Cancer Metabolism

Adapted from Edition 3 of the Tocris Cancer Product Guide
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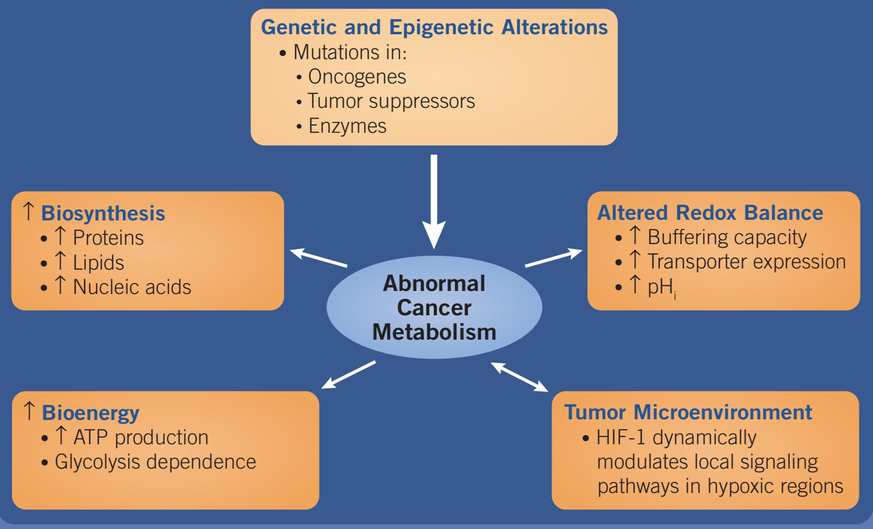
In 1924 Otto Warburg first discovered that cancer cells generated a large proportion of their ATP by metabolizing glucose via aerobic glycolysis (as opposed to mostly through oxidative phosphorylation (OXPHOS) in normal cells). Initially it was thought that this Warburg effect was a cause of cancer, but it was later established that this shift to glycolytic metabolism was an effect of cancer cell transformation. Genetic changes and epigenetic modifications in cancer cells alter the regulation of cellular metabolic pathways. These distinct metabolic circuits could provide viable cancer therapeutic targets.

Abnormal Cancer Metabolism



Main Targets in Cancer Metabolism

Glycolysis, Pentose Phosphate Pathway and Transporters

Enhanced rates of glycolysis (approximately 200-fold) produce increased levels of ATP more rapidly than OXPHOS, but this process is far less efficient, so there is an increased demand for glucose. As such, GLUT expression is frequently increased in cancer cells, as is MCT expression, which removes the increased levels of lactate from the cells. Another commonly seen adaptation is an increase in the number of glutamine transporters. The first step in glutamine catabolism is the hydrolysis of glutamine into glutamate and ammonia by GLS1, which is important in lipid biosynthesis and NADPH production.

There is also an increase in the flux through the PPP. The PPP is required to generate precursors for amino acid synthesis and NADPH (an integral component in lipid and nucleotide synthesis, as well as redox homeostasis). Depending on the requirements of the cancer cell, glucose is directed into either the PPP or glycolysis pathway (or both). For example, during high oxidative stress, cancer cells divert the flux of glucose away from glycolysis into the PPP to produce more NADPH.

Krebs Cycle

Glucose is broken down into pyruvate, which is then transported into the mitochondria. It is converted into acetyl-CoA which then enters the Krebs cycle. This produces energy in the form of ATP, precursors for amino acid synthesis and the reducing agent NADPH.

One of the major enzymes that feeds into the cycle is GDH, which converts glutamate to α-KG, an essential intermediate in the Krebs cycle. Inhibition of GDH has been shown to suppress the use of glutamine in the Krebs cycle and sensitize glioblastoma cells to glucose withdrawal. α-KG is a substrate for mutant forms of IDH, which has been linked to oncogenesis. Mutant IDH converts α-KG to D2HG resulting in high intracellular levels of D2HG. D2HG competitively blocks α-KG binding at a family of enzymes called 2-OG-dependent dioxygenases, which are regulators of important epigenetic events. Furthermore, IDH mutations impair cell redox capacity.

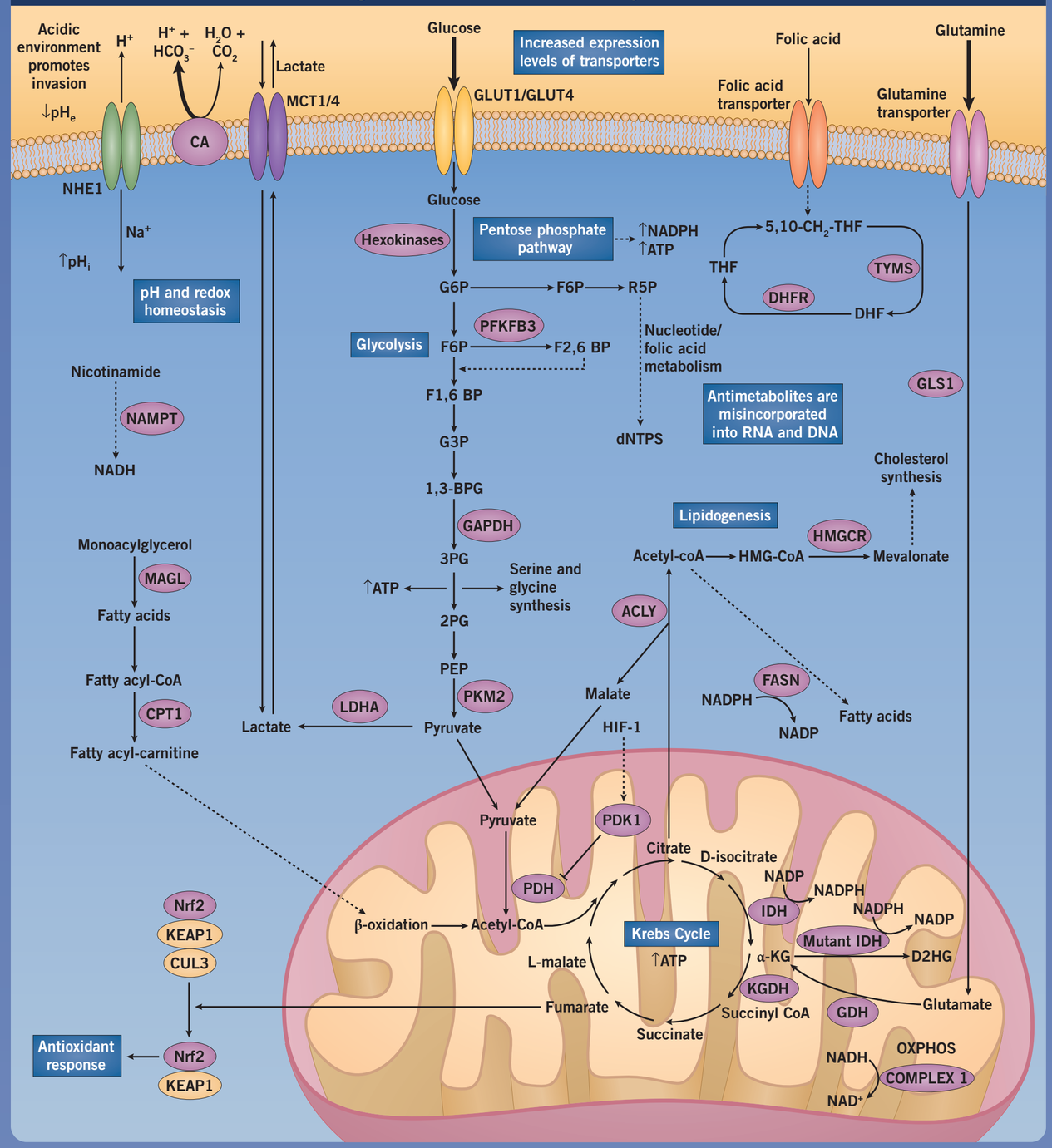
Lipidogenesis

Recent evidence suggests that in certain types of cancer such as prostate cancer, the initiation of cell proliferation relies more on lipid metabolism than glycolysis. Targeting fatty acid synthesis can cripple a cell's ability to proliferate and survive because it limits lipid membrane production, as well as blocking β-oxidation of fatty acids in mitochondria.

pH and Redox Balance

Cancer cells are able to survive in their hostile microenvironments because of increased expression of proton pumps and ion transporters. Aberrant regulation of hydrogen ions leads to a reversal of the pH gradient across tumor cell membranes, resulting in a more basic intracellular pH (pH_i) and a more acidic extracellular pH (pH_e). It is critical to cancer cell survival that the intracellular environment does not become acidified because this could induce apoptosis.

Altered Regulation of Metabolic Pathways in Cancer Cells



ACLY, ATP citrate lyase; **ATP**, Adenosine triphosphate; **1,3-BPG** 1,3-Bisphosphoglyceric acid; **CA**, carbonic anhydrase, **CPT1**, carnitine palmitoyltransferase; **CUL3**; Cullin 3; **D2HG**, D-2-hydroxyglutarate; **DHF**, dihydrofolate; **DHFR**, DHF reductase; **FASN**, fatty acid synthase; **F1,6BP**, fructose-1,6-bisphosphate; **F2,6BP**, fructose-2,6-bisphosphate; **F6P**, fructose 6-phosphate; **GAPDH**, glyceraldehyde-3-phosphate dehydrogenase; **GDH**, glutamate dehydrogenase; **GLUT**, glucose transporter; **GLS1**, glutaminase; **G3P**, Glyceraldehyde-3-phosphate; **G6P**, glucose-6-phosphate; **HIF-1**, Hypoxia-inducible factor 1; **HMGCR**, HMG-CoA reductase; **IDH**, isocitrate dehydrogenase; **α-KG**, α-ketoglutarate; **KGDH**, α-ketoglutarate dehydrogenase; **LDHA**, lactate dehydrogenase A; **MAGL**, monoacylglycerol lipase; **MCT**, monocarboxylate transporter; **NAD^+/NADH**; Nicotinamide adenine dinucleotide (oxidised/reduced forms respectively); **NADPH**, Nicotinamide adenine dinucleotide phosphate; **NAMPT**, nicotinamide phosphoribosyltransferase; **NRF2**, Nuclear factor (erythroid-derived 2)-like 2; **OXPHOS**, oxidative phosphorylation; **PDH**, pyruvate dehydrogenase; **PDK**, pyruvate dehydrogenase kinase; **PEP**, phosphoenolpyruvate; **PFKFB3**, 6-phosphofructo-2-kinase/fructose- 2,6-bisphosphatase; **2PG**, 2-phosphoglycerate; **3PG**, 3-phosphoglycerate; **PKM2**, pyruvate kinase M2 isoform; **PPP**, Pentose Phosphate Pathway; **ROS**, reactive oxygen species; **R5P**, ribose-5-phosphate; **$5,10\text{-}CH_2\text{-}THF$**, 5,10-methylene tetrahydrofolate; **THF**, tetrahydrofolate; **TYMS**, thymidylate synthase.

Products available from Tocris

ATP-citrate Lyase (ACLY)
BMS 303141, SB 204990

Carbonic Anhydrases (CA)
Topiramate, U 104

Carnitine Palmitoyltransferase (CPT)
(*R*)-(+)-Etomoxir

Dihydrofolate Reductase
CI 898, Methotrexate

Fatty Acid Synthase (FASN)
C 75, Orlistat

GAPDH
CGP 3466B

Glucose Transporters (GLUT)
STF 31

Glutaminase (GLS1)
968

Glutathione *S*-transferase
CRID3 sodium salt

Hexokinase
GKA 50, Lonidamine

HMG-CoA Reductase (HMG-CoA)
Atorvastatin, Pitavastatin calcium

Lactate Dehydrogenase A (LDHA)
GSK 2837808A

Monoacylglycerol Lipase (MAGL)
JJKK 048, JW 642, JZL 184, JZL 195, KML 29

Monocarboxylate Transporters (MCTs)
AR-C155858, CHC, UK 5099

MutT homolog-1 (MTH1)
SCH 51344

NAMPT
FK 866, GPP 78, STF 118804

Na^+/H^+ Exchanger (NHE)
Cariporide, EIPA, Zoniporide

Nrf2
CDDO Im, NK 252, TAT 14

Oxidative Phosphorylation (OXPHOS)
Rotenone

PFKFB3
3PO, PFK 15, YZ9

Pyruvate Dehydrogenase (PDH)
CPI 613

Pyruvate Dehydrogenase Kinase (PDK)
DCA

Pyruvate Kinase M2 (PKM2)
ML 202

Ribonucleotide Reductase
Gemcitabine hydrochloride

Thymidylate Synthetase
Floxuridine, 5-Fluorouracil, Trifluorothymidine

References:
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