Lecture 17-18 Cancer

Cancer cells exhibit profound metabolic reprogramming to support their rapid growth and proliferation. This reprogramming includes an increased reliance on aerobic glycolysis, known as the Warburg effect, and the utilization of alternative nutrients, driven by mutations in various metabolic regulators and signaling pathways.

Warburg Effect
The Warburg effect is characterized by the preferential uptake of glucose and its conversion to lactate in the presence of oxygen. This seemingly inefficient metabolic strategy is advantageous for cancer cells, allowing for the rapid generation of ATP and the production of biosynthetic intermediates required for cell proliferation.

Molecular Detailing of the Warburg Effect:
At the molecular level, the Warburg effect involves upregulated expression of glucose transporters (GLUT1 and GLUT4) and enzymes like hexokinase 2, which phosphorylates glucose, trapping it within the cell. The pyruvate generated is predominantly converted to lactate by lactate dehydrogenase (LDH), even when oxygen is sufficient for oxidative phosphorylation in the mitochondria.

mTOR Signaling and Cancer Cell Metabolism:
Central to cancer cell metabolism is the mammalian target of rapamycin (mTOR) pathway, which is often dysregulated in cancer. The mTOR complex 1 (mTORC1) integrates signals from growth factors, energy status, and nutrient availability to regulate cellular growth and metabolism.

Growth Factor Receptors and Ras:
Growth factor receptors activate the PI3K-AKT pathway upon ligand binding. In cancer, the Ras protein, a small GTPase and a critical mediator of growth factor signaling, is frequently mutated to an active form, contributing to continuous AKT activation.

mTOR
The mTOR signaling pathway is intricately connected to cancer cell metabolism, serving as a central hub for integrating growth signals and nutrient availability. Activation of this pathway begins at the cell membrane with growth factor receptors. When these receptors are engaged, they activate the PI3K-AKT pathway. PI3K phosphorylates PIP2 to PIP3, which then recruits and activates AKT. Activated AKT drives cancer cell growth and survival by stimulating glycolysis and biosynthesis, upregulating glucose transporters, and modulating glycolytic enzymes.
Conversely, PTEN, a tumor suppressor phosphatase, counteracts PI3K signaling by dephosphorylating PIP3 back to PIP2, serving as a brake on this growth-promoting pathway. The loss or mutation of PTEN is a common event in cancer, leading to unchecked PI3K-AKT activity and subsequent mTOR activation.
Simultaneously, the LKB1-AMPK pathway acts as a cellular energy sensor. Under conditions of low energy, AMPK inhibits mTORC1, halting biosynthetic processes and triggering catabolic pathways to conserve energy. Cancer cells often bypass this regulatory mechanism via mutations in LKB1 or alterations in the AMPK pathway, resulting in sustained mTORC1 signaling.
Myc and Cancer Metabolism:
The oncogene Myc regulates metabolism by promoting the expression of genes involved in glycolysis and glutaminolysis. It also supports the biosynthesis of nucleotides, proteins, and lipids, all necessary for the construction of new cells.
HIF-1 in Hypoxia and Normoxia:

The transcription factor HIF-1 is stabilized under hypoxic conditions, inducing the expression of glycolytic enzymes and angiogenic factors like VEGF. In many cancers, HIF-1 is aberrantly activated even in normoxia, maintaining a metabolic profile suitable for cancer progression.

Angiogenesis - Feeding the Tumor:

The growth of new blood vessels into the tumor, driven by factors like VEGF, ensures a steady supply of nutrients and oxygen, essential for the tumor's expansion. Angiogenesis also facilitates the removal of waste products such as lactate and carbon dioxide.