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Editorial

New Strategies to Overcome Drug Resistance in Clinical Therapeutics

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Chemotherapy is commonly used in cancer treatment. So far, chemotherapy agents can be categorized into three types: classical chemotherapeutic drugs, molecular target agents and cellular machineries target drugs [1]. Although the action mechanisms of these three classes of drugs are different, these drugs are facing the same challenge of drug resistance. Studies showed that mechanisms of drug resistance can be divided into three broad categories: reduced drug uptake; Changes in cells that affect the ability of drugs to kill cancer cells (such as alterations in drug targets or increased DNA damage repair) and increased energy-dependent efflux [2]. The detailed mechanisms of drug resistance have been reviewed elsewhere [2,3], here we will not discuss it further. This mini-review focused on the probable solutions to solve drug resistance in clinical therapeutics.

Multi-Drug Resistance (MDR) Modulators

Among those mechanisms as mentioned above, increased energy dependent efflux is the most common one to cause drug resistance. Drugs efflux from cancer cells is mediated by ATP-Binding Cassette (ABC) transporter. Meanwhile, ABC transporters are broadly expressed in cancer cells and strongly implicated in the regulation of drug-resistance [2]. Lots of efforts have been made to discover and synthesize modulators of ABC transporters which can reverse MDR in cancer cells [4]. P-glycoprotein (pgp) is one of the most thoroughly studied efflux pump. Within the last three decades, the inhibitors of pgp have come down through several generations. The first generation of pgp inhibitors was composed of some drugs in clinical use such as verapamil, quinidine etc [5]. Because those drugs were developed for therapeutic use rather than as inhibitors of MDR modulators, the affinity interactions between drugs and pgp were weak. When served as inhibitors of pgp, the required concentration of the first generation inhibitors was high and could cause serious side effects [6]. Based on the structures of the first generation pgp inhibitors, researchers have made some dimerization or modification to develop the second generation inhibitors. The second generation inhibitors of pgp are proved to be more selective and have a better pharmacological profile. To date, many inhibitors such as PSC833 have come into clinical trials, but they also possess moderate toxicity which limits their use [5,7]. Owning to the imperfection of the second generation inhibitors, it is necessary to develop a third generation. Prakash et al took advantage of computer aided drug design and found XR9576 as a potent and specific inhibitor of pgp. Both their laboratory experiments and phase clinical trials provided promising results [6]. It means that researchers could use Structure-Activity Relationships (QSAR) and combinatorial chemistry to design more potent inhibitors [5].

SiRNA-based therapies

It has been reported that 1481 genes were associated with drug resistance, and among them, 67 genes contributed to multi-drug resistance [8]. RNA interference (RNAi) plays a key role in analyzing the gene functions. Besides that, its therapeutic potential is also enormous [9]. For example, ABCC4 (MRP4) is a member of ABC transporter family and belongs to ABCC subfamily [2]. The ABCC4 gene was over-expressed in drug-resistance gastric cancer cells. Researchers used RNAi to attenuate the expression level of ABCC4 in drug-resistant gastric cancer cells and discovered that the use of RNAi restored sensitivity of cancer cells to chemotherapeutic agents [10]. Dönmez Y et al silenced pgp/MRP1 of doxorubicin-resistant MCF-7 breast cancer cells by siRNA, which resulted in almost completed restoration of the intracellular doxorubicin and further relocalization of the drug in the nuclei. What's more, after silencing MDR1 gene, about 70% of cells were susceptible to doxorubicin again [9]. Therefore, Small interfering RNA (siRNA) is a potential therapeutic agent in treating human disease, while the use of siRNA is hindered by instability, poor cellular uptake and inadequate bio-distribution [11].

Nanoparticulate Drug Delivery Systems (DDS)

Nanocarriers are designed as an effective delivery system to selectively deliver drugs to cancer cells. Comparing with common small drug molecules, nanocarriers exhibit more favorable characteristics such as superior pharmacokinetic profiles, prolonged half-life and better tumor accumulations [12]. Nanocarriers enter into cells mainly through endocytosis pathway and thus bypass ABC transporter. Therefore, nanocarriers might be a helpful tool for drug loading and encapsulation to overcome drug resistance [13]. It is reported that nonoparticles loaded with anticancer drugs and MDR modulators

may obtain satisfying therapeutic outcomes [14]. Doxorubicin (Dox) is a broad-spectrum anticancer drug. However, cancer cells resist Dox not long after treated with it. Curcumin (Cur) could be regarded as a MDR modulator, it is able to down regulate pgp and reverse multi-drug resistance of human leukemia HL60 cells, human osteosarcoma cells and so on [15,16]. A study found that dual drug (Dox + cur) loaded Nanoparticles (NP) not only prolonged the retention time of Dox in nucleus but also inhibited the development of drug resistance [17]. Another study also showed that the tumor growth inhibitory effect of (Dox+Cur)-PMs (Doxorubicin and curcumin polymeric micelles) was more efficient than barely combined Dox and curcumin or even Dox-PMs [18]. As we have mentioned above, siRNA owns potential in dealing with many disease while its use is constrained by some fatal shortcomings. At the moment, the advantages of nanocarries complement those shortcomings of siRNA just in time. Yong Tsuey Li et al developed a pH-sensitive carbonate apatite nanoparticle to deliver the siRNA targeting ABCG2 and ABCB1 gene in human breast cancer cells. The experimental data showed that the delivery of siRNA enhanced chemosensity of cancer cells to chemotherapeutic agents [19]. Furthermore, Nakamura K et al discovered that combination of sibcl-2 RNA-containing nanocarriers with 5-Fluorouracil (5-FU) showed better tumor growth inhibition in a colorectal cancer xenograft model, compared to single treatment [20].

Conclusion

Drug-resistance is a common clinical problem that desperately needs to be solved. A better understanding of its mechanisms will be helpful in developing efficient methods to overcome drug resistance. Compared using these three methods of MDR modulators, siRNAs and nonoparticles, it is not difficult for us to find that rational drug combinations could maximize the effect. Among them, nonoparticle is quite different from the two former methods. It doesn't possess pharmacological effect and is more like a supplementary means to get over the disadvantages of MDR modulators or siRNAs. Therefore, combination therapy of nanoparticles with chemotherapeutic agents and MDR modulators or siRNAs is the most promising way to overcome drug-resistance. However, the worry is that the selectivity of nanoparticle is not high enough and this may lead to serious side effects such as affecting the transport activities of normal cells and tissues. In conclusion, improving the selectivity of nanoparticle and applying it into clinical therapy might be the next target which we should make efforts to achieve in the future.

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