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Review article

Flexibility in metabolism bestows tenacious viability on cancer

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ABSTRACT

Cancer cells display altered metabolism distinct from non-transformed cells, which is correlated closely with malignant biocharacteristics. Flexibility remains the central feature of metabolic alteration, enabling cancer cells to survive and thrive in the challenge of inner and outer environments. In this review, we summarise how cancer reprogrammes its metabolism nimbly and adaptively. To begin with, cancer cells adapt metabolism cunningly to supply sufficient materials and energy for infinite proliferation. Further, cancer cells harness metabolism to maintain appropriate cellular redox status, providing survival benefit rather than impairment on tumor growth. Moreover, cancer can switch between different metabolic types flexibly to handle harsh conditions like hypoxia, nutrient deficiency and metabolic inhibition on the journey for expansion. Last but not least, cancer coordinates metabolism of cancerous or stromal cells well to gain support and escape immune destruction. In a word, metabolic flexibility confers indomitable viability on cancer. Exploring such plasticity will help us gain new insights into cancer pathogenesis and cancer therapy.

1. Introduction

Cancer still greatly threatens human health all over the world, forcing in-depth investigation urgent and indispensable [1,2]. Metabolism alteration is a critical hallmark of cancer and numerous researches have demonstrated reprogrammed metabolism related tightly with initiation and progression of cancer [3,4]. Although metabolic heterogeneity still exists according to genetic backgrounds, tissue origins, environmental factors and some unknown reasons, flexibility in metabolism to cope with diverse threats remains a core and universal trait, a cornerstone for cancer's expansion and flourish.

2. Meeting proliferative requirements

Infinite proliferation demands sufficient energy and biomaterials to synthesize macromolecules like nucleic acids, lipids and proteins for daughter cells assembling. Classical glucose oxidation in mitochondria seemingly provides much energy per mole of glucose, but the shortage in supplying precursors and reducing equivalents for biosynthesis hampers its prevalence in cancer cells [5]. Instead, cancer mainly takes glycolysis and usually, such preference is called “Warburg effect”. Accelerated glycolysis could satisfy the requisite energy by fast ATP generation, and, more importantly, deliver sufficient reducing equivalents and intermediates as precursors needed for biomolecules [6]. Glycolysis-derived pentose phosphate pathway (PPP), for instance, could supply plentiful NADPH, essential reducing equivalents for lipids biosynthesis, and PPP could produce riboses for nucleic acids synthesis as well [7]. Lipids and amino acids also could be derived from glycolytic intermediate products like glyceraldehyde 3-phosphate (GA3P) converted to glycerin and 3-phosphoglycerate (3PG) transformed to serine, which latter could be used in one-carbon units transformation needed for nucleotides biosynthesis [8,9]. Moreover, lactate release in this process contributes largely like refurnishing NAD^+ to fuel glycolysis, creating favorable microenvironment for metastasis and even supplying cancer cells as an alimentative source [10,11].

Cancer cells also need high-speeded tricarboxylic acid (TCA) cycle since intermediates supply acetyl-CoA pool for lipid synthesis de novo, and provide the carbon skeletons for amino acids like aspartate, which contributed to nucleotides synthesis later [12–14]. It is obvious that cancer cells must replenish materials extracted from TCA to assure this process revolves continuously. In fact, there are two major ways to accomplish anaplerosis. The first is glucose-derived pyruvate, which

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supplies acetyl-CoA via pyruvate dehydrogenase (PDH) and oxaloacetate (OAA) via pyruvate carboxylase (PC) [15,16]. The second comes to glutamine absorbed hugely by cancer cells. Glutamine first converts to glutamate via glutaminase (GLS), then transaminase or dehydrogenase transforms glutamate to α-ketoglutarate (αKG), which enters into TCA later [17,18]. Which way dominates in certain cancer is not homogenized though, high mouldability to adapt flexibly is common. For example, some cancers prefer relying on glutamine possibly for the reason that replenishing by glutamine, rather than glucose-derived pyruvate, could save energy and provide NADPH. However, once glutamine is deficient, cancer chooses to depend on pyruvate for anaplerosis [19]. Substitution effect like this may attribute to liberating inhibition of PC activity for scarcity in glutamine metabolism [20,21]. Specifically, mitochondrial respiration fueled mainly by glutamine in cancer cells still plays a part, like regenerating NAD^+ for aspartate biosynthesis, followed by nucleotides production, which is important for cell proliferation [22].

Of course, nutrients other than glucose or glutamine supply cancer either. In certain conditions, they take the principal part. Lactate fuels the leading synthesis in some cancer cells [23,24]. Intriguingly, glucose in circulation seems to fuel cancer cells by transformation to lactate first [25]. Also, lactate could directly enter into mitochondria and oxidation in mitochondria rather than the cytoplasm, through which lactate fuels as a resource as well as compensates for the relative ineffectivity of NAD^+/NADH shuttle pathways [11]. Certainly, not all cancer cells favor glycolysis or use the traditional TCA-derived precursors for biosynthesis. But almost all have their own means to maintain survival or proliferation. As for cancer cells in inactive glycolysis, they mainly generate acetyl-CoA from acetate via acetyl-CoA synthetase (ACS), while high glycolytic cancer cells use citrate by ATP citrate lyase (ACL) to maintain acetyl-CoA pool [14]. Besides, some cancer cells favor absorbing outer lipids for membrane construction rather than de novo synthesis in physiological circumstance [26]. And some amino acids could contribute more carbon mass than glucose and glutamine [27]. The direct usage of ready nutrient surpassing de novo synthesis might be more thrift and effective in light of energy and reducing equivalents.

Briefly speaking, cancer cells take advantage of diverse metabolic pathways to fuel infinite expansion (Fig. 1).

3. Optimizing redox status

Besides elements for biosynthesis, cellular reactive oxygen (ROS) influences significantly in cancer bioactivities as well. Actually, ROS functions paradoxically in cancer. On one hand, ROS causes genome instability and enables genetic mutation, triggering malignant transformation [28–30]. Certain level of ROS also activates signal pathways driving malignant progression [17,31,32]. On the other, excessive ROS damages macromolecules, impairs cellular processes and even induces cell death [33,34]. So cancer cells mediate ROS in an appropriate level to avail malignancy, mainly resorting to metabolism regulation.

Mitochondria generate the major part of cellular ROS [35]. Electron leakage in the electron transfer chain (ETC) inevitably creates ROS. Actually, mitochondria in cancer possess a high level of ROS [36]. Frequent mutation in cancerous mitochondrial DNA (mtDNA) causes dysfunction of complexes in ETC, and therewith more ROS comes from inefficacy of electron transport [36]. Also, cancer highly consuming NAD^+ can lower cellular NAD^+/NADH ratio, which may impair ETC either, thus causing ROS [3]. Besides, high-speeded metabolic processes, oncogene activation, tumor suppressor dysfunction and microenvironments like hypoxia all elevate ROS level [37–40]. As is noted above, certain ROS is essential for cancer initiation and progression.

Nevertheless, cancer also needs strategies to curb excessive ROS in case such double-edged sword damages itself. Cancer cells have the capacity indeed. The primary cellular antioxidant is reduced glutathione (GSH), whose maintenance requires replete NADPH. Cancer cells possess diverse metabolic ways to deliver NADPH, thus enhancing GSH-dependent antioxidant pathway. Accelerated PPP is the major source to deliver cellular NADPH [41], and folate metabolism could also provide NADPH for generation of GSH [42]. Besides, enzymes like malic enzyme (MC) as well as isocitrate dehydrogenase (IDH) both facilitate NADPH production [43,44]. Moreover, others work significantly in carcinogenesis either. The typical example is that nuclear factor, erythroid 2 like 2 (NFE2L2) induced inhibits ROS via transcriptional activation of downstream antioxidant genes [45]. Additionally, favorable glycolysis not mitochondrial respiration also restrains toxic ROS, helping cancer cells survive and proliferate [33,41,46].

In short, cancer harnesses metabolism neatly to maintain cellular redox status profitable for malignant characters (Fig. 2).

4. Handling fierce conditions

Also, cancer needs to overcome numerous harsh stresses in its initiation or progression. Such is the case. Immature vasculature seems unable to provide sufficient oxygen and nutrients for swift duplication of cancer, which, however, cannot impede cancer progression indeed [47]. Therapies depriving of or interfering with distinct nutrient metabolism cannot beat cancer down either [48,49]. In fact, cancer cells alter metabolism cunningly to survive and thrive in these hostile conditions.

Hypoxia is the major condition that cancer cells confronting in some initial or progressional stage. Hypoxia inhibits the hydroxylation of hypoxia-inducible factors (HIFs), reducing ubiquitination of HIFs by the von Hippel-Lindau tumor suppressor (VHL) E3 ubiquitin ligase, thus protecting HIFs from degradation [50]. Activating HIFs pathway enables cancer cells to be converted to glycolysis via transcriptional regulation of critical enzymes. The most significant mediation falls on PDH, a gate keeper deciding trend of pyruvate. HIFs trans-activate pyruvate dehydrogenase kinase 1 (PDK1), and elevated PDK1 inactivates PDH, thus shutting down pyruvate entering into TCA [51,52]. On the contrary, HIFs elevate hexokinase 2 (HK2), lactate dehydrogenase A (LDHA), monocarboxylate transporter 4 (MCT4) and other critical proteins to accelerate glycolysis [53]. Benefits for cancer cells choosing glycolysis are discussed above. Moreover, under such circumstances, glutamine takes the major part for TCA anaplerosis. There are two ways for α-KG derived from glutamine replenishing TCA. The first is oxidation running the clockwise to malic acid, OAA, etc. But such process needs pyruvate-derived acetyl-CoA to sustain the intact circle concurrently. PDH inhibition prevents acetyl-CoA produced from pyruvate. Cancer cells solve the problem indeed. Malignant cells could facilitate α-KG anti-clockwise reductive to citrate via IDH, which is the second way for α-KG independently replenishing TCA and fulfilling the subsequent biosynthesis [54,55]. Under hypoxia, cancer cells also absorb external lipids rather than de novo synthesis, for less tediousness and extravagance [56].

Diversity in feeding resources and flexibility in free switch enable cancer cells to survive in nutrients fluctuation or single resource depletion. As mentioned above, glucose contributes enormously to cancer cells, but when glucose is deprived, cancer cells rely more on glutamine for carbon source [18]. Besides, a recent research has demonstrated some amino acids contributed to metabolism outweighing glucose, but once inhibition such nutrients, cancer cells could increase usage of glucose [27]. Moreover, in the absence of free amino acids, some cancer cells can scavenge exogenous proteins for nitrogen source [57,58]. Further, cancer cells could also initiate self-autophagy to supply energy and material, when facing nutrient deficiency [59].

Also, cancer cells have diverse functional metabolic pathways, some standby silently just wait for show-up when first stringers are crippled. Once glycolysis is inhibited, oxidation of lactate fuels metabolism [48]. And pyruvate also could replenish glutaminolysis inhibition [19]. Moreover, mitochondrial respiration inhibition preventing complex 1-derived NAD^+ production, thus causing inhibition of aspartate-driven