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RESEARCH PAPER

The challenge of drug resistance in cancer treatment: a current overview

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Abstract

It is generally accepted that recent advances in anticancer agents have contributed significantly to the improvement of both the disease-free survival and quality of life in cancer patients. However, in many instances, a favorable initial response to treatment changes afterwards, thereby leading to cancer relapse and recurrence. This phenomenon of acquired resistance to therapy, it is a major problem for totally efficient anticancer therapy. The failure to obtain an initial response reflects a form of intrinsic resistance. Specific cell membrane transporter proteins are implicated in intrinsic drug resistance by altering drug transport and pumping drugs out of the tumor cells. Moreover, the gradual acquisition of specific genetic and epigenetic abnormalities in cancer cells could contribute greatly to acquired drug resistance. A critical issue in the clinical setting, is that the problem of drug resistance appears to have a negative effect on also the new molecularly-targeted anticancer drugs. Several ongoing efforts are being made by the medical community aimed to the identification of such resistance mechanisms and the development of novel drugs that could overcome them. In this review, the major drug resistance mechanisms and strategies to overcome them are critically discussed, and also possible future directions are suggested.

Keywords Drug resistance · Acquired resistance · Chemotherapy resistance · Multidrug resistance · Tumor microenvironment · Cancer

Abbreviations

MDR	Multidrug resistance
ABC	Adenosine triphosphate-binding cassette
DHFR	Dihydrofolate reductase
NER	Nucleotide excision repair
MTD	Maximum tolerated dose

Introduction

Drug resistance can be defined as the decrease in the efficacy and potency of a drug to produce therapeutic merits and represents a major impediment to the disease treatment and overall patient survival. Of note, resistance to anticancer treatments can be manifested by local or loco-regional, as well as distant tumor metastases leading in the paradox of therapy-induced metastasis (TIM) [1–3]. In many cases, tumors such as renal cancer, hepatocellular carcinoma and malignant melanoma often exhibit intrinsic resistance to chemotherapy, without prior exposure to anticancer agents, so the initial response to treatment is poor [1]. In other settings, the initial optimism after good treatment response is often followed by poor results and a devastating outcome, as tumors initially sensitive to therapy, later become unresponsive due to development of acquired drug resistance. Currently, surgery and/or radiotherapy represent the optimal treatment modalities for the management of localized tumors. Systemic treatments are required for hematologic malignancies or metastatic tumors. Current forms of systemic treatment are chemotherapy, immunotherapy and anti-angiogenic agents [6].

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The interaction between the drug and the tumor microenvironment is a complex phenomenon. Cancers have the ability to develop remarkable resistance to various treatments which target different molecular pathways [6]. Recent evidence suggests that radio- or chemotherapy for breast cancer result in a stem cell-like phenotype in non-stem tumor cells. Therefore, as it has also been suggested by a recent extensive meta-analysis, there is an urgent need to identify basic factors that determine drug resistance in cancer stem cells [7]. Of particular note, several lines of evidence have demonstrated that chemotherapy can potentially increase the levels of circulating endothelial progenitor cells (EPCs) that promote tumor growth and metastasis [3, 8].

In the "new era of targeted chemotherapy", molecules and metabolic pathways implicated specifically in the growth and proliferation of cancer cells are blocked using molecularly-targeted drugs e.g., imatinib (Gleevec) which specifically targets BCR-ABL in chronic myeloid leukemia, aiming at achieving maximum treatment response and minimum toxicity compared to other types of cancer treatment. Of importance, the more targeted a drug is, the lower the probability to elicit drug resistance [9]. The largely quantitative difference between the conventional and the molecularly-targeted drugs, that provides some therapeutic margin, is that the targets of the former are mainly cellular (e.g., cell proliferation and DNA replication) or components (e.g., microtubules, topoisomerases) that are both in normal and cancer cells [10]. As a result, the molecularly-targeted drugs are less toxic than the conventional drugs, and they achieve effective treatment at remarkably lower doses than the maximum tolerated dose [11]. However, both types of drugs (i.e., conventional and molecularly-targeted) suffer from the problem of intrinsic and acquired drug resistance [12].

In the present review, the main factors that contribute to a compromized effectiveness of systemic anticancer drug regimens, as well as the potential mechanisms underlying drug resistance, are discussed.

Intrinsic and acquired drug resistance

Drug resistance may arise due to intrinsic and/or acquired factors. Intrinsic resistance can be attributed to: (a) drug breakdown, (b) altered expression and/or function of the drug target, (c) altered drug transport across the cellular membrane or (d) reduced interaction efficiency between the drug and its molecular target [4, 5]. Intrinsic cellular resistance can be mediated through ATP-dependent membrane transporters or nuclear receptors, e.g. sxr [14]. In addition, cellular metabolic processes, such as ceramide glycosylation decrease efficacy of chemotherapeutic agents [15] Also, cell cycle regulators and DNA damage repair factors enhance cross-drug resistance, by inhibiting drug accumulation, reducing influx, increasing efflux through cell membrane transporters, or inactivating drugs [9, 16]. Of interest, inactivation of tumor-associated genes including the tumor suppressor gene *TP53* has been shown to result in resistance to chemotherapeutic drugs [17].

On the other hand, acquired drug resistance is influenced by genetic or environmental factors that facilitate the development of drug-resistant cancer cell clones or induce mutations of enzymes involved in relevant metabolic pathways [1, 5].

Genetic determinants of acquired drug resistance

Genetic instability in the form of aneuploidy, deletions, point mutations, chromosomal translocations and gene amplifications is a key factor in several aspects of cancer pathogenesis [18], including intratumor heterogeneity, which fosters primary cancers, distant metastatic lesions and cancer relapse after therapeutic failure [19, 20].

Mathematical and computational models indicate a positive correlation between chemotherapeutic resistance and the number of spontaneous genetic mutations [21, 22], which can be utilized in adjusting the administered dose or determining the type of administered treatment [23, 24]. Other models used paradigm prokaryotic organisms, such as *Escherichia coli*, in an effort to detect mutations in drug-resistant cancer cells and investigate their role in drug resistance [25–31]. These studies demonstrated that drug resistance usually results in a pattern of random mutations rather than a drug-specific effect [32–35].

Overall, resistance to drugs is directly dependent on the stability of the genetic material of the tumor cells and the level of genomic instability, the mechanism(s) of action of a chemotherapeutic drug, the dose of the administered drug and the treatment intervals [21, 22, 24]. Alterations in the genetic material such as inactive mutations may occur either before or during treatment, in small subpopulations of cancer cells. It is also possible that cancers intrinsically sensitive to chemotherapy contain at least one drug-resistant cell clone, expansion of which leads to acquired resistance and possibly recurrence. Therefore, combinatorial drug therapy provides a powerful rationale for reducing the likelihood of the development of multiple resistant clones, especially for patients undergoing adjuvant anticancer therapy with micrometastases and low-tumor burdens [36, 37].

There is an increasing interest in studying cancer clonal cell subpopulations and the evolution of resistant variants [38–40]. These studies demonstrate an intratumor heterogeneity and changes in the distribution of clonal subpopulations following treatment administration [41]. Furthermore, gene amplification (i.e., increase in gene copy number) of specific drug resistance-relevant genes was found to be associated with enhanced resistance to many molecularly-targeted drugs [18, 42].

Epigenetic determinants of acquired drug resistance

Epigenetic factors, such as DNA methylation and chromatin-remodeling, contribute greatly to drug tolerance [43–45]. Zeller at al. [46] identified a series of genes that exhibited promoter hypermethylation in the cisplatin resistant ovarian cancer cells compared to their drug sensitive counterparts. Given that hypermethylation of gene promoters can be associated with transcriptional gene silencing [47], demethylation of several of these genes led to gene re-activation and restored chemosensitivity in cancer cells. In another study by Bhatla et al. [48], inhibition of histone deacetylation and DNA methylation resulted in the activation of genes preferentially methylated and repressed in relapsed pediatric acute lymphoblastic leukemia and drug sensitivity. Of importance, targeting of DNA methyltransferases effectors of DNA methylation and histone modification was found to reverse chemoresistance in heterogeneous multiple myeloma [49].

Intrinsic drug resistance-associated membrane proteins

Multidrug resistance (MDR) is largely dependent on the activity of membrane transporter proteins, referred to as "drug resistance-associated membrane proteins" or "DRAMPs" which act either directly by extruding drug molecules out of cells to reduce intracellular accumulation, or indirectly by affecting net accumulation of drugs through physico-chemical processes [4, 50].

Two major classes of DRAMPs have been identified: (i) the ATP-binding cassette (ABC) transporter superfamily, which pumps hydrophobic chemotherapeutic drugs out of tumor cells thereby reducing the net intracellular accumulation and thus the efficacy of the drugs into tumor cells, and (ii) the solute carrier transporters which increase chemoresistance by interfering with the cellular uptake of hydrophilic anticancer agents [4, 50]. Approximately, 50 ABC transporters have been identified in the human genome which catalyze the active transport of diverse chemical compounds including anticancer drugs in an ATP-dependent way by a pair of cytoplasmic nucleotide-binding domains (NBD) [51]. There are three broad groups of ABC transporters implicated in MDR, namely, P-glycoprotein, ABCG2, and the multidrug resistance-associated proteins (MRPs) [50, 52] discussed below.

P-glycoprotein

Overexpression of the protein P-glycoprotein (or ABCB1/MDR1), an ATP-dependent efflux pump, results to MDR in several types of cancer (e.g., multiple myeloma, leukemia) [53–56], through the active translocation of drug molecules out of the tumor cells [50, 57]. The final prognosis in epithelial and solid tumors, as well as in blood malignancies, was particularly unfavorable due to enhanced ABCB1 efflux potential [58–60]. *ABCB1* overexpression has been demonstrated in cases of chemotherapeutic failure [59–63]. Moreover, a high level of *ABCB1* gene amplification was observed in MDR murine melanoma cells [64]. P-glycoprotein exhibits a very broad substrate specificity, including anthracyclines, vinca alkaloids, or taxanes, epipodophyllotoxins, which is the biochemical basis for its "MDR" property [65].

MDR-associated protein

The MDR-associated proteins (MRPs) constitute a group of 13 members, including MRP1 (ABCC1) [50, 52]. *MRP1* overexpression was shown to result to resistance to anticancer agents. The presence of reduced glutathione (GSH) is a prerequisite for the transport of unmodified chemotherapeutic agents via MRP1 [66]. A peptidomimetic glutathione-conjugate of ethacrynic acid (EA), GS-EA, was found to inhibit MRP1-mediated efflux of drugs in ovarian cancer cells which display overexpression of *MRP1*. In addition, resistance of these cells to methotrexate was reversed in part [67].

ABCG2

Another member of the broad ABC superfamily, ABCG2, was overexpressed in human-derived breast cancer cells resistant to adriamycin [68]. Furthermore, it has been reported that hypoxia can regulate *ABCG2* expression. Stem cells or cancer cells in hypoxic environment exhibit resistance to drugs due to enhanced *ABCG2* expression [69]. ABCG2 is responsible for cell resistance to many anticancer drugs, with camptothecins being the most prominent example [70, 71]. However, FL118, a camptothecin analogue, was able to overcome effectively *ABCG2*-induced resistance [72]. The substrates of ABCG2 include many molecularly targeted chemotherapy drugs, such as Gefitinib an inhibitor of epidermal growth factor receptor (EGFR), and Imatinib. However, its importance in clinical practice remains to be investigated.

Classic chemotherapeutic drugs

Methotrexate is an anticancer molecularly-targeted cytostatic drug, used either alone or in combination with other agents, to treat a variety of malignancies such as breast, lung, skin, and head and neck cancer. It is also used for the treatment of severe rheumatoid arthritis and psoriasis. Methotrexate exerts its anticancer effect through inhibiting the expression of its biochemical target dihydrofolate reductase (DHFR), a key enzyme in DNA synthesis, which facilitates cancer cell growth and proliferation. Molecular

studies have demonstrated enhanced *DHFR* expression in cells that display resistance toward methotrexate. In methotrexate-resistant cancer cells, increased *DHFR* gene copies were identified [41].

Some anticancer agents, such as vinca alkaloids and taxanes prevent cell division through altering the dynamic instability of microtubules [73]. Taxanes have been successfully used as anticancer agents over the last 25 years by destabilizing microtubules; whereas, vinca alkaloids are implicated in the inhibition of microtubule function. The synergistic effect of these agents was tested experimentally and it was observed that their microtubule-specific activity was enhanced [74]. Resistance against the taxane paclitaxel was exerted by β III-tubulin isoforms [75]. In several types of epithelial tumors, βIII-tubulin expression was linked to poor response toward paclitaxel treatment and overall patient outcome [76].

Of particular note, an initial favorable clinical response was followed by resistance to taxane treatment. This could be explained by a gradual change in microtubule dynamics and functionality [77]. Particularly, the microtubule-associated protein (MAP)-Tau interferes with the binding of taxanes to microtubules. Down regulation of MAP-Tau was shown to lead to alteration of cancer cells' chemosensitivity, rendering them more vulnerable to paclitaxel [78].

Anticancer drugs like camptothecin and epipodophyllotoxin target key enzymes involved in DNA replication and transcription such as topoisomerases. Camptothecin is a cytotoxic alkaloid administered to patients with leukemia [79, 80]. Experimental studies show that resistance to camptothecin and treatment failure are due to the activity of the enzyme topoisomerase type I [81]. Moreover, overexpression of topoisomerases type II was associated with altered efficacy of molecularly-targeted drugs [82, 83], such as Adriamycin, in chemoresistant leukemia cell lines [80].

Genetic alterations, such as mutations, in molecular drug targets like genes or proteins contribute greatly to acquired drug resistance, thereby leading to limited effectiveness or complete ineffectiveness of chemotherapy, mainly in advanced cancers [65]. For instance, Bcr-Abl kinase domain point mutations could impair or abolish imatinib binding in chemoresistant patients with chronic myeloid leukemia (CML) [84, 85].

DNA damage repair

Important determinants of response to many chemotherapy drugs and targeted therapies represent the DNA damage repair (DDR) pathways which include a complex of proteins, like Nucleotide Excision Repair (NER) machinery that processes and removes the so-called bulky lesions, such as those induced by UV light (thymine dimers and 6,4-photoproducts) and chemotherapeutic drugs such as cisplatin [86].

Two sub-pathways are involved in NER: the global genomic NER (GG-NER or GGR) which repairs DNA damage in transcriptionally silent loci and the transcription-coupled NER (TC-NER or TCR) which repairs lesions located in the transcriptionally active DNA regions. The NER pathway consists of some basic steps, including the identification of DNA damage, DNA unfolding, and other processes such as incision, polymerization, degradation, and ligation [87]. One of the most important genes related to NER is *ERCC1*, overexpression of which is usually associated with DDR induced by platinum and alkylating agent-based treatment and is correlated with negative outcomes in patients receiving cisplatin-based treatment in advanced non-small cell lung cancer (NSCLC) [88]. DNA damage caused by platinum-based drugs can also be recognized by specific proteins, such as mismatch repair (MMR) complexes, thereby resulting to transduction of DNA damage signals and various downstream effectors [89].

In addition, the DNA damage repair protein O_6-methylguanyl DNA methyltransferase (MGMT) is associated with resistance to chemotherapy with DNA alkylating anticancer drugs, such as nitrosoureas, carmustine and temozolomide in central nervous system tumors [87, 90]. The crosstalk and the signals generated between the effector molecules involved in DDR lead to either cell death or cell survival. One very important effector is the well-known *TP53* gene which triggers a major tumor abrogation mechanism via primarily the initiation of cell death, and plays a cardinal role in carcinogenesis when mutated [91]. If DNA damage is extensive and impossible to be repaired, then the apoptotic pathway becomes activated [17]. Moreover, DNA damage can result in apoptosis through the *TP73* gene, a *TP53*-related gene [89]. There is a close relationship between oncogenesis and drug resistance/sensitivity modulated by a pathway dependent on *TP53*, mutations of which are detected in many human cancers [92, 93].

Cancer stem cells

Cancer stem cells have stem-like properties and they exhibit higher resistant to chemotherapy in contrast to the differentiated tumor cells. Factors that affect CSCs' resistance to drugs include: (a) induction of pathways implicated in stem cell maintenance; (b) activation and elevated expression of ABC transporter proteins (e. g., ABCB1 and ABCG2); (c) overexpression of detoxification enzymes such as certain aldehyde dehydrogenase (ALDH) isoforms; (d) inhibition of apoptotic pathways, like the ones mediated by the pro-apoptotic TP53; (e) enhanced DNA damage repair capacity, thereby reducing the effectiveness of DNA-damaging chemotherapeutic agents; and (f) increased influence of the tumor microenvironmental niche [7, 94].

Cancer microenvironment

The cellular environment can affect greatly drug response, where the cell kinetic parameters and proliferation rate constitute important determinants of therapeutic effectiveness. Anticancer drugs and new biological agents that target these determinants have been shown to exert their antineoplastic effect by tranquilizing cancer cells [95]. Increased treatment effectiveness is usually achieved by targeting rapidly proliferating cancer cells [96]. According to a study by Hirst and Denekamp, the most effective chemotherapies are those that rapidly neutralize highly proliferating cells or selectively affect cell division [97]. Different treatments are required in the hypoxic regions of tumors or in regions with slow cell proliferation. Combination therapies with more than one anticancer agents do not necessarily guarantee treatment success because a drug can counteract or overlap the effect of another drug so that the combined effect is lower than predicted. There is a positive correlation between tumor cell proliferation and tumor vasculature, which ensures continuous blood supply to the growing tumor cells, as well as vascular permeability [97]. Reduced blood flow leads to deprivation of nutrients essential for the increased energy demands of the cell in the proliferation phase, thereby leading to delay or inhibition of proliferation. The slow cell proliferation and the poor blood supply are associated with potential resistance to molecularly-targeted drugs [98].

Novel chemosensitizing agents have been developed to counteract the phenomenon of resistance to many molecularly-targeted drugs [99]. Cell adhesion, cytokine activity, growth factors, cell proximity, oxygen and energy supply to the cells, as well as other factors, are suggested to be implicated in reduced anticancer drug response, decreased chemotherapeutic effectiveness and subsequent rapid tumor recurrence [100, 101].

Another factor which regulates the accumulation of oxygen to tumor cells is the hypoxia- inducible factor 1 (HIF1), a transcription factor [102]. HIF-1 promotes the activation of genes implicated in hypoxia signaling and inhibition of cell proliferation. HIF-1 is also implicated in the intracellular metabolism, pH regulation, inhibition of autophagy and cell death [102].

Oxygen deficiency was shown to be associated with the activation of genes encoding proteins that induce resistance to anticancer drugs, such as P-glycoprotein, especially in solid tumors [103]. Specific anticancer drugs can inhibit oxygen supply, allowing cancer cells to enter a dormant state [104]. Cells that survive drug treatment may potentially proliferate under hypoxic conditions, leading to tumor relapse in a short span of time. Additionally, the sufficient oxygenation of normal tissues is important in the mobility of anticancer drugs and favorable response to drug treatment [105]. Therefore, low oxygen concentration in tumor tissues is linked to low activity of anticancer drugs, poor tumor response to chemotherapy or rapid tumor relapse [106].

The cytotoxicity of anticancer drugs is largely affected by the pH of the tumor microenvironment. Molecules passively diffuse across the cell membrane, more effectively in the uncharged (non-ionized) form. Accordingly, alkalization of the extracellular environment increases the uptake and cytotoxicity of drugs such as Doxorubicin, with a pKa value of almost 9 [107, 108]. On the other hand, a microenvironment with acidic pH can also inhibit the active transport of certain drugs (e.g., methotrexate) [109].

Drug uptake and drug activation

Plasma membrane proteins play a very important role in intrinsic drug sensitivity or resistance, given that antineoplastic drug molecules may be expelled from cancer cells either through passive diffusion or facilitated diffusion mediated by membrane proteins [110]. The majority of antimetabolite drugs need metabolic activation to produce therapeutically effective nucleotides or nucleosides intracellularly through the activity of phosphoribosyl transferases and kinases [111].

Another component of the redistribution of anticancer drugs is the binding of drug molecules to specific intracellular proteins [112]. In blood malignancies, these proteins have been found to largely contribute to significant drug resistance and treatment failure. For example, overexpression of a major vault protein, LRP, was observed in acute myeloid leukemia (AML) patients [113]. Moreover, changes in intracellular chemical processes affect drug kinetics, leading to treatment failure [114].

Moses Judah Folkman proved first that angiogenesis and cancer are closely related [118]. Drug molecules are delivered to the target tumor cells through blood vessels. Abnormal vasculature and ultimately necrosis largely affect drug penetration and effectiveness [119, 120]. Currently, there is a number of chemotherapeutic drugs targeting the potent angiogenic factor, vascular epithelial growth factor (VEGF), such as Bevacizumab, Aflibercept, Pazopanib, Sunitinib and Sorafenib. The drugs normalize tumor vasculature, in order to increase the distribution of anticancer agents and achieve maximum therapeutic efficacy [121]. Moreover, the various physical barriers, such as the blood–brain barrier (BBB) and the blood-testis barriers, prevent the diffusion of chemotherapeutic drugs. Of note, overexpression of P-glycoprotein was observed in the endothelial cells of these barriers [122].

Strategies to overcome resistance mechanisms

Many factors and parameters must be taken into consideration for the effective cancer treatment using antineoplastic drugs. Clinicians are mainly concerned with the route of

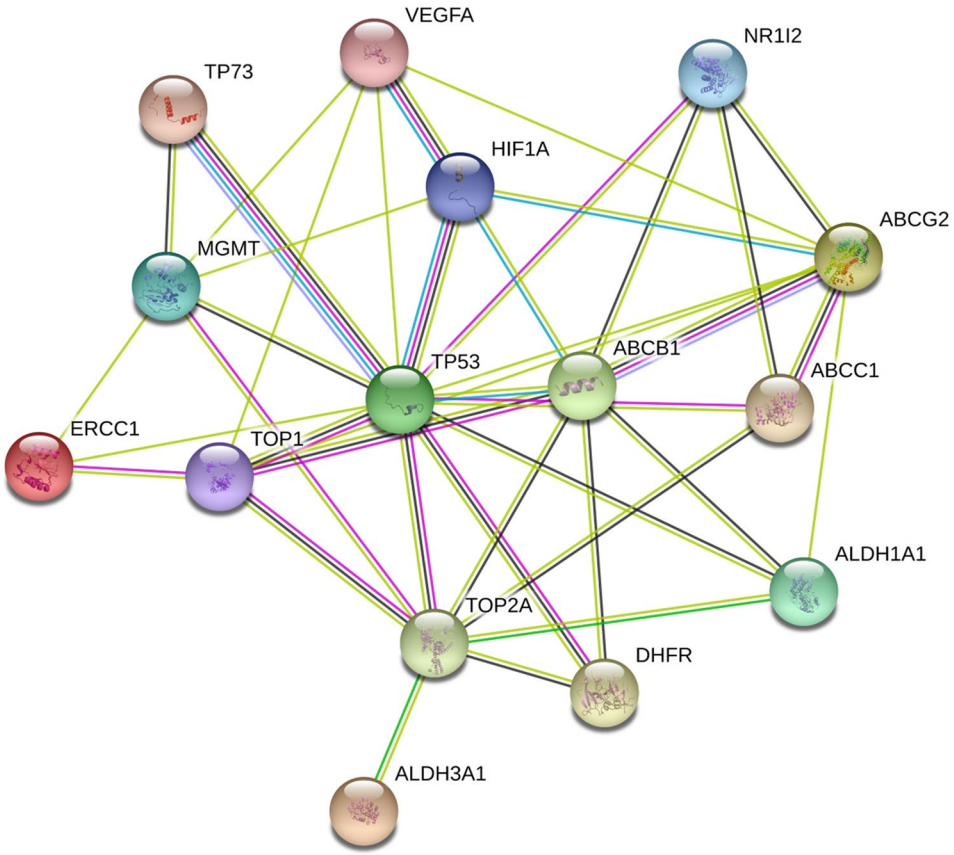

Fig. 1 An interaction network of the genes/gene products related to clinical chemoresistance with the usage of bioinformatics. The associations among them were investigated and visualized using STRING v10.5 [127]. HIF-1: HIF1A, sxr: NR1I2, VEGF: VEGFA, topoisomerase type I: TOP1, topoisomerase type II: TOP2A

drug administration as well as the maximum tolerated dose able to destroy cancer cells while minimizing adverse effects [115]. The "maximum tolerated dose", also called "maximum tolerable dose" or the "maximally tolerated dose" (MTD), can be defined as the highest single dose of an agent or treatment that does not cause significant or intolerable toxicity/adverse effects. For many drugs, the optimal dose does not necessarily coincide with the MTD; thus, determination of the optimal dose poses a great challenge [116, 117].

A novel, promising modality of drug administration has emerged, the so-called 'metronomic chemotherapy', that is, the repetitive administration of chemotherapeutic agents at low doses. It has been demonstrated that metronomic chemotherapy can be extremely beneficial in many cases; however, extended research is needed to confirm these results [124, 125]. One therapeutic strategy to overcome drug resistance is 'treatment holiday', where a patient's chemotherapy treatment is stopped for some time in order to avoid selection for drug-resistant tumor cells that could lead to cancer recurrence and relapse [115].

Of importance, special emphasis should be given to the development and optimization of molecularly-targeted drugs designed to block key genes or gene products implicated in chemoresistance. For example, resistance to chemotherapy caused by P-glycoprotein can be potentially counteracted by adding to a chemotherapy regimen the molecularly-targeted drug verapamil, a candidate competitive inhibitor of P-glycoprotein [54, 56, 126]. Moreover, a positive correlation was observed between cytidine deaminase activity in blast cells obtained from acute leukemia patients and the development of resistance to the antimetabolite drug cytosine arabinoside (ara-C) [114]. Therefore, an effective way of blocking the deamination of ara-C would circumvent resistance to ara-C.

Other potential future directions

The apparent complexity of cancer drug resistance, as discussed throughout the manuscript, leads to the suggestion that there is a pressing need for the design of novel therapeutic regimens. Unraveling the mechanisms underlying patients' response to anticancer drugs and identification of their genetic profile would enable the development of new, personalized drugs to prolong patients' overall survival, as well as quality of life.

Conclusions

Cancer patients' chemotherapeutic response and outcome depends on multiple redundant and diverse biological processes and molecular mechanisms that affect the sensitivity of cancer cells to chemotherapy drugs. Multiple molecular determinants of intrinsic and acquired resistance, including genetic/epigenetic factors, as well as membrane transporter proteins that act at the genomic or cellular level respectively, have been identified. The key genes/gene products found in this review study to be involved in chemoresistance were used to construct an interaction network (Fig. 1). These molecules are, in most cases, highly interconnected and some of them (TP53, TP73, VEGFA, HIF1A, ABCB1, ABCG2 and TOP1) act as 'hubs'. This leads to the suggestion that these genes/proteins may play a central role in drug sensitivity/resistance by interacting with each other, either functionally or physically. Novel targeted therapies for cancer must be developed that would be directed toward cellular drug resistance, and specifically to the 'hub' genes. The goal of these therapies must be to achieve maximum chemotherapeutic effect by eliminating cancer cells, with reduced normal tissue toxicity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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