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A Metabolic Shift from Normal to Cancer Metabolism

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Abstract: This work compares cancer metabolism to other metabolic situations elicited by catabolic, or anabolic hormones, or by Growth hormone. The comparison suggests that hormonal controls allowing shifting from catabolism to anabolism partially fail in cancer, leading to a hybrid metabolic situation in cancer, with enzymes phosphorylated as for catabolism, while others shift to anabolism. Markers such as AMP and DAG, differentiate the metabolic situations studied. To get markers opposite to those of cancer metabolism, a DAG lipase was implicated. This enzyme forms endocannabinoids with anti-proliferative effects.

Keywords: cancer metabolism, pancreas in cancer, ketones in cancer, AMP deaminase, AMP kinase, DAG lipase.

INTRODUCTION

Our aim was to compare cancer metabolism to catabolic and anabolic metabolic situations and to identify markers differentiating them when shifting from catabolism to anabolism. As for the special metabolic situation of cancer it would result from a partial failure of the mechanism shifting from catabolism to anabolism, giving a hybrid metabolic rewiring. We shall first recall the two opposite metabolic conditions elicited by fasting or feeding, and consider metabolic exceptions, for liver that preserves gluconeogenesis and striated muscles that need glycolysis. We will then compare catabolism and anabolism to other metabolic situations, elicited by growth hormone (GH), or to the hybrid metabolism of cancer.

Fasting elicits the release of catabolic hormones: glucagon from alpha cells of the endocrine pancreas, epinephrine and cortisol from adrenal glands. These hormones trigger the production of glucose, either from glycogen lysis, or by synthesis of glucose by gluconeogenesis, a process using several enzymes of the glycolytic pathway in the reverse direction. However, pyruvate kinase (PK) the last enzyme of glycolysis, works only in the glycolytic direction, from phosphoenolpyruvate (PEP) to pyruvate (PYR). Thus, two other enzymes have to take over, in the reverse gluconeogenic direction. These are: pyruvate carboxylase and phosphoenolpyruvate carboxykinase (PEPCK). They are fed by amino acids coming from the proteolysis of muscle proteins; the transamination of alanine produces pyruvate (PYR). In mitochondria, pyruvate carboxylase converts PYR into oxaloacetate, then (PEPCK) gives back PEP, which exits the mitochondria, starting gluconeogenesis. In order to avoid a futile cycle, in which PK would reconvert PEP into PYR, the enzyme PK has to be inhibited by phosphorylation in gluconeogenesis. In addition, the inhibition of pyruvate dehydrogenase (PDH) by phosphorylation closes the entry of PYR in the Krebs cycle and oxidative metabolism. In fasting, catabolic hormones elicit the synthesis of glucose. In parallel, glycogen stores are lysed, by glycogen phosphorylase a, the active phosphorylated form, being targeted to glycogen. In fasting, a hormonal sensitive lipase (HSL) is activated

and mobilizes lipid stores producing fatty acids, beta-oxidation and ketogenesis will then form ketone bodies. Ketogenesis involves four enzymes essentially in liver. The ketone bodies, acetoacetate and particularly Betahydroxybutyrate (BHB) are released in the blood, and are nutrients for other cells, backing up glucose when glycogen stores are emptied.

When food is available, the increase of glucose elicits the release of the essential anabolic hormone: Insulin, from pancreatic Beta cells. Insulin is released together with the inhibitory transmitter GABA, which turns off the release of catabolic hormones, when switching to anabolism. The cells will now synthesize glycogen, lipids and proteins, while glycolysis is activated. Cells may produce energy, or form membranes and substrates for new mitotic cells. In this case, citrate exits the mitochondria and feeds the cytosolic fatty acid synthesis pathway and lipogenesis, for making new membranes for mitotic cells.

The orientation of metabolic pathways depends on a set kinases and phosphatases that phosphorylate or dephosphorylate key enzymes controlling catabolism or anabolism. Catabolic hormones act on G protein coupled receptors, associated to adenylate cyclase, increasing cAMP for the Gs type receptor. This activates a protein kinase A (PKA), which stimulates other phosphorylating protein kinases, specific for the different enzymes, which become active or inhibited, for supporting catabolism. In anabolism, insulin stimulates a receptor of the tyrosine kinase type, activating protein kinase B (PKB), which stimulates a set of phosphatases able to dephosphorylate the enzymes supporting anabolism that will adopt the adequate ON or OFF configuration. Moreover, PKB blocks the specific enzyme kinases. The activation of PKB is complex, it requires the action of PI3 kinase, activated by stimulating the insulin receptor. This kinase, PI3 kinase, phosphorylates in the cell plasma membrane, phosphatidyl inositol 2 phosphates (PIP2) into PIP3, which recruits PKB, it is then activated by another membrane kinase (PDK). The other essential event in anabolism is the hydrolysis of PIP3, releasing in the cytosol inositol 3 P (IP3). The latter, will mobilize calcium from reticulum stores, and trigger back glycolysis. Calcium favours the incorporation of glucose transporters in the cell membrane by exocytosis, helping the influx of glucose. The transport is driven by hexokinase forming glucose 6 P, calcium supports the binding of hexokinase to the mitochondrial ANT site, where ATP is released in the cytosol, in exchange of ADP, boosting the hexokinase reaction. Moreover, calcium activates calcineurin phosphatase, which dephosphorylates I1, an inhibitor of PP1 phosphatase, it is activated and will dephosphorylate and activate, PK and PDH, which restores glycolysis. In addition, calcium activates a phosphodiesterase (PDE) converting cAMP into AMP, which cancels the inhibition of phospho fructokinase 2 (PFK2) by cAMP, it then produces fructose 2-6 bis P (F2-6 P) the allosteric activator of glycolysis and inhibitor of gluconeogenesis. Thus, Phospho fructo kinase 1 (PFK1) will work in the glycolytic direction converting fructose 6 P into fructose 1-6 bis P. Calcium release from the reticulum is here elicited by IP3, in anabolic conditions supporting glycolysis.

However, in liver gluconeogenesis is dominant, and cAMP must then decrease the level F2-6 P. This is achieved by a kinase that phosphorylates PFK2 and inhibits the formation of F2-6 P, Moreover, the phosphorylated PFK2 hydrolyses F2-6P, which is not the case for the dephosphorylated PFK2. Thus liver remains in gluconeogenesis and glycolysis is inhibited. This is true for liver but not for striated muscles, that need glycolysis, presumably for emergency situations. Gluconeogenesis is quite low in muscles; in active muscles, the action potential is electrically conveyed by the tubular system until ryanodine receptors of reticulum sacs in the muscle depth, and calcium release is electrically triggered, supporting

glycolysis, as discussed for anabolic insulin, where calcium release was triggered by IP3. In muscles, PFK2 is not phosphorylated by the kinase as in liver, and forms F2-6P the activator of glycolysis. Finally, insulin stimulates MAP kinase ERK mitotic pathway.

In sum, in fasting catabolic hormones, elicit the production of glucose, by gluconeogenesis and by glycogenolysis, and a phosphorylation of (PK) and (PDH) inhibiting these enzymes takes place. Glycogenolysis needs the phosphorylation of glycogen phosphorylase a, that activates the enzyme, while turning off the synthesis of glycogen, requires the phosphorylation of glycogen synthase. When food is available, anabolic insulin will elicit the de-phosphorylation of these enzymes. Having, recalled this essential background, see references (1-4), we shall compare these two basic metabolisms, to three other metabolic situations, including the effect of Growth hormone (GH), Cancer hybrid metabolism, and its modification giving opposite markers. We selected markers, involved when shifting from one situation to the other. Three of them (cAMP, AMP and DAG) seem to differentiate the five metabolic situations considered. We hope that this comparison will help the identification of new anti-cancer targets.

FOUR METABOLIC SITUATIONS COMPARED TO CANCER METABOLISM

Other essential parameters will be analysed, for comparing five different metabolic situations: catabolism anabolism, growth hormone metabolism, cancer metabolism, and a metabolism with markers opposite to cancer metabolism. They are illustrated in Figure 1. The first metabolic situation considered is catabolism Figure 1 A, as for all the metabolic situations described, the endocrine pancreas is represented and in some cases the adrenals. In catabolism, the endocrine pancreas senses the drop of blood glucose after a fasting period for example. Beta cells releasing insulin, and Delta cells releasing somatostatin (SST) have K-ATP channels in their membrane, these are inhibited by ATP, and if glucose decreases, ATP declines, which opens the K-ATP channels releasing K+, a hyperpolarization of Beta and Delta cells occurs, closing the voltage gated calcium channels, which inhibits the calcium dependent release mechanism of insulin by Beta cells and SST by Delta cells. In the case of Beta cells, the release of insulin stops, together with the co-release of GABA, the inhibitory transmitter. The decrease of GABA suppresses the inhibition of Alpha cells, mediated by GABA A receptors, via a chloride Cl^- influx. Decreasing this negative influx, depolarizes back Alpha cells, and opens their calcium channels, which triggers the release of glucagon. At some distance on adrenals, the decrease of GABA release elicits the release of epinephrine. Cortisol is also released by adrenals; it is stimulated by ACTH release from the hypophysis, induced by glucagon. Epinephrine as glucagon act on G protein coupled receptors, the Beta-adrenergic receptor activates adenylate cyclase, and it is a Gs type receptor, increasing cAMP. In parallel, epinephrine acts on alpha adrenergic receptors of (Gq type) triggering lipolysis via a hormonal sensitive lipase (HSL). Triacylglycerol (TAG) is cleaved by the lipase, into fatty acids and diacylglycerol (DAG). The fatty acids are cut by beta-oxidation, and liver ketogenesis forms Ketone bodies. The four enzymes involved in this pathway have been recalled in other works [5]. The ketone body Betahydroxybutyrate (BHB) released in the blood, is a nutrient for other cells that reconvert it by ketolysis, into acetyl CoA. The ketolytic pathway involving three enzymes, was analysed in previous publications [5]. While, ketones coming from branched chain amino acids (BCAA) were studied in ref [6].

As for the Beta type adrenergic receptors that increase cAMP, they inhibit the formation of fructose (F2-6P) an activator of glycolysis and inhibitor of gluconeogenesis. Thus glycolysis is turned off and gluconeogenesis is ON. The cAMP also activates PKA serine kinase and Src tyrosine kinase, leading to the phosphorylation and inhibition of PK and PDH, as explained above, for allowing the synthesis of glucose by gluconeogenesis. In parallel, glycogenolysis is activated by phosphorylated phosphorylase a, targeted to glycogen stores, whereas phosphorylated glycogen synthase is OFF. We also indicate that cortisol elicits proteolysis of muscle proteins providing amino acids, to feed the synthesis of glucose, alanine transamination providing pyruvate. In catabolism, glucose and ketone bodies are produced, essentially in the liver. The cAMP and DAG are two positive markers for this situation (Figure 1A). The opposite anabolic situation is illustrated in Figure 1B. Food intake, and the increase of blood glucose is sensed by K-ATP channels of Beta cells and Delta cells of the endocrine pancreas, the increase of ATP closes these channels and K+ ions are retained, cells depolarize, opening their voltage gated calcium channels, which triggers the release of insulin and GABA from Beta cells, and somatostatin (SST) from Delta cells. However, GABA will inhibit alpha cells and delta cells, closing the release of glucagon and interrupting SST release, by hyperpolarizing back these cells via their GABA A receptors that elicit a Cl^- influx. Hence, insulin will support an anabolic metabolism. The action of insulin is mediated by: Tyrosine kinase Receptors via PKB activation of phosphatases, and inhibition of enzyme kinases. Glycogen synthase is dephosphorylated and ON, while phosphorylase a, is dephosphorylated and OFF, interrupting glycogenolysis. Proteins and fatty acid are synthesized, Lipogenesis is activated, while lipolysis is OFF. Normally, fatty acids and particularly unsaturated fatty acids, inhibit AMP deaminase [7-9] but lipogenesis greatly consumes these fatty acids, cancelling the inhibition of AMP deaminase by fatty acids. Hence, AMP deaminase is activated, AMP decreases (converted to IMP). The decrease of AMP turns off another enzyme AMP kinase, removing the inhibition acetyl CoA carboxylase (ACC) by AMP kinase. This will activate ACC at the start of the fatty acid synthesis and lipogenic pathways, ACC forms malonyl CoA, the latter blocks the mitochondrial canityl transporter of fatty acids and their degradation by Beta-oxidation, closing the fatty acid source of acetyl CoA. Lipogenesis consumes DAG converted to triglycerides (TAG). This attenuates the stimulation of PKC by DAG, and inhibits the formation of CPI 17 a PP1 inhibitor normally activated by PKC. Hence, PK and PDH are dephosphorylated, Glycolysis is ON and provides acetyl CoA to the citric acid Krebs cycle. Moreover, since insulin elicits the formation of IP3, which mobilizes internal calcium stores. The calcium activates PP1 by removing another inhibitor I1 of PP1. It is a phosphatase calcineurin, activated by calcium that is involved, it dephosphorylates the I1 inhibitor, which quits PP1. The removal of the two PP1 inhibitors boosts glycolysis and the glycolytic production of acetyl CoA. In addition calcium helps the incorporation of the glucose transporter to the membrane by exocytosis. Moreover, Hexokinase moves to the mitochondrial ANT complex, receiving the ATP substrate more efficiently, which pulls the inward flux of glucose through its transporter. Finally, calcineurin activates a phosphodiesterase (PDE), which converts cAMP to AMP and then to IMP by AMP deaminase activated by the decrease of fatty acids. This cancels the inhibition of glycolysis by cAMP, since fructose 2-6 P the allosteric activator of glycolysis is formed. The insulin linked metabolic situation can be marked by the combination AMP- DAG- The next metabolic situation considered in Figure 1C, depends on Growth hormone (GH). The pancreas displays a depolarization of Beta cells releasing insulin and GABA, and of Delta cells releasing SST. The released GABA inhibits alpha cells, which stops the release of

glucagon, and inhibits Delta cells, which inhibits SST release. As indicated in the Figure 1 C, the decrease of SST increases Growth hormone (GH) (released from the hypophysis). GH elicits the synthesis and release of insulin like growth factor (IGF) from the liver. However, GH / IGF are not equivalent to insulin. GH increases lipolysis, by activating the enzyme adipocyte triglyceride lipase (ATGL), TAG is cleaved to Fatty acid and DAG. Fatty acids particularly cis unsaturated ones, inhibit AMP deaminase, increasing the level of AMP, which activates AMP kinase and turns off ACC. If ACC is at rest, malonyl CoA decreases, which cancels the inhibition of the fatty acid carnityl transporter of mitochondria, allowing the beta-oxidation of fatty acids, forming acetyl CoA. Thus, GH supports the fatty acid source of acetyl CoA. In addition, the other product of the lipolysis elicited by GH, is DAG. The latter activates PKC, which stimulates the formation of CPI 17 a PP1 inhibitor. Hence, the phosphorylation of PK and PDH is maintained, closing the glycolytic supply of acetyl CoA to the Krebs cycle, preferentially fed by acetyl CoA coming from fatty acids. The metabolic situation in Fig 1C is marked: AMP+ DAG+ .The next metabolic situation, is cancer metabolism. In Figure 1 D the pancreas is again represented, with a possible anomaly decreasing the release of GABA; [it could result from a vitamin B6 deficiency, since B6 is a cofactor of glutamate decarboxylase (GAD), the enzyme synthetizing GABA, or result from an autoimmune disease affecting Beta cells and GAD, as for type 1 diabetes, or come from pesticides affecting GAD]. Hence, the GABA deficit fails to turn off Alpha cells releasing glucagon while insulin is released. If the GABA deficiency is important, it might fail to turn off Delta cells, releasing SST. The increase of SST release might then attenuate the lipolytic effects of GH. On the other hand, adrenals will release more epinephrine as a result of the important GABA deficit. Other conditions such as stress, might stimulate epinephrine release a catabolic hormone, in parallel to anabolic insulin. In addition, a lower GABA action on GABA B auto receptors of Beta cells, probably fails to terminate the insulin release process, maintaining a chronic insulin leakage, able to desensitize insulin receptors of differentiated cells, while new mitotic stem cells with new insulin receptors, would not be affected, and would respond to insulin, epinephrine and glucagon, displaying a hybrid metabolic rewiring. The figure 1 D indicates the epinephrine and glucagon actions on Beta Gs adrenergic receptors, and alpha Gq receptors. The increase of cAMP triggered by Gs coupled receptors elicits as for a catabolic situation via PKA and Src, the phosphorylation of PK and PDH, inhibiting the glycolytic production of acetyl CoA. While the pyruvate accumulated above the PDH bottleneck forms lactate (Warburg effect) [10]. On the other hand, the GABA deficiency enhances epinephrine release, which activates a lipolysis supported by the hormonal sensitive lipase (HSL) leading to the hydrolysis of TAG into fatty acids and DAG. As indicated, fatty acids particularly unsaturated normally inhibit AMP deaminase, but since insulin elicits lipogenesis, it greatly consumes fatty acid, which cancels the inhibition of AMP deaminase by fatty acids, this decreases AMP. Hence, AMP kinase is turned off, which cancels the inhibition of ACC by AMP kinase. Thus, ACC forms malonyl CoA along the fatty acid synthesis pathway and lipogenesis. Malonyl CoA increases and blocks the fatty acid mitochondrial carnityl transporter and the degradation of fatty acids by beta-oxidation, which closes the lipolytic supply of acetyl CoA to the citric acid cycle. On the other hand, DAG will activate PKC, eliciting the formation of CPI17 an inhibitor of PP1, which keeps PK and PDH phosphorylated and inhibited, interrupting the glycolytic supply of acetyl CoA. The essential way for such cells to get acetyl CoA is to use ketone bodies via the ketolytic pathway, in which the enzyme succinyl CoA: oxoacid- CoA transferase (SCOT) plays a central part [5]. Branched chain ketogenic amino acids also form ketones and acetyl

CoA, feeding tumour cells [6]. The citrate condensation may now be supplied with acetyl CoA coming from ketones, and forms citrate, which exits the mitochondria and joins the lipogenic pathway, making new membranes for mitotic cells. The metabolic situation described in Figure 1 D could be marked AMP- DAG+ for ketolytic dependent tumour cells.

The last metabolic situation to examine will display markers opposite to the previous, it decreases the ketolytic dependency, by opening back the glycolytic and fatty acid supplies of acetyl CoA Figure 1E. Here, the Pancreas displays a depolarization of Beta and Delta cells and the release of GABA from Beta cells turns off Alpha and Delta cells, as was the case for the GH hormone metabolic situation in Figure 1C, SST declines and GH is elevated, increasing lipolysis. The enzyme ATGL is actively converting TAG into Fatty acids and DAG. As for Figure 1 C. Fatty acids (unsaturated) inhibit AMP deaminase [7], AMP increases and activates AMP kinase, which turns off ACC, malonyl CoA decreases; thus the fatty acid canityl transport of mitochondria is operational and Beta oxidation of fatty acids form acetyl CoA. But in this particular situation, DAG will decrease, presumably via the activation of a DAG lipase, PKC is no longer stimulated by DAG as in Figure 1C and CPI17 is not formed, failing to inhibit PP1. A dephosphorylation of PK and PDH takes place, activating these enzymes, which opens the glycolytic source of acetyl CoA. With two acetyl CoA sources open, one cancels the ketolytic dependency indicated for cancer in Figure 1 D. This situation is marked AMP+DAG- .

An interesting observation shows that DAG lipase forms arachidonic derivatives, 2 arachidonylglycerol (2AG) and N-arachidonoylethanolamine or anandamide, which are endogenous agonists of cannabinoid receptors (CB)1 and CB2). In mitochondria, CB1 regulates respiration [11] and inhibits human breast cancer cell proliferation [12].

CONCLUSION

Probably at an early stage of cancer, an anomaly of metabolism that could be frequent, favours the development of tumour cells, one may suggest that stem cells committed to repair an injured tissue enter in mitosis, but the daughter cells that should differentiate do not, leading to a geometric increase of their number. These new cells with new insulin receptors are still sensitive to anabolic insulin and will respond to catabolic hormones as proposed. If Beta cells, of the endocrine pancreas, release insulin with relatively lower GABA level, they might fail to inhibit Alpha cells releasing glucagon, and to terminate insulin release. Insulin receptors of differentiated cells desensitize, while the new stem cells will still respond to both insulin and glucagon or epinephrine, and display a hybrid rewiring as in Figure 1 D. They become vitally dependent of Ketone bodies, for getting their mitochondrial acetyl CoA, since the other glycolytic and fatty acid acetyl CoA sources are turned off, in this metabolic situation. Depolarized Delta cells that release SST should inhibit glucagon release and prevent the hybrid catabolic-anabolic rewiring, unless they are inhibited even at low GABA levels, or by some other mechanism discussed later. If this is the case, SST decreases and GH increases, which adds its lipolytic effects to those of epinephrine released from adrenals, since a decrease of GABA suppresses the inhibition of adrenals. In these conditions, tumour cells become vitally dependent on ketone bodies. The discussion would be easier if the K- ATP channels where not complex structures associated to other proteins that carry the sulfonyl urea inhibitor binding site, or to another potassium rectifier channel. Evidently, the models presented are to be taken cautiously.

At an early stage, the cells displaying the hybrid rewiring survive with the supply of BHB, the ketone body providing acetyl CoA via: a reductase, SCOT and thiolase (ACAT1), the three enzymes of ketolysis. However, intracellular BHB has other effects favouring the expression of embryonic isoforms of an adult gene, or the M2 embryonic mRNA splice variant isoform for PK in tumour cells. Later, of course mutations will change the course of cancer. But at this early stage, one may in theory undo the metabolic rewiring as illustrated (Figure1E), in which DAG lipase is ON, it forms in parallel, arachidonic derivatives, endogenous cannabinoids, agonists of CB1 and CB2 receptors that have anti-proliferative effects [12].

In principle, the ketogenic diet, which feeds tumour metabolism (Figure 1D), should be avoided; but again, things are more complicated, because BHB is an agonist of the niacin HCA2 receptor. Its activation by BHB, sets off inflammation, and the re-expression of embryonic proteins. Once in the cell, BHB does the opposite, supporting a juvenile phenotype (it inhibits histone deacetylase HDAC) and will in addition feed the ketolytic pathway [2, 5, 6].

A final remark concerns an early work of Brünings, we discovered in Clements' review [13]. Apparently, in his trial, Brünings observed an initial regression of tumours, following a low carbohydrate diet, with a controlled hypoglycaemia obtained by injecting insulin extracts. However, after feeding patients with a lipid enrich ketogenic diet, a disappointing rebound of tumours took place. Presently, following the work of Vegari et al. [14] we learned that insulin has a direct action on SST release from Delta cells, by activating their sodium-glucose co-transporter (SGLT) 2. The sodium entering with glucose, depolarizes Delta cells, which opens their calcium channels and triggers SST release. Hence, SST inhibits glucagon release from alpha cells. In Brünings trial, insulin presumably inhibited glucagon release via somatostatin (SST) release, which held back glucagon and ketogenesis, avoiding to feed a ketone dependent tumour. At this stage tumours regressed. Unfortunately, after two weeks of a lipid rich diet, the stimulation of (SGLT)2 of Delta cells by insulin fades down, SST release decreases failing to inhibit glucagon and ketogenesis, now feeding tumours, which presumably explains the disappointing rebound observed by Brünings, SST was not yet known.

Evidently, more works on the reciprocal interactions of islets cells in the endocrine pancreas, are needed for unravelling cancer metabolism, and helping the identification of new targets for preventing or treating cancer, bearing in mind that SST inhibits GH and its probable carcinogenicity, as suggested by A. Gernez [15] and shown by VD Longo and associates [16].

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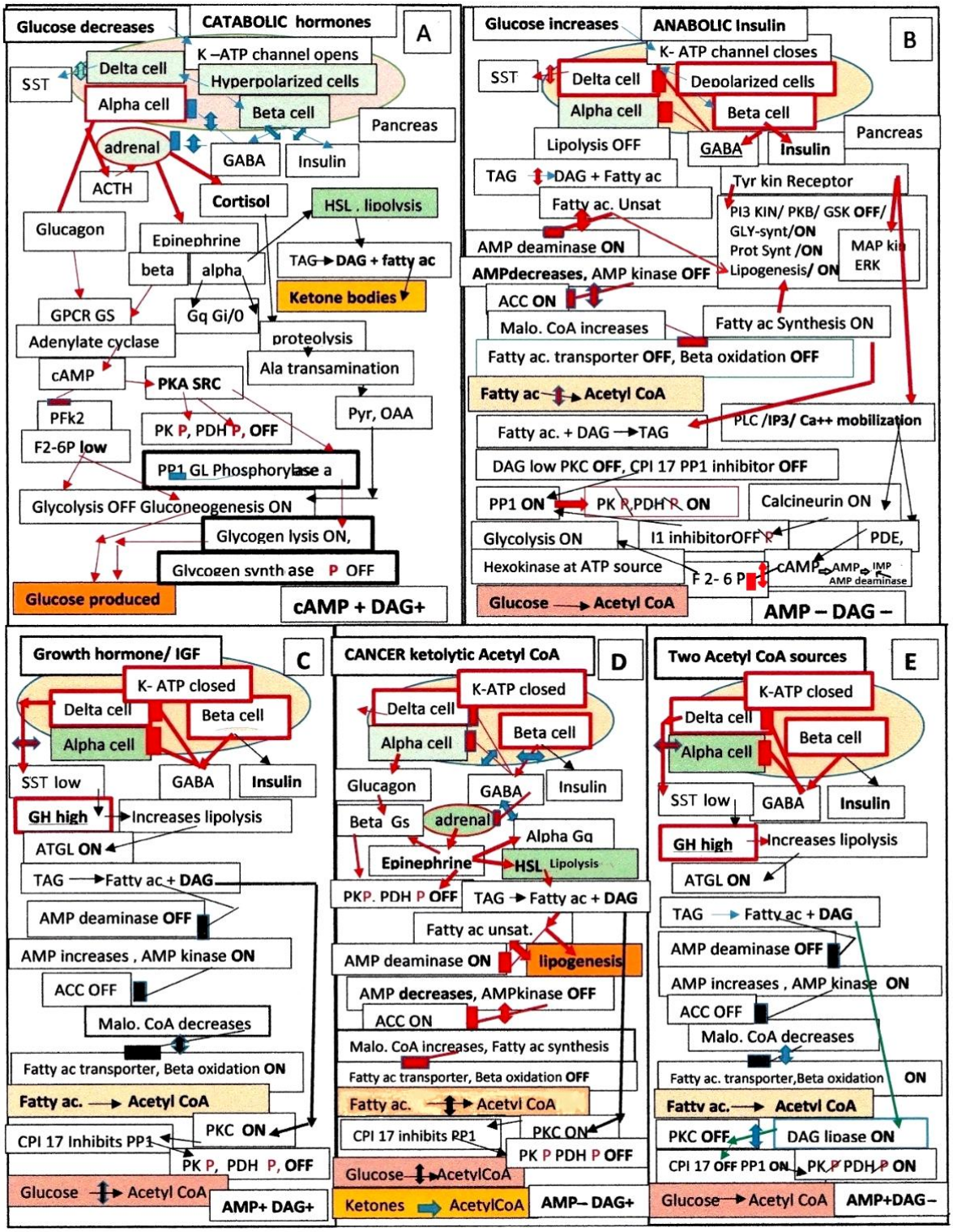

Figure 1: Normal metabolic situations compared to cancer metabolism. Note the changes in Acetyl CoA sources, the ketogenic dependency of tumour metabolism, and the markers for each metabolic situation.