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Review Article

Chemoresistance In Cancer and Novel Strategies to Overcome Therapeutic Resistance

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One of the biggest obstacles to cancer treatment is chemoresistance, which frequently results in treatment failure and disease recurrence. Resistance is increasingly recognized as a dynamic and adaptive process shaped by tumor evolution under therapeutic pressure, rather than being exclusively driven by fixed genetic mutations. Through both genetic and non-genetic means, cancer cells can alter their behavior to survive in the presence of cytotoxic medications. This adaptive behavior is the result of several interrelated pathways. These include dysregulation of cell survival signaling, increased drug efflux through transporter overexpression, epigenetic reprogramming, and improved DNA repair capacity. Tumor heterogeneity exacerbates this problem by creating diverse subpopulations with varying drug sensitivity. Furthermore, survival and resistance are supported by cancer stem cells and microenvironmental factors like hypoxia, metabolic stress, and intercellular communication. The role of drug-tolerant persister cells, a temporary, non-genetic state that enables a subset of cancer cells to endure initial therapy and subsequently develop into stable resistant clones, is also highlighted by emerging data. Current approaches are moving toward focusing on the adaptive nature of tumors in order to address this complexity. More effective disruption of resistance pathways is the goal of strategies like rational combination therapy, precision oncology, epigenetic modulation, and targeting persister cell populations. To slow the progression of tumors, adaptive dosing and microenvironment-focused treatments are also being investigated. Developing more robust and efficient cancer treatments requires a deeper comprehension of these mechanisms.

Keywords: chemoresistance, tumour microenvironment, epigenetics, drug-tolerant persister cancer cells.

INTRODUCTION

Chemoresistance remains a significant barrier in cancer therapy and is closely associated with disease progression and unfavourable clinical outcomes [1]. The diminished sensitivity of cancer cells is a complex process influenced by genetic, epigenetic, and microenvironmental factors. Several mechanisms have been identified and widely studied, including drug inactivation; decreased intracellular drug levels due to reduced uptake or enhanced efflux; modification of drug targets; activation of alternative survival pathways; alterations in DNA repair and cell death regulation; tumor plasticity; and the influence of the tumor microenvironment (TME) [2]. Approximately 90% of chemotherapy failures occur during cancer invasion and metastasis and are linked to drug resistance. After the administration of a specific chemotherapeutic agent, tumor cells in many patients gradually lose their sensitivity to the drug. As a result, drug resistance has become a critical challenge in oncology.

Depending on when it appears, drug resistance is categorized as either acquired or intrinsic. About 50% of drug-resistant cases in cancer patients are caused by either acquired resistance, which develops after therapeutic exposure, or intrinsic resistance, which

exists prior to treatment. Intrinsic resistance refers to pre-existing insensitivity prior to drug administration, often leading to poor treatment response. It may arise from: A) inherent genetic alterations in tumors that reduce responsiveness to chemotherapy and targeted agents, as seen in triple-negative breast cancer; B) tumor heterogeneity, where resistant subpopulations, including cancer stem cells, are already present and become selected during therapy, resulting in later relapse; and C) activation of natural defence mechanisms that protect cells from toxic agents, including anticancer drugs. In contrast, acquired resistance is marked by a gradual decline in drug efficacy after treatment has begun. It can result from activation of a secondary proto-oncogene that becomes a new driver gene, mutations or altered expression of drug targets, and changes in the tumor microenvironment following therapy. [4, 5].

A key objective of anticancer treatment is to control or halt tumor growth without inducing, or at least accelerating, acquired resistance. Therefore, treatment strategies should aim to prevent or delay its development. The molecular processes that drive chemotherapy resistance are studied in this review, including drug efflux, improved DNA repair, apoptosis evasion, epigenetic changes, and the function of cancer stem cells. In addition to summarizing these mechanisms, it draws attention to recent developments, especially the role that epigenetic modifications play in chemoresistance. Additionally, it highlights resistance trends in the main cancer types, pinpoints important therapeutic targets, and talks about new approaches to overcoming resistance. This review offers a foundation for enhancing therapeutic strategies against cancers resistant to chemotherapy by addressing these molecular obstacles [6].

2. CANCER AS AN EVOLVING DISEASE

The term "cancer evolution" describes how tumor cells change to fit their surroundings. The immune system's capacity to identify and eradicate tumors may be weakened by this adaptation, which may also make cancer research less predictable [7].

Cell plasticity

Cellular plasticity, sometimes referred to as phenotypic switching, allows cells to change their morphology in response to environmental changes. This capacity enables tumor cells in cancer to change reversibly into states that are not affected by drug-targeted pathways. This flexibility draws attention to cancer cells' innate ability to quickly alter their molecular and phenotypic traits in response to external stressors, such as drug exposure. Cancer cells can adapt to therapeutic stress and develop resistance to various agents thanks to this flexibility, which gives them a survival advantage. The need for a deeper comprehension of the molecular mechanisms underlying this induced plasticity is highlighted by the dynamic nature of cancer cell. To address these processes, we must move away from a static view of cancer genetics and toward a more dynamic perspective that takes genomic variability and adaptability into account within tumor populations [8, 9]. The main causes of cancer development are genetic changes, such as chromosomal rearrangements, mutations, and other anomalies. Technological developments in DNA sequencing have shown that mutations in particular genes, especially oncogenes and tumor suppressor genes (TSGs), are crucial to the development of numerous cancers [10].

In addition to genetic changes, epigenetic factors can alter chromatin accessibility, resulting in abnormal cellular reprogramming or differentiation arrest. Tumor genomes may exhibit a bivalent chromatin state, which is defined by the presence of both repressive and active markers close to specific genes, according to cancer genomic studies. Cancer stem cells (CSCs) frequently retain these characteristics, which facilitate ongoing self-renewal and phenotypic flexibility, thereby encouraging tumor growth and proliferation [11].

Understanding the molecular mechanisms underlying cancer cells' plasticity remains one of the primary objectives of cancer research. Tumor cell plasticity, which allows cells to alter their traits and adapt for survival, is largely dependent on the tumor microenvironment (TME). Interactions between tumor cells and their surroundings can facilitate the development of new phenotypes in non-malignant cells. These interactions have an impact on treatment

resistance, heterogeneity, and tumor development. Furthermore, non-genetic mechanisms often interact with the genetic landscape of the tumor to enable therapeutic escape through cellular plasticity that permits evasion of anticancer immunosurveillance and adaptive processes like modifications in transcriptional or metabolic programs. As a result, cellular plasticity and adaptation have become major obstacles to cancer treatment.

Stress-Induced Reprogramming and autophagy

The capacity of cancer cells to adapt and endure under stressful circumstances is a major challenge in cancer treatment. Tumor cells alter transcriptional, translational, and post-translational processes to reprogram their signaling pathways in a spatial and temporal manner in response to physiological and microenvironmental stresses, including oxidative stress, hypoxia, nutrient deprivation, endoplasmic reticulum and mitochondrial stress, and DNA damage. Tumor cells with unique gene expression and metabolic profiles proliferate clonally as a result of this reprogramming. Stress-induced phenotypic heterogeneity leads to treatment resistance, tumor recurrence, and metastasis [14, 15].

Two important, contextually specific stress adaptation mechanisms that promote tumor survival, metabolic adaptability, and treatment resistance are autophagy and lysosomal function. By eliminating damaged organelles, autophagy may prevent cancer during the early stages of tumorigenesis. However, in established tumors—particularly those with RAS mutations—it promotes survival through mechanisms such as mTORC1 inhibition and AMPK activation under conditions of nutrient deprivation, hypoxia, and therapeutic stress. Through lysosomal drug degradation and sequestration, these mechanisms aid in immune evasion and chemoresistance. Notably, autophagy and genes linked to autophagy play a complicated role in the development of cancer. Tumor suppressors like Beclin-1 and AMBRA1 are core regulators; autophagy is disrupted and tumorigenesis is encouraged by loss of BECN1 or decreased AMBRA1 expression [16]. In response to metabolic stress, certain pathways are activated by hypoxia. Certain cells adjust to the lack of glucose by reducing their energy requirements or by substituting other substrates for glutamine in the tricarboxylic acid (TCA) cycle. The heterogeneity of cancer metabolism is further highlighted by the various survival strategies that different cancer cells adopt [17].

TME as the Selective Pressure

The process of metastasis involves several steps, such as invasion, intravasation, circulation, bloodstream survival, extravasation, and the development of secondary tumors. The tumor microenvironment (TME) and cancer cells interact to control each of these stages. Therefore, creating successful treatment plans requires an understanding of the TME's molecular mechanisms and its function in metastasis. Conditions like hypoxia, nutrient deprivation, and acidic pH, which all contribute to tumor progression independent of genetic mutations, are characteristics of the TME. Extracellular matrix (ECM) remodelling controlled by matrix metalloproteinases (MMPs), which are upregulated in the TME, is an important step in this process. Tumor cells can infiltrate nearby tissues and travel through the circulatory system as a result of MMPs' degradation of ECM components. Furthermore, growth factors that further support tumor cell survival and proliferation are stored in the remodelled extracellular matrix. Additionally, the TME creates pathways for metastatic dissemination and promotes angiogenesis, which is essential for tumor growth. Tumor and stromal cells both secrete vascular endothelial growth factor (VEGF), which is essential to this process. Elevated levels of VEGF increase vascular permeability and cause leaky, disorganized vasculature, which makes it easier for tumor cells to enter the bloodstream. Moreover, immune cells in the TME aid in tumor growth and immune evasion. Myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) are two examples of cells that can experience functional alterations that promote tumor growth and metastasis [18- 20].

3. BIOLOGICAL BASIS OF CHEMORESISTANCE

Chemoresistance is the primary barrier to cancer treatment, contributes to disease relapse and metastasis, and hinders the improvement of clinical outcomes for cancer patients. As a result, it is critical

to understand its molecular mechanisms and discover new therapeutic approaches for cancer treatment.

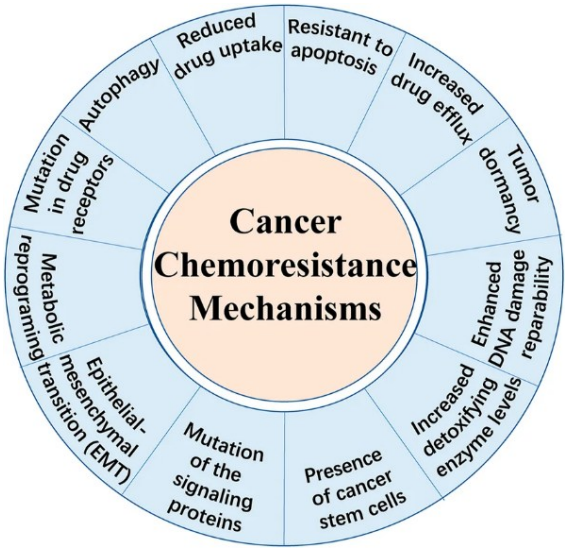

Fig 1 various mechanisms involved in chemoresistance

Microenvironment-Mediated Drug Resistance

The tumor microenvironment is made up of several elements, including ECM proteins, cancer-associated cells, and abnormal vasculature. The distinctive environmental characteristics of hypoxia, matrix rigidity, and a changed paracrine factor composition are caused by these physical elements. The different mechanisms of chemoresistance are significantly influenced by the features of the tumor microenvironment, and how this is accomplished have been investigated to varying degrees [21].

Hypoxia-inducible factor (HIF)-1α, which controls numerous cell survival and angiogenic genes, is stimulated by oxygen deprivation. This helps cancer cells resist the cytotoxic effects of chemotherapy treatments. Under chemotherapeutic pressure, such as in temozolomide resistance in GBM, HIF-1α either stimulates anti-apoptotic proteins (like c-myc, etc.) or suppresses pro-apoptotic proteins (like TRAIL). Because of a high rate of glycolysis that produces lactic and carbonic acids and inadequate clearance of these acids, the extracellular pH in solid tumors is frequently less than that in normal tissues. Resistance to anticancer medications may also be influenced by the significant pH difference between the cytoplasm of tumor cells and acidic intracellular organelles like endosomes and lysosomes. Many anticancer drugs, such as doxorubicin and mitoxantrone, are weak lipophilic bases that will build up in acidic organelles. Drugs become less effective when they are trapped in tumor cells' organelles because there is less drug available to enter the nucleus and cause cytotoxic effects. Tumor cells, CAFs, TAMs, and extracellular matrix elements make up the tumor microenvironment, an ever-evolving that promotes tumor growth and treatment resistance. Additionally, TAMs release factors that promote angiogenesis, extracellular matrix remodelling, and immune suppression, all of which contribute to chemoresistance. These factors include VEGF, MMP9, and TGF-β [22, 23, 24].

Tumor progression and chemoresistance are known to be significantly influenced by mesenchymal stem cells (MSCs), which are also present in the TME. MSCs either differentiate into tumor-associated fibroblasts (TAFs) or secrete growth factors that stimulate tumor growth. In order to protect cancer cells from chemotherapy and immunotherapy, TAFs are essential stromal cells that build physical barriers, secrete growth factors (such as TGF-β), and alter the tumor microenvironment (TME). They also promote growth, survival, and metastasis, frequently through extracellular vesicles (EVs) and signaling pathways. Additionally, MSCs can increase chemoresistance by inhibiting the apoptosis of cancer cells and secreting protective cytokines. In the tumor environment, growth factors like hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), and epidermal growth factors (EGFs) are abundant. Many of the receptors that support a chemoresistant phenotype and, consequently, malignant transformation is shared by these species [25, 26].

Overexpression of transporters

One of the main reasons behind multidrug resistance is the increased expression of ATP-binding cassette (ABC) transporters, which work by pumping anticancer drugs out of cells. In cancer, ABCB1, ABCG2, and ABCC1 are particularly important because they are closely linked to chemoresistance. P-glycoprotein (P-gp), also called ABCB1 or MDR1, is an ATP-driven efflux pump found in normal tissues such as the intestinal epithelium, liver cells, renal

proximal tubules, and capillary endothelial cells. It transports a broad variety of substances, including colchicine, tacrolimus, quinidine, etoposide, doxorubicin, vinblastine, lipids, steroids, bilirubin, digoxin, and dexamethasone. Overexpression of P-gp has been associated with resistance to chemotherapy in both hematological and solid tumors, including leukemia, neuroblastoma, ovarian cancer, and breast cancer [27, 28].

Lung resistance-related protein, or LRP, was initially identified in doxorubicin-resistant lung cancer cells as a novel 110 kD drug transporter. Additionally, it interacts with ERα, PTEN, and PARP and is restricted to nuclear pore complexes. Therefore, by modifying nucleocytoplasmic transport, including the movement of hormones, ribosomes, mRNA, and medications, MVP may mediate chemoresistance. B-cell lymphoma, gliomas, and non-small cell lung cancer (NSCLC) have all been shown to overexpress it. It is believed to mediate primary chemoresistance and transport cytotoxic drugs that target DNA [29].

Epigenetics modifications

The term "epigenetics" describes heritable variations in phenotype or gene expression that don't result from changes in the DNA sequence. Epigenetic mechanisms influence cell differentiation and aid in maintaining cellular identity both during and after cell division by regulating which genes are turned on or off, as well as when and where they are expressed. DNA methylation, histone post-translational modifications, chromatin remodelling, and non-coding RNA regulation are the four primary mechanisms of epigenetic regulation [30, 31]. Additionally, microRNAs (miRNAs) are important in controlling chemoresistance. Depending on their targets, these tiny non-coding RNAs may act as tumor suppressors or oncogenes. Chemoresistance in a number of cancers has been associated with disruption of particular microRNAs, including miR-21, miR-125b, and miR-193a-3p [32]. We discovered that one of the regulatory mechanisms of miRNA expression is silencing, which is caused by methylation of the regulatory regions of the miRNAs, leading to the overexpression of their target genes. Inhibiting miR-138 reduces cisplatin sensitivity in breast cancer cells by increasing the expression of ABCB1/MDR1 mRNA. ABCB1 and MDR1 are cytoplasmic membrane transporter proteins that contribute to resisting chemotherapy by blocking the drug's intracellular concentration [33, 34].

Tumor heterogeneity

Tumor heterogeneity is the variation observed in cancer cell populations, either within a single tumor (intratumor heterogeneity) or between tumors of the same type across multiple patients (inter-tumor heterogeneity). It is a basic characteristic of cancer and has significant effects on patient prognosis, chemotherapy response, and relapse risk. Nowadays, most people agree that tumors are clonal in origin, which means that they typically start from a single dysregulated or mutated cell. But as the tumor develops, its cells continue to change genetically, epigenetically, and phenotypically, creating several subpopulations across the same tumour [35, 36].

Intratumor heterogeneity may arise from a number of mechanisms, the majority of which take place at the cellular level, and can be seen at various levels of cancer biology. Some pre-existing resistant clones are able to withstand treatment because of these modifications, while other cells may respond to therapeutic pressure by developing new adaptive mechanisms [3].

Tumor heterogeneity consequently produces subclones with different anticancer drug sensitivity, and some of these subpopulations develop greater drug resistance than the original tumor cells. Due to this diversity, some cancer cell clones may be successfully eradicated by a treatment while resistant ones remain. The disease may then progress or reappear as a result of these resistant subclones' ability to endure, grow, and eventually repopulate the tumor. This draws attention to the shortcomings of a static treatment strategy and highlights the need for more dynamic, individualized approaches that can target several tumor cell populations at once [37, 38].

Another significant mechanism of drug resistance is adaptive resistance. After being exposed to targeted therapy, tumor cells that were initially sensitive to treatment progressively develop resistance. Studies on EGFR tyrosine kinase inhibitors (EGFR-TKIs) in non-small cell lung cancer (NSCLC), where

resistance frequently arises due to the T790M mutation in the EGFR gene, provide a well-known example [39].

Cancer stem cells

With the ability to self-renew and proliferate continuously, cancer stem cells (CSCs) are a tiny but crucial subset of tumor cells that can promote tumor initiation, metastasis, and intratumoral heterogeneity. When CSCs are transplanted into immunodeficient animals, they can generate tumors. They are also well known for being resistant to radiation and chemotherapy, which makes them significant causes of metastasis, relapse, and treatment failure. For instance, chemoresistance and recurrence in breast cancer have been linked to tumorigenic cells with high CD44 expression and low or absent CD24 expression [40, 41].

Because CSCs can both self-renew and differentiate into various cancer cell lineages in response to therapeutic stress, there is mounting evidence that they are crucial to chemoresistance. Numerous mechanisms, such as the epithelial–mesenchymal transition (EMT), quiescence, epigenetic changes, multidrug resistance, and interactions with the tumor microenvironment, adhere to their survival both during and after treatment [42].

For example, preleukemic DNMT3A-mutant hematopoietic stem cells can reconstitute the hematopoietic hierarchy and start clonal expansion as an early stage in leukemogenesis. Even after chemotherapy-induced remission, these cells have been demonstrated to endure and proliferate in the bone marrow. As cancer treatment becomes more personalized, accurately identifying and eliminating specific CSC populations may aid in drug resistance, recurrence, and survival [43].

DNA Repair and Apoptosis

One essential cellular mechanism that identifies and fixes DNA damage from both endogenous and exogenous sources is the DNA damage response (DDR). Post-translational modifications of DDR proteins, specifically phosphorylation, ubiquitination, and sumoylation, which control repair signaling and coordination, are crucial to this system's proper operation. Although DNA repair protein defects frequently result in cell death, cells may survive with genomic instability if the damage is not immediately fatal. Genomic instability syndromes are often linked to mutations in important DNA repair genes like FANCD2, BRCA1, BRCA2, and ATM, which impair normal repair mechanisms [44, 45].

One well-known example is cisplatin, which exhibits effective initial activity against a number of solid tumors but frequently loses its effectiveness due to acquired chemoresistance. DNA interstrand and intrastrand crosslinks are caused by platinum-based medications like cisplatin, and these lesions are primarily fixed by homologous recombination (HR) and nucleotide excision repair (NER). DNA repair enzyme expression and activity are frequently elevated in cisplatin-resistant tumor cells, and it has been demonstrated that NER inhibition restores cisplatin sensitivity [46, 47].

Apoptosis is typically triggered by DNA damage. Therefore, cells with damaged DNA can survive, proliferate, and develop more abnormalities when apoptosis is suppressed or evaded. Defects in apoptotic signalling are a major contributor to drug resistance because many anticancer medications work by inducing apoptosis. By upregulating anti-apoptotic proteins like Bcl-2, Bcl-xL, and Mcl-1 and downregulating pro-apoptotic proteins like Bax, Bak, Bid, and Bad, cancer cells frequently develop apoptotic resistance [48, 49, 50].

4. CLINICAL STRATEGIES TO COMBAT CHEMORESISTANCE

Combating Resistance Through Rational Combination Therapy

Combination therapies have greatly improved treatment outcomes in colorectal cancer (CRC) and BRAF^V600-mutant melanoma, showing that addressing several pathways at once can overcome adaptive resistance and improve clinical effectiveness. Inhibiting receptor tyrosine kinases (RTKs), SHP2, or downstream MAPK pathway components like MEK or ERK is a crucial strategy for preventing adaptive feedback mechanisms. These aid in preventing pathway reactivation and enhancing therapeutic response when paired with primary

inhibitors such as BRAF inhibitors [51]. Combining immunotherapy with chemotherapy, especially immune checkpoint inhibitors like nivolumab and pembrolizumab, is another promising approach. These combinations have demonstrated significant effectiveness in treating cancers such as bladder, lung, and melanoma. Chemotherapy can cause immunogenic cell death, which improves immunotherapy's efficacy by strengthening the immune system's capacity to identify and combat tumor cells. The advantages of combining traditional chemotherapeutic agents with low-toxicity compounds have also been highlighted by recent studies. For example, combining these drugs with paclitaxel (PTX) has improved lung cancer outcomes, including increased efficacy, decreased toxicity, synergistic effects, and a decreased risk of developing resistance. Combination strategies seem especially significant when it comes to cancer stem cells (CSCs). 5-fluorouracil (5-FU) monotherapy has had inconsistent outcomes and is frequently linked to tumor recurrence. However, a synergistic effect is seen when paired with salicylic acid, which increases the sensitivity of hepatocellular carcinoma (HCC) cells to 5-FU and improves tumor cell eradication. This effect is explained by salicylic acid's capacity to increase 5-FU's antitumor activity by suppressing CSC populations. Targeting epithelial-mesenchymal transition (EMT) pathways, such as blocking active β-catenin's nuclear translocation, may also lessen CSC activity and enhance therapeutic results [52- 55].

Precision Oncology–Driven Treatment Adaptation

Cancer treatment is increasingly moving away from a one-size-fits-all approach and toward more dynamic and personalised strategies. In order to better understand resistance pathways and treatment responses, signal-based medicine places a strong emphasis on the real-time mapping of molecular signaling within a patient's tumor. Additionally, this method enables the early identification of developing drug resistance, allowing therapies to be modified before resistance becomes clinically significant. Therefore, instead of depending only on standardized chemotherapy regimens, adaptive precision therapies can constantly enhance treatment decisions based on changing tumor characteristics. Advances in precision oncology and supportive statistics have accelerated this transition by shortening the time required for biomarker discovery and the clinical use of new or repurposed drugs. The goal of precision oncology is to identify patient subgroups based on particular genomic changes that affect treatment resistance or sensitivity. Predictive models are being utilized in parallel to evaluate drug response, cancer progression, survivorship, and the best combination strategies for each patient. Clinical decision support systems that incorporate multi-omics data with electronic health records are becoming more and more crucial to support this. Data-driven guidance for early detection, prevention, and individualized treatment are made possible by these systems, but because cancer is a continually evolving disease, they must be updated frequently to take into account new findings [56, 57].

While genomics has traditionally served as the foundation for precision medicine in oncology, transcriptomic and proteomic profiling are increasingly recognized as important. Oncogenic signaling pathways heavily rely on proteins, which are the main effectors of cellular function. While genomic profiling aids in the selection of therapies, it is not always able to identify resistance mechanisms or functional pathway activity. Proteomic analyses have become useful in identifying prognostic and predictive biomarkers because they offer a more direct evaluation of active signaling networks [58].

In clinical practice, tumors in patients with refractory metastatic disease have been examined using methods like immunohistochemistry and other proteomic assays. In comparison to previous treatments, these methods have been linked to better progression-free survival and have made it possible to identify actionable molecular targets. When genomic, transcriptomic, and proteomic data are combined, they provide a more thorough and efficient framework for directing tailored cancer treatment [59].

Targeting Drug-Tolerant Persister Cancer Cells

Drug-tolerant persister (DTP) cells were initially discovered in bacterial subpopulations that withstand exposure to antibiotics by reversible, non-inheritable processes linked to a brief stop in growth. A similar phenomenon was later reported in cancer; in 2010, rare DTP-like subpopulations were found in non-

small cell lung cancer (NSCLC) cell lines that entered a non-proliferative state in order to survive otherwise fatal doses of chemotherapy or targeted therapy [60].

DTPs are now acknowledged as an unusual but clinically important subset of tumors. They have reversible, non-genetic adaptations that allow them to withstand standard-of-care treatments, unlike genetically resistant cells. Even after an apparent therapeutic response, these cells may continue to exist in a dormant or slow-cycling state, serving as a hidden reservoir that may eventually cause tumor relapse. As a result, targeting DTPs has become a potentially effective treatment approach. Two primary strategies are being investigated: stopping cancer cells from transitioning into the persister state and directly eliminating DTPs by interfering with the pathways that support their survival. Both approaches usually depend on combination treatments that combine traditional anticancer medications with medications that target important DTP biology regulators. Pathway-specific targeting has demonstrated promise because DTP survival depends on several signaling pathways. Myc-suppressed, diapause-like cells, for instance, can sustain a drug-tolerant state in breast and prostate cancers; inhibition of CDK9 has been demonstrated to cancel out this phenotype and regain chemosensitivity [61- 64, 68].

DTPs rely heavily on stress adaptation mechanisms, such as improved DNA repair capacity and redox homeostasis, that are triggered under therapeutic pressure. Promising therapeutic approaches include raising cellular stress levels above acceptable thresholds. For example, combining PARP inhibitors with drugs like gemcitabine or PI3K inhibitors can increase replication stress and deplete nucleotide pools, which can ultimately result in S-phase arrest, mitotic catastrophe, and tumor cell death. Immunotherapy-based combination strategies have also demonstrated promise. By boosting immune activation, targeted treatments like MEK, ALK, or EGFR inhibitors can work in concert with immune checkpoint blockade. These combinations help eradicate immune-evasive, dormant tumor cells by increasing PD-L1 expression, stimulating STING-dependent NK and T-cell infiltration, and encouraging the recruitment of cytotoxic immune cells. Despite these advances, there are still significant challenges in optimizing treatment plans. Cytotoxic efficacy and the requirement to prevent the growth of resistant populations must be balanced in effective dosing and scheduling. Although its clinical application is still limited, mathematical modeling has been suggested as a tool to optimize treatment sequencing and drug-switching strategies. Finding credible biomarkers of drug-tolerant states, establishing ideal stress thresholds that promote tumor cell death while lowering the risk of progression, and precisely simulating tumor subpopulation dynamics are some of the major obstacles. Finally, the heterogeneity and volatile nature of these cells make it difficult to translate DTP-targeted strategies into clinical practice. Concerns regarding toxicity are raised by the fact that many of the mechanisms supporting DTP survival, including metabolic quiescence and epigenetic plasticity, overlap with regular cellular functions. Furthermore, the majority of recent research concentrates on intrinsic cellular mechanisms, while the impact of the tumor microenvironment is still poorly understood. Developing safe and effective treatments that target DTPs will require filling in these gaps with better experimental models and integrative, multifaceted approaches [65, 66, 67].

Epigenetic modifications.

Heritable changes in gene expression that take place without any changes to the underlying DNA sequence are referred to as epigenetic modifications. These mechanisms, which collectively regulate gene activity, include DNA methylation, histone modifications, chromatin remodeling, non-coding RNA regulation, nucleosome positioning, and genomic imprinting [69].

Significant changes in DNA methylation patterns are commonly seen in cancer, particularly when drug resistance is present. Studies reveal a mixture of hypermethylated and hypomethylated genes after resistance develops, and changes in CpG islands and CpG island shores are particularly frequent. DNA methyltransferases (DNMTs) catalyze DNA methylation by adding a methyl group to the 5-carbon of cytosine residues in CpG dinucleotides. This alteration frequently results in gene silencing, and when it impacts tumor suppressor genes, it directly

advances the development of cancer. For example, BRCA1 has been indicated to be silenced in breast and ovarian cancers, and the RB1 gene was among the first tumor suppressor genes discovered to be inactivated through hypermethylation [70, 71].

DNMT activity is a desirable therapeutic target because it has also been strongly associated with tumor resistance. Azacitidine and decitabine are examples of DNMT inhibitors (DNMTis), which are cytosine analogues that integrate into DNA throughout replication and bind to DNMTs, thereby deactivating them. As a result, DNA methylation gradually decreases and previously silenced genes become active again. While more recent substances like guadecitabine are presently undergoing clinical testing, these medications are already authorized for the treatment of myelodysplastic syndrome. Combination strategies have also been investigated; in early-phase trials, azacitidine and carboplatin, for instance, demonstrated modest clinical responses with low toxicity [72, 73, 74].

Histone acetylation is another crucial layer of epigenetic regulation, alongside DNA methylation. Tumor suppressor genes can be reactivated when aberrant acetylation patterns in cancer cells are reversed by histone deacetylase inhibitors (HDACIs). These agents are promising therapeutic options because cancer cells are frequently especially sensitive to HDACI-induced apoptosis. They have a wide range of effects, such as inducing cell cycle arrest, promoting differentiation, causing cell death, inhibiting angiogenesis, and modifying immune responses. However, the particular HDAC inhibitor, its dosage, and the type of cancer can all affect the precise mechanisms [75, 76].

Chemotherapy resistance has also been demonstrated to be overcome mechanistically by HDAC inhibition. For instance, HDACIs can increase treatment sensitivity in colorectal cancer by modifying chromatin structure and suppressing thymidylate synthase expression, which ultimately promotes cell death. Histone acetylation and DNA methylation function as complementary controlling layers that propel transcriptional reprogramming during drug adaptation [77].

Epigenetic therapies have limitations despite their potential. Off-target effects and toxicity continue to be major concerns because these agents can impact a variety of genes other than those directly linked to cancer. This emphasizes the need for more targeted methods to increase safety and therapeutic precision, such as biomarker-guided therapy and optimized dosing strategies [78].

CONCLUSION

With rising incidence and mortality, cancer remains a major global health concern, underscoring the urgent need for more potent and long-lasting treatment approaches. Chemoresistance, which is caused by a complex combination of genetic alterations, epigenetic changes, tumor heterogeneity, and influences from the tumor microenvironment, is one of the main challenges in cancer treatment. Crucially, resistance is a dynamic process in which cancer cells constantly adapt and change in response to therapeutic pressure. This resistance is caused by a variety of mechanisms, including increased drug efflux, activation of survival pathways, improved DNA repair, and non-genetic adaptations like drug-tolerant persister states and cancer stem cell plasticity. These interrelated mechanisms enable tumors to endure harsh therapy. Because of this, traditional single-drug strategies frequently fall short of offering long-term control. Current tactics are changing to become more integrated and flexible in order to address this. Precision medicine based on tumor profiling, combination therapies that target multiple pathways, and strategies that alter the tumor microenvironment are all becoming more and more significant. Furthermore, more recent ideas like adaptive dosing, epigenetic targeting, and removing transient resistant cell states present viable strategies to delay or stop the emergence of resistance. The tumor's distinct resistance profile and the patient's tolerance to treatment, however, continue to have a significant impact on treatment outcomes. In the end, overcoming chemoresistance is still a difficult task. In order to improve outcomes and achieve more long-lasting responses in cancer care, a deeper understanding of how tumors adapt will be essential, as will improved predictive tools and more adaptable treatment approaches.

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