Dissecting metabolic pathways in RCC mouse models

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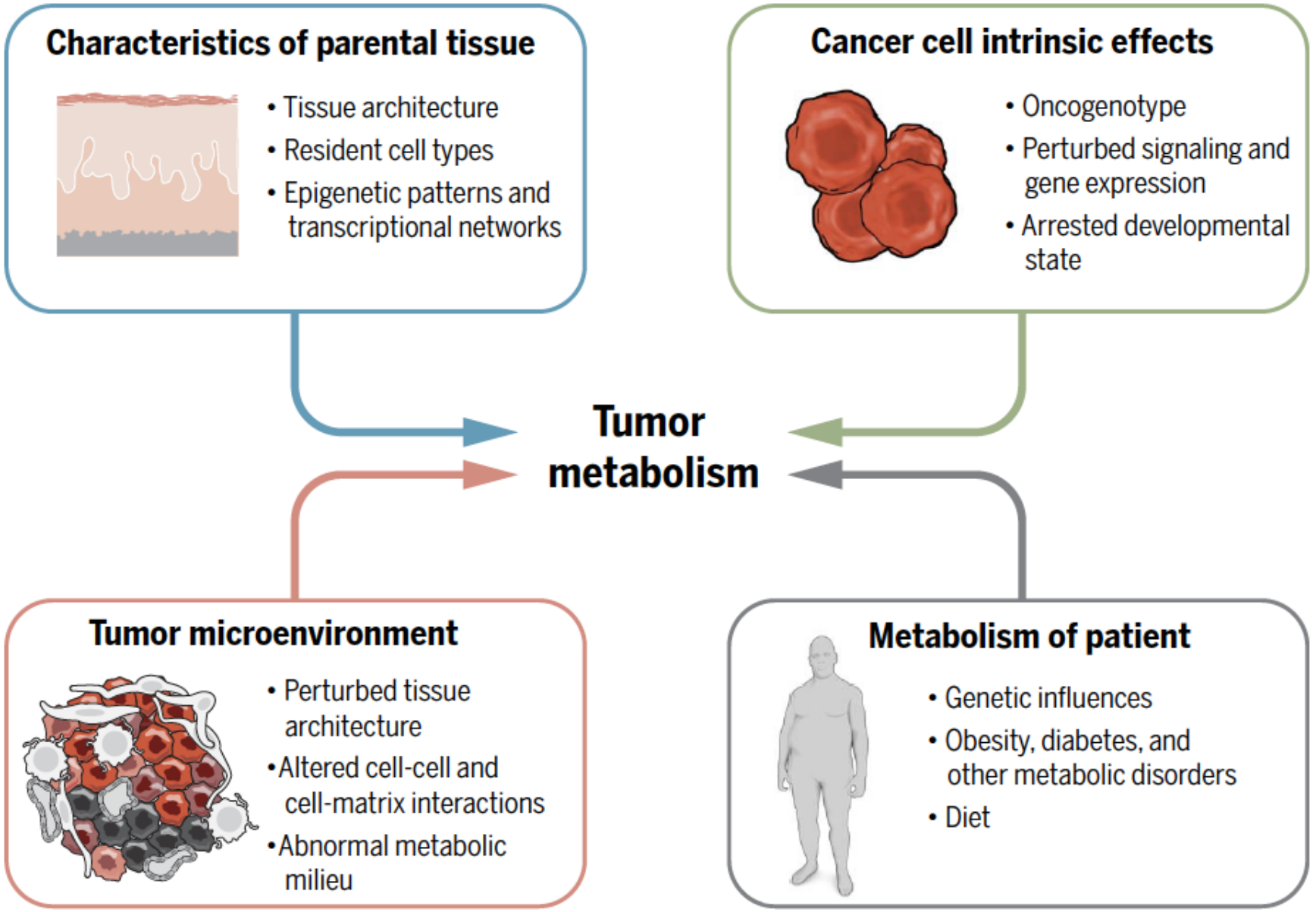
Several comments relevant to cancer metabolism

- “All models are wrong, but some are useful.”
- “Heterogeneity is a significant challenge.”
- “How do we assess a model’s fidelity to human cancer?”
- “ ‘Perfect’ can be the enemy of ‘good enough.’ ”

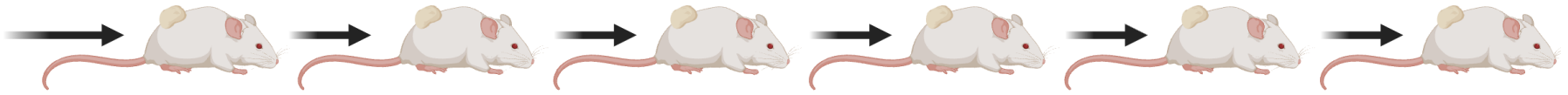
Cancer metabolism depends on factors intrinsic and extrinsic to the tumor cell



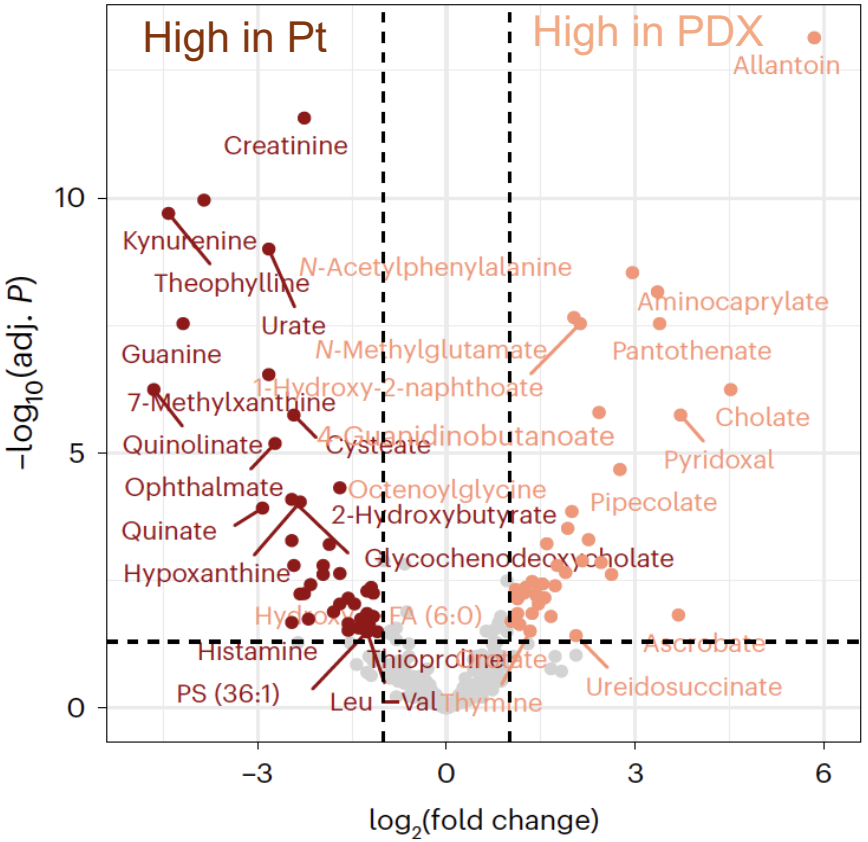
Faubert et al., 2020 (PMID 32273439)

Metabolomic divergence and conservation in patient-derived melanoma xenografts

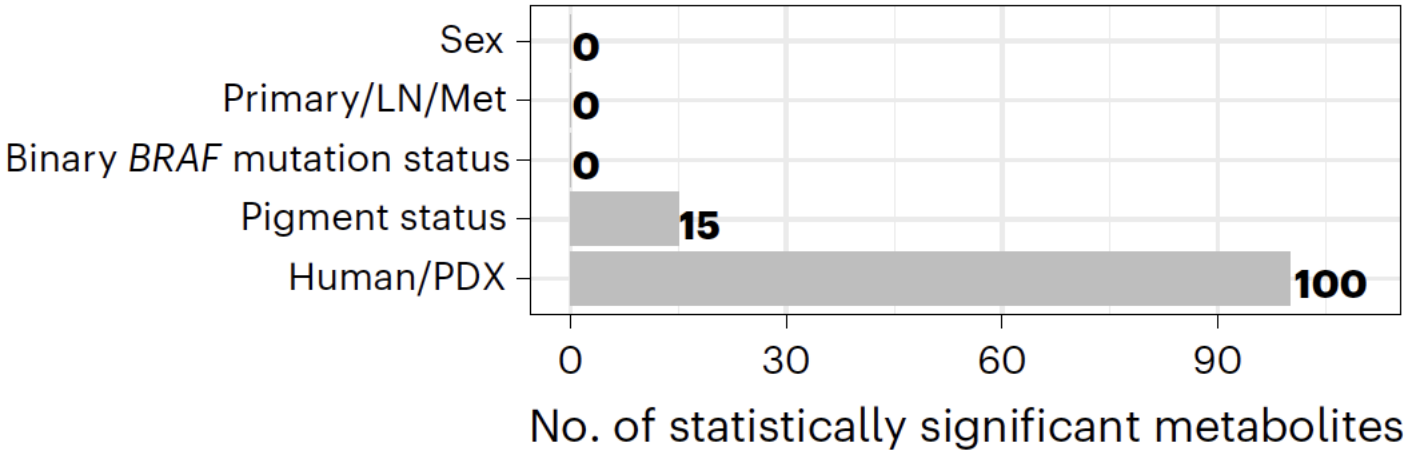
Transplant melanoma cells to mouse, then passage in mice



Rao AD et al., 2025 (PMID 40731149)



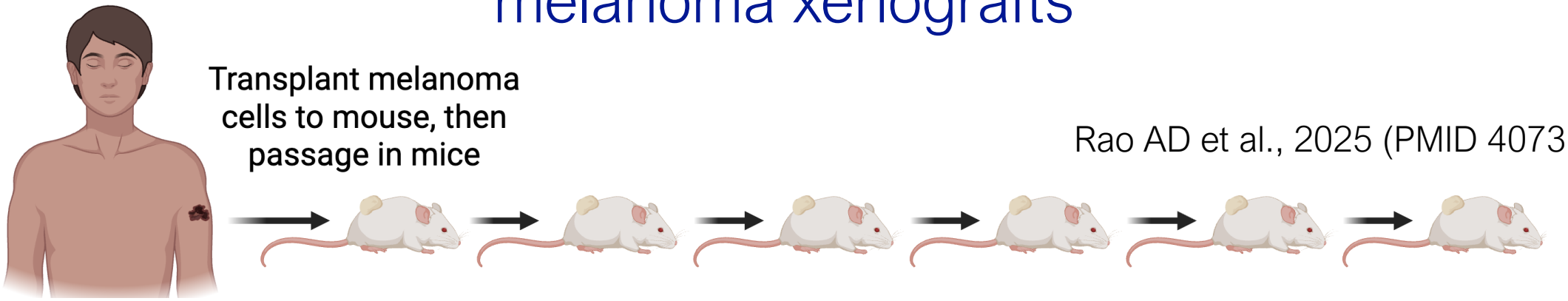
18 patients x early-passage PDX



Urate —*Urate Oxidase*→ Allantoin

(In mice but not humans)

Metabolomic divergence and conservation in patient-derived melanoma xenografts



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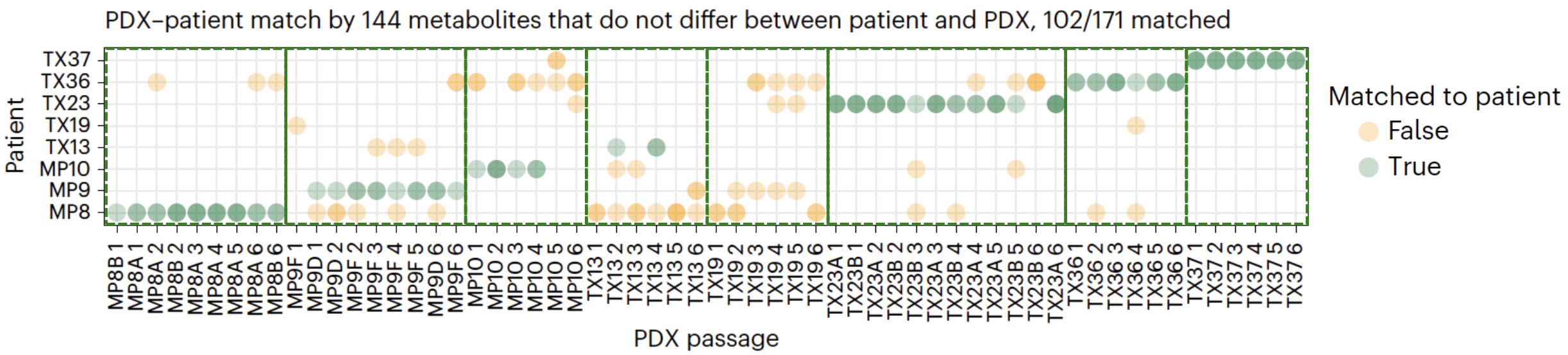


After excluding host-specific metabolites, most PDXs retain metabolic features from the patient's tumor, and these persist across many passages.

Many (but not all) metabolic aberrations are conserved between human ccRCCs and ccRCC tumorgrafts

ccRCC in 19 patients

↓

19 tumorgraft lines in mice (Brugarols lab)

↓

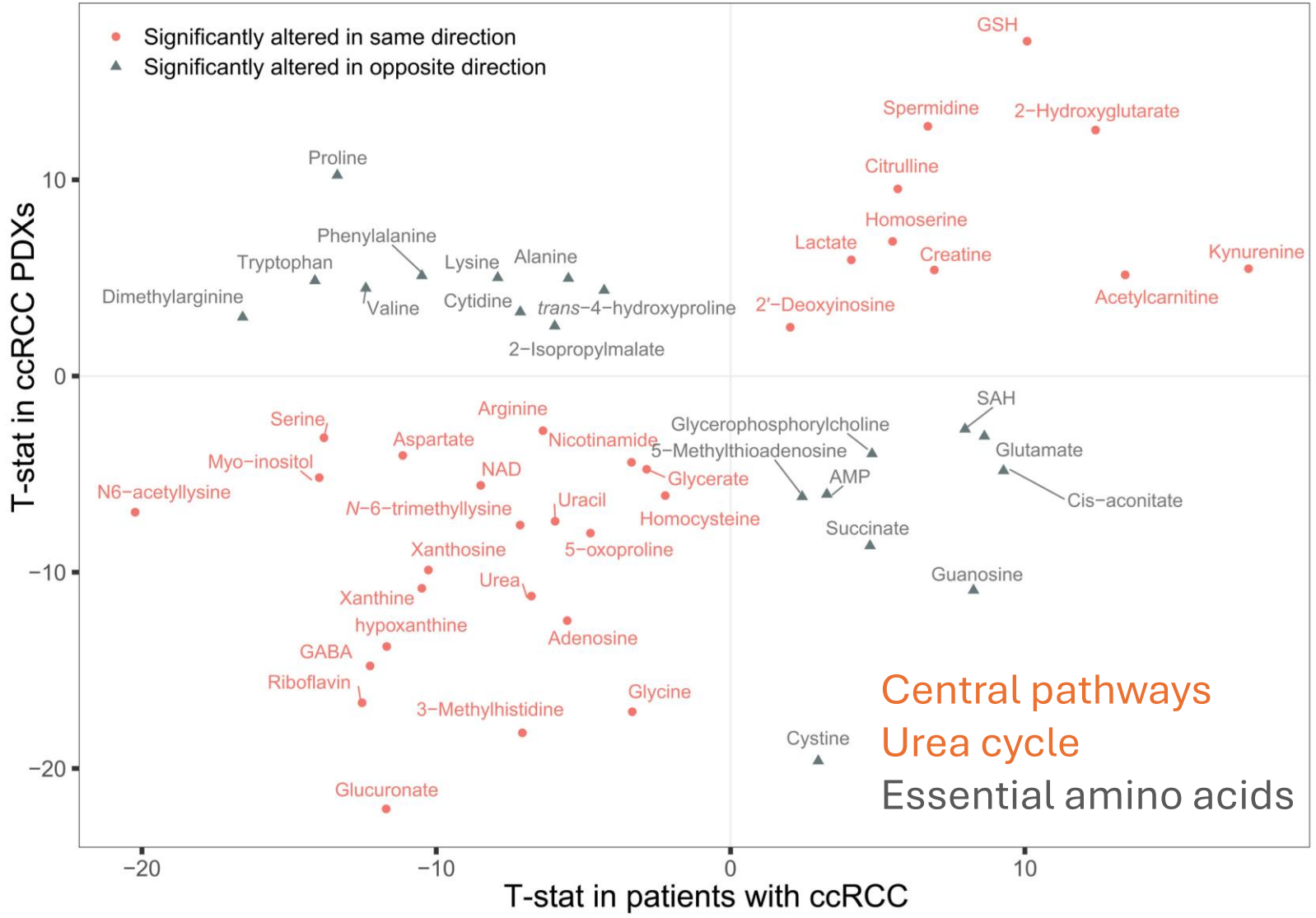
Multiple passages

↓

Metabolomics (tumor vs kidney)

↓

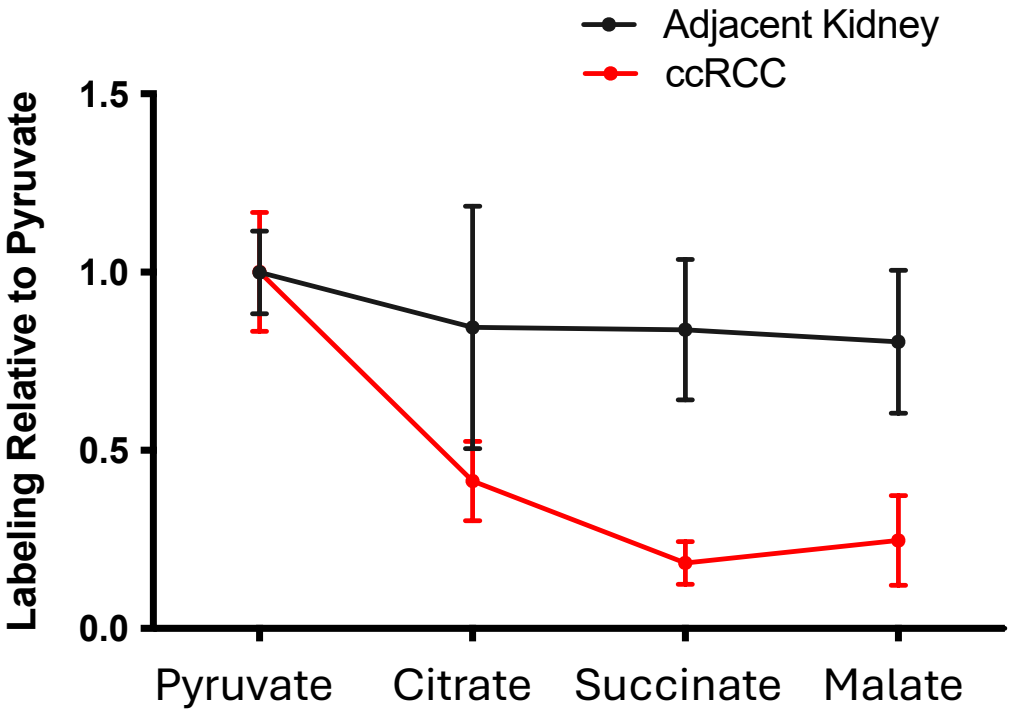
Compare to human ccRCC metabolomics (Hakimi et al., 2016, PMID 26766592)



Kaushik et al., 2022 (PMID 36525494)

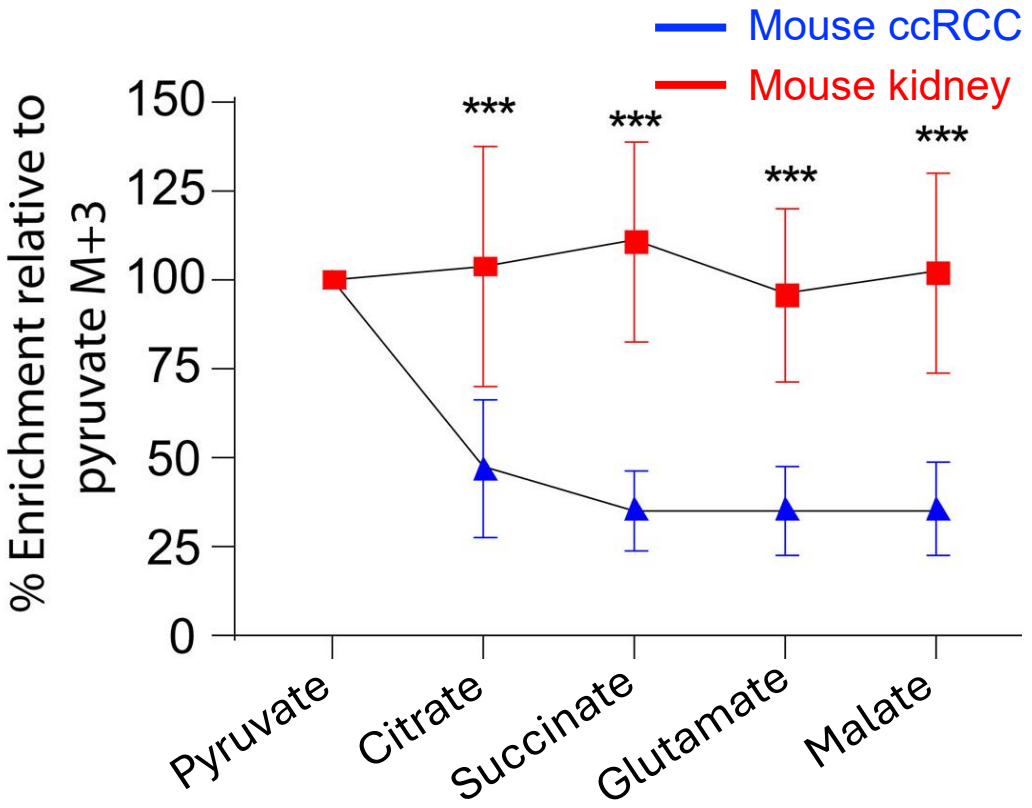
ccRCCs in patients and tumorgrafts have suppressed TCA cycle labeling from [U-^{13}C]glucose

ccRCC in patients



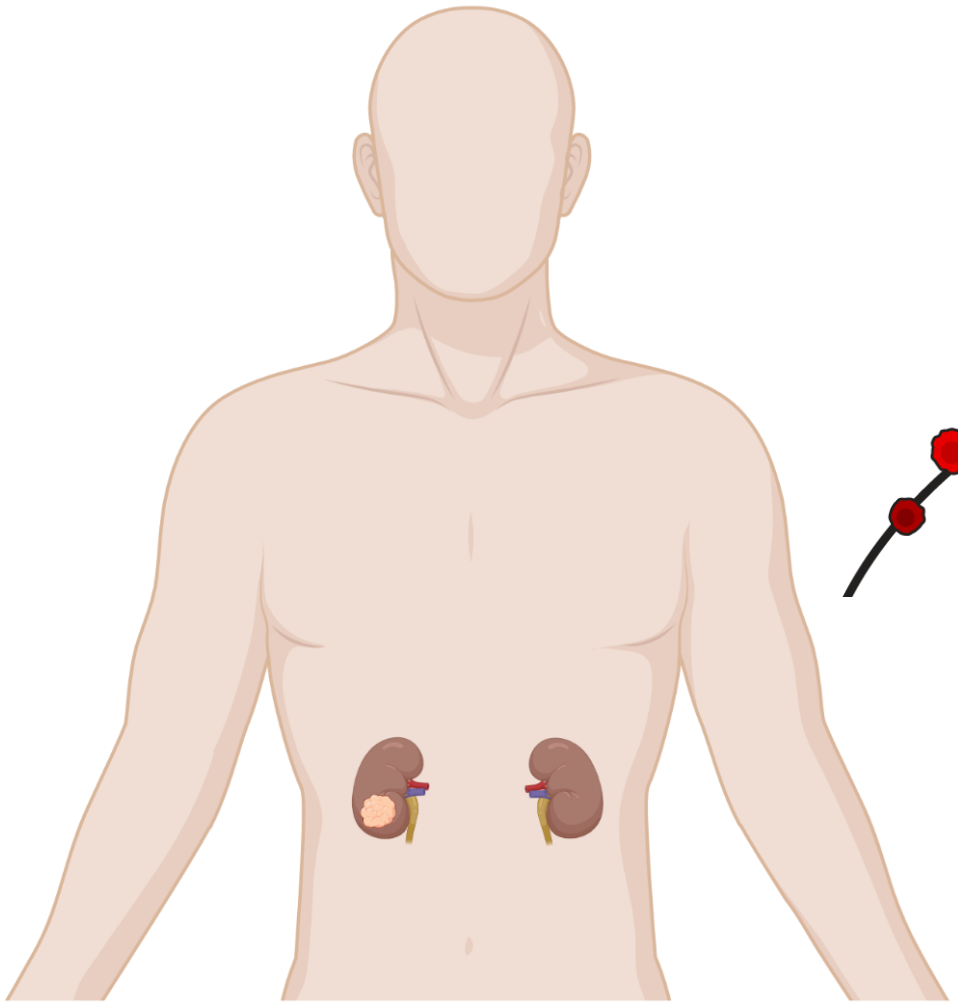
Courtney et al., 2018 (PMID 30146487)

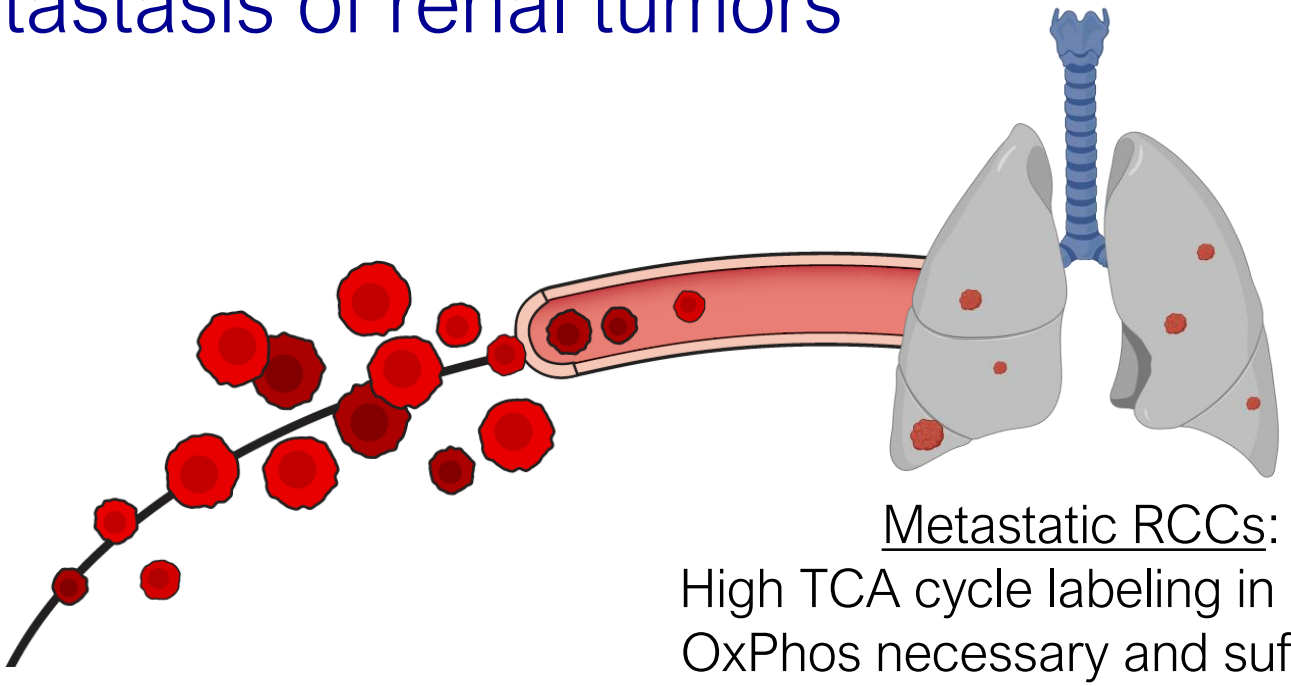
ccRCC tumorgrafts



Kaushik et al., 2022 (PMID 36525494)

Mitochondrial metabolism is a selected metabolic property during metastasis of renal tumors





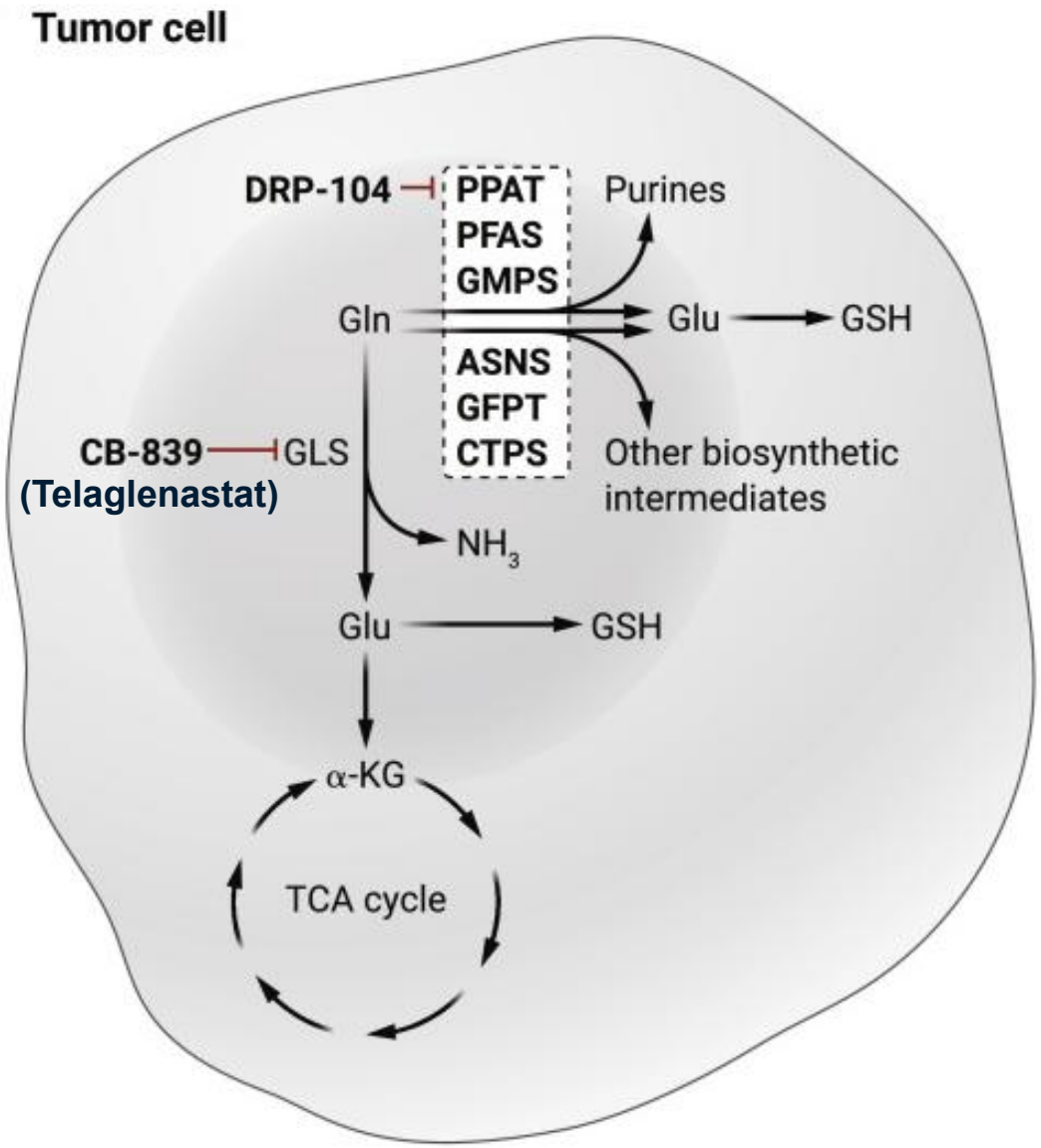
Primary RCCs:
Low TCAC labeling in patients;
Low mitochondrial respiration

Metastatic RCCs:
High TCA cycle labeling in patients;
OxPhos necessary and sufficient to enhance metastasis in mice*
…

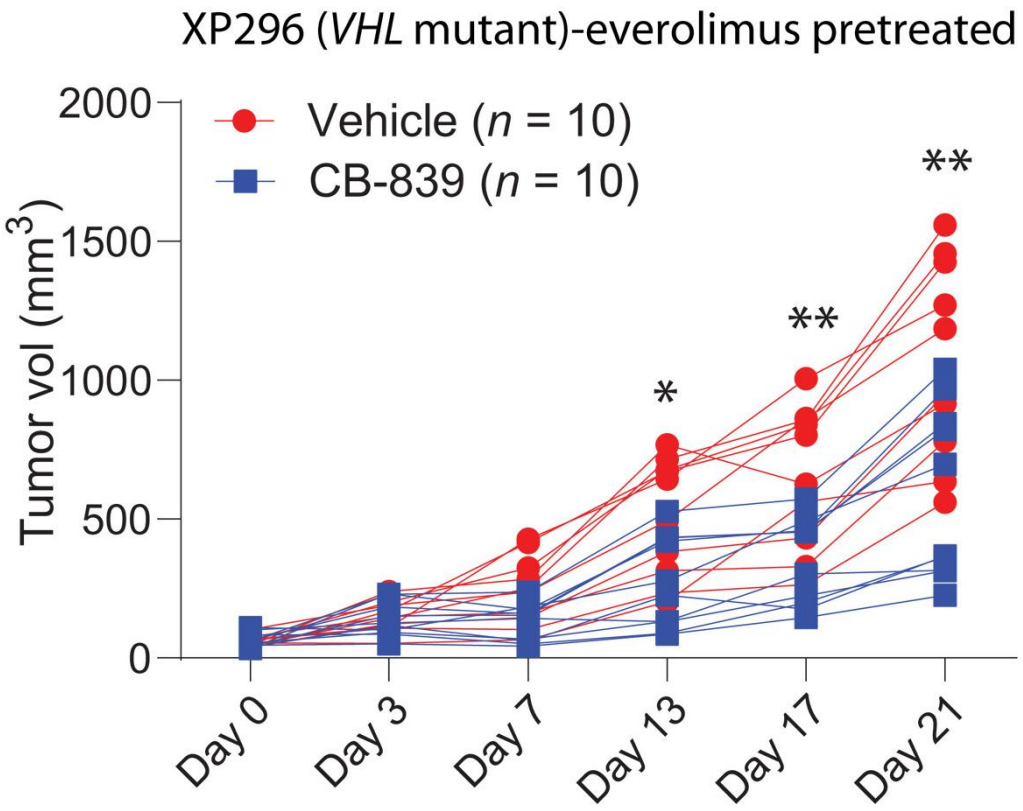
*Mouse models from Genovese lab
Cell lines from Linehan lab

Bezwada D, 2024 (PMID 39143213)

Glutamine catabolism occurs through multiple, partially redundant pathways



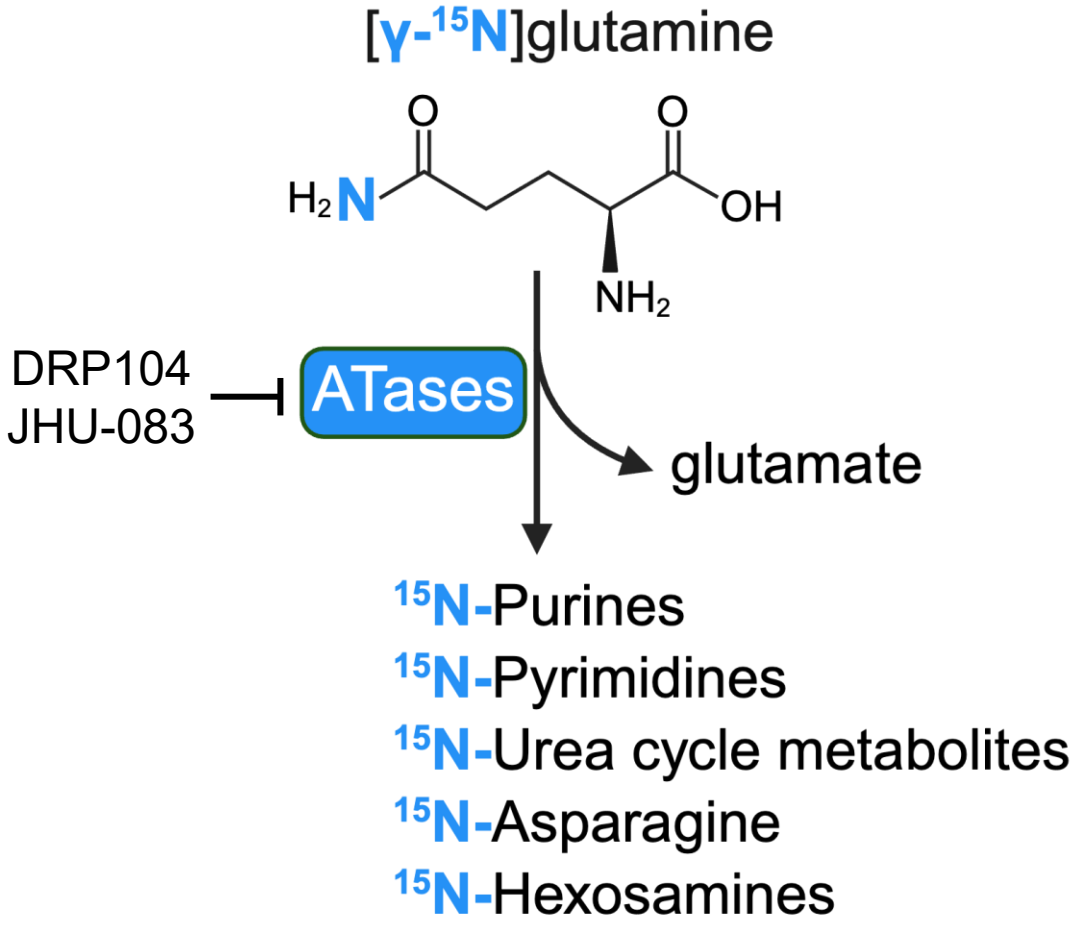
Blatt et al., 2024 (PMID 38536918)

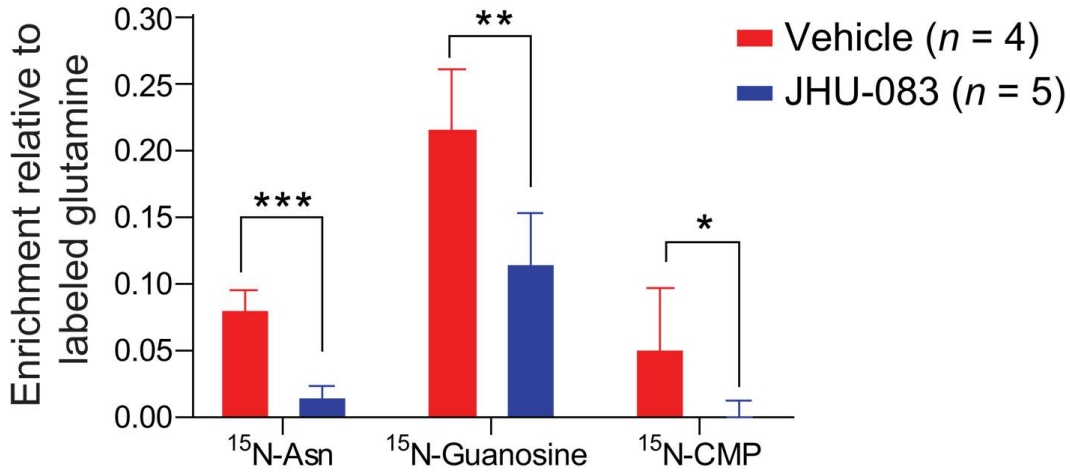


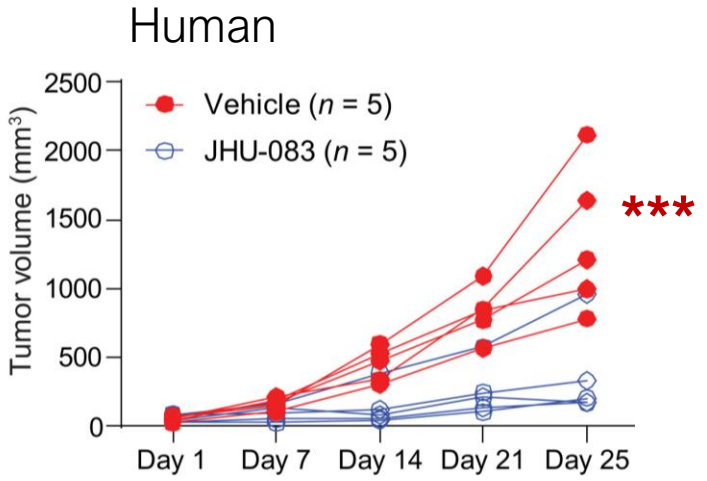
Similar effects in XP490, XP258

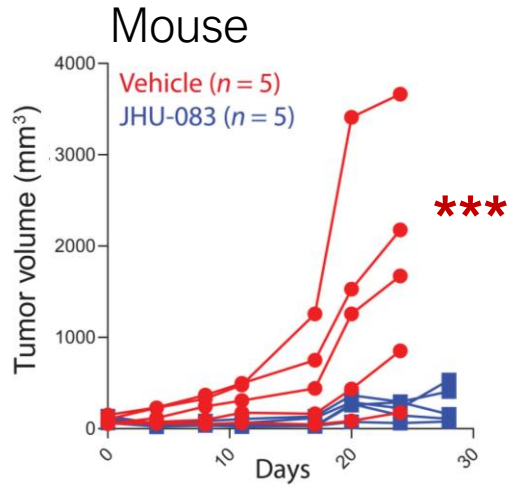
Kaushik et al., 2022 (PMID 36525494)

Amidotransferase activity can be followed in vivo using isotope labeling with [γ-^{15}N]glutamine









ATase = Amidotransferase

Kaushik et al., 2022 (PMID 36525494)

Conclusions

- Human ccRCC tumorgrafts share some metabolic properties with ccRCCs in patients, including central pathways of glucose and glutamine metabolism.
- Primary ccRCCs in patients and mice display low glucose oxidation, but activation of this pathway promotes metastasis in several models.
- Glutamine is a source of carbon and nitrogen in renal cancers.
- Amidotransferases convert glutamine to glutamate and may contribute to resistance to glutaminase inhibitors.

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