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Mini-review

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.

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

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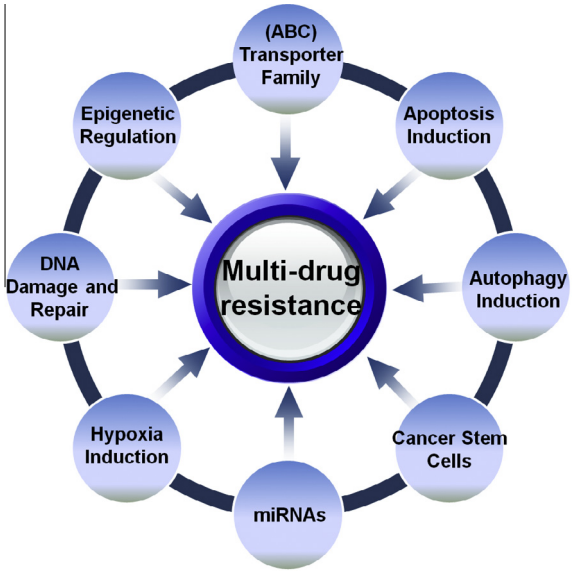

Fig. 1. Summary of the potential mechanisms of MDR.

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 (CSLCs) from the gastric cancer cell line SGC7901 using the chemotherapeutic drug vincristine (VCR). They also found that the obtained CSLCs 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, CSLCs 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 indicats 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, pacitaxel, and adriamycin, and reduced mRNA expression of the multidrug 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