Journal Club No. 709 November 24, 2015

膵管腺がんの大規模代謝物プロファイリング
－代謝阻害剤の感受性が異なる膵管腺がんのサブタイプを同定－

石山　文菜

がん細胞は好気的条件下においても解糖系を亢進して ATP を得る Warburg 効果が知られている。最近では、がんの代謝制御機構をリプログラミングするのが、がん遺伝子やがん抑制遺伝子の産物であることや、がん種によって代謝機構にかなり多様性があることが明らかとなってきた。そのため、がん特異的な代謝制御機構はがん治療の標的となり得ると考えられている。本日紹介する論文では、代謝物プロファイルを通して代謝阻害剤の感受性が異なる膵管腺がんのサブタイプを同定した。膵臓がんの代謝機構について勉強になると考え、本論文を紹介することとした。

紹介論文

Metabolite profiling stratifies pancreatic ductal adenocarcinomas into subtypes with distinct sensitivities to metabolic inhibitors.

Daemen A. et al., and Evangelista M.

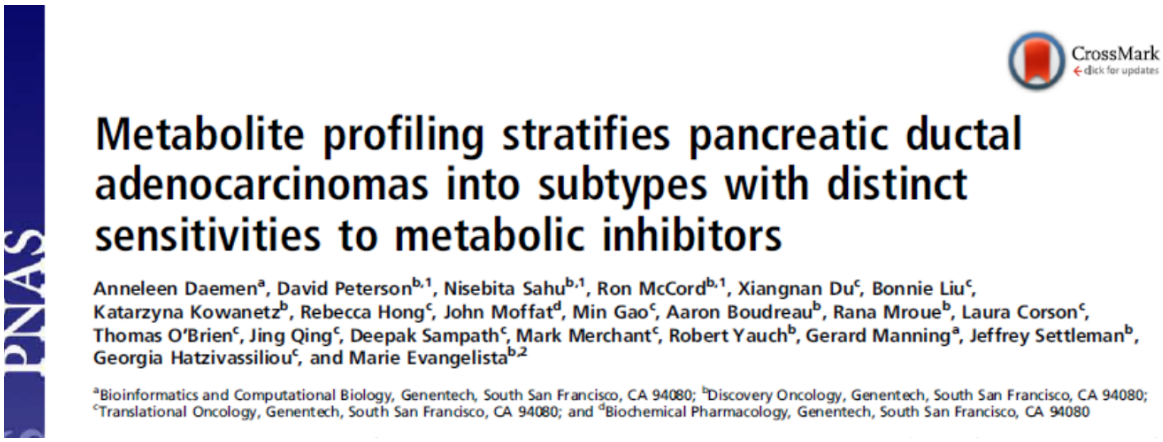
Proc. Natl Acad. Sci. USA 112, E4410-E4417 (2015)

要旨

がん代謝を標的とすることは有望な治療方針であるが、臨床での成功は代謝特異的な腫瘍サブタイプの正確な診断同定に依存する。幅広い代謝物プロファイリングを通して、著者らは膵管腺がんにおいて 3 つの代謝サブタイプ（低増殖型、解糖型、脂質合成型）の同定に成功した。解糖型と脂質合成型のサブタイプは、グルコースとグルタミンの利用やミトコンドリア機能に著しい違いが見られるだけでなく、グルタミン代謝、脂質合成、酸化還元バランス、解糖系阻害剤に対する細胞感受性にも明確な違いを示した。膵管腺がんの臨床サンプルでは、脂質合成型は上皮細胞系サブタイプ（Classical）に関連付けられたのに対し、解糖型は間葉細胞系サブタイプ（QM-PDA）に関連付けられた。さらに、約 200 の非膵管腺がん細胞株における遺伝子分類と代謝阻害剤に対する感受性結果から、今回の知見が他の腫瘍に対しても応用できることが示された。以上の結果から、代謝阻害剤の腫瘍に対する多様な感受性を予測するために、代謝物プロファイリングが有用であることが示唆された。

Journal Club No.709 (November 24, 2015) Ayana Ishiyama

Proc. Natl Acad. Sci. USA 112, E4410-E4417, July 27, (2015)



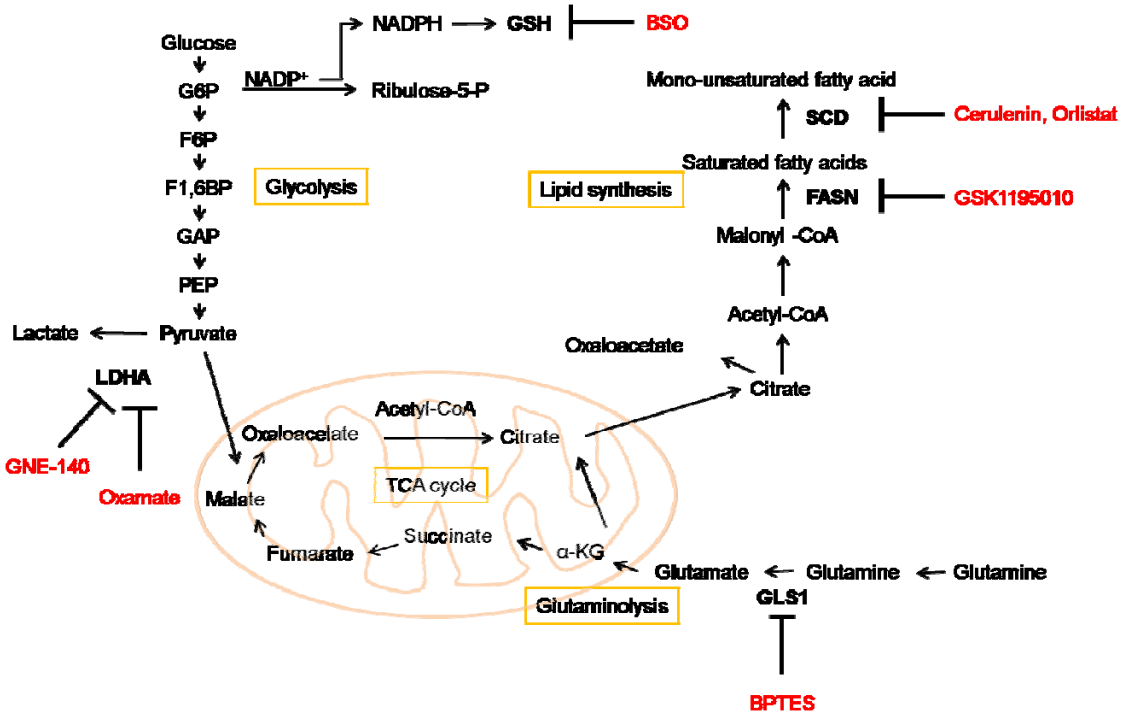
Metabolite profiling stratifies pancreatic ductal adenocarcinomas into subtypes with distinct sensitivities to metabolic inhibitors

Anneleen Daemen[a], David Peterson[b,1], Nisebita Sahu[b,1], Ron McCord[b,1], Xiangnan Du[c], Bonnie Liu[c], Katarzyna Kowanetz[b], Rebecca Hong[c], John Moffat[d], Min Gao[c], Aaron Boudreau[b], Rana Mroue[b], Laura Corson[c], Thomas O'Brien[c], Jing Qing[c], Deepak Sampath[c], Mark Merchant[c], Robert Yauch[b], Gerard Manning[a], Jeffrey Settleman[b], Georgia Hatzivassiliou[c], and Marie Evangelista[b,2]

[a]Bioinformatics and Computational Biology, Genentech, South San Francisco, CA 94080; [b]Discovery Oncology, Genentech, South San Francisco, CA 94080; [c]Translational Oncology, Genentech, South San Francisco, CA 94080; and [d]Biochemical Pharmacology, Genentech, South San Francisco, CA 94080

Genentech：South San Francisco
Research and development company that
centered on the science, oncology, immunology, neuroscience, infection.

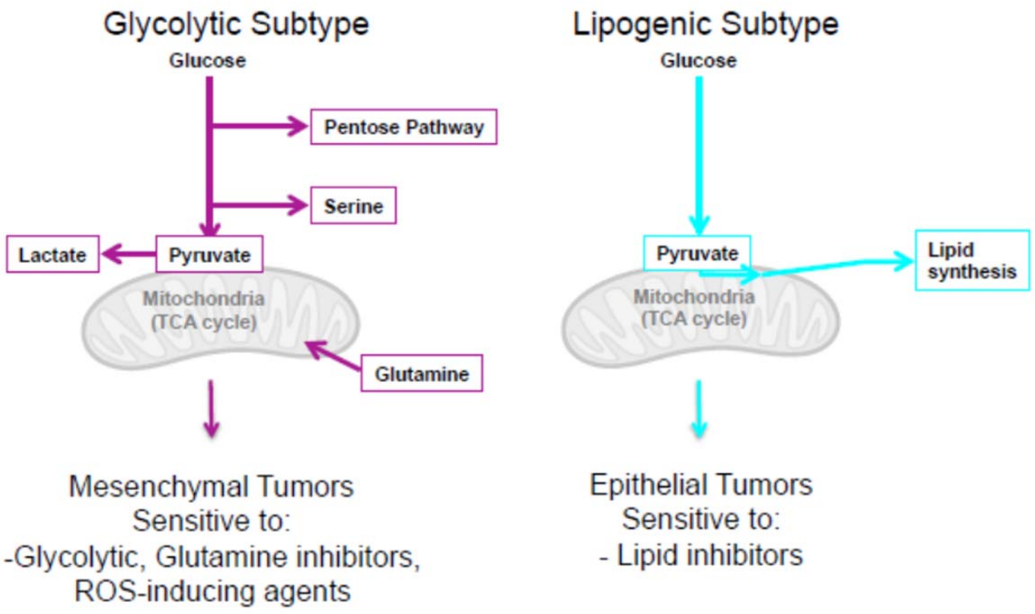
Cancer metabolism



- **Altered tumor metabolism is now a generally regarded hallmark of cancer.**
- **The detailed mechanisms remain to be fully elucidated, due to their charasteristic features of complexity, diversity and adaptability.**

Conclusion

① Metabolic characterization reveals a slow proliferating, glycolytic, and lipogenic subtype.
② Differences between glycolytic and lipogenic subtypes are sensitivity to metabolic inhibitors.
③ PDAC is split into epithelial and mesenchymal subtype, which can be applicable to other cancer types.



Metabolic characterization reveals a slow proliferating, glycolytic, and lipogenic subtype

Fig 1A

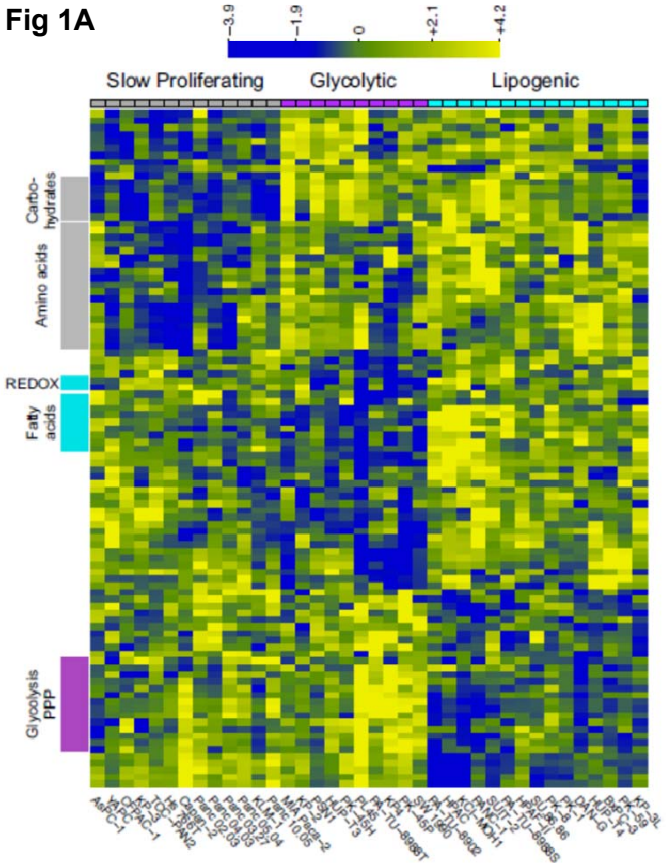


Fig S1D

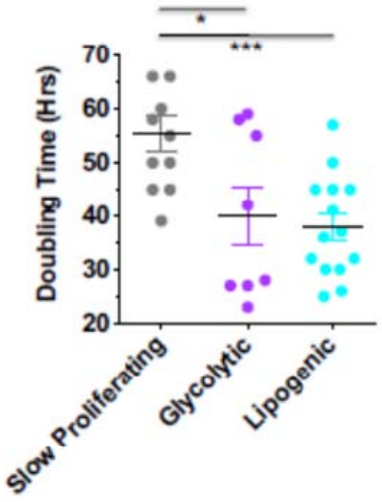


Fig 1A : Distinct metabolic subtypes in PDAC through metabolite profiling.
Fig S1D : Doubling time for all cell lines grouped by subtype.

Intracellular levels for metabolites

Fig 1C

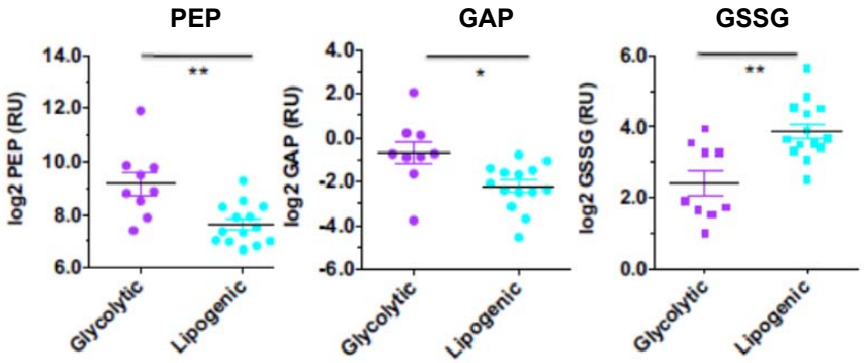


Fig 1D

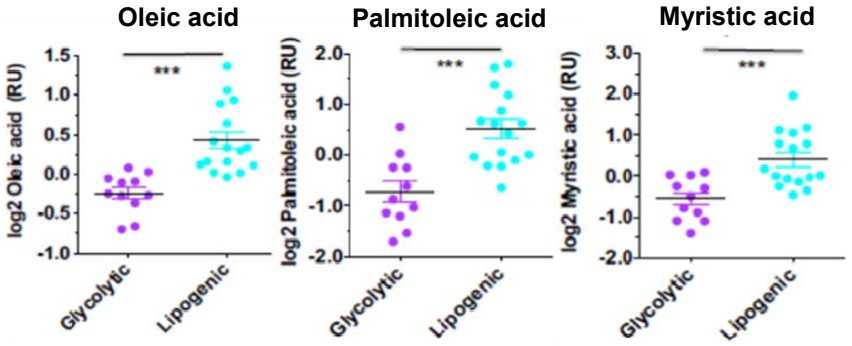


Fig 1C：Intracellular levels for metabolites involved in glycolysis, ppp and redox.
Fig 1D：Intracellular levels for metabolites involved in lipid synthesis.

Expression levels for metabolic genes

Fig 1E

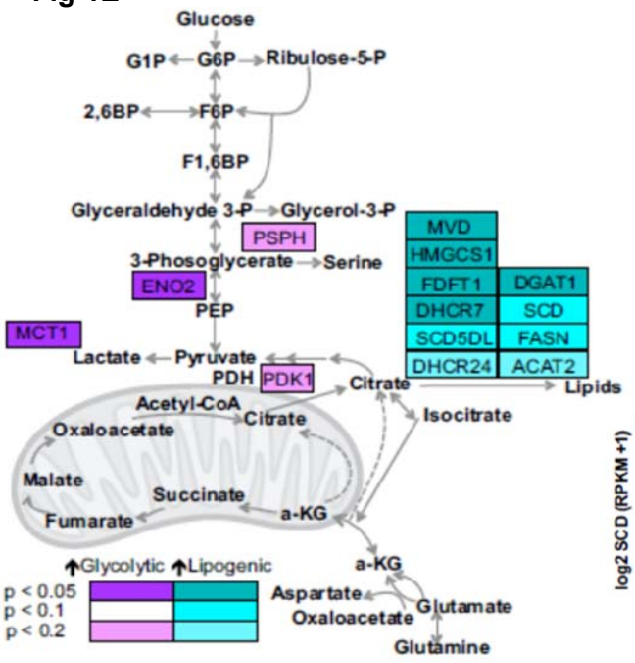


Fig S1K

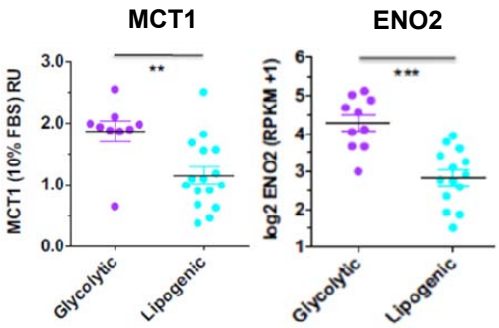


Fig 1F

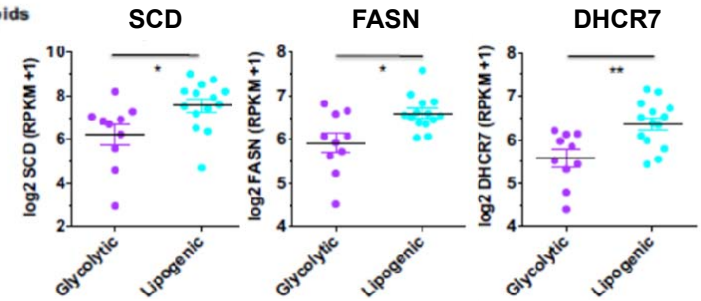


Fig 1E:Detailed metabolite map.
Fig S1K:Expression levels of metabolic genes involved in glycolysis..
Fig 1F:Expression levels of metabolic genes involved in lipid synthesis.

Glycolytic and lipogenic subtypes use glucose and glutamine in a different manner

Fig 2A

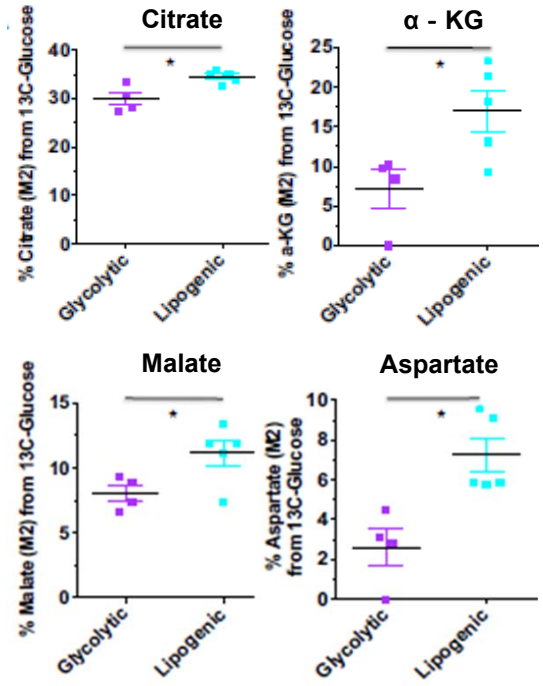


Fig 2B

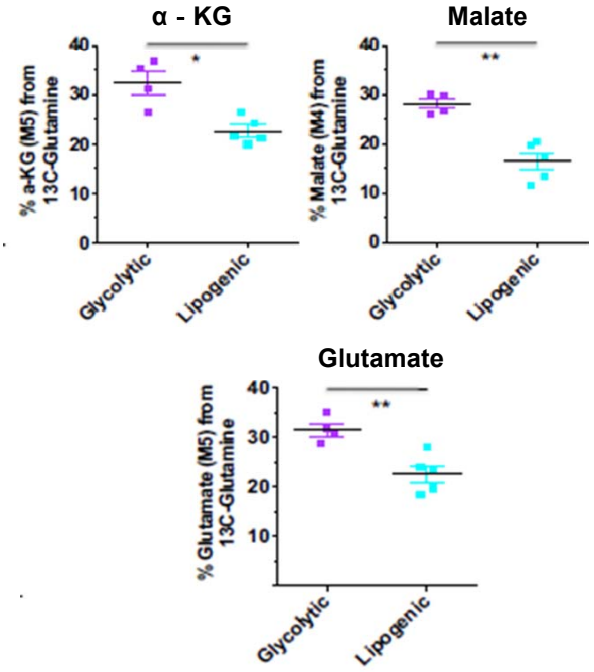


Fig 2A:Glucose oxidation to the TCA metabolites determined by M2 labeling from [U-$^{13}C_6$] glucose.
Fig 2B:Glutamine metabolism to the TCA metabolites determined by M5 labeling from [U-$^{13}C_5$] glutamine.

Glycolytic and lipogenic subtypes use glucose and glutamine in a different manner

Fig 2C

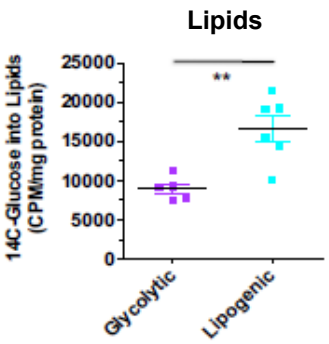


Fig 2D

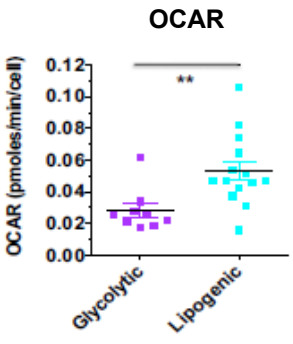


Fig 2E

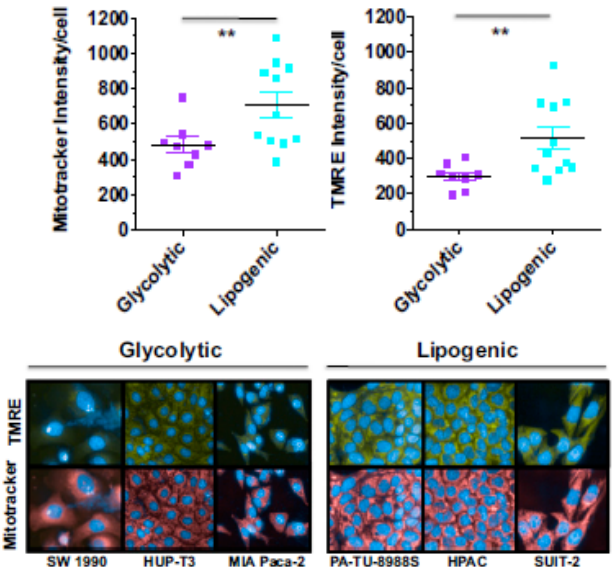


Fig 2C:The incorporation of ^{14}C glucose into lipids was determined by scintillation counting.
Fig 2D:Comparison of oxygen consumption rates.
Fig 2E:Comparison of relative mitochondria number and potential/fitness.

Glycolytic and lipogenic cell lines show distinct sensitivity to various metabolic inhibitors

Fig 3A

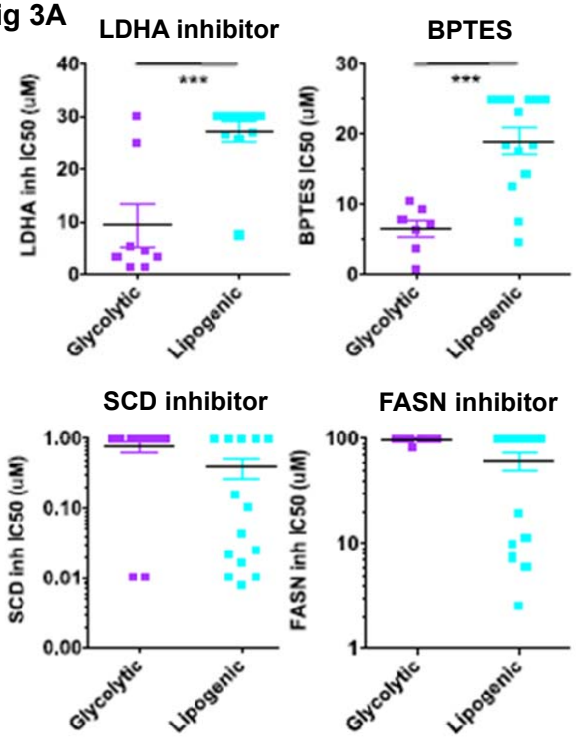
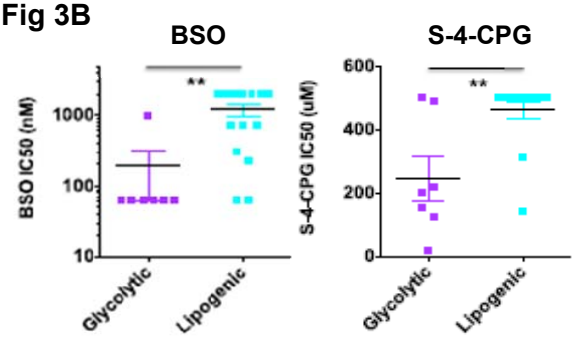


Fig 3B



- **LDHA inhibitor: GNE-140**
- **SCD inhibitor：cerulenin, orlistat**
- **FASN inhibitor：GSK1195010**

Fig 3A:Comparison of IC_{50} values to various metabolic inhibitors.
Fig 3B:Comparison of IC_{50} values to various ROS-inducing agents.

Glycolytic and lipogenic cell lines show distinct sensitivity to metabolic inhibition in vivo

Fig 3E

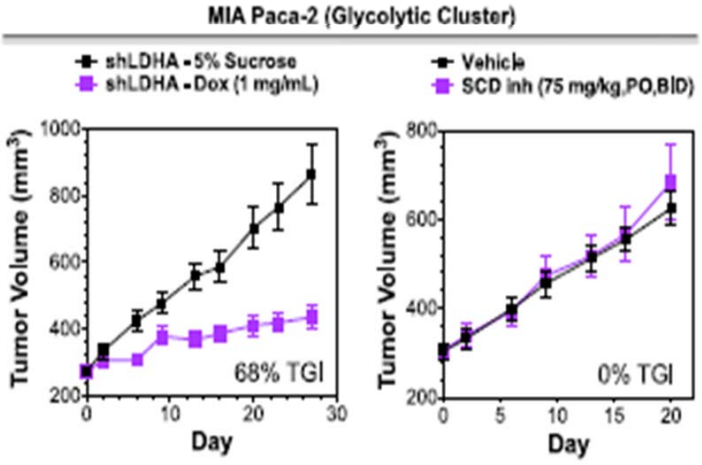
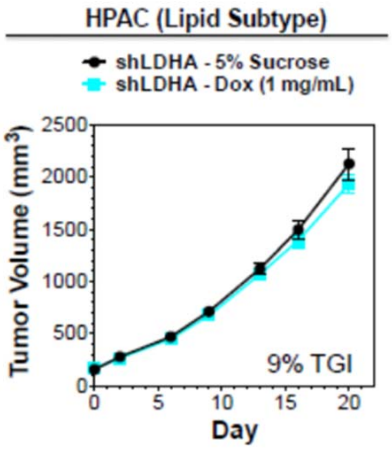


Fig S2E



US Patent WO2013056148 A2, April 18, (2013).

Fig 3E：Effect of LDHA knockdown on tumor growth in glycolytic subtype.
Fig S2E：Effect of LDHA knockdown on tumor growth in lipogenic subtype.

Glycolytic and lipogenic subtypes are associate with known subtypes of PDAC

The clinical subtypes of PDAC.

【Three subtypes】
・Classical：epithelial genes

・Quasimesenchymal (QM-PDA)：
mesenchyme-associated genes

・Exocrine-like：digestive enzyme genes

Nat Med 17, 500-503, Number 4, (2011).

Fig 4A

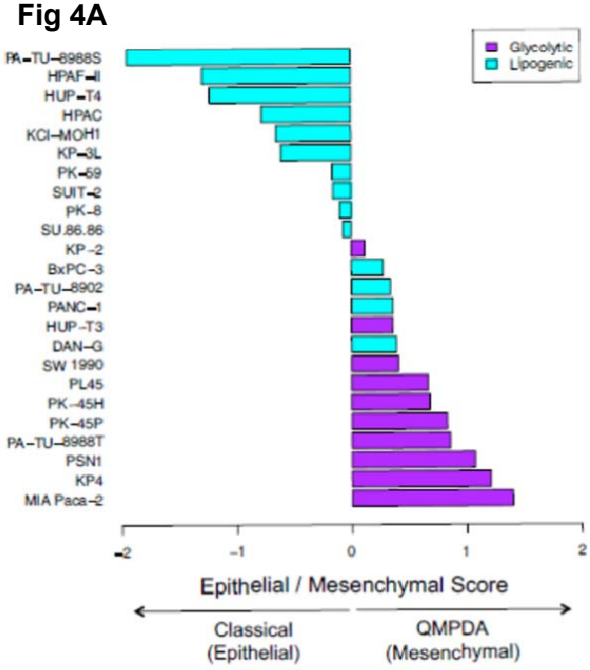
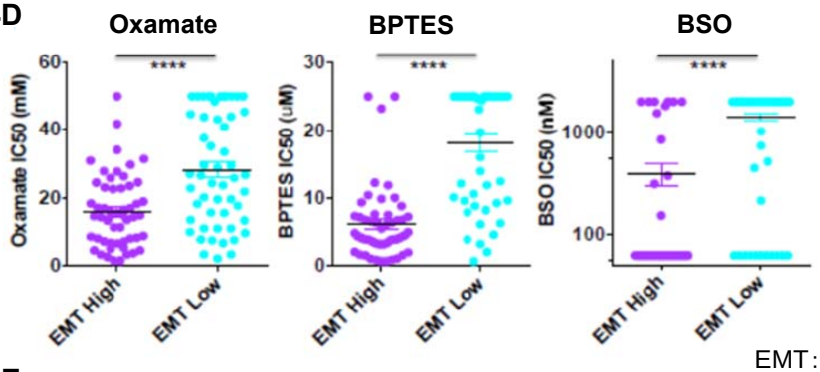


Fig 4A：Epithelial/mesenchymal score for the glycolytic and lipogenic cell lines.

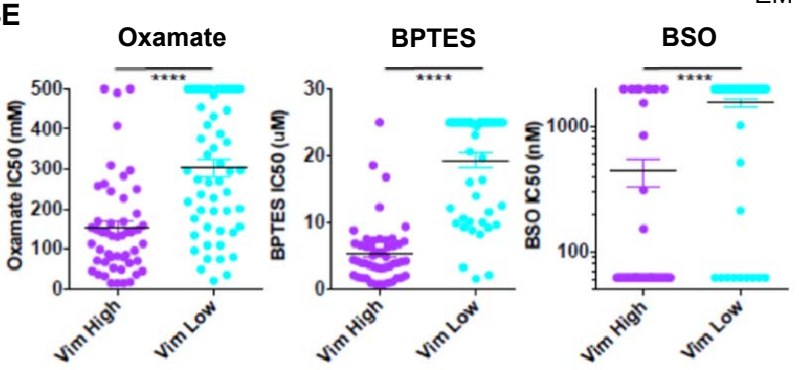
High expression of EMT or Vim associates with sensitivity to glycolytic inhibitors.

Fig 4D



EMT：epithelial-mesenchymal transition

Fig 4E

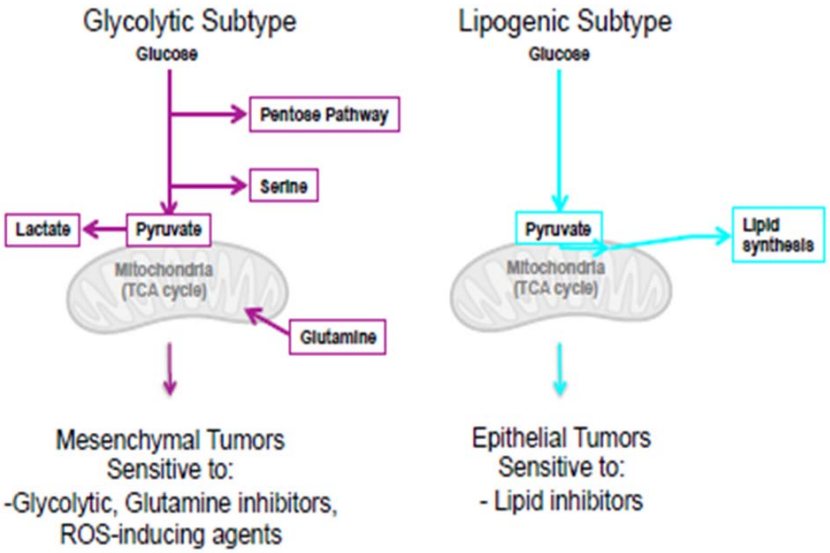


Vim：vimentin

Fig 4D:High expression of a pan-cancer EMT signature associates with sensitivity to oxamate, BPTES and BSO.
Fig 4E:High expression of mesenchymal marker vimentin associates with sensitivity to oxamate, BPTES and BSO.

Conclusion

Fig 4F



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