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SERVICES FOR SCIENCE AND EDUCATION

Respiratory Complex II and SCOT-Oxct1 Compete for Succinyl-CoA in Ketolytic Dependent Tumours

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ABSTRACT

The present work recalls main features of tumour cell metabolism, explaining their ketolytic dependency and vulnerability. We then explored the interface between the respiration chain complexes and the nutritional supply of succinyl-CoA to the ketolytic enzyme SCOT- Oxct1. We also indicate several target points in ketolysis and fatty acid synthesis pathways that would affect tumour cells, rendered vulnerable by their ketolytic dependency.

Keywords: Tumour cell metabolism, SCOT- Oxct1, Ketolysis, Respiratory complexes.

INTRODUCTION

The particular metabolism of tumour cells, in relation to general metabolism, is an essential issue to consider, for affecting specifically tumour cells, and develop a possible metabolic back-up for current cancer treatments. The initial observation of Warburg [1] on the lactic acid release by tumour cells, in spite of oxygen being available, is a particularity of tumours to be analysed in relation to nutritional or physiological changes associated to cancer.

Evidently, mitotic tumour cells need to make new lipid membranes, and have to synthesize fatty acid. In this pathway, an enzyme: Acetyl-CoA carboxylase (ACC) converts in the cytosol, acetyl-CoA into malonyl-CoA. This enzyme product inhibits the mitochondrial fatty acid carnityl-transporter and the beta-oxidative degradation of fatty acids into acetyl-CoA. Thus, when fatty acids synthesis takes place, their degradation is inhibited, which turns off, in mitotic tumour cells, the fatty acids source of acetyl- CoA.

We also know that a tumour cell has to incorporate much glucose for overcoming an abnormal bottleneck at the last enzyme of glycolysis, the pyruvate kinase PK M2 step, studied by Eigenbrodt and Mazurek [2]. Apparently, the enzyme remains phosphorylated and inhibited, unable to form active tetramers, as if it remained in the gluconeogenic configuration. In addition, just at the entry in oxidative metabolism, pyruvate dehydrogenase (PDH) is also blocked by phosphorylation, [3] forming a second bottleneck, inhibiting the conversion of

pyruvate into acetyl-CoA. The pyruvate will then be converted into lactic acid, explaining the Warburg effect. In sum, if both the glycolytic and fatty acid supplies of acetyl- CoA are turned off in tumour cells, they will become dependent of the third major source of acetyl- CoA, coming from the ketolysis of ketone bodies, formed essentially in the liver, by ketogenesis; with the support by a few ketogenic branches chained amino acids. Ketolysis is a particularly interesting feature to consider, because it depends of a single and specific ketolytic enzyme: Succinyl-CoA: 3 oxoacid-CoA transferase, (SCOT) the product of the oxct1 gene, which renders tumour cells vulnerable to SCOT inhibition. We have indeed shown that inhibiting SCOT and the ketolytic pathway in an animal cancer model, had clear anti- tumour effects and discussed the effects of ketone diets [4-6].

In the present work, we first schematize tumour cell metabolism and discuss the role of nutritional ketones supporting tumour growth, in comparison to the signalling action of ketone bodies displaying antitumour effects. Second SCOT dependent ketolysis, will be analysed in relation to the respiratory mitochondrial complexes, and to observed carcinogenic or anticancer effects related to the availability of succinyl- CoA and its metabolism. Third, we will situate some targets for several anti-cancer compounds acting on ketolysis, lipogenesis and the formation of tumour cell membranes.

A FOCUS ON TUMOUR CELL METABOLISM AND ITS KETONE DEPENDENCY

Ketone bodies formed in the liver by ketogenesis are released in the blood. Beta hydroxyl butyrate (BHB) reaches the tumour cell and is incorporated through monocarboxylate transporters, (MCT). The BHB is then converted into acetoacetate by BHB dehtdrogenase and will be processed by SCOT, which transfers the CoA of succinyl- CoA to acetoacetate, forming acetoacetyl-CoA. Then a thiolase acetyl -CoA acetyltransferase (ACAT1) converts acetoacetyl-CoA into two acetyl-CoA (Figure 1).

The succinyl- CoA is formed in the citric acid cycle from alpha ketoglutarate, itself fed by glutamate and glutaminolysis. In this way, ketolysis provides to tumour cells the acetyl-CoA they need for supporting their oxidative metabolism and the supply of citrate to the lipogenic pathway. Acetoacetate and succinyl- CoA, the two SCOT substrates, will ensure the nutrition and growth of tumour cells. In sum, a decrease of intracellular ketones and Ketolysis, should limit the SCOT pathway and slow down tumour growth. In addition, decreasing intracellular BHB attenuates its nuclear effects, such as the stimulation of NFkB transcription and inflammation triggered by intracellular BHB.

Moreover, decreasing intracellular BHB suppresses the inhibition of histone deacetylase (HDAC), and the re-expression of genes active in juvenile cells. On the other hand, extracellular BHB stimulates the HCA2 niacin receptor, which inhibits inflammation mitosis and elicits differentiation, this Gi- coupled receptor actions are mediated by prostaglandins. By decreasing BHB one may lose this favourable effect on HCA2 receptors. However, it can still be recovered by Niacin, without eliciting the development of tumour cells by intracellular BHB and ketolysis. The figure 1 summarizes the ON / OFF, nuclear NFkB transcription mechanism triggered by intracellular BHB, opposite to the action of extracellular BHB acting on HCA2 the niacin receptor. The figure 1 illustrates the mitochondrial SCOT- ACAT1 ketolytic pathway, feeding with acetyl-CoA and citrate the fatty acid synthesis pathway needed by tumour cells for making new membranes.

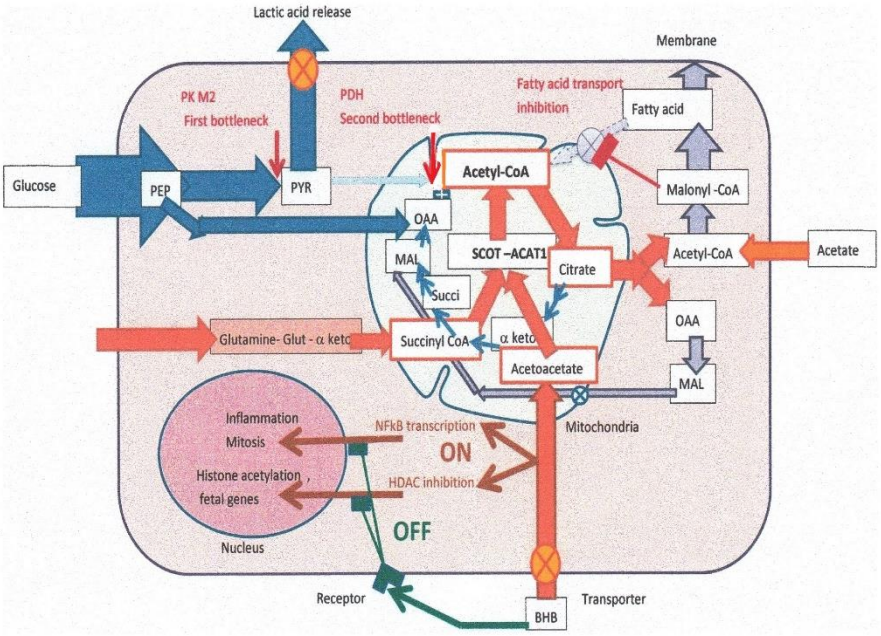

Figure 1: Ketolytic dependent tumour cells

Fatty acid and Glycolytic supplies of acetyl-CoA are interrupted in a tumour cell; note the Pyruvate kinase (PK M2) the Pyruvate dehydrogenase (PDH) bottlenecks, and the malonyl-CoA inhibition of the fatty acid carnityl transporter. Thus, Ketolysis of Beta hydroxyl butyrate (BHB), via Succinyl-CoA: 3 oxoacid-CoA transferase (SCOT) and acetyl-CoA acetyltransferase (ACAT1) becomes the essential source of mitochondrial Acetyl-CoA, feeding citrate in the fatty acid synthesis and lipogenic pathway, to form new mitotic membranes. The other intracellular effect of BHB, at the nuclear level triggers NFkB transctription, inflammation and the re-expression of embryonic genes, the system is turned OFF by exta-cellular BHB acting on the Niacin receptor.

SCOT AND THE RESPIRATORY COMPLEX II COMPETE FOR SUCCINYL-COA

A simplified representation of the mitochondrial respiration complexes in relation to the citric acid cycle is shown in figure 2. The ketolytic supply of acetyl-CoA in tumour cells via SCOT receives its two substrates the succinyl-CoA and acetoacetate, and forms acetoacetyl-CoA, then ACAT1 converts acetoacetyl-CoA into acetyl-CoA. The latter feeds the citrate condensation and the lipogenic pathway.

A carcinogenic mutation of succinodehydrogenase (SDH) complex II, interrupts the conversion of succinate into fumarate, and is carcinogenic: Carney triad tumors [7]. Indeed, if SDH is OFF, the “oncometabolite” succinate will form back succinyl-CoA, through the preceding enzyme of the Krebs cycle: succinyl-CoA synthetase, increasing the succinyl-CoA SCOT substrate and ketolysis, which then feeds the citrate condensation, lipogenesis and tumour growth. On the other hand, when Complex II is active SDH converts succinate into fumarate and consumes succinyl-CoA, which will then limit the supply of succinyl- CoA to SCOT, decreasing tumour growth.

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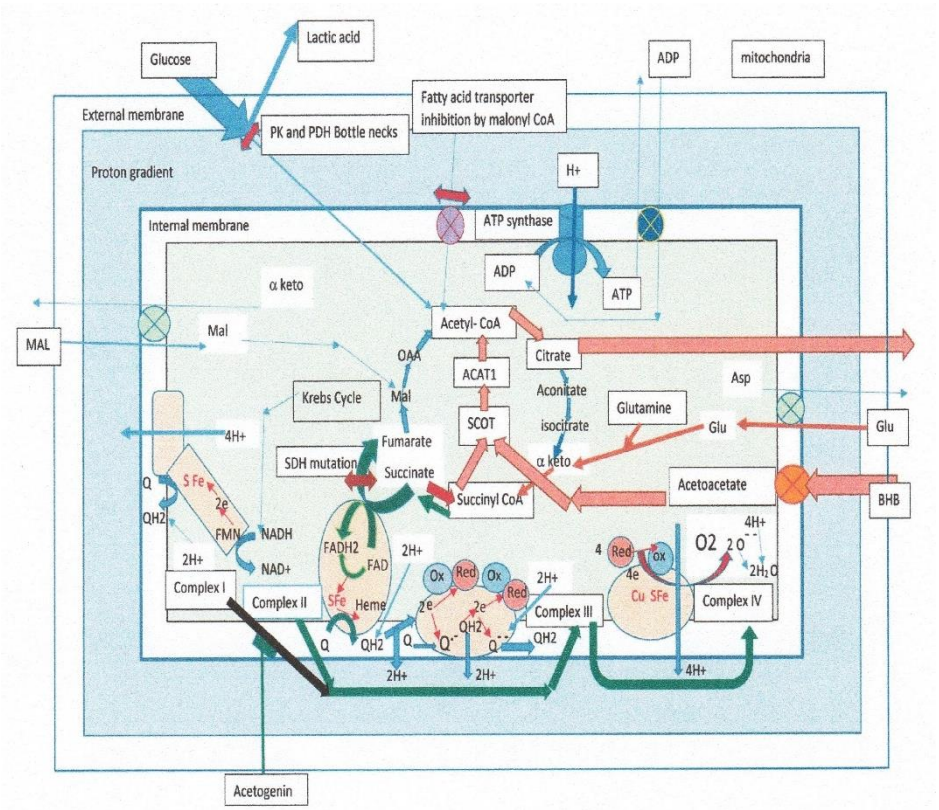

Figure 2: Ketolysis and Respiratory complex II compete for succinyl-CoA.

A simplified representation of Respiratory complexes in the mitochondrial inner membrane indicates that there are two entries for reaching complex III and IV. In black the Complex I entry, and in Green the Complex II entry. Complex II shares with the Krebs cycle the succinodehydrogenase (SDH) reaction. If a mutation inhibits SDH, succinate "an oncometabolite "increases, and more succinyl-CoA can feed ketolysis via SCOT – ACAT1, which is favourable to tumour cells (Carney triad cancers). Acetogenin, an inhibitor of complex I (as rotenone) puts all the weight on complex II, withdrawing more succinyl–CoA from the cycle, and the SCOT pathway, this has anti-cancer effects in ketolytic dependent tumours. In blue the proton gradient generated by the respiratory chain, note the reduction of cytochromes on complex III and their oxidation on Complex IV, for reducing Oxygen, it will form water, while the proton gradient flows in through the ATP Synthetase, forming ATP inside, exchanged with ADP. The figure recalls the inhibition of glycolytic and fatty acid sources of acetyl-CoA in tumour cells.

As indicated in figure 2 the respiratory chain has two entries, One through Compex I (NADH coenzyme Q reductase) the other through SDH- Complex II (succinate coenzyme Q reductase). These two entries feed Complex III and IV as indicated to generate the proton gradient between the internal and external membranes of the mitochondria, while electrons are carried through the complex cores by flavoproteins and Iron sulphur (SFe) clusters to reduce the cytochromes of complex III. These cytochromes will then be re- oxidized on Complex IV, which in turn reduces oxygen. The proton gradient will be dissipated through ATP synthase and provides the energy for synthesizing ATP in the matrix as indicated, while reduced oxygen recovers protons to form water, in accordance to Mitchell's chemiosmotic hypothesis.

Well, if the complex I entry is slowed; one can suppose that complex II will have to take over the reductive work, consuming succinyl-CoA, which is consequently discarded from SCOT. This would explain the anti-cancer effect of rotenone a classical complex I inhibitor, and the observation that acetogenins from Annones display clear anti-cancer effect, by binding as rotenone to the active center of complex I; eliciting a greater consummation of succinyl-CoA by complex II [8,9].

In sum, conditions diverting succinyl-CoA from SCOT display anti-cancer effects, in contrast conditions increasing the formation of succinyl-CoA support tumour growth; this is associated to the supply of glutamine -glutamate, and to the supply of BHB and acetoacetate to ketolytic dependent tumours.

Other points are in the same line, the formation of heme, starts with the reaction of glycine and succinyl-CoA forming aminolevulinic acid along the protoporphyrine pathway. This reaction consumes succinyl-CoA, however if the last enzyme in the pathway, the ferrochelatase step, is mutated, succinyl-CoA accumulates and feeds upstream tumours, rendered visible by protoporphyrine accumulation [10].

There are other points to consider. Of all the respiratory complexes, only complex II is the product of nuclear autosomal genes, the other complexes I, III or IV, are products of mitochondrial genes, at least for some of their numerous subunits. The translation of proteins forming complex II (autosomal genes), starts with a methionine at the N terminal. For the other complexes that depend of mitochondrial genes the starting amino acid is formylmethionine (as for bacteria). Well, it has been found that actinonin, a naturally

occurring antibacterial agent produced by Actinomyces, is an inhibitor of methionine deformylase, it will then interfere with the release of proteins encoded by mitochondrial genes, which is not the case for complex II. Thus, one expects that this will slow down the respiratory chain and complex I, while complex II will be fully active consuming succinyl-CoA, which deprives SCOT and the tumour of acetyl-CoA, explaining the anti-cancer effects of actinonin [11].

AN OVERVIEW OF TARGETS FOR SEVERAL ANTI-CANCER COMPOUNDS

We gathered in figure 3 the targets for several compounds aiming to counteract the metabolic changes supporting tumour cell metabolism. This is only a list compound, not a treatment; it is a proposal for selecting 5 or 6 compounds aiming to correct the metabolic rewiring associated to the tumour. These could be studied on animal models as we did for a few of them [4, 5] with the hope of backing-up current treatments, by acting on ketolytic dependent tumour cells. The figure 3 situates the two bottlenecks at PK M2 and PDH interrupting the glycolic supply of mitochondrial acetyl-CoA; and indicates that the active synthesis of fatty acids and lipid membranes by mitotic tumour cells interrupts the degradation of fatty acids and the lipolytic source of acetyl-CoA, rendering tumour cells dependent of the ketolysis for their acetyl-CoA supply. Ketone bodies formed essentially in the liver reach the tumour as Beta hydroxy butyrate (BHB). One may first try to decrease ketogenesis and BHB using octreotide a somatostatin analogue; we know that somatostatin inhibits, glucagon release and ketogenesis, Nigella sativa might have a similar effect [12]. The BHB is transported in the cell through MCT2/4 transporters; these are inhibited by Rauwolfia alkaloids such as Syrosingopine [13] or

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Epigallocatechin from green tea [14] or Dichloroacetate (DCA) the latter was used for inhibiting enzyme kinases phosphorylating PK or PDH, [3] in tumours. In fact, DCA may have a broader effect, on MCT transporters [15] and might compete with the supply of acetate. The MCT2/4 transporters that support the influx of BHB control the efflux of lactic acid. Quercetin inhibits this transporter leading to internal acidification [16]. As for Emodin from Aloe Vera it targets Fatty acid synthase as indicated [17]; while Rhein from rhubarb, inhibits adipocyte differentiation and adipogenesis [18]. A dehydrogenase converts intracellular BHB into acetoacetate, the substrate of SCOT, an enzyme specific for ketolysis, the other SCOT substrate being succinyl-CoA, the enzyme SCOT can be inhibited

by acetohydroxamic acid (Lithostat or Uronefrex) [19] and many siderophores, Lithotamnin from Lithotamnium Calcaneum a red alga [4] others include Phycocyanin, ferrichrome, lactoferrin the latter was, studied in earlier reports [20, 21] and probably melatonin, which displays iron binding properties. Another interesting SCOT inhibitor with anti- cancer properties is Pimozide (Orap), prescribed for Gilles de la Tourette syndrome [22]. The succinyl-CoA substrate of SCOT forms via alpha ketoglutarate in the Krebs cycle. In addition, Glutamine then glutamate; will enter in mitochondria through the Glutamate-aspartate shuttle, and contribute to the synthesis of succinyl-CoA, via Glutamate dehydrogenase (GDH) itself activated by leucine. This glutamate entry in mitochondria is inhibited by Epigallocatechin (figure 3).

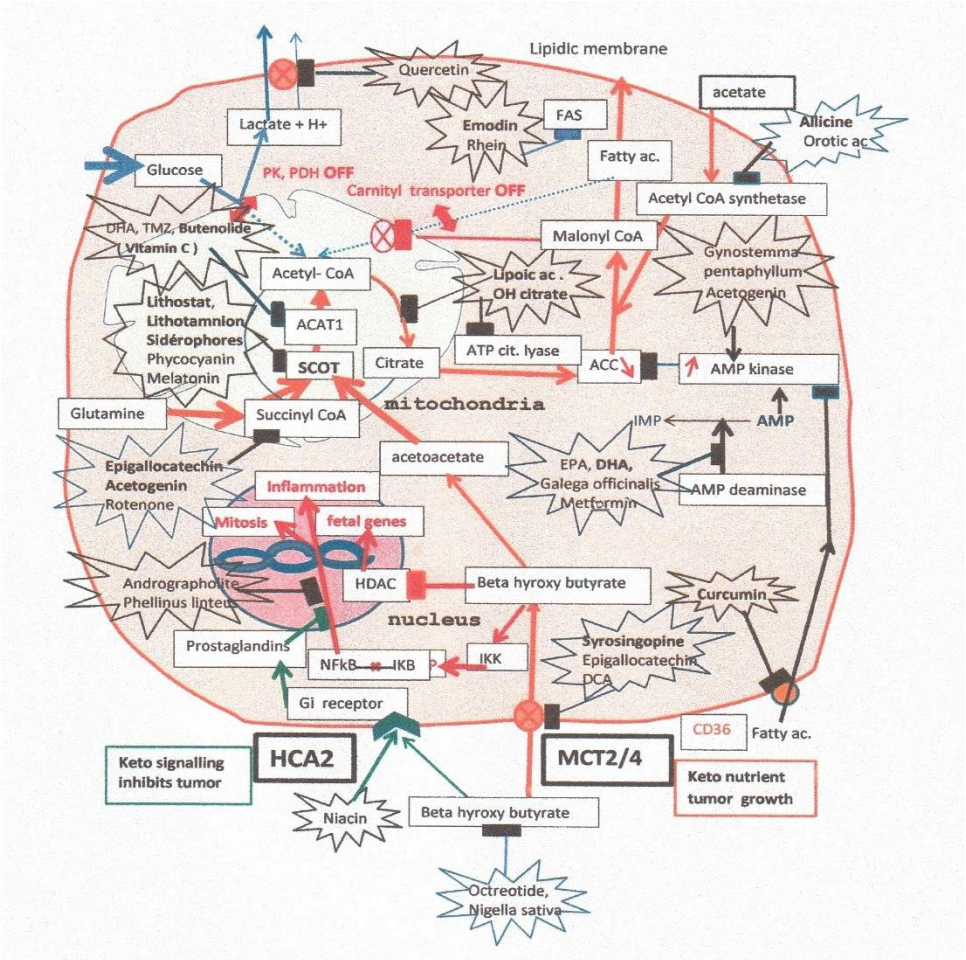

Figure 3: Drugs affecting ketolytic-dependent tumour cells.

The Ketolytic pathway forms acetyl-CoA in tumour cell mitochondria, in which the glycolytic and fatty acid acetyl-CoA sources are cut as indicated. The SCOT enzyme is the specific step in ketolysis, followed by ACAT1. For each of these 2 steps we indicate possible inhibitors (Lithostat, siderophores, and vitamin C). Upstream of SCOT, we suggest using compounds decreasing the two substrates of SCOT: succinyl-CoA and acetoacetate (Epigallocatechin acetogenin). Far upstream, the entry of beta hydroxyl butyrate (BHB) in the cell could be decreased at its transporter MCT2/4 level (Syrosingopine). The nuclear actions triggered by intracellular BHB, deserve to be decreased (andrographolite). The extracellular signalling effect of BHB over the niacin HCA2 receptor could be reinforced. Downstream of ketolysis two essential drugs decrease the citrate efflux from mitochondria and inhibit ATP citrate lyase, (lipoic acid and OHcitrate from garcinia Cambodgia), which should slow down fatty acid synthesis, also inhibited at the Fatty acid synthase (FAS) level by Emodin. The lipogenic pathway is controlled by AMP kinase, which inhibits acetyl-CoA carboxylase (ACC) a key enzyme in this pathway. An activation of AMP kinase by (Gymnostemma pentaphyllum) and an inhibition of AMPdeaminase by cis-Docosahexanoic aid (DHA) should increase AMP and activate AMP kinase, for decreasing ACC. Finally, we need to inhibit the direct supply of exogenous acetate to the lipogenic route by Allicine.

We have discussed above the role of Complex I inhibitors Acetogenin from the anonne fruit (anonna cherimola), or rotenone. In ketolysis, SCOT is followed by ACAT 1 that converts acetoacetyl-CoA into Acetyl-CoA. Vitamin C, which has a butenolide ring inhibits ACAT1, other possible inhibitors include trimetazidine (vastarel), or Docosahexanoicacid (DHA). After the citrate condensation reaction, the citrate efflux from mitochondria, feeds ATP citrate lyase and fatty acid synthesis, via acetyl-CoA carboxylase (ACC), we have earlier tested Lipoic acid and Hydroxy citrate from Garcinia cambodgia on these steps, they had impressive effects [4]. Moreover, one should inhibit the direct supply of external acetate to cytosolic acetyl-CoA synthetase, feeding the lipogenic pathway, by using Allicine or Orotic acid [23,24]. We also indicate that AMP kinase activated by AMP, down regulates fatty acid synthesis by inhibiting ACC. Gymnostemma pentaphyllum [25] or acetogenins from anonnes can directly stimulate AMP kinase [5] this will then inhibit the fatty acid synthesis and hamper the production of lipid membranes for mitotic cells. In addition, compounds that inhibit AMP deaminase will increase AMP, and stimulate AMP kinase, further inhibiting ACC and fatty acid synthesis. Apparently Cis - unsaturated fatty acids inhibit AMP deaminase [26], Other inhibitors are guanidines, galegine from Galega officinalis, very close to metformin. [27]. Note that the fatty acid membrane transporter CD36, which negatively regulates AMP kinase, is decreased by curcumin [28] this should further stimulate AMP kinase and decrease ACC.

We have seen that Niacin and BHB stimulate the HCA2 receptor, its beneficial signalling effect, mediated by prostaglandins, should attenuate the intracellular actions of BHB, which stimulate inflammation, mitosis
and tumour growth.

The niacine receptor action might be supported by Andrographolite from Andrographis paniculata a traditional Chinese medicine [29] or Phellinus linteus extracts [30].

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CONCLUSION

A presentation of tumour cell metabolism indicating its ketolytic dependency focussed our attention on SCOT and on its inhibitors. Situations forming succinyl-CoA and the transfer of CoA to acetoacetate support tumour growth, (Carney triad cancers), while conditions discarding succinyl-CoA from SCOT in relation to the respiratory complex II, explain the anti-cancer effects of complex I inhibitors. Several anti-cancer compounds were situated in a metabolic presentation targeting ketolysis and the lipogenic pathway. In previous works we have discussed the hybrid metabolic rewiring of tumour cells displaying catabolic and anabolic enzymatic features, we haves incriminated a defective regulation of the endocrine pancreas, which normally turns off catabolism in anabolic conditions; leading to a ketolytic dependent tumour cell.

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