ASCL1-DRIVEN EPIGENETIC AND METABOLOMICS PROGRAMS IN NEUROENDOCRINE PROSTATE CANCER

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Background: Androgen receptor (AR) pathway inhibitors (ARPIs), such as enzalutamide (ENZ), have significantly improved survival for castration-resistant prostate cancer (CRPC) patients. However, ~20% relapse with AR-independent tumours, exhibit activation of alternative lineage programs, and progress to aggressive neuroendocrine prostate cancer (NEPC) without targeted therapies. This progression, characterized by the limited genomic aberrations, distinct chromatin state, and DNA methylation patterns unique to NEPC, strongly suggests that NEPC is driven by lineage plasticity and epi-transcriptomic reprogramming. Our previous work identified the transcription factor (TF) ASCL1's essential role in lineage plasticity, influencing the chromatin landscape in favour of NEPC. We previously reported that ASCL1 regulates EZH2 activity and H3K27me3. However, we noticed that ASCL1 knockdown influences global histone methylation, beyond H3K27me3. Exploring the dichotomy between NEPC ASCL1-low and ASCL1-high patients, we found ASCL1-high to be associated with metabolic processes supporting the biosynthesis of S-adenosylmethionine (SAM), the universal methyl donor, suggesting that ASCL1 may mediate epigenetic plasticity via the rewiring of metabolic fluxes. Altogether, we hypothesize that ASCL1 may facilitate the interplay between metabolome and epigenome to support NEPC phenotype. However, the mechanism by which ASCL1 dictates cell fate through epigenome and metabolome is unknown.

Method: We investigated ASCL1's impact on the metabolome and epigenome by measuring changes in transcriptomic using RNA-seq, chromatin accessibility using ATAC-seq, metabolism using LC-MS and ASCL1 binding using ChIP-seq in a panel of NEPC cell lines and patient-derived xenografts.

Results: We observed that pathways related to methionine metabolism and methylation were reduced following ASCL1 knockdown. Therefore, we evaluate the metabolomic landscape of $ASCL1^{high}$ and $ASCL1^{low}$ NEPC in a small group of patient-derived NEPC xenografts. Metabolomic profiling showed a unique profile in $ASCL1^{high}$ NEPC, distinct from $ASCL1^{low}$. Further investigating this, we showed that ASCL1 regulates the methionine cycle and SAM availability, whereas ASCL1 over-expression increased methionine and SAM. Conversely, its knockdown reduced methionine and SAM, mimicking a methionine-deprived condition.

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 preliminary data suggests that ASCL1 may orchestrate a symphony of metabolic and epigenetic regulation to support methionine metabolism and NEPC phenotype.

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