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Review

Glycolysis inhibition as a cancer treatment and its role in an anti-tumour immune response

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ABSTRACT

Increased glycolysis is the main source of energy supply in cancer cells that use this metabolic pathway for ATP generation. Altered energy metabolism is a biochemical fingerprint of cancer cells that represents one of the "hallmarks of cancer". The immune system can prevent tumour growth by eliminating cancer cells but this editing process ultimately results in poorly immunogenic cells remaining allowing for unchallenged tumour growth. In this review we look at the glycolysis pathway as a target for cancer treatments. We also examine the interplay between the glycolysis modulation and the immune response as an anti-cancer therapy.

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1. Introduction

Intracellular chemical transformations sustain life and this is referred to as metabolism. Organisms grow and reproduce, respond to their environment, and maintain their structure as a result of enzyme-catalyzed metabolism. Biochemical reactions in cells ensure daily operations of a cell are accomplished. These reactions are either up- or downregulated depending on the cell's needs and functions. Monitoring of the numerous cellular anabolic (breaking down of organic matter) and catabolic (metabolic component construction) pathways is crucial to ensure they are balanced in a coordinated fashion at any given time. Cells organise these reactions into different enzyme-catalyzed pathways to achieve this goal.

Metabolic pathways are organised chemical reactions of metabolism where a chemical compound is converted into another one by a series of enzymatic activity. Enzymes are vital to metabolism. This is because they allow the organism to drive energy-consuming reactions that will not occur independently. This is achieved by coupling reactions with spontaneous reactions which release energy. Enzymes speed up reaction rates as they act as catalysts besides allowing the metabolic pathway regulation secondary to changes in the cell's environment or to other cellular signaling.

Basic metabolic pathways and their components are similar across vast different species [1]. This is exemplified by a set of carboxylic acid (citric acid intermediates) which is present in all known organisms. The early appearance in evolutionary history and efficiency in retention have likely led to the similarities in metabolism [2,3]. The process of catabolism harvests energy by means of cellular respiration, and in anabolism, cellular components are constructed using energy e.g. nucleic acids and proteins. An example of a metabolic pathway which is common in virtually all cells, both prokaryotic and eukaryotic, is glycolysis.

2. Glycolysis

Glycolysis pathway of cellular respiration is a series of reactions that constitute the first phase of most carbohydrate catabolism. The word glycolysis is derived from two Greek words and means the breakdown of something sweet. Glycolysis is an oxygen independent metabolic pathway, meaning it does not use molecular oxygen for any of its reactions. It occurs in the cellular cytosol of most organisms. *Embden–Meyerhof–Parnas (EMP pathway)* [4] is the most common type of glycolysis. Other types include the *Entner-Doudoroff pathway* and various hetero- and homofermentative pathways.

The glycolytic pathway can be divided into two phases. Firstly, the preparatory phase (or investment phase) is where ATP is utilised and followed by production of ATP in the second Pay Off phase. In the cell, glucose catabolism occurs via two main pathways, (1) one which involves mitochondrial respiration (longer but energy-efficient pathway) and (2) pathway that does not involve the mitochondria (glycolysis; less energy-efficient and a shorter pathway). Oxidative phosphorylation is a pathway involving mitochondrial respiration. Depending on intracellular requirements and available resources, cells undergo either glycolysis or oxidative phosphorylation to metabolise glucose. Glycolysis is inhibited ('Pasteur effect') by the presence of oxygen in most mammalian cells. Oxygen allows the mitochondria to oxidise pyruvate to carbon dioxide and water. The maintenance of energy production in various conditions of oxygen concentrations is met by the mammalian cells' metabolic adaptability.

'Anaerobic glycolysis' is whereby glucose is metabolised via glycolysis instead of mitochondrial oxidation in low levels of oxygen. This results in the conversion of pyruvate into lactate, which is then exported. Interestingly, 'aerobic glycolysis' (glycolysis in the presence of oxygen) is also seen in cancer cells. This almost a century-old phenomenon in cancer cells is known as the 'Warburg effect', and was hypothesised in 1924 by the German scientist Otto Heinrich Warburg.

2.1. Warburg hypothesis/effect

Cancer cells mainly produce energy by an increased rate of glycolysis (200 times more as compared to normal tissues of origin) followed by fermentation of lactate in the cytosol of the cell, even if oxygen is plentiful [5]. This is to fulfill their bioenergetic and biosynthetic demands to support rapid proliferation. This observation in oncology is called the 'Warburg effect'. In normal cells however the rate of aerobic glycolysis is lower, and is followed by oxidative phosphorylation in the mitochondria, where pyruvate is oxidated [6–8]. It was postulated by Otto Warburg that this metabolic change is the fundamental cause of cancer [9], a claim now known as the Warburg hypothesis. However, it was then discovered that mutations in oncogenes and tumour suppressor genes are responsible for malignant transformation. Instead of a cause, the Warburg effect is considered to be more of a result of these genetic mutations [10,11].

2.2. Cellular metabolism

Normal cell metabolism derives about 70% of its energy from the Krebs cycle and only 20% from glycolysis. Most of its energy production is via oxidative phosphorylation. In contrast, cancer cells exhibit a defective tricarboxylic acid (TCA) cycle and derive little or no energy from it. Instead, they derive almost all their energy from glycolysis (fermentation phosphorylation) and in the absence of oxygen. Normal cells operate at normal metabolic levels and reproduce themselves at a regulated phase by possessing hormones and enzymes behaving in balanced manner. Normal functioning cells orderly-divide to proliferate only when in demand. Cancer cells on the other hand are overactive and reproduce themselves in requiring more nutrients. These cells have overactive or underactive enzymes and hormones, and develop an aberrant