Alterations in metabolite driven gene regulation

• $\alpha$-ketoglutarate dependent dioxygenases are the TET family of DNA demethylases, Jumonji C family of histone demethylases and a family of prolyl hydroxylase (PHD) enzymes, which among other processes, regulate HIF1α levels in response to oxygen availability and oxidative stress.

• $\alpha$-ketoglutarate dependent dioxygenases are prone to inhibition by their reaction product, succinate, as well as by fumarate, the downstream product of succinate degradation in the TCA cycle
Oncometabolites: 2HG
The 6 features of cancer metabolic reprogramming

• Deregulated uptake of glucose and amino acids
• Use of opportunistic modes of nutrient acquisition
• Use of glycolysis/TCA cycle intermediates for biosynthesis and NADPH production
• Increased demand for nitrogen
• Alterations in metabolite driven gene regulation
• Metabolic interactions with the TME
Metabolic interactions with the microenvironment

- Lactate
  - attenuate the activation of dendritic cells and T cells and monocyte migration (Fischer et al 2007)
  - Stimulates M2 polarization (Colegio et al 2014).
  - Promote angiogenesis (Sonveaux et al 2012).
  - Stimulate HA production by fibroblasts, which may contribute to tumor invasiveness (Stern et al 2002)
Metabolic interactions with the microenvironment

- Numerous solid tumor types overexpress tryptophan degrading dioxygenases indoleasamine 2, 3 dioxygenase (IDO1) and tryptophan 2, 3 dioxygenase (TDO2), which catalyze the conversion of an essential amino acid, tryptophan, into its derivative, kynurenine (Munn and Mellor, 2007). As a consequence, tryptophan depletion triggers amino acid deprivation associated apoptosis of effector T cells (Fallarino et al 2002). Accumulated kynurenine acts as a ligand for aryl hydrocarbon receptor (AhR) (Opitz et al 2011).
  - In a manner dependent on AhR, kynurenine promotes Treg phenotype, further contributing to the suppression of antitumor immune responses (Fallarino et al 2006)
Carbon crosstalk?

- Energy source
- Paracrine signaling
- Juxtacrine signaling
- Immune cells
- Fibroblasts
- ECM deposition
Targeting Cancer Metabolism
<table>
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<tr>
<th>DRUG</th>
<th>TARGET(S)</th>
<th>EXAMPLE INDICATIONS</th>
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<tr>
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<td><strong>Nucleotide Metabolism</strong></td>
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<td>Methotrexate</td>
<td>Dihydrofolate Reductase (DHFR)</td>
<td>Lymphoma</td>
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<td>Breast Cancer</td>
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<td>Choriocarcinoma</td>
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<td>Osteosarcoma</td>
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<td>Pemetrexed</td>
<td>DHFR</td>
<td>Lung cancer</td>
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<td>Glycinamide ribonucleotide formyl-transferase (GARFT)</td>
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<td>5-Fluorouracil</td>
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<td>Gemcitabine</td>
<td>Ribonucleotide reductase</td>
<td>Pancreatic, lung cancer</td>
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<td>Hydroxyurea</td>
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<td>Leflunomide</td>
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<td>Rheumatoid arthritis</td>
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<td>Azathioprine</td>
<td>DNA synthesis</td>
<td>Immunosuppression for transplant</td>
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<td><strong>Amino Acid Metabolism</strong></td>
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<td>L-asparaginase</td>
<td>Asparagine depletion</td>
<td>ALL</td>
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<td><strong>Select Drugs in Trials</strong></td>
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Glutaminase inhibitor

Mutant IDH inhibitors

Inhibitors of glycolysis

Targeting redox
How we study cancer metabolism

BIOMASS
ENERGY
REDOX
ROS in cancer

- Radiation, carcinogen, inflammation, hypoxia

Extracellular

ROS

Intracellular

Genomic instability
- Orcogene activation
- Aberrant metabolism
- Mitochondrial dysfunction
- Antioxidant deficit

- Oxidative DNA damage
- Gene mutation or deletion
- Loss of functional p53
- DNA repair capacity

Cancer development and progression
OXIDATIVE STRESS

\[ \text{O}_2 \xrightarrow{e^-} \text{O}_2^- \xrightarrow{} \text{H}_2\text{O}_2 \]

\[ \text{Fe}^{2+} \xrightarrow{} \cdot\text{OH} \]

REDOX SIGNALING

\[ \text{SH} \xrightarrow{} \text{S}^\cdot \xrightarrow{} \text{SH} \]

\[ \text{H}_2\text{O} \]
Studying the redox proteome

Chio and Tuveson, TMM, 2017
MITOCHONDRIAL RESPIRATION

BIOMASS  ENERGY  REDOX

What is the purpose of respiration?