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Straight-Line to Relapse: How an Aligned Extracellular Matrix Makes Neuroblastoma Therapy-Resistant

Neuroblastoma, the most common extracranial pediatric tumor, accounts for 15% of childhood cancer-related deaths, primarily due to disease relapse. Neuroblastoma exhibits two switchable cellular identities: mesenchymal (MES) and adrenergic (ADRN). The MES state is significantly more invasive and therapy-resistant than the ADRN state, suggesting that the ADRN-to-MES transition contributes to relapse and poorer clinical outcomes. However, the mechanisms by which neuroblastoma defines the therapy-resistant MES state and modulates this transition remain poorly understood.

The extracellular matrix (ECM)—a three-dimensional network of macromolecules—acts as both a physical scaffold and a regulator of oncogenic signaling. We observed that high-risk and relapsed neuroblastoma, which likely contain a larger MES subpopulation, exhibit ECM with distinct, well-aligned structures compared to low-risk neuroblastoma. Consequently, we hypothesized that this aligned ECM drives the ADRN-to-MES transition.

To test this, we utilized a nanofabricated surface with grooved arrays as an in vitro model to replicate the topographical features of aligned ECM. Using this model, we discovered that aligned ECM induces neuroblastoma cells to adopt enhanced MES features while suppressing ADRN signatures. Specifically, the aligned ECM stimulates the YAP signaling pathway, which promotes the epigenetic silencing of ADRN signature genes and the upregulation of MES signature genes. These findings identify the tumor microenvironment's ECM as a signaling hub that drives neuroblastoma relapse, representing a promising target for future therapeutic intervention.

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