Immune Landscape of Notch Ligand Delta-Like 1 (DLL1) Overexpression in Diffuse Large B-Cell Lymphoma in The Cancer Genome Atlas

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma (1), with about 40% of cases showing resistance to standard R-CHOP therapy (2). The tumor immune microenvironment (TIME) significantly influences disease progression and treatment response. Our previous research indicated that Notch ligand Delta-like 1 (DLL1) might play a pivotal role in the prognosis of DLBCL through immune system modulation (3). In this study, we conducted in-depth immune profiling of DLL1-overexpressing DLBCL to understand its impact on the TIME.

Objectives

To investigate how DLL1 overexpression affects the tumor immune microenvironment and its potential as a prognostic marker in DLBCL.

Methods

RNA-seq expression data and clinical characteristics from the DLBCL dataset of The Cancer Genome Atlas (TCGA-DLBC) were downloaded from the UCSC Xena platform. The CIBERSORT algorithm evaluated the infiltration of immune cells among the high- and low-DLL1 expression groups. The TIMER2.0 database was used to correlate DLL1 expression with immune cell infiltration, immune inhibitory receptors, and immunosuppressive mediators.

Results

DLL1 was significantly overexpressed ($P<2.22\times10^{-16}$) in the DLBCL samples compared with controls (Fig 1). Increased DLL1 expression was significantly associated ($P<0.05$) with poor primary therapy outcome (Fig 2). The high–DLL1-expression group exhibited significant infiltration by high fractions of $CD8^+$ T cells and M1 and M2 macrophages compared with the low–DLL1-expression group (Fig 3). DLL1 expression positively correlated with M1 and M2 macrophages and $CD8^+$ T cells ($r=0.743$, $r=0.587$, and $r=0.547$, respectively; $P<0.01$ for all) (Fig 4) . DLL1 expression also strongly correlated with inhibitory receptors associated with T-cell exhaustion (PDL1, CTLA4, LAG3, CD244, TIGIT, CD160, BTLA, and TIM3) as well as immunosuppressive mediators (IDO1, IL10, and TGFB) Table1.

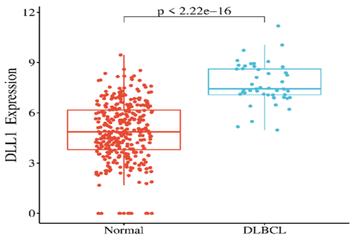


Figure 1. mRNA expression levels of DLL1 in DLBC

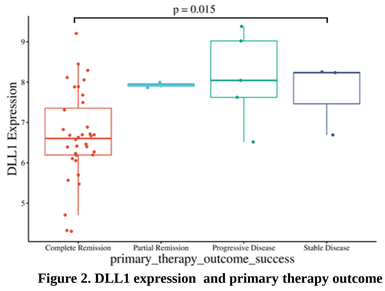


Figure 2. DLL1 expression and primary therapy outcome

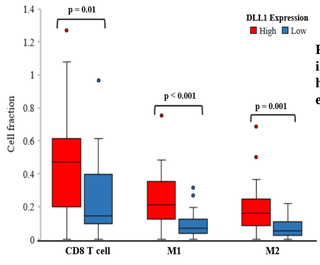


Figure 3. Boxplots of the immune cell fraction by high and low DLL1 expression groups

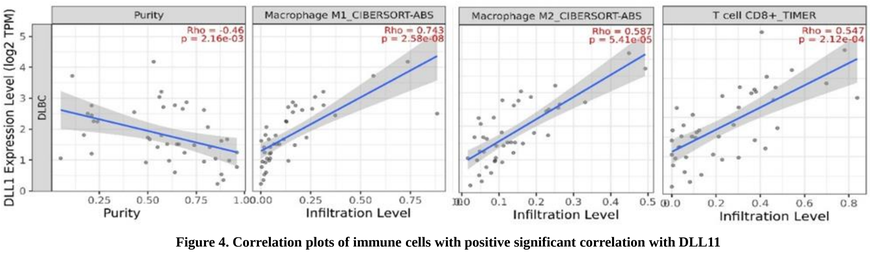


Figure 4. Correlation plots of immune cells with positive significant correlation with DLL11

Gene markers	cor	P
Inhibitory receptors		
PDL1	0.65	p<0.001
TIM3	0.63	p<0.001
LAG3	0.58	p<0.001
BTLA	0.42	p<0.001
CD160	0.55	p<0.001
CD244	0.66	p<0.001
CTLA4	0.47	p<0.001
TIGIT	0.43	p<0.001
Immunosuppressive Mediators		
IDO1	0.70	p<0.001
IL10	0.56	p<0.001
TGFB1	0.67	p<0.001

Table 2. Correlation of DLL1 expression with Inhibitory receptors & immunosuppressive mediators

Discussion

These findings suggest that DLL1 plays a pivotal role in shaping an immunosuppressive microenvironment in DLBCL, potentially contributing to therapy resistance. Further research into the mechanisms of DLL1 could establish it as a valuable prognostic marker and therapeutic target to improve immune responses in patients with DLBCL.

References

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