OA Cancer
Open Access

Basic Cancer Biology

Review

Cancer metabolism: an alteration of the anabolic–catabolic selection switch

M Israël*

Abstract

Introduction

Tumour cells display hybrid metabolic features: some of their enzymes are phosphorylated as normally observed when catabolic hormones stimulate Gs-coupled receptors, whereas other enzymes adopt a configuration normally found in anabolic situations, mediated via tyrosine kinase receptors. Consequently, tumour cells have to rewire their metabolic pathways differently, whereas differentiated cells seem to respond preferentially to catabolic hormones. This gives mitotic cells a selective advantage since they deplete other cell reserves for their benefit. The pancreatic gamma aminobutyric acid selection switch between anabolism and catabolism explains the process, that is, a deficient release of gamma aminobutyric acid from beta cells leads to a concomitant release of catabolic glucagon and anabolic insulin and to a progressive desensitisation of insulin receptors on differentiated cells. New stem cells, with non-desensitised insulin receptors, respond to the dual anabolic and catabolic signals and rewire their metabolism in cancer mode. The aim of this review was to discuss an alteration of the anabolic–catabolic selection switch.

Conclusion

Cancer metabolism can be explained by a failure of pancreatic gamma aminobutyric acid release, removing a critical selection switch between catabolism and anabolism, affecting differently, differentiated cells and stem cells.

* Corresponding author
Email: mauisrael@wanadoo.fr

2 Av. Aristide Briand 91440 Bures sur Yvette and CNRS Gif sur Yvette 91190, France

Introduction

A metabolic plan that characterises cancer was recently represented in several studies[1,2]. It was described together with a detailed analysis of signalling controls that lead to cancer metabolism. In order to explain the metabolic wiring observed in cancer, we compare cancer metabolism with normal metabolic situations elicited in different tissues and in various conditions.

The effects of starvation and catabolic hormones, on liver, muscle and lipid reserves, will be compared with anabolic metabolism elicited by insulin and anabolic hormones. The pancreatic controls for these two opposite situations will be discussed in relation to insulin receptor desensitisation and cancer metabolic feature. We conclude and suggest that a failure of gamma aminobutyric acid (GABA) release from beta cells will lead, in differentiated cells, to desensitisation of insulin receptors (recalling type 2 diabetes), and these cells will respond preferentially to catabolic signals. New stem cells with non-desensitise insulin receptors display a dual anabolic–catabolic response resulting from the pancreatic GABA failure; they will consequently rewire their metabolic pathways in 'cancer mode'.

Discussion

The author has referenced some of his own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Mobilisation of tissue stores by catabolic hormones

Let us consider the weight loss observed in cancer; weight loss mobilises tissue reserves as in starvation or fasting. In such situations, hypoglycaemia triggers the secretion of catabolic hormones such as glucagon, epinephrine and cortisol, which mobilise reserves of the organism to form glucose and ketone bodies, which in turn support muscle and brain functioning. Glucagon is released by the alpha cells of the pancreas and epinephrine and cortisol are released by the adrenal glands. Glucagon and epinephrine bind to cell membrane receptors coupled to G proteins (G protein–coupled receptor [GPCR]) of the Gs (Gs stimulates adenylate cyclase) type, which stimulate adenylate cyclase and cyclic AMP (cAMP) synthesis. The increase in cAMP stimulates protein kinase A (PKA), a serine–threonine kinase, which in turn activates Src tyrosine kinase. This elicits the phosphorylation of protein kinases that ultimately phosphorylate enzymes, which may then mobilise glycogen, protein and lipid body reserves. Thus, during fasting, glucose is produced by glycogenolysis from liver and muscle glycogen. Glycogenolysis depends on the enzyme glycogen phosphorylase, which is activated by phosphorylation; conversely, the enzyme glycogen synthase will be blocked by phosphorylation. Catabolic hormones also

FOR CITATION PURPOSES: *Israël M*. Cancer metabolism: An alteration of the anabolic–catabolic selection switch. OA Cancer 2014 Jan 18;2(1):1.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Cancer
Open Access

trigger synthesis of glucose, gluconeogenesis in the liver; from amino acids, mainly alanine coming from muscle proteolysis, which is activated by cortisol. Alanine will be transaminated to pyruvate, which will then be carboxylated to oxaloacetate (OAA). The latter, gives phosphoenolpyruvate and follows the reverse path of glycolysis until glucose is formed. To ensure gluconeogenesis, one must also avoid that OAA at the origin of the pathway gets consumed in the Krebs cycle, whose entry will be locked by a phosphorylation of pyruvate dehydrogenase (PDH). On the other hand, one must also avoid the backward reaction from phosphoenolpyruvate to pyruvate; this requires inhibiting pyruvate kinase (PK) by phosphorylation.

The compound fructose 2,6 bisphosphate determines the direction of the metabolic pathway, glycolysis or gluconeogenesis; if it rises, it supports the glycolytic direction; if it drops, it favours the opposite gluconeogenesis direction. This compound is an allosteric activator of the enzyme phosphofructokinase in its glycolytic direction. To change direction and ensure gluconeogenesis, glucagon or epinephrine will elicit a phosphorylation inhibiting the enzyme synthesising fructose 2,6 bisphosphate.

It can be assumed that the mobilisation of reserves observed in cancer depends of catabolic hormones, as it is the case for starvation, but in this context there are two cases to distinguish. Indeed, the liver and the muscle do not respond in the same way to catabolic hormones. The muscle can consume glycogen reserves as the liver, but unlike liver, there occurs a few, if any, gluconeogenesis in muscle. The reason for this is that muscles preserve glycolysis, for keeping the production of mechanical energy, which is useful if it is necessary to flee, for example. This muscular exception restores glycolysis and cancels the phosphorylations that inhibited PK and PDH. It is probably an increase in muscle calcium during activity that stimulates dephosphorylating phosphatases for PK and PDH. Calcium may also activate a phosphodiesterase that hydrolyses cAMP, which restores the formation of fructose 2,6 bisphosphate supporting the glycolytic direction.

On comparison with the tumour cell, the catabolic hormones block as for the liver, PK and PDH by phosphorylation, as should be in gluconeogenesis, but unlike the liver, tumour cells will restore glycolysis and reverse the metabolic flow, as in muscles. This is presumably due to the activation of a phosphodiesterase that hydrolyses the cAMP, which elicits the increase of fructose 2, 6 bisphosphate, the activator of glycolysis. But unlike muscle, the tumour cell is unable to dephosphorylate PK and PDH at the entrance of the Krebs cycle. If we reason from the muscle, one could tell that tumour cells activate a phosphodiesterase hydrolysing cAMP but fail to activate phosphatases that would dephosphorylate PK and PDH. To circumvent this difficulty, tumour cells must rewire in another way for entry in the Krebs cycle. The first Krebs cycle enzyme, citrate synthase, receives its acetyl coenzyme A (acetyl CoA) from ketone bodies coming from the liver; its other substrate, OAA, comes from several sources (via malate dehydrogenase or phosphoenol carboxykinase).

It is also known that glycolysis cannot function without a supply of nicotinamide adenine dinucleotide (NAD^+) to one of its enzymes: glyceraldehyde 3-phosphate dehydrogenase. If the oxygen supply is insufficient, the nicotinamide adenine dinucleotide reduced/nicotinamide adenine dinucleotide ($NADH/NAD^+$) ratio increases, this inhibits citrate synthase and the Krebs cycle and the cell switches from oxidative glycolysis to non-oxidative glycolysis. In this case, the enzyme lactate dehydrogenases will provide the NAD^+ to glyceraldehyde 3-phosphate dehydrogenase, by converting pyruvate into lactate (lactic fermentation). Recall that Warburg has described the increased lactate in cancer. However, lactate increase and release occurs in tumour cells without citrate synthase inhibition, at the start of the Krebs cycle.

An expected effect of lactic acid on red blood cells is the dissociation of oxyhaemoglobin (Bohr Effect), in synergy with the increase of 2,3 diphosphoglycerate, which also stimulates oxygen delivery. The oxygen provided is reduced in tissues and pulls electrons, which oxidises NADH to NAD^+. The decrease of the $NADH/NAD^+$ ratio suppresses the inhibition of citrate synthase and restarts the Krebs cycle.

In fasting or in cancer, glucagon and epinephrine mobilise lipid reserves via a hormone-dependent lipase activated by phosphorylation and produces fatty acids. They will be cut into acetyl CoA in liver mitochondria; acetyl CoA will form ketone bodies, acetoacetate and beta hydroxybutyrate, which enable other cells to reconvert them into acetyl CoA.

The action of anabolic hormones

An opposite situation occurs, when food becomes available, an increase in blood sugar causes insulin release and other anabolic hormones, including insulin-like growth factor (IGF), 'the armed arm of growth hormone', dixit André Gernez. The action of insulin and other anabolic hormones is transmitted via cell membrane tyrosine kinase receptors. These receptors stimulate mitogen-activated protein kinase and phosphatidylinositide 3-kinase signalling pathways, which triggers mitosis and cell survival. These receptors activate another protein kinase, protein kinase B, which phosphorylates specific serine sites and inhibit protein kinases. This will, in synergy with protein phosphatases, dephosphorylate the enzymes that were phosphorylated during catabolism via the actions

FOR CITATION PURPOSES: *Israël M*. Cancer metabolism: An alteration of the anabolic–catabolic selection switch. OA Cancer 2014 Jan 18;2(1):1.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Cancer
Open Access

of PKA and Src. Insulin stimulates glycolysis, by promoting the incorporation of the glucose transporter in membrane; dephosphorylated glycogen synthase is now activated, forming glycogen; conversely the dephosphorylation of glycogen phosphorylase blocks glycogenolysis. The model exemplified here for enzymes involved in glycogen metabolism was validated on many more enzymes for protein and lipid metabolism[1–3].

In anabolism, glycolysis is stimulated by the increase of fructose 2,6 bisphosphate. Stem cells become mitotic; there is an increase in protein synthesis, in nucleotide synthesis for DNA and RNA and in lipid synthesis to form new cell membranes.

Similarly to stem cells, subjected to anabolic actions, tumour cells, will incorporate glucose, display a high glycolysis and form new molecular building blocks for new mitotic daughter cells. However, unlike normal cells, tumour cells must overcome the blockade of PDH and PK that remain phosphorylated as for catabolic effects. We are somehow in a hybrid situation for the tumour cells, that is, the response is catabolic for these two enzymes, whereas others enzymes are normally dephosphorylated as in anabolism.

This hybrid situation reconnects metabolic pathways in tumour cells and gives them a metabolic advantage, allowing them to plunder the tissue reserves mobilised by catabolic hormones[3,4]. How do we explain this very peculiar situation?

Anabolism switches off catabolism: the GABA control mechanism and its alteration

The selection switch between anabolism and catabolism is controlled in the endocrine pancreas. When anabolic beta cells release insulin in response to an increase of glycaemia, they switch off by a parallel release of GABA, alpha cells releasing glucagon; GABA also inhibits delta cells releasing somatostatin. This reinforces the action of insulin, since the growth hormone and IGF are not inhibited by somatostatin. GABA effectively inhibits its alpha cells and delta cells via ionotropic GABA A receptors; the entry of Cl^- hyperpolarises the cells, blocks the influx of Ca^{2+} and the release of glucagon and somatostatin from alpha and delta cells, respectively. An alteration of this mechanism would explain the dual action of anabolic and catabolic hormones on tumour cells and the metabolic wiring that is its consequence. However, this does not explain why differentiated cells respond preferentially to catabolic signals, which mobilise tissue reserves for the benefit of the tumour cells with hybrid anabolic–catabolic features.

What would be the consequences of a failure of this GABA-dependent control switch?[2], this may occur if the enzyme synthesising the GABA, glutamate decarboxylase (GAD) is inhibited, or in the case of a vitamin B_6 deficiency (it is the cofactor of GAD). A deficient GABA release would no longer block glucagon release while beta cells release insulin. A hybrid message catabolic–anabolic would be sent to tissues; indeed, tumour cells display a dual hybrid response. This is illustrated by the blockade of PK and PDH, which remain phosphorylated as in a catabolic state, but this is associated to a dephosphorylation of glycogen synthase and of glycogen phosphorylase as found for insulin anabolic action. Moreover, glycolysis is very active and to overcome the blockade of PK and PDH, at the entry of the Krebs cycle, tumour cells rewire the system. They use for their citrate condensation reaction, acetyl CoA coming from ketone bodies, formed in the liver, while OAA is provided by phosphoenolpyruvate carboxykinase or malate dehydrogenase. Below the condensation of citrate, a new stop of the Krebs cycle promotes the efflux of citrate from mitochondria. This feeds cytosolic ATP citrate lyase and the fatty acids synthesis pathway, via acetyl CoA carboxylase, forming lipid membranes for dividing tumour cells[1–4]. The fatty acid synthesis route forms malonyl CoA, which blocks the mitochondrial transport of fatty acids and their degradation into acetyl CoA. Since PDH, the other potential source of acetyl CoA, is blocked in tumour cells[5], they become very dependent of liver ketone bodies that tumour cells will convert into acetyl CoA. We have in other works given more details on transamination and other features of tumour metabolism[1–4].

We have to explain here why enzymes of differentiated cells, hepatocytes or adipocytes, do not adopt a hybrid catabolic–anabolic configuration, as if they were relatively insensitive to insulin anabolic signals. Somehow, this looks like a situation observed in type 2 diabetes, where there is a desensitisation of receptors of insulin, internalised by endocytosis before proteolysis. To avoid desensitisation resulting from a tonic insulin release, beta cells normally close down insulin release. In this case, GABA acts on metabotropic GABA B autoreceptors of beta cells, which are coupled to Gi proteins (Gi inhibits adenylate cyclase). This will turn off, after several steps, the mechanism of insulin release[6]. In addition, GABA B receptor activation would increase the incorporation of K_{ATP} channels (potassium channels inhibited by ATP) in the membrane and the membrane K^+ conductance[7], which hyperpolarises the cell and turns off insulin release (Figure 1).

Conclusion

Therefore, release of GABA from beta cells works as an autocrine inhibitor to terminate the release of insulin. If the release of GABA gets deficient, there will then be a tonic release of insulin that over time desensitises the insulin receptors on differentiated cells (recalling type 2 diabetes); these cells can still respond to a phasic epinephrine or glucagon release.

FOR CITATION PURPOSES: *Israël M*. Cancer metabolism: An alteration of the anabolic–catabolic selection switch. OA Cancer 2014 Jan 18;2(1):1.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

OA Cancer
Open Access

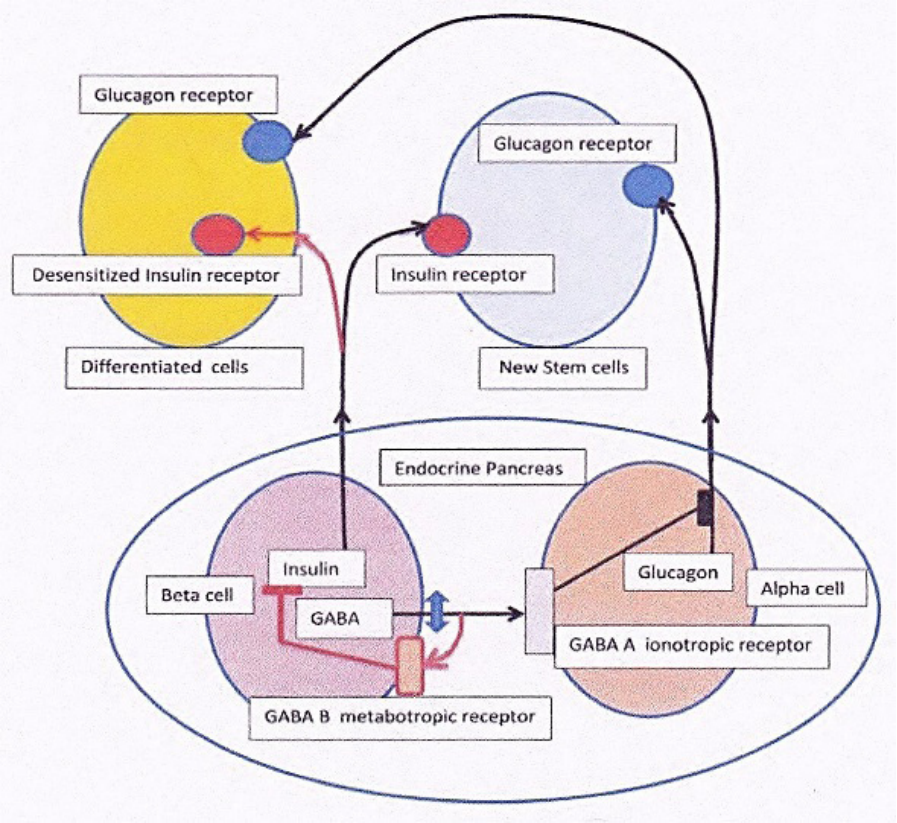

Figure 1: Gamma aminobutyric acid (GABA)-deficient release from pancreatic beta cells affects cell metabolism. A GABA-deficient release from beta cells elicits an abrupt release of glucagon from alpha cells, no longer hyperpolarised via their GABA A ionotropic receptors. Insulin is now released from beta cells together with glucagon from alpha cells. Moreover, if GABA release is deficient, GABA B metabotropic autoreceptors on beta cell are no longer activated, which prolongs insulin release. The tonic action of insulin on differentiated cells leads to a desensitisation of their insulin receptors, whereas they can still respond to a phasic release of glucagon or epinephrine, activating their catabolism. New naive stem cells that express non-desensitised insulin, and glucagon receptors, display a hybrid anabolic–catabolic response to insulin and glucagon concomitantly released after the loss of the pancreatic selection switch mediated by GABA.

In tumour cells, the situation is different, since they respond to both anabolic and catabolic signals. The simplest explanation is that unlike differentiated cells subjected to a prolonged insulin receptor desensitisation process, resulting from the GABA failure, new stem cells express new insulin receptors that have not been desensitised. And since these cells have also Gs-coupled receptor activated by catabolic hormones, they display dual anabolic–catabolic features and start their metabolic rewiring process.

In addition, in the adrenal medulla, a deficient GABA release stimulates the release of epinephrine, which inhibits the release of somatostatin; this restores the action of IGF. Glucagon also stimulates the release of cortisol. The three catabolic hormones are operational, mobilising body reserves for the benefit of mitotic cells with a hybrid metabolism rewired in a cancer mode.

Abbreviations list

acetyl CoA, acetyl coenzyme A; cAMP, cyclic AMP; GABA, gamma aminobutyric acid; GAD, glutamate decarboxylase GPCR, G protein–coupled receptor; IGF, insulin-like growth factor; NADH, nicotinamide adenine dinucleotide reduced; NAD+, nicotinamide adenine dinucleotide; OAA, oxaloacetate; PDH, pyruvate dehydrogenase; PKA, protein kinase A; PI3 kinase, phosphatidylinositide 3-kinase pathway; PK, pyruvate kinase.

References

1. Israël M. Signaling and metabolism in cancer: endocrine pancreas deficiency and hybrid anabolism-catabolism, drugs that undo the process. Cancer Therapy. 2014;10:1–12.
2. Israël M. A possible primary cause of cancer: deficient cellular interactions in endocrine pancreas. Mol Cancer. 2012 Sep;11:63–8.
3. Israël M. A primary cause of cancer: GABA deficiency in endocrine pancreas. Cancer Therapy. 2012;8:171–83.
4. Israël M, Schwartz L. The metabolic advantage of tumor cells. Mol Cancer. 2011 Jun;10(70):1–12.
5. Madhok BM, Yeluri S, Perry SL, Hughes TA, Jayne DG. Dichloroacetate induces apoptosis and cell-cycle arrest in colorectal cancer cells. Br J Cancer. 2010; 102:1746–52.
6. Braun M, Wendt A, Buchard K, Salehi A, Sewing S, Gromada J, Rorsman P. GABAB receptor activation inhibits exocytosis in rat pancreatic-beta-cells by G-protein-dependent activation of calcineurin. J Pysiol. 2004 Sep;559(Pt 2): 397–409.
7. Taneera J, Jin Z, Jin Y, Muhammed SJ, Zhang E, Lang S, et al. γ-Aminobutyric acid (GABA) signaling in human pancreatic islets is altered in type 2 diabetes. Diabetologia. 2012 Jul;55(7):1985–94.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

FOR CITATION PURPOSES: *Israël M.* Cancer metabolism: An alteration of the anabolic–catabolic selection switch. OA Cancer 2014 Jan 18;2(1):1.