New and emerging strategies for targeting cancers: Challenges and opportunities (Review)

SREENIVASA R. CHINNI[1-3], ARUN K. RISHI[3,4] and KALADHAR B. REDDY[2]

[1]Department of Urology, Wayne State University School of Medicine, Detroit, MI 48201, USA;
[2]Department of Pathology, Wayne State University School of Medicine, Detroit, MI 48201, USA;
[3]Department of Oncology, Wayne State University School of Medicine, Detroit, MI 48201, USA;
[4]John D. Dingell VA Medical Center, Detroit, MI 48201 USA

Received January 26, 2026; Accepted May 27, 2026

DOI: 10.3892/ol.2026.15735

Abstract. Despite improvements in treatment strategies for cancer patients, the response to treatment by chemotherapy or immunotherapy has benefited a small percentage of cancer patients, depending on tumor histology and other host factors. The mechanism of resistance is poorly understood because cancer cells exhibit extensive plasticity, enabling them to acquire resistance to chemo- and immunotherapy. This review summarizes the current understanding of interactions between chemo- and immunotherapy and their targets, including recent advancements in the regulatory mechanisms that control chemo- and/or immunotherapy response and resistance in cancer. Furthermore, a variety of chemotherapy and/or immunotherapies are discussed, along with recent developments aimed at preventing resistance and relapses following treatment, with a focus on upcoming initiatives to improve the efficacy of chemo- and immunotherapy for cancer patients.

Correspondence to: Professor Kaladhar B. Reddy, Department of Pathology, Wayne State University School of Medicine, 540 E. Canfield, Detroit, MI 48201, USA
E-mail: kreddy@med.wayne.edu

Abbreviations: ABCG2, ATP-binding cassette subfamily G member 2; ALDH, aldehyde dehydrogenase; anti-PD-1, anti-programmed cell death protein 1; APCs, antigen-presenting cells; B2M, beta-2-microglobulin; BRAF, B-Raf proto-oncogene serine/threonine kinase; CTLA-4, cytotoxic T-lymphocyte associated protein 4; FANCG, Fanconi anemia complementation group G; FENi, Flap endonuclease 1; ICBT, immune checkpoint blockade therapy; PD-L1, programmed death ligand protein 1; TAMs, tumor-associated macrophages; CSCs, cancer stem cells

Key words: cancers, immunotherapy, therapeutic resistance, intrinsic resistance, acquired resistance, cancer stem cells, intratumor heterogeneity

Contents

1. Introduction

Cancer management involves a range of treatment options, such as surgery, chemotherapy, targeted therapy, radiation therapy, endocrine therapy and immunotherapy. Most cancers are initially sensitive to chemotherapy and/or immunotherapy. Over time, cancer cells develop resistance, resulting in the formation of aggressive tumors (1-3). Multiple intrinsic (innate) and extrinsic (acquired) factors, intratumor heterogeneity and stromal factors all contribute to the development of resistance to cancer therapies. Tumor heterogeneity, pre-existing genetic mutations, increased DNA repair mechanisms and drug inactivation are considered key intrinsic factors (4-7). Tumor microenvironment (TME), drug-efflux proteins such as P-glycoprotein (P-gp) and ATP-binding cassette transporters (ABCG2), microRNAs, anti-apoptotic proteins (8), and oncogenic pathways are the key extrinsic factors that contribute to the development of therapeutic resistance in cancer cells. Recently, studies using targeted drugs have increasingly focused on specific molecular alterations to reduce toxicity to normal tissue. These targeted therapies demonstrate limited efficacy in treating patients due to adaptive responses and multiple mechanisms of resistance. Further elucidation of these resistance mechanisms could enable the identification of predictive biomarkers for clinical use to inform the development of optimal therapeutic strategies. Such an actionable strategy, based on insights into the mechanisms of chemotherapy and immunotherapy resistance, can improve clinical outcomes for patients.

2. Resistance to treatment

Intrinsic resistance. A lack of a significant clinical response to therapy is attributed to intrinsic, or primary, resistance. Intrinsic

resistance is natural resistance to a drug or immunotherapy that exists before the start of treatment. However, acquired resistance to chemotherapy or immunotherapy develops over time (9,10). Tumor heterogeneity, genetic mutations and the activation of defense mechanisms can cause intrinsic resistance. Some of the identified mechanisms include activation of mitogen-activated protein kinase (MAPK) or loss of phosphatase and tensin homolog (PTEN) expression, leading to enhanced PI3K signaling, increased WNT/β-catenin signaling and a loss of T-cell response. Examples of intrinsic resistance in cancer include Herceptin (trastuzumab), an anti-HER2 therapy [monoclonal antibody (mAb)] in breast cancer. In breast tumors with Herceptin resistance, there is higher PI3K/Akt activity compared to Herceptin-sensitive tumors (11,12). The difference between intrinsic and acquired Herceptin-resistant breast cancer is that intrinsic resistance tumors do not activate HER2 signaling; in contrast, HER2 signaling is activated in tumors with acquired resistance (13,14), suggesting that intrinsic resistance to Herceptin is independent of HER2 signaling, while acquired resistance depends on HER2 signaling. Patients with gastric cancer showed higher levels of HER2 expression and resistance to cisplatin treatment (15). Certain breast cancer subtypes display inherent therapy resistance. Even prior to treatment, they harbor pre-existing molecular and genetic traits-such as high CD44 and low CD24 expression-that limit treatment efficacy. Additionally, variations in the *BRAF* V600E mutation alter their sensitivity to targeted BRAF (16-18). Immune checkpoint blockade therapy (ICBT), which blocks immune-inhibitory signals to maintain antitumor responses in cancer patients, has been shown to improve clinical outcomes. The TME controls T-cell infiltration, distribution and functions in tumor tissues. However, low tumor immunogenicity or an immunosuppressive TME can lead to significant intrinsic resistance to ICBT (6). Loss of PTEN leads to increased PI3K signaling in numerous types of cancer, including 30% of melanomas, and is associated with resistance to immune checkpoint therapy (19). Drug transport and metabolism help regulate intrinsic drug resistance. The ATP-binding cassette (ABC) transporter protein family transports different drugs across the plasma membrane. This protein family comprises ~49 members, including the multidrug resistance protein 1 (MDR1). MDR1 overexpression in breast, prostate, and lung cancer is associated with intrinsic drug resistance (20-22). Breast cancer resistance protein, an MDR protein, plays a significant role in drug efflux and is associated with chemotherapeutic resistance in breast cancer and leukemias (23-25). Cancer stem cells (CSCs), naturally resistant to drugs, also exhibit higher levels of drug-efflux proteins (26).

Acquired resistance. This type of drug resistance develops gradually over time during therapy for the following reasons: i) Stress-induced driver genes that activate a second proto-oncogene, ii) modifications of drug targets due to mutations or altered expression levels, and iii) changes in the TME. Acquired drug resistance will allow the tumors to regrow (27). Some of the mechanisms are discussed below.

Drug inactivation and alteration in drug targets. Drug inactivation is a mechanism of resistance applicable to chemotherapeutic and molecularly targeted agents (Fig. 1). For instance, platinum drugs can be inactivated by the thiol glutathione (28). Capecitabine, a fluoropyrimidine prodrug, is converted into active 5-fluorouracil (5-FU) by the enzyme thymidine phosphorylase. However, inactivation of the gene encoding this enzyme can occur through methylation, leading to capecitabine resistance (29,30). Antiestrogens such as tamoxifen or aromatase inhibitors are effective initially in most estrogen receptor-positive breast tumors; however, prolonged use can lead to drug resistance (31,32). Tamoxifen resistance may arise from mutations in the estrogen receptor, decreased receptor levels or reduced conversion of tamoxifen to its active form (33,34). In prostate cancers, roughly ~30% of the patients have increased androgen receptor (AR), which is associated with acquired resistance to androgen deprivation therapy using leuprolide, testosterone-lowering drugs and AR antagonists such as bicalutamide (35). In addition to overexpression, a point mutation in AR leads to promiscuity towards other steroid ligands and the expression of variants lacking ligand-binding domains is associated with acquired resistance to newer-generation androgen/AR therapies (36). Approximately 20% of advanced cancer patients undergoing newer-generation androgen/AR therapies develop a complete loss of AR and acquisition of lineage plasticity, leading to a neuroendocrine phenotype in tumors (37). Cancer cells can alter drug targets through changes in expression levels, secondary mutations in the target protein or epigenetic alterations, leading to resistance. Tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptors (EGFR), such as gefitinib and erlotinib, show reasonable initial response rates in non-small cell lung cancer (NSCLC) (38,39). However, half of patients who respond to treatment develop resistance within a year, often with the EGFR-T790M mutation (40,41). However, tumors with an EGFR mutation at threonine 790 to methionine showed enhanced ATP affinity and impaired binding of gefitinib and erlotinib to the kinase (42). Crizotinib (a TKI) that inhibits Anaplastic Lymphoma Kinase (ALK) and Mesenchymal-Epithelial transition (MET) showed a response rate of ~60% in patients with ALK-positive NSCLC. However, some patients relapse within a year due to mutations in the tyrosine kinase domain of the ALK gene (43,44).

Enhanced DNA repair. Chemotherapeutic drugs, including cisplatin and 5-FU, as well as radiation therapy, such as X-rays, induce DNA damage and kill cancer cells. However, improving DNA repair mechanisms in response to this damage can lead to the development of drug resistance (45). Studies suggest that DNA repair genes, such as RAD23 nucleotide excision repair protein B, Fanconi anemia complementation group G and Flap structure-specific endonuclease 1, are upregulated in response to chemotherapy (46). DNA damage triggers cell cycle arrest in normal cells, allowing them to repair the damage. However, mutations or alterations in oncogenes can disrupt cell cycle arrest. However, a mutation in p53 can interrupt cell cycle arrest (47). Additionally, p53 plays a significant role in regulating apoptosis, and its mutation reduces drug-induced apoptosis, leading to resistance (48). As a therapeutic strategy, inhibition of the DNA damage response machinery has been developed, targeting the single-strand break repair enzyme poly(ADP-ribose) polymerase 1 (PARP1) (49). Breast and ovarian tumors harboring mutations in BRCA1 or BRCA2

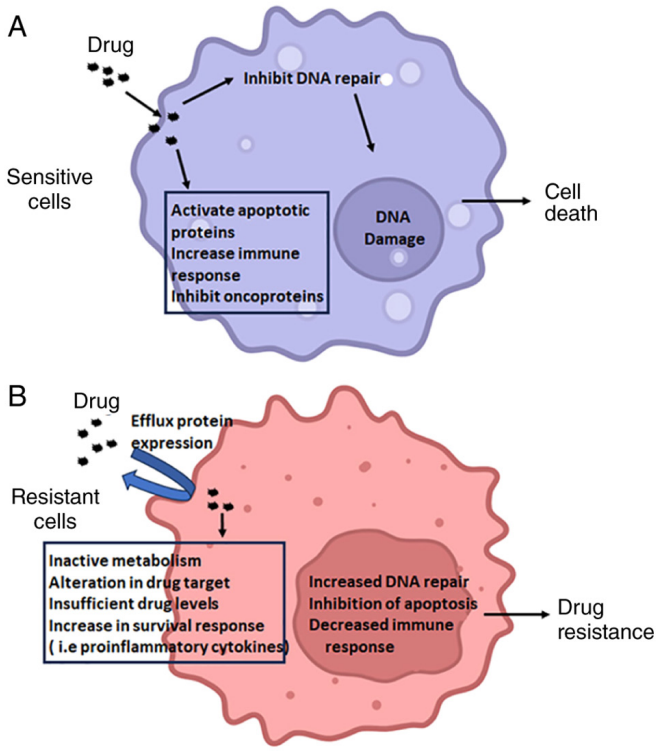

Figure 1. Mechanisms that regulate sensitivity and resistance in cancer cells. (A) Chemotherapeutic drugs are effective when they enter cancer cells and activate multiple pathways, such as inhibiting DNA repair, increasing the expression of apoptotic proteins, inducing an immune response, and inhibiting oncoproteins. These actions lead to DNA damage and cell death. (B) In resistant cells, higher levels of efflux proteins decrease drug accumulation within cancer cells, increase metabolism of inactive compounds, inhibit apoptotic proteins, alter drug targets, result in insufficient drug levels within cells, decrease immune responses, and enhance survival responses (e.g., proinflammatory cytokines). Preexisting templates were used to create figures in BioRender (https://www.biorender.com/ free online version).

are sensitive to PARP inhibitors due to impaired homologous recombination DNA repair (50). Resistance to PARP inhibitors was observed in tumors with in-frame BRCA2 deletions that restore DNA repair, allowing cells to survive treatment (51,52).

Tumor heterogeneity. Cancer cells endure constant stress and continually evolve to survive in diverse environments, resulting in a heterogeneous tumor population. Intertumoral heterogeneity arises from various germline, somatic, and/or environmental factors, as well as diverse tumor subpopulations, including cancer cells, immune cells, and stromal cells. Previous studies indicate that cancer cell subpopulations have different genetic makeups that co-exist in tumors of e.g. breast cancer, ovarian cancer and renal cell carcinoma (53-55). These clonal variants exhibit different sensitivities to chemotherapy, so the initial treatment will kill some tumor cells, while less sensitive cancer cells will survive. The genomic heterogeneity of subpopulations evolves under drug treatment through a Darwinian selection process, as evidenced by changes in subclone composition at different stages of treatment (56-58). Recent studies employing high-throughput methods, such as single-cell RNA sequencing and mutation characterization, have identified evolutionary dynamics within a tumor from the same patient and across tumors from different patients (59,60). These genomic changes were associated with tumor evolution and contributed to the development of multidrug resistance (61,62). In addition, immune analysis of HBV-associated human hepatocellular carcinoma (HCC) revealed reduced T-cell infiltration, suggesting the regulation of an intra-tumoral immune-suppressive microenvironment (63). Thus, tumor heterogeneity and altered immune landscapes, predominantly immune-suppressive, are significant challenges to understanding resistance mechanisms and treatment strategies (Fig. 2).

Cancer cell plasticity. Tumor cell plasticity, as evidenced by an epithelial-mesenchymal transition (EMT), has been shown to confer chemo- and immunotherapeutic resistance in cancers and to recapitulate stem cell characteristics (64-66). Cancer cells that undergo EMT exhibit several phenotypic changes, including increased motility, enhanced migratory capacity and resistance to apoptosis (64,67,68). A defining feature of EMT in cancer is the acquisition of mesenchymal features, characterized by increased levels of mesenchymal markers, such as vimentin and N-cadherin, and decreased expression of epithelial markers, such as E-cadherin. EMT-activating transcription factors such as snail family transcriptional repressor 1 (SNAIL1), twist family bHLH transcription factor 1 (TWIST1), and zinc finger E-box binding homeobox 1 (ZEB1) induce epithelial cells to gain mesenchymal traits, such as motility and invasiveness, without fully undergoing a phenotypic shift. This transition promotes metastasis and strengthens chemoresistance by reinforcing CSC traits that natively resist standard treatment. EMT-induced chemoresistance is driven by multiple mechanisms, including improved DNA repair, increased expression of drug efflux pumps (ABC transporters), and the activation of survival pathways such as PI3K/AKT and nuclear factor (NF)-κB (65,69,70). An example of EMT in cancer drug resistance includes breast cancer, where acetylation of Slug at lysines 166 and 211 by CREB-binding protein boosts its stability, facilitates EMT and augments breast cancer cell motility by downregulating E-cadherin and upregulating N-cadherin and vimentin (71). In cervical cancer cells, YTH N6-methyladenosine RNA-binding protein F2 facilitates motility, invasion, and EMT, while diminishing cisplatin chemosensitivity via stabilizing AXIN1; its knockdown mitigates these effects and increases drug sensitivity. Protein arginine methyltransferase 5 facilitates EMT and metastasis in high-risk neuroblastoma by modulating the EGFR and AKT pathways, activating NF-κB and upregulating ZEB1, SNAIL and TWIST1; its suppression curtails tumor proliferation and the expression of EMT transcription factors (72). In prostate cancer, Ephrin-A2 facilitates metastasis, angiogenesis and EMT by downregulating epithelial markers and upregulating mesenchymal markers; its silencing counteracts these effects (73). Immunotherapy has the advantage in the context of tumor heterogeneity, as the adaptive immune system can recognize multiple tumor antigens within a heterogeneous cancer cell population. However, tumors inhibit the immune system by upregulating suppressive ligands such as programmed death ligand 1 (PD-L1) and TGF-β, and by recruiting myeloid-derived suppressor cells

(MDSCs) and T-regulatory cells (Tregs). The tumor cell plasticity manifested as an EMT has been identified as a major obstacle in effectively treating cancer patients. New drugs are being developed to target the EMT-regulating factors to reduce EMT changes. However, it is proving difficult due to redundancy and overlap among pathways regulating tumor cell plasticity (74,75). Nevertheless, new agents that reduce EMT should be developed to combine with immunotherapies to improve treatment strategies.

Adaptive and oncogenic bypass mechanisms for resistance. Prior studies have shown that EGFR activation results in resistance to chemotherapeutic agents (63,76,77). EGFR-targeted therapies have demonstrated increased sensitivity to chemotherapeutics such as 5-FU, paclitaxel and TNF superfamily member 10 in *in vitro* and/or *in vivo* cancer models (63,76,77). However, colorectal cancer with a KRas mutation was resistant to pharmacological targeting of EGFR because oncogenic KRas functions independently of upstream EGFR activation. Data show that membrane-associated metalloproteases, ADAM, cleave and activate various growth factor ligands. They play a significant role in regulating adaptive resistance (63,78). Research has shown that inhibiting ADAM metallopeptidase domain 17, in combination with chemotherapy, results in a synergistic effect that significantly inhibits tumor growth across multiple cancer types (79,80). The erb-b2 receptor tyrosine kinase 3 (ERBB3) (or HER3)-induced PI3K-AKT pathway is essential for regulating adaptive resistance to pharmacological targeting of EGFR (81-83). This 'oncogenic bypass' occurs because the primary drug target remains unaltered and continues to inhibit tumor growth. However, when an alternative kinase is activated by an adaptive feedback loop, it results in the emergence of an adaptive resistance mechanism; for example, MET amplification activates ERBB3-dependent PI3K, leading to resistance to EGFR inhibitors in ~20% of patients with EGFR-driven lung cancer (84).

CSCs and drug resistance. Residual tumors after chemotherapy and/or radiation therapies contain more CSCs than untreated tumors, which are thought to significantly contribute to therapeutic resistance and the eventual disease relapse (85-88). CSCs are well known for their ability to self-renew and differentiate into various cancer cell types (86).

CSCs are quiescent and, therefore, resistant to chemotherapy, which targets rapidly dividing cells (Fig. 2) (89). Furthermore, CSCs are highly resistant to conventional therapies partly due to high expression of aldehyde dehydrogenase, CD44, anti-apoptotic proteins such as BCL-2 and BCL-XL, drug efflux-inducing ABC transporter proteins, DNA repair and activation of pro-survival signaling molecules, including WNT, NOTCH and NF-κB (89-94). One of the CSC markers, phosphorylated CD44 (Ser-291), inhibits ubiquitin E3 ligase F-box protein 21. As a result, proteasomal degradation of P-gp in breast and ovarian cancer cells is diminished, thereby enhancing drug efflux and reducing the cytotoxic efficacy of the drug (89-93). CSCs are known to reside in the region of tumors with hypoxic niches where the pH is low, leading to stressful conditions. Such a tumor environment leads to hypoxia-inducible factor (HIF)-1α activation, which stimulates the expression of ABC transporters, such as multidrug resistance-associated protein 1, which are downstream targets of the HIF-1α axis in CSCs (95). Furthermore, lower CSC proliferation rates and poor blood vessel formation result in insufficient drug availability to CSCs (96). The plasticity of tumors allows differentiated cells to revert to a stem cell-like state. Therefore, targeting the tumor cells and the CSC population is essential to prevent drug resistance and disease relapse.

Primary and acquired resistance to immunotherapy. The immune system continuously interacts with cancer cells during tumor progression, a process influenced by immune evasion mechanisms. T-cells are activated when major histocompatibility complex (MHC) molecules of the antigen-presenting cells present antigens to specific T-cell receptors on naïve T cells. This interaction of CD28 and B7 (CD80 and CD86) receptors is essential for T-cell activation. However, this process is tightly regulated by inhibitory checkpoints to prevent collateral damage to healthy cells and the emergence of autoimmunity. The effector T cells are inactivated by CTLA-4 receptors, which, in turn, compete with CD28 for B7 ligands, thereby inhibiting T-cell proliferation and IL-2 secretion (97,98). In metastatic melanoma, ~25-33% of the patients who respond to checkpoint blockade therapy with anti-CTLA-4 or anti-programmed cell death 1 (PD-1) agents relapse over time despite initial response to these therapies (99,100).

The loss of T-cell function, the development of escape mutations, and reduced or absent T-cell recognition due to the repression of tumor antigen presentation appear to be potential mechanisms. Immunotherapy treatments initially show a promising response, characterized by reduced IL-2 secretion and the use of tumor-infiltrating lymphocyte adoptive cell therapy. However, over time, it develops resistance due to the loss of β-2-microglobulin (B2M), a critical component shared by all human leukocyte antigen (HLA) class I molecules. B2M is essential for proper folding and transportation of HLA class I to the cell surface, and its reduction or elimination leads to diminished HLA class I presentation on the cell surface (101,102). In cases of anti-PD-1 therapy, the resistant cells often harbor a B2M truncation, leading to complete loss of cell-surface HLA class I expression (Fig. 3) (103).

In cancers such as breast cancer, lung cancer, and glioblastoma, the chemotaxis of pro-inflammatory M1 macrophages towards cytokines released by tumor CSCs results in their conversion to M2 (anti-inflammatory) macrophages at the tumor site. M2 macrophages secrete TGF-β, IL-10, IL-23, and arginase I, creating an immune-suppressive TME (103-106). For example, in HCC, CD133+ cells release the pro-inflammatory cytokine IL-8, which promotes the M2 polarization of tumor-associated macrophages (TAMs) and, in turn, stimulates therapeutic resistance (107). TAMs activated by CSCs inhibit T-cell cytotoxicity by promoting the overexpression of cancer immune checkpoint receptors, such as PD-L1 and CD80/CD86. These immune checkpoint receptors then interact with PD-1 and CTLA-4 on the surface of CD8+ T cells, leading to the subsequent impairment of the immune response and increased resistance to therapy (108,109).

The intrinsic factors that contribute to chemo and/or immunotherapy resistance include mutation(s) or nongenetic

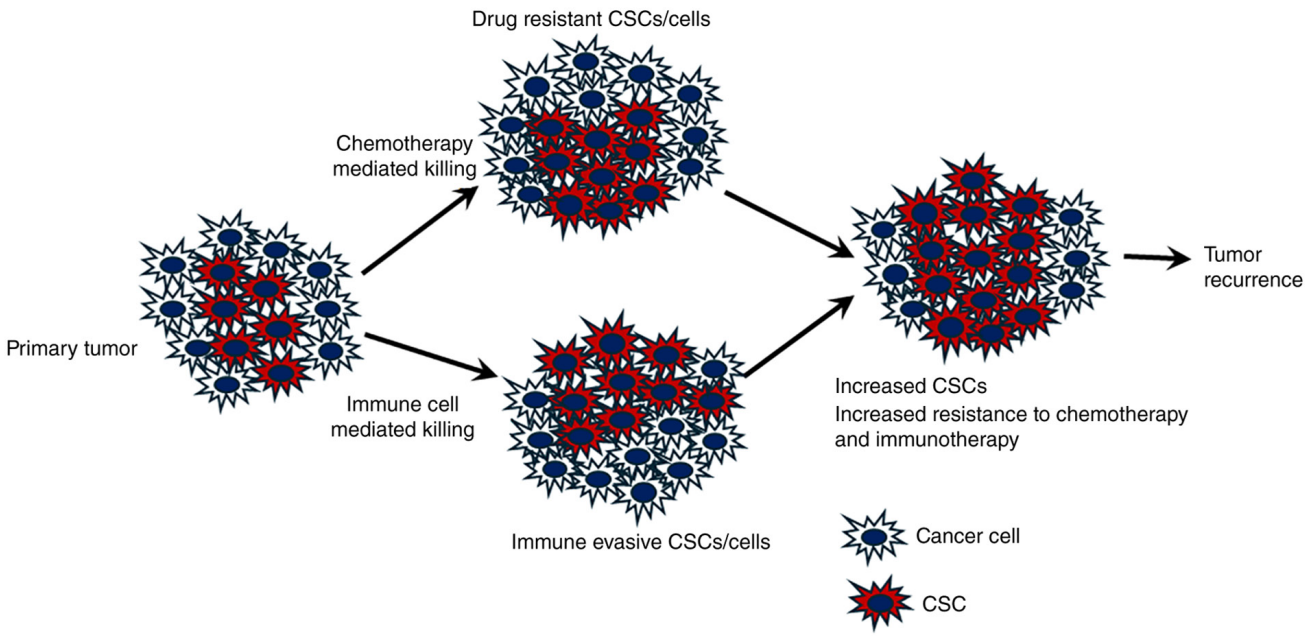

Figure 2. The CSC model demonstrates cancer cells' ability to adapt to therapeutic pressure by rerouting signaling pathways, providing a selective advantage to therapy and leading to treatment resistance. Chemotherapy or immunotherapy treatment leads to the evolution of drug-resistant CSCs due to their inherent ability to self-renew, low proliferation rates, enhanced DNA repair mechanisms, and their capacity to reside in a protective tumor microenvironment, allowing them to survive and repopulate after therapy. CSC, cancer stem cell.

alterations in the target or other proteins that interfere with drug- and/or immuno-targeting, or overexpression of the target, leading to a stoichiometric imbalance between the drug and its cellular target. Additionally, redundancy in cytokine function and in the drugs' protein targets, coupled with compensatory overexpression of another membrane receptor and its downstream signaling, often serves as a significant mechanism of resistance (110,111). Signaling through the MAPK pathway, enhanced PI3K signaling following PTEN loss, the WNT/β-catenin pathway, and interferon-γ signaling result in a diminished or absent T-cell response due to reduced or lost tumor antigen expression. These resistance mechanisms may then evolve into adaptive resistance. For example, activation of the oncogenic MAPK pathway induces suppressed T-cell recruitment and function (112).

Cancer cells have unique features that enable them to evade immune recognition by exploiting TME, thereby conferring resistance. In recent years, researchers have also explored combining immunotherapy with other treatment modalities, such as chemotherapy, radiation therapy, and targeted therapy. Overall, the development of novel immunotherapies and the combination of different treatment modalities hold great promise for improving outcomes in cancer patients, particularly those with previously untreatable or advanced diseases. Some immunotherapies approved for treatment by the Food and Drug Administration (FDA) are discussed in the following chapter.

3. Clinically approved single-agent and combination regimens for solid tumors

Overall, the development of novel therapies and the combination of different treatment modalities hold great promise for improving outcomes in cancer patients, particularly those with previously untreatable or advanced diseases. However, more research is needed to better understand the complex interactions among cancer cells, the surrounding matrix, and the immune system, and to identify new immunotherapy targets that can overcome resistance mechanisms and lead to more durable responses.

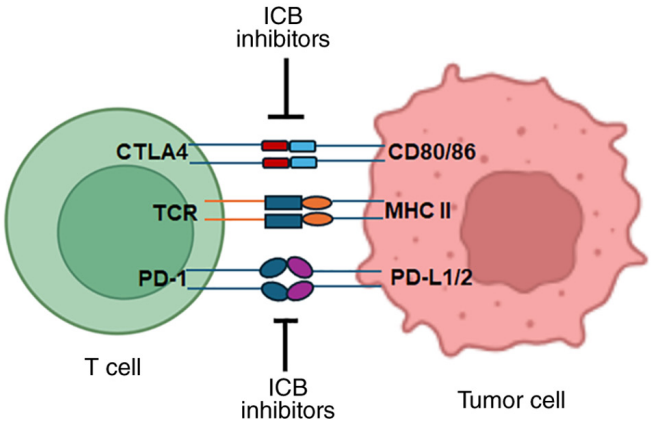

Figure 3. Tumor cells' expression of immune checkpoint blockade molecules inhibits T cell activity in the tumor microenvironment. PD-L1/2, Programmed death-ligand 1/2; and CD80/86, Cluster of Differentiation expression on tumor cells leads to binding of PD-1, Programmed death-1; and CTLA-4, cytotoxic T-lymphocyte antigen 4 on T cells. This binding inhibits TCR signaling, leading to T-cell inactivation. ICB, Immune Checkpoint Blockade inhibitors; anti-PD/PD-L1/2, and anti-CTLA-4 antibodies block the interactions between PD-1/PD-L1/2 and CTLA-4/CD80/86, respectively. This inhibition relieves the negative regulation of T cells, leading to their activation and subsequent T-cell-mediated killing of tumor cells. Preexisting templates were used to create figures in BioRender (https://www.biorender.com).

Crosstalk between CSCs and immune cells. This bidirectional process involves mechanisms that protect cancer

cells from chemotherapy and from immune attack, and *vice versa*. CSCs influence the TME by secreting specific cytokines and chemokines, which alter immune-cell infiltration and polarization within the tumor, thereby promoting therapeutic resistance and immune evasion (Fig. 4) (113-115). Chemoresistant cells activate EMT pathways, including Wnt/β-catenin (116), expression of chemokines such as C-C motif chemokine ligand-1, -2 and -5, IL-8 (115,117) and NF-κB, which also contribute to immune evasion by secreting IL-6, in turn activating the JAK/STAT3 pathway, which can drive EMT and CSC self-renewal (64), and TGF-β can activate SMAD signaling, which can reinforce stemness and promote immunosuppressive effects (113-115,118). EMT changes reduce MHC molecules, which impairs the ability of T-cells to recognize them (119). In addition, TAMs, MDSCs, and Tregs release cytokines such as IL-10, IL-6, and TGF-β, which enhance stemness and chemoresistance by activating the STAT3, NF-κB, and SMAD signaling pathways (120). This dynamic adaptation undermines the therapies targeting static CSCs in patients. Although EMT-directed therapies present significant therapeutic potential because of their complexity and microenvironmental context dependency, no effective targeting approach has been successful. A better understanding of how bidirectional interactions between EMT and the TME will be critical for improving therapeutic outcomes.

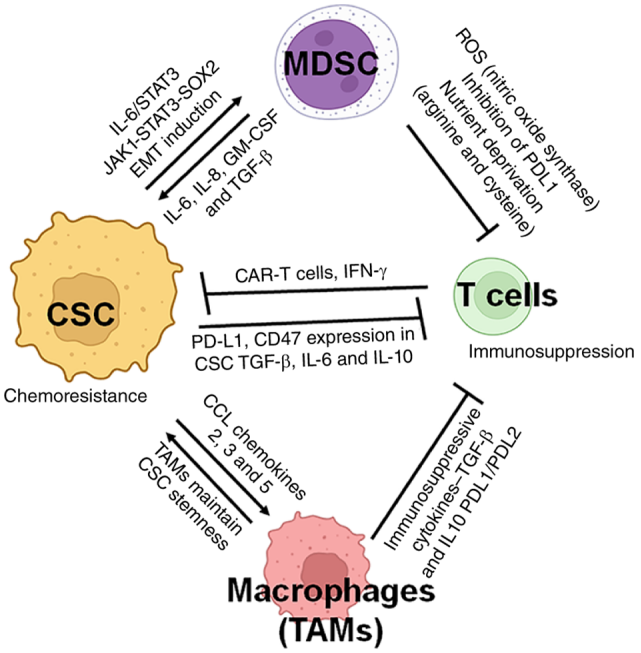

Figure 4. Mechanisms illustrate a bidirectional relationship between CSCs and immune cells: CSCs and immune cells release soluble mediators that influence each other, affecting immune cells' recruitment, function, and phenotypic changes in the tumor microenvironment and cancer stem cells. IL-6, interleukin-6; STAT3, signal transducer and activator of transcription 3; MDSC, myeloid-derived suppressor cell; CSC, cancer stem cells, EMT, epithelial-mesenchymal transition; JAK1, Janus kinase 1; GM-CSF, granulocyte-macrophage colony-stimulating factor; TGF-β, transforming growth factor-β; ROS, reactive oxygen species; PDL-1, programmed death-ligand 1; CD47, cluster of differentiation 47; TAM, tumor-associated macrophage; CCL, chronic lymphocytic leukemia.

4. Strategies to overcome drug resistance

Treatment with single drugs can lead to resistance over time due to complex interactions between heterogeneous tumor cells and the surrounding TME (4,121,122). Therefore, it is vital to understand how cancer cells regulate resistance to specific drugs or immunotherapies to improve therapeutic efficacy. Additionally, specific tumor cells can reprogram stromal and immune cells through factors such as cytokines, thereby promoting tumor progression and inhibiting cell death (123). CSCs play a crucial role in regulating resistance (124). Understanding the crosstalk between CSCs and immunotherapy is important; for example, studies have shown that low-dose chemotherapy can 'prime' the immune system by depleting MDSCs or inducing immune cell death, making the tumor more susceptible to immunotherapy (125). However, high doses can harm effector T cells, underscoring the importance of precise timing and sequencing in combination therapies. Conventionally, cancers were treated with the highest tolerated dose of chemotherapy or targeted drugs. However, such a treatment strategy leads to tumors selecting cells within tumors that are resistant to the drug. Recent cancer treatment strategies involve low-dose dose-escalating chemotherapy, followed by low-dose chemotherapy, then high-dose chemotherapy again; this cycling prevents cells from initiating an adaptive response to the drug, thereby delaying the development of drug resistance (126). For example, melanoma cells that acquired resistance after treatment with BRAF- and MEK-targeted therapy displayed robust drug addiction and were sensitive to drug withdrawal (127). A combination therapy that inhibits two crucial immune checkpoints, CTLA-4 and PD-1, significantly increased response rates and improved overall survival of patients with metastatic melanoma (128,129). Another strategy involves combining molecularly targeted therapy with immunotherapy (Table I). Targeting oncogenic BRAF alone in melanoma provided limited disease control. However, it is associated with positive effects in the TME, including increased antigen presentation, HLA expression, T-cell infiltration and improved T-cell function (2,113-116), which, in turn, increases PD-L1 expression through adaptive resistance (130). Another strategy to circumvent resistance is to block energy to tumor cells. Cancer cells appear to require higher ATP levels for survival and drug resistance. Extracellular ATP degradation or inhibition of ATP internalization can be considered for combination therapy with chemotherapy or immunotherapy to enhance the anticancer efficacy of TKIs (2,131-133).

5. Conclusions and future directions

Drug resistance to therapy is multifaceted, allowing uncontrolled cancer progression and tumor relapses, leading to reduced patient survival. Significant factors contributing to drug resistance include therapeutic pressure, tumor heterogeneity, the TME, increased drug metabolism, and altered drug targets. Targeted therapies are vital in combating cancer and reducing toxicity to normal cells (134). However, single-drug treatment strategies lead to the development of resistance over time due to complex interactions between heterogeneous

Table I. Examples of clinical trials exploring the efficacy of monotherapy and combination therapies and their outcomes in solid tumors.

A, Completed clinical trials for solid tumors

Type of cancer	Treatment monotherapy	Combination therapy	Outcomes
High risk & metastatic TNBC	Pembrolizumab (Keytruda), immune checkpoint inhibitor for PD-1 protein (NCT02447003)	Pembrolizumab plus chemotherapy (NCT03036488)	Combination therapy reduced the risk of disease progression/death by 35% and PFS to 9.7 vs. 5.6 months compared to chemotherapy alone in clinical trials
Metastatic TNBC	Atezolizumab (Tecentriq) (PD-L1 inhibitor) (NCT02425891)	Atezolizumab plus carboplatin (NCT03206203)	Combination therapy extended median PFS from 2.2 to 4.1 months and OS from 8.6 to 12.6 months compared to carboplatin alone
Prostate cancer	Ipilimumab (anti-CTLA-4 monoclonal antibody) (NCT02279862)	Ipilimumab plus ADT (NCT01194271)	Ipilimumab plus ADT has high PSA response rates; it is associated with significant immune-related adverse events and does not improve OS compared to standard treatment
		Ipilimumab plus nivolumab (NCT02985957)	Combination therapy showed a moderate ORR of 25-40% and improved survival in selected patients with mCRPC compared with single-agent ipilimumab
Glioblastoma	Anti-PD-1 plus CAR T cells (NCT03726515)	Pembrolizumab plus CART-EGFRvIII T cells (NCT03726515)	Anti-PD-1 plus CAR T cells in GBM have yielded limited long-term efficacy. Combination therapy did not significantly boost clinical efficacy due to antigen loss and tumor heterogeneity
Squamous cell carcinoma	Bintrafusp alfa (NCT04428047)	PD-L1 and TGF inhibitors (NCT02699515)	In a phase I study of pretreated advanced squamous cell carcinoma of the head and neck, bintrafusp alfa, a bifunctional fusion protein targeting both TGF-β and PD-L1 achieved an ORR of 13-30.5% (partial response), with a disease control rate of 34%.

B, Recently FDA-approved clinical trials for solid tumors

Type of cancer	Treatment monotherapy	Combination therapy	Outcomes
Ovarian cancer	Platinum	Platinum plus Pembrolizumab	For platinum-resistant ovarian cancer
Solid tumors	Augtyro (repotrectinib)	Not applicable	Its next-generation tyrosine kinase inhibitor was approved in 2024 for locally advanced or metastatic solid tumors harboring a neurotrophic tyrosine receptor kinase gene fusion
Breast cancer	Vepdegestrant (Veppanu)	Not applicable	Vepdegestrant a heterobifunctional protein degrader, for ER-positive, HER2-negative ESR1-mutated advanced or metastatic breast cancer (FDA approval 2026)
Ovarian, fallopian tube or peritoneal cancer	Not applicable	Pembrolizumab plus Paclitaxel	Pembrolizumab plus Paclitaxel for platinum-resistant cancers (FDA approval 2026)
Colorectal cancer	Not applicable	Encorafenib plus Cetuximab plus Chemotherapy	Metastatic colorectal cancer with BRAF V600E mutations (FDA approval 2026)

Table I. Continued.

B, Recently FDA-approved clinical trials for solid tumors

Type of cancer	Treatment monotherapy	Combination therapy	Outcomes
Gastric and gastroesophageal junction cancers	Not applicable	Durvalumab (Imfinzi) + chemotherapy	Early-stage gastric and gastroesophageal junction cancers to be used before and after surgery (FDA approval 2025)
Small cell lung cancer	Tarlatamab (Imdelltra)	Not applicable	Approved for small cell lung cancer (2025).

TNBC, triple-negative breast cancer; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; CAR T, chimeric antigen receptor T-cells; ADT, androgen deprivation therapy; TGF, transforming growth factor; PFS, progression-free survival; OS, overall survival; PSA, prostate-specific antigen; ORR, objective response rate; mCRPC, metastatic castration-resistant prostate cancer; GBM, glioblastoma.

tumor cells and the surrounding TME. The newer strategy of targeting multiple driver genes responsible for chemo and/or immunological resistance could significantly reduce or eliminate resistance and prolong patients' lives. Emerging strategies to overcome drug resistance include combination therapies, personalized immunotherapy, adoptive cell therapy, and the development of novel chemotherapeutic and immunotherapeutic agents. For instance, in high-risk metastatic TNBC, pembrolizumab alone is rarely used as primary treatment. However, pembrolizumab plus chemotherapy is recognized as the standard of care. Combination therapy reduces the risk of disease progression/death by ~35% and improves PFS to 9.7 vs. 5.6 months with chemotherapy alone in clinical trials. However, patients often experience the compounding side effects of both treatments. By contrast, in glioblastoma, the brain's immunosuppressive environment and tumor heterogeneity have limited the long-term efficacy of anti-PD-1 plus CAR T cells. Combination therapy did not significantly boost clinical efficacy due to antigen loss and tumor heterogeneity (Table I) (135,136). Furthermore, CSC plasticity and heterogeneity can limit the effectiveness of therapies. Ongoing research and development in these areas can lead to further improvements in cancer treatment outcomes and in the quality of life for cancer patients. Additional studies are necessary to determine if resistance mechanisms or phenotypes vary across different tissue microenvironments within the same host. Identifying distinct subpopulations with unique therapeutic vulnerabilities may lead to the development of novel strategies for cancer treatment. Advanced technologies, including high-throughput techniques, next-generation sequencing and large-scale data analysis, are crucial for identifying predictive biomarkers that facilitate patient stratification. These integrated advances will pave the way for the next generation of anticancer therapies.

Acknowledgements

Not applicable.

Funding

This work is supported by the Departments of Pathology (to KBR), Wayne State University (WSU) and Urology (to SRC), WSU, the Department of Veterans Affairs Merit Review grant (to AKR) and the Department of Veterans Affairs Basic Laboratory Research & Development Research Career Scientist award (to AKR).

Availability of data and materials

Not applicable.

Authors' contributions

All authors have substantially contributed to the writing and revision of the manuscript. KBR developed the conceptual framework of the review and wrote the manuscript. SRC and AKR contributed to the critical discussion of the literature and manuscript revision, as well as to the generation of figures and tables. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Boumahdi S and de Sauvage FJ: The great escape: Tumour cell plasticity in resistance to targeted therapy. Nat Rev Drug Discov 19: 39-56, 2020.
2. Sharma P, Hu-Lieskovan S, Wargo JA and Ribas A: Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell 168: 707-723, 2017.
3. Turner N, Tutt A and Ashworth A: Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 4: 814-819, 2004.
4. Ramón Y Cajal S, Sesé M, Capdevila C, Aasen T, De Mattos-Arruda L, Diaz-Cano SJ, Hernández-Losa J and Castellví J: Clinical implications of intratumor heterogeneity: Challenges and opportunities. J Mol Med (Berl) 98: 161-177, 2020.
5. Wang X, Zhang H and Chen X: Drug resistance and combating drug resistance in cancer. Cancer Drug Resist 2: 141-160, 2019.
6. Zhao X and Subramanian S: Intrinsic resistance of solid tumors to immune checkpoint blockade therapy. Cancer Res 77: 817-822, 2017.
7. Chen W, Li C, Liu Y and Huang H: Variations in DNA repair genes and intratumoral genetic heterogeneity in temozolomide-resistant glioblastoma. Hum Mutat 2026: 3430617, 2026.
8. Marine JC, Dawson SJ and Dawson MA: Non-genetic mechanisms of therapeutic resistance in cancer. Nat Rev Cancer 20: 743-756, 2020.
9. Aldea M, Andre F, Marabelle A, Dogan S, Barlesi F and Soria JC: Overcoming resistance to tumor-targeted and immune-targeted therapies. Cancer Discov 11: 874-899, 2021.
10. Kelderman S, Schumacher TNM and Haanen JBAG: Acquired and intrinsic resistance in cancer immunotherapy. Mol Oncol 8: 1132-1139, 2014.
11. Harris LN, You F, Schnitt SJ, Witkiewicz A, Lu X, Sgroi D, Ryan PD, Come SE, Burstein HJ, Lesnikoski BA, *et al*: Predictors of resistance to preoperative trastuzumab and vinorelbine for HER2-positive early breast cancer. Clin Cancer Res 13: 1198-1207, 2007.
12. Chen YF, Zhang QH, Zhang ZW, Zhou YJ, Liu CC, Shao ZM and Yu KD: SNX10 deficiency impairs sensitivity to anti-HER2 antibody-drug conjugates via altering HER2 trafficking in HER2-positive breast cancer. Proc Natl Acad Sci USA 122: e2417586122, 2025.
13. Ibragimova KIE, Geurts SME, Laczkó D, Meegdes M, Erdkamp F, Heijns JB, Tol J, Vriens BEPJ, Aaldering KNA, Dercksen MW, *et al*: Trastuzumab resistance in patients with HER2-positive advanced breast cancer: Results from the SONABRE registry. Clin Breast Cancer 24: 103-111, 2024.
14. Wang ZH, Zheng ZQ, Jia SC, Liu SN, Xiao XF, Chen GY, Liang WQ and Lu XF: Trastuzumab resistance in HER2-positive breast cancer: Mechanisms, emerging biomarkers and targeting agents. Front Oncol 12: 1006429, 2022.
15. Huang D, Duan H, Huang H, Tong X, Han Y, Ru G, Qu L, Shou C and Zhao Z: Cisplatin resistance in gastric cancer cells is associated with HER2 upregulation-induced epithelial-mesenchymal transition. Sci Rep 6: 20502, 2016.
16. Antonello ZA, Hsu N, Bhasin M, Roti G, Joshi M, Van Hummelen P, Ye E, Lo AS, Karumanchi SA, Bryke CR and Nucera C: Vemurafenib-resistance via de novo RBM genes mutations and chromosome 5 aberrations is overcome by combined therapy with palbociclib in thyroid carcinoma with $BRAF^{V600E}$. Oncotarget 8: 84743-84760, 2017.
17. Montero-Conde C, Ruiz-Llorente S, Dominguez JM, Knauf JA, Viale A, Sherman EJ, Ryder M, Ghossein RA, Rosen N and Fagin JA: Relief of feedback inhibition of HER3 transcription by RAF and MEK inhibitors attenuates their antitumor effects in BRAF-mutant thyroid carcinomas. Cancer Discov 3: 520-533, 2013.
18. Bot A, Scharenberg A, Friedman K, Guey L, Hofmeister R, Andorko JI, Klichinsky M, Neumann F, Shah JV, Swayer AJ, *et al*: In vivo chimeric antigen receptor (CAR)-T cell therapy. Nat Rev Drug Discov 25: 116-137, 2026.
19. Peng W, Chen JQ, Liu C, Malu S, Creasy C, Tetzlaff MT, Xu C, McKenzie JA, Zhang C, Liang X, *et al*: Loss of PTEN promotes resistance to T cell-mediated immunotherapy. Cancer Discov 6: 202-216, 2016.
20. Nooter K, Brutel de la Riviere G, Look MP, van Wingerden KE, Henzen-Logmans SC, Scheper RJ, Flens MJ, Klijn JG, Stoter G and Foekens JA: The prognostic significance of expression of the multidrug resistance-associated protein (MRP) in primary breast cancer. Br J Cancer 76: 486-493, 1997.
21. Triller N, Korosec P, Kern I, Kosnik M and Debeljak A: Multidrug resistance in small cell lung cancer: Expression of P-glycoprotein, multidrug resistance protein 1 and lung resistance protein in chemo-naive patients and in relapsed disease. Lung Cancer 54: 235-240, 2006.
22. Zalcberg J, Hu XF, Slater A, Parisot J, El-Osta S, Kantharidis P, Chou ST and Parkin JD: MRP1 not MDR1 gene expression is the predominant mechanism of acquired multidrug resistance in two prostate carcinoma cell lines. Prostate Cancer Prostatic Dis 3: 66-75, 2000.
23. Doyle LA, Yang W, Abruzzo LV, Krogmann T, Gao Y, Rishi AK and Ross DD: A multidrug resistance transporter from human MCF-7 breast cancer cells. Proc Natl Acad Sci USA 95: 15665-15670, 1998.
24. Gottesman MM, Fojo T and Bates SE: Multidrug resistance in cancer: Role of ATP-dependent transporters. Nat Rev Cancer 2: 48-58, 2002.
25. Robey RW, Shukla S, Steadman K, Obrzut T, Finley EM, Ambudkar SV and Bates SE: Inhibition of ABCG2-mediated transport by protein kinase inhibitors with a bisindolylmaleimide or indolocarbazole structure. Mol Cancer Ther 6: 1877-1885, 2007.
26. Shervington A and Lu C: Expression of multidrug resistance genes in normal and cancer stem cells. Cancer Invest 26: 535-542, 2008.
27. Aleksakhina SN, Kashyap A and Imyanitov EN: Mechanisms of acquired tumor drug resistance. Biochim Biophys Acta Rev Cancer 1872: 188310, 2019.
28. Meijer C, Mulder NH, Timmer-Bosscha H, Sluiter WJ, Meersma GJ and de Vries EG: Relationship of cellular glutathione to the cytotoxicity and resistance of seven platinum compounds. Cancer Res 52: 6885-6889, 1992.
29. Kosuri KV, Wu X, Wang L, Villalona-Calero MA and Otterson GA: An epigenetic mechanism for capecitabine resistance in mesothelioma. Biochem Biophys Res Commun 391: 1465-1470, 2010.
30. Malet-Martino M and Martino R: Clinical studies of three oral prodrugs of 5-fluorouracil (capecitabine, UFT, S-1): A review. Oncologist 7: 288-323, 2002.
31. Ahmad A, Ginnebaugh KR, Yin S, Bollig-Fischer A, Reddy KB and Sarkar FH: Functional role of miR-10b in tamoxifen resistance of ER-positive breast cancer cells through down-regulation of HDAC4. BMC Cancer 15: 540, 2015.
32. Yin S, Rishi AK and Reddy KB: Anti-estrogen-resistant breast cancer cells are sensitive to cisplatin plus TRAIL treatment. Oncol Rep 33: 1475-1480, 2015.
33. Likhite VS, Stossi F, Kim K, Katzenellenbogen BS and Katzenellenbogen JA: Kinase-specific phosphorylation of the estrogen receptor changes receptor interactions with ligand, deoxyribonucleic acid, and coregulators associated with alterations in estrogen and tamoxifen activity. Mol Endocrinol 20: 3120-3132, 2006.
34. MacGregor Schafer J, Liu H, Bentrem DJ, Zapf JW and Jordan VC: Allosteric silencing of activating function 1 in the 4-hydroxytamoxifen estrogen receptor complex is induced by substituting glycine for aspartate at amino acid 351. Cancer Res 60: 5097-5105, 2000.
35. Palmberg C, Koivisto P, Hyytinen E, Isola J, Visakorpi T, Kallioniemi OP and Tammela T: Androgen receptor gene amplification in a recurrent prostate cancer after monotherapy with the nonsteroidal potent antiandrogen Casodex (bicalutamide) with a subsequent favorable response to maximal androgen blockade. Eur Urol 31: 216-219, 1997.
36. Watson PA, Arora VK and Sawyers CL: Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer 15: 701-711, 2015.
37. Beltran H, Hruszkewycz A, Scher HI, Hildesheim J, Isaacs J, Yu EY, Kelly K, Lin D, Dicker A, Arnold J, *et al*: The role of lineage plasticity in prostate cancer therapy resistance. Clin Cancer Res 25: 6916-6924, 2019.

38. Gridelli C, De Marinis F, Di Maio M, Cortinovis D, Cappuzzo F and Mok T: Gefitinib as first-line treatment for patients with advanced non-small-cell lung cancer with activating epidermal growth factor receptor mutation: Review of the evidence. Lung Cancer 71: 249-257, 2011.
39. Wang Y, Schmid-Bindert G and Zhou C: Erlotinib in the treatment of advanced non-small cell lung cancer: An update for clinicians. Ther Adv Med Oncol 4: 19-29, 2012.
40. Bell DW, Gore I, Okimoto RA, Godin-Heymann N, Sordella R, Mulloy R, Sharma SV, Brannigan BW, Mohapatra G, Settleman J and Haber DA: Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR. Nat Genet 37: 1315-1316, 2005.
41. Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG and Halmos B: EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med 352: 786-792, 2005.
42. Ma C, Wei S and Song Y: T790M and acquired resistance of EGFR TKI: A literature review of clinical reports. J Thorac Dis 3: 10-18, 2011.
43. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, Riely GJ, Solomon B, Ou SH, Kim DW, *et al*: Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: Updated results from a phase 1 study. Lancet Oncol 13: 1011-1019, 2012.
44. Shaw AT, Yeap BY, Solomon BJ, Riely GJ, Gainor J, Engelman JA, Shapiro GI, Costa DB, Ou SH, Butaney M, *et al*: Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: A retrospective analysis. Lancet Oncol 12: 1004-1012, 2011.
45. Helleday T, Petermann E, Lundin C, Hodgson B and Sharma RA: DNA repair pathways as targets for cancer therapy. Nat Rev Cancer 8: 193-204, 2008.
46. de Angelis PM, Fjell B, Kravik KL, Haug T, Tunheim SH, Reichelt W, Beigi M, Clausen OP, Galteland E and Stokke T: Molecular characterizations of derivatives of HCT116 colorectal cancer cells that are resistant to the chemotherapeutic agent 5-fluorouracil. Int J Oncol 24: 1279-1288, 2004.
47. Enoch T and Norbury C: Cellular responses to DNA damage: Cell-cycle checkpoints, apoptosis and the roles of p53 and ATM. Trends Biochem Sci 20: 426-430, 1995.
48. Fan S, el-Deiry WS, Bae I, Freeman J, Jondle D, Bhatia K, Fornace AJ Jr, Magrath I, Kohn KW and O'Connor PM: p53 gene mutations are associated with decreased sensitivity of human lymphoma cells to DNA damaging agents. Cancer Res 54: 5824-5830, 1994.
49. Lamia MR, Perri E, Baldassarre G, Pignata S, D'Alessio C, Limongello D and Basso-Valentina F: Bevacizumab in ovarian cancer: Clinical data and predictive and prognostic biomarkers. Clin Transl Med 16: e70591, 2026.
50. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, *et al*: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434: 917-921, 2005.
51. Edwards SL, Brough R, Lord CJ, Natrajan R, Vatcheva R, Levine DA, Boyd J, Reis-Filho JS and Ashworth A: Resistance to therapy caused by intragenic deletion in BRCA2. Nature 451: 1111-1115, 2008.
52. Sakai W, Swisher EM, Karlan BY, Agarwal MK, Higgins J, Friedman C, Villegas E, Jacquemont C, Farrugia DJ, Couch FJ, *et al*: Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature 451: 1116-1120, 2008.
53. Bashashati A, Ha G, Tone A, Ding J, Prentice LM, Roth A, Rosner J, Shumansky K, Kalloger S, Senz J, *et al*: Distinct evolutionary trajectories of primary high-grade serous ovarian cancers revealed through spatial mutational profiling. J Pathol 231: 21-34, 2013.
54. Gerlinger M, Rowan AJ, Horswell S, Math M, Larkin J, Endesfelder D, Gronroos E, Martinez P, Matthews N, Stewart A, *et al*: Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 366: 883-892, 2012.
55. Navin N, Krasnitz A, Rodgers L, Cook K, Meth J, Kendall J, Riggs M, Eberling Y, Troge J, Grubor V, *et al*: Inferring tumor progression from genomic heterogeneity. Genome Res 20: 68-80, 2010.
56. Burrell RA and Swanton C: Tumour heterogeneity and the evolution of polyclonal drug resistance. Mol Oncol 8: 1095-1111, 2014.
57. Kreso A and Dick JE: Evolution of the cancer stem cell model. Cell Stem Cell 14: 275-291, 2014.
58. Turner NC and Reis-Filho JS: Genetic heterogeneity and cancer drug resistance. Lancet Oncol 13: e178-e185, 2012.
59. Levitin HM, Yuan J and Sims PA: Single-cell transcriptomic analysis of tumor heterogeneity. Trends Cancer 4: 264-268, 2018.
60. Peng J, Sun BF, Chen CY, Zhou JY, Chen YS, Chen H, Liu L, Huang D, Jiang J, Cui GS, *et al*: Single-cell RNA-seq highlights intra-tumoral heterogeneity and malignant progression in pancreatic ductal adenocarcinoma. Cell Res 29: 725-738, 2019.
61. Hata AN, Niederst MJ, Archibald HL, Gomez-Caraballo M, Siddiqui FM, Mulvey HE, Maruvka YE, Ji F, Bhang HE, Krish namurthy Radhakrishna V, *et al*: Tumor cells can follow distinct evolutionary paths to become resistant to epidermal growth factor receptor inhibition. Nat Med 22: 262-269, 2016.
62. Kazan HH, Acinan IS, Kandemir B, Karahan CP, Kayhan G and İşeri ÖD: Copy number variations of stepwise-selected doxorubicin-resistant MCF-7 cell lines. Gene 937: 149139, 2025.
63. Van Schaeybroeck S, Kelly DM, Kyula J, Stokesberry S, Fennell DA, Johnston PG and Longley DB: Src and ADAM-17-mediated shedding of transforming growth factor-alpha is a mechanism of acute resistance to TRAIL. Cancer Res 68: 8312-8321, 2008.
64. Abaurrea A, Araujo AM and Caffarel MM: The role of the IL-6 cytokine family in epithelial-mesenchymal plasticity in cancer progression. Int J Mol Sci 22: 8334, 2021.
65. Jiang M, Wang J, Li Y, Zhang K, Wang T, Bo Z, Lu S, Rodríguez RA, Wei R, Zhu M, *et al*: EMT and cancer stem cells: Drivers of therapy resistance and promising therapeutic targets. Drug Resist Updat 83: 101276, 2025.
66. Scheel C and Weinberg RA: Cancer stem cells and epithelial-mesenchymal transition: Concepts and molecular links. Semin Cancer Biol 22: 396-403, 2012.
67. Frisch SM, Schaller M and Cieply B: Mechanisms that link the oncogenic epithelial-mesenchymal transition to suppression of anoikis. J Cell Sci 126: 21-29, 2013.
68. Zhang CX, Huang RYJ, Sheng G and Thiery JP: Epithelial-mesenchymal transition. Cell 188: 5436-5486, 2025.
69. Jiang ZS, Sun YZ, Wang SM and Ruan JS: Epithelial-mesenchymal transition: Potential regulator of ABC transporters in tumor progression. J Cancer 8: 2319-2327, 2017.
70. Tian Y, Tang M, Qiao M, Wang X, Huang Y, Luo T, Nabavi N, Ashrafizadeh M, Cheng H and Tu Y: STAT3-driven EMT in cancer metastasis and chemoresistance: A review. Int J Biol Macromol 357: 151403, 2026.
71. Dai X, Xin Y, Xu W, Tian X, Wei X and Zhang H: CBP-mediated Slug acetylation stabilizes Slug and promotes EMT and migration of breast cancer cells. Sci China Life Sci 64: 563-574, 2021.
72. Wu M, Chen G, Liao X, Xiao L and Zheng J: YTHDF2 interference suppresses the EMT of cervical cancer cells and enhances cisplatin chemosensitivity by regulating AXIN1. Drug Dev Res 83: 1190-1200, 2022.
73. Zheng Y, Li P, Huang H, Ye X, Chen W, Xu G and Zhang F: Androgen receptor regulates eIF5A2 expression and promotes prostate cancer metastasis via EMT. Cell Death Discov 7: 373, 2021.
74. Qin S, Jiang J, Lu Y, Nice EC, Huang C, Zhang J and He W: Emerging role of tumor cell plasticity in modifying therapeutic response. Signal Transduct Target Ther 5: 228, 2020.
75. Shi ZD, Pang K, Wu ZX, Dong Y, Hao L, Qin JX, Wang W, Chen ZS and Han CH: Tumor cell plasticity in targeted therapy-induced resistance: Mechanisms and new strategies. Signal Transduct Target Ther 8: 113, 2023.
76. Kishida O, Miyazaki Y, Murayama Y, Ogasa M, Miyazaki T, Yamamoto T, Watabe K, Tsutsui S, Kiyohara T, Shimomura I and Shinomura Y: Gefitinib ('Iressa', ZD1839) inhibits SN38-triggered EGF signals and IL-8 production in gastric cancer cells. Cancer Chemother Pharmacol 55: 393-403, 2005.
77. Van Schaeybroeck S, Karaiskou-McCaul A, Kelly D, Longley D, Galligan L, Van Cutsem E and Johnston P: Epidermal growth factor receptor activity determines response of colorectal cancer cells to gefitinib alone and in combination with chemotherapy. Clin Cancer Res 11: 7480-7489, 2005.
78. Lee DC, Sunnarborg SW, Hinkle CL, Myers TJ, Stevenson MY, Russell WE, Castner BJ, Gerhart MJ, Paxton RJ, Black RA, *et al*: TACE/ADAM17 processing of EGFR ligands indicates a role as a physiological convertase. Ann N Y Acad Sci 995: 22-38, 2003.
79. Kyula JN, Van Schaeybroeck S, Doherty J, Fenning CS, Longley DB and Johnston PG: Chemotherapy-induced activation of ADAM-17: A novel mechanism of drug resistance in colorectal cancer. Clin Cancer Res 16: 3378-3389, 2010.

80. Zhou BB, Peyton M, He B, Liu C, Girard L, Caudler E, Lo Y, Baribaud F, Mikami I, Reguart N, *et al*: Targeting ADAM-mediated ligand cleavage to inhibit HER3 and EGFR pathways in non-small cell lung cancer. Cancer Cell 10: 39-50, 2006.
81. Holohan C, Van Schaeybroeck S, Longley DB and Johnston PG: Cancer drug resistance: An evolving paradigm. Nat Rev Cancer 13: 714-726, 2013.
82. Sergina NV, Rausch M, Wang D, Blair J, Hann B, Shokat KM and Moasser MM: Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. Nature 445: 437-441, 2007.
83. Wheeler DL, Huang S, Kruser TJ, Nechrebecki MM, Armstrong EA, Benavente S, Gondi V, Hsu KT and Harari PM: Mechanisms of acquired resistance to cetuximab: Role of HER (ErbB) family members. Oncogene 27: 3944-3956, 2008.
84. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, *et al*: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316: 1039-1043, 2007.
85. Liu L, Yang L, Yan W, Zhai J, Pizzo DP, Chu P, Chin AR, Shen M, Dong C, Ruan X, *et al*: Chemotherapy induces breast cancer stemness in association with dysregulated monocytosis. Clin Cancer Res 24: 2370-2382, 2018.
86. Reddy KB: Stem cells: Current status and therapeutic implications. Genes (Basel) 11: 1372, 2020.
87. Valent P, Bonnet D, De Maria R, Lapidot T, Copland M, Melo JV, Chomienne C, Ishikawa F, Schuringa JJ, Stassi G, *et al*: Cancer stem cell definitions and terminology: The devil is in the details. Nat Rev Cancer 12: 767-775, 2012.
88. Pan Y, Yuan C, Zeng C, Sun C, Xia L, Wang G, Chen X, Zhang B, Liu J and Ding ZY: Cancer stem cells and niches: Challenges in immunotherapy resistance. Mol Cancer 24: 52, 2025.
89. Shibue T and Weinberg RA: EMT, CSCs, and drug resistance: The mechanistic link and clinical implications. Nat Rev Clin Oncol 14: 611-629, 2017.
90. Allikmets R, Schriml LM, Hutchinson A, Romano-Spica V and Dean M: A human placenta-specific ATP-binding cassette gene (ABCP) on chromosome 4q22 that is involved in multidrug resistance. Cancer Res 58: 5337-5339, 1998.
91. Dean M: ABC transporters, drug resistance, and cancer stem cells. J Mammary Gland Biol Neoplasia 14: 3-9, 2009.
92. Resetkova E, Reis-Filho JS, Jain RK, Mehta R, Thorat MA, Nakshatri H and Badve S: Prognostic impact of ALDH1 in breast cancer: A story of stem cells and tumor microenvironment. Breast Cancer Res Treat 123: 97-108, 2010.
93. Todaro M, Francipane MG, Medema JP and Stassi G: Colon cancer stem cells: Promise of targeted therapy. Gastroenterology 138: 2151-2162, 2010.
94. Deng J, Li Y, Yin L, Liu S, Li Y, Liao W, Mu L, Luo X and Qin J: Histone lactylation enhances GCLC expression and thus promotes chemoresistance of colorectal cancer stem cells through inhibiting ferroptosis. Cell Death Dis 16: 193, 2025.
95. Lv Y, Zhao S, Han J, Zheng L, Yang Z and Zhao L: Hypoxia-inducible factor-1α induces multidrug resistance protein in colon cancer. Onco Targets Ther 8: 1941-1948, 2015.
96. Nedeljković M and Damjanović A: Mechanisms of chemotherapy resistance in triple-negative breast cancer-how we can rise to the challenge. Cells 8: 957, 2019.
97. Brunet JF, Denizot F, Luciani MF, Roux-Dosseto M, Suzan M, Mattei MG and Golstein P: A new member of the immunoglobulin superfamily-CTLA-4. Nature 328: 267-270, 1987.
98. Krummel MF and Allison JP: CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 182: 459-465, 1995.
99. Byrne EH and Fisher DE: Immune and molecular correlates in melanoma treated with immune checkpoint blockade. Cancer 123 (S11): S2143-S2153, 2017.
100. Lim SY, Shklovskaya E, Lee JH, Pedersen B, Stewart A, Ming Z, Irvine M, Shivalingam B, Saw RPM, Menzies AM, *et al*: The molecular and functional landscape of resistance to immune checkpoint blockade in melanoma. Nat Commun 14: 1516, 2023.
101. D'Urso CM, Wang ZG, Cao Y, Tatake R, Zeff RA and Ferrone S: Lack of HLA class I antigen expression by cultured melanoma cells FO-1 due to a defect in B2m gene expression. J Clin Invest 87: 284-292, 1991.
102. Restifo NP, Marincola FM, Kawakami Y, Taubenberger J, Yannelli JR and Rosenberg SA: Loss of functional beta 2-microglobulin in metastatic melanomas from five patients receiving immunotherapy. J Natl Cancer Inst 88: 100-108, 1996.
103. Zaretsky JM, Garcia-Diaz A, Shin DS, Escuin-Ordinas H, Hugo W, Hu-Lieskovan S, Torrejon DY, Abril-Rodriguez G, Sandoval S, Barthly L, *et al*: Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med 375: 819-829, 2016.
104. Müller L, Tunger A, Plesca I, Wehner R, Temme A, Westphal D, Meier F, Bachmann M and Schmitz M: Bidirectional crosstalk between cancer stem cells and immune cell subsets. Front Immunol 11: 140, 2020.
105. Najafi M, Mortezaee K and Majidpoor J: Cancer stem cell (CSC) resistance drivers. Life Sci 234: 116781, 2019.
106. Walker ND, Elias M, Guiro K, Bhatia R, Greco SJ, Bryan M, Gergues M, Sandiford OA, Ponzio NM, Leibovich SJ and Rameshwar P: Exosomes from differentially activated macrophages influence dormancy or resurgence of breast cancer cells within bone marrow stroma. Cell Death Dis 10: 59, 2019.
107. Park SY, Han J, Kim JB, Yang MG, Kim YJ, Lim HJ, An SY and Kim JH: Interleukin-8 is related to poor chemotherapeutic response and tumourigenicity in hepatocellular carcinoma. Eur J Cancer 50: 341-350, 2014.
108. Dianat-Moghadam H, Mahari A, Salahlou R, Khalili M, Azizi M and Sadeghzadeh H: Immune evader cancer stem cells direct the perspective approaches to cancer immunotherapy. Stem Cell Res Ther 13: 150, 2022.
109. Lei Q, Wang D, Sun K, Wang L and Zhang Y: Resistance mechanisms of anti-PD1/PDL1 therapy in solid tumors. Front Cell Dev Biol 8: 672, 2020.
110. Johannessen CM, Boehm JS, Kim SY, Thomas SR, Wardwell L, Johnson LA, Emery CM, Stransky N, Cogdill AP, Barretina J, *et al*: COT drives resistance to RAF inhibition through MAP kinase pathway reactivation. Nature 468: 968-972, 2010.
111. Takezawa K, Pirazzoli V, Arcila ME, Nebhan CA, Song X, de Stanchina E, Ohashi K, Janjigian YY, Spitzler PJ, Melnick MA, *et al*: HER2 amplification: A potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. Cancer Discov 2: 922-933, 2012.
112. Liu C, Peng W, Xu C, Lou Y, Zhang M, Wargo JA, Chen JQ, Li HS, Watowich SS, Yang Y, *et al*: BRAF inhibition increases tumor infiltration by T cells and enhances the antitumor activity of adoptive immunotherapy in mice. Clin Cancer Res 19: 393-403, 2013.
113. Yu G and Gong J: Targeting CSC-immune cell crosstalk to overcome chemoresistance and enhance immunotherapy efficacy. Front Immunol 16: 1620807, 2025.
114. Lei MML and Lee TKW: Cancer stem cells: Emerging key players in immune evasion of cancers. Front Cell Dev Biol 9: 692940, 2021.
115. Kobatake K, Ikeda KI, Nakata Y, Yamasaki N, Ueda T, Kanai A, Sentani K, Sera Y, Hayashi T, Koizumi M, *et al*: Kdm6a deficiency activates inflammatory pathways, promotes M2 macrophage polarization, and causes bladder cancer in cooperation with p53 dysfunction. Clin Cancer Res 26: 2065-2079, 2020.
116. Takebe N, Miele L, Harris PJ, Jeong W, Bando H, Kahn M, Yang SX and Ivy SP: Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: Clinical update. Nat Rev Clin Oncol 12: 445-464, 2015.
117. Guo X, Pan Y and Gutmann DH: Genetic and genomic alterations differentially dictate low-grade glioma growth through cancer stem cell-specific chemokine recruitment of T cells and microglia. Neuro Oncol 21: 1250-1262, 2019.
118. Batlle E and Massagué J: Transforming growth factor-β signaling in immunity and cancer. Immunity 50: 924-940, 2019.
119. Xie Y, Wang X, Wang W, Pu N and Liu L: Epithelial-mesenchymal transition orchestrates tumor microenvironment: Current perceptions and challenges. J Transl Med 23: 386, 2025.
120. Manni W and Min W: Signaling pathways in the regulation of cancer stem cells and associated targeted therapy. MedComm (2020) 3: e176, 2022.
121. Khan SU, Fatima K, Aisha S and Malik F: Unveiling the mechanisms and challenges of cancer drug resistance. Cell Commun Signal 22: 109, 2024.
122. Venkatesh J, Rishi AK and Reddy KB: Novel strategies to target chemoresistant triple-negative breast cancer. Genes Cancer 11: 95-105, 2020.
123. Vasan N, Baselga J and Hyman DM: A view on drug resistance in cancer. Nature 575: 299-309, 2019.
124. Oshimori N, Guo Y and Taniguchi S: An emerging role for cellular crosstalk in the cancer stem cell niche. J Pathol 254: 384-394, 2021.

125. Moridikia A, Montazersaheb S and Molavi O: Manipulation of tumor microenvironment by induction of immunogenic cell death and immune check point inhibitors for enhancing the efficacy of cancer treatments. Biomed Pharmacother 196: 119118, 2026.
126. Kaiser J: When less is more. Science 355: 1144-1146, 2017.
127. Moriceau G, Hugo W, Hong A, Shi H, Kong X, Yu CC, Koya RC, Samatar AA, Khanlou N, Braun J, *et al*: Tunable-combinatorial mechanisms of acquired resistance limit the efficacy of BRAF/MEK cotargeting but result in melanoma drug addiction. Cancer Cell 27: 240-256, 2015.
128. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, *et al*: Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373: 23-34, 2015.
129. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon RA, Reed K, *et al*: Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 369: 122-133, 2013.
130. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, Chen S, Klein AP, Pardoll DM, Topalian SL and Chen L: Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med 4: 127ra37, 2012.
131. Cairns RA, Harris IS and Mak TW: Regulation of cancer cell metabolism. Nat Rev Cancer 11: 85-95, 2011.
132. Filippini A, Taffs RE and Sitkovsky MV: Extracellular ATP in T-lymphocyte activation: Possible role in effector functions. Proc Natl Acad Sci USA 87: 8267-8271, 1990.
133. Koppenol WH, Bounds PL and Dang CV: Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer 11: 325-337, 2011.
134. Gu Y, Yang R, Zhang Y, Guo M, Takehiro K, Zhan M, Yang L and Wang H: Molecular mechanisms and therapeutic strategies in overcoming chemotherapy resistance in cancer. Mol Biomed 6: 2, 2025.
135. Cortes J, Rugo HS, Cescon DW, Im SA, Yusof MM, Gallardo C, Lipatov O, Barrios CH, Perez-Garcia J, Iwata H, *et al*: Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. N Engl J Med 387: 217-226, 2022.
136. Liu J, Abikenari M, Annagiri S, Ha JH, Nageeb G, Sjoholm MA, Velazhahan V, Medikonda R, Choi J, Li G and Lim M: Endogenous immune recruitment in glioblastoma CAR T therapy: Cytokine, myeloid, and chemokine circuitry. J Neurooncol 177: 50, 2026.