Biochimica et Biophysica Acta 1807 (2011) 697–706

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Review

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

Jaap Keijer [a,*], Melissa Bekkenkamp-Grovenstein [a], Dini Venema [b], Yvonne E.M. Dommels [b]

[a] Human and Animal Physiology, Wageningen University, Wageningen, The Netherlands
[b] RIKILT-Institute of Food Safety, Wageningen, The Netherlands

ARTICLE INFO

Article history:
Received 6 July 2010
Received in revised form 10 August 2010
Accepted 15 August 2010
Available online 21 August 2010

Keywords:
Nutrition
Folate
Mitochondria
Metabolic reprogramming
B-vitamin
Energy metabolism

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

☆ This article is part of a Special Issue entitled: Bioenergetics of Cancer.

* Corresponding author. Human and Animal Physiology, Wageningen University, Marijkeweg 40, PO Box 338, 6700 AH, Wageningen, The Netherlands. Tel.: +31 317484136.
E-mail address: Jaap.keijer@wur.nl (J. Keijer).

0005-2728/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbabio.2010.08.007

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