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Expression of platelet membrane glycoprotein receptor GPIb-alpha in diseases and its prognostic value

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Abstract: *Platelets play a crucial role in thrombus formation and hemostasis. Using large public databases such as TCGA, this study analyzed the expression level of GPIb-alpha in diseases and healthy controls. The results showed that compared with normal tissues, the expression level of GPIb-alpha in the disease group was significantly reduced. In addition, patients with high expression of GPIb-alpha had a shorter survival time. There was a significant correlation between the expression of GPIb-alpha and CD8+ T cells (immune infiltration) in most diseases. String analysis revealed interactions between GPIb-alpha and various molecules such as 14-3-3zeta, GPV, and Integrin, among which 14-3-3zeta may be a potential regulatory molecule for thrombosis and hemostasis. In conclusion, the data indicate that the level of GPIb-alpha in disease tissue is lower than that of control, and it may serve as a potential biomarker in diagnosis and prognosis of numerous diseases especially cancers.*

Keywords: *platelet, membrane glycoprotein receptor, GPIb-alpha, disease, expression, prognostic value*

1. Introduction

In the intricate physiological system of the human body, platelets play a pivotal role in hemostasis and thrombosis due to their unique function. GPIb-alpha, being one of the core glycoprotein receptors on the surface of platelet membranes, not only maintains blood homeostasis but is also closely associated with the development of various diseases. With the deepening research on platelet function, the potential value of GPIb-alpha in disease treatment is gradually emerging[1-2].

GPIb-alpha exhibits high affinity towards protein factors exposed after endothelial cell damage, such as VWF and collagen. This affinity enables platelets to rapidly accumulate at the injured site, initiating the hemostatic process. However, excessive activation or deregulation of this mechanism can lead to thrombus formation, thus triggering a range of cardiovascular diseases[3-5]. Therefore, understanding and regulating the function of GPIb-alpha is crucial for preventing and treating thrombotic diseases.

In recent years, the role of platelets in cancer, immune-related diseases, and cardiovascular and cerebrovascular diseases has received increasing attention. As a key receptor of platelets, the potential role of GPIb-alpha in these diseases cannot be ignored. Studying the expression level of GPIb-alpha in diseased tissues, its prognostic value, and its relationship with immune infiltration not only helps reveal the pathogenesis of diseases but also provides potential new drug targets for disease treatment[6-8].

With the rapid development of bioinformatics, big data, artificial intelligence, and machine learning, drug research and development have entered a new era. These advanced technologies provide powerful tools for in-depth research on the structure, function, and disease association of GPIb-alpha. By integrating these information, we can more precisely understand the role of GPIb-alpha in diseases and design more targeted drugs[9-10].

This study aims to comprehensively analyze the expression pattern, functional mechanism, and potential drug targets of GPIb-alpha in diseases using modern bioinformatics methods combined with clinical data. We hope that this study will provide new ideas and methods for the diagnosis and treatment of related diseases and contribute to human health.

In summary, GPIb-alpha, as a key glycoprotein receptor on the surface of platelet membranes, plays a central role in thrombus formation and hemostasis and is closely related to the development of various diseases. This study will delve into the expression level and potential prognostic value of GPIb-alpha in

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diseases, aiming to provide new strategies and methods for future disease diagnosis and treatment.

2. Materials and Methods

2.1 Database Resources

ONCOMINE (www.oncomine.org): A cancer microarray database and integrated data-mining platform for analyzing cancer genomics data. PrognoScan (http://dna00.bio.kyutech.ac.jp/PrognoScan/index.html): An online database for evaluating the relationship between gene expression and prognosis in cancer patients. GEPIA (http://gepia.cancerpku.cn/): An online interactive platform based on TCGA and GTEx projects for analyzing gene expression, mutation, copy number variation, and clinical data. Kaplan-Meier Plotter (https://kmplot.com/analysis/): An online tool for evaluating the impact of gene expression on cancer patient survival rates. TIMER (http://cistrome.org/TIMER/): An online database for analyzing immune infiltration in tumor tissues[11-12].

2.2 Statistical and Analytical Software

R software (version 3.35.0, www.r-project.org): A programming language and environment for statistical computing and graphical display.

3. Methods

3.1 Expression Analysis of GPIb-alpha in Different Diseases Using ONCOMINE

Retrieve the mRNA expression levels of GPIb-alpha in different diseases through the ONCOMINE database. Set a threshold of P-value at 0.001 and a fold change of 1.5 to screen for diseases with significant expression differences[13-15].

3.2 Survival Analysis Using PrognoScan, GEPIA, and Kaplan-Meier Plotter

PrognoScan Analysis: Search all available databases in the PrognoScan database to analyze the relationship between GPIb-alpha expression levels and overall survival (OS) and disease-free survival (DFS). Set a threshold of P-value at 0.05.

GEPIA Analysis: Utilize the GEPIA platform to explore the impact of GPIb-alpha expression on OS and DFS in various cancers.

Kaplan-Meier Plotter Analysis: Analyze the effect of GPIb-alpha expression on overall survival (OS) and recurrence-free survival (RFS) in 21 types of cancers using the Kaplan-Meier Plotter tool.

3.3 Visualization and Summary of Survival Analysis Using R Software and the "forstplot" Package from PrognoScan

Utilize R software and the "forstplot" package from PrognoScan to visualize the results of the above survival analyses and present them in the form of a forest plot.

3.4 Analysis of the Relationship between GPIb-alpha and Immune Cells Using TIMER and GEPIA

TIMER Analysis: Analyze the relationship between GPIb-alpha expression levels and the numbers of six immune infiltrating cell types (B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells) using the TIMER database. Simultaneously, investigate the correlation between GPIb-alpha expression levels and tumor purity.

GEPIA Analysis: Analyze the relationship between GPIb-alpha expression and various immune cell markers using the GEPIA platform to identify potential subtypes of infiltrating immune cells. Select immune cell marker genes from the R&D Systems website and calculate correlation coefficients using the Spearman method.

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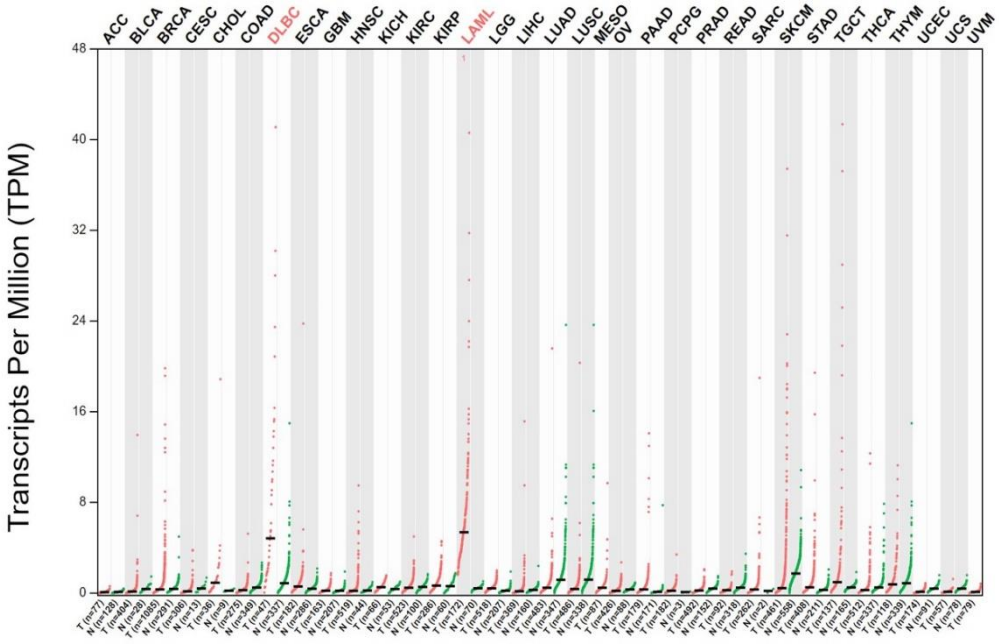
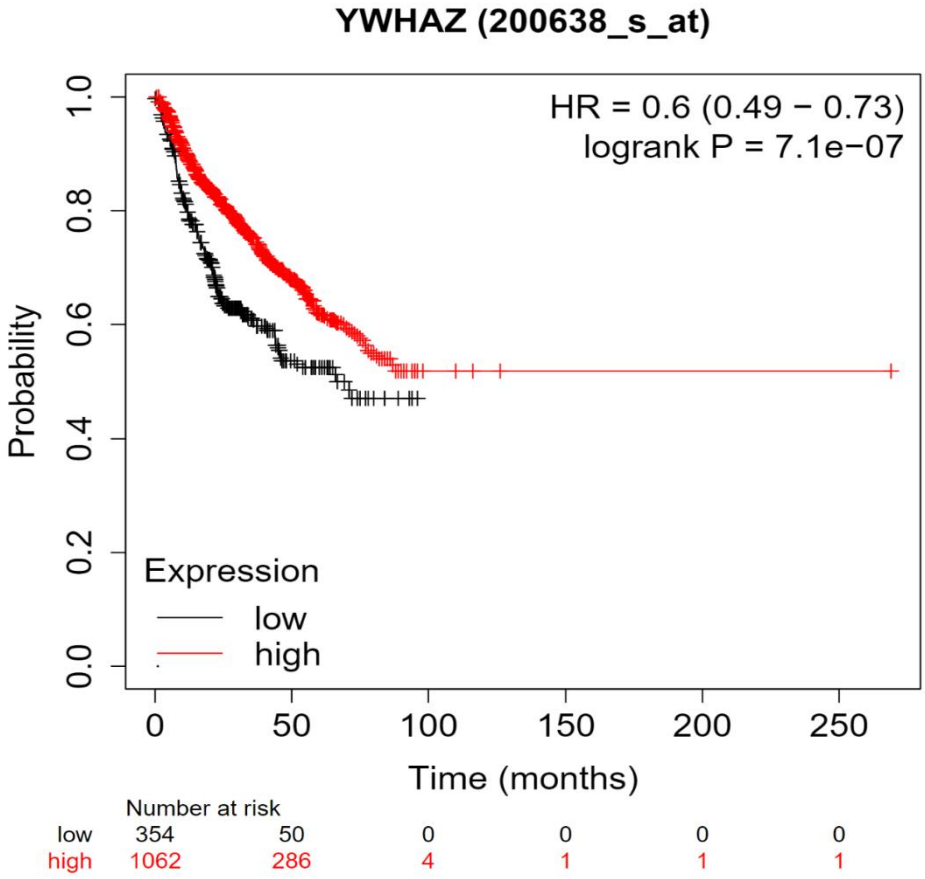
4. Results



T: Tumor, disease patients
N: Normal, healthy people

Figure 1: Comparison of GPIb-alpha expression levels in diseased and normal tissues



Red: high expression group
Black: low expression group

Figure 2: Comparison of the expression levels of YWHAZ in diseased and normal tissues

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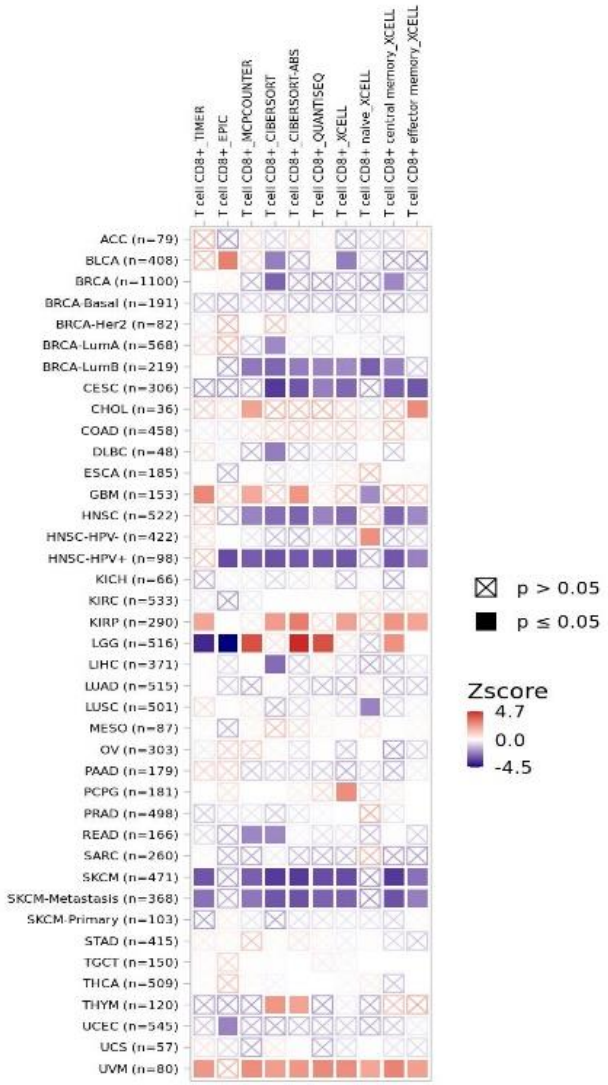

Figure 3: Relationship between GPIb-alpha expression level and immune infiltration in diseases

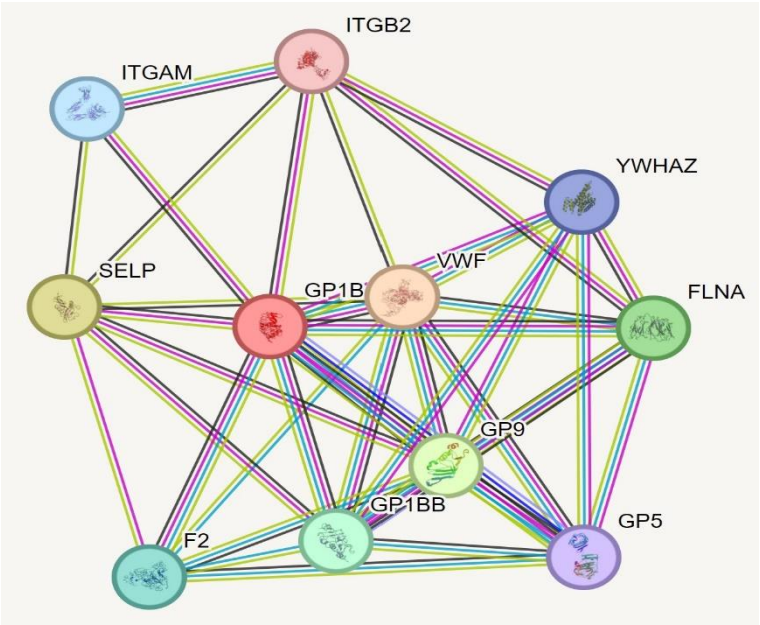

Figure 4: Interacting proteins of GPIb-alpha were analyzed by using String

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4.1 Comparison of GPIb-alpha expression levels between diseased and normal tissues

Through the analysis of the TIMER tool, we found that there are differences in the expression levels of GPIb-alpha among different diseases. When comparing the expression levels between the diseased group and normal individuals, the results in **Figure 1** showed that in most diseases, the expression level of GPIb-alpha in diseased tissues is increased compared to normal tissues. Specifically, among 33 diseases, 11 diseased groups had higher GPIb-alpha expression levels than the normal group, while 16 groups had higher expression levels for the normal group. Another 4 groups of diseases had comparable expression levels with normal tissues. It is worth noting that there is no corresponding normal tissue data for 2 diseases in the TIMER database, so direct comparisons cannot be made.

4.2 Comparison of YWHAZ (14-3-3 protein) expression levels between diseased and normal tissues

Our analysis in **Figure 2** showed that the expression level of 14-3-3 protein (YWHAZ) also varies in diseased tissues. By comparing patient survival time with survival probability, we found that patients with higher expression levels of 14-3-3 protein had a greater survival chance and longer survival time than those with lower expression levels. This suggests that the expression level of 14-3-3 protein may be positively correlated with patient survival rate and survival time, playing a positive regulatory role in the progression of the disease.

4.3 Relationship between GPIb-alpha expression level and immune infiltration

In further exploring the relationship between GPIb-alpha and immune infiltration, we found that there are different correlations between GPIb-alpha and immune cell infiltration in different diseases (as shown in **Figure 3**). In ACC disease, there was no significant difference in immune infiltration between GPIb-alpha and immune infiltration. However, in BLCA disease, GPIb-alpha was positively correlated with immune infiltration of T cell CD8+_EPIC, but negatively correlated with immune infiltration of T cell CD8+ _CIBERSORT and T cell CD8+ XCELL. Similarly, in BRCA disease, GPIb-alpha was negatively correlated with immune infiltration of T cell CD8+ CIBERSORT and T cell CD8+ central memory XCELL. These results suggest that the immune regulatory role of GPIb-alpha may vary among different diseases.

4.4 Prediction of proteins that interact with GPIb-alpha

Using the String tool for protein-protein interaction network analysis, we predicted that proteins that may interact with GPIb-alpha include VWF factor, GP9, F2, GP5, LPSE, ITGAM, ITGB2, YWHAZ, and FLNA (as shown in **Figure 4**). These proteins may participate in regulating biological processes such as cell signal transduction, immune response, coagulation, and platelet activation along with GPIb-alpha. This discovery provides potential targets and directions for further studying the mechanism of GPIb-alpha in the development of diseases.

In summary, our research results show that the expression levels of GPIb-alpha and 14-3-3 protein (YWHAZ) vary in diseased tissues, and these changes may be related to patient survival rates and immune infiltration status. Additionally, we have predicted multiple proteins that may interact with GPIb-alpha, which may play important roles in disease progression. These findings provide valuable clues and evidence for further studying the functions and regulatory mechanisms of GPIb-alpha and 14-3-3 protein in diseases.

5. Discussion

Platelets, as an essential component of blood, have long been recognized for their role in thrombus formation and hemostasis. However, with the advancement of research, platelets have been ascribed to broader functions. Recent studies have revealed that platelets not only participate in thrombus formation and hemostasis but also play a significant role in various physiological and pathological processes such as tumorigenesis, immunology, and obstetric complications. Among them, the important receptor GPIb-alpha on the surface of platelet membranes has garnered significant interest from researchers.

This study focuses on the role of GPIb-alpha in tumorigenesis and immunology, discovering its increased expression in various tumors, which is closely associated with the survival and prognosis of tumor patients. This finding provides a new perspective on tumor diagnosis and treatment. By deeply

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understanding the function and regulatory mechanism of GPIb-alpha, we hope to provide more precise treatment strategies for tumor patients.

Moreover, this study also reveals that the expression level of GPIb-alpha is involved in various physiological and pathological processes such as immune cell infiltration. This discovery provides new clues for understanding the complex mechanisms of the immune system. Immune cell infiltration is a highly complex process involving the interaction of multiple cytokines and the activation of signaling pathways. As an important participant in this process, the study of the function and regulatory mechanism of GPIb-alpha will help us better understand the working principles of the immune system and provide new insights for immunotherapy.

In terms of drug development, targeted drugs against GPIb-alpha hold huge application prospects. Due to its involvement in various physiological and pathological processes of platelets, targeting GPIb-alpha has the potential to treat platelet-related diseases such as thrombosis and tumors. Furthermore, this study identified interaction proteins of GPIb-alpha through String analysis, including 14-3-3zeta, VWF, integrin, and GPV. These interaction proteins provide valuable information for the development of novel drugs. Through further research on these interaction proteins, we hope to discover more drug targets related to GPIb-alpha, providing more options for drug development.

However, this study has some limitations. Firstly, the study mainly relies on clinical databases, lacking validation through clinical and molecular biology experiments. While the clinical databases provide ample data support, the authenticity and reliability of the data still need further experimental verification. Secondly, the study has not yet synthesized and optimized the interaction proteins of GPIb-alpha. Although we have identified proteins interacting with GPIb-alpha, the specific functions and regulatory mechanisms of these proteins require further investigation. Finally, the sample size of this study is limited, and the results need further validation. To obtain more accurate and reliable conclusions, we need to expand the sample size and conduct larger-scale studies.

To address these limitations, future research can be improved and enhanced in several aspects. Firstly, future studies should incorporate clinical and laboratory validations. Through clinical and laboratory studies, we can gain a deeper understanding of the function and regulatory mechanism of GPIb-alpha, providing a more reliable theoretical basis for drug development. Secondly, future studies should synthesize small molecule compounds for research. By synthesizing and optimizing small molecule compounds targeting the interaction proteins of GPIb-alpha, we can provide more candidate drugs for drug development. Finally, future studies need to expand the sample size to further confirm the results and conclusions. By increasing the sample size, we can obtain more accurate and reliable conclusions, providing a more solid foundation for clinical applications.

Additionally, it is worth mentioning that there is some inconsistency between the expression levels of GPIb-alpha analyzed in Oncomine across various diseases and the findings of this study. The data in Oncomine suggests that the expression level of GPIb-alpha is lower in disease groups compared to normal groups. This result conflicts with our study's findings. To explain this inconsistency, we can consider several factors. Firstly, differences in data between different databases may lead to inconsistent results. Different databases may adopt different experimental methods and standards for data collection and processing, resulting in differences in the data. Secondly, the selection and processing of samples may also affect the consistency of the results. When analyzing data, we need to fully consider the impact of sample selection and processing methods on the data results. Finally, differences in experimental methods and techniques may also lead to inconsistent results. Therefore, when analyzing data, we need to consider various factors comprehensively to obtain more accurate and reliable conclusions.

GPIb-alpha, as an important platelet membrane receptor, plays a crucial role in various physiological and pathological processes such as tumorigenesis and immunology. Through deep research on GPIb-alpha, we hope to provide new ideas and methods for the diagnosis and treatment of diseases. However, there are still some limitations in the current study, which need to be continuously improved and perfected in future research. By combining clinical and laboratory studies and expanding the sample size, we can further validate the function and regulatory mechanism of GPIb-alpha, providing a more reliable theoretical basis for drug development. At the same time, we also need to pay attention to the inconsistencies.

In conclusion, the data indicate that the level of GPIb-alpha in disease tissue is lower than that of control, and it may serve as a potential biomarker in diagnosis and prognosis of numerous diseases especially cancers.

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