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Mini Review

Inadequate Pancreatic GABA Controls that Explain Cancer Metabolism

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Abstract

In cancer, mitotic tumor cells display an active anabolic metabolism associated to a geometric increase of their number, while differentiated cells of the body, liver, adipocytes and other tissues, provide the necessary nutrients for building up the tumor, as if differentiated cells responded preferentially to catabolic signals for feeding the tumor. In fact it is slightly more complicated, since tumor cells gain such a metabolic advantage over other cells, by rewiring their metabolic pathways into a new hybrid mode, resulting from their dual sensitivity to both anabolic and catabolic signals, while differentiated cells resistant to anabolic hormones respond preferentially to catabolic ones. Stem cells committed to repair a tissue, display this dual sensitivity and become the dominant population, forming a tumor in the tissue they should have repaired.

The phosphorylation of key enzymes controlling anabolic or catabolic actions is indeed compatible with this view, but where is the starter for such a process? We came to the conclusion that an alteration of GABA controls in the endocrine pancreas, would explain the metabolic rewiring observed in cancer, with the hope that an early correction with adequate compounds will prevent or heal the disease.

Keywords: Cancer Metabolism; GABA; Glucagon; Insulin; PKC; Stem Cells

Abbreviations

PKA: Protein Kinase A; Src: Rous Sarcoma Homolog Tyrosine Kinase; PKB: Protein Kinase B; PKC: Protein Kinase C; IGF: Insulin Like Growth Factor; MAPK: Mitogen-Activated Protein Kinase; PI3 Kinase: Phosphatidylinositide 3-Kinase; PK: Pyruvate Kinase; PDH: Pyruvate Dehydrogenase; ATGL: Adipose Triglyceride Lipase; PEPCK: Phosphoenolpyruvate Carboxykinase; ACC: Acetyl-CoA Carboxylase; PDE: Phosphodiesterase; CPI- 17: C-Kinase-Activated Protein phosphatase-1 (PP1) Inhibitor; I1: PP1 Phosphatase Inhibitor; GABA: Gamma Aminobutyric acid; cAMP: Cyclic Adenosine Monophosphate; OAA: Oxaloacetic Acid; PEP: Phosphoenolpyruvate; DAG: Diacyl Glycerol; IP3: Inositol 1,4,5P.

Introduction

The fundamental discoveries of Mazurek and Eigenbrodt [1] on Pyruvate Kinase (PK) and particularly the M2 form of the enzyme associated to cancer have been reviewed in a special issue of Biomedical Research (Aligarh) on cancer metabolism in memory of E Eigenbrodt. The issue gathered many interesting contributions on cancer metabolism [2].

In cancer, the enzyme PK is blocked by phosphorylation forming a "bottle neck" interrupting the glycolytic pathway at its last step. We also know that Pyruvate dehydrogenase (PDH) is blocked by phosphorylation closing the glycolytic supply of acetyl-CoA to the citric acid-Krebs cycle; specific inhibitors of protein kinases induce a cell cycle arrest in colorectal cancer cells [3]. Normally, the phosphorylation of PK and PDH take place when catabolic hormones (glucagon, epinephrine and cortisol) elicit the formation of glucose by neoglucogenesis and glycogenolysis, but in tumor cells the PK and PDH phosphorylation is paradoxically associated to an increased entry of glucose and glycolysis until the PK bottle neck. As if the control switch reversing neoglucogenesis to glycolysis had partly failed, it did increase the glucose entry and glycolysis, but did not cancel the phosphorylation of PK and PDH, leading to the bottle neck stop. A comparison with the catabolic response of other tissues permits an identification of the regulation that failed in tumor cells [4].

Effect of catabolic hormones on liver, muscle and tumor cells

We may explain the failure of the control switch from neoglucogenesis to glycolysis in tumor cells, if we compare the effect of catabolic hormones on liver and striated muscles. The action of catabolic hormones, glucagon or epinephrine acting on Gs coupled receptors increases via adenylate cyclase, the synthesis of cAMP. This activates via PKA and Src protein kinases and the phosphorylation of PK and PDH by the respective kinases and inhibition of glycolysis. In parallel, cAMP inhibits the synthesis of fructose 2-6 bis phosphate the allosteric activator of glycolysis and inhibitor of neoglucogenesis; in the liver, glucose is formed and not consumed. In muscles the situation is very different because the neoglucogenic response is virtually absent while glycolysis is needed. How is this operated? Working muscles transmit via the T tubules the electrical signals to internal endoplasmic reticulum sacs that re-

lease calcium in the cytosol. Calcium activates a phosphodiesterase (PDE) that hydrolyses cAMP cancelling the inhibition of fructose 2-6bis phosphate synthesis, which reestablishes glycolysis. In parallel, calcium stimulates a calcium sensitive phosphatase calcineurin that removes the phosphate from an inhibitor (I1) that blocks phosphatase PP1, this will activate PP1 leading to the dephosphorylation of PK and PDH, which opens the glycolytic pathway. The serine phosphatase PP1 presumably activates other tyrosine phosphatases to act on both phosphoserine and phosphotyrosine sites. This particularity of muscles is an essential regulation keeping them ready for running and escaping predators; moreover, muscles have more epinephrine receptors coupled to Go or Gi and less of the Gs type. Well in tumor cells, the glucose entry and glycolysis is indeed activated like if the PDE, phosphodiesterase step was operational, hydrolyzing cAMP like was the case for muscles, which opens the glycolytic route and glucose entry, but in contrast to muscles, tumor cells maintain the phosphorylation of PK and PDH as if PP1 was still inhibited, in spite of the calcineurin action on I1 inhibition removal. An explanation for this was found while analyzing the effects of the calcium increase induced by anabolic insulin [5].

Effects of the calcium increase induced by anabolic insulin

Anabolic hormones such as insulin bind to tyrosine kinase receptors that get phosphorylated inducing the MAP kinase mitotic triggers and the PI3 kinase survival signals. PI3 Kinase phosphorylates membrane phosphoinositide, which elicits the membrane recruitment and activation PKB by phosphorylation. Schematically, the effects of PKB are opposite to PKA, inhibiting a set of protein kinases and activating a set of protein phosphatases, which will turn on enzymes in their anabolic configuration, producing glycogen, proteins and lipids. PI3 kinase will also activate a phospholipase PLC, which hydrolyzes membrane phospholipids into inositol 3P (IP3) and diacylglycerol (DAG). The effect of IP3 is to release calcium from the sarcoplasmic reticulum in the cytosol. Calcium triggers the incorporation of the glucose transporter by exocytosis; glucose is taken up, starting glycolysis. Again, calcium activates a phosphodiesterase (as was the case for the muscle exception) it will hydrolyze cAMP, which cancels the inhibition of fructose 2-6 bis phosphate synthesis and boost glycolysis. But here IP3 is formed together with DAG and the latter activates protein kinase C (PKC) that stimulates the formation of another inhibitor of PP1 known as CPI 17. This inhibitor cancels the effect of calcineurin that activated PP1 by neutralizing the I1 inhibitor. The result is an inhibition of PP1, which maintains the phosphorylation of PK and PDH, closing the entry of the Krebs cycle. Normally, this system allows the selection of the acetyl-CoA source, if DAG is fully hydrolyzed; the glycolytic source of acetyl-CoA prevails since the DAG-PKC dependent inhibitor CPI-17 is not formed. But if DAG increases, the acetyl-CoA will be provided by fatty acid beta oxidation instead of glycolysis. In this situation, AMP is elevated, blocking via AMP dependent kinase, acetyl-CoA carboxylase (ACC) and the synthesis of fatty acids. Since ACC is off, there is a low production of malonyl-CoA, a known inhibitor of the mitochondrial acylcarnityl transporter of fatty acid. This allows their uptake and beta oxidation splitting into acetyl-CoA, opening the fatty acid source for this compound when the glycolytic source is closed. But PKC will gradually activate AMP deaminase and 5’ nucleotidase, leading to a decrease of AMP, the stimulation of AMP kinase stops and the inhibition of ACC is terminated, for more information see [5,6]. This activates the fatty acid synthesis route, and blocks via malonyl-CoA the mitochondrial transporter and degradation route. The synthesized fatty acids are used to form lipids, and new membranes, DAG is consumed, which puts an end to the stimulation of PKC, the inhibitor CPI 17 decreases, PP1 becomes active, PK and PDH are in fine dephosphorylated, opening the glycolytic source of acetyl-CoA. It is indeed crucial to open back the glycolytic source of acetyl-CoA, when the synthesis of fatty acids turns off their degradation and the fatty acid source of acetyl-CoA. In contrast to normal cells, this regulation selecting the source of acetyl-CoA seems altered in tumor cells. Evidently, mitotic tumor cells have to synthesize their membrane lipids, their fatty acid synthesis pathway is particularly active, and ACC forms the malonyl-CoA intermediate, which inhibits the beta oxidation process closing the fatty acid source of acetyl-CoA. But unlike normal cells, tumor cells fail to open back the glycolytic source of acetyl-CoA, because PDH like PK remain blocked, as if for some reason, DAG failed to decrease and maintained the activation of PKC and the inhibition of PP1 by CPI-17. It would be interesting to find out what keeps DAG elevated [6]. But before, we have to see how tumor cells overcome this metabolic situation and how they take advantage from it.

Metabolic rewiring of tumor cells

In order to overcome their glycolytic bottle neck, tumor cells convert the PEP accumulated above PK into oxaloacetate (OAA) via the reversible phosphoenolpyruvate carboxykinase (PEPCK). But if the beta oxidation of fatty acids into acetyl-CoA is inhibited and the PDH source of acetyl-CoA is blocked, how will tumor cells find a source of acetyl-CoA for their elevated citrate condensation. Presumably, tumor cells consume ketone bodies, beta hydroxybutyrate, acetoacetate formed in the liver. They are taken up by tumor cells and reconverted in mitochondria into acetyl-CoA, via beta hydroxybutyrate dehydrogenase, ketoacyl-CoA transferase and thiolase [4].

We see here that tumor cells dependent of nutrients ketone bodies and glucose provided by the liver. In this metabolism the liver receives fatty acids from lipolysis in adipose tissue and converts them into ketone bodies. Muscle proteolysis provides amino acids such as alanine; it is transaminated in the liver into pyruvate, and then converted by mitochondria pyruvate carboxylase into OAA, then into PEP via PEPCK, following the neoglucogenic route until glucose. Glycogen in liver and muscles is also hydrolyzed providing glucose. In sum, differentiated cells in liver muscle and adipose tissues are here responding to catabolic hormones in order to feed tumor cells that display a hybrid response to both catabolic and anabolic signals. They did activate most anabolic signals but failed to reverse the catabolic blockade of PK and PDH, which led to this special metabolic rewiring, with the advantage of plundering body stores. In tumor cells, the elevated citrate condensation is followed by an efflux of citrate feeding cytosolic ATP citrate lyase; then, ACC takes the acetyl-CoA product starting the fatty acid synthesis, while OAA the other product of ATP citrate lyase, boosts the transamination chain consuming amino acids, and in fine lactic acid is released. The truncated Krebs and urea cycles, the proteolysis, the amino acid consumed, the recycling of amines and polyamine metabolism, have been discussed in other works, in relation to mitochondrial shuttles and glycolytic metabolism [4,7-14].

What are the keys that have to be controlled?

The phosphorylation of PK and PDH of tumor cells shows that catabolic glucagon has activated their kinases, but on the other hand anabolic insulin elicited all other anabolic processes, such as the synthesis of fatty acid and new membranes for dividing cells, but failed to elicit the dephosphorylating of PK and PDH, which did not reestablish the glycolytic source of acetyl-CoA. We have seen that this was attributed to a maintained inhibition of PP1 because PKC elicits the synthesis of a PP1 inhibitor, and that a decrease of DAG was necessary for putting an end to this PKC dependent inhibition. We have also to explain the selective catabolic response of differentiated tissues providing nutrients to the tumor, but also the hybrid response of tumor cells. We know that the release of insulin by pancreatic beta cells is associated to the release of GABA [15] that controls the release of glucagon from alpha cells [16-18] and somatostatin from delta cells [19]. A failure of GABA release may take place if the enzyme GAD is inhibited by pesticides, or if its cofactor Vitamin B6 is low or neutralized by toxic agents, or if autoantibodies toward GAD have decreased the synthesis of GABA. We know that such antibodies provoke diabetes type 1. It is thus quite possible to have a poor release of GABA without altering insulin release [19,20]. In such conditions, GABA will not activate its auto receptors found on beta cells. These receptors of the metabotropic type (GABA B) seem to terminate the release of insulin, and in the absence of GABA, there will be a persistent leakage of insulin that will in the long run desensitize insulin receptors of differentiated tissues, leading to insulin resistance, diabetes type 2 and metabolic syndrome are frequent diseases. On the other hand the GABA deficit will fail to block glucagon release from alpha cells, when insulin is liberated; the GABA receptors of alpha cells are ionotropic (chloride) GABA A receptors. The consequence is a dual release of glucagon and insulin, sending a mixed catabolic-anabolic message. But since differentiated cells are resistant to insulin they will respond to the catabolic signal. Only new stem cells that have not been submitted to the insulin desensitization process will respond to both glucagon and insulin. But here there is an additional element to consider, the GABA deficiency acts at some distance on adrenals, it will increase the release of epinephrine from adrenal medulla and this will selectively inhibit pancreatic delta cells that release somatostatin. The consequence is an increase of growth hormone release and IGF synthesis in the liver. Growth hormone has a direct action on adipocyte triglyceride lipase (ATGL) generating plenty of DAG, recalled in reference [6], this will then maintain the stimulation of PKC of the new stem cells that received the dual message, and maintain the PKC dependent inhibition of PP1, leading to a PK and PDH bottle neck. With a blocked PDH and an inhibited beta oxidation, these new stem cells that are not resistant to insulin, will rewire their metabolic pathways as described above, and live at the expense of tissues responding preferentially to catabolic signals. Stem cells committed to repair an organ after an injury, gain through their metabolic rewiring, a selective metabolic advantage, their number increases geometrically, a tumor is formed in the organ they should have repaired. Recall that carcinogenic phorbol esters act in the same way by increasing DAG.

In this view, cancer prevention would require a nutritional protection of the endocrine pancreas and a preservation of its GABA controls, over pancreatic cells and on adrenals. Above all, correcting with adequate compounds the rewiring process that is apparently a consequence of this GABA pancreatic failure, seems to be a promising approach that requires much work. It may eventually prevent cancer or cure the disease, as occurred for diabetes that was controlled with the discovery of insulin.

Conflict of Interest

The author declares that he has no conflict of interest.

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