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General review

Unravelling the connection between metabolism, cell growth and cancer

À la recherche d'un lien entre métabolisme, croissance cellulaire et cancer

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Abstract

This paper presents a short review of the up-to-date literature on the connection between metabolism, cell growth and cancer. A major link is aerobic glycolysis, a phenomenon termed ''the Warburg effect'', and we describe its relationship with cellular redox balance that promotes faster proliferation of cancer cells and could lead to new therapeutic approaches. We analyse signals that accelerate cancer, namely insulin and insulin-like growth factor and we briefly describe signalling pathways related to growth factor receptors. We focus on the important part played by the PI3K/Akt signalling pathway and we discuss the major role played by PTEN and treatment approaches that might result.

Keywords: Aerobic glycolysis; Signalling pathway; Tyrosine kinase receptor; Insulin; Insulin-like growth factor

Résumé

Ce texte est une revue brève et non exhaustive de la littérature récente sur les liens entre le métabolisme, la croissance cellulaire et le cancer. La relation principale provient de l'effet Warburg et nous détaillons la liaison entre glycolyse aérobie et équilibre redox qui permet à la cellule cancéreuse de se diviser plus rapidement, liaison qui pourrait déboucher sur de nouvelles approches thérapeutiques. Nous analysons les signaux accélérateurs du cancer que sont l'insuline et l'*insulin-like growth factor* et nous détaillons brièvement les voies de signalisation liées aux récepteurs des facteurs de croissance. Nous décrivons la responsabilité importante de la voie PI3K/Akt dans la prolifération tumorale, ce qui nous conduit à évoquer le rôle clé de PTEN et les approches thérapeutiques qui pourraient en découler.

Mots clés : Glycolyse aérobie ; Voie de signalisation ; Recepteur tyrosine kinase

1. Introduction

The jury is still out on a possible connection between cancer and metabolic pathway mutations. As Otto Warburg pointed out, cancer cells metabolize glucose via glycolysis, termed aerobic glycolysis, which was convincingly illustrated when positron computed tomography with ^{18}FDG came into play. The recent discoveries of citrate dehydrogenase mutation in 70% of low-grade gliomas, and of succinate dehydrogenase mutation in paragangliomas, represent the best proofs that mutations in cellular metabolism are related to cancer [1].

2. Cancer cells in culture

We are facing a growing number of evidences that indicate that insulin and a very similar hormone, insulin-like growth factor 1 (IGF1) play a key role in the nutrition and metabolism of cancer cells [2]. To grow cancer cells, breast cancer cells for

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instance, a large amount of glucose, a growth factor (for example epidermal growth factor EGF) and insulin have to be added to cultured tissues. In presence of these different factors, cancer cells multiply. If one tries to withdraw insulin, cancer cells die. Normal breast cells are poorly responsive to insulin, have no insulin receptor and thrive without insulin. Cancer cells on the other hand do not survive without insulin.

A signalling pathway activated by insulin is present in muscle, fat and liver tissues, named after its key enzymes the phospatiylinositol-3-kinase and protein kinase B, the PI3K/Akt pathway. In the above tissues, this pathway promotes migration of the glucose transporters GLUT4 to the cell surface, but this pathway's action is not restricted to insulin-modulated tissues. This pathway is the most frequently mutated in human cancer [3].

The obesity/cancer link was studied in 2004 by Kaaks and Calle who concluded that obesity is a major factor of cancer risk [4]. In 2005, Andrew Morris and fellow diabetologists at the Dundee University in Scotland noticed accordingly that diabetic patients treated with metformine had 25 to 40% less incidence of cancer compared to those treated with insulin or sulfonylurea [2]. It is not clear however whether metformine lowers cancer risk in type 2 diabetic patients or whether sulfonylurea worsens it. To find out, trials are in progress. Professor Martin Hand et al. at the Mount Sinai hospital in Toronto are planning to enrol 3500 women to study the relationship between metformine and breast cancer. The studies of M. Pollak on biguanid and cancer are also noteworthy [5,6].

3. A link between metabolism and cancer

What hides behind the insulin/cancer connection is probably the so-called Warburg effect. Unlike normal cells, cancer cells adopt a seemingly inefficient metabolic pathway termed aerobic glycolysis. Cells produce large amounts of lactate even though oxygen is present in large quantity [7,8].

In a normal cell, with enough oxygen, glucose-6-phosphate turns into pyruvate through the Embden Meyerhoff Parnas pathway. Pyruvate can enter the mitochondria as acetyl coA, the oxidative phosphorylation of which yields 36 mol of ATP for 1 mol of glucose.

When oxygen is lacking, anaerobic glycolysis is turned on and yields lactic acid plus 2 mol of ATP for 1 mol of glucose.

In cancer cells, in the presence or absence of oxygen, aerobic glycolysis (Warburg effect) yields lactate and CO_2 and an average 4 mol of ATP for 1 mol of glucose [2,9].

It was at first believed that aerobic glycolysis was specific to cancer cells. Today we know better, since it characterizes fast-growing cells, cancerous or not.

4. The Warburg effect and redox balance

In living organisms, the aerobic metabolic pathway generates reactive oxygen species (ROS), which amount to an oxidative stress at cellular level. Cancer cells have to cope with a very large oxidative stress, generated by oncogene activation, tumour suppressor loss, and through the deleterious effects of tumour microenvironment.

The key enzyme in glucose-6-phosphate (G6P) metabolism is pyruvate kinase M2 which can open a limiting ATP producing step for G6P to enter the mitochondria, a step during which phospho-enol pyruvate is turned into pyruvate [10]. In contrast with normal cells, cancer cells express the M2 form of pyruvate kinase. Against any intuition, the M2 variant is adapted better to cell proliferation, though it is less active than the M1 variant.

In regular cells with low oxidative stress, pyruvate kinase is reduced and activated, and turns PEP into pyruvate, which can enter the mitochondria (Fig. 1A) [9].

In cancer cells on the other hand, the large oxidative stress switches PKM2 to its oxidised form (under action of H_2O_2) and becomes inactive. Pyruvate production is severely impaired and G6P turns towards the pentose phosphate pathway (PPP). This pathway produces NADPH, which can reduce glutathione, restore the redox balance, and fight the oxidative stress (Fig. 1B) [10].

Moreover, the PPP could help cells resist ROS-induced apoptosis. NADPH helps restore apoptosis and increases cell growth and survival. Cell membrane NADPH oxidase produces H_2O_2, which blocks tyrosine phosphatases and activates kinases that promote cell survival and mitotic signalling [1].

Cells can store carbon skeletons of glucose molecules. In tumour cells, carbon residues will store fatty acid as triglycerides. In this way, cancer cells reach a compromise: they use the rather inefficient, at least where ATP production is concerned, aerobic glycolysis, but they can obtain resources to form new cancer cells. This possibility arises from the huge amount available of intra cellular glucose [2]. Cells that can transform glucose and glutamine into biomass will multiply more rapidly.

For cells to proliferate, glutamine with its nitrogenous group has to be available. The Myc transcription factor, downstream of several signalling pathways, as Ras or Hedgehog pathway, plays an important part in glutamine metabolism. It stimulates intracellular glutamine uptake by increasing its transporter expression. The Myc factor stimulates cellular catabolism and generates amide and amine groups that are necessary for non-essential amino acid synthesis [11].

In summary, the PPP produces anti-oxidants, nucleic acid precursors and fatty acid substrates altogether to increase cancer cell proliferation. The part played by this pathway might suggest that small molecules that activate PKM2 by restricting glycolysis product access to the PPP, such small molecules associated with radiation therapy or chemotherapy, which both increase oxidative stress, could generate a great surge in oxidative stress which would be toxic even for cancer cells [10].

5. Accelerating signals in cancer

Numerous insulin receptors are naturally present in liver, muscle and adipose tissues in man, as Lewis Cantley points out [2]. Much less numerous insulin receptors can be found in a maximum half dozen of other normal tissues. Accordingly, the