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Review

Metabolic reprogramming of carcinoma-associated fibroblasts and its impact on metabolic heterogeneity of tumors

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ABSTRACT

Tumor metabolism is characterized with up-regulated glucose uptake and glycolytic rate of tumor cells as the source of ATP and tumors growth, and regulated by a poorly defined combination of cell-intrinsic and extrinsic factors. Metabolic heterogeneity of human tumors is dependent upon the mutational status of specific oncogenes and influenced by tumor microenvironment. Carcinoma-associated fibroblasts (CAFs) adapt in a dynamic manner to the metabolic needs of cancer cells, associated with tumorigenesis and resistance to treatments. Importantly, CAFs could directly "feed" cancer cells essential nutrients and energy-rich metabolites, including lactate, ketone bodies, fatty acids, glutamine, and other amino acids through the induction of autophagy in a host-parasite pattern, to contribute to tumor growth and metastasis. To define the reciprocal metabolic interplay between CAFs and cancer cells will provide a better understanding of molecular mechanisms by which the treatment resistance occurs,and aid in the rational design of metabolism-based approaches to enhance the efficacy of immunotherapy.

Contents

1. Introduction

Tumor heterogeneity demonstrates the differentiation or variation of cell morphology, gene expression and sequence, metabolism, motility, proliferation, or metastatic potential, and contributes to low responses to therapies and to the development of drug resistance [1–3]. Of those, metabolic alterations are associated with the property of tumor tissues [4,5]. Increased glucose uptake and fermentation of glucose to lactate are commonly considered as a phenomenon and feature of altered metabolism, even in the presence of full-functioning mitochondria, and as the 'Warburg Effect' [6]. The *in vivo* microenvironment was suggested to reflect the metabolic phenotype of lung tumors, since the anatomy, cellularity, perfusion, and metabolism of tumors were monitored in patients with non-small cell lung cancer(NSCLC), using multi-parametric nuclear magnetic resonance imaging and positron emission tomography complemented by metabolomics profiling [7]. The levels of glucose oxidation elevated tumors. When the cell microenvironment changes to induce high ATP demand by altering the ATP-dependent membrane pumps, aerobic glycolysis increased rapidly, while oxidative phosphorylation remained constant [8]. Metabolic changes could support abnormal survival and growth of

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malignant cells by providing energy, macromolecular precursors, and reducing equivalents [9].

The regulation of tumor metabolism by the combination of cell-intrinsic and cell-extrinsic factors remains unclear. Oncogenic transcription factor-MYC may contribute to reprogram the nutrient utilization and drive cell-autonomous metabolism, at least partially, by the onco-genotype [5,10,11]. MYC could direct the expression of glycolytic genes, such as glucose transporter 1 (GLUT1), lactate dehydrogenase A, pyruvate kinase isozymesM2 (PKM2), hexokinase 2, or glutaminase and glutamine transporters (e.g. SLC3a2, SLC5A1, or SLC7A1) [10–13]. The intracellular metabolism can be also affected by the microenvironment where cancer cells grow. Glycolysis and glucose oxidation increased in tumors irrespective of the cancer subtype, grade, or oncogenic driver mutations [14], suggesting that the tumor microenvironment may be a better predictor for metabolic behavior than the genetic profile of cancer cells per se.

Carcinoma-associated fibroblasts (CAFs) are identified by expressions of vimentin, α-smooth muscle actin, and fibroblast activation protein, with an activated, highly contractile, myofibroblastic phenotype [15,16]. CAFs can be accumulated in tumor microenvironment and correlated with poor prognosis in a number of tumors. Recent study demonstrated that CAFs could launch metabolic reprogramming in tumor microenvironment to support cancer cell growth and metastatic dissemination [17]. Metabolic alterations of CAFs can be an important enhancer of tumorigenesis which should be more flexible to adapt to alterations of intra- or extra-cellular microenvironments in addition to cancer treatments. The present article aims to overview the importance of tumor metabolic heterogeneities, define roles of CAFs metabolic reprogramming in the formation of special characteristics and functions of cancer cells, investigate the potential of metabolic heterogeneity in the development of combined therapies, and explore molecular mechanisms by which tumor heterogeneity influences therapeutic efficacy and outcome.

2. Genetic lesions-induced metabolic heterogeneity in tumors

Metabolic profiles of tumor depend on responsible genetic lesions and tissue types. Genetic lesion–induced metabolic reprogramming of tumor cells was proposed to be an early event in oncogenesis that is an immediate consequence of an initial oncogenic mutation, and could occur even before cell invasion, e.g. in benign or early-stage lesions [18]. Glycolysis was shown to be associated with activated oncogenes (e.g. RAS and MYC) and mutant tumor suppressors (e.g. p53) [19]. Oncogenic MYC regulates the expression and activity of glycolytic enzymes, the TCA cycle, mitochondrial respiration and nucleotide synthesis, or glutamine transporters and glutaminase, the first enzyme of glutamine catabolism. The binding of hepatocyte growth factor/scatter factor with its tyrosine kinase receptor MET regulate carbohydrate metabolism and activate PI3K/AKT and RAS/MAPK signaling pathways, acting as regulators of cellular metabolism. β-catenin a central player in the Wnt pathway regulates genes of glutamine synthesis and glycolysis or mitochondrial activity. Understanding of molecular mechanisms by which the expression of oncogenes influences metabolic changes will benefit to define metabolic phenotypes and heterogeneities among tumors with distinct oncogenic lesions.

Even carrying same oncogenic lesions, regulatory effects of oncogenes on metabolic profiles are dependent upon the origin of tissue. Yuneva et al. [18] report that MYC-induced mouse liver tumors significantly increase both glucose and glutamine catabolism associated with decreased levels of glutamine synthetase (Glul) and the switch from Gls2 to Gls1glutaminase. On the other hand, MYC-induced lung tumors display increased expression of Glul and Gls1 and accumulated glutamine. It indicates that genetic factors and tissue origin are critical to design targeted therapy to tumor metabolism.

Mutant suppressors (e.g. p53) play important roles in metabolic alterations during tumorigenesis, of which the loss enhances glycolysis and anabolic synthesis from glycolytic intermediates (citrate,etc.) [19]. Such shift is able to match the tumor cell functional demands such as growth and rapid proliferation. The anti-diabetic drug metformin, an inhibitor of complex 1 in the mitochondrial electron transport chain, could block melanoma invasion and metastasis development mainly through activation of adenosine 5′-monophosphate-activated protein kinase (AMPK) and tumor suppressor protein p53 [20,21]. The liver kinase B1(LKB1) tumor suppressor is mutationally activated in about 80% of NSCLC, to activate the energy-sensing kinase AMPK and make cells more sensitive to metabolic stress. Phenformin is a mitochondrial inhibitor and analog of the diabetes therapeutic metformin, and selectively induces apoptosis in LKB1-deficient NSCLC cells [22]. Thus, oncogenes and mutant tumor suppressors may synergistically drive anabolic reprogramming and cell proliferation during tumorgenesis simultaneously. The cancer metabolism-based therapies can be an alternative for cancer treatment.

Recently, mitochondria was proposed as an critical target for the next generation of cancer therapeutics, since mitochondrial function during tumorigenesis is closely related with oncogene/suppressor genes mutations [23]. RAS is mutated in up to 30% of cancers and over-expressed to increase mitochondrial fragmentations through activation of the MAPK pathway. The knockdown of the mitochondrial fission-mediated GTPase Drp1 could inhibit tumor growth [24,25]. Such fission is driven by Erk2-mediated phosphorylation of Drp1 on Serine 616, and both the phosphorylation and mitochondrial fragmentation are increased in human pancreatic cancer [25]. Drp1(S616) phosphorylation is sufficient to phenocopy transformation-induced mitochondrial dysfunction, and dichotomizes BRAF(WT) from BRAF(V600E)-positive lesions [24]. Therefore, it is important to address and clarify routes of bioenergetic plasticity from mitochondria in cancer therapeutics and to understand the downstream of biological processes that underlie the protumorigenic activity to overcome the difficulty to directly target oncogene/suppressor genes.

3. 3The metabolic crosstalk between CAFs and cancer cells

The reciprocal interactions between cancer cells and CAFs are one of the most important metabolic crosstalk in tumor microenvironment, although the exact mechanisms remain unclear. Fibroblasts in healthy tissues are quiescent or resting with negligible metabolic activity and become activated in response to challenge [26]. CAFs are induced by cytokines produced from tumor cells. For example, hepatocellular carcinoma cells secreted lysophostatidic acid to promote trans-differentiation of Peritumoral fibroblasts to CAF phenotypes [27]. CAFs-associated metabolic reprogramming can facilitate the progression of tumor malignancy by secreting extracellular matrix proteins and providing energetic supports. CAFs actively participate the complex metabolism of tumors by providing building cell blocks, rather than act as metabolic synergistic bystanders of cancer cells. The metabolic reprogramming occurs in CAFs through activation of the transforming growth factor-β (TGF-β) pathway, with increased oxidative stress, autophagy/mitophagy, and down regulation of caveolin-1(Cav-1), to promote mitochondrial activity of adjacent cancer cells [28]. The expression of Cav-1 can inhibit cell proliferation and cell cycle progression in normal fibroblasts. A catabolic