

ASCL1-Driven Methionine Metabolism Is a Therapeutic Vulnerability in Neuroendocrine Prostate Cancer

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Introduction: Androgen receptor (AR) pathway inhibitors (ARPIs) have improved survival in patients with castration-resistant prostate cancer (CRPC). However, ~20% relapse with AR-independent tumours that activate alternative lineage programs and progress to aggressive neuroendocrine prostate cancer (NEPC), for which no targeted therapies exist. NEPC progression is characterized by limited genomic aberrations, distinct epi-transcriptomic reprogramming, and activation of lineage plasticity, which relies on intracellular metabolites as substrates and cofactors. We previously identified the transcription factor ASCL1 as a driver of lineage plasticity and neuroendocrine differentiation. Whether lineage plasticity is accompanied by a distinct metabolic program, whether ASCL1 controls this program, and whether it constitutes a therapeutic vulnerability remain unknown. We postulate that epigenetic remodelling and metabolomics rewiring may work in concert to drive lineage plasticity and NEPC progression and that ASCL1-orchestrated S-adenosylmethionine (SAM) availability is intimately linked to the chromatin state of lineage plasticity.

Method: We profiled transcriptomic and chromatin-accessibility landscapes using RNA-seq and ATAC-seq, respectively; global metabolism and methionine flux using LC-MS-based metabolomics and heavy isotope tracing; and ASCL1 binding using ChIP-seq and CUT&RUN across cell lines, patient-derived organoids, and patient-derived xenografts (PDXs) representing CRPC, lineage plasticity, and NEPC.

Results: Metabolomic profiling of PDXs and cell lines revealed a distinct metabolic state associated with lineage plasticity and NEPC compared with CRPC. Methionine and its downstream metabolite SAM, the universal methyl donor, were coordinately elevated in NEPC and metaplastic states across PDXs, cell lines, and ASCL1-high small cell lung cancer. Gain- and loss-of-function studies demonstrated that ASCL1 was both necessary and sufficient to drive methionine metabolism. Methionine tracing further demonstrated that ASCL1 loss reduced SAM and SAH flux. Targeting methionine metabolism through pharmacologic inhibition or methionine restriction depleted SAM, remodelled the chromatin landscape, reduced ASCL1 and neuronal identity programs, and suppressed proliferation.

Conclusion: While much focus has been placed on the impact of epigenetic writers and erasers, less is known about the regulation of metabolic pathways that impact epigenetics and provide the fuel for this machinery. Our findings established that ASCL1 orchestrates a coordinated metabolic and epigenetic program that facilitates the emergence of NEPC. Disrupting this axis collapses ASCL1 and neuronal identity, exposing a therapeutic vulnerability in NEPC.

Impact: By defining how ASCL1 couples a metabolic switch to epigenetic reprogramming during neuroendocrine differentiation, this work nominates methionine-cycle disruption as a strategy to target lineage plasticity and NEPC.

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