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.

**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 HIF expression, which restores the increased levels of lactate from the cells. Another commonly seen adaptation is an increase in the number of glucose transporters. The first step in glycolysis catalysed is the hydrolysis of glucose into a 6-phosphate. There is also an increase in the flux through the PPP. The PPP is required to generate precursors for the TCA cycle, and provides substrates for the biosynthesis of nucleic acids and lipids. 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. The cycle 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 2-DG-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 transport proteins and ion transporters. Alterant regulation of hydrogen ions leads to a reversal of the pH gradient across tumor cell membranes, resulting in a more basic intracellular pH (pH<sub>i</sub>) and a more acidic extracellular pH (pH<sub>e</sub>). It is critical to cancer cell survival that the intracellular environment does not become acidified because this could induce apoptosis.

**Abnormal Metabolic Regulation in Tumor Cells**

**Bioenergy**
- ATP production
- Glycolysis dependence

**Genetic and Epigenetic Alterations**
- Mutations in:
  - Oncogenes
  - Tumor suppressors
  - Enzymes

**Tumor Microenvironment**
- HIF-1 dynamically modulates local signaling pathways in hypoxic regions

**Pathways in Hypoxic Regions**

**Antimetabolites**
- Resistant: targeting cancer metabolism to

**References:**
- Gameiro et al (2014) Blocking lactate export by...