3rd Asia-Pacific Conference on Plasma Physics, 4-8,11.2019, Hefei, China

Metabolomics analysis of inactivating tumor cells by plasma treatment

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Cold atmospheric pressure plasma (CAP) is a new technology that has attracted much attention in recent years especially in biomedical applications, such as bacterial disinfection, application of skin diseases and dentistry, cell transfection, wound healing and cancer treatment. It is an ionized gas generated by electrical discharges in the atmospheric pressure at room temperature. It has reported that plasma can effectively induce cell death in various types of cancer cells, including lung cancer, leukemia, colon cancer, melanoma, cervical cancer, glioma, multiple myeloma, and pancreatic cancer[1]. However, the effect of plasma treatment on changes in tumor cell metabolism has not been reported. Cell metabolism, a general term for a series of ordered chemical reactions, is one of the most important physiological mechanism to maintain the normal growth and reproduction of organisms. Cancer cells are able to achieve rapid and explosive proliferation due to metabolic reprogramming. Metabolic reprogramming is an oncogenic signaling, which facilitates assimilation of carbons into macromolecules such as lipids, proteins and nucleic acids to generate a large number of intermediate metabolites required for the growth and proliferation of cancer cells[2]. Therefore, it's of great necessity to understand the effects of gas plasma on tumor cell metabolism, so as to treat cancer more precisely by plasma treatment.

In this paper, we used a surface plasma device, which generated the surface plasma when a sinusoidal high voltage was applied. The MOLM13 leukemia cell line was used. We totally investigated 10 samples of MOLM13 leukemia cell, of which five samples were treated with plasma for 40 s as the experimental group and the other five samples as control group were not treated. Then we investigated the metabolite profiling of plasma treatment group and control group based on Gas Chromatography Tandem Time-of-Flight Mass Spectrometry(GC-TOFMS). And we conducted a series of bioinformatics analysis of metabolites with significant differences after basic data analysis. Through using PCA and OPLS-DA, all the differential metabolites were listed and the related metabolic pathways were analyzed by KEGG pathway. By comprehensive analysis of pathways where differential metabolites were located (including enrichment analysis and topological analysis), we further screened pathways and found the key pathways with the highest correlation with differential metabolites. And then we found out that alanine, aspartate and glutamate metabolism had a significant change after plasma treatment. Meanwhile, D-glutamine and D-glutamate metabolism were significantly changed by CAP. Studies have shown that glutamine plays an important role in signal transduction and proliferation of tumor cells[3]. The first step of glutamine catabolism occurs through the activation of glutaminase (GLS), which catalyzes the conversion of glutamine to glutamic acid. Glutaminase activity was decreased after plasma treatment, which might lead to glutamine accumulation and leukemia cell death.

Our study also found that when leukemia cells were treated by jet plasma and surface plasma respectively at the same time, the cell mortality of jet treatment is much greater than that of surface treatment. By bioinformatics analysis of the metabolites and metabolic pathways of jet treatment group and surface treatment group, we analyzed the reason that the differences in killing leukemia cells between jet and surface devices at the metabolic level. The results showed that alanine, aspirate and glutamate metabolism had a significant difference. In cluster analysis, we found that glutamine of jet treatment group was up-regulated compared with surface treatment group. Previous studies have showed that glutamine could not be normally metabolized and converted to glutamic acid, which suppressed the proliferation of leukemia cells and even leaded to leukemia cells apoptosis. The result indicated that the glutamine metabolism of jet group was more inhibited than that of surface group, which might be why the cell mortality of jet was greater than that of surface group.

In conclusion, we found a crucial differential metabolite, glutamine, which was vulnerable to plasma treatment. Its changes may lead to leukemia cells apoptosis. The present study may be a meaningful finding for further screening the optimum target of plasma treatment for tumors.

References

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