Cancer as a Metabolic Disease and Diabetes as a Cancer Risk?

Nádory jako metabolická onemocnění a diabetes jako riziko nádorů?

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Summary
The prevailing aerobic glycolysis (so called Warburg effect) in cancer cells is according to current understanding the consequence of reprogramming of cellular metabolism during the process of malignant transformation. Metabolic regulation is inseparable component of cell proliferation machinery and has a tight link with activities of oncogenes and suppressor genes. The purpose of metabolic reprogramming of cancer (but also normal intensively proliferating cells) is to incorporate greater fraction of glucose metabolites into newly synthesised macromolecules. Apart from that, aerobic glycolysis confers several other selective advantages to cancer cells. Epidemiological data indicate that type 2 diabetes mellitus is associated with increased incidence of several types of cancer and that cancer mortality can be influenced by certain types of anti-diabetic treatment, however future research is needed to explain whether this relationship might be causal. Deeper knowledge about metabolic properties of rapidly proliferating cells can be exploited for further improvement of anti-cancer, immunosuppressive or anti-inflammatory therapies.

Key words
diabetes – cancer – obesity – metabolism – glyoxalase – transketolase – p53 – metformin

Souhrn
Převažující aerobní glykolýza v nádorových buňkách (tzv. Warburgův efekt) je na základě současných poznatků důsledkem přeprogramování buněčného metabolizmu během procesu maligní transformace. Regulace metabolizmu je neoddělitelnou komponentou procesu buněčné proliferace a je těsně svázána s aktivitami onkogenů a supresorových genů. Smyslem metabolické transformace nádorových buněk (a rovněž normálních intenzivně proliferujících buněk) je inkorporovat větší podíl metabolitů glukózy do nově syntetizovaných makromolekul. Mimo to aerobní glykolýza poskytuje nádorovým buňkám několik dalších selektivních výhod. Epidemiologická data naznačují, že diabetes mellitus 2. typu je asociován s rostoucí incidencí několika typů nádorů a že mortalita v důsledku nádorových onemocnění může být ovlivněna léčbou určitými druhy antidiabetik, nicméně další výzkum je nutný k vysvětlení toho, zda je tento vztah kauzální. Hlubší pochopení metabolizmu rychle proliferujících buněk může vést k dalšímu zlepšení protinádorové, imunosupresivní a protizánětové léčby.

Klíčová slova
diabetes – nádory – obezita – metabolizmus– glyoxaláza – transketoláza – p53 – metformin

This study was supported by the European Regional Development Fund and the State Budget of the Czech Republic (RECAMO, CZ.1.05/2.1.00/03.0101).

Práce byla podpořena Evropským fondem pro regionální rozvoj a státním rozpočtem České republiky (OP VaVpI – RECAMO, CZ.1.05/2.1.00/03.0101).

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE "uniform requirements" for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

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Submitted/Obdrženo: 30. 9. 2012
Accepted/Přijato: 25. 10. 2012

Introduction

Research in oncology has traditionally focused on genetic and more recently epigenetic alterations of oncogenes and tumour suppressor genes as causal factors responsible for the multistage process of malignant transformation. Recently, attention has also been paid to the tumour microenvironment and systemic factors. Metabolic properties of cancer cells – aerobic glycolysis and impairment of mitochondrial function – were originally considered to be a driving force of tumourigenesis, later a merely passive consequence or rather an essential compensation to hypoxia within the cancer mass. Nowadays we know that sustained aerobic glycolysis in cancer cells is linked to the activation of oncogenes and/or loss of function of tumour suppressor genes and represents a conditional phenotypic feature enabling all biological properties ascribed to cancer cells. However, unlike extensive genetic heterogeneity among cancer types, impairment of cancer cell metabolism represents a unifying characteristic of nearly all types of cancer regardless of tissue origin. Not the total amount of energy produced, but its' source, is the most striking difference of cancer cells from normal cells of the tissues they originate from. The thorough knowledge of the pathophysiology of impaired cancer cell metabolism has an immense clinical potential since our approach to cancer management could radically shift in the light of its' understanding and further research into the metabolic properties of cancer allowing therapeutic exploitation thus represents a promising future anticancer strategy. The aims of this mini-review are to (A) summarise the current findings explaining the metabolic phenotype of cancer cells and (B) the intimate relationship with the process of malignant transformation. Furthermore, (C) since epidemiological data suggest a relationship between diabetes and cancer, several hypothetical links are presented to explain their coincidence and the putative pathogenic mechanisms.

Cellular Metabolism and the Interplay with Cell Signalling and Proliferation

In order to maintain viability cells need to produce (i) energy in the form of ATP and (ii) precursors for synthesis of proteins, nucleic acids and membrane lipids. The main sources of energy in animal cells are glucose, glutamine and fatty acids. Most of the ATP is used by active membrane transport (ionic pumps). Cells can obtain energy from oxygen-dependent (OXPHOS) or oxygen-independent processes (anaerobic glycolysis). Since fatty acids in the form of triglycerides are the most abundant form of stored energy and OXPHOS is much more efficient in generating ATP, adult differentiated cells convert glucose to lactate (lactic acid fermentation) only in the absence of oxygen (so called Pasteur effect). In a normal cell with functioning mitochondria approximately 88% of ATP is produced by OXPHOS and the remaining 12% by glycolysis and TCA cycle [1].

Cell fate and metabolism are closely intertwined – information about nutrient and energy availability influences self-renewal, growth and division. In situations of energy depletion, cells can undergo autophagy, apoptosis or in most severe cases, necrosis. On the other hand, the activities of metabolic enzymes are under the strict control of signalling pathways and transcription factors. The effect of cellular energy (AMP/ATP ratio) and substrate status on the cell cycle is mediated by mTOR via either inhibitory AMPK/TSC2/mTOR or opposing stimulatory insulin/PI3K/AKT/ /mTOR pathway and others [2]. In fact, many other direct metabolic signals propagate the metabolic information into the cell cycle in a coordinated manner – HIF-1 oxygen sensors, sensors of NAD^+/NADH ratio (such as sirtuins or PARP-1) and others [2].

The History and Current Understanding of the "Warburg Effect"

It was shown by Otto Warburg some 90 years ago that tumour cells produce lactate despite the presence of oxygen (which would otherwise favour OXPHOS) and this phenomenon has been termed "aerobic glycolysis" or "the Warburg effect". In cancer cells pyruvate is not transported to mitochondria to be converted to acetyl-CoA and subsequently processed in the TCA cycle. Instead it is converted into lactate. Warburg originally assumed aerobic glycolysis as an epiphenomenon, a consequence of a defect in the mitochondrial respiration and he proposed primary mitochondrial dysfunction as a fundamental cause of cancer (the so called Warburg hypothesis) [3]. Naturally his hypothesis was quickly dismissed as too simplistic, not explaining the progressive nature of disease, the formation of metastases etc. [1] and cancer has become considered as a genetic rather than metabolic disease. However, the fact that most cancer cells predominantly produce energy by a high rate of glycolysis followed by lactic acid fermentation in the cytosol even if oxygen is plentiful instead of low rate of glycolysis followed by oxidation of pyruvate in mitochondria as in most normal cells (although the total amount of energy produced remains equal) has periodically regained attention and could be considered one of the hallmarks of cancer.

The asymmetry in the yield of ATP in OXPHOS compared to glycolysis (36 molecules of ATP per molecule of glucose vs only 2 in the latter) plus loss of excreted lactate has often been regarded as a sign of metabolic insufficiency of cancer cells. But this would be a problem only when resources are scarce. Proliferating mammalian cells are however continuously supplied by glucose and other nutrients from blood [4]. Malignant, rapidly growing tumour cells typically have glycolytic rates up to ten to hundred times higher than those of their normal tissues of origin. This phenomenon has a diagnostic value; the glycolytic phenotype of cancer cells is used clinically to diagnose and monitor treatment response by imaging uptake of glucose analogues (FDG, a radioactive modified hexokinase substrate) with PET.

One proposed explanation for Warburg effect is tumour hypoxia and therefore blockade of OXPHOS. Although tumour hypoxia plays an important role in cancer development it is a relatively

late occurring event and could not explain the early switch to aerobic glycolysis in cancer cells. There is another hypothetical advantage in limiting OXPHOS in cancer cells – mitochondria are an inevitable source of ROS when oxidising nutrients. ROS might cause genotoxic oxidative damage and induce apoptosis [4]. Although the original Warburg hypothesis of mitochondrial dysfunction as a primary cause of cancer has been rejected, evidence that mitochondrial function and structure in tumour cells is not normal is accumulating. There is a great controversy, though, on this subject regarding causality. Experimental evidence supports the contribution of both functional (down-regulation of ATPase and mitochondrial uncoupling) and structural (composition of membrane lipids) defects of cancer cell mitochondria to metabolic alterations (reviewed in detail elsewhere [1]). Nonetheless, mitochondria of cancer cells are functional and capable of carrying out OXPHOS. Indeed, they have to be since the contribution of glycolysis to the energy requirements of cancer cells seldom exceeds 50–60% [5]. Mitochondrial OXPHOS in cancer cells utilizes predominantly precursors produced by oxidation of glutamine. Substantial amounts of ATP in cancer cells are produced by glutaminolysis which makes up for the lower yield from glycolysis [4].

In summary, there is no evidence that ATP production in cancer cells would be limited. In fact, the amount of ATP produced in cancer cells is the same as in normal cells but the way the energy is produced is different. The shift to glycolytic phenotype is not an adaptation but an active process and serves a clear purpose – large requirements of cancer cells for synthesis of new macromolecules are met by a high rate of glycolysis (and the pentose phosphate pathway – PPP). Acetyl-CoA, glycolytic intermediates and NADPH (from PPP) are then used to produce nucleotides, amino acids and fatty acids to support cell growth and division.

Oncogenes and Tumour Suppressors Regulate Metabolism

Seemingly wasteful glucose consumption followed by excretion of lactate out of the cell has in fact – as explained above – a different purpose and is perfectly in place: glucose in cancer cells is used more for replication than for normal cell metabolism. Owing to the large body of evidence it is now clear that metabolic pathways in mammalian cells are tightly regulated by signalling pathways implicated in the regulation of cell proliferation. This allows quick switches between nutrient catabolism and their incorporation into biomass. Aerobic glycolysis is thus logically not limited to cancer cells, it is found also in non-cancerous rapidly proliferating cells such as T-lymphocytes or endothelial cells [2]. Of special interest is the fact that many cancer cells (and stem cells) express a specific isoform of pyruvate kinase (PK-M2) slowing down the last step of glycolysis and allowing the glucose intermediates to enter PPP for nucleotide and NADPH production [6]. Nowadays we know that sustained aerobic glycolysis in cancer cells is linked to the activation of oncogenes and loss of tumour suppressor genes.

There are a few exceptions, however, exemplifying reverse causality (primary metabolic derangements behaving like oncogenes and leading to cancer) such as germ-line mutations in TCA cycle enzymes (succinate dehydrogenase, fumarate hydratase) leading to familial cancer syndromes (paragangliomas, phaeochromocytomas, leiomymas or renal carcinomas) [7,8]. Other examples are mutations in isocitrate dehydrogenases 1 and 2 altering enzyme activities and producing an "oncometabolite" [9]. The pro-oncogenic mechanisms beyond these mutations are HIF-1 stabilisation (with subsequent overexpression of glucose transporters and glycolytic enzymes and inhibition of pyruvate dehydrogenase and thus down-regulation of OXPHOS) or epigenetic modifications.

There are multiple links between established oncogenes and tumour suppressors and metabolic regulation, however detailed description is beyond the focus of this mini review. The majority of imputes converge on the level of mTOR whose activation promotes protein synthesis and inhibits autophagy (response to starvation). Key regulators of mTOR are AKT – stimulated by growth factors to activate mTOR – and AMPK – activated by the lack of ATP to suppress mTOR [10]. Intuitively, every event autonomously stimulating AKT and/or suppressing AMPK could be considered tumourigenic. The activation of the cellular master switch AMPK (shutting-down mTOR and thus cell growth) is dependent on the tumour suppressor LKB1 [4]. Inactivating mutations in LKB1 lead to impaired activation of AMPK (possibly restorable by metformin – see below) and unlimited growth. Similarly, AKT is frequently activated in human cancers [10]. Furthermore, Myc (involved in glycolysis, mitochondrial biogenesis and glutamine metabolism) was one of the first oncogenes linked to metabolism [11]. Other important players are Ras, and tumour suppressors which in a wild-type form repress mTOR and once mutated activate glycolysis, including HIF-1 – PTEN, TSC 1 and2, VHL, p53 and others. Among them p53 plays a special role [10]. AMPK activation stimulates p53 and subsequent p53-mediated inhibition of proliferation is a logical response to nutrient deprivation. Conversely, wild-type p53 was found to activate AMPK (both directly and indirectly) and this way to oppose the proliferation and anabolism of cancer cells. Furthermore, p53 can also counteract established metabolic transformation of cancer cell by suppressing glycolysis and promoting OXPHOS. However, involvement of p53 in normal metabolism and metabolic transformation is much more complex and some of its actions might seem counterintuitive (for comprehensive review see [10]).

In spite of suggestive evidence of bioenergetic changes as a feature of malignant transformation we have to be cautious to think of cancer cells *in vivo* as a homogenous population (an *in vitro* perspective). Not all cells in the tumour are identical in respect to their self-renewal potential, solid tumour stroma can contribute to some extent too as well as variable proximity of cells to tumour vessels [5]. There are still many gaps to be fulfilled in our understanding to what extent the Warburg effect can be generalised.

Epidemiologic and Pathogenic Overlap of Diabetes and Cancer

People with diabetes (namely T2DM) have increased cancer incidence compared to non-diabetics [12] and mortality from cancer is increased in people with pre-existing diabetes [13]. Recently, numerous studies have been undertaken to try to investigate the previously under-recognised relationship between these two co-morbidities and this task is proving to be quite difficult. Current uncertainty rises from several reasons: (i) epidemiologic evidence linking diabetes and cancer is site-specific (observed validly for breast, endometrial, colorectal, bladder and kidney cancer and non-Hodgkin lymphoma where risk in people with T2DM appears to be 20–50% higher) [14]. Furthermore, (ii) there are methodological problems with the studies, these were not primarily designed to provide such evidence (data were mostly obtained from on-going cohort studies or by secondary analyses of RCTs) and could thus be biased [14]. Finally, (iii) the effect of glucose-lowering therapies (mainly metformin) seems to modulate the risk of cancer incidence and cancer-associated mortality and this further raises controversy in the clinical community [14].

The relationship between diabetes and cancer can be principally direct (one causing or helping to develop the other) or indirect (through shared risk factors). There are several plausible pathogenic mechanisms that can hypothetically explain the association of diabetes and cancer: (1) hyperglycaemia (favouring aerobic glycolysis [15]), (2) hyperinsulinaemia compensating insulin resistance (promoting cell proliferation and survival via insulin or IGF-1 receptors [16,17]), (3) decreased sex-hormone binding globulins (leading to excess of free oestrogens and development of oestrogen-dependent tumours [18]) and (4) others such as aberrant activity of PPP or glyoxalase. The most consistent common risk factors of diabetes and cancer comprise poor dietary habits and physical inactivity. They both contribute to the development of obesity (inevitably aggravating insulin resistance) and therefore constitute a vicious cycle feeding endogenous pathogenic mechanisms. In addition, food is an important source of dietary carcinogens and inevitable producer of mutagenic ROS as a by-product of metabolism of nutrients. Other emerging environmental risks include impaired sleeping patterns and disturbed circadian rhythmicity in general [11].

Similar to previous issues concerning the exact mechanisms linking diabetes and cancer, studies reporting that glucose-lowering treatment might modulate cancer risk have considerable methodological limitations. Metformin, an old known biguanide derivative commonly prescribed for the management of T2DM (and in some trials for its prevention or for the treatment of polycystic ovary syndrome), has recently attracted new attention due to its therapeutic potential in oncology. While meta-analyses of prospective observational studies suggest that metformin lowers the overall cancer risk by about one third [19,20], the meta-analysis of available RCTs with metformin did not confirm the reduced risk [21]. Nevertheless, there are trials in progress already of metformin as an adjuvant therapy in various cancer treatments. Studies *in vitro* and in animal models are on-going to explore potential anti-cancer mechanisms of metformin. The classical anti-diabetic effects of metformin comprise stimulation of glucose uptake by peripheral tissues (skeletal muscle and adipose tissue), inhibition of hepatic glucose production and decrease of intestinal absorption of glucose. Importantly, metformin does not stimulate insulin secretion (it improves insulin sensitivity but does not lower glycaemia) and is thus safe in non-diabetic persons. On the molecular level, metformin largely exerts its effect *via* activation of the cellular energy sensor AMPK (dependent on upstream kinase LKB1). Upon activation, AMPK acts on its down-stream targets – inhibiting mTOR pathway – and generally speaking suppresses anabolic energy-conserving reactions (gluconeogenesis, protein, fatty acid and cholesterol synthesis) and activates catabolic energy producing reactions (fatty acid beta oxidation and glycolysis). There are numerous insulin-dependent and insulin-independent effects of metformin explaining its documented anti-cancer effects (for systematic review see [22,23]) targeting cell growth, cell cycle regulation, cell survival and epithelial mesenchymal transition (EMT).

Once diabetes reaches its manifest stage, the prevention of development and progression of its late complications (diabetic micro- and macroangiopathy) becomes the urgent therapeutic aim in order to prevent the devastating outcomes (such as fatal cardiovascular events, renal failure, blindness, limb amputations etc.). There are multiple pathways contributing to the development of diabetic complications but they are all related to dysregulated intracellular glucose metabolism marked by overproduction of an array of harmful metabolites. Variable degree of fasting and/or postprandial hyperglycaemia provides substrates for several intracellular pathways (such as polyol and hexosamine pathways, dicarbonyl production and non-enzymatic glycation leading to the production of Advanced Glycation End products (AGEs) etc.) that are believed to be largely responsible for the hyperglycaemia-induced cell damage [24]. There are, however, other metabolic pathways – such as PPP, glyoxalase system and fructosamine-3-kinase pathway – potentially conferring protection from the hyperglycaemia-induced damage since they metabolise glycolytic intermediates (especially triosephosphates) into harmless metabolites [25,26]. There is obvious interest to augment their protective activity therapeutically in order to prevent development of complications, even more so since their activity appears to be insufficient or directly failing in hyperglycaemia. Our group documented impaired activity of transketolase (TKT) – the key enzyme of the non-oxidative branch of PPP – and deficient cellular availability of its co-factor thiamine diphosphate in human diabetics [27]. Evidence from experimental and clinical studies suggests that PPP activation by supplementation of the TKT co-factor thiamine may prevent and reverse early-stage diabetic complications [28]. However, PPP and namely one of the human TKT homologues, TKTL1, were

shown to play a role in aerobic glycolysis. While TKTL1 is overexpressed in a wide variety of solid cancers and its' activity positively correlates with the aggressiveness of cancer, its' inhibition mediates cell cycle arrest and apoptosis [29]. Moreover, apart from TKT there are two more enzymes utilising thiamine as a co-factor and involved in utilising glucose into biomass. Another reason for caution when considering recommendation to thiamine supplementation arises from observations that hypoxia induces up-regulation of the thiamine transporters in tumour cells *in vitro* [30]. Since conflicting reports in regard to thiamine transport in cancer cells exist, further research is needed to resolve this issue [31]. Similarly activity of the glyoxalase system was found to be disturbed under conditions of hyperglycaemia in experimental diabetes [32] and again restoring its activity would be an alluring idea in diabetology. The glyoxalase system, consisting of two enzymes, GLO1 and 2, catalyses the conversion of reactive dicarbonyl methylglyoxal (produced excessively under hyperglycaemia and contributing predominantly to the formation of AGEs) to D-lactate [33]. Without efficient degradation methylglyoxal would accumulate to levels inhibiting cell cycle and inducing apoptosis (as observed for example in endothelial cells or β-cells in diabetes). This is especially relevant for tissues with high rates of glycolysis, such as cancer. Indeed, overexpression of GLO1 and GLO1 gene amplification was recently described in many tumours and was also associated with tumour multidrug resistance [33].

In conclusion while T2DM and cancer are probably interlinked not only epidemiologically but pathogenically and successful prevention of DM or its early stabilisation (for example by metformin) might target both diseases at the same time, the management of established disease with the aim to prevent late complications by targeting pathways responsible for their development may possess risks when considering cancer as an eventual co-morbidity. Preserving cell viability and inhibition of apoptosis in target tissues affected by diabetes is a desirable effect, however – if not selective – quite unfortunate in the case of cancer.

Conclusions and Future Directions

This mini-review aims to convince the reader that the switch to aerobic glycolysis in cancer cells is an active process directed by oncogenes and tumour suppressor genes. Aerobic glycolysis confers many selective advantages for rapidly proliferating cells – a greater fraction of glucose metabolites is incorporated into newly synthesised macromolecules, it creates local acidosis suiting the cancer but not normal cells and it protects cancer cells from ROS-mediated cell death. The production of ATP by aerobic glycolysis is not lower when glucose supply is affluent, on the contrary ATP production is very fast. Suppression of the glycolytic phenotype – by substrate limitation, pharmacological intervention or genetic manipulation – confers significant anti-tumour effects. The link between cancer and diabetes has been suggested for a long time by epidemiological studies. Currently, multiple pathogenic overlaps between diabetes and cancer are suggested by experimental findings advocating for causality of the association. Considering the globally rising prevalence of diabetes and cancer, understanding the exact relationship between the two diseases is probably one of the biggest challenges for the research and clinical community in the near future. Targeting cellular metabolism more efficiently might offer a completely novel approach to the treatment of both diseases in parallel and can represent a new line of treatment synergistic with conventional chemotherapies. Metformin, a safe drug with minimal toxicity and side effects, cheap and accessible, appears to be one of the first candidates potentially suited for this task.

Abbreviations

AKT	protein kinase B
AMPK	AMP dependent protein kinase
ATP	adenosine triphosphate
FDG	2-[^{18}F] fluoro-2-deoxyglucose
GLO1	glyoxalase 1
HIF-1	hypoxia-inducible factor 1
IGF-1	insulin growth factor 1
mTORC1	mammalian target of rapamycin complex 1
OXPHOS	oxidative phosphorylation
PARP-1	poly ADP ribose polymerase
PET	positron emission tomography
PI3K	phosphatidylinositol 3 kinase
PPP	pentose phosphate pathway
RCT	randomised controlled trial
ROS	reactive oxygen species
T2DM	type-2 diabetes mellitus
TCA	tricarboxylic acid cycle
TKT	transketolase
TSC	tuberous sclerosis
VHL	von Hippel-Lindau

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