Application of Bioinformatics in Drug Activity Detection

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Abstract. Bioinformatics (BI) uses computer technology as the research means and tool, and has gradually become an interdisciplinary field between biology, statistics, mathematics, computer science and even engineering. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are involved in the regulation of neuroinflammation and thus exert neuroprotective effects. Phosphodiesterases (PDEs) are the only key enzymes that can catalyze the hydrolysis of cAMP and cGMP in vivo. Bioinformatics analysis is a crucial part of the ribonucleic acid (RNA). Therefore, this study, RNA sequencing technology was used to analyze the mechanism of the combination of rolipram (PDE4-specific inhibitor) and tadalafil (PDE5-specific inhibitor) by increasing the content of cAMP and cGMP, thereby inhibiting the secretion of inflammatory factors and upregulating the expression of neuroprotection-related factors, and playing a role in regulating neuroinflammation and neuroprotection.

Keywords: Bioinformatics, RNA sequencing, neuroinflammation

1 Introduction

BI is an emerging biological discipline. The discipline encompasses all computational methods and theories applicable to molecular biology, as well as computer techniques for solving biological problems, including model and dataset processing. In the late 20th century, with the implementation of the Human Genome Project (HGP) and the beginning of the post-genome project, more and more model organisms and microbial sequencing work were completed one after another, and biological genome data showed an explosive growth[1-3]. In the post-genome era, the rise and development of systems biology has brought severe challenges to the traditional way of thinking in molecular biology research. The research ideas and methods of systems biology are essentially multi-information fusion and the construction of system models[4]. Systems biology is not about taking the place of other scientists to figure things out at the genetic level, but about finding all kinds of connections based on the results of their experiments and then fusing them. Therefore, the essence of systems biology is to find the connections between levels and between systems. Sequencing technology

Y. Kuang et al. (eds.), *Proceedings of the 2024 5th International Conference on Education, Knowledge and Information Management (ICEKIM 2024)*, Atlantis Highlights in Computer Sciences 22,
https://doi.org/10.2991/978-94-6463-502-7_124

based on bioinformatics analysis is to decipher a large amount of sequence data generated after sequencing into reliable mutation information, help clinical to find the root cause of disease in an all-round way, and provide an important basis for disease screening, diagnosis and treatment strategy formulation.

Persistent activation of microglia in pathological settings has been associated with neuroinflammation[5-7]. cAMP and cGMP have irreplaceable effects in regulating neuroinflammation and neuroprotection, so increasing the content of cAMP and cGMP at the same time can greatly improve their anti-neuroinflammatory efficacy. PDE is the only key enzyme in the body that can hydrolyze cAMP and cGMP. In this study, RNA sequencing technology was used to confirm the ability of Rolipram and Tadalafil in combination to regulate neuroinflammation.

2 Method

BV2 cell passaging and grouping: blank control group, LPS model group, and Rolipram and Tadalafil combination group. Reference transcription methods include RNA extraction and detection, library construction and quality control, library quality detection using Agilent 2100 Bioanalyzer and Agilent High Sensitivity DNA Kit; And reference transcription analysis methods include data quality control, reference genome sequence comparison, gene expression analysis, differential expression analysis, and differential gene enrichment analysis.

Sample correlation test: The Pearson correlation coefficient is used to represent the correlation of gene expression levels between samples; Differential expression detection of two samples: The volcano map of differentially expressed genes was drawn using the R language ggplots 2 software package; Cluster analysis: use the R language Pheatmap software package to union of differentially differentiated genes of all comparison groups, and samples for two-way clustering analysis; According to the results of KEGG enrichment analysis of differentially expressed genes, the top 30 pathways with the smallest P-Value were selected for display; KO analysis: enrichment of the metabolic pathways involved in the experiment.

3 Result

3.1 Screening of Differential Genes for the Regulation of Neuroinflammation by the Combination of Rolipram and Tadalafil

In general, the correlation coefficient between 0.8 and 1 is considered to be a strong correlation. As shown in Figure 1, the correlation coefficient between groups ranged from 0.95-1, indicating that the reproducibility between samples was excellent.

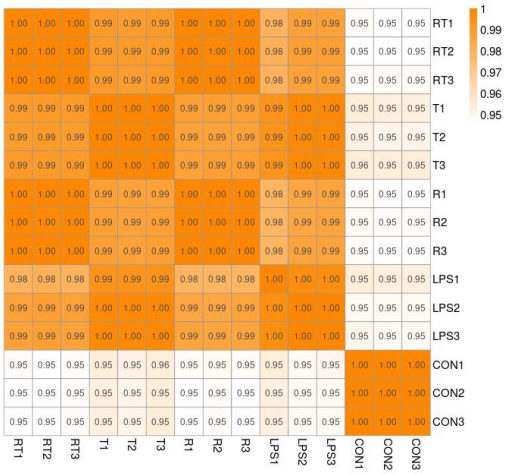
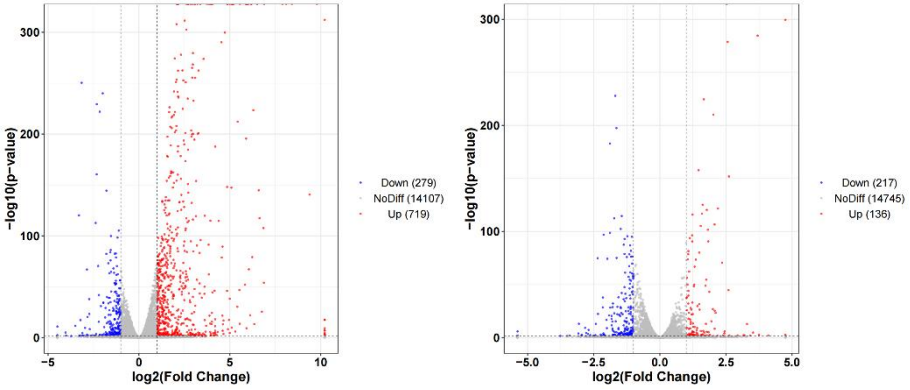


Fig. 1. Correlation analysis of samples

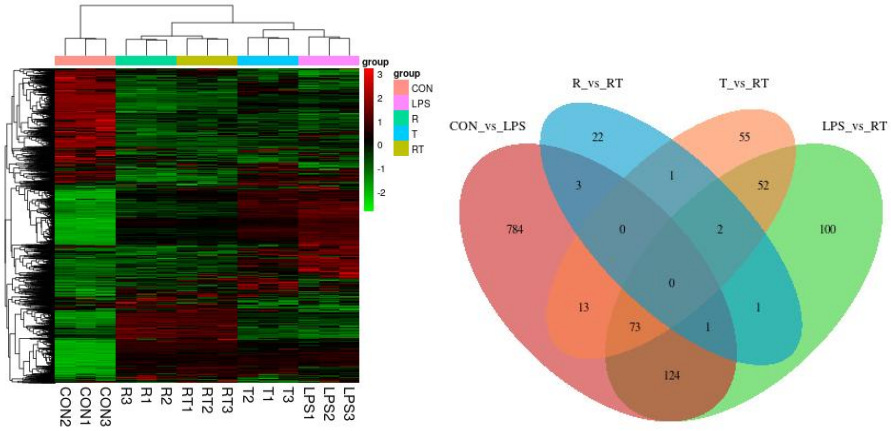
The blank control group and the LPS model group, and the LPS model group and the Rolipram + Tadalafil combination group were compared in pairs, and the number of differentially expressed genes was analyzed. The results of differentially expressed genes in each comparison group are shown in the volcano diagram in Figure 2, and the RNA sequencing results of the blank control group and the LPS model group were screened with 998 differentially expressed genes, including 279 down-regulated differentially expressed genes and 719 up-regulated differentially expressed genes. As shown in Figure 2 (2), 353 differentially expressed genes were screened by transcriptome sequencing between the LPS group and the Rolipram + Tadalafil combination group, including 217 down-regulated genes and 136 up-regulated genes.



(1) (2)

Fig. 2. Volcano diagram of differentially expressed genes. (1) Volcano diagrams of differentially expressed genes between the blank control group and the LPS group; (2) Volcano diagrams of differentially expressed genes between the LPS group and the Rolipram + Tadarafel combination group

As shown in Figure 3 (1), the mRNA expression profiles within each group were significantly clustered. The results of clustering between groups showed that the LPS was significantly different from the blank control group, suggesting that the LPS induced BV2 cell inflammation model was successful. The results of the Venn diagram showed that as shown in Figure 3 (2), there were 998 differentially expressed genes between the CON group and the LPS model group, and 353 differentially expressed genes between the LPS model group and the Rolipram + Tadalafil combination (RT) group, of which 198 genes were shared, accounting for 14.66% of the total differential genes, indicating that the combination group had a certain effect on the gene expression of LPS induced inflammation models.

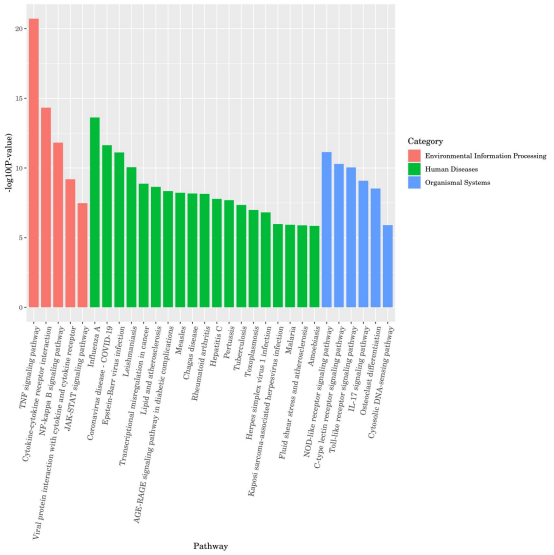


(1) (2)

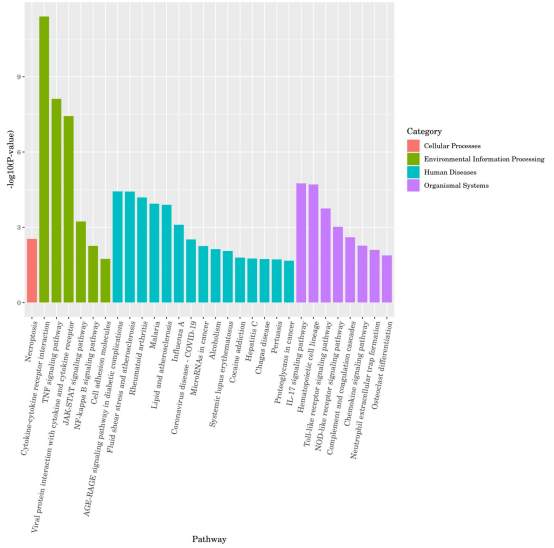
Fig. 3. Clustering and Venn diagram of differentially expressed genes between groups. (1) Cluster analysis heat map; (2) Venn Diagram

3.2 Pathway Enrichment Analysis of Differential Genes in Neuroinflammation Regulated by the Combination of Rolipram and Tadalafil

As shown in Figure 4 (1) and (2), the pathways involved in environmental information processing include TNF signaling pathway and NF-κB signaling pathway. The combination of Rolipram and Tadalafil does not play an independent role in the regulation of neuroinflammation, but is the result of synergistic interaction between various classified signaling pathways.



(1)



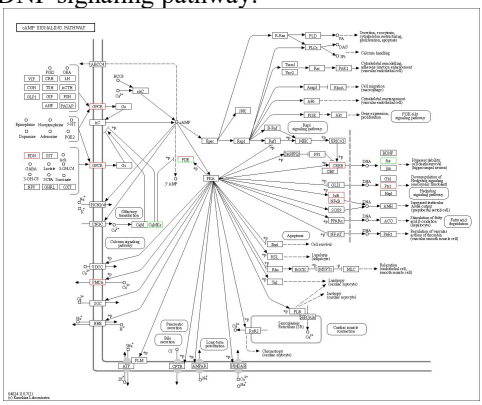
(2)

Fig. 4. KEGG Pathway enrichment results. (1) KEGG Pathway enrichment results in the blank control group and LPS group; (2) KEGG Pathway enrichment results in the LPS group and Rolipram + Tadalafil combination group

3.3 KO Analysis of Differential Genes of Rolipram and Tadalafil in the Regulation of Neuroinflammation

As shown in Figure 5 (1), the cAMP signaling pathway diagram shows that PDE further regulates the downstream signaling cascades of CREB and BDNF by acting

on protein PKA. Similarly, the cGMP signaling pathway, as shown in Figure 5 (2), shows that PDE5 regulates PKG and CREB levels, and then participates in apoptosis and other mechanistic pathways, indicating that PDE can further regulate neuroinflammation and exert neuroprotective effects by increasing the content of cAMP and cGMP, inhibiting the secretion of inflammatory factors, and activating the PKA/PKG/CREB/BDNF signaling pathway.



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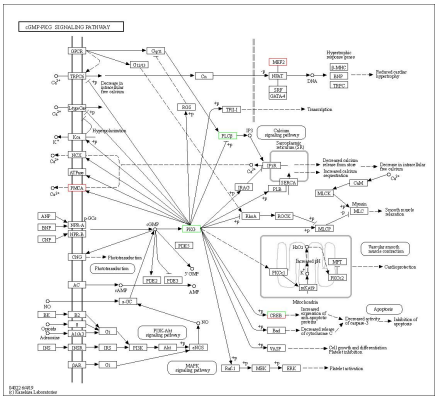

(2)

Fig. 5. Signaling Pathway. (1) cAMP signaling pathway; (2) cGMP signaling pathway

4 Conclusions

RNA sequencing analysis showed that the combination of Rolipram and Tadalafil significantly up-regulated the pathway genes affecting cAMP, cGMP and CREB, and down-regulated the genes affecting TNF signaling pathway. Combined with the analysis of biological information related to neuroinflammation and PDE, it was suggested that cAMP, cGMP, IL-1β, IL-6, TNFα, p-CREB and BDNF played an important role in neuroinflammation and neuroprotective pathways. It lays a foundation for further research on the use of bioinformatics to detect drug activity.

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