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Author: Prof.Dr. yujuan li
Beijing Institute of Technology (BIT), China

EFFECTS OF SIMULATED MICROGRAVITY ON THE EXPRESSION OF P-GP AND ITS RELATED PROTEINS

Abstract

Microgravity is an inextricable disadvantage during the space flight that induces extensively physiological changes in human body, such as body fluid shift, blood volume changes. This might affect pharmacokinetics. P-gp (Permeability glycoprotein) is a drug-efflux protein located on the cell membrane. It is widely expressed in the drug-related organs and the blood-brain barrier that can maintain the brain environment stability. It is closely related to the absorption, distribution, metabolism and excretion of drugs. Rat-tail suspension model was used to explore the P-gp under different simulated microgravity cycles. The differential proteomic analysis of brain co-immunoprecipitation (CO-IP) complexes from different simulated microgravity periods was performed by using non-standard quantitative IBAQ proteomics techniques. 66 differential proteins were identified from all of four groups. The clustering analysis of 66 different proteins was performed by using different bioinformatics tools PANTHER, DAVID, STRING. The results showed that most of the proteins were phosphatase or phosphodiesterase. Phosphorylation plays an important role in the regulation of P-gp pathway. In the biological process analysis, 66 P-gp-interacting differential proteins were mainly enriched in the processes of drug responsepotassium / calcium transport, glycoside response, ATP hydrolysis-coupled transport, cAMP catalytic processetc. The cellular components were mainly distributed in the cell membrane, cytosol, exosomes, mitochondria, protein complexes, extracellular vesicles, etc. It can be mainly bind the calcium ion kinase, ATP, ubiquitin protein ligase, glycoprotein, misfolding protein binding, with guanylate kinase, cyclic nucleotide phosphodiesterase, ATPase activity in the molecular function. KEGG pathway analysis revealed that these proteins were mainly enriched in cGMP-PKG signaling pathway, cAMP signal pathway, gap junction, estrogen signaling pathway, calcium signaling pathway and glutamatergic synapse pathway. 14 typical P-gp interacting differential proteins were found using the bioinform atics tools. The function of these 14 proteins was analyzed to explore its possible P-gp regulatory mechanisms and related signaling pathway use string software. In conclusions, all of the results showed that the protein may interact with P-gp in these pathways: (1) ATP energy supply of P-gp active transportation (2) The synthesis, transportation and degradation of P-gp in cells (3) cAMP/PKA-mediated phospho rylation of P-gp (4) Expression of P-gp in COX-2 cascade induced by glutamate.

Key words: Simulated microgravityP-gpinteractionco-immunoprecipitation proteomicssignal pathway