Abstract #43 | Poster

NR4A1 Loss Drives Immune Checkpoint Upregulation and CD8$^+$ T Cell Dysfunction in Aggressive Lymphoma

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Aggressive B-cell lymphomas remain a major clinical challenge, with approximately one third of patients relapsing after standard therapy. Immune evasion contributes substantially to treatment resistance. Low NR4A1 expression correlates with inferior survival in lymphoma patients, while its overexpression suppresses tumor growth in vivo, suggesting tumor suppressive properties. To define its role in tumor immunity, we intercrossed EμMyc mice with Nr4a1$^{-/-}$ mice and evaluated lymphoma development and immune surveillance. Nr4a1 loss significantly accelerated lymphomagenesis in vivo. Lymphoma cells derived from EμMyc Nr4a1$^{+/+}$ and Nr4a1$^{-/-}$ mice were transplanted into immunocompetent C57BL/6 or immunodeficient Fox Chase SCID beige recipients. Nr4a1-deficient lymphomas induced rapid disease progression and reduced survival in immunocompetent hosts, whereas differences were attenuated in immunodeficient recipients, indicating immune-dependent tumor control. Mechanistically, Nr4a1 loss was associated with increased expression of components of the PD-1/PD-L1/PD-L2 and CTLA-4/CD80/CD86 axes. In immunocompetent mice, Nr4a1 deficiency resulted in increased splenic malignant B-cell infiltration, reduced CD3$^+$ T-cell infiltration—including CD4$^+$ and CD8$^+$ subsets—and enrichment of M2 macrophages and regulatory T cells, consistent with an immunosuppressive tumor microenvironment. Notably, a higher proportion of CD3$^+$ T cells co-expressed multiple inhibitory receptors, including PD-1, indicative of T-cell exhaustion. Functional co-culture assays using OVA$_{257–264}$ peptide-pulsed lymphoma cells and OT-I CD8$^+$ T cells demonstrated significantly impaired T cell–mediated lymphoma cell killing in the absence of Nr4a1. Translational analysis of a human DLBCL cohort revealed that low NR4A1 expression correlated with increased immune checkpoint component expression, mirroring the murine phenotype. Collectively, these findings identify NR4A1 as a critical regulator of immune checkpoint expression and CD8$^+$ T-cell function in aggressive lymphoma. Loss of NR4A1 promotes an immunosuppressive, checkpoint-enriched tumor microenvironment that facilitates immune escape and accelerates lymphoma progression, providing a mechanistic rationale for therapeutic strategies combining immune checkpoint blockade with approaches aimed at restoring NR4A1 activity.