Expression of Notch Pathways Related Genes and their Association with Clinical Features and Immune System Modulation in Diffuse Large B-cell Lymphoma: A Study Based on TCGA Database

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Background

Diffuse large B-cell lymphoma (DLBCL) represents the most common lymphoma in adults with heterogeneous clinical features and aggressive behavior [1]. Despite that, its etiology remains unknown. Recently, the deregulation of Notch signaling has been found to be crucial for cancer biology through tumor-promoting or suppressing mechanisms [2,3].

Objective

To evaluate the RNA expression level of Notch receptors (NOTCH1-4), canonical Notch ligands either Delta-like (DLL1, DLL3, DLL4) or Serrate-like (JAG1, JAG2), as well as the Notch downstream genes (HES1, HEY1) in DLBCL utilizing online tools and publicly available databases.

Materials & Methods

Data from DLBCL patients and matched healthy controls were retrieved from the TCGA- DLBC (https://portal.gdc.cancer.gov/) and GTEx (www.gtexportal.org/). The expression of the Notch pathway-related genes in DLBCL and controls were compared using Welch's t-test, $p < 0.05$ was considered statistically significant. The association of the Notch members with immune cell infiltration and other common cancer-related pathways was assessed using the TIMER2 database (http://timer.cistrome.org) and GSCALite server (http://bioinfo.life.hust.edu.cn/GSCA/#/), respectively.

References

1. Li S et al. Diffuse large B-cell lymphoma. Pathology. 2018; 50(1):74-87.
2. D'Assoro AB et al. Roles of Notch Signaling in the Tumor Microenvironment. Int J Mol Sci. 2022; 23(11):6241.
3. Anusewicz D et al. Notch Signaling Pathway in Cancer-Review with Bioinformatic Analysis. Cancers (Basel). 2021;13(4):768.

Results

A total of 337 normal blood samples were extracted from GTEx and 48 samples were extracted from TCGA-DLBC (46% were males and 54% were females with a median age of 57.5 years). The clinical stage was available for 42 patients only.; 19% in stage I, 40.5% in stage II, 11.9% patients in stage III, and 28.6% patients in stage IV. The expression levels of NOTCH3/4, DLL1/3/4, JAG1/2, and HEY1 were significantly upregulated in the DLBCL samples compared to the controls. Figure 1.

Moreover, high expression levels of DLL1 were associated with the advanced clinical stage (stage IV). Figure 2

The association between the upregulated Notch receptors and ligands and the infiltration level of immune cells revealed that the NOTCH3, DLL1/4 and JAG1 have a positive correlation with neutrophils and a negative correlation with a regulatory T cell. Figure 3

The pathways analysis indicated that NOTCH3/4, DLL1/4, and JAG1 predominantly activate the EMT pathway. Furthermore, NOTCH4, DLL1, JAG1, and HES1 predominantly inhibit the cell cycle and apoptosis pathways. Figure 4.

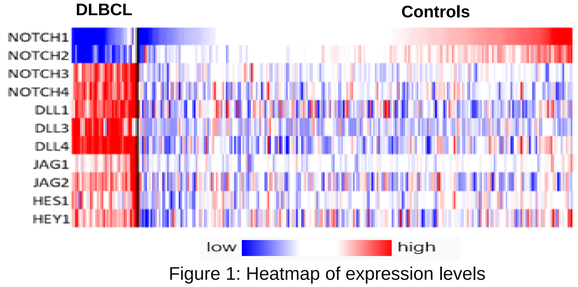


Figure 1: Heatmap of expression levels

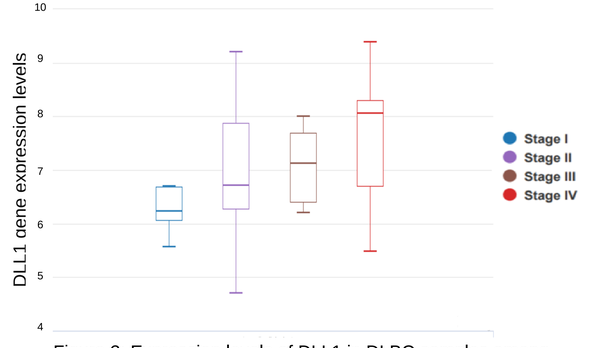


Figure 2: Expression levels of DLL1 in DLBC samples among the clinical stages

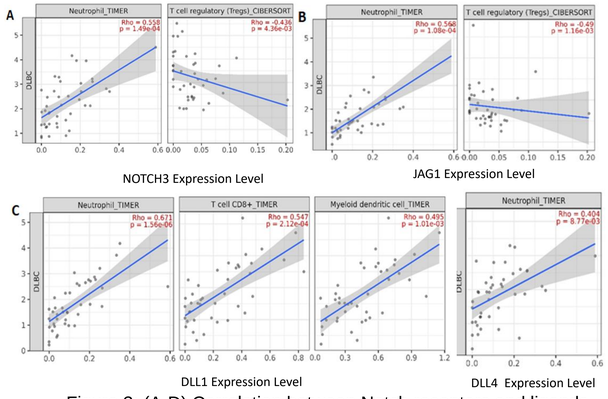


Figure 3: (A-D) Correlation between Notch receptors and ligands and immune cell infiltration in DLBC

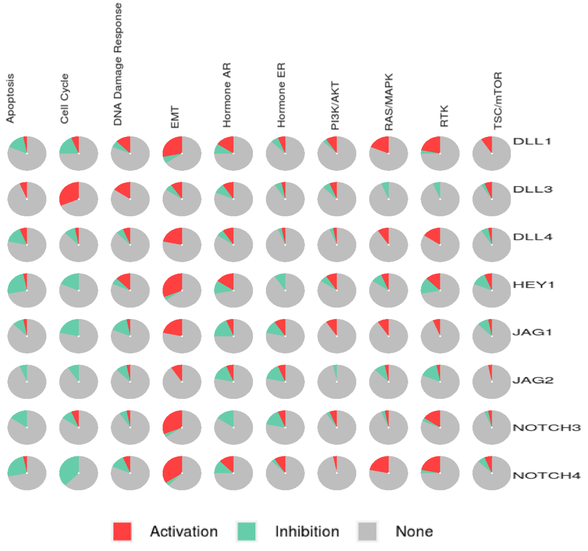


Figure 4 :The relationship between Notch members with well-known cancer-related signaling pathways

Conclusion

These data showed that DLL1 might play a pivotal role in the prognosis of DLBCL through immune system modulation and interaction with cancer-related pathways. This suggests that DLL1 could be a novel prognostic biomarker, risk stratification factor, and attractive therapeutic target for DLBCL.