A MANIFOLD-BASED TOPOLOGICAL APPROACH FOR IDENTIFYING STAGE-DIVERGENT APOPTOTIC SIGNATURES IN DLBCL

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a highly heterogeneous malignancy in which treatment failure is often driven by the complex nature of apoptotic regulatory networks. Standard linear models frequently fail to capture the complex and high-dimensional nature within these pathways across different clinical stages. This study utilized topological data analysis (TDA) to delineate the nonlinear manifold of apoptotic dysregulation in DLBCL, **aiming** to identify major transition states and clusters associated with advanced disease stages.

METHOD

Gene expression profiles with complete clinical staging for DLBCL (n=42) were obtained from The Cancer Genome Atlas (TCGA) DLBCL cohort. A curated gene set (>160 genes) defining the apoptotic signaling pathway was sourced via the Molecular Signatures Database (MSigDB). Dimensionality reduction was performed using principal component analysis (PCA) to generate a bivariate lens for the topological algorithm. A cubical cover (10 intervals, 30% overlap) was applied, with density-based spatial clustering of applications with noise (DBSCAN) serving as the local clusterer. Nodes were colored by clinical stages to visualize the topological relationship between pathway architecture and clinical stage progression.

RESULTS

The resulting mapper graph revealed distinct topological features associated with late stages (iii/iv), characterized by significant convergence in the upregulation of B-cell lymphoma 2 (BCL2)-like 10 (*BCL2L10*) and cystathionine gamma-lyase (*CTH*) genes. Conversely, early stage (i/ii) occupied a dense, lateral topological cluster, suggesting a shared predivergent apoptotic state. The analysis identified a subset of low-stage nodes positioned within high-risk stage branches, indicating a potential topological progression signature that precedes clinical stage escalation.

CONCLUSIONS

This study demonstrates that TDA can bridge the gap between clinical staging and high-dimensional gene expression data, an essential component of collaborative science. By identifying stage-divergent apoptotic signatures, this study can provide a visual framework for optimizing BCL-2 inhibitors and other proapoptotic therapies in a stage-specific manner.

TABLES AND FIGURES

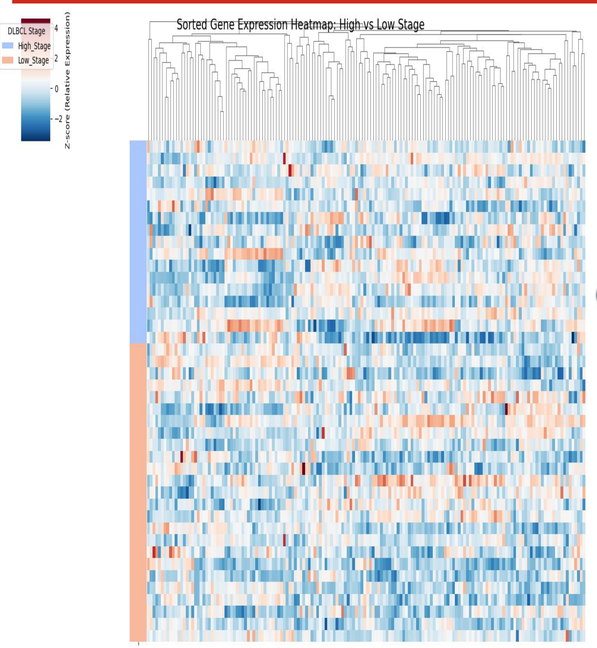

Figure 1: This heat-map shows the apoptotic pathway gene expression in low vs high DLBCL stages

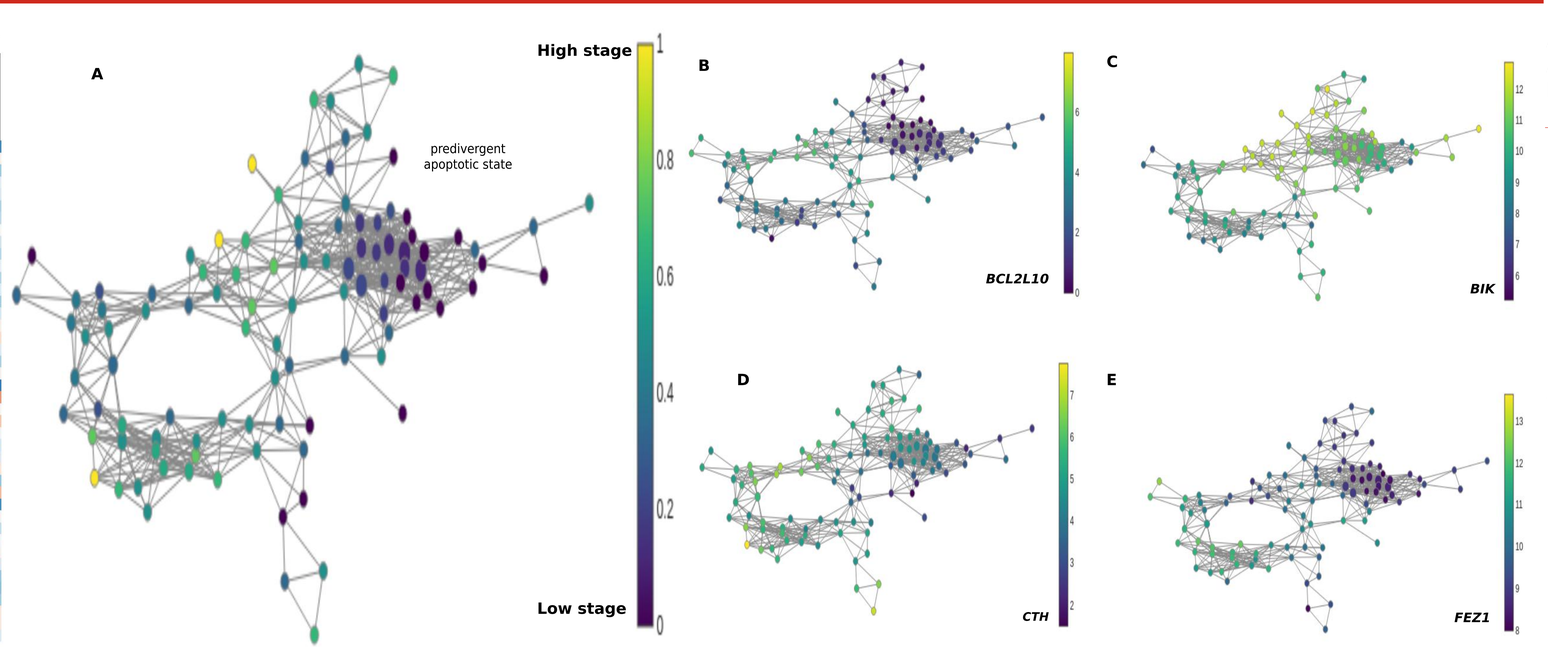

Figure 2. Topological progression signatures and marker gene expression within the study cohort. **(A)** Stage-Based Network Topology: The primary Mapper graph is color-coded by clinical stage progression ranging from Low Stage (0, dark purple) to High Stage (1, yellow). Early-stage (i/ii) samples occupy a dense, lateral topological cluster, indicating a shared, predivergent apoptotic state. Conversely, late-stage (iii/iv) samples reveal distinct topological features and branching. **(B–E)** Candidate Gene Expression Overlays: Node colors correspond to the expression intensity scales (right-hand color bars) for specific key genes across the same network topology: **(B)** *BCL2L10*: Expression profile of B-cell lymphoma 2-like 10, demonstrating convergence and upregulation in the late-stage branches compared to low stage cluster.**(C)** *BIK*: Expression profile of the BCL2-interacting killer gene across the network structure shows higher expression in low stage cluster. **(D)** *CTH*: Expression profile of cystathionine gamma-lyase, showing upregulation overlapping with the late-stage topological features. **(E)** *FEZ1*: Expression profile of fasciculation and elongation protein zeta 1 shows down-regulation in low stage cluster.

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