

# The fundamental role of the p53 pathway in tumor metabolism and its implication in tumor therapy

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## Statement of translational relevance

The tumor suppressor p53 is one of the most highly studied in the field of cancer research due to its functions on 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. On this basis, we analyzed the therapeutic strategy whereby p53 helps to prevent tumor malignant metabolic phenotype, bioenergetic, and biosynthetic processes, and blocking the reprogramming of tumor metabolism will provide new strategies for tumor therapy.

## Abstract

It is well established that the altered metabolism exhibited by cancer cell, including high rates of glycolysis, lactate production, and biosynthesis of lipids, nucleotides, and other macromolecules, 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 of aerobic glycolysis, oxidative phosphorylation, the pentose phosphate pathway, fatty acid synthesis and oxidation, glutamine metabolism, and discuss the therapeutic strategy whereby p53 helps to prevent malignant progression.

## 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 prefer to 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 also 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 regulated by p53 are ascribed to that p53 is a nuclear transcription factor to regulate the transcription of numerous target genes. Activation of p53 at the early stage of cellular stresses, such as DNA damage, can promote G1 phase cell cycle arrest and DNA repair through transactivation of p21WAF1, p53R2, and GADD45 (11). After the repair of DNA lesions, cells can then re-enter into the normal cell cycle. In this way, p53 is able to maintain the 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, p53 can activate the 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 anti-apoptotic gene survivin (15). Thus, complex regulation by p53 can prevent tumor initiation and progression.

Recent observations demonstrate 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, it was thus the first tumor suppressor 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, bioenergetic, and biosynthetic processes to repress tumor growth and proliferation, and also discuss potential metabolic targets for tumor treatment.

### **p53 and tumor glucose catabolism: the glycolysis pathway**

Cancer cells are characterized by aerobic glycolysis with the utilization of glucose and production of lactate. Several biological functions of p53 dampen 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 *TIGAR* (TP53-induced glycolysis and apoptosis regulator) 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<sub>2</sub>), thereby lowering intracellular level of this metabolite. As Fru-2,6-P<sub>2</sub> is the most potent activator of PFK-1, a p53-dependent reduction in Fru-2,6-P<sub>2</sub> levels mediated by TIGAR results in the inhibition of glycolysis (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 down-regulates PGM, mutation of p53 can enhance PGM activity and glycolytic flux. Thus, p53-dependent down-regulation 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 which regulate the enzymes involved in glycolysis are different in species and tissues.

Besides inhibition of glycolytic enzyme reactions via TIGAR and PGM, p53 can also 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 also represses GLUT3 gene expression indirectly by preventing activation of the 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**

It is described by Otto Warburg that cancer cells preferentially utilize glycolytic pathways for energy generation while downregulating mitochondrial respiration, and one reason he proposed is that cancer cells have irreversible damages 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 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 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 mitochondrial respiratory chain, p53 plays an important role in enhancing mitochondrial oxidative phosphorylation in cancer cells.

In addition, activation of p53 can also 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  $\alpha$ -ketoglutarate, which is a key intermediate in the TCA cycle. Thus, GLS2 mediates the role of p53 in regulating the mitochondrial tricarboxylic acid 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, whether this interaction has an impact on mitochondrial respiration need to be further investigated (32). Interestingly, failure of DNA repair in the ATM<sup>+/−</sup> mice impairs p53 activity and results in mitochondrial dysfunction, p53<sup>−/−</sup> 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**

The pentose phosphate pathway (PPP) is important for both glucose catabolism and biosynthesis, PPP can generate NADPH (nicotinamide adenine dinucleotide phosphate, reduced) and ribose 5-phosphate, the essential precursors of nucleotides. The p53 tumor suppressor inhibits the pentose phosphate pathway, 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 towards ribose 5-phosphate and NADPH biosynthesis when p53 mutates in many human tumor cells (2,35) (Fig. 1).

### **p53 and tumor fatty acid metabolism**

Besides aerobic glycolysis, increasing de novo synthesis of fatty acids is another characteristic of tumor metabolism, which is essential for lipid 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) (39). AMPK is a heterotrimeric enzyme complex consisting of a catalytic subunit ( $\alpha$ ) and two regulatory subunits ( $\beta$  and  $\gamma$ ) that maintains cellular energy homeostasis. AMPK  $\beta$  subunit is transcriptionally induced by p53, leading to increased AMPK  $\beta$  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 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 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 wt p53 protein level is regulated by HDM2 ubiquitin ligase, which targets p53 for degradation via ubiquitylation (56,57). Therefore, HDM2 inhibitors HLI98 can stabilize p53 and and Nutlin 3A rescue tumor suppression function in cancer cells (58,59). Unfortunately, this approach has the risk to enhance the pro-survival adaptation functions of p53 in some tumors (60,61), and clarify the mechanism by which p53 coordinates adaptation could discover new therapeutic targets in cancer expressing wild-type p53.

Tumor metabolic alterations meet the bioenergetic and biosynthetic demands of increased cell proliferation, and targeting of tumor metabolism may appear on the stage of tumor therapy. Thus, drugs that mimic the metabolic effect of p53 are able to perturb cancer cell metabolism and inhibit cancer cell proliferation. Since tumor cells rely on glycolysis for ATP production for their survival, the molecular targets of p53 in the glycolytic pathway might be the potential therapeutic targets in cancer. Indeed, the non-metabolizable glucose analogs, 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



chemotherapeutic drug daunorubicin (64). As p53 repression of GLUT3 expression is mediated by IKK–NF- $\kappa$ B pathway, thereby inhibition of the activation of IKK–NF- $\kappa$ B pathway can be another target for cancer treatment. It has been demonstrated R-roscovitine can inhibit the function of IKK and downregulate NF- $\kappa$ B activation. In addition to NF- $\kappa$ B 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 tumor (65-67).

Silencing of mitochondria is another characteristic feature of tumor cells. Hence, mimic the metabolic effect of p53 to maintain mitochondrial respiration chain and shift 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 anti-cancer 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, showing that pharmacological AMPK activators, such as metformin, phenformin, and AICAR attenuate cancer cell growth and inhibit tumorigenesis in animal models (72,73). Therefore, recover the activity or mimic the metabolic effect of p53 is the potential strategy in cancer therapy.

## Concluding remarks

The proliferation of malignant cancer cells needs nutrients, energy, and biosynthetic activity. Therefore, metabolic reprogramming fuels cancer cell malignant growth and proliferation. Mutation and inactivation of tumor suppressor genes contributes not only to cancer initiation, proliferation, and progression, but also to metabolic reprogramming in cancer cells. This review attempts to summarize the current state of 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 pentose phosphate pathway, 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 always believed that the cancer cell genotype is a manifestation of six 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 tumor limitless replication and growth, might be added to this list (75). The p53 plays an important inhibitory role in this metabolic reprogramming, and p53 pathway components involved in this aspect of p53 function should therefore be considered as novel targets for tumor therapy.

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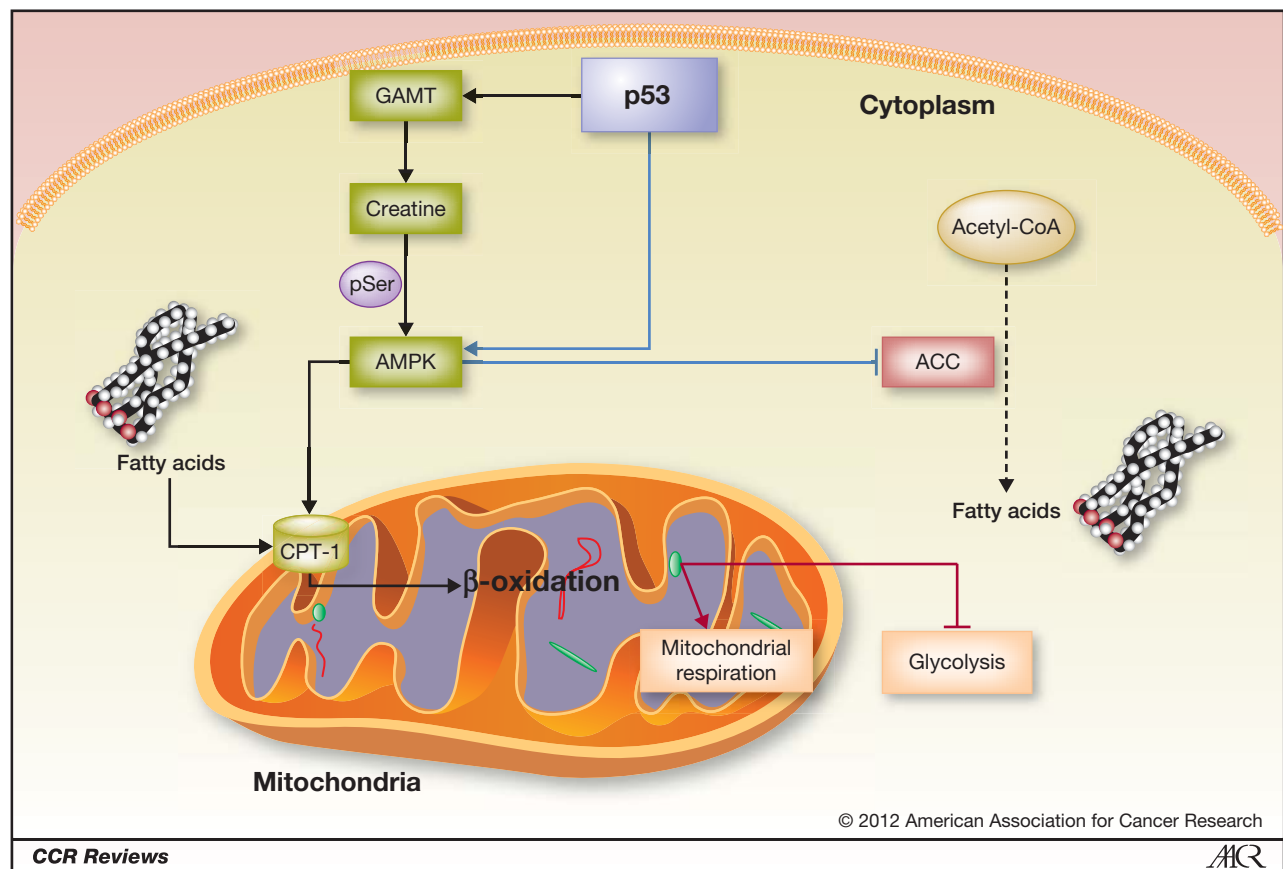
## Figure Legends

**Fig. 1** p53 regulates glucose catabolism in cancer cells. Several metabolic effectors of p53 are involved in the glucose metabolic processes, such as TIGAR, PGM, GLUT1/4, IKK, Hexokinase, SCO2, AIF, GLS2, and G6PD, which finally inhibit the glycolytic pathway and the pentose phosphate pathway while enhancing mitochondrial respiration. Please see text for details.

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







# Clinical Cancer Research

## The fundamental role of the p53 pathway in tumor metabolism and its implication in tumor therapy

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