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Review

A global view of the biochemical pathways involved in the regulation of the metabolism of cancer cells

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ABSTRACT

Cancer cells increase glucose uptake and reject lactic acid even in the presence of oxygen (Warburg effect). This metabolism reorients glucose towards the pentose phosphate pathway for ribose synthesis and consumes great amounts of glutamine to sustain nucleotide and fatty acid synthesis. Oxygenated and hypoxic cells cooperate and use their environment in a manner that promotes their development. Coenzymes (NAD^+, $NADPH,H^+$) are required in abundance, whereas continuous consumption of ATP and citrate precludes the negative feedback of these molecules on glycolysis, a regulation supporting the Pasteur effect. Understanding the metabolism of cancer cells may help to develop new anti-cancer treatments.

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1. Introduction

In contrast to normal cells which arrest glycolysis in the presence of oxygen and favor oxidative phosphorylation-ATP production (OXPHOS), cancer cells lose this regulation and favor glycolysis-producing lactate. This "aerobic glycolysis" was first observed by Otto Warburg in the 1920s [1]. The Warburg effect has led to increasing data focusing on the signaling pathways that conduct this reprogramming [2–6]. Understanding the biochemical routes that redirect the metabolism towards biosynthesis may be a source of inspiration for developing new anticancer treatments. The aim of this review is to dissect the main biochemical routes involved, although some of them remain partly deductive, emphasizing the importance of molecules such as NAD^+, ATP and citrate, for regulating and driving these pathways.

2. The metabolism of cancer cells: The importance of the Warburg effect and loss of the Pasteur effect

The biochemical metabolism of cancer cells is disrupted in order to promote the production of lactate, despite the presence of O_2.

2.1. The Warburg effect

Cancer cells synthesize great amounts of nucleotides, macromolecules and lipids, and these biosynthesis require continuous production of NAD^+, $NADPH,H^+$ and ATP. They consume at least 10 times more glucose than normal cells [5,7,8] and produce lactic acid, even in the presence of oxygen. High rates of glucose uptake have been clinically used to detect tumours by positron emission tomography with a glucose analogue tracer (PET) [9]. Aerobic glycolysis was considered by Warburg as a defect in mitochondrial respiration [8] and/or in ATP production by others (for review [5]) implying: - F1/F0 ATPase defect or mitochondrial content depletion [10]–SCO2 (synthesis of cytochrome c oxidase 2) defect, since aerobic glycolysis is reversed by re-expressing SCO2, an assembly factor controlled by p53 entering in complex IV [11]; an abrogation of proton gradient by uncoupling proteins (UCP) such as UCP2, which are overexpressed in various cancer cells [12,13]; cardiolipin abnormalities also favoring the dissipation of energy [14]; and mutations in certain electron transport chain (ETC) complexes encoded by mtDNA exposed to ROS damage because mtDNA is not surrounded by histones [15–18]; however, mitochondrial mutations are inconsistently observed [19–26] or remain silent [27].

In contrast to these hypotheses, many cancer lines may not be inherently more glycolytic than normal cells [28], and/or may not generate defective OXPHOS production [29]; their aerobic glycolytic phenotype could be a normal adaptation to a hypoxic environment. The ATP production mode of cancerous and normal cells of the same origin should be compared [28–30], and it is likely that the part of glycolysis depends on the type of cancer cell and on microenvironment, which may or may not provide oxygen and nutrients in abundance. Interestingly, the Warburg effect is not believed to exclusively concern cancer cells, but also embryonic proliferative cells [21].

Cancer cells located in well-oxygenated areas divide the most rapidly, thus favoring OXPHOS production of ATP, in contrast to more hypoxic cells [29,31–33], which need to consume larger amounts of glucose, since OXPHOS is slowed down or arrested, a downregulation which might avoid excessive ROS production [34,35]. In the highly hypoxic core areas of tumors [36,37], glycolysis necessarily becomes the main, if not the unique cause of ATP generation. It is not so surprising that these "hardy cells" correspond to higher malignancy grades [32,38], because hypoxia forces them to adapt and develop several strategies to avoid apoptotic or necrotic death: overexpression of oncogenes, such as hypoxia-inducing factor-1 (HIF-1) which promotes hypoxic metabolism [39,40]; overexpression of UCP2 which can reduce ROS production [12,13]; over-activation of cytosolic dehydrogenases, in particular of lactate dehydrogenase A (LDH-A) which produces more NAD^+ which is crucial for glycolysis function [13,41–43]; overexpression of anti-apoptotic proteins such as Mcl-1 and Bcl-x_L [44–46]; and activation of a mitochondrial autophagy protective effect [47–50].

2.2. Lactic acid production

Lactate production is an essential feature of cancer cells. The isoform LDH-M, which is regulated by the c-Myc [51] and/or HIF-1 target gene *LDH-A* [43], transforms pyruvate into lactate. This route is favored because the conversion of pyruvate in acetyl-CoA through pyruvate dehydrogenase (PDH) is inactivated by pyruvate dehydrogenase kinase 1 (PDK1) [52–54]. This blockade leads to an uncoupling between glycolysis and the TCA cycle (Fig. 1), which drives pyruvate away from acetyl-CoA generation and causes a reduction in the quantities of NADH and $FADH_2$ delivered to ETC, decreasing ROS production, especially when limited levels of O_2 are present [18,43].

2.3. The main role of HIF-1α in the loss of the Pasteur effect

In the presence of O_2, normal cells arrest glycolysis (Pasteur effect) in favor of OXPHOS, producing 18 times more ATP than glycolysis. This effect may be related to HIF-1α [40,43,55], which modifies the expression of numerous genes involved in glycolysis, lactate production and extrusion, angiogenesis and metastasis [56,57]. The kinase mTOR stimulated by AKT favors HIF-1α transcription [58]. HIF-1α is a major determinant of the glycolytic phenotype because it activates glucose transporters (GLUT), several key enzymes of glycolysis such as hexokinase II (HKII), phosphofructokinase (PFK) and pyruvate kinase M2 (PKM2) [4,6,43,52,55,59–61]. It also stimulates LDH-A and PDK1, promoting lactic acid production [52,53,59,62]. HIF-1α is normally inactivated in an oxygen-dependent manner by prolyl hydroxylase domain protein (PHD), which allows HIF-1α recognition by the von Hippel–Lindau (VHL) protein complex, the latter addressing HIF-1α for poly-ubiquitylation and destruction at the proteasome [63,64]. In hypoxia (defined as $\leq$2% O_2), HIF-1α protein expression levels increase gradually with O_2 concentration [32,65,66]. The potential reasons for HIF-1α escaping inactivation in normoxia include mutation of the von Hippel–Lindau (VHL) protein [67] and inhibition of PHD by succinate and fumarate as a result of mutations in succinate dehydrogenase (SDH) and/or fumarate hydratase (FH) [68–70], which act as suppressor genes since their mutations lead to the development of many tumours [71,72]. Moreover, pyruvate or oxaloacetate (OAA), which accumulate in hypoxia, activate HIF-1α in a feedback loop, even upon re-oxygenation [73]. Lactate also induces HIF-1α activation [74].

3. Major catabolic pathways

3.1. Glycolysis

To provide essential molecules (ribose, glycerol, serine, etc.) for biosynthesis, glycolysis is slowed down at its end, where pyruvate kinase (PK) converts phosphoenolpyruvate (PEP) into pyruvate, which leads to the production of ATP. This blockade is related to re-expression of PK in its embryonic form (PKM2), which is less active than the adult form. PKM2 plays a key role in the Warburg effect [75–77], and favors the transcription of HIF-1α in the nucleus [78]. The dimeric phosphorylated form of PKM2 is inactive and causes a bottleneck, favoring glucose metabolism towards biosynthesis. In contrast, the dephosphorylated tetrameric form leads to ATP and lactic acid production [21,76,77]. The switch from the inactive to the active form is an oscillating process, controlled by allosteric regulation implying the concentration of F1,6P and serine [79,80], and by covalent regulation through protein kinase A [75,76,79]. The binding of phosphotyrosine peptides to PKM2 results in the release of its main allosteric activator F1,6P [81,82], whereas phosphatase PP2A deficiency is thought to play a key role in the modulation activity of PKM2 [22]. Due to PKM2 dimeric preponderance in