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Review

Bioactive food components, cancer cell growth limitation and reversal of glycolytic metabolism ☆

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ABSTRACT

Cancer cells are resistant to apoptosis and show a shift in energy production from mitochondrial oxidative phosphorylation to cytosolic glycolysis. Apoptosis resistance and metabolic reprogramming are linked in many cancer cells and both processes center on mitochondria. Clearly, mutated cancer cells escape surveillance and turn into selfish cells. However, many of the mechanisms that operate cellular metabolic control still function in cancer cells. This review describes the metabolic importance of glucose and glutamine, glycolytic enzymes, oxygen, growth cofactors and mitochondria and focuses on the potential role of bioactive food components, including micronutrients. The role of B- and A-vitamin cofactors in (mitochondrial) metabolism is highlighted and the cancer protective potential of omega-3 fatty acids and several polyphenols is discussed in relation to metabolic reprogramming, including the mechanisms that may be involved. Furthermore, it is shown that cancer cell growth reduction by limiting the growth cofactor folic acid seems to be associated with reversal of metabolic reprogramming. Altogether, reversal of metabolic reprogramming may be an attractive strategy to increase susceptibility to apoptotic surveillance. Food bioactive components that affect various aspects of metabolism may be important tools to reverse glycolytic to oxidative metabolism and enhance sensitivity to apoptosis. The success of such a strategy may depend on several actors, acting in concert. Growth cofactors may be one of these, which call for careful (re)evaluation of their function in normal and in cancer metabolism. This article is part of a Special Issue entitled: Bioenergetics of Cancer.

1. Introduction: Nutrition, nutrients and cancer

Nutrition is in many ways related to cancer. It is estimated that 30% or more of all cancers may be due to dietary factors [1]. The view that the general nutritional status changes cancer risk is strongly supported by association of obesity with increased risk of colon cancer [2], breast cancer [3] and many other types of cancers [4]. In many cases changes in hormone homeostasis are implicated as the mediating factor. As a consequence, life style interventions targeting obesity have been proposed as a means to reduce cancer risk [5]. Cancer risk can also, beneficially or adversely, be modulated by specific nutrients. Often this relation is complex. For example, two large human clinical intervention studies, the ATBC and the CARET study, have shown an increase in lung cancer risk and mortality upon high dose supplementation with beta-carotene of smokers, but no such effect was seen in non-smokers [6,7]. Later also an increased colon cancer risk was reported [8]. On the other hand, two other large trials, the PHS study and the Linxian study, with mainly (but not only) non-smokers, showed no increased cancer risk [9,10]. Furthermore, many indications exist that high natural intake of beta-carotene is associated with a cancer protective effect [11–13]. The mechanisms underlying the increased cancer risk upon high dose beta-carotene supplementation in smokers are still not known, but most likely result from a combination of a high dose supplementation, a long duration of continuous supplementation and an inflammatory condition that is characteristic for the at risk groups [14]. Many aspects of the relation between nutrition (and nutrients) and different types of cancer are excellently reviewed in the second WRCF/AIR expert report [15].

2. Reprogramming of energy metabolism

While it is clear that an association exist between nutritional status, nutrition and nutrients and cancer, much less is known about the specific mechanisms involved, in particular where mitochondria are concerned. Cancer cells are characterized by unrestricted growth, which is facilitated by altered mitochondrial function in two different manners; with respect to apoptosis surveillance and metabolism. First, cancer cells are mutated cells. Mitochondria have an important role in surveying the cell condition and to initiate apoptosis to eliminate mutated and potential deleterious cells [16], but apparently this

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function is compromised in tumor cells. Indeed targeting mitochondria for induction of apoptosis is a valid anti-cancer strategy [17–19], for which bioactive food components have been suggested [20]. Second, as described already in the 1920s by Otto Warburg, cancer cells show a shift in energy production from mitochondrial oxidative phosphorylation (OXPHOS) to cytosolic glycolysis [21]. This so-called 'aerobic glycolysis', in which glucose is converted to pyruvate and lactate in the presence of oxygen, is a major characteristic of most tumor cells, including colon tumors. Aerobic glycolysis not only provides the cell with ATP from the readily available substrate glucose, but the rapid glycolytic flux can also provide the cells with the necessary substrates, intermediates for lipid, amino acid and DNA synthesis, that are needed for growth in particular, NADPH, ribose, acetylCoA and glucose-derived non-essential amino acids. In addition to an altered use of glucose, cancer cells make energetically inefficient use of glutamine to supply the nitrogen for the synthesis of nucleotides and non-essential amino acids, to facilitate import of essential amino acids and to drive the TCA cycle and support NADPH production. Many aspects of altered substrate use are described in detail in [22]. The altered metabolic phenotype usually does not result from mutations in specific metabolic genes, but rather is the result from mutations in metabolic regulators. For example, p53 and LKB1, which help cells to adapt to their glucose and glutamine supply, are often mutated in cancer cells. The role of p53 and LKB1 in cancer cell metabolism is described in detail in recent reviews: [23] and [24], respectively. Other regulators that have an important role in the altered cancer cell metabolism are phosphatidylinositol-3-kinase (PI3K), Akt, AMP-kinase (AMPK), mammalian target of rapamycin (mTOR) and, likely, sirtuins. PI3K/Akt signaling mediates nutrient uptake by activating hypoxia inducible factor (HIF-1) and c-Myc. Both increase the expression of glycolytic enzymes and glucose transporters. HIF-1 further diverts pyruvate from the TCA cycle, by activation of PDK1 resulting in inhibition of pyruvate dehydrogenase [25,26], and c-Myc facilitates glutamate uptake and metabolism [27]. Both HIF-1 and c-Myc are over-expressed in tumor cells. Together, the metabolic changes take care of supply of NADPH and acetylCoA, in addition to ATP, as building blocks for the synthesis of macromolecules and satisfy the need of tumor cells to grow (Fig. 1). Glycolytic metabolism and the associated metabolic reprogramming not only support rapid growth, although at the expense of other cells, but they also make the cancer cell less dependent of oxygen availability and generates a favorable (acidic) micro-environment. More detailed descriptions of the altered cancer cell metabolism, from different perspectives, can be found in recent reviews [28–34]. Inhibition of glycolysis may have therapeutic implications in cancer treatment as a strategy to kill cancer cells [17,35–38]. Such a strategy may also make use of bioactive food components [39]. It is conceivable that such a strategy may only work if many actors operate in concert to attain the goal of metabolic reprogramming. It is therefore important to consider, as reviewed here, the various roles that bioactive food components, including micronutrients, may have. One class of bioactive food components that affect energy metabolism and may have anti-cancer effects are polyphenols. Indeed, dietary quercetin, a polyphenol present in apples, onions, tea and wine, that affects energy metabolism [40], was able to inhibit azoxymethane induced colon carcinogenesis in rats [41]. This was accompanied with lower expression of glycolytic enzymes, suggestive of inhibition of glycolytic metabolism [42]. It should be noted that quercetin is fully gluceronidated in intestinal cells upon entry in the body, a process that changes is bioactivity [43], which makes it questionable that the many potential anti-cancer effects observed *in vitro* are of relevance *in vivo*. Another polyphenol with anti-cancer potential is resveratrol. Resveratrol is well known as a compound that is present in red wine and is suggested to be responsible for the 'French paradox' [44]. Dietary resveratrol was shown to beneficially affect energy metabolism of mice fed a high fat diet. Addition of resveratrol to a high fat diet resulted in reduced weight, increased oxygen consumption, increased mitochondrial density in muscle and increased physical endurance [45,46]. Recently, topical administration of resveratrol was shown to protect against 7,12-dimethyl-benz(a)anthracene induced mouse skin tumor genesis, by up-regulation of mitochondria mediated apoptosis, involving PI3K/Akt signaling [47]. Resveratrol is also implicated in other cancer protective effects, involving various mechanisms [48,49]. On the other hand, a cancer stimulatory effect of resveratrol has also been reported [50]. It should be noted that food bioactives which affect energy metabolism may work as anti-cancer agents using mechanisms distinct from their effect on energy metabolism. One example is the polyphenol epigallocatechingallate (EgCG), the dominant polyphenol present in green tea. EgCG [51], as well as green tea extracts [52], has been shown to possess weight lowering effects in rodents and humans. Oral intake of green tea polyphenols prevents photocarcinogenesis in the skin of mice, but the mechanisms most likely involve the up-regulation of nucleotide excision repair genes [53], rather than altering energy metabolism. Another potential mechanism of anti-tumor action of EgCG is through its binding to the laminin receptor [54], which is over-expressed in many cancers cells [55]. Indeed, over-expression of the laminin receptor sensitizes cancer cells to EgCG [56]. Recently, it was shown that vitamin A derived all-trans retinoic acid enhances the anti-tumor effect of EGCG in an retinoic acid receptor (RAR)-alpha dependent manner [57]. Polyphenols are anti-oxidants. The current view is that these and most other dietary anti-oxidant compounds exhibit their functional effects through specific cellular mechanisms, rather than though general, direct anti-oxidants effects [58], possibly except in the intestinal lumen.

3. Oxygen, an essential growth substrate

Glycolytic metabolism and the associated metabolic reprogramming make the cancer cell less dependent on oxygen [30]. This was beautifully supported by a recent study of Chen et al. [59]. These authors identified the loss of a mitochondrial ribosomal protein as one of the factors underlying accelerated pancreatic tumor growth *in vivo*. This mutation decreased mitochondrial function, increased glycolysis and increased tumor growth *in vivo*, where oxygen availability is limited, but not *in vitro*, with an abundant presence of oxygen. They showed that knock down of cytochrome c oxidase, which limits the need for oxygen, had a similar effect, while the reverse, a need for oxygen and reduced tumor growth *in vivo*, was seen with over-expression of the uncoupling protein UCP-1. In agreement, one of the principal mechanisms underlying the metabolic shift is the activation of HIF-1 [60], a transcription factor that activates the conversion of glucose to lactate [61–63] and facilitates adaptation of mitochondria to hypoxia [64,65]. Among others, HIF-1 up-regulates hexokinase (HK) and lactate dehydrogenase A (LDHA), two metabolic enzymes that are considered to be of functional relevance in 'aerobic glycolysis'. Inhibition of LDHA indeed increases mitochondrial reactive oxygen production, reduces ATP production and limits cancer progression [66,67]. HK is of importance not only as a rate limiting factor in glycolysis, but also because of its role in resistance to apoptosis. HK has been shown to associate more tightly to the voltage dependent anion channel (VDAC) in tumors [68], governed by Akt [69–71], which may result in increased resistance of mitochondrial membrane transition [72], a crucial factor in mitochondrial mediated apoptosis. Indeed, it was shown that inhibition of glycolysis sensitizes tumor cells to apoptosis in an Akt dependent manner [73]. HIF-1 levels increase by hypoxia through inhibition of its degradation (reviewed in: [74]). However, under conditions of chronic hypoxia, HIF-1 levels decrease [75], which is thought to underlie the necrosis that is observed in the center of solid tumors [76]. Most of the hypoxic regions of tumors are exposed to fluctuating oxygen levels [77], which stabilize HIF-1 (for details:[78]). This also accommodates the angiogenesis promoting role of HIF-1, which is needed to supply nutrients as well as oxygen to

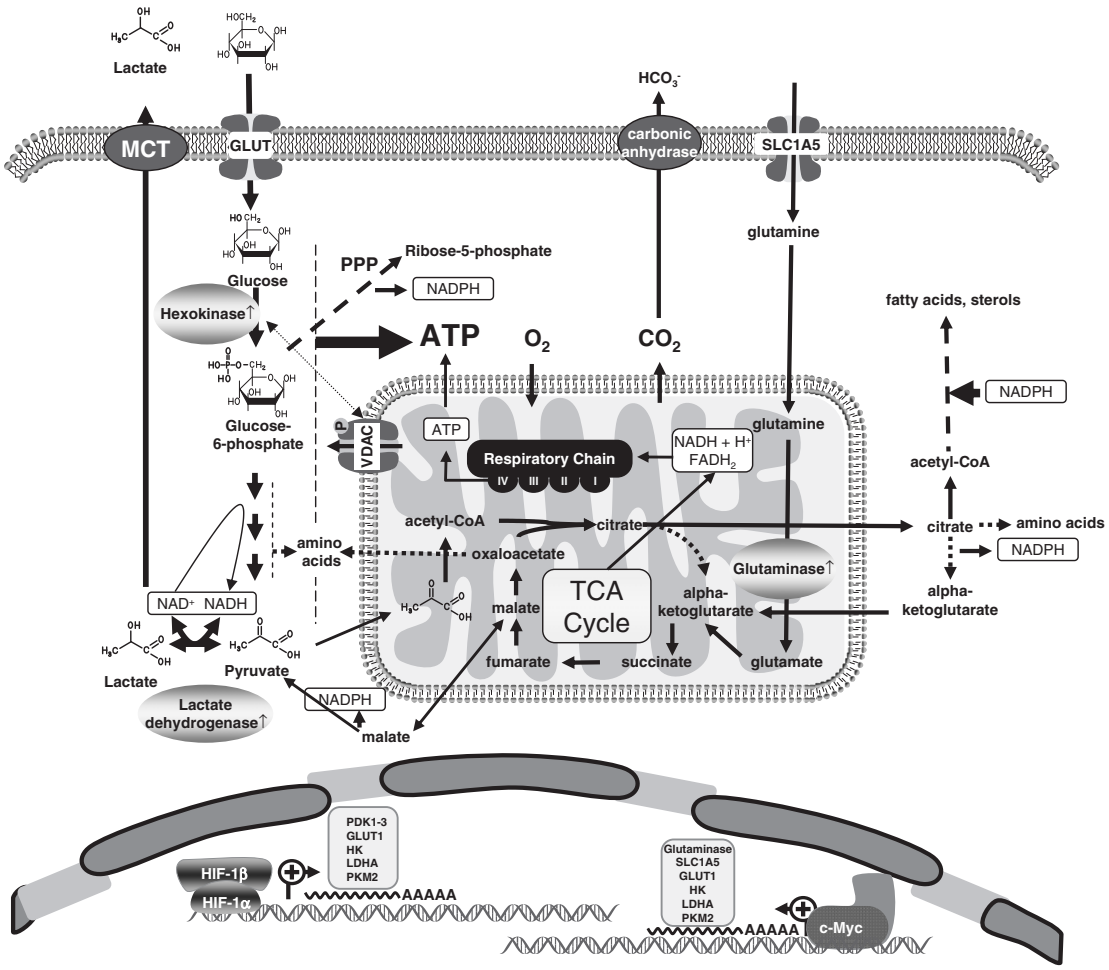

Fig. 1. Metabolic reprogramming of cancer cells. Cancer cells are metabolically reprogrammed towards 'aerobic' glycolyis. Glucose is converted into pyruvate and then to lactate, which renders 2 ATP molecules of ATP per molecule of glucose. This is in contrast to normal cells where pyruvate enters the mitochondria and is oxidized to CO_2, which is far more energy efficient and renders 32 molecules of ATP per molecule of glucose. Cancer cells compensate for the loss in energetic efficiency by using the high capacity of glycolysis, at the expense of the organism. The advantage to the cancer cell is that it renders the cells less dependent on oxygen and less sensitive to apoptotic surveillance, by various mechanisms including the association of hexokinase to voltage dependent anion channel (VDAC). A truncated tricitric acid (TCA) cycle functions to deliver the necessary building blocks for cell growth; e.g. citrate is transported to the matrix where it is converted in oxaloacetate and acetylCoA. Inhibition of hexokinase as well as lactate dehydrogenase contributes to reversal of the metabolic reprogramming of cancer cells, and both enzymes thus have an essential role in 'aerobic' glycolysis. Glutamine metabolism is also altered to facilitate the supply building blocks for protein, nucleotide and lipid synthesis. Indicated is the production of acetylCoA and NADPH for lipid synthesis. The transcription factors hypoxia inducible factor (HIF-1) and c-Myc have an important role in these changes. This figure presents a simplified version of the altered metabolism of cancers cells, which also involves other regulators and metabolic switches, such as p53, PI3K/Akt/mTOR, LKB1/AMPK, and others, possibly including sirtuins.

cancer cells and to prevent full hypoxia. In addition, the more aerobic tumor cells may use lactate produced by the more hypoxic tumor cells [31]. Although cancer cells have a glycolytic metabolism, oxidative metabolism, including lipid oxidation, is usually still functioning to contribute to ATP production [22]. However, the limited amount of oxygen that is available requires a reduced pyruvate influx into mitochondria to prevent the production of excess reactive oxygen species at complex III of the respiratory chain. Reduction of ROS is further supported increased expression of UCP-2, most likely induced by the higher ROS levels in tumor cells, and possibly also by increased lipid turnover. UCP-2 may have a role in apoptosis resistance by preventing detrimental amounts of ROS (reviewed in: [79]).

4. B- and A-vitamins and mitochondria

For their functioning, mitochondria need energy substrates, glucose and oxygen, but also cofactors (non-protein compounds needed for enzyme activity) to perform essential biochemical tasks. Deficiencies in these cofactors are associated with cancer, but generally this does not result from their role in energy metabolism. Rather this is due to specific metabolic alterations, such as the formation of toxic metabolites, altered mechanisms that protect against reactive oxygen species, and so on. Among the essential cofactors facilitating energy metabolism are B-vitamins and A-vitamins. This is briefly described later, focusing on the role of these vitamins in mitochondrial energy metabolism and indicating how deficiency or excess may result in cancer. Additional information on the role of B-vitamins in mitochondrial function can be found in extensive reviews by Depeint et al. [80,81]. Thiamin pyrophosphate, the coenzyme form of thiamin (vitamin B1), is essential for functioning of the mitochondrial enzymes pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, branched chain ketoacid dehydrogenases as well as for transketolase and thus has a central role in energy metabolism. Indeed, 30% of cellular thiamin is estimated to be located in mitochondria (30 μM) [82] and thiamin deficiency results in increased plasma levels of pyruvate and lactate [83]. Thiamin deficiency in rats is associated with an increase in aberrant crypt foci, an indication of an increase in colon cancer risk, possibly by increasing genotoxic alpha-oxoaldehydes [84]. Thiamine pyrophosphate is a cofactor in the rate limiting step of alpha-ketoglutarate (oxo-glutarate) dehydrogenase, an enzyme at the crossroads of energy metabolism, nitrogen assimilation and ROS signaling [85], with a possible role in modulation of the activity of HIF-1 [86], all aspects that are deregulated in tumor cells. Riboflavin (vitamin B2) is a precursor of flavin

adenine dinucleotide (FAD) and flavin mononucleotide, and as such provides essential prosthetic groups in flavoenzymes. Flavoenzymes function in many metabolic processes, including anti-oxidant metabolism (e.g. glutathione reductase [87]), lipid metabolism (e.g. acyl CoA reductases [88]) and energy metabolism (heme/cytochrome synthesis [89]). Decreased FAD levels affect folate metabolism by inhibition of methylene tetrahydrofolate reductase and may thus increase cancer risk [81]. Flavin is also a coenzyme of the histone lysine specific demethylase 1 (LSD1), with an important role in tumor genesis [90,91]. Niacin (vitamin B3) covers two vitaminers, nicotinamide and nicotinic acid, and both are precursors to NAD(+) and NADP(+) and thus involved in numerous enzymatic reactions. All energy producing processes, glycolysis as well as oxidative energy metabolism, depend on enzymes needing this coenzyme. Niacin deficiency can lead to impaired DNA repair and thus predisposes to cancer, since NAD(+) is required for poly(ADP)ribose mediated protection against DNA damage [92]. It should be noted that niacin deficiency is rare in diets with adequate tryptophan, a precursor of nicotinic acid. Of particular relevance to energy metabolism is the discovery of sirtuins (SIRT1–7), a family of NAD(+) dependent deacetylases that may serve as sensors for NAD(+)/NADH in cells and mitochondria [93–95]. SIRT1 is associated with increased life span in many organisms [96] and, together with AMP-kinase is one of the gatekeepers of PGC1-alpha, the master regulator of mitochondrial biogenesis [97]. Three sirtuins, SIRT3, SIRT4 and SIRT5, are located in mitochondria [98]. SIRT3 is located in the mitochondrial matrix and was recently shown to have an important role in the regulation of mitochondrial fatty acid oxidation [99]. Furthermore, SIRT3 was shown to function as a tumor suppressor by enhancing the expression of mitochondrial MnSOD. Loss of SIRT3 leads to increased mitochondrial ROS, which can enhance cellular transformation and tumor growth [100]. Cytochrome c was identified as a target of SIRT5 deacetylase function, providing SIRT5 with a direct role in the regulation of energy production [101]. Unlike most other sirtuins, SIRT4 has no deacetylase function, but is an ADP-ribose transferase with a function in insulin secretion [102]. Pantothenic acid (vitamin B5) is the precursor of coenzyme A (CoA) and as such is involved in 4% of all enzymatic reactions, including heme synthesis, cellular, mitochondrial and peroxisomal lipid metabolism, the citric acid cycle and mitochondrial leucine metabolism. Panthotenic acid is present in two cellular pools, as CoA and as acyl carrier proteins, with CoA being predominantly present in mitochondria (2.2 mM), but also in peroxisomes (20–140 μM) and in the cytoplasm (less than 15 μM) [103]. Pantothenic acid is shown to protect against reactive oxygen species and may thus protect against cancer [104]. Pryridoxal/pyridoxamine phosphate are the coenzyme form of vitamin B6 (pyridoxine), which is involved in aminotransferase reactions and is essential for the ureacyle, the malate aspartate shuttle and in linking amino acid metabolism to energy production [81]. Vitamin B6 is also intimately involved in one carbon metabolism, as are vitamins B9 and B12. One carbon metabolism is essential for protein and DNA methylation and the synthesis of nucleotides and links these vitamins to cancer. Biotin (vitamin B7) plays a role in lipid metabolism, with 4 of the 5 biotin dependent carboxylases being located in mitochondria. Biotin also has a role in gene regulation through histone modification [105]. Histone biotinylation by carboxylase synthase is sensitive to biotin levels and, among others, has an important role in the cellular response to double strand DNA breaks [106]. Biotin deficiency can result in heme deficiency and because of this, biotin-deficient cells may selectively loose mitochondrial complex IV [107]. Folate (vitamin B9), which is further discussed later, has no function in mitochondrial energy metabolism, but has a central role in one carbon metabolism [81,108]. Cobalamin (vitamin B12) also has an essential role in one carbon metabolism [109], and as such, like folate, is associated with (colon) cancer risk. In the form of 5-deoxyadenosylcobalamin (coenzyme B12), vitamin B12 is required as prosthetic group in methylmalonylCoA mutase for the synthesis of succinyl-CoA and as such plays an important role in the TCA cycle and energy metabolism [81,110]. Rapid growing tumor cells require higher amounts of vitamin B12, and bioconjugation to vitamin B12 is used to deliver anti-tumor agents to tumor cells [110]. Beta-carotene (pro-vitamin A) and its metabolites, retinol (vitamin A), retinaldehyde and retinoic acid, most likely affect mitochondria and energy metabolism through effects of different retinoic acid derivatives via RAR or the retinoic X receptor (RXR), the latter an obligatory heterodimeric partner of many nuclear receptors involved in transcriptional regulation of energy metabolism [111,112]. Recently, it was found that retinol is an essential cofactor of mitochondria located PKC-delta, which regulates the pyruvate dehydrogenase complex. Retinol can thus enhance energy flux into the citric acid cycle [113]. This provides the first evidence of a fundamental role of retinol in (regulation of) energy homeostasis. As described previously, beta-carotene supplementation is associated with increased lung cancer risk in at risk individuals through a still unresolved mechanism. Vitamin A derivatives play a crucial role in embryonic development, tissue homeostasis, lipid metabolism, cellular differentiation and proliferation and as such are also linked to cancer development as well as protection [114].

5. Folic acid

While excess or deficiency of cofactors may be associated cancer initiation, cofactors may also play a role in tumor progression. Rapid growth of cells not only requires energy substrates, but also sufficient amounts of essential cofactors, such as folate or vitamin B12. Folate is a water-soluble B-vitamin (vitamin B9) that naturally occurs in foods, such as green leafy vegetables, beans, peas and many other types of vegetables and fruits. Natural folates are pteroylglutamate compounds that are conjugated to a polyglutamyl chain of different length, depending on the type of food. This polyglutamyl chain is removed by the intestinal folate conjugase enzyme before folate-monoglutamate is taken up by the intestine. If food folates are not in the 5-methyl-tetrahydrofolate (MTHF) form already, they will be converted to this form in intestinal mucosa cells [115]. Folic acid, the synthetic form of folate, is a monoglutamate (pteroylglutamic acid, PGA). This form does not require cleavage by the intestinal folate conjugase enzyme before uptake. Folic acid is used for fortification of grain products and is present in vitamin supplements because it is chemically more stable and is supposedly better bioavailable than natural folates [116]. For physiological activity, folic acid needs to be reduced by the enzyme dihydrofolate reductase to dihydro- and tetrahydrofolate (DHF and THF). This occurs within intestinal mucosal cells and MTHF is released into the plasma [115]. The function of folate is strongly relate to cell growth, since it has an essential role in the generation of S-adenosylmethionine, which is required for methylation of DNA and other substrates, for the synthesis of purines and pyrimidines and for the metabolism of several amino acids [117–119]. 30–50% of cellular folate is located in mitochondria, which constitutes a separate pool that does not equilibrate with the cytosolic folate pool [120–123]. One carbon metabolism in mitochondria is relatively poorly understood. Many of the same enzymes are present in mitochondria as in cytoplasm, but the reactions are more oxidative and use different reducing equivalents [121,124]. In mitochondria, reduced folates are required for synthesis of formyl-methionyl t-RNA, and are thus required for initiation of mitochondrial protein synthesis. Mitochondrial one carbon metabolism supplies folate for cytoplasmic one carbon metabolism and generates glycine. Serine/glycine cycling is thought to occur primarily in mitochondria, while its role in purine and methionine synthesis occurs mainly in the cytoplasm. Folate is thus essential for normal cell growth and cancer prevention, while, on the other hand, it is an essential cofactor permitting the rapid growth of established cancer cells. Indeed, animal intervention studies of Song et al. [125,126], using genetically predisposed murine models of intestinal tumor genesis, support the dual modularly role of folate in carcinogenesis. These authors found that folic acid supplementation suppressed intestinal tumor development in normal healthy epithelial tissues of Apc+/− and Apc+/−Msh−/− mice, whereas folate deficiency predisposed the animals to neoplastic

transformation. In contrast, if intestinal neoplasms were already established, PGA supplementation had a promoting effect and deficiency inhibited progression into tumors. This has been supported by later studies in different models [127] and resulted in a debate on the potential risk of cereal fortification for people with pre-existing neoplastic lesions [128]. The inhibitory effect of folate deficiency in tissues with rapidly replicating cells shows that sufficient amounts of folate are essential for tumor growth under physiological relevant conditions.

6. Is cancer cell growth and glycolytic metabolism interdependent?

When cells turn into tumor cells, they become selfish. Their metabolism is reprogrammed towards aerobic glycolysis, with a rapid glycolytic flux supporting rapid growth at the expense of the whole organism. This diminishes the need for oxygen, relaxes metabolic control and requires energy substrates (e.g. glucose), but it also requires essential cofactors needed for growth. While metabolic reprogramming is well established, many aspects of associated regulatory alterations and metabolic interdependencies are still not fully understood. For example, will energy metabolism be altered under conditions of limiting cofactor availability, or is it a fixed tumor cell characteristic? Later, as an example, we examine this for folic acid, a vitamin with no direct role in energy metabolic pathways. While rapid cancer cell growth is associated with glycolytic metabolism, we question whether the reverse is also true; whether growth restriction by limitation of an essential cofactor, such as folic acid, will result in reduced aerobic glycolysis (and increased oxidative metabolism). We examine this using the highly glycolytic HT-29 human colon cancer cell line [129] as an *in vitro* model.

7. Low folate retards the growth rate of HT-29 cells and alters its metabolism

HT-29 cells are rapidly growing tumor cells. HT-29 cells cultured in 10 ng/ml PGA, grow significantly slower (approximately 2.7 fold, $p=0.0008$) compared to HT-29 cells cultured in 100 ng/ml PGA (Fig. 2A). Intracellular folate levels are lower at 10 ng/ml ($p=0.008$ for MTHF and $p=0.018$ for THF) (Fig. 2B). Since increase of PGA above 100 ng/ml, up to levels that are present in standard culture media, did not result in increased intracellular folate levels (data not shown), nor in increased growth rates (data not shown), it can be concluded that cofactor limitation inhibits the growth rate of HT-29 human colon cancer cells. We then hypothesized that lower growth would result in a decreased glycolytic metabolism and hence a lower amount of lactate in the culture medium, relative to the amount of cellular protein as a measure for cell mass, which was found ($p=0.045$) (Fig. 2C). To assess whether this was indeed accompanied by increased respiration, the mitochondrial respiratory capacity was analyzed in a standardized experimental regime. Strikingly, we observed that the routine respiration of HT-29 cells with low intracellular folate levels cultured at 10 ng/ml was significantly higher compared to culturing at 100 ng/ml folic acid ($26.8 +/- 5.8$ vs $17.9 +/- 2.6$ (expressed as pmol $O_2/s/1\times10^6$ cells $+/-$ SD); $n=5$, $p=0.0.014$). Carbonylcyanide p-trifluoromethoxyphenylhydrazone (FCCP) stimulated respiration, which reflects the maximum respiratory capacity of uncoupled mitochondria in intact cells was also significantly higher in the HT-29 cells cultured in 10 ng/ml folic acid ($87.5 +/- 16.3$ vs $51.5 +/- 4.9$ pmol $O_2/s/1\times10^6$ cells $+/-$ SD; $n=5$, $p=0.0015$, Fig. 2D). The extent of respiration inhibition by both oligomycin (inhibits ATP synthase, so respiration due to leak is measured) and rotenone (inhibits complex I, so mainly respiration via complex II is measured) was not statistically different under both conditions ($10.9 +/- 2.1$ and $6.9 +/- 1.3$ vs $12.1 +/- 0.8$ and $6.9 +/- 1.5$ pmol $O_2/s/1\times10^6$ cells; $n=5$, $p=0.28$ and $p=0.7$, respectively). The respiratory control ratios are shown in Fig. 2E. Respiratory control ratio (RCR) values greater than 10 are indicative of well-coupled mitochondria, lower values are indicative of "loose coupling" of the processes of substrate oxidation and ATP synthesis [130]. The RCR are all lower than 10, but HT-29 human colon cancer cells cultured in 10 ng/ml folic acid have significantly ($8.1 +/- 0.6$ vs $4.3 +/- 0.4$; $n=5$, $p<0.0001$, Fig. 2E) the highest value. Also the phosphorylation respiratory control ratio (RCRp) values were significantly different. ($0.18 +/- 0.04$ vs $0.11 +/- 0.05$; $n=5$, $p=0.04$). There was no significant difference in the uncoupling control ratio (UCR) ($3.3 +/- 0.4$ vs $2.9 +/- 0.4$; $n=5$, $p=0.8$). Blue native gels established intactness of all OXPHOS complexes (Fig. 2F). Together this provides evidence that the lower growth rate induced by limitation of a cofactor that is required for growth, but not for energy metabolism, results in a shift from glycolytic to oxidative metabolism. This strongly suggests a reciprocal relationship between the type of metabolism and the growth of cancer cells. Growth cofactor limitation resulting in a shift to oxidative metabolism may result in enhanced sensitivity of the cell to apoptosis and/or in an enhanced oxygen requirement. This is especially attractive since cancer cells have a higher requirement for cofactors than normal cells.

8. Will nutritional stimulation of mitochondrial biogenesis counteract glycolytic metabolism in cancer cells?

As mentioned previously, targeting glycolytic metabolism may be an effective strategy in the cancer therapy. This may be done in several manners, including inhibition of enzymes involved in glucose or lactate metabolism [67]. Indeed, inhibition of glucose metabolism by 2-deoxyglucose not only inhibited the growth of human mammary tumor MCF-7 cells *in vitro*. Feeding of 2-deoxyglucose also delayed the appearance of mammary tumors in rats [35]. Metabolic normalization of cancer cells and concomitant inhibition of carcinogenesis may potentially also be attained by induction of mitochondrial biogenesis. Mitochondrial biogenesis is mediated by the transcriptional coactivator peroxisome proliferator activated receptor (PPAR)-gamma coactivator-1alpha (PGC-1alpha) [131–134]. Indeed it has been suggested that PGC1 activation may be effective in cancer therapy [135]. In mitochondrial biogenesis, PGC-1alpha associates with nuclear respiratory factor 1 (NRF-1), Estrogen Related Receptor alpha (ERR-alpha) [136] and also the PPAR-gamma-RXR dimer. Further, it induces transcription of NRF-2 and is a cofactor for the mitochondrial transcription factor A (Tfam) [137]. Two PGC-1alpha related co-activators have been cloned, PGC-1beta and PGC-1-related coactivator (PRC), which display partially similar functions, including NRF-1 [138–141] and ERR-alpha activation [141,142]. PGC-1alpha activity can be increased by transcriptional activation as well as by deacetylation, mediated by SIRT1 [132,143,144], while it can be inhibited by acetyltransferase GCN5. Indeed its acetylation state is tightly correlated with its activity [145]. A number of polyphenols are able to activate SIRT1 [43,146], including resveratrol. In particular, dietary resveratrol was shown to be able to deacetylate PGC1-alpha, induce mitochondrial biogenesis and increase metabolic fitness [45,46]. This was accompanied by increased expression of ERR-alpha, NRF-1 and Tfam [46]. At this moment it is not clear to which extent this mechanism contributes to the many reported anti- (or even pro-) cancer effects of resveratrol [48–50]. Also the marine omega-3 fatty acids docosahexanoic acid (DHA) and eicosapentanoic acid (EPA) are able to increase expression of PGC-1alpha and induce mitochondrial biogenesis [147,148]. Since DHA and EPA have been implicated in various anti-cancer effects [149,150], it is tempting to speculate that induction of mitochondrial biogenesis underlies these effects. However, other mechanisms are strongly implicated, in particular the induction of apoptosis [151], but also inhibition of angiogenesis [152], inhibition of inflammation [153]. The anti-inflammatory and immuno-regulatory effects are thought to be largely mediated by resolvins and protectins, specific metabolic products derived from DHA and EPA [154,155]. Furthermore, DHA and EPA are able to activate AMP-kinase (AMPK) [147,156] leading to activation of fatty acid metabolism. AMPK is a central regulator of the

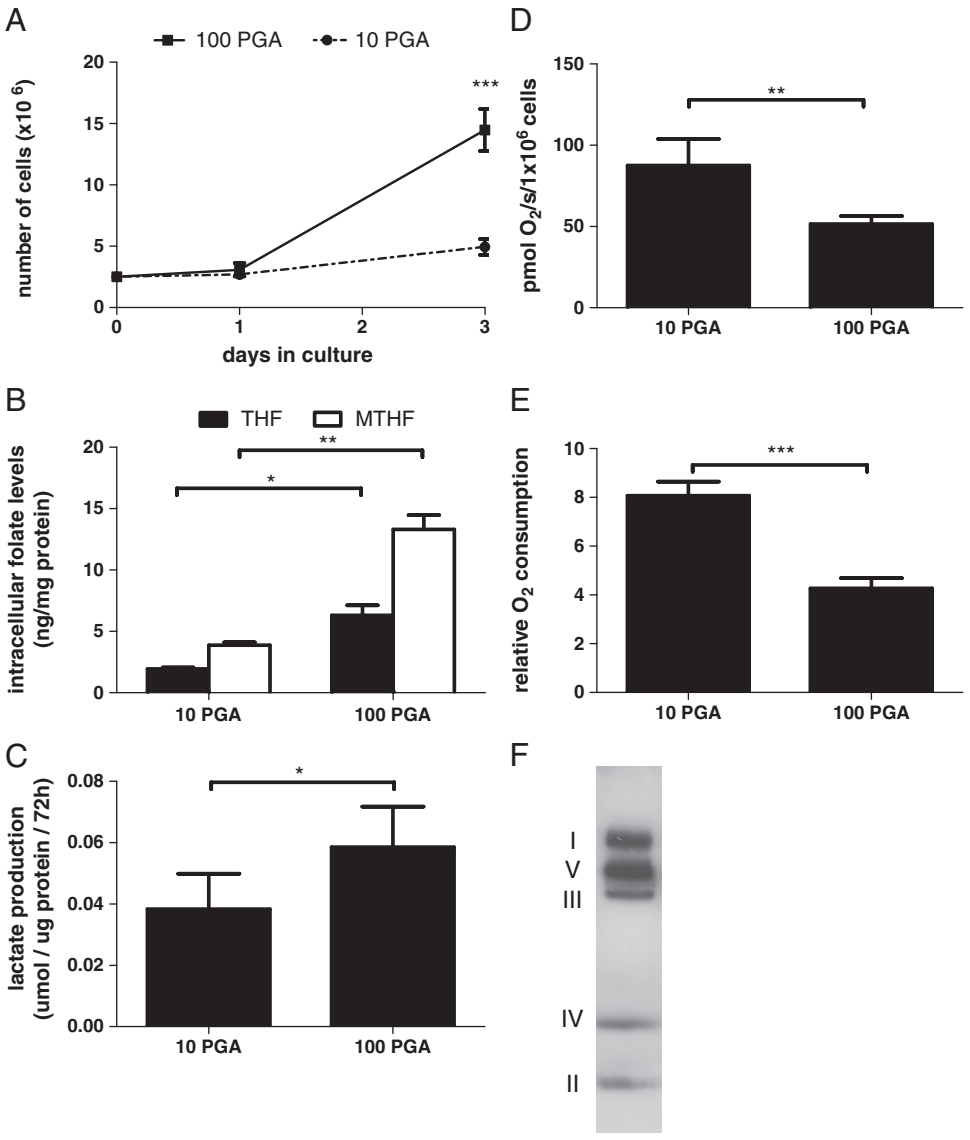

Fig. 2. Effects of folate limitation on growth and metabolism of HT-29 cells. HT-29 human colon cancer cells were cultured in 10 ng/ml PGA (10 PGA) or 100 ng/ml PGA (100 PGA, Control) for 3–3.5 weeks (after habituation at 25 ng/ml PGA) at the start of the analyses. Panel A) For growth determination the cells were re-plated in 75 cm^2 cell culture flasks and the number of cells were counted after 1 and 3 days. Results represent the means +/− SD of 3 independent replicate determinations. Student's t-test gave a significant difference in the number of cells between the groups at day 3 ($p = 0.0008$). Panel B) Intracellular tetrahydrofolate (THF) and 5-methyl-tetrahydrofolate (MTHF) levels (ng per mg protein). Results represent the means +/− SD of duplicate determinations of 2 independent experiments. Student's t-test gave a significant differences for both THF ($p = 0.018$) and MTHF ($p = 0.008$). Panel C) Lactate was measured in a 72 hour culture medium. Results represent the means +/− SD of 4 replicate determinations of 3 independent experiments. Student's t-test gave a significant difference between the groups ($p = 0.045$). Panel D) FCCP uncoupled respiration. Results represent the means +/− SD of 5 independent duplicate determinations. Student's t-test gave a significant difference between the groups ($p = 0.0015$). Panel E) The respiratory control ratio. Results represent the means +/− SD of 5 independent duplicate determinations. Student's t-test gave a significant difference between the groups ($p < 0.0001$). Panel F) Blue native gel electrophoresis of mitochondria isolated from HT-29 cells. Complexes I–V are indicated and are at the correct position.

cell metabolism [157,158], that senses the cytosolic ATP over AMP ratio. Physiologically, AMPK can be activated by its upstream kinase LKB1, a bona fide tumor suppressor. In turn, AMPK can activate PGC-1alpha and thus activate mitochondrial biogenesis [159]. By phosphorylation of phosphofructokinase it can stimulate glycolysis and it can increase the expression of HK and GLUT4. One of the major targets, direct, and indirect via tuburin (TSC2), is the mTORC1 complex, a major regulator of cell growth [160,161]. While AMPK inhibits mTORC1, phosphorylation by Akt stimulates this complex through TSC2 phosphorylation, which is one of the manners in which Akt is implicated in the Warburg effect [162]. A role of the energy sensor AMPK as a tumor suppressor is supported by the observation that patients on treatment with metformin, an activator of AMPK, have a lower cancer incidence [163–165]. Of interest, oxidized DHA derivatives have been shown to be effective ligands of PPAR-gamma [166]. As mentioned, PPAR-gamma associates with PGC-1alpha to mediate mitochondrial biogenesis, but it is also a target of SIRT1 and stimulates PGC-1alpha expression. Indeed, it was shown that thiazolidinediones (TZDs), selective activators of PPAR-gamma, promote the biogenesis of mitochondria and up-regulate PGC-1alpha, NRF-1, Tfam and cytochrome c oxidase subunits I and IV [167]. TZDs have been endowed with anti-cancer properties. The anti-cancer effects of TZDs include induction of apoptosis, cell cycle arrest and apoptosis [168] as well as energy restriction responses [169]. However, recent evidence indicates that these effects are largely independent of transcriptional activation of PPAR-gamma. TZDs are also able to activate AMPK [170] and these effects may possibly be mediated by AMPK. Alternatively, TZDs were shown to reduce phosphorylation of PPAR-gamma by CDK5 [171]. The resulting altered metabolic regulation may constitute part of the mechanisms

underlying the anti-cancer properties of TZDs. Another bioactive food component that impinges on AMPK/PGC1alpha signaling, and that can, in combination with other cofactors, induce mitochondrial biogenesis, is lipoic acid [172,173]. Whether this explains in the anti-cancer properties of lipoic acid is not known [174]. Lipoic acid also has a role in anti-oxidant defence and is a cofactor for mitochondrial alpha-ketoacid dehydrogenase complexes, functions which may contribute to in its anti-cancer properties. Other anti-cancer mechanisms of lipoic acid include the induction of apoptosis, mediated by the Akt signaling pathway [175], which also mediates the effects of lipoic acid on glucose metabolism [176]. It should be noted that lipoic acid is synthesized in the body, a process that is essential and cannot be complemented by dietary lipoic acid [177].

Altogether there is no strong evidence for activation of mitochondrial biogenesis as a mechanism in the protection against cancer by bioactive food components. However, at this point it cannot be concluded that activation of mitochondrial biogenesis could not play a role in cancer protective effects or even that targeting mitochondrial biogenesis may not be part of cancer protective strategies involving bioactive food components.

In targeting specific metabolic alterations, it should be realized that many counteracting, homeostatic and partly redundant mechanisms exist. For example, activation of mitochondrial biogenesis may be counteracted by up-regulation of HIF1-alpha, since increased oxygen consumption may result in hypoxia [178]. Also, cross-talk exists between different energy sensors in the cell, such as AMPK and SIRT1 [179] and mTORC1 mediated growth responses are balanced by Akt and AMPK activities [180]. Furthermore, while both Akt and c-Myc promote aerobic glycolysis, Akt mediated glycolysis inhibition sensitizes cells to apoptosis, while c-Myc mediated glycolysis inhibition sensitizes inhibition of mitochondrial function [73].

9. Conclusion and future perspective

Cancer cells are resistant to apoptosis and show a shift in energy production from mitochondrial oxidative phosphorylation to cytosolic glycolysis. The cancer cell uses glucose and the high glycolytic flow for ATP production and to produce TCA cycle intermediates for lipid, amino acid and DNA synthesis. This metabolic reprogramming also makes the cancer cell independent of oxygen availability and generates a favorable micro-environment. Apoptosis resistance and metabolic programming are linked in many cancer cells and both processes center on mitochondria. Clearly, mutated cancer cells escape surveillance and turn into selfish cells. However, many of the mechanisms that operate metabolic control still function in cancer cells. Glucose, glycolytic enzymes, oxygen and growth cofactors are all needed and mitochondria are a metabolic necessity. This opens the possibility of reversal of metabolic reprogramming as an attractive strategy to increase susceptibility to surveillance. Nutritional compounds may support this, by altering metabolism and induction of apoptosis. One example of the potential of nutritional components is the supportive role of omega-3 fatty acids in cancer therapy [181]. Modulation of one pathway will, most likely, in most cases not be effective. Different bioactive food components, separate or in support of pharmaceutical interventions, affecting various aspects of metabolism may, alone or in synergy, provide an important tool to reverse glycolytic to oxidative metabolism and enhance sensitivity to apoptosis. Carefully evaluating the need for metabolic cofactors and their function in metabolism, including B- and A-vitamins, should be part of this strategy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.bbabio.2010.08.007.

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