Multi-drug resistance in cancer chemotherapeutics: Mechanisms and lab approaches

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ABSTRACT
Multi-drug resistance (MDR) has become the largest obstacle to the success of cancer chemotherapies. The mechanisms of MDR and the approaches to test MDR have been discovered, yet not fully understood. This review covers the in vivo and in vitro approaches for the detection of MDR in the laboratory and the mechanisms of MDR in cancers. This study also envisages the future developments toward the clinical and therapeutic applications of MDR in cancer treatment. Future therapeutics for cancer treatment will likely combine the existing therapies with drugs originated from MDR mechanisms such as anti-cancer stem cell drugs, anti-miRNA drugs or anti-epigenetic drugs. The challenges for the clinical detection of MDR will be to find new biomarkers and to determine new evaluation systems before the drug resistance emerges.

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Introduction

Multi-drug resistance (MDR) is defined as the resistance of cancer cells to one chemotherapeutic drug accompanied by resistance to other chemotherapeutic drugs that may have different structures and mechanisms of action [1]. Specifically, once cancer cells gain resistance to drugs that are structurally and functionally unassociated, even to the drugs that have not been exposed previously, they are said to have an MDR phenotype [2]. Once MDR is acquired, the anti-cancer effects of chemotherapeutic drugs decrease. MDR is the most significant reason for the failure of cancer chemotherapeutics and is crucial to cancer metastasis and recovery. The chemo-resistance of a tumor can be divided into primary resistance, which arises before the use of chemotherapeutic drugs, and acquired resistance, which happens after the exposure to chemotherapeutics.

Mechanisms of MDR in cancer chemotherapy

The potential mechanisms of MDR currently reported are shown in Fig. 1, which includes the ABC transporter family, apoptosis induction, autophagy induction, cancer stem cell regulation, miRNA regulation, hypoxia induction, DNA damage and repair, and epigenetic regulation.

Adenosine triphosphate (ATP)-binding cassette (ABC) transporter family

The ABC transporter family is known to have at least 48 members in humans [3], and 12 of these are recognized to be putative drug transporters [4], including the well known P-glycoprotein (Pgp, encoded by the ABCB1 gene), MDR-associated protein 1 (MRP1, encoded by the ABCC1 gene) and ABC subfamily G member 2, also known as breast cancer resistance protein, BCRP, which is encoded by the ABCG2 gene [5]. Cancer patients who do not respond to chemotherapy usually have a high expression of various ABC transporter pumps, which are located on the cytoplasmic side of the resistant cell membrane, resulting in an increased drug efflux. The discovery of these various ABC transporters made potential targets for the pharmacologic down-regulation of efflux-mediated chemotherapy resistance available [6].

Chemoresistance to apoptosis induction

Apoptosis is one of the main mechanisms by which chemotherapeutic drugs kill cells. However, many cancer cells have been found to have primary or acquired resistance to apoptosis, resulting in chemoresistance. For example, BYL719, a novel and specific
PI3KCA inhibitor, inhibited the survival of primary MM (multiple myeloma) cells and induced the apoptosis of MM cells and inhibited their cell cycle by causing G1 arrest. BYL719 inhibited PI3K signaling, decreased proliferation and cells cycle signaling, and induced apoptosis signaling in MM cells. Finally, BYL719 synergized with bortezomib and carfilzomib, and overcame drug resistance induced by bone marrow stroma [7]. Shao et al. found the anti-apoptotic role of AGS3 in MM by developing a cell apoptotic model induced by doxorubicin in MM. The negative role of AGS3 in cell apoptosis was further confirmed by knocking down AGS3. The microenvironment has been shown to influence tumor cell phenotype in response to chemotherapy. AGS3 siRNA reversed the high rate of MM cell adhesion and reduced drug resistance to doxorubicin, mitoxantrone, and dexamethasone [8].

**Autophagy induced chemoresistance**

Autophagy refers to the process in which cytoplasmic components are delivered to lysosomes for bulk degradation in response to intracellular and extracellular pressures. Autophagy is an evolutionarily conserved mechanism for degradation for the maintenance of intracellular homeostasis [9]. Accumulating evidence suggests that autophagy plays significant roles in chemoresistance. Chemotherapeutic drugs induce autophagy along with apoptosis, and autophagy exerts its cyto-protective effect by degrading the drug molecules, helping cancer cells evade apoptosis [9]. In response to 5-fluorouracil (5-FU) and cisplatin, chemosensitive cell lines exhibited apoptosis, whereas chemoresistant populations exhibited autophagy and a morphology resembling type II programmed cell death (PCD). Cell populations that respond to drugs by inducing autophagy are more drug-resistant and will recover after the withdrawal of the chemotherapeutic agent(s) [10]. In response to tamoxifen, 31 kinases were identified that conferred drug resistance on sensitive cells using high-throughput cell-based screens. HSPB8 (Heat shock protein beta-8) was one of these kinases, and its expression predicted poor clinical outcome in one cohort of patients. Further studies revealed that the basal level of p53 is important to autophagy activation in nutrient-deprived HCC cells. Furthermore, combining p53 inhibition and nutrient deprivation or 5-FU treatment resulted in a marked increase in reactive oxygen species generation and mitochondrial damage. Antioxidants reduced nutrient deprivation or 5-FU-induced cell death of HCC after p53 inhibition. In conclusion, the p53 contributes to cell survival and chemoresistance in HCC under nutrient-deprived conditions by modulating autophagy activation [11].

**Regulation of MDR by cancer stem cells**

Cancer stem cells are known to be a subpopulation of cancer cells with self-renewal and differentiation properties. They were recognized to be the origin of cancer and the basis of cancer malignant phenotypes, including MDR. Xue et al. reported an approach to obtain cancer stem-like cells (CSCs) from the gastric cancer cell line SGC7901 using the chemotherapeutic drug vincristine (VCR). They also found that the obtained CSCs displayed mesenchymal characteristics, including the up-regulation of the mesenchymal markers Snail, Twist, and vimentin, and the down-regulation of the epithelial marker E-cadherin. Using a Matrigel-based differentiation assay, CSCs formed 2D tube-like and 3D complex lumen-like structures that resembled differentiated gastric crypts. More interestingly, drug sensitivity assays and xenograft experiments demonstrated that these cells developed MDR and significant tumorigenicity in vivo [12]. In small cell lung cancer, CD133 expression was correlated with chemoresistance and increased tumorigenicity in vitro and in vivo, and was increased in mouse and human SCLC after chemotherapy, an observation confirmed in clinical specimens isolated longitudinally from a patient receiving chemotherapy. The above evidence indicates that CD133+ cancer stem-like cells in small cell lung cancer are highly tumorigenic and chemoresistant [13]. These findings indicated that there are direct relationships between cancer stem cells and MDR.

Because current evidences have indicated that cancer stem cells are responsible for multi-drug resistance, the eradication of the cancer stem cells is therefore essential and convincing to overcome multi-drug resistance and to help achieve a good prognosis in cancer patients. For example, the combination of melatonin and chemotherapeutic drugs (including temozolomide, current treatment for malignant gliomas) has a synergistic toxic effect on Brain tumor stem cells and A172 malignant glioma cells. This effect is correlated with a downregulation of the expression and function of the ABC transporter ABCG2/BCRP [14]. In ovarian cancer, the CD44(+)/CD117(+) stem cells, are highly proliferative, have a low degree of differentiation, and are resistant to chemotherapeutics. Cheng et al. found that miR-199a significantly increased the chemosensitivity of ovarian cancer stem cells to cisplatin, paclitaxel, and adriamycin, and reduced mRNA expression of the multi-drug resistance gene ABCG2 as compared with miR-199a mutant-transfected and untransfected cells. The expression of stemness markers was also significantly reduced in miR-199a-transfected cancer stem cells as compared with miR-199a mutant-transfected and untransfected ovarian cells. They also found that miR-199a may exert the effects by regulating expression of its target gene CD44 [15].

**Regulation of MDR by miRNAs**

miRNAs are non-coding 18-24nt RNAs that regulate the expression of target genes by binding to the 3’ un-translated regions of these target genes. miRNAs have been reported to play significant roles in the malignant phenotypes of cancers such as metastasis, MDR, proliferation or even in the self-renewal or differentiation of cancer stem cells. miRNAs tend to regulate malignant phenotypes by modulating the aberrant functions of their target genes. For example, miR-19a and miR-19b, members of the miR-17-92 cluster, were found to be upregulated in MDR cell lines, and modulated MDR in gastric cancer cells by targeting PTEN [16]. For another example, miRNA profiling revealed that miR-153 was highly expressed in colorectal cancer. In colorectal cancer patients
followed for 50 months, 21 of 30 patients with high levels of miR-153 had disease progression compared with others in this group with low levels of miR-153. Functional studies revealed that miR-153 upregulation increased colorectal cancer invasiveness and resistance to oxaliplatin and cisplatin both in vitro and in vivo. Mechanistic investigations indicated that miR-153 promoted invasiveness indirectly by inducing matrix metalloproteinase enzyme 9 production, whereas drug resistance was mediated directly by inhibiting the Forkhead transcription factor Forkhead box O3a (FOXO3a) [17].

Except for oncomiRs, some tumorsuppressive miRNAs have been found to sensitize for multi-drug resistance in the treatment of cancers. Xia et al. found that miR-15b and miR-16, members of miR-15/16 family, were down-regulated in the MDR gastric cancer cell line SGC7901/VCR compared with parental SGC7901 cells. In vitro drug sensitivity assays demonstrated that the over-expression of miR-15b or miR-16 sensitized SGC7901/VCR cells to anticancer drugs, whereas the inhibition of these factors using antisense oligonucleotides conferred MDR in SGC7901 cells. Moreover, the over-expression of miR-15b or miR-16 could sensitize SGC7901/VCR cells to VCR-induced apoptosis by targeting BCL2 [18]. As another example, Shang et al. found that the overexpression of miR-508-5p was sufficient to reverse cancer cell resistance to multiple chemotherapeutics in vitro and sensitize tumors to chemotherapy in vivo. Furthermore, miR-508-5p could directly target the 3'-untranslated regions of ABCB1 and ZNRD1 (DNA-directed RNA polymerase I subunit RPA12) [19]. The overexpression of miR-27a by transfecting with miR-27a mimics in the BEL/S-FU cells could reduce the MDRI/P-glycoprotein and β-catenin expressions, enhance the sensitivity of these cells to 5-fluorouracil and 5-fluorouracil-induced apoptosis. Moreover, up-regulation of miR-27a did not decrease the FZD7 (Frazzled-7) mRNA level, but significantly reduce its protein expression in BEL/S-FU cells. It was also confirmed that reduction of FZD7 by RNA interference induced inhibitory effects on the expression of MDRI/P-glycoprotein and β-catenin, similar to miR-27a [20].

Studies also found miRNAs can not only regulate and sensitize the multi-drug resistance phenotype, but also might serve as diagnostic markers for multi-drug resistance. Chen et al. demonstrated that serum miR-19a was detected to be significantly up-regulated in resistance-phase serum in colorectal cancer patients. The ROC curve analysis showed that the sensitivity of serum miR-19a to discriminate the resistant patients from the response ones was 66.7%, and the specificity was 63.9% when the AUC was 0.679. The serum miR-19a was also observed to have a complementary value for cancer embryonic antigen (CEA). Stratified analysis further revealed that serum miR-19a predicted both intrinsic and acquired drug resistance [21].

**Hypoxia induced chemoresistance**

The hypoxia-inducible factor 1 (HIF-1) pathway was shown to have a profound effect on the response to radiotherapy. It was also demonstrated that this pathway also played significant roles in resistance to chemotherapy. For example, Liu et al. found that HIF-1, the major transcriptional factor significantly activated by hypoxia, was over-expressed in gastric vincristine-resistant cells SGC7901/VCR under normoxic conditions, suggesting that that HIF-1 was associated with drug resistance in gastric cancer cells [22]. They also found that blocking the expression of MGr1-Ag/37LRP by siRNA in gastric cancer cells effectively reversed the multidrug resistance phenotype induced by hypoxia, while the up-regulation of MGr1-Ag/37LRP was abolished by HIF-1 inhibition with siRNA. Further studies demonstrated a functional HIF-1 binding site within the MGr1-Ag/37LRP regulatory sequence located at -16 to -11 relative to the transcriptional initiation point [23][24].

DNA damage and repair contributing to MDR

Most antitumor therapies damage tumor cell DNA either directly or indirectly. Without repair, this damage can result in genetic instability and eventually cancer. Generally, DNA repair in cancer cells excises lethal DNA lesions, thus it is intuitive that the efficient repair of DNA within cancers will contribute to intrinsic drug resistance [25]. A dysfunction of one DNA repair pathway may be counteracted by the function of another compensatory DNA damage response pathway, and this may contribute to the resistance to DNA-damaging chemotherapy. For example, the inhibition of endoglin decreases cell viability, increases apoptosis, induces double-stranded DNA damage, and increases cisplatin sensitivity. Targeting endoglin down-regulates the expression of numerous DNA repair genes, including BARD1 (BRCA1-associated RING domain protein 1), H2AFX (H2A histone family, member X), NBN (Nibrin), NTHL1 (nth endonuclease III-like 1), and SIRT1 (Sir-tuin 1). BARD1 was also associated with platinum resistance and was induced by platinum exposure [26]. Metnase is a component of the non-homologous end-joining DNA double-strand break repair pathway. Wray et al. have found that in acute myeloid leukemia (AML) and breast cancer cells, Metnase expression levels may predict resistance to Topo II-alpha inhibitors; Metnase is therefore a potential therapeutic target for small molecule interference [27][28]. Elizabeth et al. further identified eight compounds as possible Metnase inhibitors. Among them, ciprofloxacin inhibits the ability of Metnase to cleave DNA and inhibits Metnase-dependent DNA repair. Interestingly, ciprofloxacin on its own did not induce DNA damage, but it did reduce the repair of chemotherapy-induced DNA damage. Ciprofloxacin increased the sensitivity of cancer cell lines and a xenograft tumor model to clinically relevant chemotherapy [29].

**Epigenetic regulation of chemoresistance**

Epigenetic changes such as DNA methylation and histone modification are also believed to regulate the malignant phenotypes of cancers including MDR. The de-methylation or low methylation of some tumor suppressor genes might cause the malignant phenotypes of cancer cells including MDR. Martín et al. reported that brain tumor stem cells (BTSCs) over-express members of the adenine triphosphate-binding cassette (ABC) family transporters, and this overexpression is responsible for multidrug resistance and tumor relapse. Combinations of melatonin and chemotherapeutic drugs (including temozolomide) have a synergistic toxic effect on BTSCs and A172 malignant glioma cells. Melatonin increased the methylation levels of the ABCG2/BCRP promoter, and the effects on ABCG2/BCRP expression and function were prevented by pre-incubation with a DNA methyl-transferase inhibitor [14]. To identify genes that regulate cisplatin resistance, 20 gastric cancer cell lines were subjected to gene expression profiling, DNA methylation profiling and drug-response assays. Epigenetic analysis identified bone morphogenetic protein 4 (BMP4) as an epigenetically regulated gene that is highly expressed in cisplatin-resistant cell lines. In primary tumors, BMP4 promoter methylation levels were inversely correlated with BMP4 expression, and patients with high BMP4-expressing tumors exhibited significantly poorer prognosis. Therapeutically, the targeted genetic inhibition of BMP4 caused a significant sensitization of GC cells to cisplatin [30]. Oehme et al. provided in vitro and in vivo evidence that histone deacetylase (HDAC) 10 promotes the autophagy-mediated survival of neuroblastoma cells. They showed that both the knockdown and inhibition of HDAC10 effectively disrupted the autophagy associated with the sensitization to cytotoxic drug treatment in a panel of highly malignant N-Myc (V-MYC myelocytomatosis viral-related
oncogene, neuroblastoma derived)-amplified neuroblastoma cell lines, in contrast to nontransformed cells [31].

**Laboratory approaches for determination of cancer drug resistance**

To date, many of the multidrug resistant tumor phenotypes can only be detected by isolating cancer cells from primary tissues and testing their tolerance to chemotherapeutic drugs due to the lack of in vivo drug resistance detection methods. Commonly used tumor resistance indicators include the half inhibitory concentration (IC50), resistance index (RI), cytotoxic drug pump out rate, cell proliferation index, cell growth curve, and apoptosis index. Commonly used assays to test tumor cell resistance are MTT assays, doxorubicin accumulation and retention experiments, drug sensitivity tests, detection of multidrug resistance genes and pathways, high-content instrument technology, gene chip technology, and high-throughput screening technology.

**The establishment of drug-resistant tumor cell lines**

Drug-resistant cell lines are cell lines in which permanent resistance to chemotherapeutic drugs is induced by repeated exposure. Generally, a parental tumor cell line is treated with a small dose of chemotherapeutic drugs, and the dose of chemotherapeutic drugs is increased continually over a period of time. The drug dose can be increased until the cells can stably live without the drug for more than a week. The commonly used drug-resistant human tumor cell lines that have been established are summarized in Table 1.

**Half inhibitory concentration (IC50) and resistance index (RI)**

In multidrug resistant tumor cells, higher IC50 values mean more resistance. The IC50 ratio of drug-resistant tumor cells to that of the parental tumor cells is called the resistance index, which reflects the degree of chemoresistance in the experimental cells compared to the control cells. IC50 and RI may be detected by the MTT assay to test the activity of the cell growth state and can be calculated by reading the OD value of cells from cell culture plates. The formula for calculating cell viability is (absorbance of experimental group – absorbance of control group)/(absorbance of negative control group – absorbance of control group) × 100%. To evaluate the in vitro antitumor efficacy of the LMWC (low molecular weight chitosan)-conjugated DTX (docetaxel) [32] compared to that of unmodified DTX, the IC50 values of the drugs were evaluated by MTT assays using two human cancer cell lines. The LMWC–DTX conjugate showed similar IC50 value to the parent DTX, indicating that the conjugate has comparable antitumor efficacy to DTX in vitro [32].

**Drug efflux assays**

The drug efflux assay is to assess the functional activity of membrane pumps such as MDR1, MRP1, MRP2 and BCRP in living cells under physiologic conditions by directly measuring the relative fluorescence of cell populations that actively exclude fluorescent multidrug resistance transport probes. The probes used for detection are fluorescent small molecules, such as the classic fluorescence dyes DiOC2, rhodamine 123, and calcein AM. Also the selectivity of probes is different according to the individual transporters. For example, DiOC2, rhodamine 123 [33], fexofenadine [34], digoxin [35], were commonly used to detect MDR1 expressing cells. The main substrate of the efflux pump BCRP reported was doxorubicin [36], while tariquidar can be used for both MDR1 and BCRP probes [37]. The substrate leukotriene was able to transport for MRP1 and MRP2, while calcein can be used for MRP 1 and bilirubin glucuronosides for MRP2 transportation [38,39]. Several other dyes with broad coverage, such as daunorubicin and mitoxantrone, lack sensitivity due to overall dimness and thus may yield a significant percentage of false negative results [40].

**Drug sensitivity test**

The drug sensitivity test, also known as drug susceptibility test, can be measured by testing the ability of cells to proliferate in the presence of chemotherapeutic drugs or small molecule agents on xenograft tumors in nude mice in vivo to evaluate the anti-tumor functions of these drugs in animals [45]. Primary cultured tumor cells or passaged tumor cells are usually used to prepare fibrin clots and then transplanted under the renal capsule, in situ organs or subcutaneous. After randomization and tail vein injection of chemotherapeutic drugs for several days, the animals are sacrificed and the size of the tumor masses (L and W) is measured. The following formula is used for the calculation of tumor size for in vivo drug sensitivity: $V = (LW^2)/2; \Delta TS = −V_1 − V_2$, where:

(a) $\Delta TS$: tumor volume before and after treatment the rate of change (mm3);
(b) $−V_1$: the day of transplantation tumor volume (mm3);
(c) $V_2$: 6 days after transplantation tumor volume (mm3).

**High-content screening and analysis**

High-content screening and analysis system is an integrated platform which can biologically evaluate and obtain information about intracellular and intercellular conditions under drug stimulation. The system does not destroy the structure of the cells and...
Commonly used drug resistant human tumor cell lines.

<table>
<thead>
<tr>
<th>Source of organs and tissues</th>
<th>Name of cell lines</th>
<th>Parental cell line and tumor name</th>
<th>Chemotherapeutic drug</th>
<th>Institution</th>
<th>Reference</th>
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</thead>
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<td>Bleomycin</td>
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<td>KB-C2</td>
<td>Nasopharyngeal epithelial carcinoma KB cell line</td>
<td>Colchicine</td>
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<td>Chronic myelogenous leukemia K562 cell line</td>
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<td>With high expression of P-glycoprotein</td>
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<td>[77]</td>
</tr>
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</table>

Table 1

Because the majority of tumors express the classical molecular resistance genes or the downstream signaling pathways, the status of these factors can be detected by Western blotting and immunohistochemistry to evaluate the drug resistance of tumor cells or tissues. There are two human multidrug resistance genes, MDR-1 and MDR-2 [51]. MDR-1 encodes the drug transporter P-glycoprotein (P-gp) and is associated with multidrug resistance. The MDR-2 gene encodes a P-gp that is specifically involved in the phthalocyanine phospholipid cholrine. P-gp protein encoded by MDR-1 is a transmembrane glycoprotein with a molecular weight of 170 KD and functions as an energy-dependent drug pump. P-gp can bind to both the drug and ATP; ATP provides the energy to pump intracellular drugs out of cells, reducing the intracellular drug concentration and causing the drug resistance [52]. Tumors with higher expression of this protein can pump intracellular chemotherapeutic drugs to extracellular environments and is responsible for the mechanism of producing tumor multidrug resistance.

In addition, some other drug resistance-related genes such as multidrug resistance associated protein (MRP), lung resistance protein (LRP), intracellular glutathione (GSH), glutathione S transferase (GST) and DNA topoisomerases I and II (TOPO I, TOPO II), can also be used to detect multidrug resistance [53,54].

High-throughput screening technology for MDR related genes

High-throughput screening technology uses molecular and cellular methods and micro-plates as experimental tools; these systems can be used to conduct experiments automatically so that a large number of tests can be completed and experimental data can be collected rapidly. Tens of thousands of samples can be measured simultaneously, and the experiments are rapid, sensitive, accurate and traceable. These methods can therefore be used to obtain a lot of information from a single experiment and generate valuable data.

Detection of multi-drug resistant genes and their molecular signaling pathways

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The high-throughput screening system can be used to screen phenotypic or functional data. For example, multidrug resistance-related genes or miRNAs can be screened using random small interfering RNA (siRNA) retrovirial libraries or miRNA inhibitor libraries. Drug resistance phenotypes can be detected after the infection of viral vectors carrying siRNAs or a miRNA library to select certain genes or miRNAs with drug resistance characteristics [55].

Array-based high throughput drug screening including gene chip, cDNA chip, RNA chip, protein chip, and protein modification chip (protein phosphorylation chip or protein glycosylation chip) can also be applied to analyze multidrug resistance genes, RNAs or proteins [56]. For example, a comparison between a normal cell line and a drug-resistant cell line using an array-based high-throughput screen can identify the differential expression of genes, RNAs or proteins that may have certain drug resistance functions to be explored [57].

Clinical applications of MDR

Biomarkers for MDR

Despite the urgent need to improve the current biomarkers for MDR or targeted therapies, the rate of advances in these fields has been slow. There has also been little progress over the past years (since the identification of KRAS mutations) in predicting resistance to epidermal growth factor receptor (EGFR) monoclonal antibodies. Recent approved therapeutics such as regorafenib and aflibercept or label extensions for existing therapies such as bev-acizumab lack companion biomarkers [58]. Global gene expression methods such as gene microarrays and RNA sequencing enable the study of thousands of genes simultaneously and allow scientists to examine molecular pathways of cancer pathogenesis [59]. To identify potential biomarkers predicting paclitaxel sensitivity, a laryngeal cancer cell line, untreated or treated with lower dose of paclitaxel, was applied to DNA microarray chips for gene and miR expression profile analysis. In the four up-regulated genes, ID2 and BMP4 were implicated to be involved in sensitivity to several drugs [60]. Even though most of the meta-analyses in cancer have yielded contradictory results, a number of potential biomarkers for sensitivity or resistance to conventional chemotherapeutic agents such as gemcitabine, platinum-compounds, pemetrexed and taxanes have been proposed [61].

The application of MDR inhibitors or reversal agents in the clinic

Although MDR is still a big obstacle in the treatment of cancers, there is already MDR inhibitors or reversal agents applied in clinical trials in the treatment of cancers. For example, as the inhibitor of P-glycoprotein (P-gp), XR9576 (Tarivid) was previously demonstrated to reverse P-gp dependent multi-drug resistance in tumor cell lines and tumor-bearing animals [62]. The XR9576 was demonstrated to help increase the retention of (99 m) Tc-sestamibi with other chemotherapeutic drugs such as doxorubicin, vinorelbine, or docetaxel in tumors to look for a better application of XR9576.

The need for a clinical evaluation system to determine MDR

The clinical usefulness of the prediction of MDR is limited due to the lack of MDR biomarkers and the limited approaches to evaluating in vivo MDR sensitivity or resistance. To date, the resistance of tumors to certain chemotherapeutic drugs could only be discovered after the resistance has been acquired. However, if the drug resistance phenotype could be detected prior to the acquisition of MDR using biomarkers from the circulatory system or from in vivo imaging detection, the tumor patients would have better clinical outcomes. Thus, approved approaches are needed to clinically evaluate MDR before drug resistance is acquired.

Future directions

Newly discovered elements such as cancer stem cells and miRNAs have been proposed as novel mechanisms of MDR in cancers and have inspired cancer research in the past decade. The great challenges for MDR-related cancer therapy in the years to come will be to determine the contribution of certain mechanisms to the resistance of chemotherapeutics, to find the underlying molecules or pathways and to use this information to design more effective and curative therapies. Future therapeutic drugs to improve the outcomes for cancer patients will likely combine the existing chemotherapeutic drugs with targeted drugs such as anti-cancer stem cell drugs, anti-miRNA drugs or anti-epigenetic drugs. The challenges for the clinical diagnosis of MDR will be to find new biomarkers for MDR and to determine new evaluation systems to test for MDR before the drug resistance arises.

In conclusion, the future of anti-MDR therapy for cancer patients will rely on our endeavors to develop new anti-MDR drugs, new diagnostic methods and optimized treatment conditions.

Conflict of Interest

We declared that we have no conflicts of interest.

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Reference


