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Review

Managing lipid metabolism in proliferating cells: New perspective for metformin usage in cancer therapy

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ABSTRACT

Cancer cells metabolically adapt to undergo cellular proliferation. Lipids, besides their well-known role as energy storage, represent the major building blocks for the synthesis of neo-generated membranes. There is increasing evidence that cancer cells show specific alterations in different aspects of lipid metabolism. The changes of expression and activity of lipid metabolising enzymes are directly regulated by the activity of oncogenic signals. The dependence of tumour cells on the deregulated lipid metabolism suggests that proteins involved in this process could be excellent chemotherapeutic targets for cancer treatment. Due to its rare side effects in non-cancerous cells, metformin has been recently revaluated as a potential anti-tumourigenic drug, which negatively affects lipid biosynthetic pathways. In this review we summarised the emerging molecular events linking the anti-proliferative effect of metformin with lipid metabolism in cancer cells.

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1. Introduction

Since Warburg's discovery, in the 1950s, that cancer cells preferentially utilize glycolysis rather than the more efficient oxidative phosphorylation (OXPHOS) to produce ATP [1], more than five decades of research have made it clear that tumour cells present several alterations at the level of metabolic pathways [2]. Overall, these alterations are

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aimed at increasing the incorporation and usage of nutrients, necessary to fulfil their high energetic requirements. The addiction to either glucose or glutamine, or even both, is now a well-established hallmark of many tumour cells. Indeed, glutamine and glucose are two extremely versatile molecules which can provide cancer cells not only ATP but also substrates for the synthesis of macromolecules (proteins, nucleic acids, lipids) and reducing equivalents (NADPH). The higher dependence of cancer cells to a continuous supply of nutrients with respect to non-transformed cells opens the possibility for cancer therapies which targets tumour-specific metabolic network. Indeed, many molecules and drugs have been developed and tested so far, with some of them that have reached clinical trial phases [3]. The demonstration that nutrient incorporation by cancer cells greatly exceeds the requirement of ATP, reveals that the production of biomass could be even more crucial than the synthesis of ATP in sustaining cancer cell proliferation and growth [4]. In this context, along with the key role of glucose and glutamine, a growing body of evidence is emerging about the deep involvement of lipid metabolism in tumours. Lipid metabolism, particularly that regarding fatty acids (FAs), is tightly linked to those of glucose and glutamine, since both fuel FA synthesis by continuously providing substrates such as NADPH and acetyl-CoA. *De novo* synthesis of FAs in adult normal tissues mainly occurs in the liver and in the adipose tissue. However, several studies revealed that tumour cells reactivate lipid neo-synthesis, making a high degree of FA synthesis, defined as lipogenesis, a key metabolic footprint of nearly all cancers that is required for both tumourigenesis and cancer progression [5–9]. An enhanced expression of lipogenic genes has been found in association with several types of cancers with aggressive phenotypes [10,11]. The function of FAs in tumour cells is not only limited to their well-known role as storage of energy. Indeed, like other macromolecules, energy production is only one, and probably not the most important, aspect of lipid contribution in sustaining tumour growth. Other crucial roles that lipids exert within the cells include: *i*) supply of building blocks for membrane biosynthesis; *ii*) second messengers and signalling molecules; and *iii*) involvement in post-translational modifications of proteins. Considering the role of FAs in many cellular functions, targeting enzymes involved in or related to their metabolism may be a feasible and winning strategy for preferentially targeting cancer cells, with a reduced side-effect for normal cells and the entire organism. In this review we provide an overview of the main alterations associated with lipid metabolism and the current advances in the development of anti-cancer strategies, which target lipid-related pathways. Particular attention will be directed to the emerging role of an old anti-diabetic drug metformin, as a promising anti-cancer therapeutic treatment.

2. Tumour-specific dysregulation of lipogenesis in cancer cells

The exacerbated lipogenesis in cancer cells is not only caused by the up-regulation of lipid metabolising enzymes, but is also directly coupled to other common metabolic pathways such as those related with glycolytic or glutaminolytic flux (Fig. 1). In particular, glucose meets lipid synthesis into mitochondria at the point of citrate, an intermediate of the Krebs cycle. During aerobic glycolysis, glucose carbons are funnelled into the mitochondria as pyruvate leading to an increase in the mitochondrial concentration of citrate. In highly proliferating cells, mitochondrial citrate is exported to the cytosol via the tricarboxylate transporter, wherein citrate is used as a biosynthetic precursor for lipogenic pathways. Citrate is cleaved by ATP-citrate lyase (ACLY) to generate acetyl-CoA and oxaloacetate. Cytosolic oxaloacetate is reduced to malate, which can then return to the mitochondria, recycling carbon and shuttling reducing equivalents into the mitochondria [12]. The conversion of cytosolic oxaloacetate to malate is driven by the relatively high cytosolic NADH/NAD^+ ratio present in glycolytic cells [13,14]. Malate can enter the mitochondrial matrix and be converted to oxaloacetate to complete the substrate cycle. In parallel, acetyl-CoA represents the start-up molecule for newly synthesized lipids [15]. In cellular compartment a well-organized enzymatic structure is engaged to metabolize carbons from cytosolic citrate to FAs. ACLY, acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and sterol regulatory element-binding proteins (SREBPs) are the best characterized metabolic checkpoints involved in the progression of cancer development and for which several pharmacological approaches are under evaluation. Hereinafter, these pivotal components of lipid metabolism will be reviewed.

2.1. ACLY

Proliferating cells require lipid building blocks for membrane formation. It has long been established that most normal tissues obtain the bulk of their required lipids from the diet and the circulation. However, many human tumours meet this need in a largely self-sufficient manner by overexpression of several lipogenic enzymes and activation of lipogenic pathways [16]. One of these enzymes is ACLY, a homotetrameric enzyme that links glucose with lipid metabolism by shuttling metabolites from the glycolysis and the citric acid cycle to the FAs and cholesterol synthesis pathways by converting cytosolic citrate into oxaloacetate and acetyl-CoA, which is the key building block for *de novo* lipogenesis. High levels of glucose and growth factors (*i.e.* insulin/insulin-like growth factor-1 (IGF-1)) activate PI3K/Akt/mTOR oncogenic pathways promoting cancer progression, consequentially to ACLY induction [17–20]. It thus becomes evident that signalling pathways that contribute to a glycolytic phenotype and play an important role in tumourigenesis can also lead to increased ACLY levels and/or activity. These de-regulated pathways may partly account for the evidence that ACLY activity is found to be significantly elevated in lung, prostate, bladder, breast, liver and stomach tumours [21–23]. Interestingly, by using Oncomine and unbiased proteomic profiling, it has been found that ACLY was up-regulated in colorectal cancer compared with its levels in normal mucosa. Moreover, overexpression and activation of ACLY were found to be statistically significant negative prognostic factors for at least lung and colon cancers [22,24]. Furthermore ACLY acetylation at three lysine residues (Lys 540, 546 and 554) is increased in human lung tumours. Indeed it has recently been demonstrated that acetylation of these residues enhances ACLY activity by preventing its ubiquitination and degradation, resulting in increased FA biosynthesis and tumour cell growth under high glucose conditions [25].

2.2. ACC

ACC is a rate-limiting enzyme in *de novo* FA synthesis, catalysing the ATP-dependent carboxylation of acetyl-CoA to malonyl-CoA. Malonyl-CoA is a substrate of FAS for acyl chain elongation and an inhibitor of carnitine palmitoyltransferase I (CPT-I) for FA β-oxidation. ACC is positively and allosterically regulated by citrate and glutamate and negatively and allosterically regulated by long- and short-chain fatty acyl-CoAs such as palmitoyl-CoA. There are two isoforms of ACC, namely ACC1 and ACC2, which, although encoded by separate genes, exhibit considerable sequence identity and have the same domain structure responsible for enzyme activity. However, ACC1 seems to be the limiting enzyme in proliferating cancer cells [26]. This could be related with an unlike biochemical role of ACC1 and ACC2. In particular, ACC1 is functional to regulate FA synthesis whereas ACC2 mainly regulates FA oxidation and similarly to ACLY, ACC1 is under the insulin/IGF-1 signal transduction pathway [27]. ACC1 has been found up-regulated in proliferating cancer cell lines such as prostate, breast and liver. Indeed, it has been shown that knock-down of ACC1 by siRNA promotes apoptosis in prostate cancer and breast tumour cells but not in control noncancerous cells, underlining cancer cells' higher reliance on this enzyme than normal tissues [28,29]. ACC1 is up-regulated in breast cancer cell lines overexpressing the tumour aggressiveness marker Human Epidermal Growth Factor Receptor 2 (HER2), with respect to breast cancers with low or normal levels of the receptor. HER2 enhances ACC1 expression