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Cancer cells and alpha-ketoglutarate

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ABSTRACT

Uncontrolled and irregular metabolism is a characteristic of cancer cells. At the center of different metabolic pathways integrated into mitochondrial functions, the alpha (α)-ketoglutarate dehydrogenase complex is an important regulator of electron transport chain activity and tricarboxylic acid (TCA) cycle and a key enzyme for cancer cells. Different methods have been found in the fight against cancer, which is one of the greatest problems of our age. Alpha-ketoglutarate and α-ketoglutarate dehydrogenase have contributions to modulating the epigenetics of cancer cells. In this review, we will discuss the effects of the TCA cycle enzyme and its substrate on cancer, the development of cancer cells, and their orientation to other tissues.

Keywords: Alpha-ketoglutarate, alpha-ketoglutarate dehydrogenase complex, cancer cells, cancer metabolism, epigenetics, hypoxia, tumor progression.

FORMATION AND DEVELOPMENT OF TUMOR CELLS

Genes control the division of cells, and while some of these genes enable cells to proliferate, some inhibit excessive cell production. Renewal and division of cells is a significant factor for living things to survive. Cells that have expired are replaced by new cells.[1]

As a result of the changes caused by environmental factors in cell deoxyribonucleic acid (DNA) and genes, cells begin to divide uncontrollably, form abnormal cell populations, and potentially spread to neighboring tissues and distant organs. Cell populations that have these features are called cancer. Other malignant characteristics, such as invasion (invading healthy tissue) and metastasis (spreading to healthy tissues through the circulatory system), are significant factors in the emergence of cancer.[2,3]

The cell cycle is a period during which the effects of mutagenesis appear and cells become vulnerable to mutation. The cell cycle comprises 4 phases: the S phase, where DNA synthesis takes place; the M phase, where mitosis takes place; G1 and G2 phases, the temporary pause phases between these two fundamental processes. Most of the cells in the body are in the G0 (resting) phase until they receive signals like stem cells in the bone marrow or liver cells. Terminal solid tumors are generally in this group. Changes in the checkpoints of the cell cycle is one of the causes of cancer development. The function of tumor suppressing, DNA repair, and apoptosis are sensitive and critical points in cancer development. Cyclins and cyclin-dependent kinases in the cell cycle lead cells to not only cell growth and cell proliferation but also cell death with their effects on the tumor suppressor genes.[4]

Mutations give rise to replication of DNA, transcription, translocation, or activation of genes. Oncogenes facilitate the formation of cancer by disrupting the regulation of their expression or activities due to changes in their structure and function. Tumor suppressor genes are necessary for the control of proliferation in

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the normal cell, and when they are damaged or eradicated, they cause the cell to multiply uncontrollably. Proto-oncogenes play a role in the growth, differentiation, and proliferation of cells. While mutations occurring in these cells lead to tumor development, mutations occurring in tumor suppressor genes lead to abnormal cell growth by preventing inhibition of the cell cycle.[2-5]

Doubling time, or the growth rate of the tumor, is the time needed for the tumor cells to double numerically. Solid tumor cells initially proliferate by a geometric increase. As time progresses, growth rate decelerates, and in some cases, cells that die and reproduce become equal.[5,6]

When the tissue formed by the proliferating tumor cells reaches a certain size, some of the cancer cells leave this tissue and begin to progress within the tissue. When these cells come across the vessels, they melt the vessel wall and enter the vessel and then begin to circulate throughout the body with the blood. While circulating in the vein, tumor cells attach to the surface of the vein in certain organs. The cancer cell dissolves the vessel wall in the region where it is attached and then begins to multiply in the target tissue.[1,4,7,8]

Cancer cells are recognized and broken down by the body's immune system. Mutated cells have less chance of survival than normal cells and therefore die. Most of the mutant cells have a feedback control mechanism (tumor suppressor genes) that prevents excessive growth. Therefore, fewer of these cells survive and turn into malignant cells. These cells, which have cancer potential, are eradicated before they grow and develop cancer. The role of the cellular immune response mechanism in clearing cells is called the "immune control" of the immune system against cancer. The immune system controls the formation of the tumor and, in the meantime, creates an immune response to the tumor cell and its antigens. When cellular immune response is suppressed, formation of cancer increases. The genetic changes involved in the physiopathology of cancer, the identification of signaling pathways, oncogene and tumor suppressor genes, and apoptosis not only help to elucidate the basic mechanisms that lead to disease but also help to understand how processes, such as cell proliferation, differentiation, and death, occur. Thus, it has led to the development of new treatments against the disease by enabling the use of molecular methods in the diagnosis of cancer and monitoring of patients.[1,4]

Cancer cells need to acquire some biological properties to survive, proliferate, and spread. These functional properties or characteristics of cancer include maintaining proliferative signaling (signaling the growth or production of cells by the proliferation of fragments), escaping cell death, and activating metastasis. Consequently, they lead to a pathological amount of cell survival and growth and ultimately tumor formation.[9]

THE RELATIONSHIP BETWEEN CANCER AND ALPHA-KETOGLUTARATE (α-KG)

A common property of tumors is that the cells rapidly accumulate as a cluster on the blood supply, and hence they withstand changes in oxygen and nutrition, forcing them to modulate their mitochondrial function.

It has been established that neither hypoxia nor oxidative phosphorylation (OXPHOS) defects require complete interruption of mitochondrial metabolism, and in both cases the tricarboxylic acid (TCA) cycle can exert metabolic fluxes to promote a glutamine-dependent biosynthetic pathway that perpetuates tumor progression. For this reason, the TCA cycle represents a metabolic center that directs the use of substrate on changes in resource utilization. Regarding this, the discovery of mutations in genes encoding key enzymes of the TCA cycle has revealed the significance of intracellular TCA cycle metabolite levels in altering both the metabolic and epigenetic landscape of cancer cells. Modification of metabolite levels and metabolic flows of TCA as a response to environmental pressure can explain tumor adaptation and plasticity in changing environments. Alpha-ketoglutarate dehydrogenase complex (α-KGDC) has emerged as a modulator of the signal metabolite α-KG, which is deeply associated with the respiratory chain and tightly regulated according to tumor microenvironmental changes.[10,11]

The TCA cycle is nourished by substrates entering diverse gateways to carry carbon resources for energy production and biosynthesis.

Acetyl coenzyme A (CoA) is generally produced by the oxidation of glucose and fatty acids, and subsequently, it is intensified with oxaloacetate to create citrate. Subsequent oxidative reactions provide the production of the reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide, which feed respiratory complex I and respiratory complex II, respectively, to create the mitochondrial membrane potential ($\Delta\Psi m$) required for adenosine triphosphate production. Glutamine, the most abundant amino acid in plasma, has been widely identified as an additional important source of carbon and nitrogen, particularly for rapidly proliferating cells. Glutaminolysis results in the production of α-KG with the aid of a transamination reaction, followed by the dehydrogenation of glutamate.[10,12-14]

The α-ketoglutarate dehydrogenase (E1) subunit, a dehydrogenase encoded by the human OGDH gene, is required to produce succinyl-CoA and catalyzes the decarboxylation of α-KG. The second step is the reductive succinylation of the dihydrolipoyl groups. It is a reaction carried out by the dihydrolipoamide succinyltransferase (E2) subunit encoded by the human DLST gene. Dihydrolipoamide dehydrogenase (E3) subunit encoded by DLD gene catalyzes reoxidation of E2 dihydrolipoyl groups and dihydrolipoamide dehydrogenase that reduce NAD+ to NADH.[15]

Glutamine and glucose are two fundamental nutrients used by cancer cells. In addition, unlike glucose, which only manages to provide carbon for biosynthesis, glutamine can provide both carbon and nitrogen for anabolic reactions and thus significant additional benefits. Besides, cancer cells depend on lipid biosynthesis for an increase in biomass.[12,16-18]

An important precursor of fatty acid biosynthesis is citrate, which is accepted by glucose and glutamine metabolism via the forward TCA cycle. Instead, in neoplastic cells under hypoxic conditions or in the presence of electron transport chain (ETC) defects, citrate is produced from the reductive carboxylation of glutamine-derived α-KG by cytosolic and mitochondrial reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent isocitrate dehydrogenase 1 (IDH1) and 2, respectively.[10,13,19]

Conversion of α-KG to isocitrate leads to decreased α-KGDC activity and an imbalance of the α-KG/citrate ratio, resulting in a reversed TCA cycle, and therefore, supports the synthesis of acids and tumor growth.[18-20]

Inactivation of α-KGDC is reduced by hypoxia-inducible factor 1 (HIF1)-mediated degradation of a splice variant of the E1 subunit, which renders cancer cells dependent on citrate or proliferation of exogenous lipids and inhibits tumor growth *in vivo*.[18]

Hypoxia-inducible factor 1, which is the primary regulator of hypoxic response in malignant cells, inhibits the activity of pyruvate dehydrogenase (PDH), and thus, citrate formation, causing it to increase the α-KG/citrate ratio.[21-23]

These findings suggest that HIF1 has a substantial role in modulating TCA metabolite levels and reconnecting α-KG cadherin from oxidative to reductive metabolism. In addition, it has been indicated that structure activation of HIF1 alone can support reductive carboxylation of α-KG in normoxia. Hypoxia-inducible factor 1 is not necessary to induce a reduction of α-KG, as any condition leading to a high α-KG/citrate ratio may favor this with a mass effect on the TCA cycle flux.[13,14,20]

For instance, in cancer cells with hypoxia and ETC defect, a decrease in α-KG oxidation may be due to differences in the levels of reducing equivalents. Consequently, modifications of the mitochondrial redox state may be responsible for the inhibition of the TCA dehydrogenase α-KGDC and PDH and the promotion of NADPH-dependent IDHs. In addition, ETC defects or hipoxia may often contribute to the increase of reactive oxygen species (ROS) and the reduction of α-KGDC and aconitase activations. In this way, ROS-mediated inhibition of α-KGDC can promote α-KG accumulation and its deviation towards lipid biosynthesis, while aconitase inactivation may contribute to citrate accumulation and extrusion from mitochondria.[13,14,24-28]

THE EFFECTS OF α-KG ON EPIGENETICS OF CANCER CELLS

Epigenetic changes at the level of DNA and histone have increasingly been approved as a

modifier of tumorigenesis. Unmethylated CpG islands are extensively hypermethylated compared to the corresponding normal tissue in many types of cancer, while the remainder of the genome is more demethylated. Hypermethylation of CpG islands has been utilized as a criterion to distinguish different types of tumor from non-malignant tissue. Tumors characterized by high levels of DNA methylation were classified as having a CpG island methylator phenotype. It is associated with a worse prognosis, primarily due to the silencing of potentially tumor suppressor genes. In general, this phenotype results from early periods of many kinds of tumorigenesis such as glioblastomas, acute myeloid leukemia, gastric cancer, and ependymomas. Therefore, medicines targeting DNA methylation mechanism had an encouraging strategy.[29-32]

The α-KG-dependent dioxygenase family includes two classes of enzymes that participate in the demethylation and hydroxylation reactions of DNA and histones. Ten-eleven translocation (TET) hydroxylases 1 and 3 catalyze DNA demethylation. The Jumonji C domain (KDM 2 to 7)-containing lysine demethylases (KDMs) are the largest family of histone demethylases.[11,33,34]

Both L-2-hyxdroxyglutarate (HG) and R-2-HG are competitive inhibitors of TET enzymes and KDMs. Thus, they are significant modifiers of epigenetics of cancer cells. Accordingly, L-2-HG and R-2-HG have been associated with a variety of cancer types. Similarly, along with 2-HG, succinate and fumarate can cause changes in DNA and histone methylation, and this way, they increase the development of cancer.[35-43]

It indicates that cytosolic α-KG concentrations influence the methylation of histones and DNA, thus triggering epigenetic changes. The studies on this subject demonstrated that maintaining an appropriate α-KG/succinate ratio is a priority for determining the identity and fate of embryonic stem cells (ESCs). Specifically, a high α-KG/citrate ratio increases DNA and histone demethylase activation, which is sufficient for modifying this ratio and regulating multiple chromatin modifications. Treatment with α-KG supports self-renewal of ESC, which is known to exhibit an abnormal "open" chromatin structure associated with hypertranscription. Hence, high cytosolic α-KG levels will promote high energy-consuming processes, a hypothesis supported by the presence of α-KG-mediated prolyl hydroxylasePHD-driven mammalian target of rapamycin activation that promotes anabolic processes. On the contrary, in cancer cells facing hypoxia, while promoting HIF1α stabilization for hypoxic adaptation, hypoxia inhibits the activity of the demethylase KDM4C (L) trimethylation of histone H3 at lysine 9 (H3K9me3), which is known to suppress gene expression through the accumulation of 2-HG, which also causes an increase.[35,44,45]

Recent studies have revealed that lack of oxygen in cancer cells directly causes DNA hypermethylation by intensely reducing TET activation at the gene promoters. Nevertheless, while TET enzymes and KDMs are a transcriptional target of HIF1 by themselves, specific HIF1 may stimulate transcription of target genes. Therefore, oncometabolites and low oxygen levels cause a decrease in global gene expression with closed chromatin and α-KG-dependent dioxygenase activation. It causes a specific genetic reaction in cells by restricting the transcription mechanism of these enzymes to HIF1-target genes.

Likewise, given the role of α-KG as an indicator of the availability of amino acids, it is more plausible to speculate that an epigenetic remodeling occurs upon glutamine deprivation, which may be encountered in cancer. Accordingly, a study conducted recently has demonstrated that lack of glutamine is associated with a low level of α-KG, which can determine the inhibition of KDMs in the nucleus of a tumor. As a result, an increase in histone methylation induces the differentiation of cancer cells and may lead to treatment resistance.

The result of epigenetic modifications is the conversion of external stimuli into a transcriptional response, thereby adjusting the phenotype of cells without affecting their genotype.[43,46-49]

In conclusion, the α-KGDC enzyme, as a gatekeeper of the OXPHOS system, responds to OXPHOS activity fluctuations and is a key regulator of mitochondrial metabolism. It also controls mitochondrial redox status through the balance of NADH and ROS levels and directs TCA metabolite flows into anabolic, energetic, and signaling pathways. Although the anti-tumorigenic properties of α-KG have attracted attention, its mechanisms of action are still not fully determined. It has been illustrated to be

highly dependent not only on the impaired HIF1 signaling pathway but also on the effects of α-KG on tumor growth. Alpha-ketoglutarate-mediated interactions have presented a perspective that may be used to limit cancer progression.

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