International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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An overview of molecular mechanisms in cancer drug resistance and therapeutic strategies

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International Journal of Science and Research Archive, 2024, 12(02), 1243–1258

Publication history: Received on 14 June 2024; revised on 23 July 2024; accepted on 26 July 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.12.2.1353

Abstract

Cancer resistance refers to the ability of cancer cells to evade the effects of treatments, such as chemotherapy and radiation, making it challenging to eliminate tumors. Cancer cells develop resistance through genetic modifications, alterations in cellular pathways, or microenvironmental adaptations that allow cancer cells to persist, proliferate, and even thrive despite the application of therapies designed to eradicate them. Despite efforts to create more potent target-based drugs, the flexibility of acquired resistance necessitates advanced options. Combination therapy and precision immunotherapy has revolutionized treatment but is limited by patient specificity and requires further development. New approaches like small molecules, peptides, and nanotherapeutics aim to overcome resistance by enhancing site-specific delivery and increasing drug concentration inside cancer cells. This review provides a comprehensive overview of the molecular mechanisms underlying cancer drug resistance, including genetic mutations, epigenetic alterations, efflux pump activity, and the influence of the tumor microenvironment. Additionally, the roles of microRNAs, long noncoding RNAs, and cellular processes such as autophagy and hypoxia in mediating resistance are examined. This review seeks to improve patient care and help to the development of more effective cancer medicines by explaining these complicated systems and investigating novel therapeutic alternatives.

Keywords: Cancer drug resistance; Chemotherapy; Cancer therapy; Stem cell based therapy

1. Introduction

Cancer is a generic term for a large group of diseases that can affect any part of the body, characterized by unregulated growth of abnormal cells and defective immune system recognition, often referred to as "a wound that never heals." According to a report from the World Health Organization, cancer was responsible for an estimated 10 million deaths worldwide in 2020, accounting for nearly one in six deaths [1]. Though there are numerous treatment available, such as immunotherapy, endocrine therapy, gene therapy, radiation therapy, and surgery, chemotherapy remains the most common cancer treatment. However, cancer drug resistance continues to pose a significant challenge in achieving effective treatment outcomes. Cancer cells exhibit behaviors like recurrence, dormancy, and resistance due to cancer stem cells (CSCs). New chemotherapeutic drugs and altered dosing strategies have shown some success in preventing tumor regrowth. However, understanding resistance mechanisms and developing targeted therapies is crucial. Although the efficacy of this treatment is constrained by drug resistance. According to statistical data, drug resistance is responsible for more than 90% of cancer patients' deaths [2]. Drug resistance, which poses a significant obstacle to the treatment of disease and the overall survival of patients, is described as a decline in a drug's efficacy and potency to elicit therapeutic benefits. There are two types of factors in cancer resistance: Intrinsic and extrinsic. The intrinsic factors include genetic mutations, tumor heterogeneity and defense pathways [3, 4]. Intrinsic resistance means that the majority of tumor cells already contain resistance-mediating elements that render the treatment ineffective before chemotherapy is administered. Mutations that occur during therapy as well as other adaptive responses, such as

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increased expression of the therapeutic target and activation of alternative compensatory signaling pathways, can result in acquired drug resistance in tumors that were previously responsive [5]. The extrinsic factors are primarily target tumor microenvironment (TME) that impact the biology of cancer cells and response to treatment. These components are the extracellular matrix (ECM), cancer-associated fibroblasts (CAFs), and extracellular vesicles (EVs), contribute to cancer resistance.

Targeting both intrinsic and extrinsic factors may enhance treatment efficacy. Advances in drug-resistance research have led to therapies, targeting receptor tyrosine kinases (RTKs), androgen and HER2 receptors, and more. Precision immunotherapies, such as anti-CTLA [6] and anti-PD-1/PD-L1 [7,8], have shown success in recognizing and destroying cancer cells, although resistance and limitations remain including issues with patient response variability, immune-related side-effects, and the emergence of resistance mechanisms. Cancer cells develop drug-resistant traits by undergoing Darwinian selection, which means that the cells with genetic, epigenetic, and protein changes that help them survive treatment are more likely to persist and proliferate [9,10]. This process allows cancer cells to adapt to and resist the effects of chemotherapy and other treatments, ensuring that only the most resilient cells survive and continue to grow. Combination chemotherapy became a new standard in cancer treatment, leading to more complex regimens. Approaches to dose intensity like shorter intervals between doses or higher doses with growth factor support to prevent bone marrow suppression improved success by preventing early tumor regrowth [11,12]. This review discusses how cancer cells resist treatment, a significant clinical challenge. We explore multidrug-resistant pathways across various cancers to support the development of next-generation therapies, including more potent drugs and immunotherapies. Additionally, the review identifies successful strategies to target emerging resistance mechanisms.

2. Common anticancer drugs and their mode of action

Anticancer drugs play a crucial role in the treatment of various malignancies. Chemotherapy, which targets fast-growing cells like cancer cells but also harms healthy cells and causes severe side effects, is a treatment option for cancer. Several chemotherapeutics are frequently combined to address issues like drug resistance, molecular instability, and poor water solubility, which limits cell membrane permeability. Other strategies involve small molecules like genes, small RNAs, and plasmids, though these also face challenges due to poor stability in vivo [13]. The most significant clinical advances in anticancer therapeutics have emerged from treatments with novel mechanisms of action. New classes of cytotoxic chemotherapies, such as anthracyclines and taxanes, have notably improved outcomes across various tumor types. Imatinib, a pioneering kinase inhibitor, has revolutionized the treatment of chronic myeloid leukemia. Additionally, monoclonal antibodies have made substantial progress by effectively targeting CD20 in B-lymphoma, ERBB2 in breast cancer, and immune checkpoints, leading to enhanced therapeutic efficacy [14,15,16]. Here, a number of anticancer drugs are listed according to their class (**Table 1**). Their mode of action and the types of cancer that are used to treat are also mentioned below.

Table 1 List of anticancer drugs and their mode of action

Class	Drug Name	Mode of Action	Cancer Types Treated
Alkylating Drugs	Cyclophosphamide	Cross-links DNA, leading to DNA strand breaks and apoptosis.	Lymphomas, leukemias, breast cancer
	Cisplatin	Forms DNA adducts, causing DNA cross-linking and strand breaks.	Testicular, ovarian, bladder cancer
	Ifosfamide	Similar to cyclophosphamide; forms DNA cross-links, leading to cell death.	Sarcomas, lymphoma and lung cancer.
	Melphalan	Alkylates DNA, leading to cross-linking and apoptosis.	Multiple myeloma, ovarian cancer
	Chlorambucil	Cross-links DNA, interfering with DNA replication and transcription.	Chronic lymphocytic leukemia, lymphomas
	Busulfan	Cross-links DNA, leading to DNA damage and cell death.	Chronic myeloid leukemia and myelofibrosis
	Carmustine (BCNU)	Alkylates DNA and RNA, causing cross-linking and strand breaks.	Brain tumor, multiple myeloma

	Dacarbazine	Methylates DNA, inhibition of DNA replication and transcription.	Melanoma, Hodgkin's lymphoma
Antimetabolites	Methotrexate	Inhibits dihydrofolate reductase, blocking DNA synthesis and cell division.	Leukemia, breast cancer, osteosarcoma
	5-Fluorouracil (5-FU)	Inhibits thymidylate synthase, disrupting DNA synthesis.	Colorectal cancer, breast cancer
	Cytarabine	Inhibits DNA polymerase, preventing DNA replication.	Acute myeloid leukemia
	Gemcitabine	Incorporates into DNA, causing chain termination and apoptosis.	Pancreatic cancer, non-small cell lung cancer
	Capecitabine	Converted to 5-FU in the body, inhibiting thymidylate synthase.	Breast cancer, colorectal cancer
	6-Mercaptopurine	Inhibits purine synthesis, interfering with DNA and RNA synthesis.	Acute lymphoblastic leukemia
	Pemetrexed	Inhibits multiple folate-dependent enzymes involved in nucleotide synthesis.	Non-small cell lung cancer, mesothelioma
	Fludarabine	Inhibits DNA polymerase, ribonucleotide reductase, and DNA primase, blocking DNA synthesis.	Chronic lymphocytic leukemia
	Cladribine	Incorporates into DNA, causing strand breaks and apoptosis.	Hairy cell leukemia
	Nelarabine	Converted to arabinosylguanine nucleotide, incorporating into DNA and causing chain termination.	T-cell acute lymphoblastic leukemia
Topoisomerase Inhibitors	Topotecan & Camptothecin	Inhibits topoisomerase I, preventing DNA unwinding and replication.	Ovarian cancer, small cell lung cancer
	Irinotecan	Inhibits topoisomerase I, leading to DNA damage and cell death.	Colorectal cancer
	Etoposide (VP-16) & Epipodophyllotoxin	Inhibits topoisomerase II, causing DNA strand breaks and apoptosis.	Testicular cancer, lung cancer
	Teniposide (VM-26)	Inhibits topoisomerase II, leading to DNA damage and inhibition of cell division.	Acute lymphoblastic leukemia
	Doxorubicin	Inhibits topoisomerase II, causing DNA damage, and also intercalates into DNA.	Breast cancer, leukemia
	Daunorubicin	Inhibits topoisomerase II, causing DNA damage, and also intercalates into DNA.	Acute myeloid leukemia, acute lymphoblastic leukemia
	Mitoxantrone	Inhibits topoisomerase II and intercalates into DNA, causing DNA damage.	Prostate cancer, breast cancer
	Amsacrine	Inhibits topoisomerase II and intercalates into DNA, causing strand breaks.	Acute lymphoblastic leukemia

Mitotic Inhibitors	Paclitaxel (Taxol)	Stabilizes microtubules, preventing their disassembly, inhibiting mitosis.	Breast cancer, ovarian cancer, lung cancer
	Docetaxel (Taxotere)	Promotes microtubule assembly and inhibits disassembly, leading to mitotic arrest.	Breast cancer, prostate cancer, lung cancer
	Vincristine	Binds to tubulin, inhibiting microtubule formation and preventing mitosis.	Leukemia, lymphoma, multiple myeloma
	Vinblastine	Inhibits microtubule formation, causing mitotic arrest and apoptosis.	Hodgkin's lymphoma, testicular cancer
	Vinorelbine	Inhibits microtubule formation, leading to mitotic arrest.	Non-small cell lung cancer, breast cancer
	Ixabepilone	Binds to tubulin and promotes microtubule stabilization, inhibiting cell division.	Breast cancer
	Eribulin	Inhibits microtubule growth, leading to mitotic blockage and apoptosis.	Breast cancer, liposarcoma
	Cabazitaxel	Stabilizes microtubules, inhibiting their disassembly and preventing mitosis.	Prostate cancer
Hormonal Therapies	Tamoxifen	Selective estrogen receptor modulator (SERM); blocks estrogen receptors.	Breast cancer
	Anastrozole, Letrozole & Exemestane	Aromatase inhibitor; reduces estrogen production.	Breast cancer
	Leuprolide & Goserelin	Gonadotropin-releasing hormone (GnRH) agonist; reduces testosterone production.	Prostate cancer
	Flutamide & Bicalutamide	Nonsteroidal anti-androgen; blocks androgen receptors.	Prostate cancer
	Megestrol acetate	Progestin; inhibits pituitary gonadotropin secretion and lowers estrogen levels.	Endometrial cancer, breast cancer
	Abiraterone acetate	Inhibits CYP17 enzyme, reducing androgen production.	Prostate cancer
Immunotherapeutic Drugs	Pembrolizumab, Nivolumab, Avelumab & Atezolizumab	PD-1 inhibitor; enhances T-cell activity against cancer cells.	Melanoma, lung cancer, Merkel cell carcinoma others
	Ipilimumab	CTLA-4 inhibitor; stimulates immune system to attack cancer cells.	Melanoma
	CAR-T Cell Therapy (e.g., Kymriah)	Genetically engineered T-cells to target specific cancer cells.	Leukemia, lymphoma
	Sipuleucel-T	Personalized vaccine stimulating immune response against cancer.	Prostate cancer
	Trastuzumab	HER2 inhibitor; blocks HER2 receptor and mediates ADCC.	Breast cancer

Monoclonal antibody therapy	Rituximab	CD20 inhibitor; induces B-cell cytotoxicity.	Non-Hodgkin lymphoma
	Bevacizumab	VEGF inhibitor; inhibits angiogenesis.	Colorectal cancer, lung cancer
	Cetuximab & Panitumumab	EGFR inhibitor; blocks epidermal growth factor receptor.	Colorectal cancer, head and neck cancer
	Daratumumab	CD38 inhibitor; induces cytotoxicity in multiple myeloma cells.	Multiple myeloma
	Alemtuzumab	CD52 inhibitor; depletes targeted lymphocytes.	Chronic lymphocytic leukemia
	Ofatumumab	CD20 inhibitor; targets B-cells in chronic lymphocytic leukemia.	Chronic lymphocytic leukemia
	Pembrolizumab	PD-1 inhibitor; enhances immune system's ability to fight cancer.	Melanoma, lung cancer, others
	Ipilimumab	CTLA-4 inhibitor; activates T-cells to attack cancer cells.	Melanoma

Understanding the molecular mechanisms of drug resistance involves comprehensive genomic analysis of multi-drug resistant (MDR) cancer cells, including studying the epigenetics and identifying MDR genes. Factors like hypoxia and autophagy in cancer cells also contribute to drug resistance and reduced drug efficacy [17]. Identifying affordable and effective treatment of cancer is one of the primary goal for researchers and clinicians. However, chemotherapy is promising, it is ineffective in nearly 90% of patients due to resistance in cancer cell, resulting in increased invasion and metastasis. Both developing and developed countries are critically facing challenges in treatment due to emerging resistance to chemotherapeutic agents and targeted therapies. Genetics, micro RNAs (miRNAs), cancer stem like cells and long noncoding RNAs (lncRNAs) contribute to develop multidrug resistance (MDR) in cancer cells [18,19,20]. MDR genes, such as MDR1 (ABCB1), which encodes P-glycoprotein (P-gp), are key in drug resistance. Increased P-gp expression has been shown to induce MDR in previously sensitive cells [21]. However, the development of resistance to these drugs poses a significant challenge in cancer therapy. Understanding the mechanisms of action and the corresponding resistance mechanisms is essential for developing strategies to overcome drug resistance.

3. Drug resistance mechanism in cancer

Drug resistance in cancer is a significant obstacle to effective treatment. Notably, most cancer patient deaths are due to resistance against anticancer drugs. Cancer cells can acquire several mechanisms of drug resistance during therapy. Understanding these mechanisms is critical for developing novel therapeutic approaches. The primary mechanisms of drug resistance in cancer are as follows.

3.1. Tissue heterogeneity

The transformation of normal cells into cancer cells is explained at genetic, epigenetic, and proteomic levels. However, cancer initiation, development, and progression are complex and variable processes involving dysregulation of key cellular functions [22]. Cancer cells constantly evolve under stress, leading to a heterogeneous population within tumors, with varying responses to anti-cancer drugs. Tumor heterogeneity can be intertumoral (differences between patients) or intratumoral (differences within a patient). Advances in genomic analysis, especially for aggressive cancers like non-small-cell lung cancer (NSCLC), have improved personalized treatment strategies [23]. Although initial success, cancer cells often develop resistance to targeted therapies, highlighting their dynamic nature. Intratumoral heterogeneity, driven by genomic variability from factors like mutagen exposure, DNA repair dysregulation, and redox balance disruptions, plays a crucial role in cancer progression and drug resistance [24,25]. High-throughput genome sequencing has identified genetic signatures associated with instability and variability. For instance, lung cancer caused by smoking shows specific genomic changes. Rapid mutation rates disrupt the balance between oncogenes and tumor suppressor genes, promoting diversity. Clonal evolution, following Darwinian selection, leads to genetic diversity as competitive sub-clones and cancer stem cells (CSCs) emerge [26,27]. These clones expand that generates further diversity and acquire the traits like growth and resistance. Techniques like single-cell RNA sequencing and mutation characterization help to examine evolutionary dynamics within tumors, aiding personalized therapy. Genomic changes contribute to drug resistance and tumor recurrence. Tumor evolution creates a subpopulation of multi-drug resistant (MDR) cells with different treatment responses as compared to the primary cells. Chemotherapy pressures further

evolve resistant sub-clones [28]. Recent studies on HBV-associated human hepatocellular carcinoma (HCC) show that tumor heterogeneity and immune landscape inhibit T-cell infiltration, creating an immune-suppressive microenvironment [29]. This finding is crucial for designing effective immune therapies, either alone or with existing treatments, to sensitize resistant cancer cells. Understanding tumor heterogeneity and immune landscape challenges is essential for advancing cancer therapy.

3.2. Genetic and epigenetic modifications

Numerous aspects of cancer pathogenesis, such as intratumoral heterogeneity—which promotes primary cancers, distant metastatic lesions, and cancer relapse following therapeutic failure—are significantly influenced by genetic instability. This instability manifests as aneuploidy, deletions, point mutations, chromosomal translocations, and gene amplifications [30,31]. Losing drug-sensitive genes or causing alterations in biochemical pathways, both of which appear to be essential in the development of chemotherapeutic drug resistance, may be caused by regularly losing chromosomes or their reassortments during mitosis. The treatment is further complicated by the fact that normal cells, which seldom gain or lose a chromosome, typically remain receptive to medications. Cytotoxic medicines work by disabling cell components whose survival-critical functions must be maintained. Tumor cells frequently have gene mutations, which give them the ability to modify target molecules in a way that renders them resistant to a certain medication. The gene's product still has action, but it no longer has the ability to attach to the medication due to alterations in its stereochemical structure. Antiestrogen therapy for breast cancer patients is a well-known instance of this resistance mechanism [2]. The presence of at least one drug-resistant cell clone in malignancies that are naturally susceptible to chemotherapy raises the possibility that these tumors will develop resistance to chemotherapy over time and may return. Epigenetic mechanisms alter the expression and function of genes without altering the DNA sequence, which may produce heritable traits. In addition to traditional genetics, epigenetics plays a crucial regulatory function in the transgenerational transmission of acquired traits, the fate of stem cells, and the development of cancer. Epigenetic modifications are significantly influenced by alterations in the internal and external environment [32,33]. Epigenetic variations occur when gene expression and function are altered by changes such as histone modifications including acetylation, ubiquitination, sumoylation, and DNA methylation. Studies have shown that these epigenetic modifications are crucial for drug-tolerant persister (DTP) cells, which can withstand higher drug pressures [34]. The most recent research highlights the critical contribution of epigenetic changes in cancer cells to anticancer treatment resistance. The epigenome experiences a variety of changes during tumorigenesis, including a genome-wide loss of DNA methylation, localized hypermethylation (especially in CpG promoter islands of tumor suppressor genes), global modifications to histone modification marks, and changes in the expression of miRNAs [35, 36]. Hypermethylation of the miR-129-5p CpG island suppresses miR-129-5p, promoting chemoresistance in gastric carcinoma cells. Treatment with 5-azacytidine (5-AzaC) decreases chemoresistance to cisplatin, 5-FU, and vincristine in the gastric carcinoma MDR cell line SGC7901/VCR by restoring miR-129-5p activity through reduced gene methylation [37]. Hypomethylation in several genes' promoter regions can lead to chemotherapy resistance. The GSTp, MDR1, uPA, and MGMT promoter regions were hypomethylated in drug-resistant MCF-7 cells, contributing significantly to resistance. Hypomethylation of the MDR1 gene has been associated to upregulation of the drug efflux protein P-glycoprotein (P-gp), resulting in doxorubicin resistance [38,39]. Apoptosis sensitivity or resistance is influenced by epigenetic control of anti- and pro-apoptotic signaling components. Baharudin et al. (2017) found that hypermethylated genes linked to the MAPK signaling pathway regulate apoptosis and therapeutic resistance to 5-fluorouracil (5-FU) in colorectal carcinoma patients [40].

3.3. Drug transporters

Drug resistance-associated membrane proteins, or "DRAMPs," are membrane transporter proteins that act either directly by pushing drug molecules out of cells to reduce intracellular accumulation or indirectly by influencing net drug accumulation through physico-chemical processes. Reduced uptake of cytotoxic drugs into cancer cells is a primary cause of chemotherapy resistance. Drugs enter cells by receptor/transporter interactions, endocytosis, or diffusion across the plasma membrane. Alterations or mutations in these receptors/transporters can limit medication absorption, resulting in pharmacological insensitivity. For example, lower expression of the MTX transporter in osteosarcoma, human breast cancer cells (MDA-MB-231), and cisplatin-resistant cells is associated with low folate transporter expression, resulting in decreased cellular absorption [41]. Two MDR genes, MDR-related proteins and *P-gp* genes, are found in humans. They are structurally similar and members of the ABC transporter family. Multidrug resistance (MDR) is largely dependent on the activity of these membrane transporter proteins. The ATP-binding cassette (ABC) transporter superfamily, which pumps hydrophobic chemotherapeutic drugs out of tumor cells to reduce net intracellular accumulation and, consequently, the efficacy of the drugs into tumor cells, and the solute carrier transporters, which increase chemoresistance by preventing the cellular uptake of hydrophilic anticancer agent, are the two main classes of DRAMPs that have been identified. P-glycoprotein, ABCG2, and the multidrug resistance-associated proteins (MRPs) are three major categories of ABC transporters that are associated to MDR [42]. P-gp has long been

acknowledged as a feasible target to combat MDR in cancer as it was the first identified and most thoroughly characterized MDR transporter. P-gp expression was found in more than 50% of the NCI-60 tumor cell lines, including all melanomas, tumors of the central nervous system, and renal and colon cancers at high levels. Reduced chemotherapeutic responses and poor clinical outcomes in a variety of cancer types, including both solid tumors and blood malignancies, have been associated to higher P-gp expression in cancer cells. Leukemia and breast cancer are two examples of malignancies with low levels of P-gp expression at baseline that had upregulated P-gp as the disease progressed after receiving chemotherapy [43]. The active efflux function of P-gp exhibited a key defense mechanism of drug resistance in ovarian cancer and down-regulations of P-gp were proved to restore the sensitivity of tumor cells to chemotherapy [44]. Numerous anticancer medications that are essential to many chemotherapeutic regimens are susceptible to P-gp-mediated efflux, including vinca alkaloids and taxanes that target microtubules (such as vinblastine and vincristine), DNA-chelating anthracyclines (such as doxorubicin and daunorubicin), topoisomerase inhibitors (such as topotecan and etoposide), and tyrosine kinase inhibitors (dasatinib and gefitinib). Chemoresistance in prostate, lung, and breast cancer has also been linked to MRP1 overexpression [45]. BCRP, the third main MDR drug efflux pump to be discovered, has been linked to chemoresistance in leukemia and breast cancer [46]. According to recent research, molecularly targeted treatments including imatinib, erlotinib, sunitinib, and nilotinib also act as substrates for MDR1 and BCRP19 as well as modulators of these two receptors [47]. A better understanding of the chemical characteristics that turn a medication into a substrate for ABC transporters may make it possible to avoid those characteristics when developing novel anticancer treatments by taking them into account while designing the medicinal chemistry.

3.4. DNA damage repair

Numerous chemotherapy medications cause DNA damage either direct mechanism, such as platinum- based medications) or through indirect mechanism, such as topoisomerase inhibitors. Normal cells follow strict cell cycle regulation to repair DNA damage at G1/S, intra-S, and G2/M checkpoints. Cancer cells, on the other hand, circumvent this regulation and alter DNA repair. DNA damage-induced cell cycle arrest has evolved as a mechanism to provide cells with the required time to repair the damage. It makes sense to combine DNA-damaging drugs with a therapy strategy that prevents cancer cells from repairing DNA damage. Additionally, at least one DNA damage repair mechanism is commonly dysfunctional in malignancies, which can result in total reliance on an alternate repair process that is redundant in normal cells and can be suppressed to cause cancer-cell- specific death [5]. Some anticancer drugs, like platinum drugs, damage DNA directly, while others like irinotecan and DOX do so indirectly by inhibiting topoisomerase. The ability of cancer cells to repair DNA damage affects chemotherapy effectiveness. Enhanced DNA damage response (DDR) mechanisms can increase DNA repair activity, leading to greater drug resistance. ERCC1, an essential component of nucleotide excision repair (NER), is overexpressed in many malignancies, including colorectal and breast cancer. It helps to repair DNA damage caused by platinum medications. Liu et al. discovered that ERCC1 expression in gastric cancer is regulated by the ERK1/2 and p38 signaling pathways via the transcription factor c-jun/AP-1 [48]. Similarly, Tung et al. demonstrated that elevated ERCC1 expression causes mitomycin C resistance in gastric cancer via MAPK signaling, which activates the transcription factor Sp [49]. The DNA damage repair (DDR) pathways, which include a complex of proteins like NER machinery that processes and eliminates the so-called bulky lesions, are key indicators of response to many chemotherapeutic treatments and targeted therapies. The two sub-pathways of nucleotide excision repair (NER) are transcription-coupled NER (TC-NER or TCR), which fixes damage in active DNA regions, and global genomic NER (GG-NER or GGR), which repairs damage in non-active regions. Detection of DNA damage, DNA unwinding, and other procedures like slicing, polymerization, degradation, and ligation are some of the fundamental stages that make up the NER pathway [42]. Mismatch repair (MMR) systems are critical for preserving genomic integrity, and mutations in MMR genes can cause microsatellite instability. MMR deficiencies can result in resistance to certain platinum medications. Overexpression of miRNA-21 also inhibits the MMR proteins, like MSH2 and MSH6, which are required for recognizing and repairing DNA damage [50].

3.5. Cancer stem like cells

Enormously diverse populations make up tumors, and it has been hypothesized that some of these groups contain tumor-initiating cells or cancer stem-like cells (CSCs). Because they exhibit normal tissue stem-like characteristics such as self-renewal and the ability to produce differentiated cell populations. CSCs are regarded to have a high tumorigenic potential. CSCs resist chemotherapy through many pathways such as Notch, Wnt, TGF-β, and Hedgehog. Targeting these pathways can assist in overcoming resistance. For example, Notch1 expression enhances trastuzumab resistance in BT474, SK-BR3, and MCF-7 cells, whereas decreasing it makes these cells more susceptible to therapy [51]. Furthermore, it is discovered that PF-03084014 inhibits the Notch-1 pathway in prostate CSCs, increasing the efficiency of docetaxel via inhibiting cell proliferation and promoting cell death [52]. Conventional therapy can stimulate CSCs, resulting in tumor recurrence and resistance. Radiation therapy, for example, stimulates glioblastoma CSCs (CD133+/Prominin-1), which increase radioresistance by activating DNA checkpoints. Combining checkpoint inhibitors (Chk1 and Chk2) with radiation increases radiosensitivity [53]. Although bevacizumab initially shrinks glioblastoma

tumors, its efficacy decreases with time due to the formation of resistant lineages and VEGF-VEGFR2-Neuropilin-1 signaling, culminating in tumor relapse [54, 55].

Numerous studies have demonstrated that the CSC population exhibits a high level of resistant to radioactive treatments and traditional chemotherapy drugs as a result of variety of unique characteristics. Since recurrences and metastasis are the main causes of poor patient prognosis, it is very likely that CSCs survive after treatment with conventional therapy regimens and are responsible for those events even if the quantity of survived cancer cells reaches an undetectable level. CSCs are believed to be in a quiescent state (also known as the G0 phase), particularly after the tumor development. Consequently, they are challenging to eradicate with traditional anti-cancer medications or radioactive rays that aim at actively proliferating cell. Some cancer forms, particularly CSCs, have been found to overexpress these ABC transporters [56]. According to reports, CSCs frequently exhibit elevated amounts of membrane ABC transporters, which pump medications out of the cell, contributing to drug resistance and tumor relapse. For example, in triple-negative breast cancer (TNBC) CSCs, ABCG2 overexpression is associated with chemoresistance. Furthermore, it is found that ABCG2 protects different cancer cells against 5-FU and doxorubicin by expelling these medicines and inhibiting apoptosis [57, 58]. CSCs rely on the signaling pathways that help keep them from going through apoptosis. Anti-apoptotic signaling has been demonstrated to be activated by two key stemness-related signaling pathways, Notch and Hedgehog, which are frequently highly activated in CSCs [59].

3.6. Exosomes

Exosomes are spherical or cup-shaped extracellular vesicles that range in size from 40 to 150 nm and have a density of 1.13 to 1.19 g/mL. A small portion of the cytosolic substance is encased within the phospholipid bilayer that makes up an exosome. However, no cytoplasmic organelles are present. The mother cell's physiological state is directly correlated with the exosome content [60]. Extracellular vesicles (EVs) can transport drug-resistant proteins, nucleic acids, and metabolites to cancer cells or directly package and sequester drugs, resulting in drug resistance. Evidence suggests that the tumor microenvironment (TME) contributes to medication resistance. (P-gp carried by exosomes can bind to the plasma membrane of osteosarcoma cells, enriching tumor cells and triggering pharmacological desensitization. In prostate cancer, exosomal P-gp in serum may be a biomarker of docetaxel resistance [61]. Chemo-resistance can be transmitted between cells via exosomes. For example, exosomes from cisplatin-resistant lung cancer cells caused drug resistance in recipient cells via miRNA-100-5p, which altered mTOR expression levels [62]. In liver cancer, multidrug-resistant cells delivered miRNA-32-5p to susceptible cells via exosomes, activating phosphatidylinositol kinase via the Akt pathway and leading to treatment resistance [63].

Recent researches suggest that exosomes play an important role in the response of cancer cells towards chemotherapy. Hedgehog, Wnt, Notch, β-catenin, and other CSC-specific proteins and mRNAs are found in exosomes generated from CSCs, and these substances promote the survival and growth of tumor cells. Exosomes sustain CSCs' ability to self- renew and other stemness characteristics by transporting these cargos, which increases resistance to many cancer therapies. Exosome intercellular transfer between drug-resistant and drug-sensitive cells changes the gene expression of the drug-sensitive cell population. Tumor-derived exosomes can also protect target cells by neutralizing the drug's effects on target cells. Another mechanism of acquired drug resistance in cancer involves the transmission of proto-oncogenes via exosomes that activate the PI3K/Akt signaling pathway. Proteomics investigation of TEXs in this context revealed essential signaling proteins, such as the Ras, Src, and MAPK families. Such proteins enter recipient cells where they activate anti apoptotic signaling cascades, increasing the number of drug-resistant cells. Ji et al. discovered that exosomes from mesenchymal stem cells (MSCs) caused fluorouracil resistance in gastric cancer cells via activating the CaMKs/Raf/MEK/ERK pathway [64]. Sansone et al. demonstrated that cancer cell-derived exosomes transfer mitochondrial DNA (mtDNA), resulting in therapeutic resistance [65]. They discovered the whole mitochondrial genome in EVs from the blood of metastatic breast cancer patients who were resistant to hormone therapy. Exosomal mRNAs actively regulate cancer progression. The TP73 gene isoform ΔNp73 plays a role in the development of cancer at various stages. Soldevilla et al. found that CRC-derived exosomes have larger quantities of ΔNp73 mRNA than their original cells, which can promote oncogenic potential and chemoresistance in recipient cells [66]. Another method of resistance in cancer cells is the transfer of certain miRNAs via exosomes.

3.7. Non coding-RNA

Small noncoding RNAs (sncRNAs, 18–200 nt) and long noncoding RNAs (lncRNAs, >200 nt) are two types of noncoding RNAs that do not encode any proteins. There are several kinds of sncRNAs, such as microRNAs (miRNAs), small nuclear RNAs (snRNAs), piwi interacting RNAs (piRNAs), and small nucleolar RNAs (snoRNAs). LncRNAs have a role in controlling different cellular functions. Numerous lncRNAs have been found to exhibit aberrant expression in gastric cancer and to contribute to chemoresistance through the regulation of many target genes. Many oncogenic lncRNAs, including nuclear paraspeckle assembly transcript 1 (NEAT1), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), urothelial carcinoma-associated 1 (UCA1), and prostate cancer-associated transcript 1 (PCAT-1), as well as some tumor suppressor lncRNAs, have been shown to play a role in gastric cancer chemoresistance [67]. The lncRNA

CDKN1A antisense RNA is often deregulated in various gastrointestinal tumors. MALAT1, a conserved lncRNA present in many cancers, is silenced by miR-101 and miR-217, which help inhibit the proliferation, migration, and invasion of esophageal cancer [68]. LncRNAs are classified as linear or circular based on their structure, as compared to miRNAs, which do not have 5' caps or 3' poly(A) tails. Inhibition of medication-induced apoptosis is an important mechanism in cancer treatment resistance. MiR-633 prevents doxorubicin/cisplatin-induced apoptosis in SGC-7901 and AGS cells via downregulating FADD in the 3′-UTR [69]. Furthermore, miR-92a-3p is increased in cervical cancer tissues and cisplatin-resistant HeLa and SiHa cells, reducing apoptosis via targeting Krüppel-like factor 4 (KLF4) and thereby increasing resistance. Knocking down miR-92a-3p improves cisplatin sensitivity in these cells [70]. Emerging evidence shows that circular RNA (CircRNA) dysregulation contributes to cancer drug resistance through mechanisms like drug transport, cell death, DNA repair, and cancer stemness. CircRNA_101277 is highly expressed in colorectal cancer (CRC), facilitating cisplatin resistance by upregulating IL-6 via miR-370 sequestration [71]. Similarly, circAKT3 is highly expressed in cisplatin-resistant Gastric Cancer, promoting resistance by upregulating PIK3R1 through miR-198 sequestration, enhancing DNA repair, and inhibiting apoptosis [72].

3.8. Epithelial-to-mesenchymal transition (EMT) program

EMT (epithelial-mesenchymal transition) occurs when epithelial cells shift into motile mesenchymal cells. It is necessary for development and wound healing, and it has a crucial function in cancer progression [5]. EMT is a conserved biological program that improves cell mobility and drug efflux pumps by altering epithelial cells into mesenchymal or CSC-like ones. This transition is caused by hypoxia, cytokines, or activation of TGF-β, Notch, Hedgehog, and Wnt pathways. Cancer metastasis and drug resistance are both driven by EMT signaling pathways [73]. Key EMT markers include Snail, TWIST, ZEB, N-cadherin, and fibronectin. ZEB1, an EMT activator, represses genes that promote the epithelial phenotype (i.e. miR-200 and miR-203), increasing stemness and chemotherapy resistance [74,75]. The EMT transcription factor ZEB1 reduces BIM expression by binding to the BIM promoter, limiting apoptosis and inducing resistance [76]. TWIST1 activation via Metadherin (MTDH) generates CSC attributes and drug resistance in MCF-7 cells [77]. In TNBC cells, the SOX2-ABCG2-TWIST1 pathway plays an important role in tumorigenicity and chemoresistance. Wilson et al. discovered that TGF-β therapy generated EMT-associated resistance in EGFR-mutated non-small cell lung cancer, resulting in higher resistance and lower apoptosis in mesenchymal cells relative to epithelial cells when treated with the EGFR inhibitor erlotinib [78]. Withaferin-A limits cell migration, invasion and metastasis in lung cancer (H1299) and breast cancer including MDA-MB-231, MCF-7, T47D cell lines while exhibiting mild proapoptotic and antiproliferative effects. This drug actually induce vimentin disassembly and serine 56 phosphorylation that exerts dose-dependent inhibition of metastatic lung nodules in human [79].

3.9. miRNA-related drug resistance

The post-transcriptional effect of miRNA gene expression, known as gene silence, happens via mRNA destruction, translational repression, or DNA methylation. miRNAs modulate DNA methylation by targeting methyltransferase enzymes. This epigenetic alteration has been associated to cancer development. miRNAs often attach to the 3' untranslated regions of their target genes, inhibiting their function. Numerous studies in recent years have demonstrated that miRNAs play a role in the drug resistance of tumor cells by targeting genes associated with drug resistance or by affecting genes involved in cell proliferation, the cell cycle, and apoptosis. It is recently demonstrated that miR-221, miR-222, and miR-30b/c are controlled by both epidermal growth factor (EGF) and MET receptors, but miR-103 and miR-203 are only regulated by MET. MiR-221/222 and miR-30b/c target APAF-1 and BIM to cause gefitinib resistance, while miR-103 and miR-203 inhibit lung cancer by targeting PKC-ε and SRC, respectively [80]. Ahmad and colleagues demonstrated that Hedgehog signaling leads to lung cancer treatment resistance. Inhibiting this pathway using siRNAs improved NSCLC cell responsiveness to erlotinib by increasing miR-200b and let-7c levels. Furthermore, miR-34a inhibits HGF-mediated gefitinib resistance in EGFR mutant NSCLC by targeting MET [81]. miRNAs have been demonstrated to play a significant impact in the efficacy of cancer chemotherapy. Zhong et al. identified 123 dysregulated miRNAs in vinorelbine-resistant breast cancer cells, 31 of which were downregulated and 92 of which were elevated, suggesting that miRNA expression tightly controls drug resistance [82]. Further, they found that 17 specific miRNAs and their target genes are involved in key oncogenic pathways like TGFβ, mTOR, Wnt, and MAPK, which play major roles in breast cancer chemotherapy response. Epithelial-mesenchymal transition (EMT) is frequent in CSCs, which are metastatic and resistant to therapy. Chen et al. discovered that the CSC marker ALDH1 promotes paclitaxel resistance in colon cancer [83]. However, miR-125a/b expression restored paclitaxel sensitivity in HT29 cells by downregulating ALDH1 [83]. Both miR-146b and miR-218 inhibit cisplatin resistance in NSCLC cells [84, 85]. MiR-15b and miR-27a, on the other hand, increase cisplatin resistance by blocking PEBP4 and RKIP-mediated EMT [86]. Overexpression of miR-199a-5p suppresses autophagy and lowers susceptibility to several chemotherapeutic drugs. Furthermore, miRNAs such as miR-133a-3p influence drug resistance in lung cancer through interactions with EGFR signalling networks [87]. These miRNAs control a variety of target genes, including those that influence how cells react to chemotherapy. One kind of miRNA can target several mRNAs due to the tissue specificity of miRNA regulation,

and one mRNA can also be targeted by multiple miRNAs [88,89]. As a result, the same miRNA may have varied, even conflicting, roles in regulating drug resistance in various cancer cells. A review of recent studies reveals that miRNAs largely affect cell survival and death signaling pathways to determine drug resistance in cells. Additionally, Synthetic mRNAs with multiple binding sites for a specific microRNA, called microRNA sponges, can bind and sequester the microRNA, preventing it from interacting with its natural targets. The benefits of microRNAs over siRNA/shRNA are that they can control several targets simultaneously, impacting a complex network of interacting molecules [90].

4. Discussion

Chemotherapy is still an effective method for getting rid of cancerous cells. Nevertheless, the frequent occurrence of innate and acquired multidrug resistance compromises the effectiveness of chemotherapy. Understanding and overcoming drug resistance in cancer treatment remains a major obstacle. Therefore, one of the main goals of cancer research is to develop innovative methods to combat cancer medication resistance. Comprehensive genomic and epigenetic analyses have shown the multiple mechanisms that underpin resistance, including genetic mutations, altered expression of MDR genes, and the function of noncoding RNAs such microRNAs and long noncoding RNAs. Furthermore, cellular circumstances such as hypoxia and autophagy exacerbate therapy efficacy. An innovative and effective cancer-targeting technique is nanomedicine. First off, nanomedicine could easily reach tumors and accumulate at sufficient drug concentrations to increase the effectiveness of cancer treatment [91, 92]. Thanks to the enhanced permeability and retention (EPR) effect or active transport mediated by endothelial pathways. Second, surface decoration of nanoparticles with specific ligands, such as small molecules, peptides, aptamers, and antibodies, which target particular tumor biomarkers on the surface of cancer cells, could improve the specific accumulation of nanomedicine in tumors, reducing off-target effects and harmful toxicity to healthy tissues. Notably, the most well-known nano-based medications are Hensify® (NBTXR3), Pazenir®, Vyxeos®, and Doxil®, which were approved by the FDA several years ago and have been used successfully in clinical practice [93]. To address these issues, future research must focus on establishing personalized therapy regimens that take into account each tumor's distinct genetic and molecular profiles. Personalized medicine (PM) in cancer tailors tumor treatment and prevention to individual genetic diversity, tumor environment, lifestyle, and comorbidity. PM seeks to optimize tumor response, reduce therapy-induced toxicities, preserve organ function, and improve quality of life, eventually improving patient care [94]. Furthermore, investigating combination therapies that target many pathways at once could improve treatment outcomes [95]. The effectiveness of chemotherapy for cancer patients depends on a variety of molecular mechanisms and biological processes that influence how sensitive cancer cells are to chemotherapy medications. The development of novel targeted cancer medicines that selectively target the "hub" genes and target cellular drug resistance is necessary. These treatments must aim to eliminate as many cancer cells as possible while having less of an adverse effect on healthy tissue.

5. Conclusion

Cancer remains the second leading cause of death globally, with around 9.8 million fatalities annually. A major challenge in cancer treatment is the development of drug resistance, which complicates the effective management and eradication of the disease. This resistance arises through various molecular and biophysical mechanisms, including genetic mutations, changes in drug targets, and alterations in cellular pathways that allow cancer cells to evade therapy. These factors limit the efficacy of standard treatments, highlighting the need for novel therapeutic strategies. Understanding these resistance mechanisms is crucial for designing more effective therapies. Recent advances, such as combination therapy and precision medicine, have shown promise in addressing these challenges. This study provides a comprehensive overview of the key molecular mechanisms in cancer drug resistance and explores innovative therapeutic strategies, offering potential benefits to society.

Compliance with ethical standards

Acknowledgments

We strongly acknowledge the study participants and Gautam Buddha University for facilitating the academic platform.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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