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Review

Emerging concepts in bioenergetics and cancer research: Metabolic flexibility, coupling, symbiosis, switch, oxidative tumors, metabolic remodeling, signaling and bioenergetic therapy

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ABSTRACT

The field of energy metabolism dramatically progressed in the last decade, owing to a large number of cancer studies, as well as fundamental investigations on related transcriptional networks and cellular interactions with the microenvironment. The concept of metabolic flexibility was clarified in studies showing the ability of cancer cells to remodel the biochemical pathways of energy transduction and linked anabolism in response to glucose, glutamine or oxygen deprivation. A clearer understanding of the large-scale bioenergetic impact of C-MYC, MYCN, KRAS and P53 was obtained, along with its modification during the course of tumor development. The metabolic dialog between different types of cancer cells, but also with the stroma, also complexified the understanding of bioenergetics and raised the concepts of metabolic symbiosis and reverse Warburg effect. Signaling studies revealed the role of respiratory chain-derived reactive oxygen species for metabolic remodeling and metastasis development. The discovery of oxidative tumors in human and mice models related to chemoresistance also changed the prevalent view of dysfunctional mitochondria in cancer cells. Likewise, the influence of energy metabolism-derived oncometabolites emerged as a new means of tumor genetic regulation. The knowledge obtained on the multi-site regulation of energy metabolism in tumors was translated to cancer preclinical studies, supported by genetic proof of concept studies targeting LDHA, HK2, PGAM1, or ACLY. Here, we review those different facets of metabolic remodeling in cancer, from its diversity in physiology and pathology, to the search of the genetic determinants, the microenvironmental regulators and pharmacological modulators.

Contents

Abbreviations: ACLY, ATP citrate lyase; AKT, protein kinase B; ATP, adenosine triphosphate; ANT, adenine nucleotide translocator; AMPK, AMP-activated protein kinase; COX, cytochrome c oxidase; EGFR, epidermal growth factor receptor; ERRα, estrogen-related receptor alpha; ETC, electron transfer chain; ETF, electron-flavo-protein; FADH2, flavin adenine dinucleotide; FOXO, forkhead transcription factor; $F_{1,6}$BP, fructose$_{1,6}$-biphosphate; GDH, glutamine dehydrogenase; GSEA, Gene Set Enrichment Analysis; GOT, glutamic-oxaloacetic transaminase; G6P, glucose 6 phosphatex; HIF1α, hypoxia inducible factor 1; HK2, hexokinase 2; HNF4a, hepatocyte nuclear growth factor a; KEGG, Kyoto Encyclopedia of Genes and Genomes; LDHA, lactate dehydrogenase isoform A; LKB1, liver kinase B1; mTORC, mammalian target of rapamycin complex; MMTV, Mouse mammary tumor virus; NADH, nicotinamide dinucleotide; NMR, nuclear magnetic resonance; NSSN, nutrient-sensing signaling network; OXPHOS, oxidative phosphorylation; OPA1, optic atrophy protein 1; PGAM1, phosphoglyceric acid mutase; PDH, pyruvate dehydrogenase; PGC1α, peroxisome proliferator-activated receptor-gamma coactivator; PKM2, pyruvate kinase M2 isoform; PPARs, peroxisome proliferator-activated receptors; PSPs, pathway switching proteins; PDK1, pyruvate dehydrogenase kinase 1; PTEN, phosphatase and TENsin homolog; PI3K, phosphoinositide 3-kinase; RHEB, Ras homolog enriched in brain; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding transcription factor; SCO2, cytochrome c oxidase assembly protein; TIGAR, TP53-inducible glycolysis and apoptosis regulator; TP53, tumor protein p53; UCP, uncoupling protein.

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1. Introduction

The basic principles of energy metabolism regulation were deciphered in the late 50s with the pioneering work of Warburg, Lenhinger, Krebs, Chance, Petersen, Weinhouse, and Vaupel among several others (Scheffler, 1999; Weinhouse, 1956). The regulation of controlling enzymes belonging to glycolysis, the pyruvate dehydrogenase complex (PDH) and Krebs cycle, all involved in ATP synthesis mostly occurs by metabolic intermediates as ATP itself, citrate, fructose$_{1,6}$-bisphosphate ($F_{1,6}$-BP), and inorganic phosphate (Pi). Another level of regulation of mitochondrial energy fluxes (ATP synthesis and respiration) was identified by Chance and Williams in the 50s with the so-called 'respiratory control' by ADP (Chance and Williams, 1955, 1956). Thereafter, a large number of additional molecular regulations of oxidative phosphorylation (OXPHOS) were identified, as the recently discovered OPA1 dependent-stabilization of the respiratory supercomplexes (Cogliati et al., 2013), the ATP-synthase dependent assembly of complex III (Ostojić et al., 2013), the energy-state dependent RHEB-induced control of mitochondrial turnover (Melser et al., 2013) and the regulation of respiratory chain complexes by acetylation (Finley et al., 2011) and glutathionylation (Mailloux et al., 2014). Consideration of the numerous means to regulate ATP transduction in the cell led to the notion of a 'multi-step control' of energy metabolism (Benard et al., 2010). More recently, the regulation of energy metabolism was closely linked, in a mutual way, with the control of cell growth and division. For instance, a signaling pathway central to cell biology and governed by the hypoxia-inducible factor 1 alpha (HiF1α) transcription factor, was shown to mediate a shift in respiratory chain complex IV subunit 4 (Fukuda et al., 2007). Conversely, succinate accumulation in the cytosol can inhibit HiF1α degradation and promote its stabilization (Pollard et al., 2005). Likewise, the AMP-activated protein kinase (AMPK) pathway stimulates the expression of several OXPHOS proteins when ATP needs are increased, as initiated by a higher ADP/ATP ratio in the cytosol (Hardie et al., 2003). Another central pathway in the control of energy metabolism is the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) pathway, a transcription co-activator, which participates in OXPHOS stimulation in cooperation with the estrogen-related receptor alpha (ERRα), or to the induction of gluconeogenesis in cooperation with the hepatocyte nuclear factor 4 alpha (HNFAa) (Lustig et al., 2011). The RAS protein, involved in the control of cell mitogenic activities, also controls OXPHOS, both in cancer and non-cancer tissues (Wei et al., 2012; Palorini et al., 2013; Gough et al., 2009; Telang et al., 2007). A role in the modulation of OXPHOS capacity was also discovered for MYC and for p53, both of which play central functions in the control of cell growth and division, leading to the emerging concept of oncobioenergetics (Jose et al., 2013). The communication between mitochondria and the nucleus was defined as the retrograde response, suggesting that changes in mitochondrial physiology can induce specific gene expression. This was shown in the context of respiratory chain deficiency, where the retrograde activation of mitochondrial biogenesis was observed through the activation of a nitric-oxide dependent mechanism (Benard et al., 2012). Central to this review article, a new layer of upper- or meta-regulation of energy metabolism was recently identified with the discovery of rewiring of metabolic circuits, governed by genetic determinants connected or not with changes in cell microenvironment. In particular, this upper level of bioenergetic control links catabolism with anabolism, thereby providing a more integrated view of cell metabolic plasticity. Prior to discussing the molecular bases and the physiology of metabolic remodeling, we provide below a rapid overview of cellular bioenergetics.

In most human tissues, mitochondria provide the energy necessary for cell growth, and biological activities. It has been estimated that about 90% of mammalian oxygen consumption is mitochondrial, which primarily serves to synthesize ATP, although in variable levels according to the tissue considered and its activity status. Mitochondria intervene in the ultimate phase of cellular catabolism, following the enzymatic reactions of intermediate metabolism that degrade carbohydrates, fats and proteins into smaller molecules such as pyruvate, fatty acids and amino acids, respectively (Fig. 1). Mitochondria further transform these pro-energetic elements into NADH and/or $FADH_2$, through β-oxidation and the Krebs cycle. Those reduced equivalents are then degraded by the mitochondrial respiratory chain in a global energy converting process (OXPHOS) where the electrons liberated by the oxidation of NADH and $FADH_2$ are passed along a series of carriers regrouped under the name of "respiratory chain" or "electron transport chain" (ETC), and ultimately transferred to molecular oxygen (Fig. 2). ETC is located in mitochondrial inner membrane, with an enrichment in the cristae. ETC consists of four enzyme complexes (complexes I–IV), and two mobile electron carriers (coenzyme Q and cytochrome c). These complexes are composed of numerous subunits encoded by nuclear and mitochondrial genes, at the exception of complex II (nuclear only). It was demonstrated that these complexes assemble into supramolecular assemblies called "supercomplexes" or respirasome (Schägger and Pfeiffer, 2000; Schagger, 2001). It is still debated whether some complexes, as complex I, can be found alone or if all are embedded in supercomplexes. In addition to the classic ETC components, other proteins are involved in the oxidation of nutrient-derived reduced equivalents and the subsequent reduction of coenzyme Q, used for ultimate ATP synthesis. This is the case for the electron-flavo-protein (ETF) system, composed of the $ETF_{A/B}$ and the ETF-QO proteins, which connect fatty-acid oxidation with coenzyme Q reduction. The glycerol-3-phosphate dehydrogenase, which oxidizes cytosolic NADH to reduce mitochondrial FAD also supports oxidative phosphorylation and participates to REDOX homeostasis. Lastly, the NADH-shuttling system, as the malate-aspartate shuttle also fuels OXPHOS and supports REDOX homeostasis *via* the delivery of cytosolic NADH to the mitochondrial matrix. The oxidation of NADH or $FADH_2$ by complex I or complex II, respectively, triggers the transfer of electrons from complex I (or II) to complex IV and mediates the extrusion of protons from the matrix to the inter-membrane space, thus generating an electrochemical gradient of protons ($\Delta\tilde{u}_H^+$) which is finally used by the F_1F_0 ATP synthase (*i.e.*, complex V) to produce adenosine triphosphate (ATP), the main energetic currency of the cell. This gradient has two components: an electric potential ($\Delta\Psi$) and a chemical potential ($\Delta\mu_H^+$) that can also be expressed as a pH gradient (ΔpH). According to the chemiosmotic theory proposed by Peter Mitchell in 1961 (Mitchell, 1961), $\Delta\tilde{u}_H^+ = \Delta\Psi - Z\Delta$pH, with $Z = -2.303\,RT/F$.

Under physiological conditions, mitochondrial energy production can alternate between two energy steady-states: basically, at state 4 (also denominated the "leak respiration state"), respiration is slow and ATP is not produced ($\Delta\Psi$ is high), while during state 3, respiration is rapid and ATP is largely produced ($\Delta\Psi$ is lower). However, it should be stated that the definition of state 3