Cancer Cell Metabolism

Nadi Wickramasekera, Ph.D.
Dept. of Pharmacology and Therapeutics (L4-107)
Nadi.wickramasekera@RoswellPark.org
Acquired Abilities for Cancer Progression: Cancer Hallmarks 2000 vs 2011

- Deregulating cellular energetics
- Avoiding immune destruction
- Genome instability and mutation
- Tumor-promoting inflammation

Discuss and review the biochemical pathways involved in anaerobic and aerobic production of ATP

How is cancer-cell metabolism different? Warburg theory of cancer or "Warburg hypothesis -1924"

Cancer cell metabolism: Warburg and beyond. The possible drivers and advantages of the altered metabolism of cancer cells

Linking oncogenes and tumor suppressor's to tumor cell metabolism

Inhibiting the high glycolytic activity in cancer cells for therapeutic purposes

Mitochondria in cancer cells

Application and integration of tools to study tumor metabolism
Metabolism:

Collection of controlled intracellular biochemical reactions that convert nutrients and endogenous molecules to energy and matter (proteins, nucleic acids, and lipids) that sustain life.

A sequence of chemical reactions, where the product of one reaction serves as a substrate for the next, is called a metabolic pathway or biochemical pathway.

Most metabolic pathways take place in specific regions of the cell.
Map of Metabolic Pathways

Figure 15-1
Lehninger Principles of Biochemistry, Fifth Edition
© 2008 W. H. Freeman and Company
Basic Chemical Reactions Underlying Metabolism

Catabolism and Anabolism

Two major classes of metabolic reactions

Catabolic pathways
- Break larger molecules into smaller products
- Exergonic (release energy)

Anabolic pathways
- Synthesize large molecules from the smaller products of catabolism
- Endergonic (require more energy than they release)
Metabolism Composed of Catabolic and Anabolic Reactions

- Catabolism: Decomposition of larger molecules into smaller molecules, releasing energy.
- Anabolism: Synthesis of larger molecules from smaller molecules, requiring energy.

- Nutrients are broken down into smaller molecules during catabolism.
- Energy is released and stored as ATP (Adenosine Triphosphate).
- ATP is used for cellular processes and energy storage.
- Anabolism synthesizes larger molecules from smaller ones, providing energy for cellular structures and processes.
- Energy is lost as heat during catabolism.

Diagram shows the flow of energy and molecules from catabolism to anabolism, highlighting the role of ATP as an energy carrier.
Bioenergetics

Cell Energy
ATP is the main energy currency of cells

Formation of ATP
Degradation of glucose and glycogen
- Glycolysis
Oxidative formation of ATP
- Oxidative phosphorylation

Anaerobic pathways
- Do not involve $O_2$
- Glycolysis

Aerobic pathways
- Require $O_2$
- Oxidative phosphorylation
Basic Steps Involved

1. Glycolysis

2. Acetyl CoA Formation

3. Krebs Cycle

4. Electron Transport System
ATP Generating Metabolic Pathways

**Anaerobic**

**Aerobic**

**Glycolysis**
- Glucose \( \rightarrow \) Pyruvate

**Krebs Cycle**
- 2 NADH
- 2 Acetyl CoA

**Electron Transport Chain and Oxidative Phosphorylation**
- 6 NADH
- 2 FADH

**Cytoplasm**
- Electron shuttle across membrane

**Mitochondrion**
- Electron transport chain

**Electron Transport Chain**
- + about 34 ATP

**ATP Generation**
- + 2 ATP

**Substrate-Level Phosphorylation**
- by substrate-level phosphorylation
  - + 2 ATP
- depending on shuttle that transports electrons from NADH in cytosol
  - - 0 to about 2 ATP

**Oxidative Phosphorylation**
- by oxidative phosphorylation
  - + about 34 ATP

Maximum per glucose: About 38 ATP
Glycolysis

Glycolysis (“splitting of sugar”) breaks down glucose into two molecules of pyruvate

- Occurs in the cytoplasm and has two major phases
  - Energy investment phase
  - Energy payoff phase

- Occurs whether or not O\textsubscript{2} is present

- Glycolysis harvests chemical energy by oxidizing glucose to pyruvic acid

- The oxidation of glucose to pyruvic acid produces ATP and NADH

Energy yield: 2 ATP and 2 NADH
## Balance Sheet for Glycolysis

### Input
1. Glucose
2. ADP + P\textsubscript{i}
2. NAD\textsuperscript{+}

### Output
2. Pyruvate
2. ATP
2. NADH
Fate of Pyruvate

**Anaerobic Respiration**

- No O\(_2\) present
- Fermentation
- Pyruvate → Ethanol or lactate

**Glucose → 2 lactic acid + 2 ATP**

**Aerobic Respiration**

- O\(_2\) present
- Cellular respiration
- Pyruvate → Acetyl-CoA
- Acetyl-CoA → Citric acid cycle
Transition Reaction

The diagram illustrates the conversion of pyruvate to acetyl CoA in the mitochondrial matrix. The steps involved are:

1. Pyruvate is dehydrogenated to yield CO₂ and NAD⁺.
2. NAD⁺ is reduced to NADH and H⁺.
3. Acetyl CoA is produced from the reaction product.

The reaction involves transport proteins that facilitate the movement of pyruvate into the mitochondrial matrix, where it undergoes further biochemistry.
Transition Reaction

Krebs Cycle (Citric Acid Cycle)

Transition reaction:
- Pyruvate $\rightarrow$ Acetyl CoA
- CO$_2$

Citric acid cycle:
- 3 NADH
- 3 NAD$^+$
- FAD
- FADH$_2$
- 2 CO$_2$

(a) Pyruvate $\rightarrow$ Acetyl CoA, (b) Citric acid cycle producing ATP.
Oxidative Phosphorylation

Glycolysis → Krebs cycle → Electron transport chain and oxidative phosphorylation → ATP

Intermembrane space → Inner mitochondrial membrane

NADH + H⁺ (carrying e⁻ from food) → NAD⁺ → Electron Transport Chain

2 H⁺ + \( \frac{1}{2} \) O₂ → H₂O

ADP + Pi → ATP

Mitochondrial matrix → Electron Transport Chain → ATP Synthase
ATP Generating Metabolic Pathways

Glycolysis (in cytoplasm)

Glucose → (Several steps) → (2) pyruvate → (2) ATP

Preparatory step and Krebs Cycle (in mitochondria)

(2) pyruvate → (2) Acetyl groups → CO₂ → Krebs cycle → (2) ATP

Electron Transport System (in mitochondria)

(8) NAD⁺ (4) FAD (8) NADH (4) FADH₂ → Electron transport system → O₂ → H₂O → (32) ATP
### Overall ATP Production

<table>
<thead>
<tr>
<th>Process</th>
<th>ATP Produced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electron Transport System</td>
<td>34</td>
</tr>
<tr>
<td>Citric Acid Cycle</td>
<td>2</td>
</tr>
<tr>
<td>Glycolysis</td>
<td>2</td>
</tr>
<tr>
<td><strong>SUBTOTAL</strong></td>
<td><strong>38</strong></td>
</tr>
<tr>
<td>NADH Transport into Mitochondrion*</td>
<td>-2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>36</strong></td>
</tr>
</tbody>
</table>

(-2) some ATP is used to pump NADH across membrane so ~ **36 ATP**

The high-energy ATP molecules store 7.3 kcal of energy per mole
34 to 36 molecules ATP for every glucose molecule

about 40% efficiency

The high-energy ATP molecules store 7.3 kcal of energy per mole
What Feeds a Tumor?

- Normal genes (regulate cell growth)
- Tumor suppressor genes
- 1st mutation (susceptible carrier)
- Tumor suppressor genes
- Active oncogene
- 2nd mutation or loss (leads to cancer)
- No brakes
- No brakes
- Active oncogene

NCI web site
How is Cancer Cell Metabolism different?

Normal Tissue

- Lactate production
- No lactate production

Tumor Tissue

- Lactate production
- Lactate production

Matthew G. Vander Heiden, Science Webinar.
The Warburg Theory of Cancer or "Warburg hypothesis"

**Warburg hypothesis 1924**

“Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar…” -- Dr. Otto H. Warburg in Lecture

Observation that most cancer cells predominantly produce energy through a high rate of glycolysis followed by lactic acid fermentation, rather than through oxidative phosphorylation in the mitochondria
The uncontrolled growth and division of cancer cells relies not only on the deregulation of cell proliferation, but also on the reprogramming of cellular metabolism, including increased aerobic glycolysis (known as the Warburg effect).

Tumor Metabolism: How is it Different?

Glycolysis

Differentiated tissue

\[ \text{Glucose} + O_2 \rightarrow \text{Pyruvate} \rightarrow \text{CO}_2 \]

\[ \text{Glucose} - O_2 \rightarrow \text{Pyruvate} \rightarrow \text{Lactate} \]

Oxidative phosphorylation
~36 mol ATP/mol glucose

Anaerobic glycolysis
2 mol ATP/mol glucose

Proliferative tissue

\[ \text{Glucose} + O_2 \rightarrow \text{Pyruvate} \rightarrow \text{CO}_2 \]

Tumor

\[ \text{Glucose} + /- O_2 \rightarrow \text{Pyruvate} \rightarrow \text{Lactate} \]

Aerobic glycolysis (Warburg effect)
~4 mol ATP/mol glucose

### Warburg Effect

The higher the malignancy, the greater the fermentation and the smaller the respiration.

<table>
<thead>
<tr>
<th>Cells</th>
<th>$Q_{O_2}$</th>
<th>$Q_{M^{O_2}}$</th>
<th>$Q_{M^{N_2}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites cancer cells</td>
<td>-7</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>Earle’s cancer cells</td>
<td>-7</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>(high malignancy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earle’s cancer cells</td>
<td>-13</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>(low malignancy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorion of young embryos</td>
<td>-17</td>
<td>0</td>
<td>35</td>
</tr>
</tbody>
</table>

$Q_{O_2}$: oxygen consumed/ml

$Q_{M^{O_2}}$: lactic acid produced aerobically /ml

$Q_{M^{N_2}}$: lactic acid produced anaerobically /ml

---

Science 1956;124: (3215) 269-70
Higher Glucose Uptake Correlates With More Aggressive Phenotypes and Poorer Clinical Outcomes
Cancer cells must compensate for the ~18-fold lower efficiency of ATP production afforded by glycolysis relative to mitochondrial oxidative phosphorylation.

Cancer cells upregulate glucose transporters, which substantially increases glucose import into the cytoplasm.

Cancer Cell Metabolism: Warburg and Beyond
The Possible Drivers, Advantages, and Potential Liabilities of the Altered Metabolism of Cancer Cells

Hsu PP et al. Cell. 2008 Sep 5;134(5):703-7
The Possible Advantages of the Altered Metabolism of Cancer Cells

Altered Metabolism Provides Substrates for Biosynthetic Pathways

- Aerobic glycolysis is about 100 times faster than oxidative-phosphorylation in the mitochondria
- Increased glycolysis allows the diversion of glycolytic intermediates into various biosynthetic pathways
- Facilitates the biosynthesis of the macromolecules and organelles required for assembling new cells
- Ensures that cancer cells have a ready supply of the building blocks needed for macromolecule synthesis
Cell Proliferation Requires the Conversion of Nutrients into Biomass

Non-proliferating Cells

Proliferating Cancer Cells
Glucose and Glutamine Feed Cell Growth and Proliferation
Most of the Increased Nutrient Uptake in Cancer is Used to Support Biosynthesis

Pyruvate Kinase (PK-M2) Activity is Regulated by cell Growth Signals and Promotes Anabolic Metabolism

Normal differentiated cells
Oxidative Phosphorylation

Proliferating cells
Aerobic Glycolysis
PKM2 Regulates an Anabolic Program to Support Cancer Cell Proliferation

Nature Reviews | Cancer
The Possible Drivers of the Altered Metabolism of Cancer Cells

The tumor microenvironment selects for altered metabolism

**Hypotheses:** Hypoxic conditions (A decrease in ambient $O_2$ availability and levels)

Persistent metabolism of glucose to lactate even in aerobic conditions is an adaptation to intermittent hypoxia in pre-malignant lesions

Upregulation of glycolysis leads to microenvironmental acidosis requiring evolution to phenotypes resistant to acid-induced cell toxicity

Subsequent cell populations with upregulated glycolysis and acid resistance have a powerful growth advantage, which promotes unconstrained proliferation and invasion
Hypoxia-Inducible Transcription Factor (HIF)

Tumors outgrows the diffusion limits of its local blood supply, leading to hypoxia and stabilization of the hypoxia-inducible transcription factor, HIF.

HIF-1 is critical to glycolysis, induces nearly all enzyme transcription.

- pH regulation
- Inflammatory cell recruitment
- Angiogenesis
- Proliferation
- Motility
- Survival
- Extracellular matrix function
- Metabolism/mitochondrial function
The Control of the Metabolic Switch in Cancers by Oncogenes and Tumor Suppressor Genes

Arnold J. Levine¹,²* and Anna M. Puzio-Kuter²

OXPHOS- Oxidative Phosphorylation
Linking Oncogenes and Tumor Suppressor's to Tumor Cell Metabolism

<table>
<thead>
<tr>
<th>Gene</th>
<th>Effects</th>
<th>Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3K</td>
<td>Activates Akt via PI3; reduces (via Akt) expression of the β-oxidation</td>
<td>Ovarian and gastrointestinal cancer</td>
<td>Deberardinis et al. (2006)</td>
</tr>
<tr>
<td></td>
<td>enzyme carnitine palmityltransferase 1A (CPT1A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akt</td>
<td>Uregulates fatty acid synthase (FASN); activates mTOR complex 1</td>
<td>Breast and ovarian cancer</td>
<td>Wang et al. (2005)</td>
</tr>
<tr>
<td>Her2</td>
<td>Increases, through activation of PI3K, Akt, and mTOR, expression of</td>
<td>Mammary carcinoma</td>
<td>Yoon et al. (2007)</td>
</tr>
<tr>
<td></td>
<td>FASN and acetyl-CoA carboxylase α (ACCα) at the translational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrosine kinases</td>
<td>Generate phosphotyrosines that can bind to pyruvate kinase</td>
<td>Multiple cancers</td>
<td>Christofk et al. (2008b)</td>
</tr>
<tr>
<td></td>
<td>isoform PKM2, converting it from a tetramer to a less active dimer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E7 from HPV16</td>
<td>Binds PKM2, converting it from a tetramer to a less active dimer</td>
<td>Cervical carcinoma</td>
<td>Mazeuk et al. (2005)</td>
</tr>
<tr>
<td>p53</td>
<td>Required for expression of SCO2 and hence optimal OXPHOS; enhances the</td>
<td>Multiple cancers</td>
<td>Matoba et al. (2006);</td>
</tr>
<tr>
<td></td>
<td>expression of TIGAR, a glycolysis inhibitor; reduces the expression of</td>
<td></td>
<td>Benssaad et al. (2006);</td>
</tr>
<tr>
<td></td>
<td>the glycolytic enzyme phosphoglyceromutase</td>
<td></td>
<td>Kondoh et al. (2005)</td>
</tr>
<tr>
<td>VHL</td>
<td>Ubiquitin ligase required for degradation of HIF-1α</td>
<td>Clear cell renal carcinoma</td>
<td>Shaw and Cantley (2006)</td>
</tr>
<tr>
<td>TSC1 (hamartin) and TSC2 (tuberin)</td>
<td>Negative regulators of Rheb (which inhibits mTOR)</td>
<td>Tuberous sclerosis complex and lymphangioleiomyomatosis</td>
<td>Shaw and Cantley (2006)</td>
</tr>
<tr>
<td>PTEN</td>
<td>Negative regulator of class I PI3K</td>
<td>Cowden syndrome and prostate cancer</td>
<td>Shaw and Cantley (2006)</td>
</tr>
<tr>
<td>LKB1</td>
<td>Required for activation of AMPK</td>
<td>Peutz-Jeghers syndrome and sporadic lung</td>
<td>Shaw and Cantley (2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>NF1</td>
<td>Negative regulator of RAS and PI3K-Akt pathway</td>
<td>Neurofibromatosis</td>
<td>Shaw and Cantley (2006)</td>
</tr>
<tr>
<td>PML</td>
<td>Negative regulator of mTOR complex 1</td>
<td>Promyelocytic leukemia and lung cancer</td>
<td>Shaw and Cantley (2006)</td>
</tr>
<tr>
<td>Succinate dehydrogenase subunits SDHB, C, and D</td>
<td>Accumulated succinate competitively inhibits HIF-1α</td>
<td>Paraganglioma (SDHB, C, and D) and pheochromocytoma (SDHB and D)</td>
<td>Gottlieb and Tomlinson (2005)</td>
</tr>
<tr>
<td>Fumarate hydratase (fumarase)</td>
<td>Accumulated fumarate inhibits PHDs</td>
<td>Leiomyomatosis and papillary renal carcinoma</td>
<td>Gottlieb and Tomlinson (2005)</td>
</tr>
</tbody>
</table>
Signalling and Transcriptional Machinery that Regulate Metabolism: PI3K/Akt Pathway


©2012 by American Association for Cancer Research
p53 turns on the energy switch

...p53, one of the most frequently mutated genes in human cancers, regulates... glycolytic pathways through its direct transcriptional targets.

p53 Regulates Mitochondrial Respiration

Satoaki Matoba,¹ Ju-Gyeong Kang,¹ Willmar D. Patino,¹ Andrew Wragg,¹ Manfred Boehm,¹ Oksana Gavrilova,² Paula J. Hurley,³ Fred Bunz,³ Paul M. Hwang¹*

16 JUNE 2006 VOL 312 SCIENCE
p53 and Mitochondrial Respiration

![Graph showing O2 consumption for Liver mito and HCT116 cell with p53 genotypes: (+/+), (+/-), (-/-)]

![Diagram illustrating mitochondrial dysfunction with SCO2, SCO1, VDAC, and p53 expression levels for Liver mito and HCT116 cell with p53 genotypes: (+/+), (+/-), (-/-)]
p53 and Mitochondrial Respiration

HCT116

![Graph showing O2 consumption with siRNA, Mock NS, p53](image)

![Graph showing O2 consumption with p53 +/+, --/-- --/-- --/--](image)

![Western blot images of p53, SCO2, VDAC](image)

![Table showing pcDNA and pcDNA-SCO2 expression levels](image)
p53 and Mitochondrial Respiration

![Bar chart showing oxygen consumption and ATP source](image-url)
P53 Regulates Cellular Metabolism


©2012 by American Association for Cancer Research
Wild-type p53 and Mutant- p53 have Opposing Roles in Cellular Metabolism
Summary: Factors Affecting Cancer Metabolism

Genetic alterations (affecting p53, MYC, AMPK, PI3K and HIF1) → Abnormal metabolic phenotype → Bioenergetics, Biosynthesis, Redox → Tumour microenvironment (hypoxia, pH, nutrients and autophagy)

TW Mak et al., Nat Rev Cancer, 2011
Glycolytic Inhibitors With Anticancer Activity

## Glycolytic Inhibitors With Anticancer Activity

### Table 1 Chemicals targeting glycolysis-related enzymes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Tumor Type</th>
<th>Response</th>
<th>Concentration</th>
<th>Trial</th>
<th>N° Trial or Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-DG</td>
<td>HK</td>
<td>Prostate Cancer</td>
<td></td>
<td>30 mg/kg daily</td>
<td>Phase I/II</td>
<td>NCT00633087</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Advanced solid tumors</td>
<td></td>
<td></td>
<td></td>
<td>(suspended)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovarian carcinoma</td>
<td>Apoptosis</td>
<td>5 mM</td>
<td>Pre-clinical</td>
<td>(Zhang et al. 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mesothelioma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alveolar Rhabdomyosarcoma</td>
<td>Apoptosis</td>
<td>2-10 mM</td>
<td>Pre-clinical</td>
<td>(Ramirez-Peinado et al. 2011)</td>
</tr>
<tr>
<td>Lonidamine</td>
<td>HK</td>
<td>Glioblastoma multiforme</td>
<td>Partial stabilization</td>
<td>450 mg daily (+15 mg daily diazepam)</td>
<td>Phase II</td>
<td>(Oudard et al. 2003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benign Prostatic hyperplasia</td>
<td>Tumor volume Reduction</td>
<td>150 mg daily</td>
<td>Phase II</td>
<td>(Ditomno et al. 2005)</td>
</tr>
<tr>
<td></td>
<td>Bcr-Abl</td>
<td>Chronic myeloid leukemia</td>
<td></td>
<td>400 mg daily</td>
<td>Approved agent</td>
<td>(Druker et al. 2006)</td>
</tr>
<tr>
<td></td>
<td>KIT</td>
<td>Gastrointestinal stromal tumor</td>
<td></td>
<td>400 mg daily</td>
<td>Approved agent</td>
<td>(Demetri et al. 2002)</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td>HK</td>
<td>Glioblastoma multiforme</td>
<td>Partial stabilization</td>
<td>450 mg daily (+15 mg daily diazepam)</td>
<td>Phase II</td>
<td>(Oudard et al. 2003)</td>
</tr>
<tr>
<td>Oxythiamine</td>
<td>TKTL-1</td>
<td>Lewis lung carcinoma</td>
<td>Anti-metastatic effect</td>
<td>500 mg/kg daily</td>
<td>Pre-clinical</td>
<td>(Yang et al. 2010)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ehrlich’s ascites tumor cells</td>
<td>Tumor growth inhibition</td>
<td>400 mg/kg daily</td>
<td>Pre-clinical</td>
<td>(Boros et al. 1997)</td>
</tr>
<tr>
<td>FXII</td>
<td>LDH-A</td>
<td>Human lymphoma Human pancreatic cancer</td>
<td>Tumor growth inhibition</td>
<td>42 μg daily</td>
<td>Pre-clinical</td>
<td>(Le et al. 2010)</td>
</tr>
<tr>
<td>CHC</td>
<td>MCT1</td>
<td>Colon and lung carcinoma</td>
<td>Necrosis Radiosensitization</td>
<td>125 mM</td>
<td>Pre-clinical</td>
<td>(Sonveaux et al. 2008)</td>
</tr>
</tbody>
</table>
The possible effects of loss of supercomplex organization on mitochondrial function during oncogenesis.
Application and Integration of Tools to Study Tumor Metabolism
Summary

- Reprogramming energy metabolism is an emerging hallmark in deregulation of cell proliferation.
- The Warburg effect, or aerobic glycolysis, is the observation that most cancer cells produce energy through a high rate of glycolysis followed by lactic acid fermentation, even in the presence of oxygen.
- ~90 years after Warburg’s idea, aerobic glycolysis indeed play important roles in cancer biology.
- Using glucose analog FDG, PET can pinpoint the location of cancer cells.
- Changes in the tumor microenvironment, oncogene activation, transcription rate of enzymes and transporters involved in glycolysis and oxidative metabolism are believed to push cancer cells into adopting aerobic glycolysis.
- These changes are a result of transcription factors such as HIF and p53.
- Drugs currently in development/clinical trials to disrupt aerobic glycolysis in cancer cells, are focused on blocking glucose uptake, or inhibiting specific glycolytic enzymes.
- Cancer metabolism can cooperated into signal transduction, and serve as a route to study cancer biology.
- Solid tumor is heterogeneous, and each cancer cell is a function of oxygen, glucose, pH, HIF-1, and p53…, which make targeting therapy more challenging.
References

**Recommended Reading:**


**Required Reading:**