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The Evolving Landscape of Drug Resistance: From Mechanisms to Therapeutic Strategies

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ABSTRACT

Drug resistance is a major obstacle in the effective treatment of cancer, severely impacting patient outcomes and complicating therapeutic strategies. The development of resistance is multifactorial, involving a combination of genetic and epigenetic changes within cancer cells, alterations in drug metabolism, increased DNA repair mechanisms, overexpression of drug efflux pumps, and complex interactions with the tumor microenvironment. These factors work synergistically to render traditional chemotherapy and targeted therapies less effective over time.

Recent advances in molecular biology, particularly next-generation sequencing and the CRISPR-Cas9 gene-editing tool have significantly enhanced our understanding of the underlying mechanisms driving resistance. These technologies have enabled researchers to identify novel genetic mutations and signaling pathways that cancer cells exploit to evade treatment, offering new potential targets for therapeutic intervention. Additionally, the dynamic role of the tumor microenvironment, including immune cells, stromal cells, and extracellular matrix components, has emerged as a key factor influencing drug resistance, further complicating treatment strategies.

To address these challenges, several innovative therapeutic approaches are being explored. Combination therapies, which involve the use of multiple drugs targeting different pathways simultaneously, hold promise in overcoming resistance by attacking cancer cells from multiple fronts. Immunotherapy, which harnesses the body's immune system to target cancer cells, is also showing significant potential in resistant cancers. Furthermore, nanomedicine, which uses nanoparticles to deliver drugs directly to tumors, may improve drug efficacy and minimize resistance.

Despite these advancements, much remains to be done. Ongoing research focused on identifying reliable biomarkers, developing personalized medicine approaches, and understanding the intricate relationship between cancer cells and their microenvironment is essential. This review aims to provide a comprehensive overview of the current state of knowledge regarding drug resistance in cancer, emerging therapeutic strategies, and future research directions in this critical field.

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INTRODUCTION

Cancer is a complicated condition defined by the uncontrolled proliferation and dissemination of aberrant cells. It is caused by damage to DNA, the genetic material that regulates cell activity and development (1, 2). Mutations in DNA may arise in a variety of genes, such as oncogenes (which drive cell development) and tumor suppressor genes. Mutations

in these genes allow cells to develop unrestrained, creating tumors that may invade neighboring tissues and spread to distant regions (3). Cancer has several origins, including genetic, environmental, and lifestyle factors. Genetic alterations may be passed down from parents, raising a person's vulnerability to certain malignancies. Environmental factors including tobacco smoke, asbestos, and UV radiation may affect DNA and contribute to the occurrence of cancer (4). Diet, physical exercise, and alcohol intake all contribute significantly to cancer risk.

Cancer therapy has improved tremendously, providing a variety of alternatives based on the kind and stage of the disease (5). Common methods involve surgery to eliminate malignant tissue, radiation treatment to kill cancerous cells with high-energy beams, chemotherapy to utilize medications that target fast-proliferating cells, and tailored therapies to tackle particular weaknesses in cancer cells (6). Immunotherapy, which uses the body's immune system to combat cancer, is an increasingly essential therapeutic option. However, cancer therapy presents several obstacles (7). Many therapies, although effective against cancer cells, may harm healthy tissues, resulting in symptoms such as tiredness, nausea, and hair loss. Drug resistance is another key barrier since cancer cells might develop methods to avoid the effects of therapies (8).

Drug resistance is a serious impediment to effective cancer therapy, often causing disease recurrence and worse patient outcomes. Cancer cells, owing to their intrinsic genetic instability and fast multiplication, might develop methods to resist the damaging impacts of anticancer treatments (9). This resistance can manifest in a variety of ways, including decreased drug absorption by the cell, increased drug efflux (pushing the drug out of the cell), modifications in the targeted pathway (so the drug no longer connects successfully), stimulation of substitute signaling networks that bypass the drug's intended operation, and improved DNA repair processes that counteract the DNA damage caused by some chemotherapies (10). Drug resistance develops via a complicated process that is influenced by selection pressure. When malignant cells undergo exposure to a treatment, those cells that develop resistance responses have a survival advantage and are more likely to multiply, ultimately becoming the majority group within the tumor (11).

Several pathways are associated with the emergence of drug resistance. Genetic changes may occur spontaneously or be caused by the medicine, resulting in changed proteins that impact drug action or metabolism (12). Epigenetic alterations, which modify gene expression without altering the DNA sequence, may also have an impact. Modifications in DNA methylation or histone changes, for instance, might influence gene expression related to drug metabolism or cell viability. In addition, the tumor environment may lead to medication resistance (13). Hypoxia (low oxygen concentrations), nutritional restriction, and the existence of specific immune cells may all contribute to a selection pressure that promotes the persistence of drug-resistant cells (14). Addressing the intricate interaction of these processes is critical for creating methods to avoid or overcome drug resistance and enhance cancer treatment results. This study investigates the complicated processes behind medication resistance in cancer, a key hindrance to effective therapy, as well as the problems it presents. Furthermore, it looks into new alternative treatment tactics for overcoming resistance and increasing patient results (15).

Mechanisms involved in drug resistance

Efflux pumps

Efflux pumps, especially those from the ATP-binding cassette (ABC) transporter superfamily, are critical in the emergence of multidrug resistance (MDR) in cancer cells (16). These pumps are transmembrane proteins that actively transport a diverse range of materials, notably various chemotherapeutic medicines, out of the cell. Efflux pumps reduce the intracellular concentration of these medicines, limiting their capacity to communicate with their cell targets and producing cytotoxic consequences (17).

This lower dosage enables tumor cells to survive and grow in the presence of chemotherapeutic resulting in chemotherapy failure. Numerous ABC transporters, including P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated protein 1 (MRP1/ABCC1), and breast cancer resistance protein (BCRP/ABCG2), have been extensively researched and linked to MDR in diverse kinds of cancer (18). The increased expression of these efflux pumps is common in drug-resistant malignancies, and it is directly related to decreased drug efficacy and a poorer prognosis for patients. Additional resistance mechanisms, including changed drug targets or increased DNA repair, may work along with efflux pump activity to increase drug resistance (19). Recognizing the individual efflux pumps implicated in a given cancer type, as well as the variables that influence their expression and activity, is critical for devising ways to avoid MDR and increase cancer treatment efficacy (20).

Epigenetic modifications

Epigenetic changes, heritable variations in gene expression that do not entail modifications to the DNA sequence itself, play a crucial role in the establishment and maintenance of treatment resistance in cancerous cells (21). These alterations, which include DNA methylation, histone modifications, and changes in microRNA expression, may impact the expression

of genes that regulate drug metabolism, therapeutic targets, cell survival, and DNA repair, resulting in diminished medication effectiveness (22). For instance, hypermethylation of a tumor suppressor gene's promoter region might quiet its expression, eliminating a major barrier to cell proliferation and possibly granting resistance to treatments that target quickly expanding cells (23). On the other hand, hypomethylation of oncogenes may result in their overexpression, which promotes cell proliferation and treatment resistance. These epigenetic changes may be reversible, presenting prospective therapeutic options to restore medication sensitivity (24).

One extensively investigated instance of epigenetic regulation in drug resistance is the gene that encodes P-glycoprotein (P-gp), a notable efflux pump that leads to multidrug resistance. Elevated P-gp expression may efficiently pump chemotherapy medicines out of tumor cells, lowering their intracellular concentration and efficacy (25). Epigenetic changes, like DNA hypomethylation in the P-gp promoter region, may boost P-gp expression and develop drug resistance (26). Likewise, histone changes, such as enhanced histone acetylation, may promote P-gp gene transcription. Knowing the particular epigenetic alterations that control drug resistance mechanisms such as P-gp expression is critical for creating innovative treatment techniques to reverse these changes and restore drug sensitivity in malignant cells (27). These tactics may include the application of epigenetic medicines, like DNA methyltransferase inhibitors or histone deacetylase inhibitors, to remodel cancer cells' epigenomes and make them more receptive to chemotherapy (28).

Tumor microenvironment

The tumor microenvironment (TME), a complicated and ever-changing ecology around cancer cells, serves a vital role in cancer growth, metastasis, and, crucially, the emergence of treatment resistance (29). It encompasses some cellular and non-cellular elements, involving fibroblasts, immunological cells, endothelial cells (lining blood vessels), and extracellular matrix (ECM) constituents (30). This sophisticated network of connections has the potential to greatly alter cancer cell activity by supplying growth factors, viability signals, and protection from treatments (31). The TME may exert selective pressure on drug-resistant tumor cells, failing to treat. For example, the TME may be hypoxic, nutrient-deprived, or acidic, all of which might generate or choose tumor cells with improved drug resistance pathways (32). Likewise, physical characteristics of the TME, like thick ECM or aberrant blood vessel development, might impede medication delivery to the tumor site, hence lowering the drug's therapeutic effectiveness (33).

Different cell types in the TME are associated with drug resistance. Cancer-associated fibroblasts (CAFs), which frequently appear in the TME, may release growth hormones and ECM components that help tumor cells survive and fight drugs (34). They may also alter the ECM, forming a physical barrier that prevents drug entry. Immune cells, which are perfectly designed to kill cancerous cells, might paradoxically lead to treatment resistance (35). Tumor-associated macrophages (TAMs), for example, may adopt a pro-tumor character by secreting substances that promote tumor cell proliferation, angiogenesis (new blood vessel creation), and treatment resistance (36). Myeloid-derived suppressor cells (MDSCs) are another kind of immune cell that may inhibit anti-tumor response and cause treatment resistance via a variety of methods (37). Endothelial cells, which line blood arteries, can also lead to medication resistance by restricting drug delivery to tumors or supporting the survival of tumor cells that have spread to distant areas (38). The relationship between cancerous cells and the many cell types within the TME is complicated and bidirectional. Cancer cells may affect the activity of stromal cells, which can then offer assistance and defense to cancer cells, therefore developing treatment resistance (39). Knowing the intricate interactions that occur inside the TME is critical for creating innovative treatment techniques that target not just cancer cells but also supporting cells and the surrounding environment in general (40). Interfering with the TME's protective function, for example, by attacking CAFs, TAMs, or the ECM, may increase drug delivery and restore drug sensitivity in tumor cells, resulting in improved cancer therapy (41).

DNA repair pathways

DNA repair processes are key biological systems that preserve the integrity of the genome by identifying and fixing different forms of DNA damage, such as single-strand breaks, double-strand breaks, base alterations, and DNA crosslinks (42). These pathways rely on an intricate structure of proteins to identify DNA damage, activate repair processes, and restore the original DNA sequence. There are many unique DNA repair mechanisms, each specialized for fixing certain kinds of DNA damage (43). For example, nucleotide excision repair (44) eliminates large DNA adducts caused by UV radiation or chemical carcinogens, whereas base excision repair (BER) addresses destroyed or altered bases (45). The homologous recombination (HR) and non-homologous end joining (NHEJ) processes are crucial for mending double-strand breaks, which are especially harmful since they may lead to chromosomal instability and cell death. The capability and accuracy of DNA repair are critical for proper cell function and survival, and

abnormalities in these pathways may lead to higher mutation frequencies and cancer formation (46).

Cancer cells, although frequently described by genomic instability, may also demonstrate improved DNA repair capability as a strategy of resistance to DNA-damaging treatments, such like chemotherapy and radiation (47). These medicines produce DNA damage in cancer cells, prompting cell death by apoptosis. Yet, tumor cells with increased DNA repair function can effectively repair this damage, enabling them to survive and multiply despite therapy (48). This improved repair capability may occur via a variety of methods, such as increased production of DNA repair proteins, overexpression of certain repair pathways, or changes in the signaling pathways that control DNA repair (49). Elevated expression of ERCC1, a DNA repair protein, has been linked to resistance to platinum-based chemotherapies that cause DNA cross-links. Comparably overexpression of the HR pathway may provide resistance to ionizing radiation, which causes double-strand breaks (50).

The connection between DNA repair processes and drug resistance is complicated and multifaceted. Although improved DNA repair can protect tumor cells from the toxic properties of DNA-damaging therapies, it can also make them more susceptible to other kinds of therapies (51). For example, tumors cells with errors in specific DNA repair pathways, like BRCA1/2 in the HR pathway, can be more susceptible to PARP inhibitors, which block single-strand break repair (52). This synthetic lethality technique takes advantage of a defect in one DNA repair mechanism to make cancer cells more susceptible to blockage of another process (53). In addition, the tumor microenvironment might affect DNA repair ability. Hypoxia, for instance, may cause DNA damage and alter the expression of DNA repair proteins. Addressing the complex interaction of DNA repair, drug resistance, and the tumor environment is critical for designing customized cancer treatments that target particular tumor susceptibility (54).

Drug Resistance: A Challenge in Cancer Therapy

Drug resistance dramatically influences cancer therapy across many malignancies, reducing therapeutic effectiveness and influencing patient results. Resistance may turn a curable malignancy into a potentially fatal illness, restricting therapy choices and often resulting in disease progression and recurrence (55). This problem emerges variably among cancer types, mirroring the varied causes of resistance and therapies used. Drug resistance is a significant issue in hematological malignancies like acute myeloid leukemia (56, 57). AML cells may exhibit resistance to chemotherapy via a variety of processes, such as raised drug efflux via ABC transporters, mutations in drug targets like the FLT3 receptor tyrosine kinase, and changes in apoptotic routes (58). These mechanisms of resistance frequently result in relapse, necessitating more intensive and possibly less efficient salvaging therapies. Similarly, mutations in the BCR-ABL1 fusion gene, which drives chronic myeloid leukemia (CML), may cause resistance to tyrosine kinase inhibitors (TKIs) such as imatinib. These mutations could hinder the TKI from binding efficiently, enabling leukemic cells to grow uncontrolled (59).

Solid cancers also confront considerable issues with treatment resistance. In lung cancer, resistance to EGFR inhibitors, including gefitinib and erlotinib, usually develops owing to secondary mutations in the EGFR gene, most notably the T790M mutation (60). This mutation modifies the EGFR protein, rendering it insensitive to the inhibitor. Likewise, in breast cancer, resistance to HER2-targeted treatments such as trastuzumab may develop via a variety of processes, such as a higher level of alternative growth factor receptors, activation of downstream signaling pathways that bypass HER2, and loss of PTEN, a tumor suppression gene (61). Melanoma resistance to BRAF inhibitors, such as vemurafenib and dabrafenib, targeting the BRAF V600E mutation, may appear via reactivation of the MAPK system, either through mutations in other elements of the pathway or through activation of bypass signaling loops (62). Colorectal cancer is another instance of how drug resistance has an important effect on controlling patients. Resistance to treatment strategies like FOLFOX or FOLFIRI may develop via a variety of pathways, involving increased production of DNA repair enzymes, modifications to drug metabolism, and alterations in the tumor microenvironment (63). Resistance to targeted therapy, such as EGFR inhibitors (Cetuximab, Panitumumab) or VEGF inhibitors (bevacizumab), may also emerge via changes in downstream signaling pathways, like KRAS or NRAS, or by activation of alternative angiogenic variables (64). Platinum resistance in ovarian cancer is a significant clinical issue. Mechanisms involve enhanced DNA repair, altered drug delivery, and changes in glutathione levels. This resistance generally leads to disease recurrence and a worse prognosis (65). The emergence of medication resistance has a significant influence on patient outcomes. It often entails the application of more harmful and ineffective medicines, which leads to higher side effects and a worse quality of life. Furthermore, medication resistance might restrict treatment choices, making illness management challenging and eventually leading to lower survival rates (66). Addressing medication resistance requires continued study into the underlying processes, the development of innovative therapeutic tactics, and the deployment of personalized treatment methods that customize therapy to the unique features of every patient's tumor (67).

Molecular insights into drug resistance: advancing cancer therapy

Recent advancements in molecular biology have transformed our knowledge of drug resistance pathways in cancer, presenting tremendous prospects for creating more efficient treatments (68). Technologies like next-generation sequencing provide thorough genomic profiling of tumors, exposing a complicated landscape of genetic abnormalities, epigenetic alterations, and gene expression variations that lead to medication resistance (69). Single-cell sequencing tools contribute to this knowledge by showing the heterogeneity of treatment resistance inside a tumor, detecting discrete groups of resistant cells, and determining their unique genetic properties (70). These developments allow scientists to dissect the complex networks of signaling and molecular connections that cause drug resistance, paving the way for the discovery of novel targets for therapy and markers (71).

Moreover, CRISPR-Cas9 gene editing technology has become known as an effective tool for investigating drug resistance pathways. Scientists may use CRISPR to carefully introduce particular mutations into cancer cells or knock out genes of interest, allowing them to directly examine the effect of these genetic alterations on treatment sensitivity (72). The combination of CRISPR with additional developed molecular methods, like proteomics and metabolomics, offers systems-level knowledge of drug resistance, showing how tumor cells change and adapt under selective pressure (73). This method may be utilized to model drug resistance in vitro, detect new resistance genes, and confirm potential targets for therapy (74).

Emerging therapies to combat drug resistance

The fight against drug resistance in cancer drives therapeutic development. Many interesting treatments are developing; including the invention of next-generation inhibitors that target resistant mutations, such as the application of third-generation EGFR inhibitors (e.g., osimertinib) for lung cancer patients with the T790M resistance mutation (44). Combination treatments are also gaining popularity, attempting to simultaneously address various resistance pathways or to avoid the establishment of resistance. For instance, the combination of a BRAF inhibitor with a MEK inhibitor in melanoma targets two important components of the MAPK pathway, lowering the risk of resistance development (75). Immunotherapy, which utilizes the body's immune system to attack cancer, provides another path for overcoming resistance, especially in tumors with high mutational loads (76). Strategies to modify the tumor microenvironment, including targeting cancer-associated fibroblasts or reprogramming immune system cells, are also being researched to disturb the defensive niche that supports treatment resistance (77). Lastly, personalized medicine techniques, informed by genetic profiling of individual malignancies, are becoming more crucial for identifying the most successful medicines and predicting future resistance mechanisms. Some of these cases are mentioned in the next section (78).

Effective therapeutic combinations for overcoming drug resistance in cancer

The emergence of drug resistance remains an important hurdle in cancer treatment, frequently causing the progression of the disease and treatment disappointment. A promising approach for tackling this obstacle is the application of combination treatments, which involve using two or more drugs concurrently to target various routes or mechanisms inside tumor cells (79). Combination treatment works by targeting cancer cells from numerous sides, making it harder for them to build resistance to all of the medications at once. Ideally, medications in combination ought to have synergistic impacts, which means that their combined impact exceeds the sum of their impacts (80). This synergy may occur via a variety of reasons, including as one treatment sensitizing cancer cells to the other, or medicines targeting complementary pathways required for tumor cell survival. Combination treatment may also assist combat pre-existing resistance processes or inhibit the formation of new resistance mutations (81).

The development of successful combination treatments necessitates an in-depth knowledge of the molecular processes that drive cancer progression and drug resistance. Rational medication combinations frequently depend on the unique genetic changes and signaling networks that are dysregulated in a certain tumor type (82). For example, in tumors with mutations in the RAS-RAF-MEK-ERK pathway, combining a BRAF inhibitor with a MEK inhibitor has been quite successful. BRAF mutations, such as the V600E mutant, persistently stimulate the MAPK system, resulting in excessive proliferation of cells (83). Although BRAF inhibitors might be beneficial initially, resistance frequently arises due to reactivation of the MAPK pathway, which can occur via mutations in MEK or other downstream elements. Combining an MEK inhibitor that targets another stage in the pathway could avoid reactivation while delaying or overcoming resistance (84). Similarly, in tumors with abnormalities in DNA repair routes, combining a PARP inhibitor with a DNA-damaging drug may take advantage of the "synthetic lethality" concept, which states that inhibiting two critical DNA repair pathways results in cancer cell death (85).

Besides directly targeting cancerous cells, combination treatments are being investigated to modify the tumor environment and improve drug delivery. The tumor microenvironment promotes

cancer cell proliferation, survival, and medication resistance. It encompasses many cell types, such as cancer-associated fibroblasts, immunological cells, and endothelial cells, as well as extracellular matrix elements (86). These elements can form an inhibitory microenvironment for tumor cells, shielding them from medications and increasing drug resistance. Combining chemotherapy with medications that target the tumor microenvironment, like angiogenesis inhibitors or fibroblast depleters, may increase drug penetration and therapeutic success (87). In addition, combination therapy may be used to boost anti-tumor immunity and overcome the immunosuppressive environment prevalent in malignancies. Scientists want to harness the immune system's potential to eliminate cancer cells, particularly those resistant to drugs, through the use of immune checkpoint inhibitors with other immunomodulatory medicines or chemotherapy (88).

Checkpoint Inhibitors: Unleashing the Immune System to Overcome Drug Resistance

Immune checkpoint inhibitors are an innovative method of cancer treatment, with the potential to combat medication resistance by reactivating the body's immune system to target and eliminate tumor cells (89). These inhibitors target particular checkpoint proteins including CTLA-4, PD-1, and PD-L1, which usually control immune cell activation and hinder autoimmunity. Cancerous cells often use these checkpoints to elude immune monitoring, essentially placing a brake on immune cell assault. Checkpoint inhibitors function by inhibiting these inhibitory signals, enabling immune cells, notably cytotoxic T lymphocytes (CTLs), to detect and destroy cancer cells (90). This method of action varies greatly from standard chemotherapy or targeted medicines, which often directly target tumor cells and are vulnerable to drug resistance pathways. Since checkpoint inhibitors activate the patient's immune system, the anti-tumor response may persist even after therapy is stopped, possibly resulting in permanent remissions (91).

Checkpoint inhibitors have been effective in a variety of different cancer types, such as melanoma, lung cancer, bladder cancer, and renal cell carcinoma. For instance, ipilimumab, a CTLA-4 inhibitor, has demonstrated considerable activity in melanoma, resulting in increased overall survival for certain patients (92). Likewise, PD-1 inhibitors like nivolumab and pembrolizumab have transformed the management of non-small cell lung cancer, especially in cancers with high PD-L1 expression or a high mutational load (92). These inhibitors have also shown potential in other malignancies, such as Hodgkin lymphoma and MSI-H colorectal cancer. Checkpoint inhibitor effectiveness is often related to the presence of tumor-infiltrating lymphocytes (TILs), suggesting that these medicines need a pre-existing immune response to be effective. Nevertheless, even in tumors with modest TIL levels, checkpoint inhibition may occasionally trigger an immune response, resulting in tumor regression (93).

Furthermore, checkpoint inhibitors may be utilized to combat or avoid medication resistance against additional cancer treatments. For example, in melanoma, combining a BRAF inhibitor with a PD-1 inhibitor demonstrated improved effectiveness in comparison to BRAF inhibitor monotherapy, delaying the formation of resistance to BRAF treatment (94). This shows that inhibiting checkpoints may limit the emergence of resistant clones as a result of targeted therapy's selectivity. In addition, in certain malignancies, checkpoint inhibition has been demonstrated to restore chemotherapy sensitivity in tumors that have become resistant. The methods by which checkpoint inhibitors overcome drug resistance are complicated and poorly understood, but they are most likely a mix of direct immune-mediated death of resistant cells and tumor environment manipulation (95).

Although checkpoint inhibitors have demonstrated exceptional efficacy, they are not without limits. Some individuals react to these treatments, and some may have immune-related side effects (96). The current study aims to uncover biomarkers that forecast responsiveness to checkpoint inhibition, develop techniques to combat resistance to these medicines, and investigate innovative immunotherapeutic approaches like conjunction immunotherapies and adoptive cell therapies. The combination of checkpoint inhibitors with other immunomodulatory drugs, including agonists of stimulatory immunological receptors or inhibitors of immunosuppressive molecules shows potential for improving immunity against tumors and overcoming resistance (97). Continued research and improvement of immunotherapeutic techniques are vital to enhancing results for cancer patients and tackling the ongoing problem of medication resistance.

Nanomedicine: a novel approach to overcoming drug resistance

Nanomedicine offers innovative strategies to combat drug resistance in cancer by improving drug delivery, enhancing drug efficacy, and modulating the tumor microenvironment (98). Nanocarriers, such as liposomes, polymeric nanoparticles, and dendrimers, can encapsulate chemotherapeutic drugs, protecting them from premature degradation and non-specific distribution in the body (56). This targeted delivery minimizes off-target toxicity and allows for higher drug concentrations to reach the tumor site, including drug-resistant cancer cells. Furthermore, nanocarriers can be engineered to actively target cancer cells by attaching ligands, such as antibodies or peptides, that bind specifically to receptors overexpressed on cancer

cell surfaces (99). This active targeting enhances drug uptake by cancer cells, improving the therapeutic index and reducing the exposure of healthy tissues to cytotoxic drugs. Nanomaterials can also be designed to be responsive to specific stimuli within the tumor microenvironment, such as changes in pH, redox potential, or enzyme activity. These stimuli-responsive nanocarriers can release their drug payload specifically at the tumor site, maximizing drug efficacy and minimizing systemic toxicity (100).

Beyond improving drug delivery, nanomedicine can also be used to overcome specific drug resistance mechanisms. For example, multidrug resistance (MDR) often involves the overexpression of efflux pumps, like P-glycoprotein, which actively pumps drugs out of cancer cells (101). Nanocarriers can protect drugs from these efflux pumps, allowing them to bypass this resistance mechanism and reach their intracellular targets. Furthermore, nanocarriers can be designed to deliver multiple drugs simultaneously, including drugs that target different resistance pathways (101). This combination therapy approach can be highly effective in preventing or overcoming drug resistance, as it becomes more difficult for cancer cells to develop resistance to multiple drugs at once. Nanomaterials can also be used to deliver gene therapy agents, such as siRNAs or miRNAs, that can silence genes involved in drug resistance, restoring drug sensitivity in cancer cells (102). For instance, nanoparticle-mediated delivery of siRNA targeting P-glycoprotein has been shown to reverse MDR in various cancer cell lines. The versatility of nanomedicine makes it a promising platform for developing personalized cancer therapies that can be tailored to the specific drug resistance mechanisms present in individual tumors (103).

DISCUSSION AND CONCLUSION

Drug resistance remains a challenging barrier in cancer therapy, with substantial implications for therapeutic effectiveness and patient outcomes. As previously stated, the processes producing drug resistance are diverse and multidimensional, including genetic changes, epigenetic alterations, altered drug metabolism, increased DNA repair, efflux pump function, and interactions with the tumor environment (104). This complexity needs a multifaceted strategy for combating drug resistance, which includes the discovery of new medicines, the optimization of current treatment regimens, and a better understanding of the complicated interaction between cancer cells and their environment (105). Advances in molecular biology, including next-generation sequencing and CRISPR-Cas9 gene editing, have offered crucial tools for unraveling the genetic basis of drug resistance, opening the door for the discovery of novel therapeutic targets and biomarkers (105, 106). These findings have fuelled the development of novel treatment techniques, including next-generation inhibitors, combination therapies, immunotherapies, and nanomedicine approaches, all targeted at combating or avoiding drug resistance (107).

Combination therapy rationally developed based on the unique molecular changes that drive cancer development and resistance, has shown great promise. These combinations may avoid or overcome resistance by addressing numerous routes or processes at the same time (108). Immunotherapy, especially immune checkpoint inhibitors, has transformed cancer treatment by utilizing the immune system's capacity to target and eliminate cancer cells, including those that have gained medication resistance. Nanotechnology provides another novel strategy by improving medication delivery, increasing treatment effectiveness, and altering the tumor environment (109). Nanocarriers may prevent medications from degradation, deliver them directly to cancer cells, and even circumvent efflux pump function, providing fresh hope for overcoming multidrug resistance. The combination of these novel techniques, led by personalized medicine tactics based on genetic profiling of individual tumors, has enormous potential to improve cancer treatment results (110).

Despite tremendous development in the past few years, certain limits persist. It is difficult to predict which patients will acquire medication resistance and to determine the exact resistance systems involved (111). While certain biomarkers have been found, additional study is required to provide more accurate and complete predicting systems. Furthermore, the development of new drugs and therapies is often a lengthy and expensive process (112). Clinical trials are essential for evaluating the safety and efficacy of new treatments, but they can be time-consuming and may not always be successful. Finally, access to these advanced therapies can be limited by cost and availability, creating disparities in cancer care (113).

Looking to the future, several promising avenues of research are being explored. Liquid biopsies, which detect circulating tumor DNA or RNA in blood samples, offer a non-invasive way to monitor treatment response and detect the emergence of drug resistance (114). Artificial intelligence and machine learning are being applied to analyze vast amounts of data from cancer genomics, proteomics, and clinical trials to identify new drug targets and predict treatment outcomes (115). The development of more sophisticated Nanocarriers, capable of delivering multiple drugs or gene therapy agents simultaneously, holds great promise for overcoming complex drug resistance mechanisms (116). Continued research into the tumor microenvironment and its role in drug resistance will pave the way for new therapeutic strategies that target

not only cancer cells but also the supporting cells and the microenvironment itself. By addressing the current limitations and pursuing these future directions, we can move closer to a future where drug resistance is no longer a major obstacle to successful cancer treatment.

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Yousef Roosa and Neda Abedi were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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