Proliferating versus nonproliferating cells have different metabolic needs.

**NONPROLIFERATING CELLS**
- quiescent or differentiated

Housekeeping functions

Glucose → ATP → NADPH → Amino acids

**PROLIFERATING CELLS**

Glucose → ATP → NADPH → PROTEIN → LIPIDS → CARBOHYDRATES → Amino acids

Housekeeping functions + anabolic reaction + antioxidant functions
Proliferating cells require glycolysis (aerobic glycolysis) and mitochondrial metabolism.

Hexosamine pathway

- NADPH from:
  - PPP
  - One carbon metabolism
  - IDH
  - Malic enzyme

- ATP from:
  - TCA
  - glycolysis

Glycosylation of proteins
Glutamate generates multiple amino acids.
Cell proliferation requires nutrient transporters
# GLUTs: Glucose transporters

<table>
<thead>
<tr>
<th>Name</th>
<th>Distribution</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLUT1</td>
<td>Is widely distributed in fetal tissues. In the adult, it is expressed at highest levels in erythrocytes and also in the endothelial cells of barrier tissues such as the blood–brain barrier. However, it is responsible for the low level of basal glucose uptake required to sustain respiration in all cells.</td>
<td>Levels in cell membranes are increased by reduced glucose levels and decreased by increased glucose levels. GLUT1 expression is upregulated in many tumors.</td>
</tr>
<tr>
<td>GLUT2</td>
<td>Is a bidirectional transporter, allowing glucose to flow in 2 directions. Is expressed by renal tubular cells, liver cells and pancreatic beta cells. It is also present in the basolateral membrane of the small intestine epithelium. Bidirectionality is required in liver cells to uptake glucose for glycolysis and glycogenesis, and release of glucose during gluconeogenesis. In pancreatic beta cells, free flowing glucose is required so that the intracellular environment of these cells can accurately gauge the serum glucose levels. All three monosaccharides (glucose, galactose, and fructose) are transported from the intestinal mucosal cell into the portal circulation by GLUT2.</td>
<td>Is a high-frequency and low-affinity isoform.(^{[12]})</td>
</tr>
<tr>
<td>GLUT3</td>
<td>Expressed mostly in neurons (where it is believed to be the main glucose transporter isoform), and in the placenta.</td>
<td>Is a high-affinity isoform, allowing it to transport even in times of low glucose concentrations.</td>
</tr>
<tr>
<td>GLUT4</td>
<td>Expressed in adipose tissues and striated muscle (skeletal muscle and cardiac muscle).</td>
<td>Is the insulin-regulated glucose transporter. Responsible for insulin-regulated glucose storage.</td>
</tr>
<tr>
<td>GLUT14</td>
<td>Expressed in testes</td>
<td>similarity to GLUT3(^{[12]})</td>
</tr>
</tbody>
</table>
T cells engage in different types of metabolism depending on their functions.

**Naïve T cells**
- Proliferation
- Cytokines antigen

**Effector T cells**
- Switch to memory T cells

**Memory T cells**

Catabolic metabolism → Anabolic metabolism → Catabolic metabolism
Cancer metabolism heterogeneity

A. Gradients
- Acidosis
- Hypoxia
- Apoptosis

Vasculature
- Nutrients and oxygen
- Stromal interaction

B. Global view
- Necrotic zone
- Quiescent zone
- Proliferative zone

Tissue matrix

C. Regional view

Clone A
Clone B
Clone C
Clone D
Clone E

Glucose metabolism diagram:
- Glucose to PPP (Glycolysis)
- Pyruvate to Lactate
- Glycerolipid synthesis
- Essential amino acids
- Protein synthesis
- Lipid synthesis
- Nucleotide biosynthesis
- Methylation
- One-carbon metabolism
- Acetyl-CoA
- Acetate
- Glutamine
- Glutaminolysis
Other example cancer metabolism

Hyperplasia

Blood vessel recruitment
Dense hypoxic core formation

Basement membrane invasion
Metastasis

Solid tumor progression

Invasive Front
↑ Mitochondrial respiration
↓ Lipogenesis

Highly Perfused Region
↑ Fuels other than glucose

Hypoxic core
↑ Glucose uptake & addiction
↑ Lactate
↓ Pyruvate

Regions differing in terms of metabolite composition

Stem cell enriched region
↑ Mitochondrial respiration
↑ Protein anabolism
↑ Lipid metabolism

Trailing follower cells
↑ Glycolysis & Lactate
↑ Lipogenesis
Cancer cells maintain redox balance

- **ROS GENERATORS**
  - Oncogenes
  - Oxidative metabolism
  - Hypoxia
  - Loss of tumour suppressors

- **ROS SCAVENGERS**
  - SODs
  - Nrf2
  - Catalase
  - GSH/GPX
  - PRXs
Signaling pathways that regulate cancer cell metabolism

mTOR
Kras
Myc
Proliferating cancer cells express PKM2 to regulate glycolysis
Metabolic adaptation in hypoxia
Alterations in certain metabolic enzymes drive cancer

Folate and NADPH

TCA CYCLE

FH

SDH

SDH

mIDH2

mIDH1

Isocitrate

Succinate

Fumarate

HIF

2HG

Succinate

Fumarate

OH

JmjC HISTONE DEMETHYLASE

TET2 DNA HYDROXYLASE

EPIGENETIC REGULATION

NUCLEUS

MITOCHONDRIUM

Glucose

3-Phosphoglycerate

PHGDH

Serine

ONE-CARBON METABOLISM

Folate and NADPH
Metabolism and cancer spreading

**Primary Tumour**

- CTC Formation
  - Anoikis
  - Ferroptosis
  - EMT
  - Glutamine
  - NADPH
  - PPP
  - Lipids

- Acetyl-CoA
- TCA cycle
- Metastasis initiating Ability

**CTCs**

- Survival in Circulation
  - Glutamate
  - GSH
  - ATP
  - G6PD
  - Serine Biosynthesis
  - HK2
  - Glutamine

- Fatty Acid Oxidation
- Mitochondrial Biogenesis
- PGC1α

**Secondary Tumour**

- Extravasation and Colonisation
  - Glucose
  - 3-PG
  - Pyruvate
  - mTORC1
  - Establishment of Metastatic Niche
  - Brain/Lung Colonisation

Macrometastasis
Metabolism can be targeted for cancer therapy

Repurposing the antidiabetic drug metformin to reduces tumorigenesis through multiple mechanisms