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From tumor cell metabolism to tumor immune escape

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Abbreviations:

antigen processing machinery (APM)

body mass index (BMI)

cytotoxic T-cells (CTLs)

dendritic cells (DC)

dichloroacetate (DCA)

Extracellular signal-regulated kinases (ERK)

glyceryl trinitrate (GTN)

histone acetyltransferases (HAT)

human leukocyte antigen (HLA)

hypoxia inducible factor 1 α (HIF-1 α)

interferon- γ (IFN- γ)

indoleamine 2,3-dioxygenase (IDO)

liver X receptors (LXR)

major histocompatibility complex-I (MHC-I)

Mitogen-activated protein (MAP) kinases (MAPK)

MHC class I-related proteins (MICs)
Myeloid-derived suppressor cells (MDSCs)
natural killer (NK)
nitric oxide (NO)
nitrotyrosine (NT)
non-Hodgkin's lymphoma (NHL)
oxidative phosphorylation (OXPHOS)
peroxisome-proliferator-activated receptors (PPARs)
postload plasma glucose (PLG)
prostate-specific antigen (PSA)
pyruvate dehydrogenase kinase isozyme 1 (PDK1)
pyruvate dehydrogenase isozyme 1 (PDH1)
positron emission tomography (PET)
peroxynitrite (PNT)
Reactive oxygen species (ROS)
T cell receptor (TCR)
regulatory T cells (T_{reg})
transforming growth factor- β (TGF- β)
tricarboxylic acid (TCA)
tumor-associated antigen (TAAs)

Abstract

Tumorigenesis implies adaptation of tumor cells to an adverse environment. First, developing tumors must acquire nutrients to ensure their rapid growth. Second, they must escape the attack from the host immune system. Recent studies suggest that these phenomena could be related and that tumor cell metabolism may propel tumor immune escape. Tumor cell metabolism tends to avoid mitochondrial activity and oxidative phosphorylation (OXPHOS), and largely relies on glycolysis to produce energy. This specific metabolism helps tumor cells to avoid the immune attack from the host by blocking or avoiding the immune attack. By changing their metabolism, tumor cells produce or sequester a variety of amino acids, lipids and chemical compounds that directly alter immune function therefore promoting immune evasion. A second group of metabolism-related modification targets the major histocompatibility complex-I (MHC-I) and related molecules. Tumor MHC-I presents tumor-associated antigens (TAAs) to cytotoxic T-cells (CTLs) and hence, sensitizes cancer cells to the cytolytic actions of the anti-tumor adaptive immune response. Blocking tumor mitochondrial activity decreases expression of MHC-I molecules at the tumor cell surface. And peroxynitrite (PNT), produced by tumor-infiltrating myeloid cells, chemically modifies MHC-I avoiding TAA expression in the plasma membrane. These evidences on the role of tumor cell metabolism on tumor immune escape open the possibility of combining drugs designed to control tumor cell metabolism with new procedures of anti-tumor immunotherapy.

Introduction

During the process of tumorigenesis cells are confronted to an adverse environment in two contexts: they must obtain nutrients for their rapid growth and they must escape the attack from the host immune system. Otto Warburg found in the 1920s that, even in the presence of ample oxygen, cancer cells prefer to metabolize glucose by glycolysis (Warburg, 1930, Warburg, 1956). Glycolysis is the metabolic pathway that converts glucose into pyruvate, which later on and in a simple description, can be burnt in the mitochondria (OXPHOS) or reduced to lactate (fermentation). This anaerobic glycolysis or fermentation is less efficient for producing ATP than oxidative phosphorylation (OXPHOS; respiration). However, fermentation is much quicker than respiration on producing ATP and offers a selective advantage to rapidly growing tumor cells. This Warburg effect has been observed in a wide variety of rapidly dividing human cancers and constitutes the physiological basis for the use of positron emission tomography (PET) scans in clinical oncology. Recent developments in the field indicate a wide remodeling of the metabolic pathways of cellular energy production although the molecular mechanisms still remain unclear and are probably tumor cell specific (Jezek et al., 2010, Bellance et al., 2009). Moreover, tumor cell metabolism is most likely linked to tumor cell development because several waves of gene regulation constantly modify the metabolism during tumorigenesis (Smolkova et al., 2011).

Paul Ehrlich in 1909 was one of the first to conceive the idea that the immune system could repress a potentially “overwhelming frequency” of carcinomas. However this idea was not pursued until the establishment of the existence of tumor-associated antigens (TAAs). In the 1960s, Sir Macfarlane Burnet and Lewis Thomas proposed the hypothesis of “cancer immunosurveillance” (Burnet, 1970), which stated that “inheritable genetic changes must be common in somatic cells and a proportion of these changes will represent a step toward malignancy. It is an evolutionary necessity that there should be some mechanism for eliminating or inactivating such potentially dangerous mutant cells and it is postulated that this mechanism is of immunological character”. In our days this hypothesis is commonly accepted (Dunn et al., 2002, Dunn et al., 2006). Initial descriptions of both cancer immunosurveillance and the Warburg effect were done at least forty years ago. Both processes occur early in tumor development suggesting that they could be linked, either directly or indirectly. New data reviewed herein suggest that these phenomena could indeed be related and that changes in tumor cell metabolism may propel tumor cell immune escape.

Tumor cell metabolism

The vast percentage of tumor cells increase aerobic glycolysis and decrease OXPHOS compare to their non-oncogenic counterparts. Even in normoxia they mainly rely in aerobic glycolysis a phenomenon called the Warburg effect. This was initially linked to the low O₂ concentration found in the inner region of the nascent tumors that become progressively distanced from the vasculature. These increasing hypoxic conditions could gear the metabolic shift from OXPHOS to fermentation. However, although hypoxia could select aggressive tumor cell clones, several results now challenge the hypothesis that it is essential for metabolic remodeling. Firstly, leukemic cells that should develop in a well-oxygenated environment also show a Warburg-like metabolism (Samudio et al., 2009). Second, at the microregional level, lactate production and hypoxia do not overlap (Yaromina et al., 2009). Third, hypoxia inducible factor 1 α (HIF-1 α), which is the master regulator of genetic adaptation to hypoxia, can be stabilized in tumors under normoxic conditions. Hence, tumors can express HIF-1–regulated genes and enhance flux of glycolysis in an oxygen-independent manner (Lu et al., 2002). As a consequence or a cause of this metabolism tumor cells enhance expression of glucose transporters and monocarboxylate transporters to ensure glucose delivery and guarantee lactate secretion out of the cell, respectively. Nevertheless, a certain quantity of pyruvate, the main “fuel” used by mitochondria, still enters the tricarboxylic acid (TCA) cycle for bioenergetic and biosynthetic purposes (Levine and Puzio-Kuter, 2010). Indeed, most tumor cells continue to use their mitochondria to produce ATP, although at slower rate. In addition glutaminolysis also increases in tumor cells and glutamine is largely used for anabolism and catabolism (Dang, 2009). In summary, the Warburg effect, which is currently called aerobic glycolysis because of the increase rate of glycolysis in the presence of oxygen, is not the only feature of tumor cell metabolism.

A significant proportion of tumor cells also increase glutamine metabolism (DeBerardinis et al., 2007, Dang, 2009, Smolkova et al., 2011). Glutamine, with a concentration around 700 μ M, is the amino acid with the highest circulating levels in human blood. It serves as an important source of cellular energy through OXPHOS and of anabolic carbon and nitrogen (Curthoys and Watford, 1995). Activation of oncogenes or loss of tumor suppressors could drive these changes in glutamine metabolism. One example is induction of mitochondrial glutaminase (GLS) expression by the oncogene c-Myc (Gao et al., 2009, Wise et al., 2008). The catabolism of glutamine is initiated by GLS, which catabolyzes the conversion of glutamine to glutamate, which can enter into the Krebs cycle as α -ketoglutarate (Curthoys and Watford, 1995). Interestingly, GLS is probably the rate-limiting enzyme for glutamine consumption in proliferating T cells as well as leukemic cells (Carr et al., 2010).

The mechanisms controlling GLS in tumor cells are poorly understood but it has recently

emerged that microRNAs (miRNAs), a class of short, non-coding RNA molecules, regulate GLS-mediated glutamine metabolism. miRNAs play a central role in regulating posttranscriptional gene expression by annealing to the 3' untranslated regions of target mRNAs to generally promote mRNA degradation or translational repression (Chhabra et al., 2010). c-Myc transcriptionally represses miR-23a and miR-23b, which target GLS mRNA, resulting in greater expression of GLS protein (Gao et al., 2009). We have recently observed that the MAPK ERK5 is essential for leukemic cell survival in glutamine medium (Charni et al., 2010). Glutamine increases ERK5 expression and activation (Charni et al., 2010). ERK5 activation induces p65 translocation to the nucleus and increases its transcriptional activity (Garaude et al., 2006). Moreover, cells growing in glutamine increase p65 translocation to the nucleus where it controls glutamine metabolism by downregulating miR-23a levels. This leads to increase GLS expression (M.G.Rathore and M. Villalba, IJBCB (in revision). Hence, the constitutive activation of NF- κ B found in leukemic cells could provide them with a selective metabolic advantage. In summary, during tumorigenesis different metabolic adaptations can occur and the physiological implications will change.

How metabolic changes that appear in tumor cells can therefore impact neoplasticity and tumorigenesis? Recent work from Wellen et al. provided new evidences (Wellen et al., 2009). They demonstrate that Acetyl-CoA, which is a key intermediate in several metabolic pathways, is a substrate of histone acetyltransferases (HAT). Interestingly, in absence of ATP-citrate lyase, which ensures the production of acetyl-CoA from citrate, global histone acetylation is reduced. Therefore, the cellular pool, or more specifically the nuclear pool, of citrate-acetyl-CoA controls gene expression (Wellen et al., 2009). Thus, tumor cell metabolism might modulate tumor genetic reprogramming.

However, tumor metabolism may vary over the course of tumor development. A new hypothesis proposes that tumor cells can change their metabolism by waves of gene regulation to adjust to their different needs (Smolkova et al., 2011). Some of these waves are originated by deregulated expression of oncogenes, which have already been linked to metabolic remodeling. Thus, tumor metabolic shift is probably due to several processes including overexpression of glycolytic enzymes and metabolite transporters, defects in cellular respiration and oncogenic alterations. However, besides the growth advantage given by the tumor metabolic shift, it is now clear that this phenomenon offers other advantages. One of them is probably facilitating immune escape by a kind of 'Darwinian' selection of the clones able to perform the appropriate metabolic changes.

Immune system and tumor formation

A key feature of cancer is the failure of the immune system to control tumor growth (Dunn et al., 2002, Dunn et al., 2006). These data derived from murine tumor models, but also from correlative data obtained by studying human cancers (Vesely et al., 2011). Between these observations, we highlight that transplanted tumors grow more robustly in mice treated with neutralizing monoclonal antibodies for interferon- γ (IFN- γ ; (Dighe et al., 1994)) and that immunodeficient mice lacking either IFN- γ responsiveness or a functional T cell compartment are more susceptible to chemical-induced sarcomas (Engel et al., 1997a, Engel et al., 1996, Engel et al., 1997b, Svane et al., 1997a, Svane et al., 1996, Svane et al., 1997b, Kaplan et al., 1998). The immune system also controls tumor immunogenicity (Shankaran et al., 2001). Tumors that develop in immunocompromised mice are rejected when transplanted into immunocompetent syngeneic wild-type mice. However, tumors derived from immunocompetent wild-type mice grow when transplanted into syngeneic wild-type hosts (Shankaran et al., 2001, Garaude et al., 2008, Aguilo et al., 2009). Thus, the notion of cancer immunoediting proposes that the immune system sculpts the tumor immunogenicity. This has been observed in several kinds of tumors including in blood-borne cancers. For example, the essential role of immunosurveillance and cancer immunoediting in leukemia progression is highlighted by the anti-leukemic defects found in PKC θ -deficient mice (Garaude et al., 2008, Aguilo et al., 2009). These mice fail mounting an appropriate immune response against MHC-I positive and negative tumor cells because they show impaired activation of both CTLs and natural killer (NK) cells. The appearance of clinically detectable tumors may be the result of the proliferation of cells that have developed sophisticated strategies to escape the immune response even though immune cells efficiently infiltrate tumors. In fact, in some established tumors these infiltrating immune cells do not mount an effective anti-tumor response and often they can provide positive assistance to tumor growth for instance by secreting pro-angiogenic factors or matrix metalloproteinases. Tumor immune escape and tumor immunoediting have been reviewed elsewhere (Vesely et al., 2011). Therefore, we will focus our discussion on immune escape mechanisms related to tumor metabolic changes. We divide these mechanisms in two groups: those actively blocking function of immune cells and those allowing tumor cell to hide from the attack of the immune system.

Blocking the immune attack

Tumor cells produce different metabolites that promote immunosuppression. We will limit this review to some relevant examples.

Aminoacids:

Tryptophan and L-arginine. . Several tumors express the enzyme Indoleamine 2,3-dioxygenase (IDO), which depletes the extracellular medium of tryptophan, leading to T cell anergy (Mellor et al., 2003) .

Myeloid-derived suppressor cells (MDSCs) represent the predominant population of tumor-associated myeloid cells (Gabrilovich and Nagaraj, 2009). They metabolize L-arginine with the enzymes arginase and nitric oxide synthase (NOS) generating products that inhibit the function of infiltrating lymphocytes and, in addition, depriving lymphocytes of arginine. Arginase produces urea whereas NOS produces nitric oxide (NO). Activated myeloid cells greatly produced reactive oxygen species (ROS) i.e. radical superoxide (O_2^-), which reacts with NO to produce the free radical peroxynitrite (PNT). Thus, during tumor development some myeloid cells can produce PTNs when activated under oxidative stress, which is thought to constitute a feature of tumor-associated myeloid cells (Gabrilovich and Nagaraj, 2009). PNTs in turn induce activated T lymphocytes to undergo apoptosis (Bronte et al., 2003) and T cell tolerance via nitration/nitrosylation of TCRs and CD8 molecules. Nitrosylated TCRs lose the ability to recognize specific peptide/MHC (pMHC) complexes and therefore limit the antitumor activity of CD8 T cells (Nagaraj et al., 2007). Interestingly, there is evidence for a role of PNT in masking tumor cells from the immune system (see below).

Macrophages also constitute an important part of the myeloid cell population present in the tumor mass. Tumor-associated macrophages (TAMs) are mainly composed of 'alternatively activated' macrophages (or M2 macrophages) that exert a tumor promoting function (Gabrilovich et al., 2012). Notably, TAMs accumulate in hypoxic regions of the tumor where they can support angiogenesis, impair T cell activation and eliminate M1 macrophages, which are tumoricidal and support T cell mediated immunity (Gabrilovich et al., 2012). M2 macrophages produce IDO and therefore lower T cell responses and promote immune tolerance through tryptophan catalysis. In addition, accumulating evidences suggest that, upon contact with apoptotic tumor cells in tumor microenvironment, M2 macrophages downregulate NO production and upregulate arginase metabolism, thereby contributing to tumor development (Weigert and Brune, 2008).

Lipid metabolism:

Several immune cells such as macrophages and dendritic cells (DCs) can uptake tumor cells and tumor cell debris in a process termed phagocytosis. Upon cell-internalization, phagocytes face an important increase in their intracellular contents of metabolites such as lipids, cholesterol or nucleotides (Ravichandran and Lorenz, 2007). In 'normal' settings, macrophages can re-use

cholesterol from engulfed cell and/or increase cholesterol efflux (Kiss et al., 2006, Ravichandran and Lorenz, 2007). Interestingly, this cholesterol efflux was not observed when engulfed cells trigger inflammatory signaling (i.e. Fc Receptor engagement or necrosis sensing) suggesting that cholesterol load may depend on inflammatory condition encountered by the phagocytes. In line with this, the group of D. I. Gabrilovich recently demonstrated that DCs accumulate cholesterol and other lipids through their scavenger receptors in tumor bearing hosts. This lipid accumulation impairs DC function therefore preventing priming of an efficient anti-tumor immune response (Herber et al., 2010). Interestingly, normalization of DC lipid content using an acetyl-CoA carboxylase inhibitor restores DC function demonstrating that tumor cells can indirectly impact metabolism of antigen-presenting cells to dampen anti-tumor immunity. Molecular mechanisms governing immune cells responses to metabolism changes are now being deciphered. For example, high levels of cholesterol and oxysterols (oxidized derivatives of cholesterol) trigger peroxisome-proliferator-activated receptors (PPARs) and liver X receptors (LXR), which in turn can affect DC maturation and migration and promote anti-inflammatory responses (Russo, 2011, Torchinsky et al., 2010, Mukundan et al., 2009, N et al., 2009). In addition, LXRs are also implicated in PNT formation and therefore can affect T cell activation as described above (Russo, 2011).

Lactate.

As previously described lactate is the last and more abundant product of tumor cell fermentation and serves as a marker for metastases and overall survival of patients (Hirschhaeuser et al., 2011). Some of the effects of extracellular lactate include: (i) blocking the differentiation of monocytes to DCs (Gottfried et al., 2006) ; (ii) inhibiting cytokine release from DCs (Gottfried et al., 2006) and cytotoxic T lymphocytes (CTLs ;(Fischer et al., 2007)) ; (iii) dampening the migration of monocytes (Goetze et al., 2011) and (iv) reducing cytotoxic T-cell function (Fischer et al., 2007, Diel et al., 2010). More than this, because cellular lactate secretion via monocarboxylate transporters (MCTs) is accompanied by H⁺ transport, a decrease in extracellular pH results in a reduction of CTL function due to intracellular accumulation of lactate (Fischer et al., 2007, Diel et al., 2010). Interestingly, regulatory T cells (T_{reg}) do not appear to be affected by the presence of lactate or an acidic microenvironment, because their metabolism relies on fatty acid oxidation (Michalek et al., 2011). In contrast to the inhibition on motility observed in immune cells, lactate led to a concentration-dependent increase in random migration of various cancer cell lines (Goetze et al., 2011). This increased migration could be important to avoid immune response or to produce metastases.

Avoiding the immune attack:

As mentioned above, tumor cells can block immune function. An interesting alternative is to avoid being seen by effector immune cells. Clinical tumors show some different strategies. These include decreasing or shedding the expression of TAAs, absence of expression of costimulatory receptors, lack of expression of adhesion molecules, expression of Fas ligand (FasL) and/or TGF- β (transforming growth factor- β) and impaired expression of MHC-I, which is called human leukocyte antigen (HLA) in humans.

This is a general overview because some adhesion molecules, such as like mucin-1 (MUC1), are usually overexpressed in tumors and functions as a TAA (Pashov et al., 2010). MUC1 primary function is to protect the body from pathogen's infection (Moncada et al., 2003). However, MUC1 is a marker of tumor malignancy, especially in mammary epithelial tumors. Antigen shedding allows the tumor to escape from the host immune response, and MUC1, is one of these shed antigens by a pathway regulated by gamma-secretase (Julian et al., 2009).

The molecular mechanism underlying abnormal MHC class I expression include mutations or epigenetic changes in genes encoding the MHC-I light chain β 2-microglobulin (β 2m), HLA class I heavy chain, and antigen processing machinery (APM). The expression of one or more of these proteins is often altered in tumor cells, leading to a decrease of surface expression of MHC-I. This selective loss of MHC-I expression, which is found in the majority of cancers (Aptsiauri et al., 2007, Campoli and Ferrone, 2008), allows tumor cells to avoid CTLs and thereby prevents anti-tumor adaptive immune response (Aptsiauri et al., 2007, Campoli and Ferrone, 2008). However, a small amount of surface MHC-I must be maintained, because its absence would make tumor cells targets of natural killer (NK) cells (Vivier et al., 2008). Therefore, two important immune cells in charge of killing tumor cells are influenced by the expression of MHC-I in the plasma membrane. Tumor cells use some approaches analogous to virus, which target proteins implicated in MHC-I expression and antigen presentation machinery (Alcami and Koszinowski, 2000), to avoid immune recognition, suggesting that immune responses targeting infected cells and tumor cells might be shared.

The role of tumor cell metabolism on avoiding immune attack.

MHC-I. The mechanisms responsible for the lost of MHC-I surface expression in tumor cells are being elucidated (see above) and new mechanisms related to tumor cell metabolism have recently been described (Charni et al., 2010, Lu et al., 2011). Cancer cells are metabolically adapted to generate energy by anaerobic glycolysis in preference to OXPHOS (Warburg, 1956). When glucose is no longer available, cells are forced to use alternative energy substrates such as

the oxidation of glutamine that is present in most culture media. This process called glutaminolysis requires OXPHOS for ATP production (Reitzer et al., 1979, Rossignol et al., 2004). We hypothesized that associated to this metabolic change there were a differential expression of genes involved in immune escape (Figure 1). Altered MHC-I expression is arguably the most efficient because its downregulation allows tumor cells to avoid the adaptive immune response mediated by CTL (Aptsiauri et al., 2007). Mouse L1210 B leukemic or human Jurkat T leukemic cells growing in 25 mM glucose were changed to glucose-deprived medium supplemented with 10 mM galactose plus 4 mM glutamine as respiratory substrate (Charni et al., 2010). Galactose was added to glutamine containing media to allow generation of nucleic acids through the pentose phosphate pathway (Reitzer et al., 1979, Rossignol et al., 2004). Cells growing in glucose-free medium for three days showed a 3-fold increase in MHC-I expression. OXPHOS-induced MHC-I upregulation was totally reversible and after placing OXPHOS-growing cells in glucose-containing medium they recovered their usual MHC-I expression (Charni et al., 2010). Finally, cells growing in the presence of 25 mM glucose and dichloroacetate (DCA) increased MHC-I expression. DCA inhibits pyruvate dehydrogenase kinase isozyme 1 (PDK1; (Whitehouse et al., 1974) and, therefore, activates pyruvate dehydrogenase isozyme 1 (PDH1; (Bartrons and Caro, 2007). This forces pyruvate to enter the Krebs's cycle and therefore switching metabolism to respiration (Bartrons and Caro, 2007). Tumor metabolism regulates MHC-I expression at the transcriptional level because glutamine-growing cells expressed high mRNA levels of both the heavy and the light ($\beta 2m$) MHC-I chains (Charni et al., 2010). The molecular mechanism involves OXPHOS-induced ERK5 expression, which controls MHC-I expression at the transcriptional level (Charni et al., 2009).

Interestingly, DCA shows a strong anti-tumoral effect (Bonnet et al., 2007). It is believed that by inducing a metabolic change from fermentation to OXPHOS, DCA specifically induces apoptosis in tumor cells. DCA has clinical benefits for the treatment of certain cancer patients (Flavin, 2010, Michelakis et al., 2010), although its use is under debate (Stockwin et al., 2010, Heshe et al., 2011). In view of our results (Charni et al., 2010), it should be interesting to investigate the clinical association of DCA with CTL-mediated immunotherapy because DCA-induced MHC-I expression should facilitate plasma membrane expression of TAAs allowing proper recognition by CTLs.

As previously described some cancer immunotherapeutic protocols obtain a satisfactory infiltration of CTLs. However, a clinical benefit is observed in a low number of patients, probably because tumors produce some immunomodulators that block CTL activity (see above). However, a new mechanism has been described that involved chemical modifications of MHC-I,

and hence, reducing tumor cell recognition by CTLs (Lu et al., 2011). MDSCs produce PNT that induces nitrosylation of tyrosine residues in target proteins. Elevated nitrotyrosine (NT) levels are associated with poor prognosis (Nakamura et al., 2006). The conversion of tyrosine to NT in MHC-I molecules blocks the binding of peptides to them and favors tumor immune escape (Lu et al., 2011). This has strong implications in the current context of immunotherapy where CTLs are generated in vitro against TAAs. However, these in vitro-generated CTLs will not find the same antigen-MHC-I context once they are engrafted in vivo. Perhaps, CTLs should be developed against TAAs but in the presence of MDSCs to reproduce the tumor environment. To give an idea of the relevance of this phenomenon, in pancreatic, lung or breast cancers, myeloid cells are the main source of PNT (Lu et al., 2011).

MHC class I-related proteins (MICs). MICs (MICA and MICB) are induced upon cell stress in normal cells; however, they are constitutively expressed in many tumors. MICs are recognized by NK cells, NKT cells, and most of the subtypes of T cells (Siemens et al., 2008). Surface expression of MICs is under the control of extracellular as well as intracellular events. For example, hypoxia increases tumor cell shedding of MICs at their surface (Siemens et al., 2008). Clinical observations have suggested that shedding of MICA and MICB may be one of the mechanisms by which tumors evade host immunosurveillance and progress. A phase II clinical trial was conducted to attenuate hypoxia-induced progression of prostate cancer (Siemens et al., 2009). Because nitric oxide (NO) blocks prostate cancer hypoxia and increases expression of MICs (Siemens et al., 2008), patients were treated with a slow-release transdermal glyceryl trinitrate (GTN) patch that locally increase NO (Siemens et al., 2009). The results suggest that GTN has a consistent, inhibitory effect on prostate-specific antigen (PSA)-expressing tumor progression in men with recurrent prostate cancer after primary treatment failure. However, there were not evidences of cytotoxic activity against neoplastic cells (Siemens et al., 2009). In animal models (Wu et al., 2009), obstructing shedding of the immunostimulatory MICB also prevents prostate tumor formation. MICB is recognized by the NK cell-activating receptor NKG2D. Therefore, in mice prostate tumor cells hide MICB to avoid NK cell recognition. Conversely, NKG2D deficiency results in a higher incidence of highly malignant prostate adenocarcinomas (Guerra et al., 2008). Moreover, aggressive tumors arising in NKG2D-deficient mice expressed higher amounts of NKG2D ligands than did similar tumors in wild-type mice, suggesting an NKG2D-dependent immunoediting of tumors in this model (Guerra et al., 2008).

MUC1. As described before, one of the main characteristics of metabolic reprogramming in tumor cells is glutamine addiction (Wise et al., 2008)(DeBerardinis and Cheng, 2010). As described before, One mechanism used by tumors to avoid the immune attack is by shedding

MUC1. Silencing GLS expression inhibits MUC1 shedding (Segura et al., 2001), suggesting that the increase in GLS activity found in most tumor cells should favor tumor immune escape.

Epidemiological studies: diabetes and cancer

The pathophysiological implications of the bioenergetic remodeling of tumor cells remains poorly understood, and no conclusive link between this metabolic reprogramming and tumor stage, or the microenvironment has been clearly established. Perhaps because tumor metabolism can constantly change (Smolkova et al., 2011). The higher risk of developing cancer in obese individuals, particularly those who develop type 2 diabetes, suggests an important role in energy metabolism, including environmental (circulating glucose) in tumorigenesis. The metabolic status of the cells can regulate gene expression, i.e. in the absence of OXPHOS succinate accumulates, leading to stabilization of factor HIF1 α , and induction of target genes (Bellance et al., 2009). Therefore, the tumor metabolism and the metabolic environment (glucose and oxygen) are associated to the gene expression program in cancer cells. We postulate that some of these genes are implicated in immune evasion (Figure 2). This also suggests that therapeutic approaches designed to modulate tumor cell metabolism or nutritional approaches could reactivate the anti-tumor immune response.

Of relevance for human health the effect of tumor cell metabolism on immune evasion could help explaining why certain fat- or glucose-rich diets are a tumor risk factor. In particular, they could explain clinical and epidemiology results (Chiu et al., 2006, Jee et al., 2005). Postload plasma glucose (PLG) levels are positively associated with high body mass index (BMI). High BMI and/or abnormal PLG is associated with higher risk of mortality from several hematopoietic cancers including non-Hodgkin's lymphoma (NHL), leukemia and myeloma (Chiu et al., 2006). Similarly, elevated fasting serum glucose levels and a diagnosis of diabetes are independent risk factors for several major cancers, and the risk tends to increase with an increased level of fasting serum glucose (Jee et al., 2005). Diabetic patients show higher risk of developing several kinds of cancer (Vigneri et al., 2009). Hyperinsulinemia might favor cancer in diabetic patients because insulin acts as a growth factor with metabolic and mitogenic effects in malignant cells. However, obesity, hyperglycemia and increased oxidative stress may also contribute to increase cancer risk in diabetes. The results discuss in this review offer an additional clue to explain why hyperglycemia is a risk factor: by facilitating a different tumor metabolism (fermentation), it may favor immune evasion (Figure 2). Moreover, the recent findings described above might have public health significance because BMI and glucose levels are amenable to modification and therefore they could be controlled in patients at risk of developing certain cancers.

Conclusions or “Future prospects”

Advances in tumor biology, i.e. discovery of oncogenes and tumor suppressor genes, shifted cancer research away from studies of energy metabolism and cancer immunosurveillance. However, the physiological importance of the Warburg effect is now revisited (Gogvadze et al., 2008) and the cancer immunosurveillance hypothesis is commonly accepted (Dunn et al., 2002, Dunn et al., 2006). New clinical approaches geared toward inducing an immune response against tumors will probably need to be combined with drugs designed to control metabolism of tumor cells.

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Figure legends:

Figure 1. Tumor metabolism controls MHC-I expression. Tumor cells choose glycolysis metabolism to generate ATP rather than mitochondrial metabolism even in the presence of oxygen (Warburg effect). The pyruvate generated in the glycolysis is reduced to lactate (fermentation). Surface expression of MHC-I is often reduced in tumor cells to avoid the immune attack. Oxidative phosphorylation (OXPHOS) induces expression of ERK5, which increases MHC-I expression at the transcription level.

Figure 2. Diabetes and cancer risk. In the classical model of how diabetes propels cancer (left side), hyperglycemia and insulin resistance (IR) induce an accumulation of circulating insulin, which can interact with the Insulin-like growth factor 1 receptor, inducing mitogenic and transforming effects. Insulin binds also the insulin receptor (IR), more expressed in tumour cells, causing cell growth and cancer progression due to its mitogenic effect. In the new and not excluding approach (right side), hyperglycemia can induce a change in tumour cell metabolism, which leads to the escape of tumour cells from the immune system. This metabolic change affects ultimately the whole body.

Graphical abstract. Mechanisms of the tumor cells to avoid the immune attack. Tumor cells produce several metabolites to prevent the immune recognition: aminoacids (tryptophan, L-arginine and peroxynitrite (PNT)), lipid metabolism (cholesterol and oxysterol) and lactate. Also tumor metabolism downregulates the expression of MHC-I, which helps tumor cells to avoid recognition by CTLs.