MINI REVIEW

Actuality of Warburg's views in our understanding of renal cancer metabolism

Catherine Godinot · Elodie de Laplanche · Eric Hervouet · Hélène Simonnet

Abstract More than 50 years ago, Warburg proposed that the shift in glucose metabolism from oxidative phosphorylation (OXPHOS) to glycolysis occurring in spite of an adequate oxygen supply was at the root of cancer. This hypothesis often disregarded over the following years has recently stirred up much interest due to progress made in cancer genetics and proteomics. Studies related to renal cancers have been particularly informative to understand how abnormal use of glucose and decrease in OXPHOS are linked to cell proliferation in tumors. Indeed, in aggressive tumors such as clear cell renal carcinoma, the von Hippel–Lindau factor invalidation stabilizes the hypoxia-inducible factor (HIF) in the presence of oxygen. HIF stimulating glycolytic gene expression increases the glycolytic flux. Deficiencies in genes involved in oxidative phosphorylation that can explain the down-regulation of OXPHOS components also begin to be identified. These findings are important in the search for novel therapeutic approaches to cancer treatment.

Keywords Hypoxia-inducible factor · Glycolysis · Oxidative phosphorylation · Renal cancer

C. Godinot (✉) · E. de Laplanche · E. Hervouet · H. Simonnet
Center of Molecular and Cellular Genetics (CGMC), UMR 5534,
CNRS, University Claude Bernard of Lyon 1,
43, Bvd du 11 novembre 1918, 69622 Villeurbanne, France
e-mail: godinot1@yahoo.com

Present address:
E. Hervouet
Inserm U601, Institute of Biology,
9 quai Moncousu, F-44035 Nantes, France

Introduction

As early as the 1930s, Otto Warburg observed that tumor cells utilized glycolysis instead of oxidative phosphorylation for producing ATP, even when oxygen supply was sufficient (Warburg et al. 1930). He made the hypothesis that this shift in energy metabolism could be at the root of cancer (Warburg 1956). This view has been progressively disregarded over the following years while the genetic basis of cancer became widely recognized by identification of many oncogenes and tumor suppressor genes. Changes in tumor metabolism were then considered as the consequence of lack of oxygen availability due to an inadequate blood supply to the tumor core rather than a cause of cancer development. Recent progresses in cancer genetics and proteomics have however renewed our interest towards Warburg's views.

It has been shown about 30 years ago that oncogenic viral transformation (Kawai and Hanafusa 1971; Birnbaum et al. 1987) and growth factors (Diamond et al. 1978) increase glucose transport and glycolysis; therefore, a cellular shift toward rapid proliferation seemed to be associated to incomplete substrate oxidation and preferential ATP synthesis from glycolysis. It is not surprising that regulatory mechanisms involved in shifts from oxidative to glycolytic metabolism were discovered in kidney cancers because this organ has a remarkable capacity to withstand transient periods of hypoxia (Rowell 1974) and to shift under hypoxia from oxidative, lactate consuming, glucose producing metabolism to anaerobic glycolysis and lactate production (Simonnet 1999; de Laplanche et al. 2006). Kidney also has a remarkable capacity to switch from quiescence to cell proliferation (for review, see: Shankland and Wolf 2000). Recent studies have identified oncogenes

and tumor suppressor genes that link energy metabolism and substrate utilization to the cell cycle. The deficiency of these genes is prone to constitutively reorient cell metabolism towards hypoxic features in spite of a normal oxygen supply (Dang and Semenza 1999; Kaelin and Maher 1998).

One of the first discovered genes encodes the von Hippel Lindau protein that is inactivated in most clear cell renal carcinomas (CCRC) (Iliopoulos et al. 1995). We'll see in this review how such inactivation stabilizes the hypoxia-inducible transcription factor (HIF) that targets genes involved in the glycolytic flux (Iliopoulos et al. 1996). The mechanism by which mitochondrial oxidative phosphorylation (OXPHOS) can be decreased also begin to be better understood. Different mechanisms can be observed in various types of kidney tumors.

Glycolysis activation induced by HIF stabilization in renal cancers

One of the first mechanisms describing how glycolysis was increased in cancer was unveiled by the study of the von Hippel–Lindau disease. Biallelic inactivation of the von Hippel–Lindau (VHL) tumor suppressor gene are observed as well in sporadic CCRCs as well as in tumors of patients affected by the hereditary VHL syndrome that predisposes patients to CCRCs and to pheochromocytomas (for review, see Kim and Kaelin 2003). The best understood function of pVHL is to regulate a network of target mRNAs in response to oxygen. PVHL is a subunit of the E3-ubiquitin ligase complex that binds ubiquitin to the α subunit of the hypoxia-inducible transcription factor, HIF. HIF is a heterodimer made of a labile α subunit and of a constitutively expressed β subunit. There are three isoforms of HIF-α that all bind pVHL. In addition, a natural antisense RNA complementary to HIF-1α 3′-UTR mRNA is overexpressed in CCRCs (Thrash-Bingham and Tartof 1999), as well as other types of high grade malignant tumors (Rossignol et al. 2002; 2004). Although its function is still enigmatic, aHIF is a poor prognostic marker in breast cancer (Cayre et al. 2003).

In the presence of oxygen, the HIF-α moiety can be hydroxylated at the level of two conserved prolyl residues located in an oxygen-dependent degradation domain (ODDD) and at the level of an asparagyl residue located in its C-terminal transactivation domain (CTAD). The proline hydroxylation is catalyzed by three different HIF prolyl hydroxylases (PHD) that require molecular oxygen since the oxygen atom in the hydroxyl group comes from molecular oxygen. PHDs are members of the super family of iron and α-ketoglutarate-dependent dioxygenases (see Kaelin 2005; Berra et al. 2006, for reviews). HIF-α hydroxylation is sensitive to physiological changes in oxygen concentration. Prolyl hydroxylation generates a

binding site for the E3-ubiquitin ligase complex containing pVHL. This ubiquitination results in HIF-α degradation by the proteasome. Under hypoxia or in the absence of functional pVHL, the HIF-1α or HIF-2α subunits are stabilized and translocated into the nucleus to form a dimer with HIF-β. This dimer recruits a number of co-activators such as p300 and CBP. HIF can then bind to the hypoxia response element (HRE) motif (minimal consensus: 5′-RCGTG-3′) of target genes and activate their transcription (Fig. 1). A factor inhibiting HIF1 (FIH) prevents such recruitment by catalyzing asparagine hydroxylation. This hydroxylation occurs at higher oxygen concentration than proline hydroxylation, which differentially regulates some specific HIF-dependent genes (Pouyssegur et al. 2006). Among more than 60 known HIF targets are genes involved in glucose metabolism: glucose transporter, Glut-1 and at least one isoform of all enzymes involved in the glycolytic pathway. Other genes control oxygen supply (erythropoietin), angiogenesis (VEGF, PDGF-β, FLK-1), iron metabolism, cell cycle regulation (p21/WAF, cyclin D1) or cell differentiation (TGF-β), and acetyl-CoA formation (for reviews, see Dang and Semenza 1999; Semenza 2003; Wenger et al. 2005; Bardos and Ashcroft 2005). The increase in glycolytic enzyme amounts speeds up the glycolytic flux, as predicted in the Warburg's hypothesis.

The end product of glycolysis is pyruvate that enters the Krebs cycle via the pyruvate dehydrogenase complex (PDH)
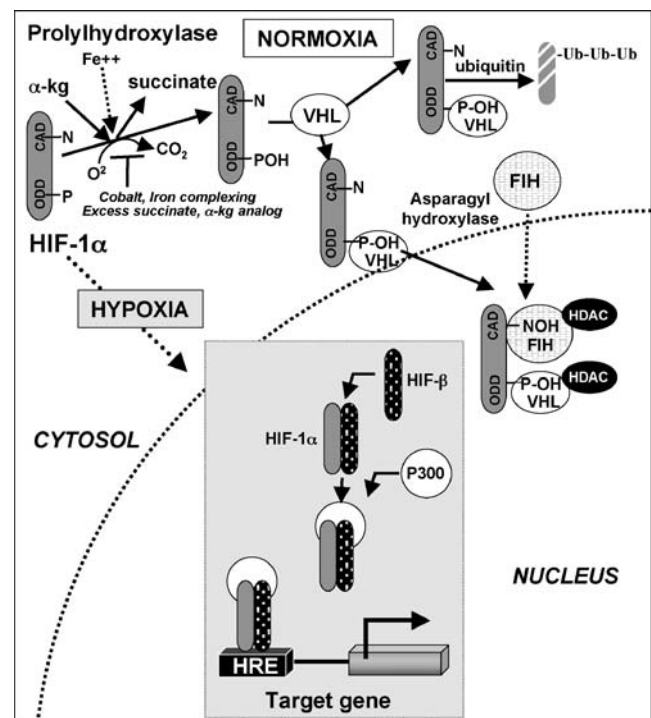

Fig. 1 Regulation of HIF-induced transcriptional activity

Fig. 2 Energetic metabolism changes in renal cancers. *Upward arrows* indicate HIF-induced increased transcription of genes involved in glycolytic flux stimulation or decreased acetyl-CoA provision to the citric acid cycle. *Downward arrows* indicate decreased expression or activity coming either from genetic mutations or ROS-induced inactivation or else from unknown origin and resulting in a decreased OXPHOS efficiency
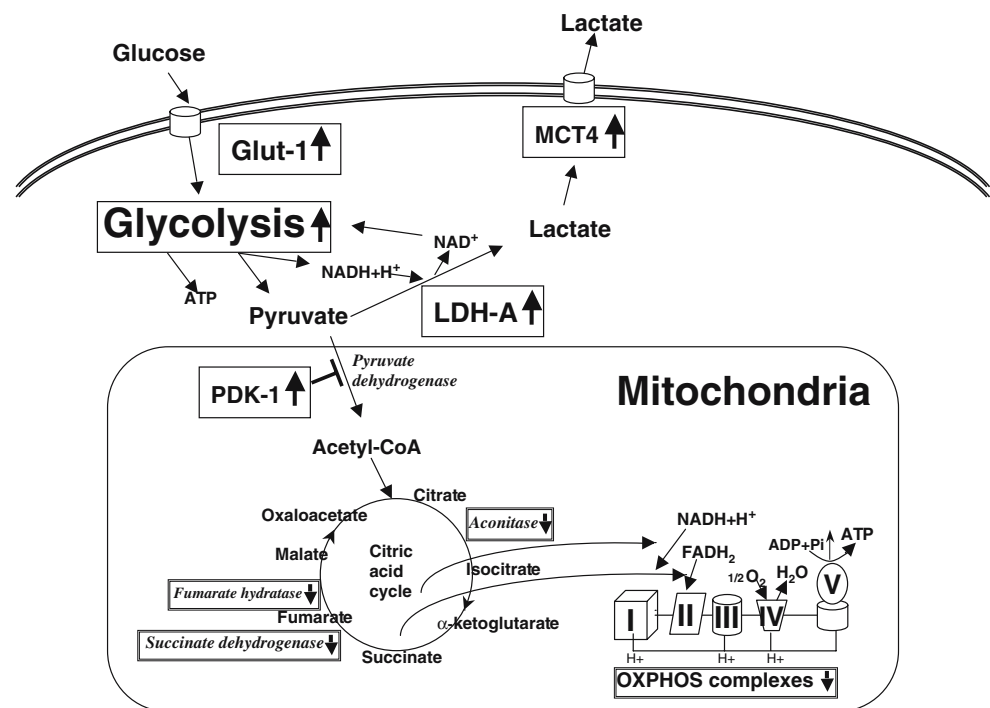
to form acetyl-coenzyme A. PDH activity is inhibited through phosphorylation by the pyruvate dehydrogenase kinase (PDK1) that is also a HIF target (Kim et al. 2006; Papandreou et al. 2006). Thus, inhibiting PDH via PDK activation decreases substrate provision to the Krebs cycle and then decreases OXPHOS.

When NADH accumulates, pyruvate is transformed into lactate by the lactate dehydrogenase (LDH) to regenerate the NAD+ that is necessary to feed glycolysis. LDH-A gene (Semenza 2003) and protein (Unwin et al. 2003) expression are also increased by HIF. In Her-2/neu transformed tumor cells, experimental inhibition of LDH-A reduced glycolysis, increased OXPHOS and decreased cell growth and tumorigenicity (Fantin et al. 2006). Since HIF also increases the lactate transporter MCT4 (Ullah et al. 2006), lactate does not accumulate in the cell. In conclusion, HIF increases glycolysis and contributes to OXPHOS down-regulation by diminishing pyruvate oxidation (Fig. 2). This can be observed either under hypoxia, or, in the presence of oxygen, when HIF is stabilized by pVHL inactivation in CCRCs. HIF also increases the synthesis of vascular endothelial growth factor (VEGF) mRNA improving blood supply to ischemic tissues and thus raising oxygen as well as substrate delivery. Preliminary data from our laboratory have shown that a low glucose content up-regulates the expression of HIF target transcripts such as VEGF, FLK-1, TIE-2, Glut-1 or Aldolase A and HIF-1α mRNA itself (de Laplanche et al. 2005). As a result, ischemia could regulate HIF-1α content at two levels: a lack of glucose increases HIF-1α mRNA and lack of oxygen stabilizes the

protein. In addition, in different types of cancers, HIF can also be activated through different mechanisms by a number of oncogenes even under normoxic conditions (for review, see Shaw 2006).

OXPHOS inhibition in renal cancers

As shown above, HIF can decrease acetyl CoA production and therefore substrate provision to the citric acid cycle by up-regulating PDK-1 that inhibits pyruvate dehydrogenase. However, this is not the only cause of OXPHOS decrease in cancer. Indeed, OXPHOS protein contents, respiratory chain activities and mitochondrial DNA amounts are strongly decreased when compared to normal adjacent tissue in aggressive renal cancers such as the CCRCs (Simonnet et al. 2002; Meierhofer et al. 2004). They were also decreased in chromophilic carcinomas, although to a lower extent. On the contrary, mtDNA, citrate synthase, OXPHOS complexes III, IV and V were increased in oncocytomas when compared to their normal counterpart. The only point of similarity between oncocytomas and CCRCs was their deficiency in complex I (Simonnet et al. 2003). CCRCs that are more aggressive renal cancers than chromophilic cancers exhibited the lowest respiratory chain activities and oncocytomas which are the most benign contained increased amounts of complex III, IV and V, suggesting a correlation between mitochondrial OXPHOS and tumor aggressiveness. However, in CCRCs, there was no apparent correlation between the cancer grade and the mitochondrial density, as attested by electron microscopy

(Molinie et al. 1998; Tickoo et al. 2000) or citrate synthase activity (Simonnet et al. 2002). OXPHOS decrease extent was not either dependent on the cancer grade, as also reported by Meierhofer et al. (2004). F1-ATPase was the only OXPHOS complex to be less diminished in low grade CCRCs than in high grade CCRCs. This is in agreement with observations made in various cancers by the group of Cuezva (Cuezva et al. 2002, 2004; Isidoro et al. 2004) and showing that cancer aggressiveness in tumors of various origins can be defined by a bioenergetic index that is the ratio between the mitochondrial ATPase activitiy and the glycolytic glyceraldehyde-3-phosphate dehydrogenase activity. The patient survival time was the shortest when this ratio was the lowest.

The decrease in respiratory chain activities is associated with the presence of HIF. Indeed, when cells coming from CCRC are transfected with wild type vhl, which restores HIF-α degradation and prevents tumor growth in nude mice, respiratory chain subunit levels are increased (Hervouet et al. 2005; Craven et al. 2006a,b). This HIF-related increase does not seem to be directly caused by important changes in transcripts encoding repiratory chain subunits. Indeed, neither microarray studies, nor direct titration by RT–PCR experiments could put forward significant differences in the amount of those transcripts when comparing cells devoid of active vhl to cells transfected with wild-type vhl (Hervouet et al. 2005; Hervouet 2006). However, recently, Matoba et al. (2006) have shown that p53, the most frequently mutated tumor suppressor gene in cancers, stimulates mitochondrial respiration by activating the transcription of SCO2 (Synthesis of Cyto-chrome Oxidase-2 gene). SCO2 is a copper-binding protein presumably involved in formation of the Cu(A) centre of the COX-2 subunit. Copper binding being an essential step in the process of COX assembly, when SCO2 is lacking, not only COX will be inactive but also its biogenesis will be impaired (Stiburek et al. 2005). Since in metastatic CCRCs, HIF increase is correlated with p53 decrease, HIF can indirectly decrease COX by decreasing SCO2. There-fore, in the presence of HIF, the decrease in COX subunits and COX activity observed by enzymatic analysis (Simonnet et al. 2002) and immunological studies (Hervouet et al. 2005) might be indirectly explained by HIF increase. Very recently, Fukuda et al. (2007) have shown that, in some cells under hypoxia, HIF1 could induce the transcription of the COX-4 subunit isoform 2 and of the mitochondrial LON protease, which accelerated COX-4 subunit isoform 1 degradation. In Hela or 293T cells, such switch between COX-4 isoforms optimized OXPHOS efficiency. Since COX-4 isoform 2 mRNA expression could not be detected in HIF1-deficient 786-0 cells (Hervouet et al. 2006), this regulation is likely to be specifically related to HIF1 and not to HIF2-induced gene transcription.

Other nuclear encoded germline mutations have also been observed in three subunits of OXPHOS Complex II (succinate dehydrogenase subunits B, C and D) in familial paraganglioma and pheochromocytoma (Maher and Eng 2002; Bryant et al. 2003; Eng et al. 2003). Similarly, fumarate hydratase that catalyses the next step of succinate oxidation in the Krebs cycle is the gene mutated in hereditary leiomyomatosis and renal cell cancer (Pollard et al. 2003; Gottlieb and Tomlinson 2005). In these types of cancers, the increase in succinate level is accompanied by an increase of HIF, likely through a feedback inhibition of PHD (Selak et al. 2005), although this is still being discussed.

In the above-mentioned studies in which a specific respiratory chain deficiency has been put forward, there is no explanation of the down-regulation of the other OXPHOS complexes observed in CCRCs. Indeed, in mitochondrial diseases in which SCO2 or SDH subunits are mutated, the COX activity is strongly decreased but the other respiratory chain complexes are still active and normally synthesized. On the contrary, in CRCCs, the decrease in respiratory chain complexes concerns all respiratory chain activities. Another mechanism must interfere to down regulate the biogenesis of these com-plexes. As a hypothesis, we propose that this could be due to an increased ROS production. This is supported by the fact that the Mn-SOD (mitochondrial Mn–superoxide dismutase) that generates H_2O_2 from superoxide anions is among the most overproduced proteins observed when comparing cells devoid of active pVHL to cells expressing pVHL (Unwin et al. 2003; Shi et al. 2004; Hervouet 2006). This suggests that the presence of HIF is associated with mitochondrial production of ROS that would in turn be deleterious for all respiratory chain protein located at the vicinity of the ROS production in a kind of vicious circle. Indeed, the main site for mitochondrial ROS production is complex III that is able to stabilize HIF during hypoxia (Chandel et al. 2000). A more detailed discussion of the important role played by ROS in both the hypoxic and non-hypoxic signaling processes which control HIF activity has been reviewed by Kietzmann and Gorlach (2005).

Renal oncocytomas are generally characterized by a proliferation of mitochondria inside the cell. In these relatively benign tumors, the mitochondrial NADH-coen-zyme Q oxidoreductase activity (complex I) is strongly decreased (Simonnet et al. 2003) and there is an important reduction in the amount of assembled complex I, as shown by two-dimensional blue native-PAGE and/or immunolog-ical titration of some Complex I subunits. On the contrary, the amounts of subunits belonging to other OXPHOS complexes were increased (Simonnet et al. 2002; Hervouet 2006). We proposed that complex I deficiency might stimulate mitochondrial biogenesis, as observed in the

ragged red fibers of patients suffering from mitochondrial diseases (Heddi et al. 1999). Savagner et al. (2003) have shown that, PGC-1, the nuclear respiratory factor NRF-1 and the mitochondrial transcription factor TFAM, essential to control mitochondrial biogenesis and important in mitochondrial DNA gene expression, are over expressed in thyroid oncocytomas in which mitochondria also proliferate. Mitochondrial DNA amounts and levels of most studied OXPHOS subunits being increased in both types of oncocytomas, it is likely that the accumulation of mitochondria is due in both cases to the over expression of these transcription factors. Indeed NRFs and PGC-1 family co-activators control mitochondrial biogenesis, likely via the AMP kinase that activates their expression in response to low ATP (Atherton et al. 2005). The reason why Complex I depletion is predominant in renal oncocytomas (Simonnet et al. 2003) while complex III deficiency associated with cytochrome b mutations seems more frequent in thyroid oncocytomas (Bonora et al. 2006) remains to be determined. Combined efforts from our laboratory and that of G. Romeo (Bologna, Italy) suggest that clonal mitochondrial DNA mutations in NADH dehydrogenase genes might be responsible for complex I deficiencies in renal oncocytomas (unpublished observations). Since mitochondrial proliferation in oncocytomas comes from a deficiency in one of the respiratory chain complexes, this type of cancer is also consistent with the Warburg's hypothesis suggesting that a decrease in OXPHOS may be responsible for most cancers.

It is worth mentioning that genetic deficiencies in genes encoding various OXPHOS complexes can either predispose to inherited neoplasia or be at the origin of severe neurological impairment. For example, complex I, complex II, complex IV or pyruvate dehydrogenase deficiencies can be the cause of Leigh syndrome (Smeitink et al. 2001; Houstek et al. 2006) or that of different types of cancers (see above). The mechanisms by which mutations in genes encoding similar respiratory chain proteins lead either to this neurodegenerative devastating mitochondrial disease in early infancy or to tumor development in the kidney later in life will need to be better elucidated.

Perspectives for treatment

CRCCs are characterized with poor prognosis in patients because of their high resistance to classical anti-mitotic agents and high levels of multi-drug resistance channels. CRCCs being generally highly vascularized, angiogenesis inhibition is one of the most studied strategies in clinical trials to cure renal cancers (for reviews: Hervouet and Godinot 2006; van Spronsen et al. 2005).

Curing cancer by targeting glucose metabolism, has proved efficient in rapidly growing hepatomas (Gwak et al. 2005; Pedersen et al. 2002). Nevertheless, the treatment of mice developing adenocarcinoma with 2-deoxyglucose that blocks hexokinase II activity didn't reduce the tumors. The combination of deoxyglucose with an anti-proliferative agent such as Paclitaxel significantly reduced the growth of tumors implanted in *nude* mice (Maschek et al. 2004). This could be accounted for by the fact that a small decrease in glycolytic ATP synthesis in cancer cells might reduce the ATP-dependent activity of multi drug resistance channels that are often over-expressed in tumors resistant to anti-mitotics. The analog of lactate/pyruvate, 3-bromopyruvate, seemed to block even more efficiently hexokinase II activity than deoxyglucose. Recent studies in highly glycolytic hepatocellular carcinoma with this drug have shown resorption of tumors in all treated animals (Geshwind et al. 2004; Ko et al. 2004).

Modica-Napolitano and Singh (2004) and Dias and Bailly (2005) have recently reviewed possible drugs targeting mitochondria. The efficiency of these drugs for curing renal cancers either alone or in combination with other drugs should now be evaluated at the clinical level.

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