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Short Communication

How Cancer Outsmarts Treatments: Assessing Drug Resistance in Tumors

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Abstract

Drug-resistance remains one of the main challenges for cancer chemotherapy. The failure of treatments due to drug-resistant tumors accounts for much of the relapse and cancer mortality seen today. What makes it challenging to address this issue is that tumor resistance to anticancer drugs has multiple and complex mechanisms, shaped by the intrinsic tumor cell and environmental context in which it has developed. At the primary tumor site, a heterogeneous population of cells may contain tumor cells that are inherently chemoresistant even before treatment (intrinsic resistance). Other tumor cells are initially responsive, but acquire mutations that allow rapid resistance to therapeutic agents (secondary resistance). The following review will conceptually classify the mechanisms of secondary drug resistance into 1) cellular mechanisms in tumor cells promoting drug-resistance and 2) extracellular mechanisms prohibiting drugs from gaining access to tumor cells. We will also discuss strategies to address these drug resistance mechanisms.

Cellular mechanisms of drug resistance

High efflux rate prevents drug from staying in tumors: A major drug resistance mechanism involves amplification of pumps that actively export drugs out of tumor cells (Figure 1). Many efflux pumps with wide-ranging specificity belong to the ATP-binding cassette (ABC) transporter family. The most common examples of ABC transporters associated with multidrug resistance include P-glycoprotein (MDR, PgP or ABCB1), multidrug resistance protein 1 (MRP1 or ABCC1) and ABCG2 [1]. Pumps typically bind and transport endogenous molecules. However, under drug selection, those transport pumps can become more efficient in pumping out anticancer drugs. Ultimately, the increased drug efflux confers resistance by lowering the concentration of anticancer agents inside the tumor cell, thus lowering the toxic responses of the drug [2].

Target mutations alter drug-binding in tumors: Mutations that modify target-drug interactions contribute to drug resistance and are the common cause for relapse in patients (Figure 1). Types of mutations include point mutations, deletions of extracellular domains, and alternative splicing of receptors [3]. A receptor that is commonly mutated is the tyrosine kinase receptor responsible for deregulated proliferation of cancer cells. While inhibitors have been created to target the ATP pocket of the kinase domains, the extracellular domain of the receptor, the ligands, and even the intermediates of downstream signaling pathways (Ras, Raf, PTEN), deletions on various targets may prevent various inhibitors from binding to their target sites, thereby conferring drug resistance. A well-known example of drug-resistance in chronic myeloid leukemia patients involves imatinib. Imatinib is a Bcr-Abl tyrosine-kinase inhibitor that works by binding constitutively active Bcr-Abl, thereby impeding abnormal proliferation of white blood cells. A mutation in the BCR-Abl enzyme, however, causes resistance to imatinib [4].

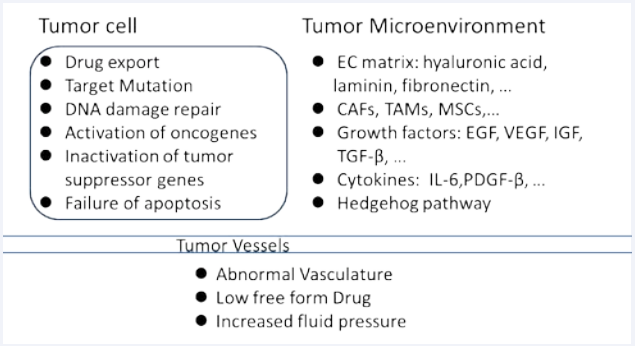

Figure 1 Multiple mechanisms of drug resistance in cancer therapy.

Adding to the complexity, the mutation can be located either directly at the binding site of the imatinib drug and Bcr-Abl or scattered throughout the extracellular domain of the tyrosine kinase receptor altering the enzyme's conformation state, thereby preventing drug binding [5]. Overcoming drug resistance will require a deeper understanding of the factors that control the conformational changes in proteins [6].

Alterations in DNA Damage Responses confer drug resistance: Cancer cells may acquire drug resistance resulting from numerous genetic and epigenetic changes that promote cell survival or resistance to cell death (Figure 1). Chemotherapy serves as an effective anti-cancer agent by causing DNA damage and interrupting the cell cycle of cancer cells. As a result, the cancer cells may activate DNA damage responses (DDR), which are a complex network of kinases, phosphatases, and ubiquitin ligases that contribute to permanent arrest of cancer cells in the short term or cell death in the long term. Cancer cells treated with DNA-damaging agents, however, can acquire sequential mutations in their DDR that accumulate over time [7]. Abnormal pathways, not individual genes, are the key to understanding cancer drug resistance. Cancers resist therapy because they may have 1) altered cell cycle checkpoints leading to increased proliferation or 2) inhibition of apoptosis pathways.

Altered cell cycle checkpoint genes leading to increased proliferation: Oncogenes and tumor suppressor genes play an important role in cell cycle regulation. Oncogenes normally stimulate growth but can become over activated making cancer cells drug resistant by causing cells to survive and proliferate when they ought to die. Examples of nuclear oncogenes include src, myc, ras, wnt, beta-catenin, erk, trk, Bcr-Abl, and notch. A well-described example of mutations in oncogenes is the alteration of the Ras/Raf/MAPK pathway. Overactivated tyrosine kinase receptors activate Ras GTP protein that activates mitogen activated protein kinase (MAPK) cascade starting with the Raf enzyme. Activating mutations in a gene encoding Ras, Raf, or downstream transcription factors can lead to pro-survival signals contributing to drug resistance [8]. In addition, tumor suppressor genes normally inhibit growth but can become inactivated making cancer cells drug resistant. Notable tumor suppressor genes include BRCA1/2, CHK2, ATM, P53, PTEN, RB1, WT1, VHL, and APC. To elaborate on a well-known tumor suppressor gene, retinoblastoma (Rb) is a protein that typically regulates cell cycle progression by sequestering the EF2 transcription factor that expresses cyclin E and A. When this gene is disrupted by an inactivating mutation, however, the cancer cell can enter the cell cycle and become more sensitive to different chemotherapeutic molecules [9,10]. PTEN is another tumor suppressor gene that is often disrupted by an inactivating mutation. A mutation in the PTEN gene can result in unregulated activation of the PI3K/AKT/mtor pathway, thus conferring acquired drug resistance through potent cancer cell survival signaling [11,12]. Thus, altered cell cycle checkpoints may impact the drug resistance related to DNA damage.

Inhibition of apoptosis pathways: Cancer cells can also overcome the lethal effects of chemotherapy by affecting the apoptosis pathway through various mechanisms, including genetic changes. An insufficient amount of apoptosis, however, results in uncontrolled cell proliferation in cancers. A well-known example of mutations that affect apoptosis in tumors is the alteration of the PI3K/AKT/mTOR pathway [13]. Growth factor receptors can activate Phosphatidylinositol-3-kinases (Pi3K) that lead to downstream AKT and mTOR kinase activation, which are involved in regulating anti-apoptotic proteins, BcL2 and BcLXL. Activating mutations in PI3K, AKT, or mTOR, thus inhibit activation of the cytoplasmic caspase cascade and inactivate transcription factors that transcribe genes involved in apoptosis [14]. Another example is the activating mutation in NF-kappa B transcription factor that enhances the expression of anti-apoptotic proteins, including BCL-XL and several IAPs [15]. Therefore, the acquisition of mutations that affect the apoptotic pathway serves as an important mechanism for drug resistance.

Extracellular mechanisms prohibiting drug effects

Inhibition of drug delivery : In order for a drug to be effective, the drug must reach the tumor site at adequate concentration to perform its therapeutic effect. Effective drug delivery fails for numerous reasons [16] (Figure 1). First, if a cancer patient has a uniquely high concentration of plasma proteins that bind drugs and hinder its systemic transport to the tumor, such situation may reduce the drug's final concentration in the tumor. Second, tumors may also develop barriers that make it difficult for drugs to reach the tumor. For instance, bulky tumors may compress surrounding blood vessels to diminish the drug supply to many tumor areas [17,18]. Third, tumors may attract abnormal vasculature with high resistance and viscosity that limits drug supply by slowing blood flow [19]. Endothelial cells also contribute to tumor chemoresistance by secreting vascular endothelial growth factor (VEGF) that promotes tumor cell resistance to apoptosis by up-regulating anti-apoptotic proteins, Mcl-1 and XIAP [20,21]. Fourth, the chemical characteristic of a drug may also determine its distribution since the drug's pKa may affect its conformation or cellular uptake at varying pH levels in the body. Fifth, enzymes in the extracellular matrix may contribute to drug inactivation or modification. Finally, the drug may accumulate at a reduced dose through less perfused tissues, such as dense tumors. For instance, enzymatic degradation of hyaluronan, an extracellular (EC) matrix protein in the desmoplastic stroma of pancreatic adenocarcinoma, resulted in increased chemotherapy efficacies in mouse models due to relief of vascular collapse [22]. These data have led to the development of PEGPH20, a pegylated recombinant human hyaluronidase- an enzyme that degrades hyaluronan, in combination with chemotherapy for pancreatic

cancer treatment. Thus, many factors outside of tumor cells may impact the drug delivery to tumor cells, contributing to drug resistance.

Drug resistant mechanisms in tumor microenvironment: Cancer cells live in a microenvironment that is comprised of various types of stromal cells, including endothelial cells, adipoctes, mesenchymal stem cells (MSCs), immune cells, and a bulk of carcinoma-associated fibroblasts (CAFs). The tumor microenvironment plays an important role in drug resistance from multiple aspects (Figure 1). First, within the cancer cell population, the cancer stem cell (CSC) subpopulation is defined by its ability to self-renew, differentiate, and initiate tumor development [23] and displays several drug-resistant phenotypes, including a high level of ABC transporters and potent anti-apoptotic proteins, which allow it to survive chemotherapy [24,25]. CSCs rely on their "niche," which controls their self-renewal and differentiation. Moreover, CSC features can be induced in more differentiated tumor cells by the microenvironment of their niche. The tumor microenvironment also protects CSCs against genotoxic insults from the chemotherapy treatment. Second, stromal cells participate in drug-resistance by instigating a reciprocal signaling dialogue between tumor cells and with each other [26,27]. For instance, sonic hedgehog (SHh) secreted by pancreatic cancer cells functions on the stromal compartment through a paracrine signaling network and promotes the proliferation of stromal fibroblasts [28]. It was demonstrated that treating a preclinical mouse model of pancreatic cancer with a SHh inhibitor resulted in a better delivery of gemcitabine through reduction of stroma and increase of vascular density [29]. Third, cancer cell-extracellular matrix interactions affect drug resistance by influencing the cancer cell sensitivity to apoptosis [30]. For instance, integrins on the cancer cell surface bind to extracellular matrix components like fibronectin or laminin resulting in enhanced resistance to drugs [31]. Fourth, CAFs contribute to apoptosis resistance by secreting prostaglandin E2 and sphingosine-1-phosphate, which activate the PI3K-Akt/PKB pathway in tumors. Tumor and stromal cells also locally release cytokines such as IL-6 and PDGF-b and growth factors such as IGF and TGFb that promote tumor growth and block apoptosis. Lastly, immune cells, including tumor-associated macrophages (TAM) and Foxp3+ regulatory T cells, present a highly immunosuppressive phenotype that protects tumors from cell death induced by chemotherapeutic drugs, and thus may also serve as promising targets for therapies [32].

PERSPECTIVES

Over the past 50 years, we have made major technological advances identifying multiple mechanisms critical for the drug-resistant phenotypes of cancers. For instance, high-throughput DNA sequencing technology has allowed systematic screening of the cancer genome, which have helped escort in a new wave of treatments for cancer targeting cancer-causing genes. In the near future, it is quite likely that most of the mechanisms driving drug-resistance in tumors will be characterized. With a better understanding of the drug resistant mechanisms, we will enter the era of personalized therapies that will allow us to design targeted drugs with less drug resistance compared to current chemotherapy. Furthermore, next generation sequencing platforms will revolutionize medicine by allowing us to measure personalized biomarkers for monitoring tumors. Identification of predictive biomarkers associated with cancer drug-resistance will assist in categorizing patients who are likely to benefit from one or another drug. The effectiveness of a single drug may be limited in some cases because tumor cells may acquire resistance to that drug. Thus, a combination of drugs targeting alternative pathways simultaneously will likely be the most promising approach to reverse this secondary resistance and compensatory rewiring. Another line of future investigation to bypass drug resistance is the employment of immunotherapy in the form of monoclonal antibodies or vaccine therapy that can augment immune responses against cancer. If we can address the problem of drug-resistance through extensive research, we may be able to save the lives of countless patients with recurrent drug-resistant cancers.

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