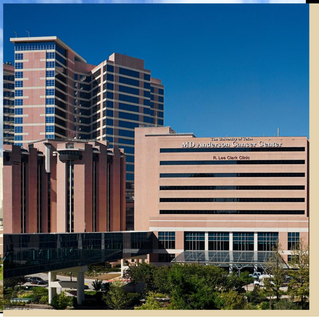

Investigating Glucose Uptake Prognostic Effects On Pan Cancer TCGA by METAFLUX

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Introduction

- One major hallmark of cancer is deregulation of cellular metabolism, which allows cancer cells to undergo metabolic reprogramming to sustain their uncontrolled growth, such as upregulated glycolysis.
- Higher uptake of glucose into cancer cells has been associated with more aggressive tumors due to increased expression of glucose transporters[1].
- PET scans have been leveraged to infer changes in glucose metabolism, **but pan-cancer glucose uptake studies for large cohorts are still lacking[2]**.
- To study metabolic processes, we developed METAFlux (METAtabolic Flux balance analysis) to derive metabolic fluxes for 13,082 reactions for bulk RNA-seq datasets. METAFlux relies on three major steps: calculating the metabolic reaction activity score (MRAS), flux balance analysis (FBA), and optimization of biomass reaction.

Objective

- Use METAFlux to analyze
  1. The association of predicted glucose uptake with clinical outcomes
  2. If these effects are homogenous across different types of cancer.

Methods

- Gene expression data downloaded from The Cancer Genome Atlas
- Data passed through the METAFlux pipeline to calculate flux
  1. Calculate the metabolic reaction score (MRAS) using the gene expression data.
  2. Use the MRAS to set the bounds for flux balance analysis (FBA)
  3. Use quadrating programming and the OSQP package[3] to minimize the function $\frac{1}{2}v^T v - \alpha C^T v$ (v is the flux vector, $C^T v$ is the biomass reaction and $\frac{1}{2}v^T v$ represents the sum of squared fluxes of all metabolic reactions)

Methods

- Extract glucose uptake data and sort into “High” and “Low” groups
- Use the TCGABiolinks package[4] to analyze survival

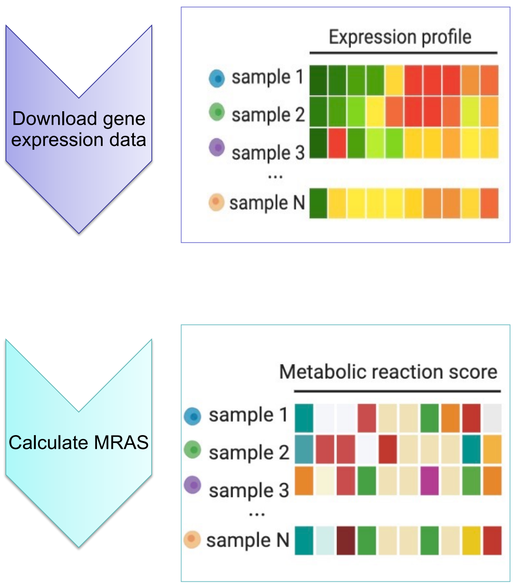

Figure 1: Project pipeline – download expression data, METAFlux algorithm, analyze results

Results

- Highest mean glucose uptakes: lung squamous cell carcinoma (LUSC, mean = 0.0057), uterine carcinosarcoma (UCS, mean = 0.0061), and uveal melanoma (UVM, mean = 0.0064)
- Lowest mean glucose uptake were kidney chromophobe (KICH, mean = 0.0024), kidney renal clear cell carcinoma (KIRC, mean = 0.0026), and kidney renal papillary cell carcinoma (KIRP, mean = 0.0027)
- LUSC glucose uptake > LUAD glucose uptake, consistent with the literature[5]

Cancer Type	Mean Glucose Uptake	Survival P Value	High Uptake Glucose Effect
ACC (77)	0.0039	0.05	Detrimental
BLCA (407)	0.0054	0.23	NS
LGG (509)	0.0041	0.0037	Beneficial
BRCA (1092)	0.0047	0.34	NS
CESC (304)	0.0047	0.85	NS
CHOL (36)	0.0038	0.15	NS
COAD (288)	0.0049	0.92	NS
ESCA (181)	0.0047	0.12	NS
GMB (153)	0.0035	0.48	NS
HNSC (518)	0.0050	0.35	NS
KICH (66)	0.0024	0.33	NS
KIRC (530)	0.0026	0.087	NS
KIRP (288)	0.0027	0.47	NS
LIHC (369)	0.0048	0.67	NS
LUAD (513)	0.0040	0.015	Detrimental
LUSC (498)	0.0057	0.77	NS
MESO (87)	0.0043	0.041	Detrimental
OV (419)	0.0055	0.8	NS
PAAD (178)	0.0038	0.73	NS
PCPG (177)	0.0041	0.24	NS
PRAD (495)	0.0040	0.28	NS
READ (92)	0.0051	0.99	NS
SARC (258)	0.0056	0.59	NS
SKCM (102)	0.0049	0.27	NS
STAD (414)	0.0042	0.63	NS
TGCT (148)	0.0053	0.42	NS
THYM (119)	0.0052	0.038	Beneficial
THCA (504)	0.0031	0.049	Detrimental
UCS (180)	0.0061	0.91	NS
UCEC (57)	0.0046	0.85	NS
UVM (79)	0.0064	0.82	NS

Table 1: Pan-Cancer Glucose Uptake Results

Key:
Highest mean glucose uptakes
Lowest mean glucose uptakes
Lower glucose uptake was significantly better
Higher glucose uptake was significantly better

Results

- Twenty-five cancers showed an insignificant difference; may depend on other nutrients (glutamine, amino acids, etc.)[6]
- Four cancers showed that survival for patients with lower glucose uptake was significantly better ($p = 0.05$): mesothelioma (MESO), lung adenocarcinoma (LUAD), adrenocortical (ACC), thyroid carcinoma (THCA)

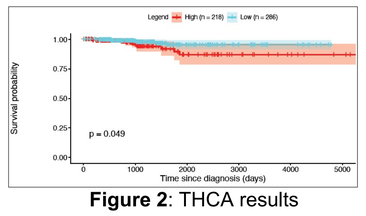

Figure 2: THCA results

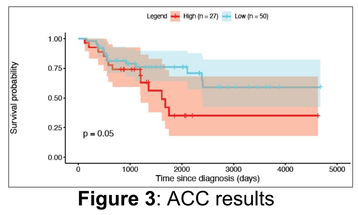

Figure 3: ACC results

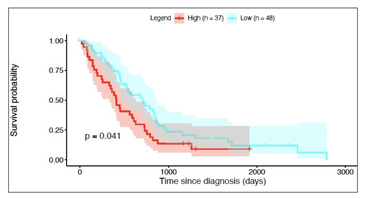

Figure 4: MESO results

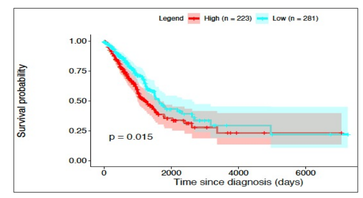

Figure 5: LUAD Results

- Two cancers showed that survival for patients with higher glucose uptake was significantly better ($p = 0.05$): brain lower grade glioma (LGG), thymoma (THYM)

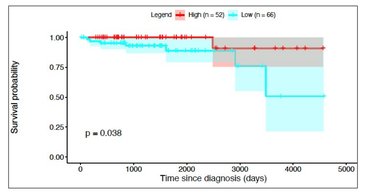

Figure 6: THYM results

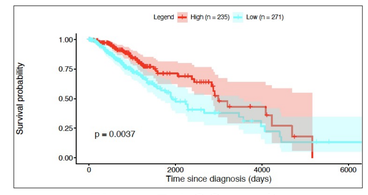

Figure 7: LGG results

Discussion

- Four cancers were consistent with previous knowledge, but two were opposite
- Found a shared and cancer-specific pattern in large cohorts
- Demonstrated the utility of METAFlux in determining metabolites of interest for therapeutics
- **Limitations:** mean was used to determine ”High” and “Low” groups, future studies with a systematic way of determining a cutoff would be useful

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