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Opinion Article

Targeting Cancer Metabolism: From the Warburg Effect to Modern Therapeutic Approaches

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DESCRIPTION

Cancer is a complex disease characterized by uncontrolled cellular growth, invasion into surrounding tissues, and metastasis to distant organs. The past few decades have seen substantial advances in understanding cancer biology, with metabolism emerging as a key area of interest. Cancer cells rewire their metabolism to support rapid proliferation, survival, and invasion, often differing significantly from the metabolic pathways employed by normal cells. This altered metabolism provides both challenges and opportunities for cancer therapy, making cancer metabolism a potential therapeutic target.

One of the earliest discoveries linking cancer and metabolism was made by Otto Warburg in the 1920s. He observed that cancer cells exhibit a high rate of glycolysis followed by lactic acid fermentation, even in the presence of sufficient oxygen: A phenomenon termed aerobic glycolysis or the Warburg effect. While normal cells predominantly produce energy through oxidative phosphorylation in mitochondria, cancer cells rely heavily on glycolysis to meet their energy and biosynthetic demands. This shift in metabolism supports rapid proliferation by providing cancer cells with metabolic intermediates for nucleotide, amino acid, and lipid biosynthesis. The Warburg effect, while initially controversial, has since become a foundation of cancer metabolism research. However, it is now understood that the Warburg effect is not the only metabolic alteration in cancer cells. Cancer cells can utilize multiple metabolic pathways to fuel growth and resist stress, which complicates efforts to develop targeted therapies.

Metabolic reprogramming in cancer

Cancer cells undergo metabolic reprogramming to adapt to the changing environment and sustain their uncontrolled growth. Several factors contribute to this reprogramming, including genetic mutations, Tumor Microenvironment (TME), and oncogenic signaling pathways.

Mutations in key oncogenes and tumor suppressor genes, such as *MYC*, *KRAS*, and *TP53*, alter metabolic pathways. For example, mutations in *IDH1* and *IDH2* lead to the production of 2-hydroxyglutarate, an oncometabolite that promotes tumorigenesis by interfering with DNA and histone methylation. Tumors often grow in hypoxic conditions, where oxygen supply is limited. Hypoxia-Inducible Factors (HIFs) activate under low-oxygen conditions and promote glycolysis while inhibiting oxidative phosphorylation. This allows cancer cells to survive in the hard TM and continue proliferating. Several signaling pathways involved in cancer, such as the PI3K/AKT/mTOR and MAPK pathways, directly regulate metabolic processes. These pathways increase glucose uptake and glycolysis, while also promoting lipid and protein synthesis, which are essential for sustaining rapid cell division. The reprogramming of cancer metabolism not only fuels the energy needs of cancer cells but also allows them to avoid apoptosis, invade surrounding tissues, and evade the immune system.

Key metabolic pathways in cancer

In Glycolysis and glutaminolysis as mentioned, cancer cells preferentially use glycolysis, even in the presence of oxygen. In addition to glycolysis, many cancer cells rely on glutaminolysis, the breakdown of glutamine, as a carbon source for biosynthetic pathways. Glutamine provides nitrogen for nucleotide and amino acid synthesis, as well as replenishing the Tricarboxylic Acid (TCA) cycle.

Lipid metabolism are essential for membrane biosynthesis and energy storage. Cancer cells often upregulate fatty acid synthesis and lipid desaturation to meet their increased demand for membranes during rapid cell proliferation. In some cancers, Fatty Acid Oxidation (FAO) is also upregulated, providing an additional source of energy. While cancer cells predominantly use glycolysis, mitochondria remain important for cancer metabolism. The TCA cycle provides precursors for biosynthesis and supports redox balance through the production of Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH), which is important for detoxifying Reactive Oxygen Species (ROS). Furthermore, oxidative phosphorylation can be important for certain types of cancer, particularly in metastatic cells.

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Certain amino acids, like serine and glycine, are important for cancer cell growth and survival. These amino acids are involved in one-carbon metabolism, which is essential for DNA methylation, nucleotide synthesis, and redox regulation. Cancer cells also rely heavily on arginine, methionine, and proline metabolism to support their growth.