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Cancer metabolism in space and time: Beyond the Warburg effect☆

Pierre Danhier [a,b], Piotr Bański [a], Valéry L Payen [a], Debora Grasso [a], Luigi Ippolito [c], Pierre Sonveaux [a], Paolo E Porporato [a,d,*]

[a] Pole of Pharmacology and Therapeutics, Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain (UCL), Avenue Emmanuel Mounier 52 box B1.53.09, 1200 Brussels, Belgium
[b] Louvain Drug Research Institute (LDRI), Université catholique de Louvain (UCL), Avenue Emmanuel Mounier 73 box B1.73.08, 1200 Brussels, Belgium
[c] Department of Experimental and Clinical Biomedical Sciences, University of Florence, Viale Morgagni 50, Florence, Italy
[d] Department of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Torino, Via Nizza 52, 10126 Torino Italy

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ABSTRACT

Altered metabolism in cancer cells is pivotal for tumor growth, most notably by providing energy, reducing equivalents and building blocks while several metabolites exert a signaling function promoting tumor growth and progression. A cancer tissue cannot be simply reduced to a bulk of proliferating cells. Tumors are indeed complex and dynamic structures where single cells can heterogeneously perform various biological activities with different metabolic requirements. Because tumors are composed of different types of cells with metabolic activities affected by different spatial and temporal contexts, it is important to address metabolism taking into account cellular and biological heterogeneity. In this review, we describe this heterogeneity also in metabolic fluxes, thus showing the relative contribution of different metabolic activities to tumor progression according to the cellular context. This article is part of a Special Issue entitled Mitochondria in Cancer, edited by Giuseppe Gasparre, Rodrigue Rossignol and Pierre Sonveaux.

1. Introduction

The notion that cancer cells harbor a different metabolic profile with respect to somatic cells dates back to the seminal observation by Otto Warburg almost 100 years ago on glucose metabolism [1]. While glucose consumption in normal cells is refrained by energy-rich metabolites produced in the presence of oxygen, a phenomenon known as the Pasteur Effect, Warburg reported that cancer cells behave differently. Indeed, by comparing cancerous and normal tissues, he found that cancer cells are able to maintain a high rate of glycolysis, thus converting glucose to lactate at high speed, even in the presence of oxygen, a phenomenon known as 'aerobic glycolysis' that has also been termed the 'Warburg effect' [2,3]. This observation is at the basis of [^{18}F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) scans of tumors, which allows to detect a tumor tissue because of its generally high avidity for the glucose analogue FDG. Another metabolite that has been identified as being important for tumor growth is glutamine, which is pivotal for biomass production, most notably as a nitrogen donor [4]. Nevertheless, it is overly reductive to assume that cancer metabolism can be summarized as an upregulation of glucose and glutamine metabolism for energy production.

As will be detailed hereafter, our understanding of cancer cell metabolism drastically advanced in the recent years. Despite the key roles of aerobic glycolysis and glutamine metabolism in fostering

Abbreviations: ACL, ATP citrate lyase; AMPK, adenosine monophosphate kinase; ARG1, L-arginine-metabolizing enzyme arginase 1; BCAA, branched-chain amino acid; Bcl2, B-cell lymphoma 2; CAF, cancer-associated fibroblast; CIC, cancer-initiating cell; COX2, cytochrome oxidase; CSC, cancer stem cell; CREB, cyclic adenosine monophosphate response element binding protein; DEC1, differentially expressed in chondrocytes 1; EMT, epithelial-to-mesenchymal transition; FAK, focal adhesion kinase; FAS, fatty acid synthase; FBP, fructose 1,6-bisphosphate; FDG-PET, [^{18}F]-fluorodeoxyglucose-positron emission tomography; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HIF-1, hypoxia-activated factor-1; HK2, hexokinase 2; HMGB1, high-mobility group box 1; HUVEC, human umbilical vein endothelial cell; IFN-γ, interferon gamma; LDH, lactate dehydrogenase; MEF, murine embryonic fibroblast; MET, mesenchymal to epithelial transition; MRI, magnetic resonance imaging; mTORC1, mammalian target of rapamycin complex 1; NSCLC, non-small cell lung cancer; OXPHOS, oxidative phosphorylation; PDAC, pancreatic ductal adenocarcinoma; PHD, prolylhydroxylase; pHe, extracellular pH; pHi, intracellular pH; PK, pyruvate kinase; PPP, pentose phosphate pathway; REDD1, regulated in development and DNA damage response 1; RhoA, Ras homolog gene family, member A; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCO2, synthesis of cytochrome oxidase 2; SGK-1, serum and glucocorticoid-regulated kinase-1 Sirt1, sirtuin 1; TAM, tumor-associated macrophage; TIGAR, TP53-induced glycolysis and apoptosis regulator; TSC2, tuberous sclerosis 2; VDAC, voltage-dependent anion channel; VEGF, vascular endothelial growth factor; ZEB, Zinc finger E-box-binding homeobox.

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* Corresponding author at: Department of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Torino, Via Nizza 52, 10126 Torino, Italy.
E-mail address: paolo.porporato@unito.it (P.E. Porporato).

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tumor growth, several other metabolic pathways have been identified and characterized in cancer. Consequently, it is no longer tenable to claim that alterations of cancer metabolism can be simply summarized as accelerated glycolysis and glutaminolysis. Several factors contribute to such complexity: (i) the perfusion of a tumor is not optimal, thus the delivery of nutrients is often insufficient for cancer cells to rely on few metabolic fuels; (ii) in addition to cancer cells, different cellular populations contribute to the tumor tissue, defining the tumor stroma; (iii) cancer cells present a variety of mutational backgrounds making them heterogeneous; (iv) different activities are performed by cancer cells at different times, ranging from proliferation, to dormancy and invasion. It is thus reductive and even incorrect to picture cancer metabolism unidimensionally as a metabolically homogenous entity. On the contrary, one must study tumor metabolism as being heterogeneous, both in space and in time.

From the spatial standpoint, different tumor areas present various degrees of perfusion, immune infiltration and clonal evolution. This overall complexity results in the development of different metabolic adaptations, such as metabolic symbiosis [5,6], related to a cooperation between cancer cells with different metabolic needs and adaptation to limited perfusion and acidosis [7,8]. This metabolic heterogeneity is also mirrored by the biological heterogeneity of tumors, where cells will have diverse metabolic requirements according to the specific biological activity occurring in that particular area, *e.g.* whether it is at the invasive front or close to the necrotic core, or interacting with specific stromal population. Metabolic heterogeneity can also be interpreted in time, as cancer cells adapt their metabolic activities according to specific requirements bound to ongoing processes. A paradigmatic example of temporal influences is metastasis formation, during which cancer cells undergo sequential metabolic reprogramming according to the specific steps that are involved in the metastatic process, ranging from decreased mitochondrial respiration following early cell detachment [9] to higher mitochondrial oxygen consumption to promote migration and invasion [10,11].

In this review we will address this complexity by explaining how single metabolic alterations might differentially affect the various activities of a tumor.

2. Metabolic contribution to cell proliferation

Normal cells proliferate to sustain their population, and this process is limited to a defined number of replication cycles. Comparatively, cancer cells are able to replicate indefinitely, as they circumvent the checkpoints controlling replication (hence the term neoplasia: new formation) [12]. A complex network of regulation is altered in order to allow cancer cells to proliferate at a high rate even in harsh conditions (*i.e.*, nutrient and oxygen limitation, immune attack). In order to develop this particular set of skills, cancer cells need to alter specific metabolic pathways [13] (Fig. 1).

In order to proliferate, a cancer cell must generate a biomass sufficient to sustain both daughter cells produced during division. Proliferating cells therefore need to gather high levels of lipids, nucleotides and amino acids. Cells can produce this biomass by using precursors and products of the TCA (tricarboxylic acid) cycle. This leads to a situation where more ATP is used and cataplerosis provides a constant outflow of intermediates [14,15]. Indeed, cataplerosis in proliferating cells is observable with the synthesis of lipids that are mainly derived from glucose [13,16]. A constant supply of lipids is indeed necessary for membrane production [13]. In hematopoietic cells, glucose conversion to lipids is regulated by cytokines and the PI3K/AKT signaling pathway. In these cells, IL-3-mediated activation of PI3K/AKT signaling is considered to be necessary and sufficient for the conversion of glucose to lipids [17]. Moreover, citrate originating from mitochondria is an important precursor of lipogenesis in the cytosol.

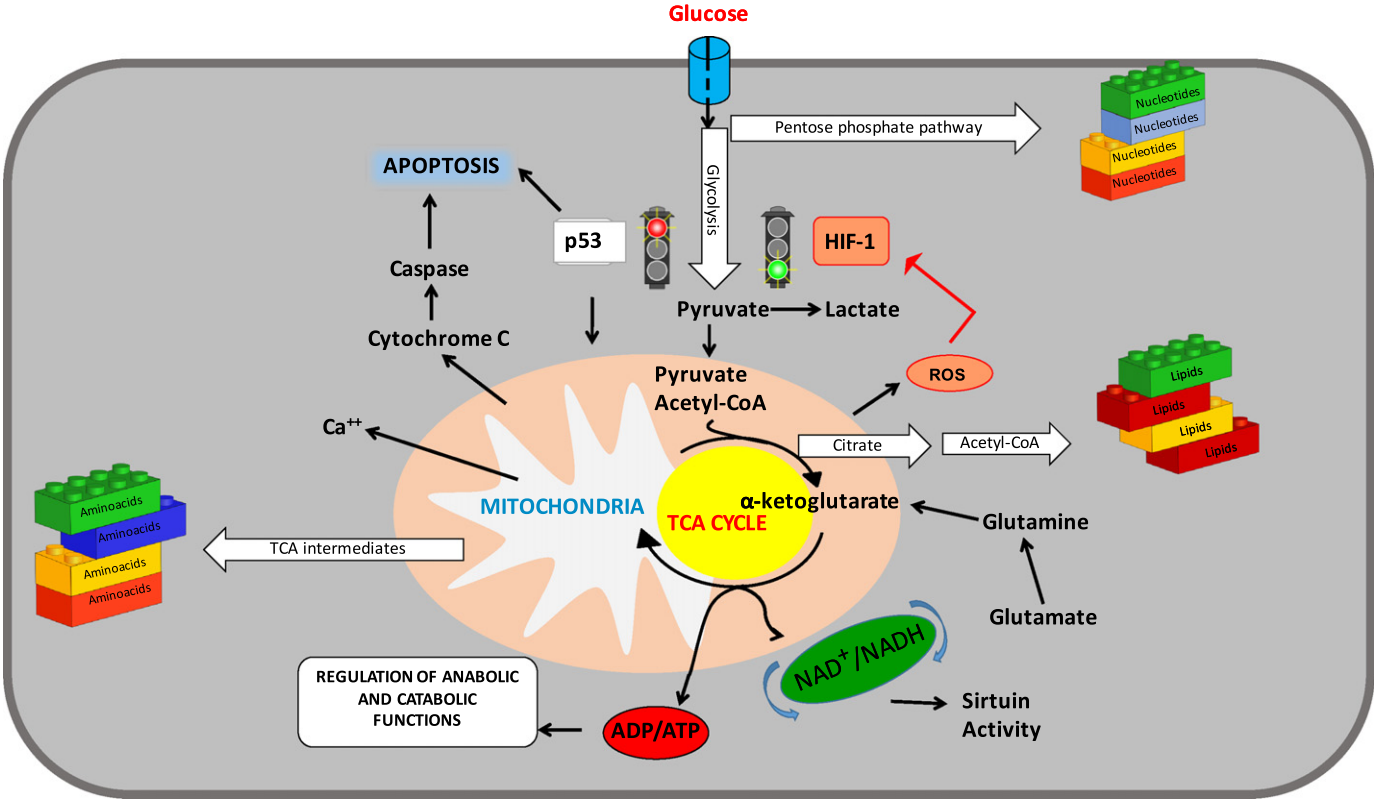

Fig. 1. Simplified version of metabolic pathways leading to the production of metabolic intermediates required for cellular growth. P53 and HIF-1 act as pivotal regulators leading to regulation of glycolysis (positive and negative respectively). Mitochondria stand at the cross-road between energy metabolism and signaling regulation acting both as a cellular "factory" and signalling organelle by regulating the availability of various factors, *e.g.* ROS, Ca^{++}, cytochrome C, ATP and NAD^{+}.