

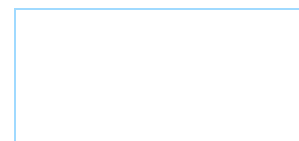


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## Establishment of a high-efficiency screening method for potential inhibitors of P-glycoprotein and its evaluation in vitro and in vivo

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**【Summary】** Multidrug resistance (MDR) is a serious drug resistance phenomenon in tumor cells, which is an important reason for the failure of chemotherapy. P-Glycoprotein (P-gp) is the earliest discovered ABC transporter. The overexpression of P-gp in tumor cells is one of the common mechanisms of MDR, which will lead to the failure of clinical chemotherapy. The combined use of anticancer drugs and P-gp inhibitors can increase the accumulation of chemotherapeutic drugs in tumor cells, thereby improving the therapeutic effect of chemotherapeutic drugs and reversing MDR. At present, P-gp inhibitors have been developed to the third generation, and they have stopped in preclinical or clinical research due to serious toxic and side effects. Therefore, the development of P-gp inhibitors with high selectivity and low toxicity is of great significance for reversing the MDR mediated by P-gp in tumor therapy. Traditional Chinese Medicine (TCM) has the advantages of novel chemical structure and less toxicity, and is an important source of P-gp inhibitor screening. At present, the interaction research between small molecules and P-gp mainly stays at the cellular level. The experimental methods are time-consuming and labor-intensive, and the accuracy is limited. In addition, the evaluation of P-gp inhibitors is still in the in vitro stage, and there are relatively few in vivo studies. Aiming at the problems faced in the screening of P-gp inhibitors, this thesis takes P-gp as the research core, and uses a variety of membrane protein stabilization strategies to obtain P-gp proteins with correct conformation and good activity, combined with surface plasmon resonance (Surface Plasmon Resonance), SPR technology has the advantages of high specificity and rapidity, and established a new method for efficient screening of P-gp inhibitors and an evaluation system for the interaction between potential inhibitors and P-gp from in vitro to in vivo. The research content of this subject is mainly divided into the following three parts: 1. Establishment of a screening method for potential inhibitors of traditional Chinese medicine P-gp based on lentiviral vector membrane protein stabilization strategy combined with SPR. Lentiviral particles (LVP) stabilized membrane protein strategy and Combined with SPR technology, a P-gp specific ligand screening system was constructed to screen potential inhibitors of P-gp from TCM, and to verify its biological activity in vitro. First, lentiviral particles with different P-gp expression levels were constructed, and the expression of P-gp on the lentivirus was identified. Then, the lentiviral particles with high and low expression of P-gp were immobilized on different channels of CM5 chip for affinity detection. The positive drugs Valspodar and cyclosporine (Cyclosporine A, The  $K_D$  values for binding between Cs A) and P-gp on the chip were  $14.09 \mu\text{M}$  and  $16.41 \mu\text{M}$ , respectively. Using this screening system, 3 compounds were screened as potential P-gp ligands from 40 TCM monomers. Affinity experiments showed that the  $K_D$  values of honokiol, honokiol and resveratrol were  $15.88$ ,  $6.44$  and  $70.01 \mu\text{M}$  for binding to P-gp on the chip, respectively. Subsequently, in vitro verification experiments were carried out, and the bidirectional transport experiments of Rhodamine 123 (Rhodamine 123, Rh123) showed that these three compounds could inhibit the efflux of Rh123. In addition, honokiol and resveratrol can reduce the  $IC_{50}$  value of Adr on MCF-7/ADR cells from  $17.54 \pm 4.54 \mu\text{g/mL}$  to  $9.56 \pm 0.60 \mu\text{g/mL}$  and  $8.00 \pm 1.60 \mu\text{g/mL}$ , respectively, indicating that these two compounds have the activity of reversing MDR in MCF-7/ADR cells. Western blot (WB) and flow cytometry analysis showed that both honokiol and honokiol could down-regulate the expression level of P-gp in drug-resistant cancer cells. In this experiment, a novel P-gp ligand screening system was constructed based on lentiviral membrane protein stabilization technology combined with SPR biosensor. Using lentivirus as the carrier of P-gp, it can maintain its natural conformation. The method is highly specific and can be used for In vitro studies of small molecule interactions with P-gp. Compared with traditional cell experimental screening, the experimental time is greatly shortened. 2. The strategy of SMA polymer extraction of cell membrane proteins combined with SPR to establish a new method for rapid screening of potential P-gp inhibitors to study the use of styrene-co-maleic acid (SMA) membrane protein stabilization strategy,





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