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MYC Drives Temporal Evolution of Small Cell Lung Cancer Subtypes by Reprogramming Neuroendocrine Fate

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Summary

Small cell lung cancer (SCLC) is a neuroendocrine tumor treated clinically as a single disease with poor outcomes. Distinct SCLC molecular subtypes have been defined based on expression of ASCL1, NEUROD1, POU2F3, or YAP1. Here, we use mouse and human models with a time-series single-cell transcriptome analysis to reveal that MYC drives dynamic evolution of SCLC subtypes. In neuroendocrine cells, MYC activates Notch to dedifferentiate tumor cells, promoting a temporal shift in SCLC from ASCL1+ to NEUROD1+ to YAP1+ states. MYC alternatively promotes POU2F3+ tumors from a distinct cell type. Human SCLC exhibits intratumoral subtype heterogeneity, suggesting that this dynamic evolution occurs in patient tumors. These findings suggest that genetics, cell of origin, and tumor cell plasticity determine SCLC subtype.