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From tumor cell metabolism to tumor immune escape☆

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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 histocompatibility 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.

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"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