The International Journal of Biochemistry & Cell Biology xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

From tumor cell metabolism to tumor immune escape☆

Martin Villalba*, Moeez G. Rathore, Nuria Lopez-Royuela, Ewelina Krzywinska, Johan Garaude, Nerea Allende-Vega

INSERM, U1040, Université de Montpellier 1, UFR Médecine, Institut de Recherche en Biothérapie, Montpellier, France

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Warburg effect
Cancer immunosurveillance
Cancer immunoediting
MHC-I
OXPHOS

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.

This article is part of a Directed Issue entitled: Bioenergetic Dysfunction, adaptation and therapy.

1. 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, 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

Abbreviations: APM, antigen processing machinery; BMI, body mass index; CTLs, cytotoxic T-cells; DC, dendritic cells; DCA, dichloroacetate; ERK, extracellular signal-regulated kinases; GTN, glyceryl trinitrate; HAT, histone acetyltransferases; HLA, human leukocyte antigen; HIF-1α, hypoxia inducible factor 1α; IFN-γ, interferon-γ; IDO, indoleamine 2,3-dioxygenase; LXR, liver X receptors; MHC-I, major histocomatibility complex-I; MAP, mitogen-activated protein; MAPK, kinases; MICs, MHC class I-related proteins; MDSCs, myeloid-derived suppressor cells; NK, natural killer; NO, nitric oxyde; NT, nytrotyrosine; NHL, non-Hodgkin's lymphoma; OXPHOS, oxidative phosphorylation; PPARs, peroxisome-proliferator-activated receptors; PLG, post-load plasma glucose; PSA, prostate-specific antigen; PDK1, pyruvate dehydrogenase kinase isozyme 1; PDH1, pyruvate dehydrogenase isozyme 1; PET, positron emission tomography; PNT, peroxynitrite; ROS, reactive oxygen species; TCR, T cell receptor; T_{reg}, regulatory T cells; TGF-β, transforming growth factor-β; TCA, tricarboxylic acid; TAAs, tumor-associated antigen.

☆ This article is part of a Directed Issue entitled: Bioenergetic Dysfunction, adaptation and therapy.

* Corresponding author at: INSERM, U1040, Institut de Recherche en Biothérapie, 80, avenue Augustin Fliche, 34295 Montpellier Cedex 5, France. Tel.: +33 467 330 465; fax: +33 467 330 113.

E-mail address: martin.villalba@inserm.fr (M. Villalba).

1357-2725/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.biocel.2012.04.024

"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, 2006). Initial descriptions of both cancer immunosurveillance and the Warburg effect were done at least 40 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.

2. 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 O_2 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 1α (HIF-1α), 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 μM, 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 (Rathore et al., in press). Hence, the constitutive activation of NF-κB 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.

3. 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, 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., 1996, 1997a,b; Svane et al., 1996, 1997a,b; Kaplan et al., 1998). The immune system also controls tumor immunogenicity (Shankaran et al., 2001). Tumors that develop in

Please cite this article in press as: Villalba M, et al. From tumor cell metabolism to tumor immune escape. Int J Biochem Cell Biol (2012), http://dx.doi.org/10.1016/j.biocel.2012.04.024

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 immunogenecity. 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 PKCθ-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.

4. Blocking the immune attack

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

4.1. Aminoacids

4.1.1. 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 CD8T 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).

4.2. 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; González et al., 2009). In addition, LXRs are also implicated in PNT formation and therefore can affect T cell activation as described above (Russo, 2011).

4.3. 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; Dietl 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; Dietl 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

Please cite this article in press as: Villalba M, et al. From tumor cell metabolism to tumor immune escape. Int J Biochem Cell Biol (2012), http://dx.doi.org/10.1016/j.biocel.2012.04.024

(Goetze et al., 2011). This increased migration could be important to avoid immune response or to produce metastases.

5. 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 β2-microglobulin (β2m), 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.

6. The role of tumor cell metabolism on avoiding immune attack

6.1. 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 (Fig. 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 3 days showed a 3-fold increase in MHC-I expression. OHPHOS-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 (β2m) 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).

6.2. 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 immunosurveillace and progress. A phase II clinical trial was conducted to attenuate hypoxia-induced progression of prostate cancer (Siemens et al., 2009). Because nitric

Please cite this article in press as: Villalba M, et al. From tumor cell metabolism to tumor immune escape. Int J Biochem Cell Biol (2012), http://dx.doi.org/10.1016/j.biocel.2012.04.024

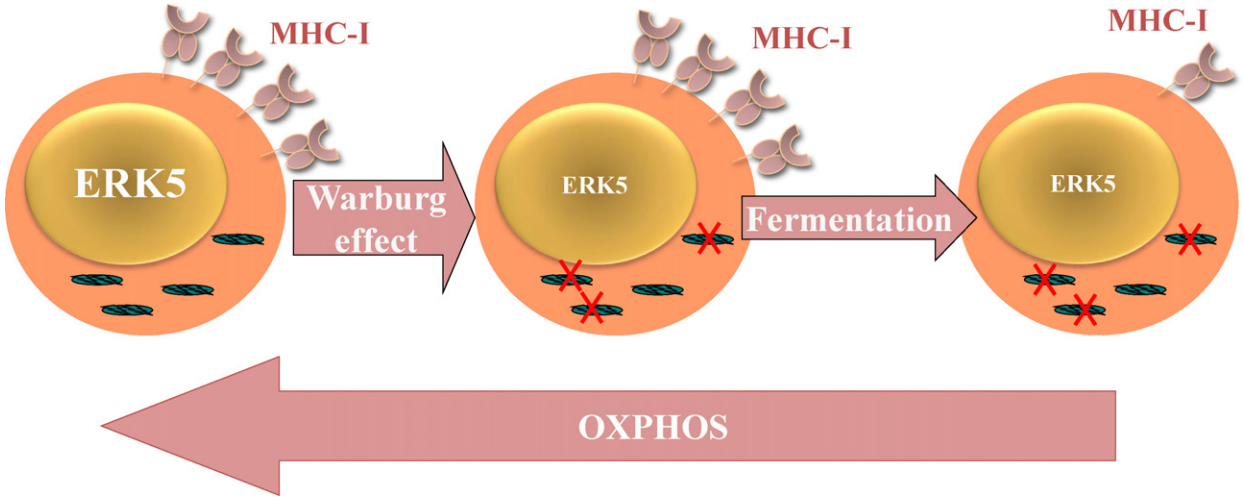

Fig. 1. Tumor metabolism controls MHC-I expression. Tumor cells choose glycolysis metabolism to generate ATP rather than mitochondrial metabolism even in the presence of oxygen (Warburg effect). The pyruvate generated in the glycolysis is reduced to lactate (fermentation). Surface expression of MHC-I 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.

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

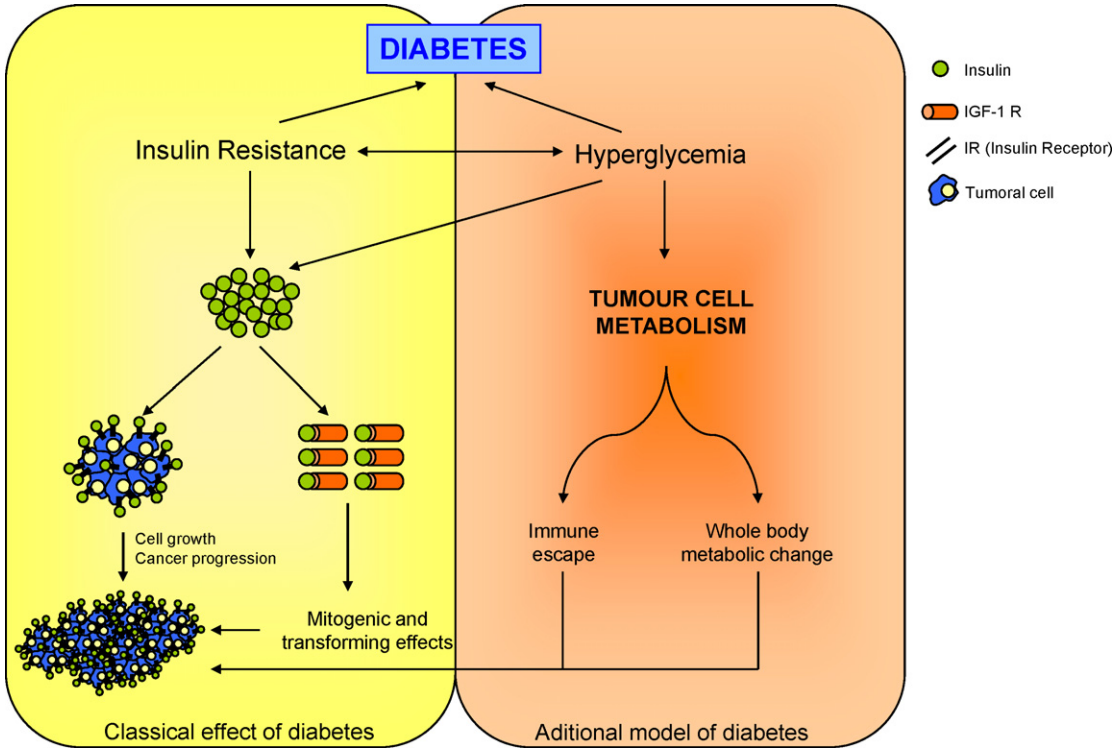

Fig. 2. Diabetes and cancer risk. In the classical model of how diabetes propels cancer (left side), hyperglycemia and insulin resistance (IR) induce an accumulation of circulating insulin, which can interact with the Insulin-like growth factor 1 receptor, inducing mitogenic and transforming effects. Insulin binds also the insulin receptor (IR), more expressed in tumor 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 tumor cell metabolism, which leads to the escape of tumor cells from the immune system. This metabolic change affects ultimately the whole body.

Please cite this article in press as: Villalba M, et al. From tumor cell metabolism to tumor immune escape. Int J Biochem Cell Biol (2012), http://dx.doi.org/10.1016/j.biocel.2012.04.024

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.

7. 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 HIF1α, 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 (Fig. 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 (Fig. 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.

8. 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, 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.

Conflict of interest

The authors declare no competing financial or other interests.

Acknowledgements

This work was supported by the program "Chercheur d'avenir" from the Region Languedoc-Rousillon (MV), a scientific program from the "Communauté de Travail des Pyrénées" (CTPP10/09 to MV), the Association pour la Recherche contre le Cancer (MV), the Fondation pour la Recherche Medicale (MV), a grant FEDER Objectif competitivite (MV), a grant from European Community Program SUDOE (MV) and a fellowships from the ARC and Higher Education Commission, Pakistan (MGR), and Ligue contre le cancer (NLR).

References

Aguilo JI, Garaude J, Pardo J, Villalba M, Anel A. Protein kinase C-theta is required for NK cell activation and in vivo control of tumor progression. Journal of Immunology 2009;182:1972–81.
Alcami A, Koszinowski UH. Viral mechanisms of immune evasion. Trends in Microbiology 2000;8:410–8.
Aptsiauri N, Cabrera T, Garcia-Lora A, Lopez-Nevot MA, Ruiz-Cabello F, Garrido F. MHC class I antigens and immune surveillance in transformed cells. International Review of Cytology 2007;256:139–89.
Bartrons R, Caro J. Hypoxia, glucose metabolism and the Warburg's effect. Journal of Bioenergetics and Biomembranes 2007;39:223–9.
Bellance N, Lestienne P, Rossignol R. Mitochondria: from bioenergetics to the metabolic regulation of carcinogenesis. Frontiers in Bioscience 2009;14:4015–34.
Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, Lee CT, Lopaschuk GD, Puttagunta L, Harry G, Hashimoto K, Porter CJ, Andrade MA, Thebaud B, Michelakis ED. A mitochondria-K+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer Cell 2007;11:37–51.
Bronte V, Serafini P, Mazzoni A, Segal DM, Zanovello P. L-Arginine metabolism in myeloid cells controls T-lymphocyte functions. Trends in Immunology 2003;24:302–6.
Burnet FM. The concept of immunological surveillance. Progress in Experimental Tumor Research 1970;13:1–27.
Campoli M, Ferrone S. HLA antigen changes in malignant cells: epigenetic mechanisms and biologic significance. Oncogene 2008;27:5869–85.
Carr EL, Kelman A, Wu GS, Gopaul R, Senkevitch E, Aghvanyan A, Turay AM, Frauwirth KA. Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK during T lymphocyte activation. Journal of Immunology 2010;185:1037–44.
Charni S, Aguilo JI, Garaude J, de Bettignies G, Jacquet C, Hipskind RA, Singer D, Anel A, Villalba M. ERK5 knockdown generates mouse leukemia cells with low MHC class I levels that activate NK cells and block tumorigenesis. Journal of Immunology 2009;182:3398–405.
Charni S, de Bettignies G, Rathore MG, Aguilo JI, van den Elsen PJ, Haouzi D, Hipskind RA, Enriquez JA, Sanchez-Beato M, Pardo J, Anel A, Villalba M. Oxidative phosphorylation induces de novo expression of the MHC class I in tumor cells through the ERK5 pathway. Journal of Immunology 2010;185:3498–503.
Chhabra R, Dubey R, Saini N. Cooperative and individualistic functions of the microRNAs in the miR-23a~27a~24-2 cluster and its implication in human diseases. Molecular Cancer 2010;9:232.
Chiu BC, Gapstur SM, Greenland P, Wang R, Dyer A. Body mass index, abnormal glucose metabolism, and mortality from hematopoietic cancer. Cancer Epidemiology, Biomarkers and Prevention 2006;15:2348–54.
Curthoys NP, Watford M. Regulation of glutaminase activity and glutamine metabolism. Annual Review of Nutrition 1995;15:133–59.
Dang CV. MYC microRNAs and glutamine addiction in cancers. Cell Cycle 2009;8:3243–5.
DeBerardinis RJ, Cheng T. Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer. Oncogene 2010;29:313–24.
DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, Thompson CB. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proceedings of the National Academy of Sciences of the United States of America 2007;104:19345–50.
Dietl K, Renner K, Dettmer K, Timischl B, Eberhart K, Dorn C, Hellerbrand C, Kastenberger M, Kunz-Schughart LA, Oefner PJ, Andreesen R, Gottfried E, Kreutz MP. Lactic acid and acidification inhibit TNF secretion and glycolysis of human monocytes. Journal of Immunology 2010;184:1200–9.

Please cite this article in press as: Villalba M, et al. From tumor cell metabolism to tumor immune escape. Int J Biochem Cell Biol (2012), http://dx.doi.org/10.1016/j.biocel.2012.04.024

Dighe AS, Richards E, Old LJ, Schreiber RD. Enhanced in vivo growth and resistance to rejection of tumor cells expressing dominant negative IFN gamma receptors. Immunity 1994;1:447–56.
Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nature Immunology 2002;3:991–8.
Dunn GP, Koebel CM, Schreiber RD. Interferons immunity and cancer immunoediting. Nature Reviews Immunology 2006;6:836–48.
Engel AM, Svane IM, Madsen MW, Pedersen M, Werdelin O. Molecular aberrations in the MHC class I-restricted pathway for antigen presentation in methylcholanthrene sarcomas from nude mice: discrepancies between MHC mRNA and surface protein. Clinical and Experimental Immunology 1997a;109:323–31.
Engel AM, Svane IM, Mouritsen S, Rygaard J, Clausen J, Werdelin O. Methylcholanthrene-induced sarcomas in nude mice have short induction times and relatively low levels of surface MHC class I expression. Apmis 1996;104:629–39.
Engel AM, Svane IM, Rygaard J, Werdelin O. MCA sarcomas induced in scid mice are more immunogenic than MCA sarcomas induced in congenic, immunocompetent mice. Scandinavian Journal of Immunology 1997b;45:463–70.
Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, Gottfried E, Schwarz S, Rothe G, Hoves S, Renner K, Timischl B, Mackensen A, Kunz-Schughart L, Andreesen R, Krause SW, Kreutz M. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood 2007;109:3812–9.
Flavin DF. Non-Hodgkin's lymphoma reversal with dichloroacetate. Journal of Oncology 2010.
Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nature Reviews Immunology 2009;9:162–74.
Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nature Reviews Immunology 2012;12:253–68.
Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, Zeller KI, De Marzo AM, Van Eyk JE, Mendell JT, Dang CV. c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. Nature 2009;458:762–5.
Garaude J, Cherni S, Kaminski S, Delepine E, Chable-Bessia C, Benkirane M, Borges J, Pandiella A, Iniguez MA, Fresno M, Hipskind RA, Villalba M. ERK5 activates NF-kappaB in leukemic T cells and is essential for their growth in vivo. Journal of Immunology 2006;177:7607–17.
Garaude J, Kaminski S, Charni S, Aguilo JI, Jacquet C, Plays M, Hernandez J, Rodriguez F, Hipskind RA, Anel A, Villalba M. Impaired anti-leukemic immune response in PKCtheta-deficient mice. Molecular Immunology 2008;45:3463–9.
Goetze K, Walenta S, Ksiazkiewicz M, Kunz-Schughart LA, Mueller-Klieser W. Lactate enhances motility of tumor cells and inhibits monocyte migration and cytokine release. International Journal of Oncology 2011;39:453–63.
Gogvadze V, Orrenius S, Zhivotovsky B. Mitochondria in cancer cells: what is so special about them? Trends in Cell Biology 2008;18:165–73.
Gottfried E, Kunz-Schughart LA, Ebner S, Mueller-Klieser W, Hoves S, Andreesen R, Mackensen A, Kreutz M. Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. Blood 2006;107:2013–21.
Guerra N, Tan YX, Joncker NT, Choy A, Gallardo F, Xiong N, Knoblaugh S, Cado D, Greenberg NM, Raulet DH. NKG2D-deficient mice are defective in tumor surveillance in models of spontaneous malignancy. Immunity 2008;28:571–80.
Herber DL, Cao W, Nefedova Y, Novitskiy SV, Nagaraj S, Tyurin VA, Corzo A, Cho HI, Celis E, Lennox B, Knight SC, Padhya T, McCaffrey TV, McCaffrey JC, Antonia S, Fishman M, Ferris RL, Kagan VE, Gabrilovich DI. Lipid accumulation and dendritic cell dysfunction in cancer. Nature Medicine 2010;16:880–6.
Heshe D, Hoogestraat S, Brauckmann C, Karst U, Boos J, Lanvers-Kaminsky C. Dichloroacetate metabolically targeted therapy defeats cytotoxicity of standard anticancer drugs. Cancer Chemotherapy and Pharmacology 2011;67:647–55.
Hirschhaeuser F, Sattler UG, Mueller-Klieser W. Lactate: a metabolic key player in cancer. Cancer Research 2011;71:6921–5.
Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202.
Jezek P, Plecita-Hlavata L, Smolkova K, Rossignol R. Distinctions and similarities of cell bioenergetics and the role of mitochondria in hypoxia, cancer, and embryonic development. International Journal of Biochemistry and Cell Biology 2010;42:604–22.
Julian J, Dharmaraj N, Carson DD. MUC1 is a substrate for gamma-secretase. Journal of Cellular Biochemistry 2009;108:802–15.
Kaplan DH, Shankaran V, Dighe AS, Stockert E, Aguet M, Old LJ, Schreiber RD. Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. Proceedings of the National Academy of Sciences of the United States of America 1998;95:7556–61.
Kiss RS, Elliott MR, Ma Z, Marcel YL, Ravichandran KS. Apoptotic cells induce a phosphatidylserine-dependent homeostatic response from phagocytes. Current Biology 2006;16:2252–8.
Levine AJ, Puzio-Kuter AM. The control of the metabolic switch in cancers by oncogenes and tumor suppressor genes. Science 2010;330:1340–4.
Lu H, Forbes RA, Verma A. Hypoxia-inducible factor 1 activation by aerobic glycolysis implicates the Warburg effect in carcinogenesis. Journal of Biological Chemistry 2002;277:23111–5.
Lu T, Ramakrishnan R, Altiok S, Youn JI, Cheng P, Celis E, Pisarev V, Sherman S, Sporn MB, Gabrilovich D. Tumor-infiltrating myeloid cells induce tumor cell resistance to cytotoxic T cells in mice. Journal of Clinical Investigation 2011;121:4015–29.
Mellor AL, Munn D, Chandler P, Keskin D, Johnson T, Marshall B, Jhaver K, Baban B. Tryptophan catabolism and T cell responses. Advances in Experimental Medicine and Biology 2003;527:27–35.
Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, Sullivan SA, Nichols AG, Rathmell JC. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. Journal of Immunology 2011;186:3299–303.
Michelakis ED, Sutendra G, Dromparis P, Webster L, Haromy A, Niven E, Maguire C, Gammer TL, Mackey JR, Fulton D, Abdulkarim B, McMurtry MS, Petruk KC. Metabolic modulation of glioblastoma with dichloroacetate. Science Translational Medicine 2010;2:31–4.
Moncada DM, Kammanadiminti SJ, Chadee K. Mucin and Toll-like receptors in host defense against intestinal parasites. Trends in Parasitology 2003;19:305–11.
Mukundan L, Odegaard JI, Morel CR, Heredia JE, Mwangi JW, Ricardo-Gonzalez RR, Goh YP, Eagle AR, Dunn SE, Awakuni JU, Nguyen KD, Steinman L, Michie SA, Chawla A. PPAR-delta senses and orchestrates clearance of apoptotic cells to promote tolerance. Nature Medicine 2009;15:1266–72.
González NA, Bensinger SJ, Hong C, Beceiro S, Bradley MN, Zelcer N, Deniz J, Ramirez C, Diaz M, Gallardo G, de Galarreta CR, Salazar J, Lopez F, Edwards P, Parks J, Andujar M, Tontonoz P, Castrillo A. Apoptotic cells promote their own clearance and immune tolerance through activation of the nuclear receptor LXR. Immunity 2009;31:245–58.
Nagaraj S, Gupta K, Pisarev V, Kinarsky L, Sherman S, Kang L, Herber DL, Schneck J, Gabrilovich DI. Altered recognition of antigen is a mechanism of CD8+ T cell tolerance in cancer. Nature Medicine 2007;13:828–35.
Nakamura Y, Yasuoka H, Tsujimoto M, Yoshidome K, Nakahara M, Nakao K, Nakamura M, Kakudo K. Nitric oxide in breast cancer: induction of vascular endothelial growth factor-C and correlation with metastasis and poor prognosis. Clinical Cancer Research 2006;12:1201–7.
Pashov A, Monzavi-Karbassi B, Raghava GP, Kieber-Emmons T. Bridging innate and adaptive antitumor immunity targeting glycans. J Biomed Biotechnol 2010;2010:354068.
Rathore MG, Saumet A, Rossi JF, De Bettignies C, Tempe D, Lecellier CH, Villalba, M. The NF-κB member p65 controls glutamine metabolism through miR-23. Int J Biochem Cell Biol, http://dx.doi.org/10.1016/j.biocel.2012.05.011, in press.
Ravichandran KS, Lorenz U. Engulfment of apoptotic cells: signals for a good meal. Nature Reviews Immunology 2007;7:964–74.
Reitzer LJ, Wice BM, Kennell D. Evidence that glutamine, not sugar, is the major energy source for cultured HeLa cells. Journal of Biological Chemistry 1979;254:2669–76.
Rossignol R, Gilkerson R, Aggeler R, Yamagata K, Remington SJ, Capaldi RA. Energy substrate modulates mitochondrial structure and oxidative capacity in cancer cells. Cancer Research 2004;64:985–93.
Russo V. Metabolism, LXR/LXR ligands, and tumor immune escape. Journal of Leukocyte Biology 2011;90:673–9.
Samudio I, Fiegl M, Andreeff M. Mitochondrial uncoupling and the Warburg effect: molecular basis for the reprogramming of cancer cell metabolism. Cancer Research 2009;69:2163–6.
Segura JA, Ruiz-Bellido MA, Arenas M, Lobo C, Marquez J, Alonso FJ. Ehrlich ascites tumor cells expressing anti-sense glutaminase mRNA lose their capacity to evade the mouse immune system. International Journal of Cancer 2001;91:379–84.
Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature 2001;410:1107–11.
Siemens DR, Heaton JP, Adams MA, Kawakami J, Graham CH. Phase II study of nitric oxide donor for men with increasing prostate-specific antigen level after surgery or radiotherapy for prostate cancer. Urology 2009;74:878–83.
Siemens DR, Hu N, Sheikhi AK, Chung E, Frederiksen LJ, Pross H, Graham CH. Hypoxia increases tumor cell shedding of MHC class I chain-related molecule: role of nitric oxide. Cancer Research 2008;68:4746–53.
Smolkova K, Plecita-Hlavata L, Bellance N, Benard G, Rossignol R, Jezek P. Waves of gene regulation suppress and then restore oxidative phosphorylation in cancer cells. International Journal of Biochemistry and Cell Biology 2011;43:950–68.
Stockwin LH, Yu SX, Borgel S, Hancock C, Wolfe TL, Phillips LR, Hollingshead MG, Newton DL. Sodium dichloroacetate selectively targets cells with defects in the mitochondrial ETC. International Journal of Cancer 2010;127:2510–9.
Svane IM, Engel AM, Nielsen M, Werdelin O. Interferon-gamma-induced MHC class I expression and defects in Jak/Stat signalling in methylcholanthrene-induced sarcomas. Scandinavian Journal of Immunology 1997a;46:379–87.
Svane IM, Engel AM, Nielsen MB, Ljunggren HG, Rygaard J, Werdelin O. Chemically induced sarcomas from nude mice are more immunogenic than similar sarcomas from congenic normal mice. European Journal of Immunology 1996;26:1844–50.
Svane IM, Engel AM, Thomsen AR, Werdelin O. The susceptibility to cytotoxic T lymphocyte mediated lysis of chemically induced sarcomas from immunodeficient and normal mice. Scandinavian Journal of Immunology 1997b;45:28–35.
Torchinsky MB, Garaude J, Blander JM. Infection and apoptosis as a combined inflammatory trigger. Current Opinion in Immunology 2010;22:55–62.
Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annual Review of Immunology 2011;29:235–71.
Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocrine Related Cancer 2009;16:1103–23.
Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. Nature Immunology 2008;9:503–10.
Warburg O. Metabolism of Tumors. London: Arnold Constable; 1930.
Warburg O. On respiratory impairment in cancer cells. Science 1956;124:269–70.

Please cite this article in press as: Villalba M, et al. From tumor cell metabolism to tumor immune escape. Int J Biochem Cell Biol (2012), http://dx.doi.org/10.1016/j.biocel.2012.04.024

Weigert A, Brune B. Nitric oxide, apoptosis and macrophage polarization during tumor progression. Nitric Oxide 2008;19:95–102.
Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. ATP-citrate lyase links cellular metabolism to histone acetylation. Science 2009;324:1076–80.
Whitehouse S, Cooper RH, Randle PJ. Mechanism of activation of pyruvate dehydrogenase by dichloroacetate and other halogenated carboxylic acids. Biochemical Journal 1974;141:761–74.
Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang XY, Pfeiffer HK, Nissim I, Daikhin E, Yudkoff M, McMahon SB, Thompson CB. Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. Proceedings of the National Academy of Sciences of the United States of America 2008;105:18782–7.
Wu JD, Atteridge CL, Wang X, Seya T, Plymate SR. Obstructing shedding of the immunostimulatory MHC class I chain-related gene B prevents tumor formation. Clinical Cancer Research 2009;15:632–40.
Yaromina A, Quennet V, Zips D, Meyer S, Shakirin G, Walenta S, Mueller-Klieser W, Baumann M. Co-localisation of hypoxia and perfusion markers with parameters of glucose metabolism in human squamous cell carcinoma (hSCC) xenografts. International Journal of Radiation Biology 2009;85:972–80.

Please cite this article in press as: Villalba M, et al. From tumor cell metabolism to tumor immune escape. Int J Biochem Cell Biol (2012), http://dx.doi.org/10.1016/j.biocel.2012.04.024