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ORIGINAL ARTICLE

Identification of Hub Genes and Pathways Associated with CAR-T Cell-Mediated Neurotoxicity in DLBCL

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SUMMARY

Background: **Severe neurotoxicity after chimeric antigen receptor T cell (CAR-T) therapy can be a crucial life-threatening event in diffuse large B-cell lymphoma (DLBCL), and management of those toxicities is still a serious clinical challenge. The underlying mechanisms of CAR-T cell-mediated neurotoxicity remain poorly elucidated because very few studies examine the intact tumor microenvironment before CAR-T cell infusion. Herein, we purposed to identify differentially expressed genes (DEGs) related to CAR-T cell-mediated neurotoxicity in the DLBCL microenvironment before CAR-T cell infusion and reveal their potential mechanisms.**

Methods: **The mRNA expression profile data of GSE153438 were obtained from the GEO database. The GSE153438 dataset includes 26 samples with non-severe neurotoxicity (grade 0 - 2) and 10 samples with severe neurotoxicity (grade 3 or higher). Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) patway enrichment assessment was carried out. We screened the hub gene by protein-protein interaction (PPI) network analysis and Cytoscape software. Gene set enrichment analysis (GSEA) was also analyzed with the GSEA software. Moreover, the predictive value of the hub gene for severe neurotoxicity was evaluated via receiver operating characteristic (ROC) curve analysis.**

Results: **We identified a total of 25 up-regulated DEGs and 26 downregulated DEGs associated with CAR-T cell-mediated neurotoxicity in the DLBCL microenvironment before CAR-T cell infusion. Results of GO analysis showed that DEGs were mainly enriched in T cell activation, leukocyte cell-cell adhesion, and positive regulation of cell adhesion. The KEGG analysis revealed that DEGs were significantly enriched in T cell receptor signaling pathway, cell adhesion molecules, and Epstein-Barr virus infection. GSEA revealed that the glycolysis pathway was significantly associated with severe neurotoxicity. The top centrality hub gene GZMB was identified from the PPI network. ROC curve analysis showed that GZMB had a potential predictive value for severe neurotoxicity.**

Conclusions: **In DLBCL microenvironment before CAR-T cell infusion, we identified T cell activation and glycolysis pathways significantly associated with CAR-T cell-mediated severe neurotoxicity. GZMB might be used as a predictive and therapeutic molecular marker for neurotoxicity. The study suggested that the tumor microenvironment before CAR-T cell infusion plays an essential role in the early prediction of neurotoxicity.**

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Supplementary Tables and Figures

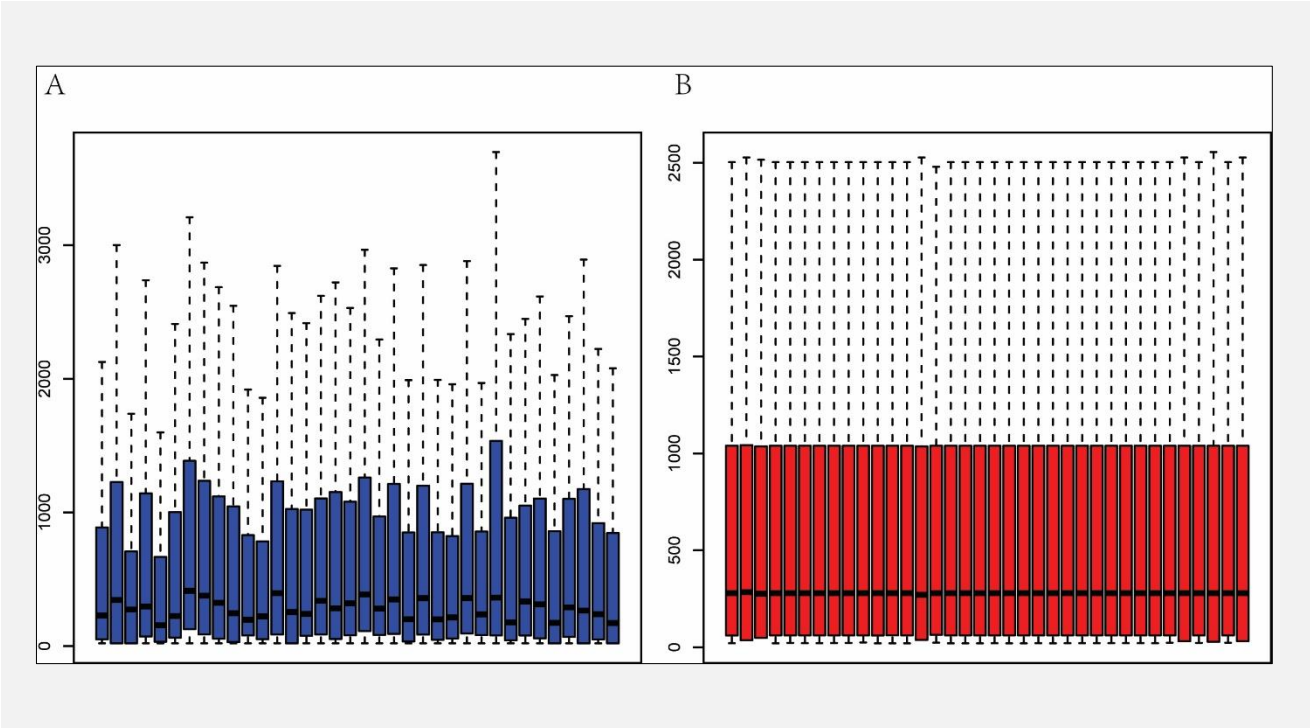

Figure S1. Cassette figures before (A) and after (B) data standardization.

The color scale shown at the top illustrates the relative expression level of an mRNA. Red color represents a high relative expression level, and blue color represents a low relative expression level.