Integrative transcriptomic and metabolomic analysis provides insights into metabolic reprogramming by UDP-glucose dehydrogenase

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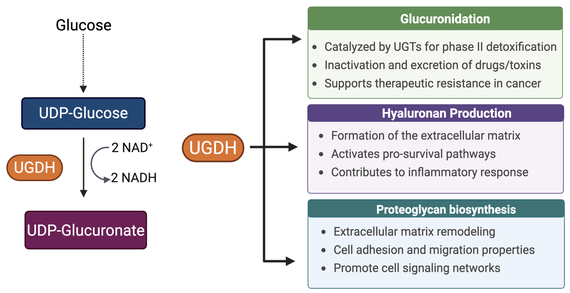
Background

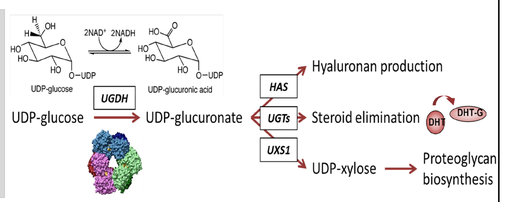
- Increased glucose consumption is a hallmark of tumorigenesis
- UDP-GlcA is a precursor for glucuronidation, proteoglycan production, and hyaluronan biosynthesis
- UGDH is elevated in prostate cancer (PC) tumor biopsies and important for maintaining androgen homeostasis[1,2]
- Knockdown of UGDH restores sensitivity of castration resistant PC cells to therapeutic resistance[2,3]
- UGDH promotes cell migration, invasion, and metastasis[4]
- Understanding its impacts on multiple signaling pathways in prostate cancer will support its role as a therapeutic target[4]

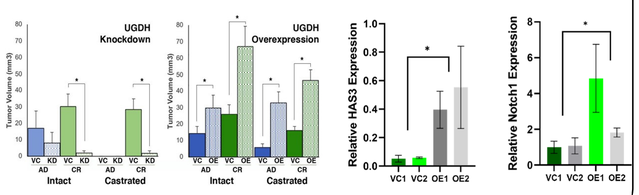
UDP-GlcA priority is directed by UGDH



UGDH drives transition to CRPC

UGDH OE drives tumorigenesis via UDP-GlcA production along with increased expression of HAS3 and ECM components, Notch1





**Dr. Brenna Zimmer

Hypothesis

UGDH is a dynamic sensor that integrates cellular metabolic needs to direct UDP-GlcA priority. UGDH activity influences downstream canonical and noncanonical signaling pathways to promote tumorigenesis.

Experimental design and differential gene expression analysis

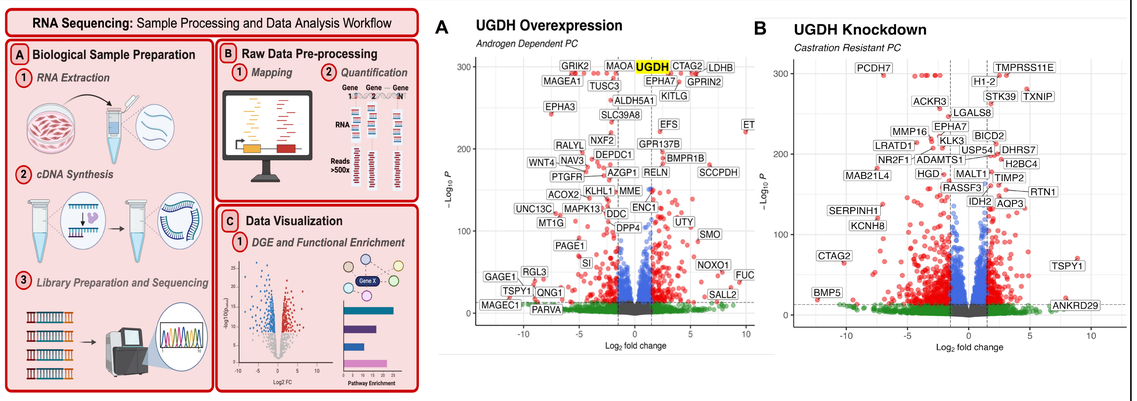


Figure 2. UGDH expression significantly alters the transcriptome. Volcano plots of differentially expressed genes (DEGs) in AD clones overexpressing UGDH (A) and (B) CR clones with UGDH knockdown, all compared to vector control. Cutoff for DEGs set to FDR<0.05 and $log_2FC>1.5$

UGDH significantly impacts key growth control and oncogenic pathways

Figure 3. Gene Set Enrichment Analysis (GSEA) of hallmark pathways impacted by UGDH expression. UGDH AD cell model with UGDH overexpressed (A), UGDH KD (B), and CR line with UGDH KD (C). Analysis done in R using *enrichR*. Genes ranked by stat metrics, adj. P-value cutoff set to <0.05 and NES> 1

UGDH manipulation alters cellular priorities and results in cellular dysfunction

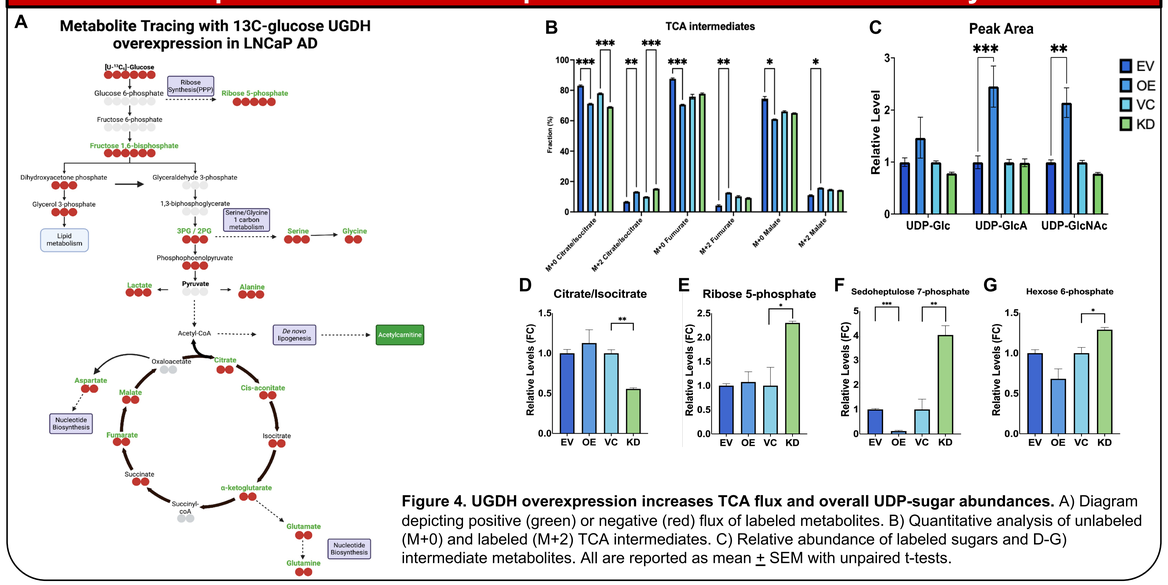


Figure 4. UGDH overexpression increases TCA flux and overall UDP-sugar abundances. A) Diagram depicting positive (green) or negative (red) flux of labeled metabolites. B) Quantitative analysis of unlabeled (M+0) and labeled (M+2) TCA intermediates. C) Relative abundance of labeled sugars and D-G) intermediate metabolites. All are reported as mean ± SEM with unpaired t-tests.

UGDH influences key noncanonical pathways

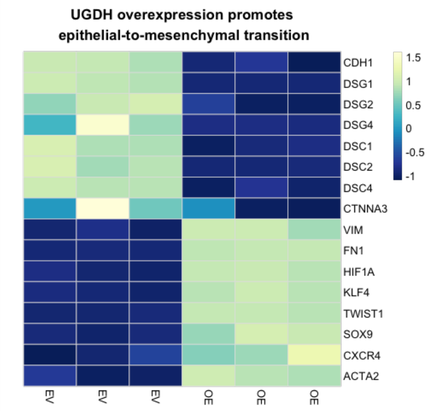


Figure 4. EMT marker expression impacted by UGDH overexpression. Enrichment of EMT markers and downregulation of tumor-suppressor and epithelial-related genes. Plotted using *pheatmap* in R. Unsupervised clustering of Z-score from normalized counts

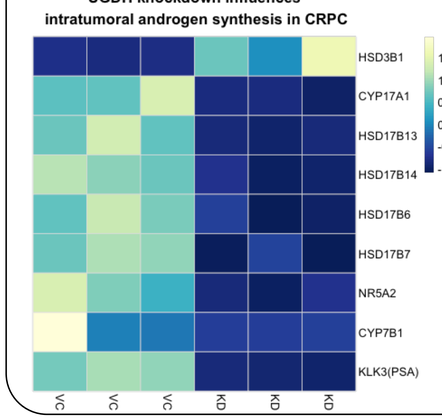


Figure 5. UGDH knockdown alters backdoor androgen synthesis pathways. Intratumoral androgen synthesis markers upregulated in CRPC to circumnavigate androgen dependence. Plotted in R. Unsupervised clustering of Z-score from normalized counts.

Conclusions

1) UGDH significantly influences the PC transcriptome.
2) Increased UGDH expression elevates pro-tumorigenic pathways and metabolites, promoting tumor aggressiveness.
3) Targeting UGDH expression in CRPC results in reduced expression of backdoor androgen synthesis genes, providing new insight to the mechanisms underlying increased CR sensitivity to androgen deprivation therapy with UGDH knockdown.

References

1. Huang, D, et al. (2010). Udp-glucose dehydrogenase as a novel field-specific candidate biomarker of prostate cancer. International Journal of Cancer, 126(2), 315-327.
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Acknowledgements

Next-generation sequencing was performed by NCSU Genomic Sciences Laboratory (Raleigh, NC, USA) using the Illumina NovaSeq 6000.