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Commentary

Glycolysis Inhibition in Hypoxic Tumor Microenvironment: Natural Compounds and their Mechanisms of Action

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DESCRIPTION

The Tumor Microenvironment (TME) plays a crucial role in the development and progression of cancer. One of the hallmarks of the TME is hypoxia, which is a condition where the oxygen supply to the tumor cells is reduced. Hypoxia causes a shift in the metabolism of cancer cells from oxidative phosphorylation to glycolysis. This shift in metabolism is known as the Warburg effect, and it provides cancer cells with the energy and building blocks necessary for their growth and survival. However, this metabolic shift also creates an opportunity for therapeutic intervention. Natural compounds have been shown to regulate glycolysis in hypoxic TME and may provide a promising approach for cancer treatment. In this article, we will discuss the natural compounds that regulate glycolysis in hypoxic TME and their potential as cancer therapeutics.

Glycolysis in hypoxic TME

Glycolysis is a metabolic process that breaks down glucose to produce energy in the form of ATP. In normal cells, glucose is metabolized through oxidative phosphorylation, which is a more efficient process for energy production. However, in hypoxic TME, the oxygen supply to the cells is reduced, which impairs oxidative phosphorylation. To compensate for the lack of oxygen, cancer cells shift their metabolism towards glycolysis, which provides a less efficient but faster way to generate ATP. This shift in metabolism also allows cancer cells to produce the building blocks necessary for their growth and proliferation.

The Warburg effect is a phenomenon where cancer cells rely on glycolysis even in the presence of oxygen. This metabolic shift is believed to be a result of genetic alterations in cancer cells that activate glycolysis and suppress oxidative phosphorylation. The upregulation of glycolysis in cancer cells creates a dependency on glucose and other nutrients that are required for the process. As a result, glycolysis has become an attractive target for cancer therapy.

Natural compounds that regulate glycolysis in hypoxic TME

Several natural compounds have been shown to regulate glycolysis in hypoxic TME. These compounds have different mechanisms of action, but they all target glycolysis to inhibit cancer cell growth and survival. Here, we will discuss some of the most promising natural compounds that regulate glycolysis in hypoxic TME.

Resveratrol: Resveratrol is a polyphenolic compound found in grapes, berries, and other plants. It has been shown to have antioxidant, anti-inflammatory, and anticancer properties. Resveratrol targets glycolysis by inhibiting the activity of Hexokinase 2 (HK2), which is a key enzyme in glycolysis. HK2 is upregulated in cancer cells and is required for the glycolytic flux. Resveratrol inhibits HK2 by binding to its active site and preventing glucose from entering the glycolytic pathway. This leads to a decrease in ATP production and an increase in apoptosis in cancer cells. Resveratrol has been shown to inhibit tumor growth in several cancer types, including breast, prostate, and colon cancer.

Curcumin: Curcumin is a polyphenolic compound found in turmeric. Anti-inflammatory, antioxidant, and anticancer effects have all been demonstrated. Curcumin targets glycolysis by inhibiting the activity of Pyruvate Kinase M2 (PKM2), which is another key enzyme in glycolysis. PKM2 is upregulated in cancer cells and is required for the glycolytic flux. Curcumin inhibits PKM2 by binding to its active site and preventing the conversion of phosphoenolpyruvate to pyruvate. This leads to a decrease in ATP production and an increase in apoptosis in cancer cells.

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