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Therapeutic Potential of Sel1L and Its Correlation with Immune Cell Profiles in Hepatocellular Carcinoma

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Abstract: The objective of this study is to elucidate the expression patterns of the Sel1L gene and its association with immune cells in hepatocellular carcinoma (HCC), thereby assessing the potential clinical relevance of Sel1L in the diagnosis and targeted treatment of HCC. Utilizing bioinformatics analysis of large-scale data and tissue microarray analysis, we discovered a marked increase in Sel1L protein expression within HCC tissues, implying a significant role in the initiation and progression of liver cancer. Furthermore, we performed enrichment analysis, immunoinfiltration analysis, TISCH and PheWAS analysis to delve into the possible pathways influenced by Sel1L in HCC, its correlation with immune cells, its expression across various cell types, and the potential for pleiotropic effects and side effects as a therapeutic target. Our findings reveal a strong positive correlation between Sel1L expression and the presence of macrophages, CD8+ T cells, and neutrophils, suggesting that elevated Sel1L expression is intricately linked to immune cell quantity and functionality. The PheWAS analysis failed to identify any significant links between Sel1L and other phenotypes, indicating a low likelihood of severe adverse drug reactions or unintended pleiotropic consequences associated with targeting Sel1L in treatment regimens. In conclusion, the Sel1L gene exhibits significantly heightened expression in liver cancer, potentially impacting immune cell counts and functions, positioning it as a promising candidate gene for diagnostic and therapeutic applications in HCC.

1. Introduction

Liver cancer, due to its poor prognosis, high mortality rate, and difficulty in early diagnosis, is a

collective term for various histological types of primary liver tumors, including hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, hepatoblastoma, and gallbladder adenocarcinoma. HCC accounts for approximately 90% of primary liver cancers[1]. China, being significantly impacted by liver diseases, also bears a substantial burden of liver cancer cases. Surgical treatments show potential efficacy in early-stage liver cancer, yet the 5-year survival rate is modest at 50-70% [2-3]. There is a critical need for effective targeted therapies for patients with early-stage liver cancer and poor prognosis, underscoring the significance of identifying new targets for precision medicine in liver cancer.

The Endoplasmic Reticulum (ER) is a structurally complex and functionally adaptable organelle that is pivotal in the regulation of protein homeostasis, lipid metabolism, gluconeogenesis, and calcium homeostasis. As the primary site for protein and lipid synthesis within the cell, the ER also plays a critical role in the distribution of lipids to the cytoplasm and other cellular organelles[4]. The presence of unfolded and misfolded proteins within the ER initiates the Unfolded Protein Response (UPR), a signaling cascade that can induce ER stress, mediated by UPR sensors including PERK, ATF6, and IRE1α. The UPR is designed to reestablish cellular homeostasis; however, if the stress persists, it can precipitate apoptosis[5-6]. The Endoplasmic Reticulum-Associated Degradation (ERAD) system is instrumental in maintaining cellular balance by degrading misfolded proteins, thus preserving ER homeostasis. Sel1L, a core component of the ERAD system, facilitates the transfer of substrates and lectins to the HRD1 protein complex and orchestrates the recruitment, translocation, and ubiquitination of ERAD substrates. Downregulation of Sel1L impairs the degradation of substrates within the ER lumen and membrane[7].

The genesis and progression of HCC are intricately linked to the ERAD system. However, the specific expression patterns and functional roles of Sel1L in HCC remain to be elucidated. This study employs bioinformatics and tissue microarray analysis to assess Sel1L expression in liver cancer and to explore its potential role in the disease's pathogenesis.

2. Materials and methods

2.1 Expression analysis

Downloaded the TPM data of TCGA-LIHC from the UCSC Xena database (https://xenabrowser.net/hub/), which includes data from 369 patients and 50 normal control samples. Additionally, downloaded HCC protein expression data from the NCI Cancer Research Data Commons (CRDC) (https://pdc.cancer.gov/pdc/).

2.2 Tissue microarray immunohistochemistry

A total of 170 cases of hepatocellular carcinoma tissue microarrays were included in the study. After conditional screening of the immunohistochemically stained tissue microarrays and excluding necrotic and exfoliation parts of the tissue, 149 cases of hepatocellular carcinoma patients' tissue samples with corresponding para-cancerous tissues were left. The pathological scoring of the sections was mainly divided into two items: (1) The staining intensity scoring criteria are as follows: No staining 0 points (negative), light yellow 1 point (weakly positive), dark yellow 2 points (moderately positive), and brown 3 points (strongly positive); (2) The scoring criteria for the proportion of positively stained cells are as follows: less than 5% 0 points, 5% to 25% 1 point, 26% to 50% 2 points,

51% to 75% 3 points, and greater than 75% 4 points. The final score is the product of the two. The result judgment rules are: 0 points are counted as (-), 1 to 3 points are counted as (+), 4 to 5 points are counted as (++), and 6 to 9 points are counted as (+++). In this experiment, a total score of ≤1 for the tissue microarray is considered low protein expression, and a score greater than 1 is considered high protein expression.

2.3 Enrichment analysis

To explore the potential pathways of SEL1L in HCC, we first divided the patients with HCC into two groups based on the expression levels of SEL1L, and performed differential analysis. Subsequently, we conducted Gene Set Enrichment Analysis (GSEA) based on the log fold change (lgFC) values obtained from the differential analysis. The gene sets for GSEA were downloaded from the KEGG dataset on the GSEA official website (https://www.gsea-msigdb.org/).

2.4 Immunoinfiltration analysis

Considering the significant role of immune cells in the development and progression of HCC, we subsequently analyzed the correlation between SEL1L and various immune cells in HCC samples using TIMER (http://timer.cistrome.org/).

2.5 TISCH

The TISCH database (http://tisch.comp-genomics.org/) aggregates various public datasets, including 190 datasets and 6,297,320 cells from tumor patients and healthy donors. In this study, we utilized datasets from TISCH to investigate the expression levels of SEL1L in various cell types within Hepatocellular Carcinoma (HCC) at the single-cell level.

2.6 Phenome-wide association analysis

To further assess the polypharmacological potential and possible side effects of SEL1L as a drug target, a Phenome-Wide Association Study (PheWAS) was conducted on the PheWAS website (https://azphewas.com/).

3. Results

3.1 The expression of SEL1L was significantly increased in HCC

After downloading and organizing the TCGA-LIHC data, our analysis found that the mRNA expression of the SEL1L gene was significantly elevated in liver cancer tissues (see Figure 1A). Additionally, we calculated the changes in SEL1L protein expression levels in HCC and similarly discovered a significant increase in SEL1L protein content (see Figure 1B).

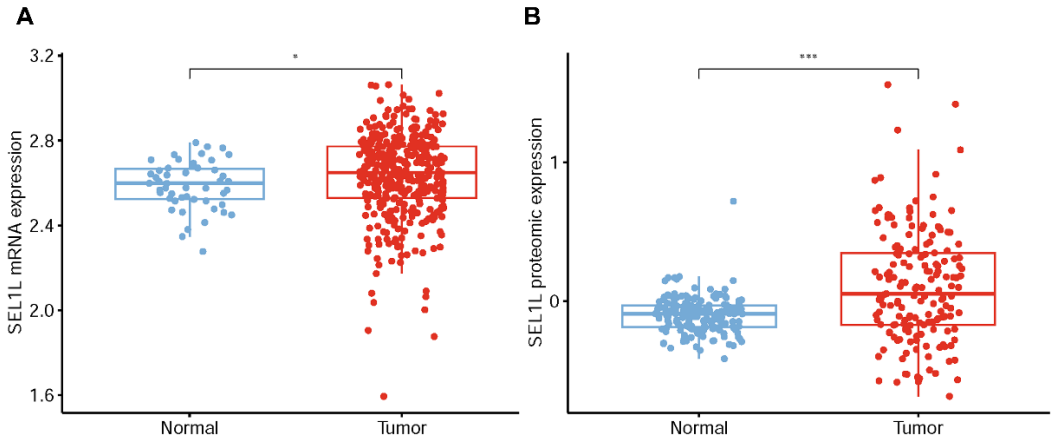

Figure 1: The expression of SEL1L was significantly increased in HCC. (A) The mRNA expression of SEL1L was significantly increased in HCC; (B) The protein expression of SEL1L was significantly increased in HCC (* indicates $P<0.05$, *** indicates $P<0.001$).

Simultaneously, an immunohistochemical study conducted on tissue microarrays from 149 liver cancer samples revealed that the expression of Sel1L protein in hepatocellular carcinoma tissues was higher than in adjacent non-cancerous tissues (see Figure 2A, B). This result suggests that Sel1L plays a certain role in the occurrence and development of liver cancer, and it is worth further investigating the mechanisms by which Sel1L is involved in regulating the onset and progression of liver cancer.

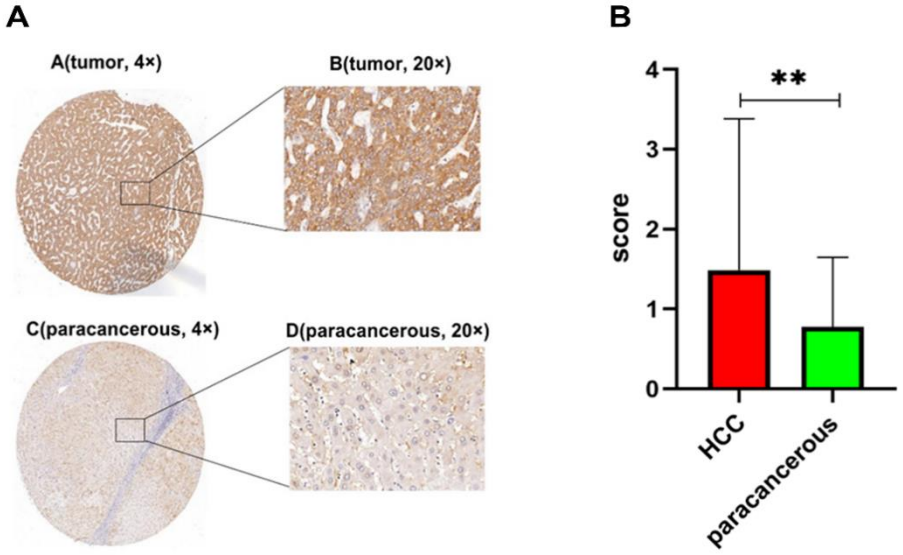

Figure 2: Expression of Sel1L protein in paracancerous and liver cancer tissues. (A) Immunohistochemical expression of Sel1L protein in liver cancer and paracancerous tissues at magnifications of 4x and 20x respectively; (B) Microarray scoring assessment reveals that the protein expression level of Sel1L in liver cancer tissues is significantly higher than in paracancerous tissues (** indicates P<0.01).

3.2 Enrichment Analysis Results

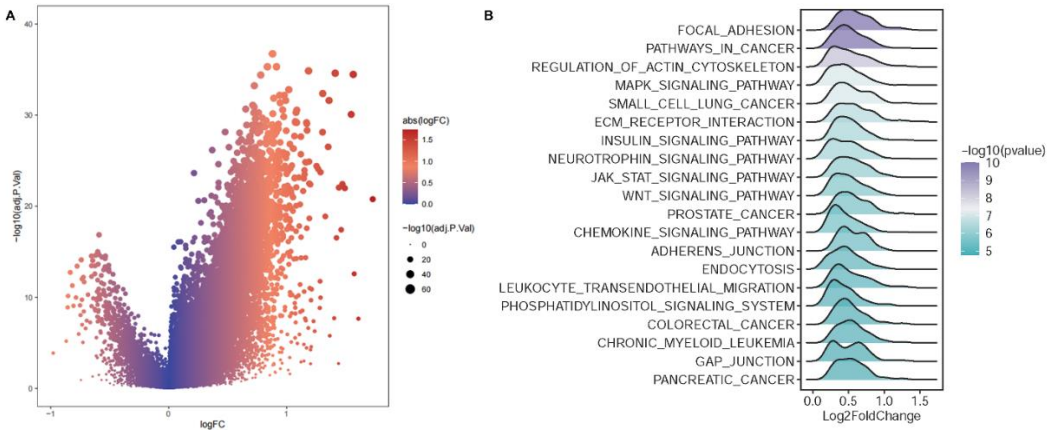

Figure 3: Functional Enrichment Results of SEL1L in HCC. (A) Volcano plot showing the differential analysis between high and low expression groups of SEL1L in HCC; (B) Landscape plot of GSEA enrichment results.

To explore the potential pathways of SEL1L in HCC, we divided the HCC data into two groups based on the expression levels of SEL1L and performed differential analysis (see Figure 3A). We then conducted enrichment analysis on the results and found enrichment in pathways such as Focal adhesion, Pathways in cancer, Regulation of actin cytoskeleton, MAPK signaling pathway, Small cell lung cancer, ECM-receptor interaction, Insulin signaling pathway, Neurotrophin signaling pathway, JAK-STAT signaling pathway, and Wnt signaling pathway, providing clues to understand the potential functions of SEL1L (see Figure 3B).

3.3 Analysis of the Correlation between SEL1L and Immune Cells in HCC

Using the TIMER database, it was found that the expression level of SEL1L in HCC is significantly positively correlated with the content of macrophages, CD8+ T cells, and neutrophils (see Figure 4).

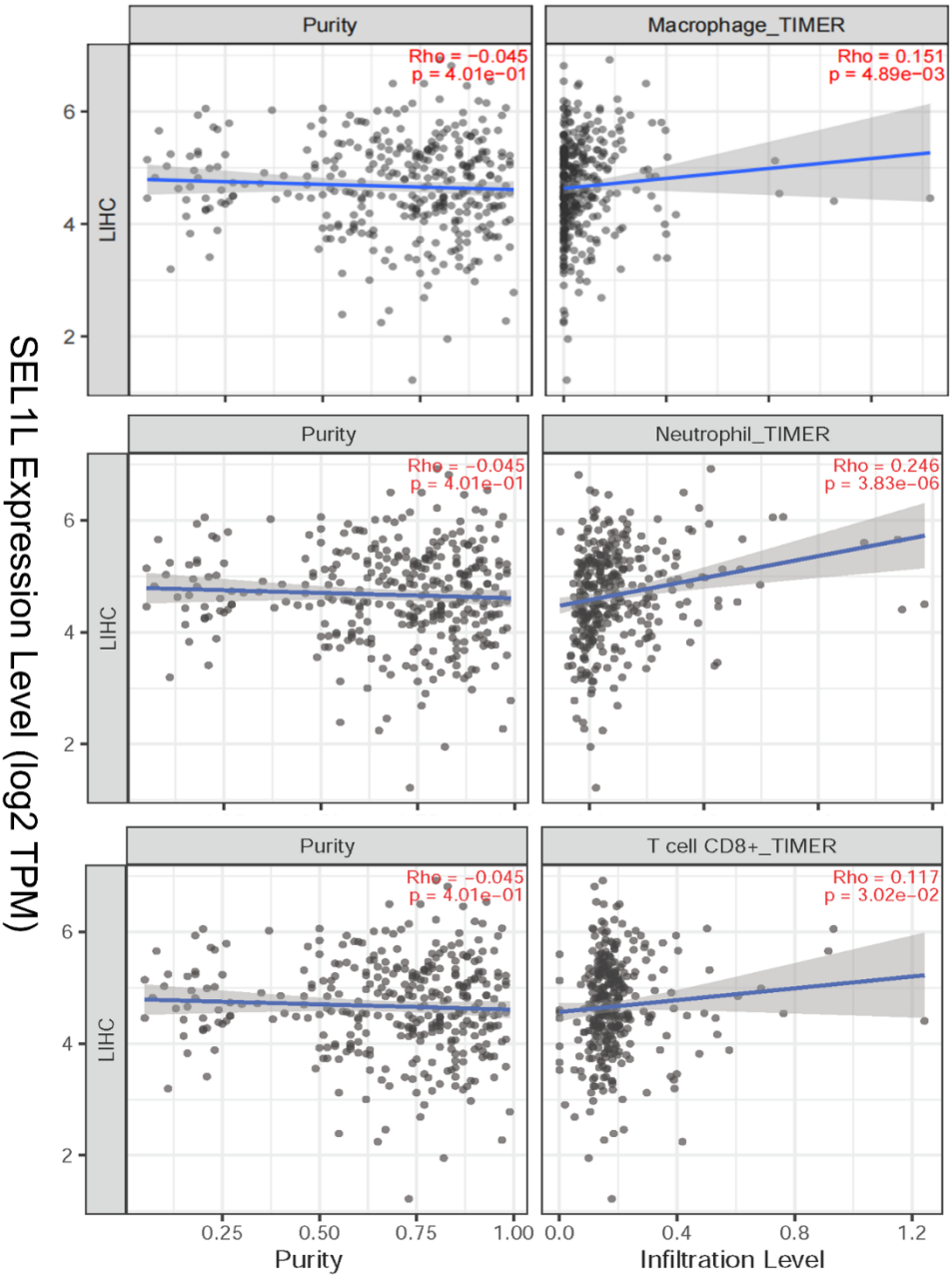

Figure 4: Scatter plots showing the correlation between SEL1L and various immune cells in HCC.

3.4 TISCH

Next, through the TISCH database, it was discovered that the SEL1L gene is primarily expressed in various immune cells in HCC (see Figure 5).

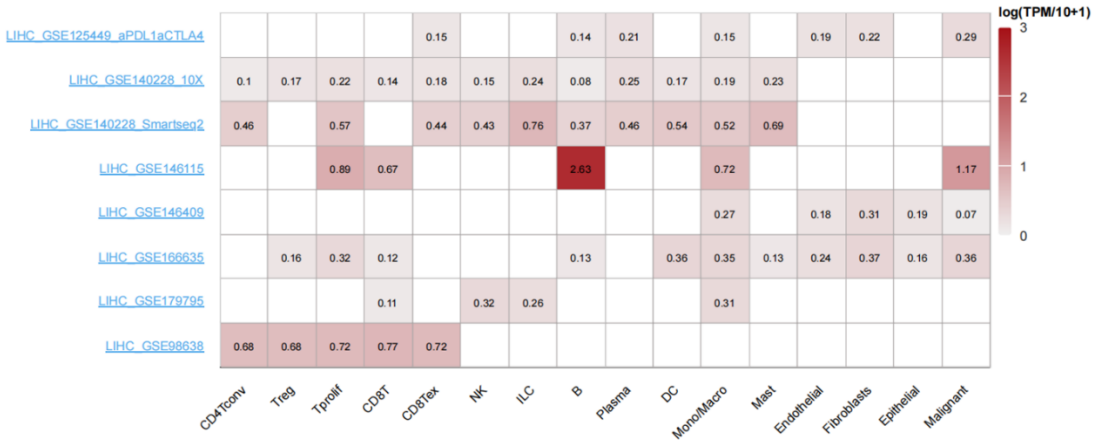

Figure 5: Heatmap of SEL1L expression levels in various cell types in HCC.

3.5 Phewas analysis

To explore whether targeting SEL1L for the treatment of HCC has significant adverse effects on other tissues and organs, we utilized the PheWAS Portal website to conduct a phenome-wide Mendelian Randomization (MR) analysis to identify potential side effects of targeting SEL1L. The results did not find evidence of a significant relationship between SEL1L and other phenotypes. These results suggest that the risk of adverse drug reactions or unexpected pleiotropic effects in the treatment pathway targeting SEL1L is low (see Figure 6).

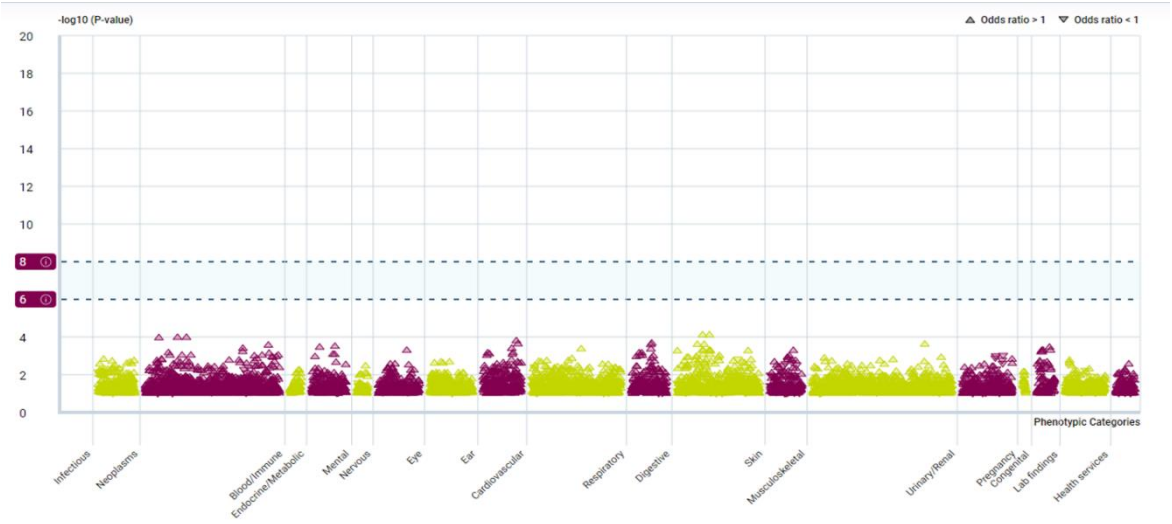

Figure 6: Binary traits PheWAS association with SEL1L.

4. Discussion

The endoplasmic reticulum (ER) is an important site for protein synthesis and lipid metabolism in cells, and ER homeostasis is extremely important for maintaining normal cellular physiological functions [5-6]. The ERAD system is a crucial mechanism within the cell for degrading misfolded and unfolded proteins, thereby maintaining ER homeostasis. Dysfunction of the ERAD system is one of the factors leading to numerous diseases, including viral infections and tumorigenesis. Sel1L is

one of the core genes of the ERAD system and is closely related to pancreatic development, lipid metabolism, and replication of the hepatitis B virus [7-8]. This study, through bioinformatics big data and tissue microarray analysis, found that Sel1L protein is highly expressed in liver cancer tissues, indicating that it plays a certain role in the occurrence and development of liver cancer. In breast cancer patients, the downregulation of Sel1L is significantly correlated with poor prognosis. However, Mellai et al. found that Sel1L is highly expressed in gliomas and is associated with the migration and proliferation of glioma cells [9]. This indicates that the role of Sel1L varies in different types of tumors. Furthermore, Wang et al. found that the expression of endoplasmic reticulum (ER) stress-related markers (including DERL2, EDEM1, SEL1L and HRD1) was significant decrease in HCC tissues[10], This conclusion is contrary to the results of this study, and possible reasons may include the small sample size of their research and the heterogeneity of liver cancer.

HCC is a highly heterogeneous malignant tumor, and its development involves complex interactions with immune cells. HCC can evade immune system surveillance through various mechanisms, including reducing the activity of immune cells and altering the tumor microenvironment, thereby promoting immune escape of the tumor. At the same time, the composition and functional status of immune cells in liver cancer tissue also have a significant impact on the development and prognosis of the tumor[2]. This study found that the expression level of SEL1L in HCC is significantly positively correlated with the content of macrophages, CD8+ T cells, and neutrophils, implying that high expression of Sel1L in liver cancer is closely related to the number and function of immune cells[11].

In summary, the expression of the Sel1L gene is significantly increased in liver cancer, which may affect the number and function of immune cells. The Sel1L gene can be considered a candidate gene for the diagnosis or targeted therapy of liver cancer.

Acknowledgements

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