# Warburg效应研究识别抑制癌症转移的代谢靶标

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# Background

- **Studies** about the cancer
- Altered **tumor metabolism**
- Otto Warburg's early studies:**Warburg effect**
- The role of **tumorigenic metabolic rewiring** in supporting **cancer proliferation**
- **Cellular migration** has received far less attention

# Background

- Treatment
- **Contemporary cytotoxic cancer treatment**
- **Drug targets**
- The growing availability of **high‐throughput measurements**
- Integrate pertaining data with a **genome‐scale mechanistic model** of human metabolism

# Synopsis

- **Research objectives:**
- **The first** genome - scale computational study of the metabolic underpinnings of cancer migration.
- The extent of the **Warburg effect** is highly associated with **cancer cell migration** across different cell lines and **identifies anti - migratory targets**.

# Synopsis

- **<u>The Outline</u>:**
- **1.Genome - scale metabolic models** of each the NCI - 60 cell lines correctly **capture the Warburg effect**.
- **2.The extent of the Warburg effect**, as **quantified** by the ratio between **glycolytic** and oxidative **ATP flux rate (AFR)**, positively associates with cancer cell migration across the different cell lines.

# Synopsis

- **3.Experiments test**:**siRNA knockdown** of 13 genes predicted to reduce the AFR attenuates cell migration while having almost no effect on cell proliferation.

- **4.Theoretical analysis**:In agreement with the predictions, a significant reduction in the ratio of **glycolytic/oxidative capacity** is observed following these gene perturbations.

# Results

- **1.Validating the basic function** of our NCI - 60 models

- An important hallmark of cancerous cells is the **production of lactate** through the Warburg effect (Warburg, 1956).

- **GSMM** and **cell-specific metabolic models**

# Results

$$Sv = 0 \tag{1}$$

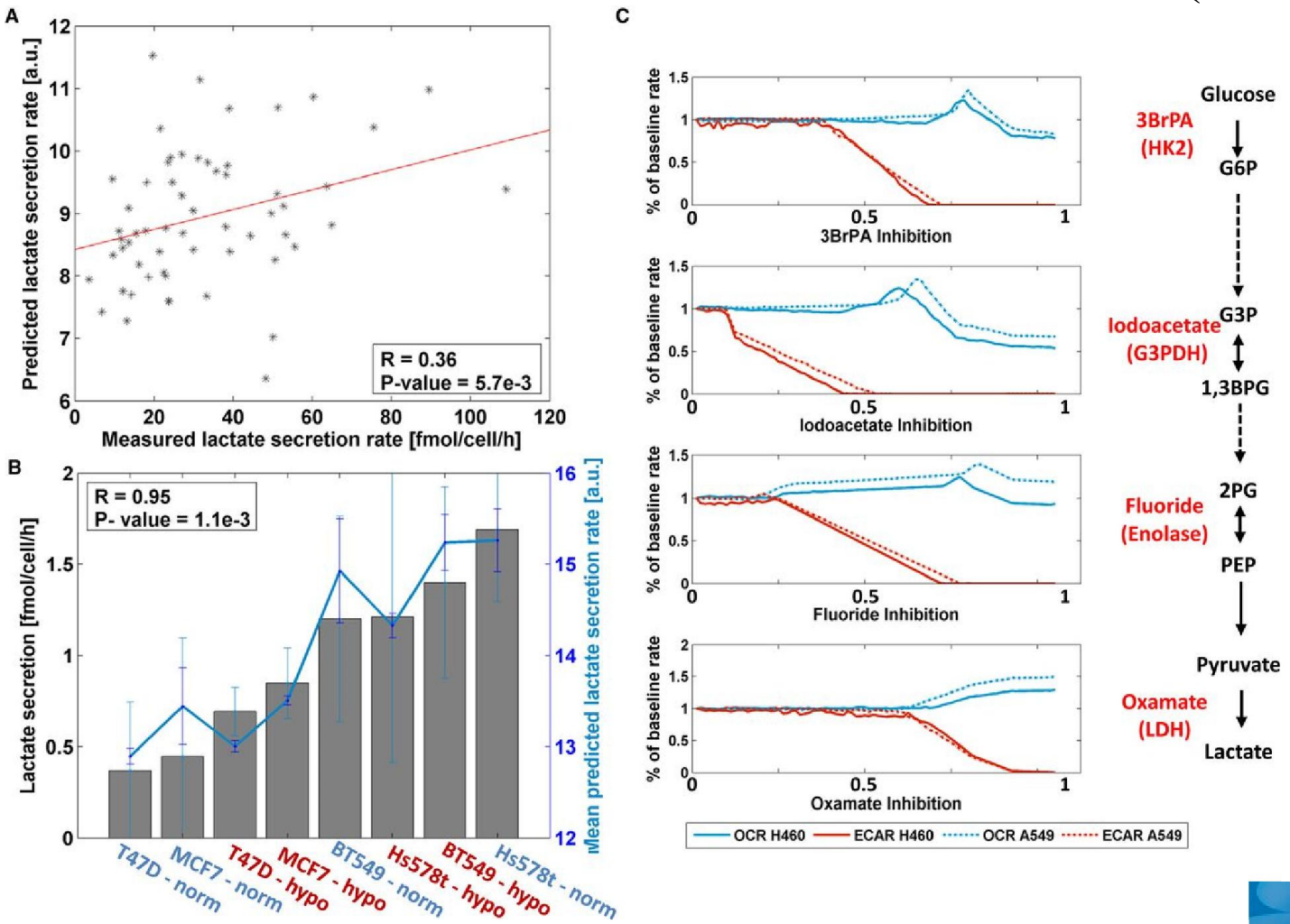
$$v_{\min} \leq v \leq v_{\max} \tag{2}$$

- **Several key inputs**:
- (a) the generic human model (Duarte et al, 2007), (b) gene expression data for each cancer cell line from (Lee et al, 2007), and (c) growth rate measurements.

# Results

- **2.**Comparing **predicted** versus **experimentally measured** bioenergetics capacity
- obtaining a moderate but significant correlation
- To further test the models' performance under different environmental conditions
- To further examine how well our cell line models capture measured Warburg - related activity

# A comparison between experimental and predicted in silico measurements of lactate secretion (or ECAR) and OCR across different cancer cell lines Measured versus predicted lactate secretion rates across the 59 cell lines available at Jain et al (2012).



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# Results

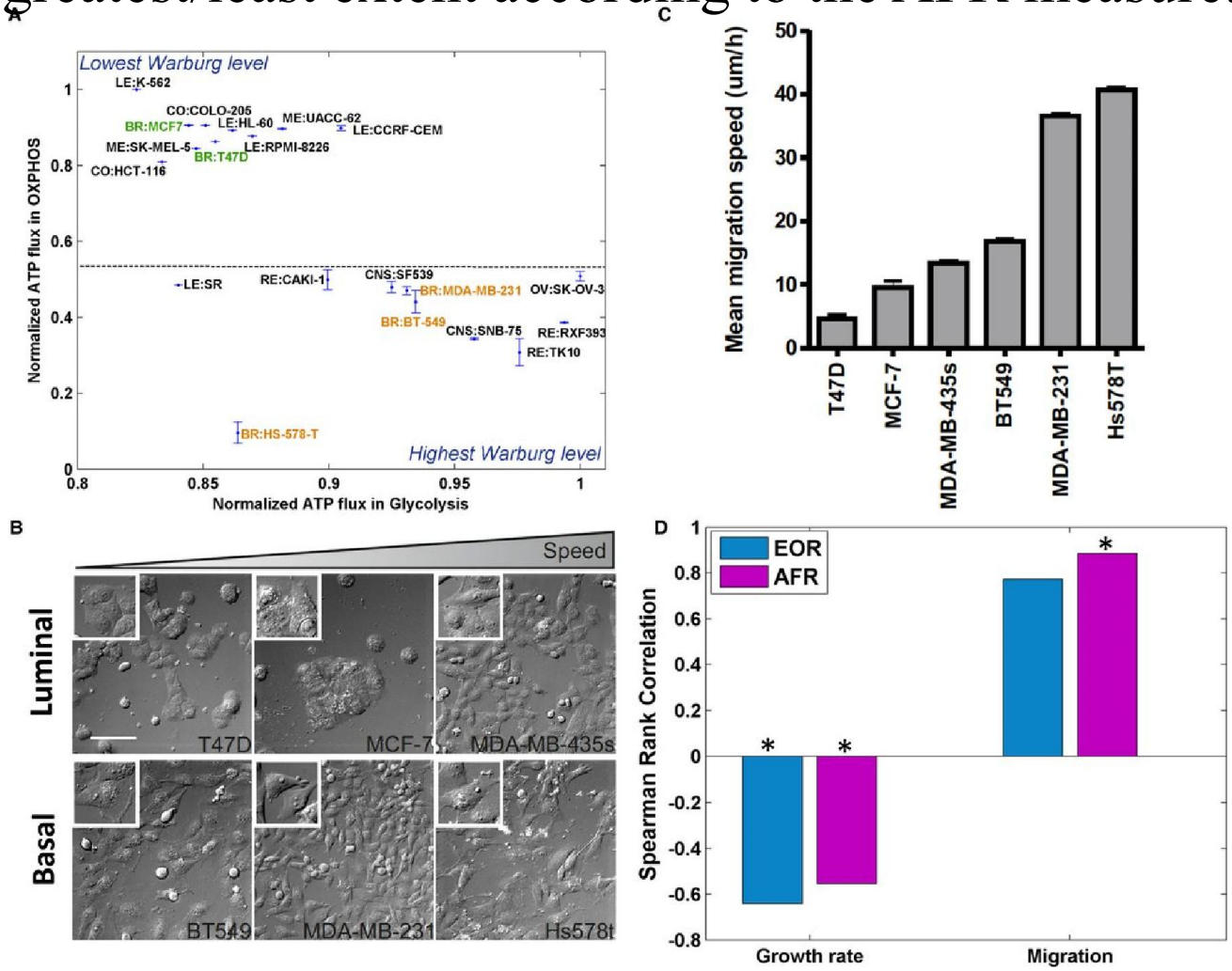
- **3.Quantifying** the Warburg effect and its relation to proliferation and migration across the NCI‐60 cell lines

- OXPHOS

- GI50

# Association between AFR levels and cell proliferation and migration

The 20 cell lines that are predicted to exhibit the Warburg effect to the greatest/least extent according to the AFR measure.

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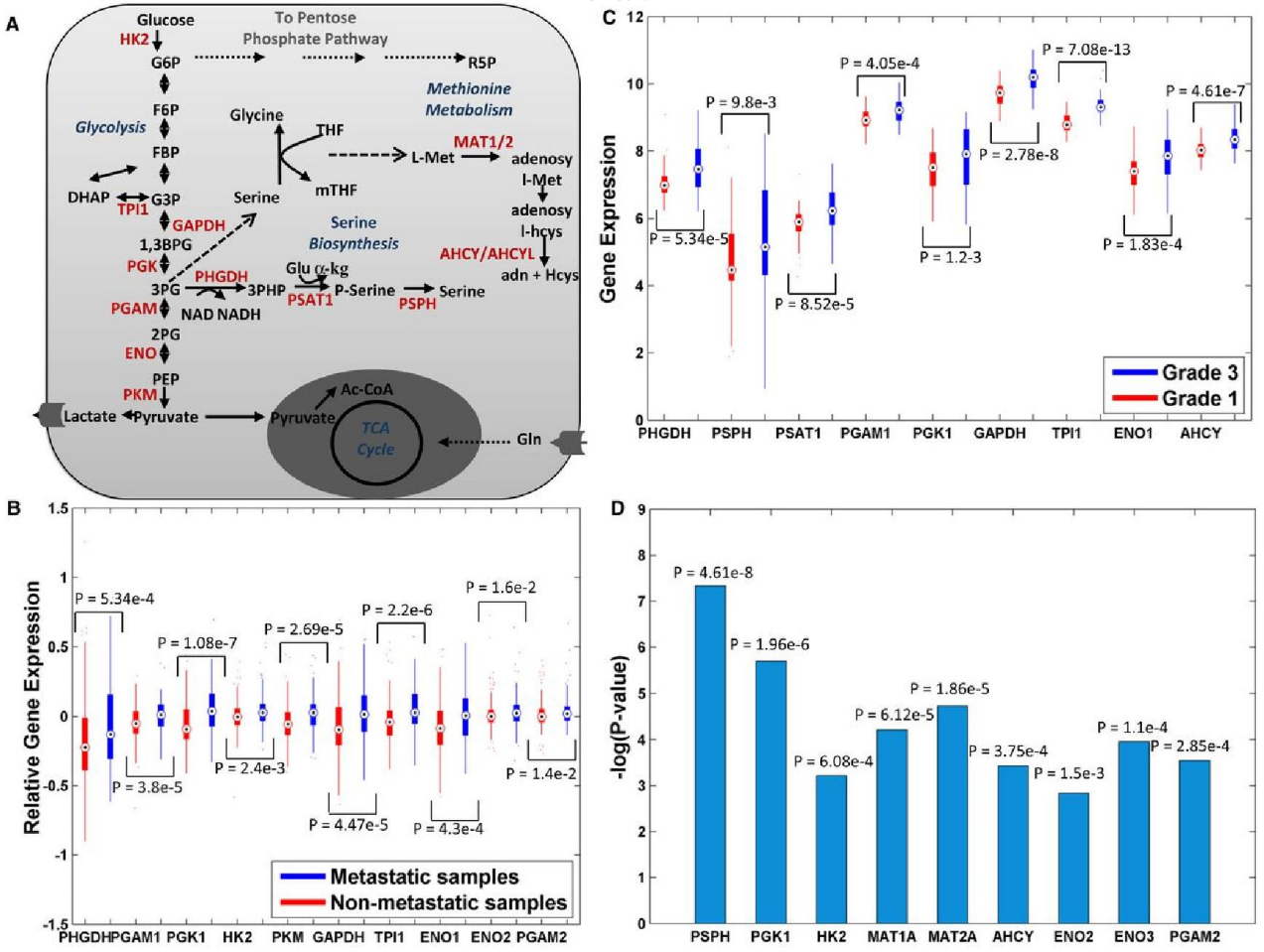
# Results

- **4.Predicting drug targets** that **revert** the AFR and hence may inhibit cancer migration
- The first identified a set of 113 reactions
- The knockout of 12 of 113
- The final list of predicted gene targets includes 17 metabolic enzymes

# Gene targets that are predicted to reduce the AFR and their association with prognostic markers of breast cancer patients A schematic representation of the 12 predicted gene targets, marked in red.



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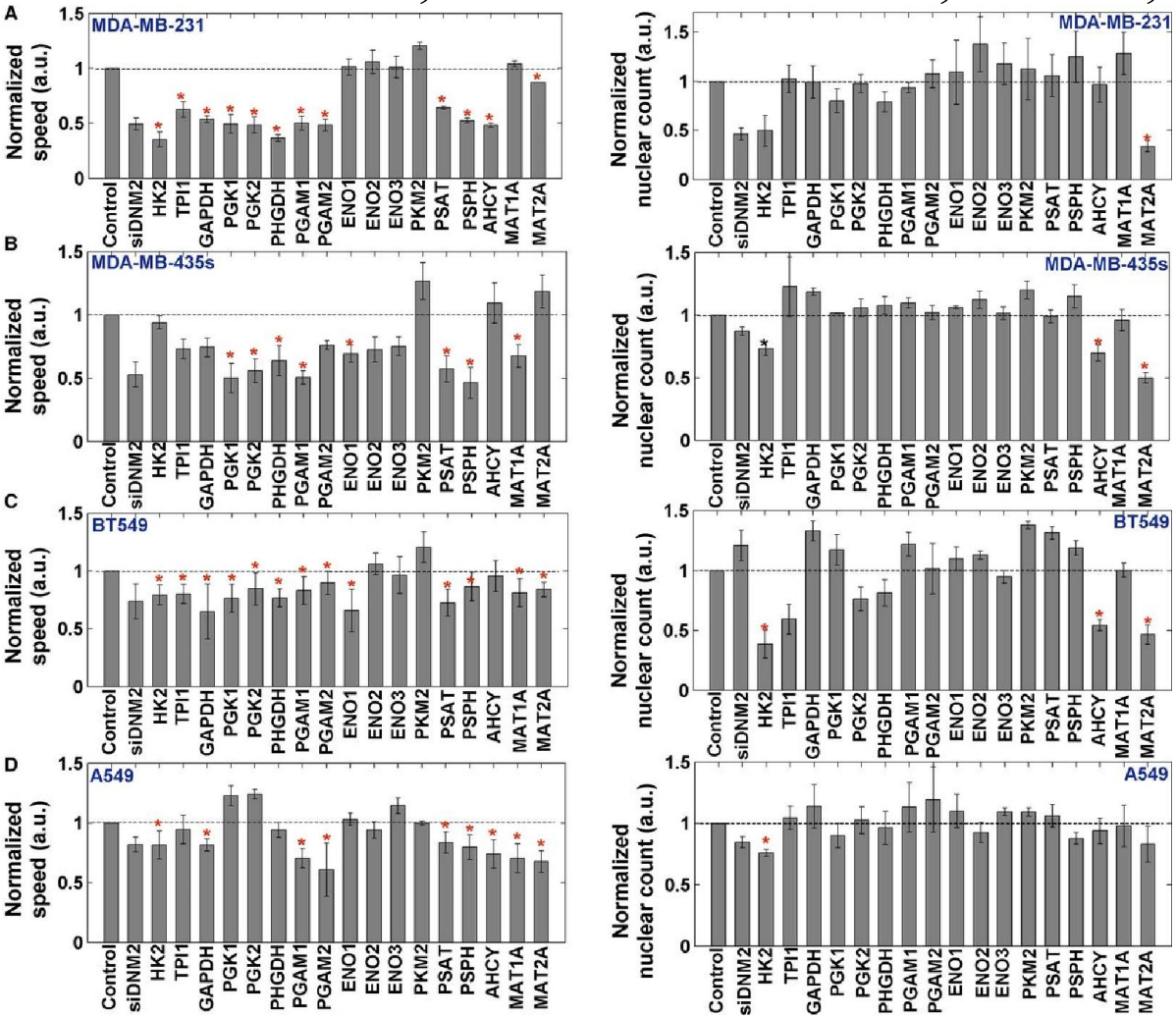
# Results

- **5.Experiments test**
- SmartPool gene silencing
- **Two different controls** are used:
- (1) non‐targeting siRNA (= negative control); and
- (2) a positive control DNM2 which is known to block both migration and proliferation (Ezratty et al, 2005).

Normalized to control mean speed per SmartPool gene silencing of the predicted targets A–DThe four different cell lines that were analyzed: MDA - MB - 231, MDA - MB - 435s, BT549, and A549.

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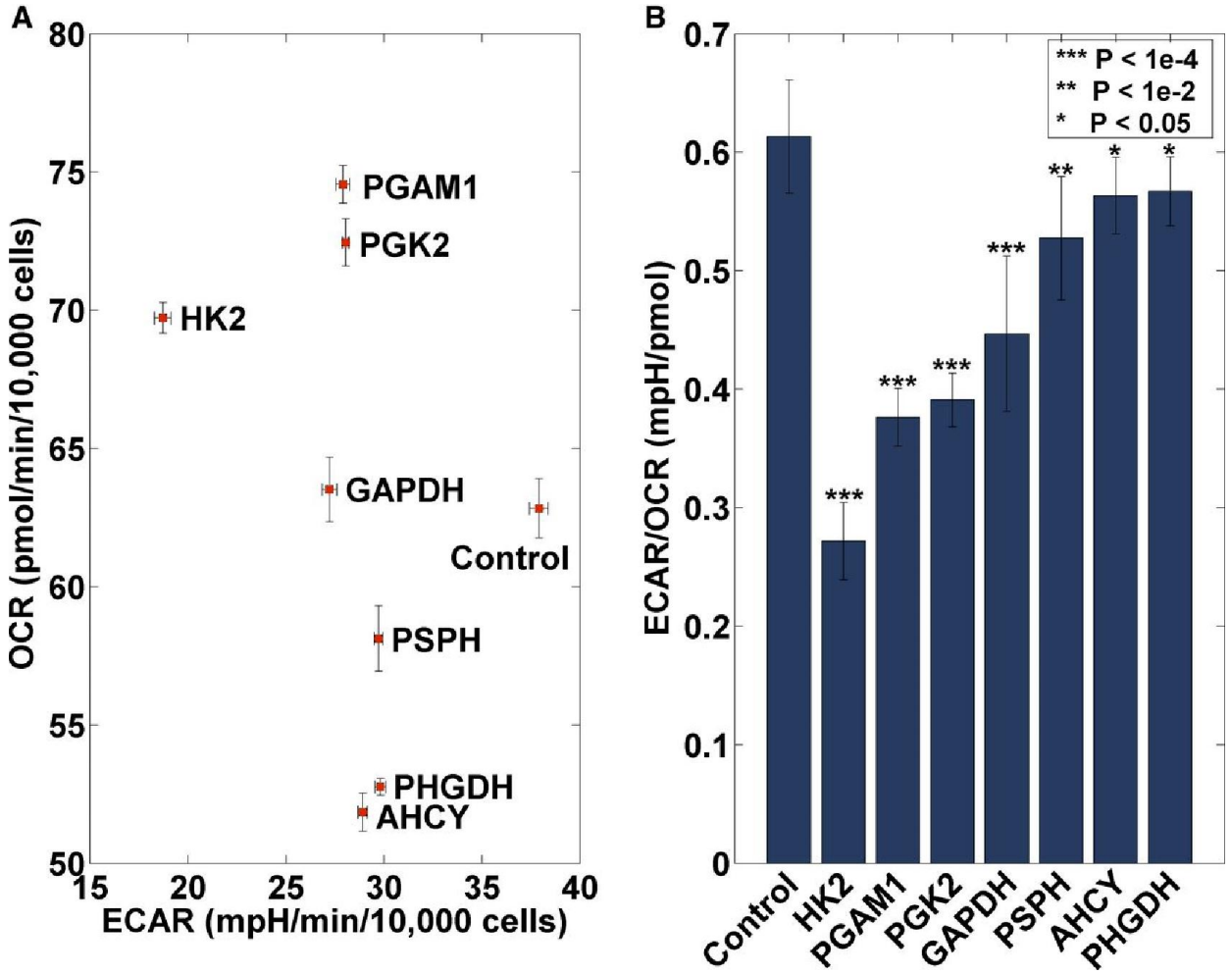
# Results

- **6.Theoretical analysis**
- ECAR and OCR levels of top predicted gene targets
- To further study the association between reduced AFR levels and impaired cell migration
- Seahorse XF96 extracellular flux analyzer

# ECAR and OCR levels of top predicted gene targets Mean and SEM (normalized to nuclear count) ECAR and OCR levels after silencing of seven different genes (HK2, PGAM1, PGK2, GAPDH, PSPH, AHCY, and PHGDH) compared to the control.

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# Conclusions and Discussions

- （1）一句话总结
- 这是第一个关于癌症转移代谢基础的基因组范围的计算研究，研究结果表明Warburg效应与癌细胞转移高度相关，并且鉴别了抗转移的相关靶标。
- （2）启发
- 实验与生物信息相结合（数据分析指导，实验验证）；分析问题的流程（数据-模建-预测-验证-再分析）；发展的角度（随着研究发展而变化，代谢基因组）。

# Conclusions and Discussions

- （3）改进
- 数据不全、准确性不足（模建通病）；且需增加和优化受测体系，因研究依赖基因表达特异性，没有考虑到每种细胞系具体的吸收率（原因：研究材料不能测这一参数），因此食欲捕捉定性而非定量的不同。
- 虽然可避免细胞毒治疗（化疗等）的副作用，但细胞转移在正常生理活动中也很重要，例如：免疫应答、组织修复等。所以要在药物选择方面做更多的工作。
- 需要从癌细胞转移表型向机理层次做更深入的研究（如各代谢基因对转移的贡献来提高药靶的可靠性等）。