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Exploring NR4A1-associated transcriptional programs in lymphoma at single-cell resolution

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Diffuse large B-cell lymphoma (DLBCL) represents the most frequent aggressive non-Hodgkin lymphoma and is associated with a five-year survival rate of approximately 50%. The nuclear receptor NR4A1 has been described as a tumor suppressor in DLBCL. In a Myc-driven murine lymphoma model, Nr4a1 deficiency accelerates lymphoma development and induces features of T-cell exhaustion. In human disease, reduced NR4A1 expression correlates with increased PD1/PDL1/PDL2 levels, supporting a link to immune escape. However, the cellular and transcriptional consequences of differential NR4A1 expression within the DLBCL tumor microenvironment remain incompletely defined.

To address this question, we assembled an integrated single-cell atlas combining two public scRNA-seq datasets, one public CITE-seq dataset, and a newly generated dataset from the Graz Lymphoma Cohort. In total, the analysis included 33 DLBCL samples (ABC and GCB subtypes), 18 follicular lymphoma cases, and 13 reactive lymph nodes as non-malignant controls.

Malignant B cells were delineated using inferred copy number variation profiles. Sample-wise NR4A1 expression was quantified through a pseudobulk strategy, and cases were classified as NR4A1-low or NR4A1-high based on first- and third-quartile thresholds. Transcriptomic stratification showed concordance with available immunohistochemical data for the Graz cohort.

NR4A1 status was associated with substantial differences in microenvironmental composition, particularly among T-cell subsets. NR4A1-low samples displayed increased frequencies of exhausted T cells. Differential expression analyses across malignant B cells, exhausted T cells, T helper, and regulatory T-cell populations identified recurrently regulated genes, including RAMMET, SMIM37, and POLR2J3, which were consistently reduced in NR4A1-high cases. Functional enrichment highlighted pathways related to cytokine-mediated cytoskeletal dynamics and cilium organization.

Overall, NR4A1 expression delineates biologically distinct DLBCL subgroups characterized by coordinated tumor-intrinsic transcriptional programs and immune landscape remodeling, supporting a role for NR4A1 in shaping tumor–immune interactions and may inform future therapeutic strategies targeting immune evasion in DLBCL.