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Mini-review

Metabolic adaptation to cancer growth: From the cell to the organism

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ABSTRACT

Tumour cells proliferate much faster than normal cells; nearly all anticancer treatments are toxic to both cell types, limiting their efficacy. The altered metabolism resulting from cellular transformation and cancer progression supports cellular proliferation and survival, but leaves cancer cells dependent on a continuous supply of energy and nutrients. Hence, many metabolic enzymes have become targets for new cancer therapies. In addition to its well-described roles in cell-cycle progression and cancer, the cyclin/CDK–pRB–E2F1 pathway contributes to lipid synthesis, glucose production, insulin secretion, and glycolytic metabolism, with strong effects on overall metabolism. Notably, these cell-cycle regulators trigger the adaptive "metabolic switch" that underlies proliferation.

1. Introduction

Cyclins, cyclin-dependent kinases (CDKs), retinoblastoma proteins (pRBs), and the transcription factors E2F are the core regulators of cellular growth and proliferation, sensing external signals that require precise metabolic responses. Cell-cycle progression has been intensively studied in recent years. The cell cycle is divided into four major phases: G0/G1, S, G2, and M; every transition between phases is strongly regulated. Transition from G0/G1 to S is tightly regulated and depends on the activation of the G1 cyclins/CDKs and the pRB–E2F pathway.

CDKs are kinases that phosphorylate serine or threonine residues of their targets in a cell cycle-specific manner. To be active, CDKs must be complexed with cyclins, with the complex functioning as a holoenzyme; cyclins select the specific targets for phosphorylation. Additionally, the activity of cyclin/CDK complexes is determined by the presence or absence of two families of CDK inhibitors (CKIs). The first family includes the inhibitors of Cdk4 (INK4) proteins, which specifically bind and inhibit the catalytic subunits of Cdk4 and Cdk6. The INK4 family includes p16, p15, p18, p19, and p19ARF. The Cip/Kip family, including p21, p27, and p57, is the second family of CKIs. These proteins exhibit broad inhibitory function, including inhibition of the activities of the cyclins and CDKs. Active cyclin/CDK hyperphosphorylates the pRBs, mediating the release of the E2F transcription factor and the subsequent expression of several genes involved in cell-cycle progression, apoptosis, and DNA synthesis [6]. In this scenario, cells are able to progress to the next phase of the cell cycle [57].

E2Fs modulate the transcription of several genes through heterodimerization with DP-1 and DP-2 [20], activating the transcription of E2F-responsive genes. Nevertheless, in the presence of a larger complex of unphosphorylated members of the retinoblastoma protein family pRBs (RB1, p107 and, p130), the transcription of these genes is repressed. E2F activity is frequently increased in several human cancers, contributing to the uncontrolled proliferation of cancer cells [13].

Here we review the role of the cyclin/CDK–pRB–E2F axis as a master regulator of the metabolic adaptive response triggered by growth factors. We also consider how cancer cells switch their metabolism, as well as the molecular mechanisms implicated in this process.

2. The "metabolic switch"

An adapted "metabolic switch" accompanies most physiological and pathological changes in cellular functions. A fine-tuned and regulated cascade of molecular events senses changes in the environmental conditions of the cell and delivers a proper and specific response via the metabolic pathways of the cell. In this way, metabolism is adapted to the necessities of the cell; intermediary metabolism must be coupled to either biosynthetic or oxidative metabolism.

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For tumour progression, cancer cells undergo high rates of biosynthesis of lipids and other macromolecules to construct new cells [37,77]. Large amounts of energy are required to carry out these processes. However, a subset of cancer stem cells has long doubling times, for that reason we will focus in this review in the context of late metastasis. In late-stage cancer, when the mass of the tumour is large, energy consumption becomes quantitatively important. An estimated ~17,700 kcal are required over 3 months to support metastatic colorectal cancer. To obtain this large amount of energy, the bulk of cancer cells become highly glycolytic, undergoing non-aerobic fermentation of glucose to lactate. Lactate accumulates inside cancer cells and is exported out of the cells by the monocarboxylate transporter family; the resulting lactic acidosis is quite common in cancer patients [17]. Impaired functioning of the monocarboxylate transporters causes substantial defects in cancer-cell proliferation and tumour growth, indicating that cancer cells depend on efficient lactate secretion. Therefore, cells use glycolysis to obtain most of their energy in the form of ATP, as well as the intermediate metabolites necessary for the biosynthesis of macromolecules.

Under aerobic conditions, complete fermentation of glucose to lactate is not the most efficient way to obtain energy. When glycolysis occurs in the presence of oxygen, it is called "aerobic glycolysis" or the "Warburg effect" [79–81]. Warburg suggested that alterations in the metabolism of cancer cells were due mainly to the malfunction of mitochondria. However, this idea of a "metabolic switch" in cancer cells has been reformulated to include the relationships between cancer genes and metabolic alterations. The molecular mechanisms underlying the "metabolic switch" observed in cancer cells are not completely understood.

Energy metabolism is therefore gaining attention as an alternative therapeutic target for tumours [51]. Glucose is essential for cancer-cell proliferation, not only because it is the main energy source for the cell, but because glucose may be equally important as a substrate for the pentose phosphate pathway [85], an essential component of the generation of new nucleotides and a source of NADPH equivalents required for the synthesis of fatty acids. Aerobic glycolysis remains the major pathway used by cancer cells. Glycolysis offers several advantages to highly proliferating cancer cells: (1) It enables use of the most abundant extracellular source of energy, glucose, and (2) glycolysis-derived ATP production can exceed that obtained during oxidative phosphorylation.

3. The cancer-host metabolic dependance

Data about diet are not consistent between *in vitro* and *in vivo* experiments. In this way, glucose deprivation induces oxidative stress and cytotoxicity in cancer cells, which indicates a positive role of diet fighting against proliferation [71]. Nevertheless, this fact presents a limited action *in vivo* and sometimes with contradictory results because subjected animal models to a low-carbohydrate diet exhibited just a reduced inhibition of tumour growth [18]; but on other studies, diet significantly prolonged the survival of a mouse prostate cancer xenograft model [48]. With a nutritionally balanced diet low in carbohydrates and high in fat, human patients experienced long-term tumour management [54,64]. Therefore, use of this restricted diet partially controls glucose levels in the organism, reducing the rapid proliferation of cancer cells via a decrease in glycolysis rates and in the availability of intermediate metabolites for macromolecule synthesis. Unfortunately, this treatment is not sufficient for cancer therapy for several reasons. First, a chronically restricted diet is expected to delay but not to stop the progression of the disease [11,52,66], and this delay may only occur for some cancers types [34]. Second, moderate diet restriction produces a long-term loss of body weight caused by the loss of adipose tissue and muscle cachexia, which may be tolerated by only a small percentage of cancer patients [74] [25] [24,61]. Third, long-term dietary restriction was accompanied by delayed wound healing and immunological impairment in *in vivo* studies [35,62]. Thus, in addition to controlling dietary glucose, treatment could also target liver gluconeogenesis, which is an important secondary source that can generate significant amounts of glucose from glycerol, glucogenic amino acids, or lactate, as is the case for cancer cachexia [32].

The best diagnostic sign of cancer cachexia is involuntary weight loss [5]. Cancer cachexia could be considered to be an initial adaptive response for accessing body stores of energy and protein [72]. Cachexia is clinically obvious in its advanced phase (gross loss of adipose tissue and skeletal muscle). Cachexia is divided into three phases: precachexia, cachexia, and refractory cachexia. Cancer cachexia therapy focuses on the time of cancer diagnosis because the latter phases are less amenable to reversal [23]. Cancer cachexia is a multifactorial syndrome that is defined by a progressive reduction of skeletal muscle mass (with or without loss of adipose tissue) that cannot be reversed by conventional nutritional support. Cachexia is characterized by a negative energy balance and protein insufficiency, which are driven by a variable combination of reduced food intake and abnormal metabolism [38]. In cancer patients, reduced food intake is caused by primary anorexia. Simultaneous high rates of metabolism and catabolism as well as lower rates of anabolism exacerbate the weight loss and triggering systemic inflammation. Cachexia is thus a combination of dietary and metabolic factors [38,55,67]. Cancer cachexia is a complex syndrome, and can often occur in the presence of malnutrition, age-related changes in anabolism, physical deconditioning, and comorbidity [19].

The effects of cancer cachexia and the complications after cancer therapy are not easy to differentiate because weight loss can be due to several features of cancer treatment [4,7,8,69]. Mobilization of resources from skeletal muscle and adipose tissue is an appropriate response. Cancer cells alter energy regulation by eliciting an excessive inflammatory response that augments both central and peripherally mediated catabolic events [72]. Cancer therapy is progressively targeted against molecular pathways that are responsible for cellular proliferation, such as the PI3K, AKT, and mTOR pathways; these pathways are involved in the activation of muscle protein anabolism. Consequently, these treatments result in muscle wasting, a significant side effect of drugs that target these pathways [10,27,75]. Unfortunately, cachexia is rarely treated actively, mainly due to a lack of knowledge about clinical nutrition in cancer [70]. However, current progress in cachexia therapy promises to improve the systematic treatment of cachexia.

Cachexia is a good model of how cancer cells force the host organism to change metabolism. Another argument to prove that cancer cells takeover the host metabolism is lactate cycle. Lactate secretion is also a hallmark of cancer cells. Lactate is secreted, and since it cannot be fully excreted it is transported to liver cells, where is used as substrate for gluconeogenesis. Tumors may take advantage of this pathway. Lactate is secreted by cancer cells to signal to liver the requirement of glucose by the tumor and facilitates glucose recycling through lactate conversion in liver. This is strikingly similar to the Cory cycle implemented between liver and muscle during acute exercise. We propose that tumor cells customize the metabolism of the whole organism to receive enough glucose. Increased glucose requirement is likely provided by excess glucose production in liver of the host organism. Glucose is also synthesized from other substrates than lactate such as aminoacids, which are also increased during cancer progression. Interestingly some studies from the 60's already proposed inhibition of gluconeogenesis as a treatment of cancer [28]. Furthermore, increased glucose turnover is typically observed in cancer patients

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