Review

Clinical Cancer Research

The Fundamental Role of the p53 Pathway in Tumor Metabolism and Its Implication in Tumor Therapy

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Abstract

It is well established that the altered metabolism exhibited by cancer cells, including high rates of glycolysis, lactate production, and biosynthesis of lipids, nucleotides, and other macromolecules, and which may occur either as a consequence or as a cause of tumorigenesis, plays an essential role in cancer progression. Recently, the tumor suppressor p53 was found to play a central role in this process. Here, we review the role of p53 in modulating tumor metabolism. Specifically, we focus on the functions of p53 in regulating aerobic glycolysis, oxidative phosphorylation, the pentose phosphate pathway, fatty acid synthesis and oxidation, and glutamine metabolism, and we discuss the therapeutic strategy whereby p53 helps to prevent malignant progression. *Clin Cancer Res; 18(6); 1561–7. ©2012 AACR.*

Introduction

The rapid proliferation of tumors consumes large quantities of bioenergy and biomaterials, which drive metabolic reprogramming to maintain tumor malignant behavior. The first alteration in tumor metabolism was discovered by the Nobel Prize winner Otto Warburg in the 1920s. He found that cancer cells preferentially metabolize glucose by glycolysis, even in the presence of ample oxygen. Compared with mitochondrial respiration, glycolysis is a less efficient pathway for producing ATP (1). In addition to aerobic glycolysis, another major pathway of glucose metabolism, the pentose phosphate pathway (PPP), is enhanced in tumor cells (2). Furthermore, both fatty acid metabolism and glutamine metabolism are also altered during tumor development (3, 4). During the course of tumor metabolic reprogramming, oncogene activation and tumor suppressor gene inactivation cause alterations to multiple intracellular signaling pathways that affect tumor cell metabolism (5, 6).

p53 is one of the most highly studied tumor suppressor genes in the field of cancer research (7). The tumor suppressive function of p53 is mainly attributed to dual mechanisms; p53 can either promote the repair and survival of damage cells or promote the permanent removal of irreparable damage cells through apoptosis or autophagy (8–10). These cellular processes are ascribed to the fact that p53 is a nuclear transcription factor that regulates the transcription of numerous target genes. p53 activation at the early stage of cellular stresses, such as DNA damage, can promote G_1-phase cell-cycle arrest and DNA repair through transactivation of p21WAF1, p53R2, and GADD45 (11). After DNA lesions are repaired, cells can then reenter the normal cell cycle. In this way, p53 is able to maintain genomic integrity to prevent tumor occurrence and development. Alternatively, p53 may exert its proapoptotic function, leading to the removal of cells with extensive and irreparable DNA damage. For this role, p53 can activate transcription of various proapoptotic genes, including those genes encoding the BH-3–only proteins Bax, Noxa, and Puma (12–14), which promote apoptosis. Furthermore, p53 can also trigger apoptosis by the transcriptional repression of the antiapoptotic gene survivin (15). Thus, complex regulation by p53 can prevent tumor initiation and progression.

Recent observations show that many tumor suppressor genes play important roles in metabolic regulation, in addition to their established roles in cell survival and apoptosis. As p53 is the most frequently mutated tumor suppressor gene in human cancers, its function is relatively well characterized; thus, it was the first tumor suppressor that was recognized to regulate tumor metabolism. In this review, we focus on the metabolic functions of the p53 tumor suppressor gene and on p53-related therapeutic strategies. We discuss how the p53 tumor suppressor influences the tumor metabolic phenotype and bioenergetic and biosynthetic processes to repress tumor growth and proliferation, and we also discuss potential metabolic targets for tumor treatment.

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doi: 10.1158/1078-0432.CCR-11-3040

Translational Relevance

The tumor suppressor p53 is one of the most highly studied in the field of cancer research because of its role in tumor cell survival and apoptosis. However, tumor metabolic reprogramming fuels cancer cell malignant growth and proliferation. In this review, we systematically document the mechanisms of p53 in tumor metabolism regulation. We analyze the therapeutic strategy whereby p53 helps to prevent tumor malignant metabolic phenotype and bioenergetic and biosynthetic processes, and how blocking the reprogramming of tumor metabolism will provide new strategies for tumor therapy.

p53 and Tumor Glucose Catabolism: The Glycolysis Pathway

Cancer cells are characterized by aerobic glycolysis with the use of glucose and production of lactate. Several biologic functions of p53 decrease the glycolysis pathway in cells. In the third step in glycolysis, 6-phosphofructo-1-kinase (PFK-1), which acts as a key rate-limiting enzyme, converts fructose-6-phosphate to fructose-1,6-bisphosphate. p53 induces TP53-induced glycolysis and apoptosis regulator (*TIGAR*) expression via transcriptional activation. The TIGAR protein has sequence similarity with the bisphosphatase domain of the bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK-2/FBPase-2) and can dephosphorylate fructose-2,6-bisphosphate (Fru-2,6-P_2), thereby lowering the intracellular level of this metabolite. As Fru-2,6-P_2 is the most potent activator of PFK-1, a p53-dependent reduction in Fru-2,6-P_2 levels mediated by TIGAR results in glycolysis inhibition (5, 16). A second p53 metabolic effector is phosphoglycerate mutase (PGM), which converts 3-phosphoglycerate to 2-phosphoglycerate at a later step in glycolysis. Wild-type p53 downregulates PGM, and mutation of p53 can enhance PGM activity and glycolytic flux. Thus, p53-dependent downregulation of PGM expression and activity can inhibit the glycolysis pathway (17, 18). However, p53 is also a transcriptional activator of the muscle-specific *PGM* gene and involved in myocyte differentiation (19). It seems likely that the pathways that regulate the enzymes involved in glycolysis are different in species and tissues.

In addition to inhibition of glycolytic enzyme reactions via TIGAR and PGM, p53 can reduce intracellular glucose levels by inhibiting the expression of glucose transporters. For example, p53 directly represses the transcriptional activity of the *GLUT1* and *GLUT4* gene promoters (20). In addition, p53 represses *GLUT3* gene expression indirectly by preventing activation of the inhibitor of κB kinase (IKK)–NF-κB pathway (21, 22). Therefore, p53 recovery and activation in tumor cells can attenuate aerobic glycolysis by reducing glucose uptake through the glucose transporters.

However, this inhibitory function of p53 in tumor glycolysis is contradicted by other studies that show an opposing activity. It was reported that, at least under some circumstances, p53 can significantly activate the type II hexokinase promoter leading to increased expression of type II hexokinase, which facilitates a high rate of glycolysis (23). Although this p53 activity may increase the survival of tumor cells under this circumstance (6), the complex p53-dependent mechanisms that regulate glycolysis need further investigation (Fig. 1).

p53 and Tumor Glucose Catabolism: Mitochondrial Respiration

Warburg described how cancer cells preferentially use glycolytic pathways for energy generation while downregulating mitochondrial respiration; one reason he proposed is that cancer cells have irreversible damage to mitochondrial oxidative phosphorylation. Interestingly, the key component involved in oxidative phosphorylation is the synthesis of cytochrome c oxidase 2 (SCO2), which can be directly transactivated by p53. SCO2 is required for the assembly of mitochondrial DNA-encoded cytochrome c oxidase (COX) II subunit into the COX complex of the mitochondrial electron transport chain, where it is the site of mitochondrial oxidative phosphorylation in mammalian cells. Therefore, disruption of SCO2 with p53 in human cancer cells aggravated the metabolic switch to glycolysis, and activation of p53 could increase SCO2 expression and, thereby, stimulate mitochondrial respiration and ATP production (24, 25). In addition to participating in the assembly of the COX II subunit via SCO2, p53 is also involved in the posttranscriptional regulation of the COX II subunit and, therefore, contributes to the stability of COX II protein and the structural integrity of mitochondria (26). Furthermore, p53 can directly upregulate the gene encoding the COX I subunit of the COX complex in colon cancer cells (27), which may contribute to the maintenance of mitochondrial cytochrome c oxidase, the complex IV in the electron transport chain. Finally, p53 can transcriptionally activate the apoptosis-inducing factor (AIF) to maintain the integrity of complex I in the mitochondrial electron transport chain (28–30). Thus, through maintaining the mitochondrial respiratory chain, p53 plays an important role in enhancing mitochondrial oxidative phosphorylation in cancer cells.

In addition, activation of p53 can enhance the mitochondrial tricarboxylic acid (TCA) cycle rate. Glutaminase 2 (GLS2) can be directly transactivated by p53 and can, therefore, mediate p53-dependent regulation of cellular energy metabolism. GLS2 encodes a mitochondrial glutaminase that catalyzes the hydrolysis of glutamine to glutamate, and deamination of glutamate generates α-ketoglutarate, which is a key intermediate in the TCA cycle. Thus, GLS2 mediates the role of p53 in regulating

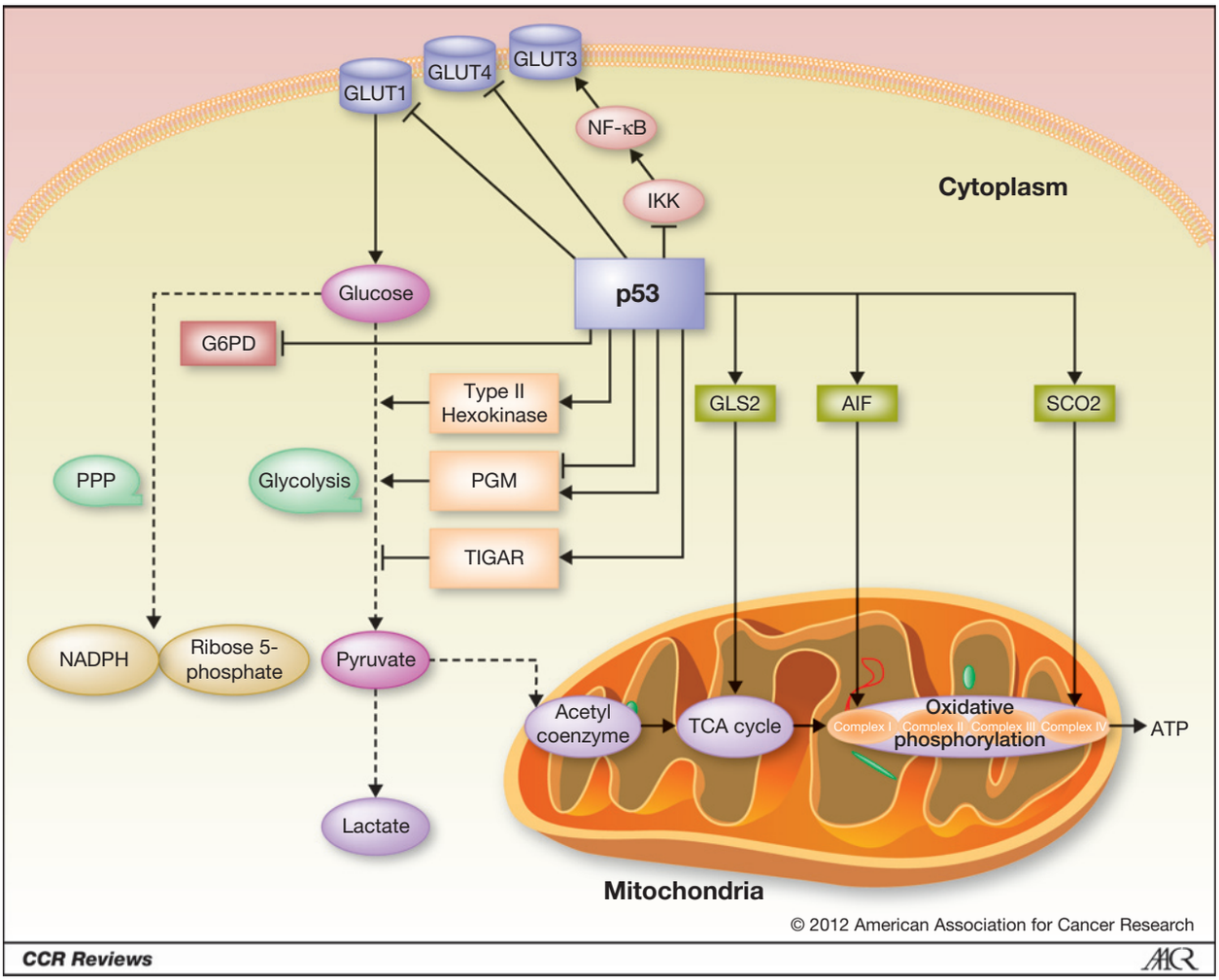

Figure 1. p53 regulates glucose catabolism in cancer cells. Several metabolic effectors of p53, such as TIGAR, PGM, GLUT1/4, IKK, hexokinase, SCO2, AIF, GLS2, and G6PD, are involved in glucose metabolic processes and inhibit the glycolytic pathway and PPP, while enhancing mitochondrial respiration. See text for details.

the mitochondrial TCA cycle and, thus, in regulating mitochondrial respiration (4, 31). Another potentially significant role is that p53 physically interacts with mitochondrial transcription factor A to maintain mitochondrial DNA and regulate apoptosis; the impact of this interaction on mitochondrial respiration needs to be further investigated (32). Interestingly, failure of DNA repair in the $ATM^{+/-}$ mice impairs p53 activity and results in mitochondrial dysfunction, and $p53^{-/-}$ mice also display impaired mitochondrial biogenesis and respiration in mixed muscle (33, 34). Therefore, p53 may have several intricate roles to promote mitochondrial respiration (Fig. 1).

p53 and Tumor Glucose Catabolism: The Pentose Phosphate Pathway

PPP is important for both glucose catabolism and biosynthesis: PPP can generate NADPH and ribose 5-phosphate, the essential precursors of nucleotides. The p53 tumor suppressor inhibits PPP, thereby suppressing glucose consumption and the production of NADPH and ribose 5-phosphate. The tumor suppressor p53 binds to glucose-6-phosphate dehydrogenase (G6PD), the unique and rate-limiting enzyme of the PPP, and inhibits the activity of G6PD. Therefore, the enhanced PPP glucose flux may direct glucose toward ribose 5-phosphate and NADPH biosynthesis when p53 mutates in many human tumor cells (Fig. 1; refs. 2, 35).

p53 and Tumor Fatty Acid Metabolism

In addition to aerobic glycolysis, increasing *de novo* synthesis of fatty acids is another characteristic of tumor metabolism, which is essential for liquid synthesis and protein modification (36–38). Acetyl-CoA carboxylase (ACC), the key rate-limiting enzyme catalyzing *de novo* fatty acid synthesis from acetyl-CoA, is phosphorylated

and inactivated by AMP-activated protein kinase (AMPK; ref. 39). AMPK is a heterotrimeric enzyme complex consisting of a catalytic subunit (α) and 2 regulatory subunits (β and γ) that maintains cellular energy homeostasis. AMPK β subunit is transcriptionally induced by p53, leading to increased AMPK β expression (40). Therefore, p53 upregulates AMPK expression to inactivate ACC and, thereby, inhibits *de novo* fatty acids synthesis.

The tumor microenvironment is characterized by chronic hypoxia, as well as deprivation of nutrients, such as glucose (41). When glucose is unavailable, fatty acid oxidation is the preferred alternative pathway used to generate energy (42). The increased fatty acid oxidation in response to glucose deprivation requires p53 and its transcriptional target gene guanidinoacetate methyltransferase (*GAMT*), which encodes an essential enzyme involved in creatine synthesis. The GAMT metabolite creatine could increase fatty acid oxidation by AMPK phosphorylation and activation, associated with ACC inactivation and decreased *de novo* fatty acids synthesis (43). In addition, fatty acid oxidation is connected to the TCA cycle by converting acyl-CoA to acetyl-CoA, contributing to the maintenance of oxidative phosphorylation. Further, increased fatty acid oxidation can also inhibit glycolysis (44, 45). Thus, it might be that p53 modulates both fatty acid anabolism and catabolism to maintain cellular energy levels (Fig. 2).

Current Strategies to Target the p53 Pathway in Tumor Metabolism

In tumor cells, the p53 pathway is often disrupted. Therefore, recovering the function of wild-type p53 and its targets in tumor cells is a key therapeutic objective. In head and neck cancer, p53 mutations are frequent, and the incidence of p53 mutations increases with progression of head and neck cancer (46, 47). Therefore, a recombinant human adenovirus that expresses functional wild-type p53 has been approved by the Chinese government for the treatment of head and neck carcinoma (48–50). Treatments showed that antitumor efficacy was associated with the expression and activity of functional p53, and adverse effects were also significant (51–54). Recently, pharmacologically activated wild-type p53 by small-molecule compound RITA is

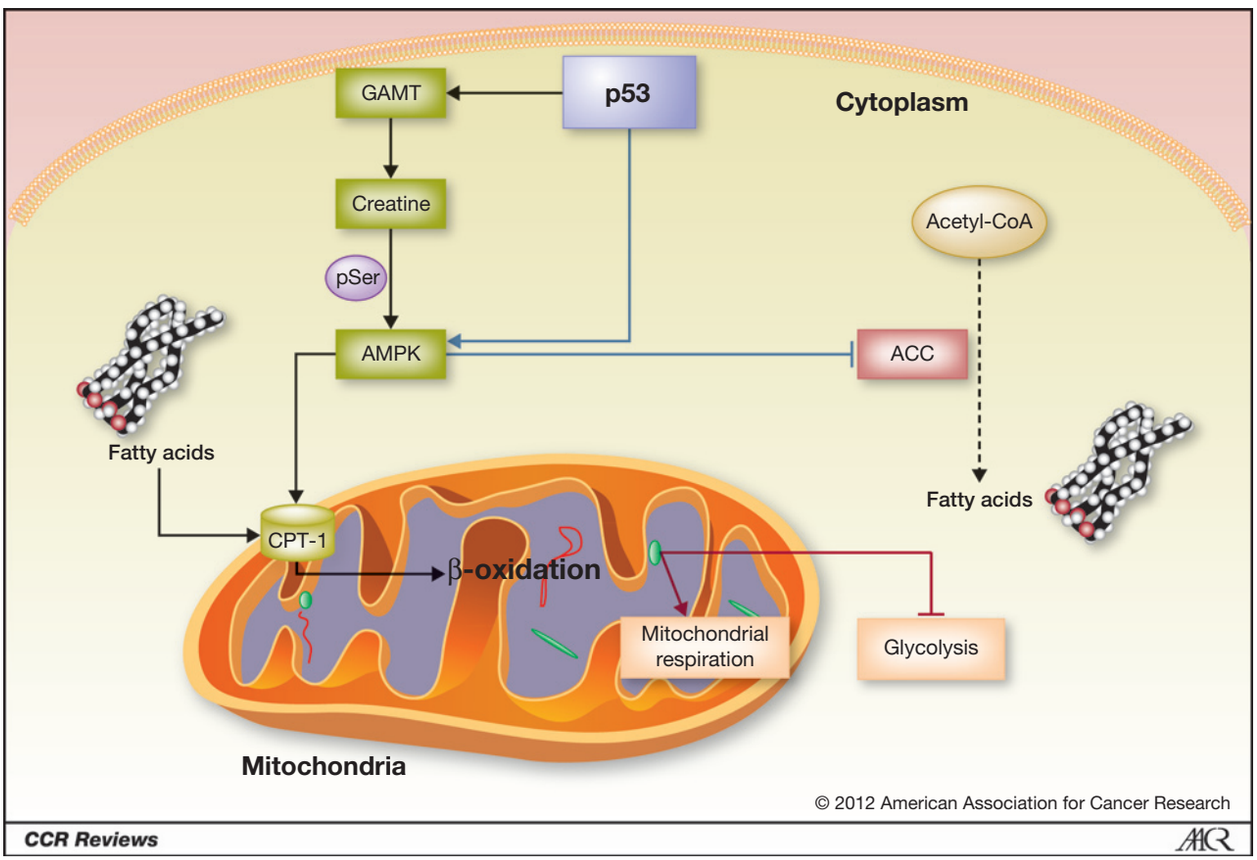

Figure 2. p53 regulates fatty acid metabolism in cancer cells. p53 regulation in fatty acid anabolism and catabolism is partially mediated by the activation of AMPK. p53 upregulates AMPK expression to inactivation of ACC and, thereby, inhibits *de novo* fatty acid synthesis. In addition, p53 increases fatty acid oxidation by promoting AMPK expression and activation.

reported to inhibit glycolytic enzymes and, therefore, induce robust apoptosis in cancer cells (55). In addition, enhancement of p53 protein stability is also a target in restoring wild-type p53 activity in cancer cells. The protein level of wild-type p53 is regulated by HDM2 ubiquitin ligase, which targets p53 for degradation via ubiquitylation (56, 57). Therefore, HDM2 inhibitors HLI98 and Nutlin 3A can, respectively, stabilize p53 and rescue tumor suppression function in cancer cells (58, 59). Unfortunately, this approach carries the risk of enhancing the prosurvival adaptation functions of p53 in some tumors (60, 61), clarifying the mechanism by which p53 coordinates adaptation could lead to the discovery of new therapeutic targets in cancer expressing wild-type p53.

Tumor metabolic alterations meet the bioenergetic and biosynthetic demands of increased cell proliferation, and targeting tumor metabolism may become part of tumor therapy. Thus, drugs that mimic the metabolic effect of p53 are able to perturb cancer cell metabolism and inhibit cancer cell proliferation. Because tumor cells rely on glycolysis for ATP production for their survival, the molecular targets of p53 in the glycolytic pathway might be potential therapeutic targets in cancer. Indeed, the nonmetabolizable glucose analogues 2-deoxyglucose or 3-bromopyruvate can inhibit glycolysis and ATP production (62, 63). Moreover, the glucose transporter inhibitor phloretin inhibits glucose uptake and sensitizes tumor cells to the chemotherapeutic drug daunorubicin (64). As p53 repression of GLUT3 expression is mediated by the IKK–NF-κB pathway, inhibition of the activation of the IKK–NF-κB pathway can, thereby, be another target for cancer treatment. *R*-roscovitine has been shown to inhibit the function of IKK and downregulate NF-κB activation. In addition to the NF-κB pathway, the cyclin-dependent kinase inhibitor roscovitine can also dramatically enhance the expression of p53 and block the degradation of p53 mediated by MDM2, thereby activating the p53 pathway and inhibiting glycolysis in tumors (65–67).

Silencing of mitochondria is another characteristic feature of tumor cells. Hence, mimicking the metabolic effect of p53 to maintain the mitochondrial respiration chain and shifting energy production from glycolysis to mitochondrial respiration might be a therapeutic strategy for cancer. Overexpression of the Friedreich ataxia-associated protein, frataxin, promotes mitochondrial oxidative metabolism in colon cancer cells via stimulation of the synthesis of the Fe-S clusters that maintain the integrity of complexes in the mitochondrial electron transport chain. Through stimulation of mitochondrial activity, frataxin inhibited colony formation and suppressed tumor formation in nude mice (68, 69). Thus, the induction of mitochondrial energy conversion is a potential therapeutic approach in cancer. In addition, mitochondrial uncoupling contributes to the dysfunction of wild-type p53 and metabolic reprogramming of cancer cells. Therefore, inhibition of mitochondrial uncoupling by selective inhibitors or some other ways may help restore the functions of p53 to inhibit aerobic glycolysis and provide novel targets for anticancer therapy (70, 71).

In the course of fatty acid metabolism regulated by p53, AMPK is a key factor linking fatty acid synthesis and oxidation. The activation of AMPK induces fatty acid oxidation and mitochondrial respiration and represses fatty acid synthesis and glycolysis. Thus, AMPK may be a beneficial target for cancer treatment. Recent studies support this finding, showing that pharmacologic AMPK activators, such as metformin, phenformin, and AICAR, attenuate cancer cell growth and inhibit tumorigenesis in animal models (72, 73). Therefore, recovering the activity of or mimicking the metabolic effect of p53 is a potential strategy in cancer therapy.

Conclusions

The proliferation of malignant cancer cells requires nutrients, energy, and biosynthetic activity. Therefore, metabolic reprogramming fuels cancer cell malignant growth and proliferation. Mutation and inactivation of tumor suppressor genes contribute not only to cancer initiation, proliferation, and progression but also to metabolic reprogramming in cancer cells. This review summarizes the current state of the tumor suppressor gene p53 in tumor metabolism, especially its role in tumor glucose catabolism and fatty acid metabolism, and highlights therapeutic strategies targeting the p53 pathway in tumor metabolism. In general, p53 suppresses aerobic glycolysis, while enhancing mitochondrial respiration. In addition, p53 also suppresses the biosynthetic PPP, thereby inhibiting the synthesis of nucleotides and lipids in tumor cells. Moreover, p53 promotes fatty acid oxidation and inhibits the synthesis of fatty acids, and the metabolic products of fatty acid oxidation can enhance mitochondrial oxidative phosphorylation in cancer cells.

It is generally accepted that the cancer cell genotype is a manifestation of 6 essential alterations: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis (74). Tumor metabolic reprogramming, which fuels limitless tumor replication and growth, might be added to this list (75). p53 plays an important inhibitory role in this metabolic reprogramming, and the p53 pathway components involved in this aspect of p53 function should, therefore, be considered novel targets for tumor therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported by the National Natural Science Foundation of China (30600314, 30830054, 31070681, and 31171112).

Received December 1, 2011; revised December 30, 2011; accepted January 6, 2012; published OnlineFirst February 3, 2012.

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