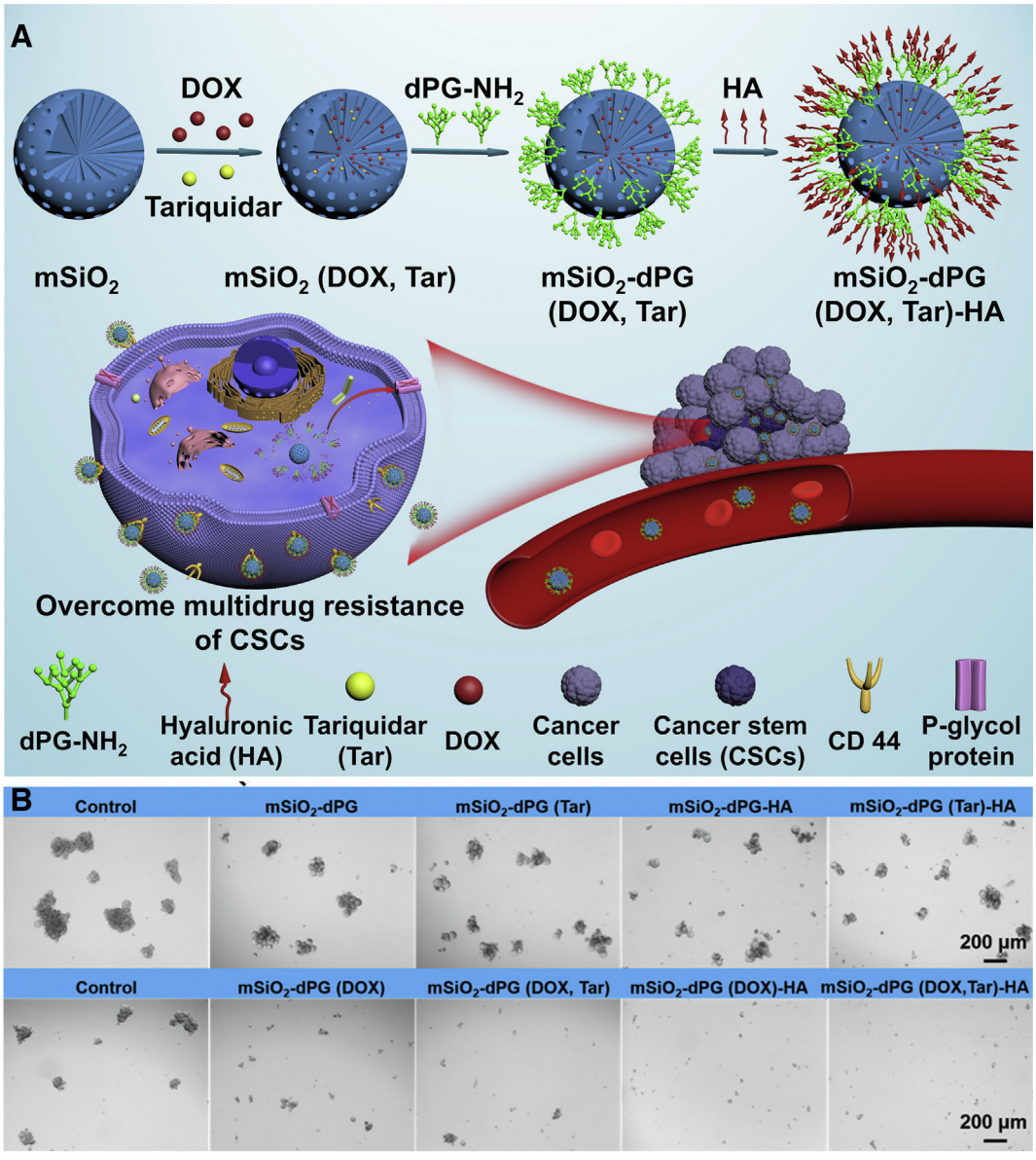

FIGURE 4

Targeted delivery of doxorubicin (DOX) using novel nanomedicines for the selective targeting of P-glycoprotein (P-gp). **(a)** Schematic of dendritic polyglycerol-conjugated mesoporous silica-based targeting nanocarriers co-delivery of DOX and tariquidar to overcome multidrug resistance in breast cancer stem cells. **(b)** Optical micrographs of the formation of tumorspheres after 2 (i) and 10 days (ii) after administration. Reprinted, with permission, from[282].

In addition to HA, folic acid (FA) can be used for surface modification of nanocarriers, because cancer cells express high levels of the FA receptor (FAR). FA is a safe and non-immunogenic agent,[202–203] and FA-modified liposomes can selectively internalize in cancer cells; following nuclear delivery of DOX and nitrooxy, DNA damage and cell cycle arrest occur. Furthermore, mitochondrial function is impaired, resulting in activation of the mitochondrial apoptotic pathway.[204] Another study used FA-functionalized core–shell nanomicelles for the delivery of small interfering (si)RNA-P-gp to promote DOX accumulation at tumor cells, mediating their chemosensitivity.[205] Thus, nanoarchitectures can provide a platform for the co-delivery of DOX with other antitumor agents, simultaneously enhancing their internalization in cancer cells. For example, bovine serum albumin nanocarriers were used for the co-delivery of DOX and cyclopamine to increase the sensitivity of breast cancer cells to DOX. Using these polymeric NPs leads to an increased intracellular accumulation of DOX in cancer cells, reducing P-gp expression and subsequent inhibition of distant metastasis and proliferation.[206]

Aptamers are short oligonucleotide sequences [single-stranded (ss)DNA or RNA] that can bind to specific receptors on the cell surface. Cancer cells have mutations that result in expression of certain receptors that can be targeted by apta-

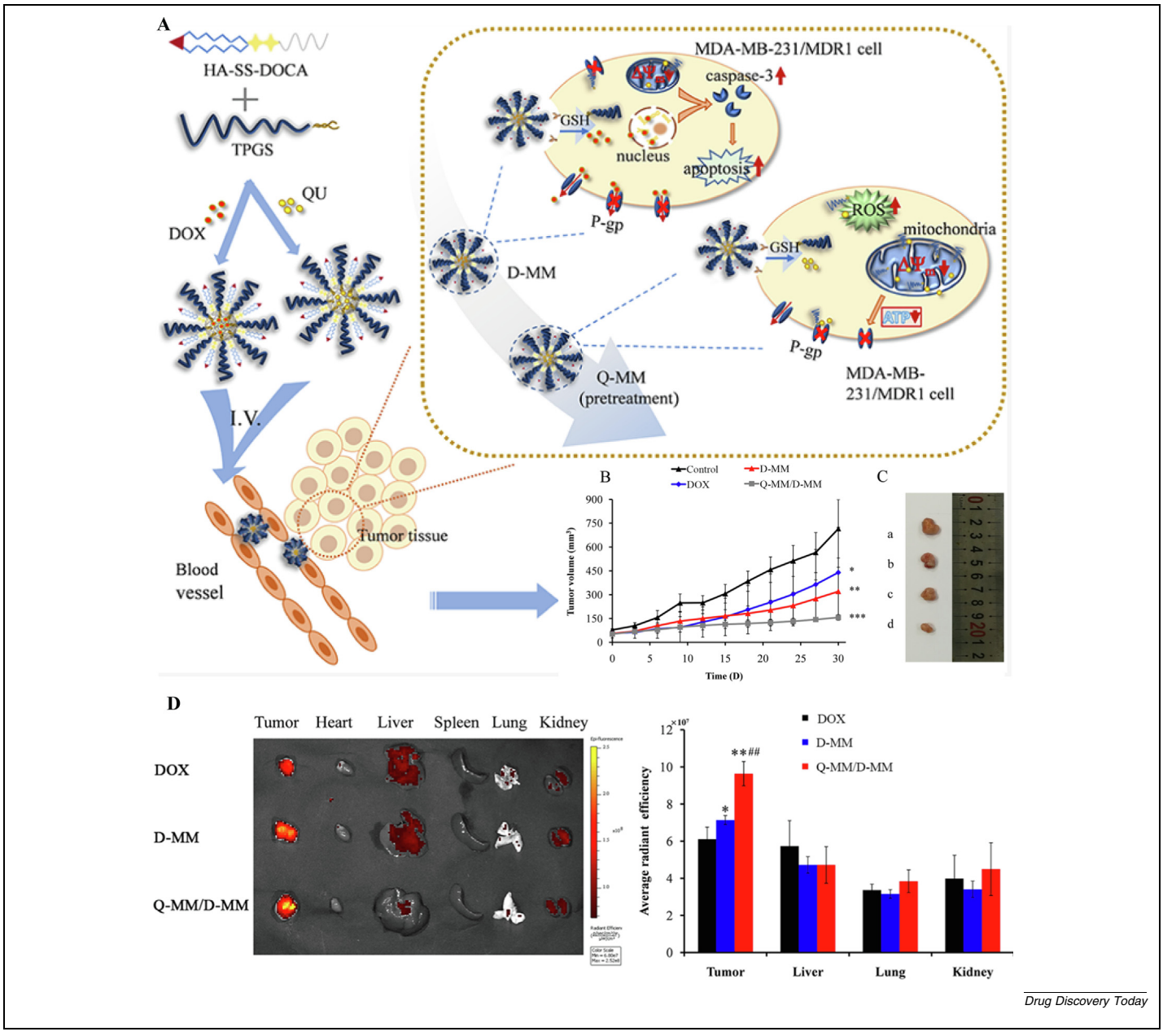

FIGURE 5

Targeting the tumor microenvironment in breast cancer using nanostructures for the co-delivery of anticancer drugs targeting P-glycoprotein (P-gp). **(a)** Schematic of anticancer activity. **(b)** Change in tumor volume as a function of time. **(c)** Tumor sizes after various treatments. **(d)** *Ex vivo* fluorescent images and qualification of tissue distribution of doxorubicin (DOX) 24 h after injection of DOX, DOX-loaded cells (D-MM), and quercetin-loaded cells (Q-MM)/DMM (Q-MM were injected 24 h in advance). Reprinted, with permission, from[283].

mers.[207–208] A recent study applied aptamer-functionalized hybrid NPs for the co-delivery of DOX and siRNA-P-gp. The study demonstrated that these targeted NPs promoted the internalization of DOX and siRNA and, upon P-gp downregulation by siRNA, increased the internalization of, and sensitization of breast cancer cells to, DOX chemotherapy.[209] Another study used micelles for the co-delivery of DOX and siRNA-P-gp in liver cancer therapy. The high cellular uptake of micelles by the cancer cells increased the efficacy of siRNA in downregulating P-gp, leading to enhanced DOX penetration. DOX then exerted its antitumor activity by significantly reducing the proliferation and viability of the cancer cells.[210]

The application of siRNA in reversing DOX resistance via targeting P-gp has also been reported. However, two important issues associated with siRNA are off-targeting and degradation by enzymes, which can be solved by using nanocarriers for its delivery. By enhancing the intracellular accumulation of siRNA, nanostructures enhance the potential of siRNA in gene silencing.[211–213] For example, polymeric micelles have been used for siRNA-P-gp delivery. The encapsulation of DOX by NPs is performed via π-π stacking interactions, with the resulting nanocarriers demonstrating a particle size of 78 nm. These 'smart NPs' were pH-responsive and released siRNA and DOX under mild acidic conditions. Given their biocompatibility, these siRNA-P-

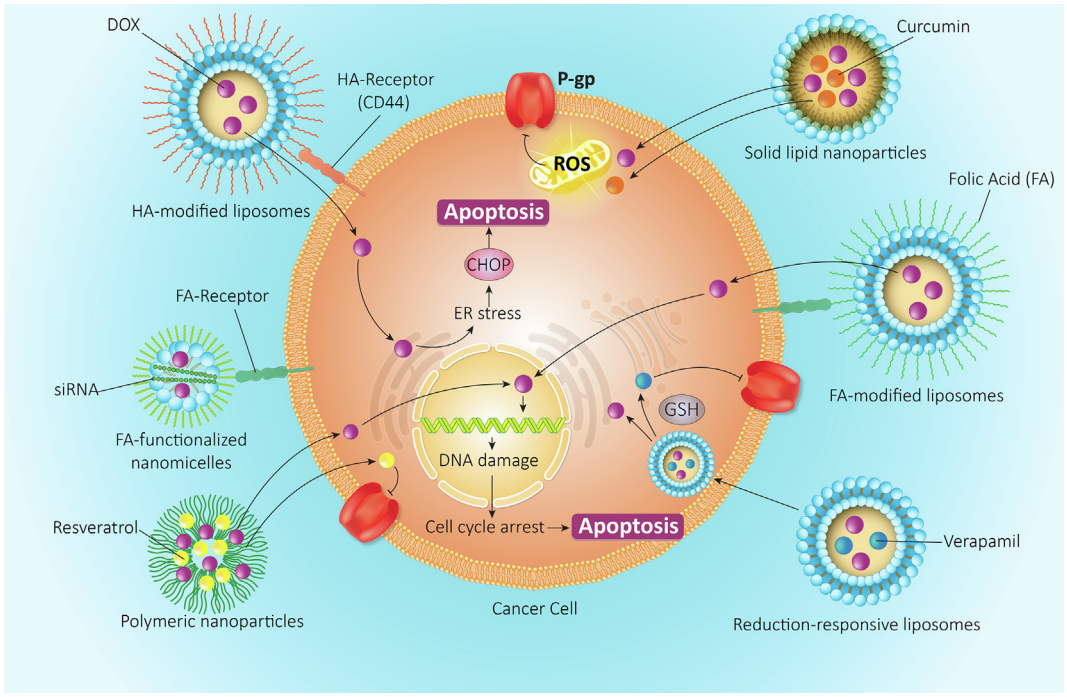

FIGURE 6

Nanocarriers for doxorubicin (DOX) delivery with antitumor agents and genetic tools to suppress P-glycoprotein (P-gp) expression. Surface modification of nanocarriers with ligands, such as folic acid (FA) and hyaluronic acid (HA), can significantly promote the internalization into cancer cells of nanoparticles containing DOX. Upon cellular accumulation, these nanocarriers reduce P-gp activity and expression, reversing DOX resistance. Furthermore, nanocarriers can simultaneously deliver both DOX and other antitumor compounds, such as resveratrol and curcumin, to promote the antitumor activity of DOX. As a genetic tool, small interfering (si)RNA can be loaded onto nanocarriers to reverse DOX resistance.

gp- and DOX-loaded NPs retarded the growth and viability of breast cancer cells.[214] In addition to pH-sensitive NPs, light-responsive NPs can be developed for DOX delivery. For this purpose, agents should be undergo structural changes upon radiation. Wu and colleagues synthesized photoresponsive nanocarriers that, when exposed to 405 and 365 nm light irradiation, degraded coumarin and o-nitrobenzyl ester to release DOX and P-gp short-hairpin RNA (shRNA), rendering cancer cells chemosensitive.[215] The delivery system used for DOX and gene delivery should be simple and easy to prepare. Furthermore, it should be biocompatible and capable of loading DOX at high concentrations. Designing smart NPs, such as pH-responsive NPs, further improves the efficiency of nanocarriers for DOX and siRNA delivery, resulting in increased capacity to downregulate P-gp and improving the DOX sensitivity of cancer cells.[216] Another strategy is to prepare smart nanocarriers that are reduction responsive and release DOX at response to glutathione (GSH) levels. Reduction-responsive liposomes have been synthesized for the co-delivery of DOX and a P-gp inhibitor (verapamil). The encapsulation efficiency of NPs was up to 95% and enhanced the cellular uptake of these antitumor agents through clathrin-mediated and macropinocytosis-mediated endocytosis, followed by efficient lysosomal escape. This led to the increased sensitivity of cancer cells to DOX.[217] Overall, nanostructures have opened a new way in DOX chemotherapy, suppressing P-gp by providing targeted delivery.[218–219]

The combination of natural products with antitumor activity can significantly promote the antitumor activity of DOX and prevent the development of drug resistance. The co-delivery of DOX with resveratrol (Res) using polymeric NPs enhanced DOX cytotoxicity against breast cancer cells and inhibited chemoresistance by downregulating P-gp. *In vivo* studies on tumor-bearing mice demonstrated decreased cancer growth that was partially attributed to P-gp downregulation.[220] The strategy of loading both DOX and antitumor compounds in a nanocarrier is known as 'all-in-one' strategy. Although promising in promoting DOX sensitivity and impairing normal function of P-gp,[221] why has the focus been on synthesizing simple nanocarriers for this purpose? Future work should focus on surface modifications or rendering them stimuli responsive to promote their capacity to reverse DOX resistance and target P-gp.

Autophagy is an important mechanism in cancer therapy. This programmed cell death (PCD) can be activated under starvation and stress conditions to provide energy. However, there is no consensus about its exact role in cancer as a prosurvival or pro-death mechanism. Autophagy induction can pave the road to DOX resistance,[222] whereas another study demonstrated that it is involved in the antitumor activity of DOX.[223] Therefore, the role of autophagy appears to be cancer type dependent, although more studies are required to clarify this. DOX- and chloroquine-loaded NPs can penetrate lung cancer cells through autophagy. However, because autophagy can prevent the antitu-

TABLE 2

Doxorubicin-loaded NPs for suppressing P-gp as an effective cancer chemotherapy.

Nanovehicle	Drug/gene	Cancer	Surface modification	Particle size (nm); Zeta potential (mV); encapsulation efficiency (%)	Remarks	Refs
Lipid-polymer hybrid NPs	DOX; psoralen	Liver	–	64.8 nm; –27.86 mV; 72.2%	Enhances antitumor activity of DOX by 17 fold; enhances ROS levels; stimulates apoptosis stimulation; partial impact of P-gp	271
Mesoporous silica NPs	DOX; quercetin	Gastric	–	100 nm; –28.56 mV; up to 85%	Potentiates gastric cancer chemotherapy; high cellular uptake of DOX; decreases P-gp expression	273
Micelles	DOX	Breast	–	150 nm	Smart nanocarriers sensitive to pH; releases up to 60% of DOX in mild acidic pH; biocompatible and high loading efficiency; enhances circulation in blood; induces apoptosis; overcomes P-gp-mediated DOX resistance	260
	DOX; curcumin	Breast	–	102.5–110 nm; –9.03 to –13.03 mV; 80%	Provides platform for co-delivery of curcumin and DOX; suppresses ATP activity; induces significant decrease in expression of P-gp; potentiates cancer chemotherapy	261
Pegylated liposomes	DOX	Breast	–	–	Overcomes P-gp-mediated DOX resistance; enhances survival of mice	270
Peptides	DOX	Breast	–	–22.8 mV	pH-responsive behavior of peptides; intracellular accumulation through endocytosis; escapes from P-gp efflux; promotes DOX internalization	268
Polymeric micelles	DOX; apatinib	Breast	–	104 nm; –40.4 mV; 68%	ROS and light responsive; provides simultaneous chemotherapy and phototherapy; inhibits P-gp activity	266
Polymeric NPs	DOX	Colon	TAT and poly (aspartic acid)	150 nm; +15 mV	Increases intracellular accumulation of DOX by as much as 86.3%; bypasses P-gp-mediated efflux of DOX; enhances antitumor activity of DOX	262
	DOX; adjudin	Breast	–	100 nm; 50%	pH responsive; overcomes DOX resistance *in vitro* and *in vivo;* induces apoptosis; decreases P-gp expression	263
	DOX; Kras-siRNA	Lung	–	81.8 nm; –18.62 mV	Prolongs release; downregulates P-gp and c-Myc; upregulates p53 expression; potentiates antitumor activity of DOX	265
	DOX; quercetin	Breast	Biotin	105.8 nm; –9.56 mV; 86%	Decreases activity and expression of P-gp; significant increase in internalization of DOX; synergistic effect of DOX and quercetin	267
Polymeric/gold NPs	DOX	Lung	Polyethylene glycol	71.2 nm; –12.83 mV; 73.14%	Prolongs release of DOX; pH sensitive; exerts antiproliferative activity; challenges P-gp activity in DOX efflux; increases DOX internalization	264
Polymersomes	DOX; combretastatin-A4 phosphate	Breast	–	50.3 nm; 90%	Increases cellular uptake; promoting cytotoxicity against cancer cells; enhances apoptotic cell death rate; depletes ATP to suppress P-gp activity	269
Solid-lipid NPs	DOX; α-tocopherol	Breast	–	74–80 nm; –27 to –32 mV; 99%	Bypasses P-gp efflux; overcomes chemoresistance; enhances cytotoxicity against cancer cells	272

mor activity of DOX, its inhibition by chloroquine protects DOX, leading to effective cancer therapy by reducing P-gp expression.[224] Thus, although no direct interaction between autophagy and P-gp has been reported, they might indirectly affect DOX sensitivity.

The tumor microenvironment is a suitable target for cancer therapy. pH-responsive multifunctional micelles were designed for DOX delivery at pH 5.5, resulting in superior antitumor activity by reducing the activity of P-gp and preventing DOX efflux from breast cancer cells. The decrease in activity of P-gp resulted from the depletion of ATP.[225]

The route of administration of chemotherapeutic agents is also important. A popular route of administration of chemotherapeutic agents is intravenous, although this can result in systemic toxicity.[226] Oral administration of chemotherapeutic agents is preferred because of the ease of application and patient compliance.[227–228] However, poor bioavailability, low penetration of the gastrointestinal tract, and efflux by P-gp are disadvantages of this route.[229–230] Consequently, the development of nanocarriers can aid the oral administration of chemotherapeutic agents. Polymeric NPs were synthesized for oral administration of DOX. Enoxaparin sodium (ES; negatively charged) was used to interact electrostatically with DOX (positively charged) in the NPs, which demonstrated a encapsulation efficiency of 93.78%, with sustained DOX release. These nanocarriers also improved the permeability of DOX through caveolin- and clathrin-mediated endocytosis. The amount of DOX efflux was reduced because of P-gp inhibition by the polymeric NPs. *In vivo* research demonstrated as much as a 2.47–3.63-fold increase in DOX bioavailability, increasing its antitumor activity.[231]

Microneedles (MNs) are an emerging technology for the transdermal delivery of drugs.[232–235] They are smaller in size compared with conventional hypodermic needles, being less than 1 nm in length.[236] MNs do not need complex equipment for administration compared with, for example, transdermal delivery methods such as ultrasound or iontophoresis, which need specific electronic equipment.[237–238] Furthermore, MNs reduce the risk of infection and do not damage the epidermal layer, capillaries, or neurons.[232,239–241] Recently, dextran methacrylate hydrogel MNs were designed for the sustained transdermal delivery of DOX and trametinib (Tra). As an antitumor agent, Tra reduces the expression level of P-gp to suppress MDR, leading to enhanced DOX sensitivity. The application of MNs also diminishes systemic delivery-mediated toxicity against normal cells.[242]

The focus for research enhancing DOX sensitivity should be on reducing P-gp activity and expression, and further improvements can be made via the surface modification of NPs to increase their cellular uptake by cancer cells.[209] In addition, the stability of nanocarriers and their high encapsulation efficiency are important parameters for DOX delivery in cancer therapy.[243] Surface modification of nanocarriers can include the use of naturally occurring compounds, such as chitosan, because they are biocompatible.[244] Given that increased ROS generation can inhibit P-gp activity,[245–246] electrodynamic therapy by porous platinum NPs significantly enhanced ROS levels to inhibit P-gp, resulting in combined chemo- and electrodynamic therapy, and enhancing the DOX sensitivity of cancer cells.[247] However, more studies are needed to shed light on the potential of nanoarchitectures for reversing DOX resistance by targeting P-gp.[248–259] Table 2 provides an overview of nanoarchitectures applied for the delivery of DOX alone or in combination with other antitumor agents to reverse P-gp expression and activity.

In summary: (i) a solution to the poor bioavailability of antitumor agents is NPs that enhance their therapeutic impact (e.g., a five-to-tenfold increase for curcumin) to reduce P-gp expression and potentiate the effects of DOX chemotherapy; (ii) nanostructures can protect siRNA and shRNA from degradation and enhance their internalization and also induce P-gp downregulation and mediate DOX sensitivity; (iii) for selective targeting of tumors, surface modifications of NPs with HA and FA have been performed to promote their potential to decrease P-gp expression and trigger DOX sensitivity; and (iv) future work should focus on multifunctional NPs and using sustainable methods for their synthesis.

Concluding remarks

Although tumor-promoting factors undergo upregulation to mediate the resistance of cancer cells to DOX, it appears that drug transporters that induce efflux of DOX are also important in chemoresistance. Therefore, attention should focus on revealing the role of drug transporters in mediating DOX resistance and revealing upstream mediators. As a well-known transporter involved in chemoresistance, P-gp diminishes the internalization of DOX in cancer cells to induce chemoresistance. A variety of molecular pathways regulate P-gp in response to DOX and targeting them is vital to prevent DOX resistance. Various strategies have been used to trigger DOX sensitivity. Antitumor compounds capable of decreasing P-gp expression and activity, such as guggulsterone, DHA, ascorbate, and Tan IIA, enhance the intracellular accumulation of DOX to potentiate its antitumor activity. P-gp requires ATP for its function and, by depleting ATP, antitumor compounds can also improve DOX sensitivity. Genetic tools, such as siRNA, have been also applied to reduce P-gp expression and trigger DOX sensitivity. However, both genetic tools and antitumor compounds suffer issues including degradation and poor bioavailability, respectively. NPs have been developed to overcome such issues. By protecting siRNA circulating in blood and enhancing the bioavailability of antitumor compounds, nanocarriers promote the efficient reduction in P-gp expression and activity to potentiate DOX chemotherapy. Nanoarchitectures designed for DOX delivery can penetrate cancer cells via endocytosis, bypassing P-gp efflux. Surface modification of NPs can enhance their selectivity toward cancer cells, increasing their efficiency in terms of P-gp inhibition and increasing sensitivity to DOX. However, studies have so far been limited to preclinical research, and more experiments will be needed for their clinical translation.

Given that chemotherapy failure is common in the clinic and leads to death of many patients with cancer, it is necessary to translate results from preclinical experiments to the clinic. The optimal option for reversing drug resistance and improving the potential of chemotherapy in the treatment of cancer is combination therapy with antitumor compounds suppressing P-gp activity and/or genetic tools reducing P-gp expression. However, clinical trials are required to investigate this approach in patients.

Challenges to this approach do exist that require solutions. Most antitumor compounds targeting P-gp activity against DOX are phytochemicals. Despite showing potent antitumor activity, phytochemicals suffer poor bioavailability, which needs to be addressed to improve their therapeutic impact.[274–277] NPs are one such way of achieving tumor-targeted therapy. Loading antitumor compounds on multifunctional NPs that are pH, redox, or light responsive, can improve their potential to reduce P-gp expression and decrease DOX resistance, as is also true for genetic tools. Although genetic tools, such as siRNA, are potent gene regulators *in vitro*, their efficiency reduces *in vivo* because of enzyme degradation and lack of targeted delivery.[278–280,213,281] Nanostructures can also be beneficial for the delivery of siRNA and other genetic tools to suppress P-gp and reverse DOX resistance. However, main obstacles to their use in the clinic are the biocompatibility of NPs and their large-scale production. However, overcoming these issues could pave the way for the clinical application of drug- or gene-loaded nanostructures for targeting P-gp to improve the effects of DOX chemotherapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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