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GAMT joins the p53 network

Branching into metabolism

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The p53 protein functions to prevent tumor development by restricting proliferation, motility and survival of abnormal or stressed cells. In addition to well-established roles, recent discoveries indicate a role for p53 in the regulation of pathways involved in energy metabolism. The metabolic functions of p53 can inhibit the shift to glycolysis that is characteristically seen in cancer cells, while favoring the energy production by mitochondrial oxidative phosphorylation. Identification of guanidinoacetate methyltransferase (GAMT) as a new p53 target connects p53 to creatine metabolism critical in the regulation of ATP homeostasis. The involvement of GAMT in both genotoxic and metabolic stress-induced apoptosis, as well as the requirement of p53-dependent upregulation of GAMT in glucose starvation-mediated fatty acid oxidation (FAO), demonstrate a further role of p53 in coordinating stress response with changes in cellular metabolism. Such activities of p53 would help to bring a better understanding of how cancer cells acquire unique metabolic features to maintain their own survival and proliferation, and might provide interesting clues toward the development of novel therapies.

Key words: p53, cancer cell metabolism, GAMT, creatine metabolism, fatty acid oxidation

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Introduction

Since its discovery 30 years ago, the p53 protein has emerged as a key tumor suppressor protein, and beyond doubt, a crucial player in cancer biology. p53 invokes its tumor-suppressive ability by acting as a mediator of various kinds of stress, such as DNA damage, oxidative stress and oncogene activation.[1] Through its activity as a transcription factor, p53 regulates the expression of various target genes to prevent tumor development, mainly by inducing cell cycle arrest and DNA repair or triggering cell death and senescence to maintain genomic stability.[2-6] Under mild or transient stress conditions, activated p53 targets several genes involved in cell cycle arrest and DNA repair to stop cells from proliferating and allow repair of any damaged DNA, preventing potentially oncogenic mutations from being passed on to the daughter cells. However, when stress-induced DNA damage is too severe to be reparable, p53 initiates programmed cell death/apoptosis and cellular senescence to eliminate or permanently arrest cells, respectively, that may have acquired irreparable and potentially oncogenic mutations. Relevantly, the human p53 gene (*TP53*) is frequently mutated or inactivated in more than 50% of human cancers of different types.[7] Furthermore, mice with a p53 gene (*Trp53*) deletion can develop normally but develop cancer before the age of 6 months.[8] Thus, the importance of p53 in the inhibition of tumor development is indisputable; however, the function of p53 is far from simplicity. To date, emerging evidence indicates that p53 is involved in numerous pathways and is capable of much broader cellular functions, ranging from fertility, development and aging to energy metabolism and autophagy.[9-14] Furthermore, it is clear that the activity of p53 by modulating metabolic pathways

will have consequences beyond cancer, influencing various other aspects of disease and longevity.

Cancer Cell Metabolism

Rapid cell growth and proliferation are representative features of tumor cells. Consequently, tumor cells need ample amount of energy to generate macromolecules (DNA, RNA, proteins and lipids) necessary for cell proliferation. To fulfill such demand for energy, tumor cells undergo modifications in cellular metabolism and metabolic adaptation to support its enhanced cell growth and proliferation and to survive periods of metabolic stress and maintain viability. Among various nutrients, glucose is the primary energy source for most normal cells. Under conditions of normal oxygen level, glucose is metabolized via mitochondrial oxidative phosphorylation to efficiently generate 32 molecules of ATP per one molecule of glucose. However, when oxygen level is low, mitochondrial function is suppressed and normal cells undergo anaerobic glycolysis to produce only a fraction of the maximum energy from glucose (two molecules of ATP per one molecule of glucose). Thus, normal cells would not use this less efficient pathway to produce energy under aerobic conditions. On the contrary, tumor cells, which require substantial amount of energy, preferentially utilize the less efficient glycolytic pathway even though sufficient level of oxygen is available (also known as "aerobic glycolysis"). This striking discovery was first documented by Otto Warburg in the 1920s when he observed that liver cancer cells, compared to normal liver cells, displayed an increase in glycolytic activity despite the presence of oxygen.[15] He further hypothesized that this increase in aerobic glycolysis is due to mitochondrial dysfunction and may be the prime cause of cancer.[16] Whether this metabolic shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis is the origin of cancer or a consequence of tumorigenesis, this phenomenon, termed the "Warburg effect," has been reported in most cancers and is recognized as a key metabolic hallmark of virtually all cancer cells.[17,18] This metabolic change is now widely used in diagnosing human solid tumors using fluorodeoxyglucose positron emission tomography (FDG-PET) to detect the much higher uptake of glucose by the tumor than the adjacent normal tissues. In addition, an increasing understanding of the molecular mechanisms that control metabolism highlights the realization that metabolic transformation can have an essential role in maintaining tumorigenic state.

Role of p53 between Glycolytic and Respiratory Pathways

Recent studies have demonstrated the ability of p53 in the regulation of both glycolysis and oxidative phosphorylation, consequently contributing to prevent the increase in glycolysis that is characteristic of cancers. p53 can reduce glucose uptake into the cells through inhibiting the expression of glucose transporters GLUT1 and GLUT4 as the first defense.[19] Glucose uptake is further limited by p53's regulation of NFκB pathway.[20] Expression of p53 can restrict the activity of IκB kinase-α (IKKα) and IKKβ, thereby leading to a reduction in NFκB activity and decreased expression of GLUT3. p53 can also repress the levels of PGM (phosphoglycerate mutase), which acts at the later stages of the glycolytic cascade,[21] and TIGAR (TP53-induced glycolysis and apoptosis regulator), which functions to direct glucose to an alternative pathway, the pentose phosphate pathway (PPP).[22] Loss of p53 is associated with increased PGM and decreased TIGAR expression, which can enhance glycolysis and the Warburg effect.

The modulation of glycolytic rate by p53 is paralleled by the ability of p53 to help maintain mitochondrial function and promote oxidative phosphorylation. SCO2 (synthesis of cytochrome oxidase 2), a target gene of p53, regulates the cytochrome c oxidase complex, which is essential for mitochondrial respiration and utilization of oxygen to produce energy (ATP).[23] Another p53 target gene AIF (apoptosis-inducing factor) plays a role in regulating various cell death pathways and, as an oxidoreductase, is a key factor in maintaining the integrity of complex 1 in the electron transport chain.[24] Thus, cells that lack functional p53 show lower oxygen consumption by mitochondrial respiration and a shift to glycolysis for the production of energy.

p53 has been further implicated in metabolic control through its communication with two key regulatory factors, AMPK (AMP-activated protein kinase) and mTOR (mammalian target of rapamycin).[25,26] Reduced nutrient or energy levels result in the activation of AMPK and failure to stimulate the AKT-mTOR pathway, both of which can induce p53, leading to enhanced macroautophagy and fatty acid oxidation.[27,28] The aforementioned p53 regulation of energy metabolism is merely a subset among the various aspects of metabolism that p53 can regulate, and without a doubt, this complex network of p53 will have more additions.

p53 and Creatine Metabolism

The creatine-phosphocreatine system plays an important role in phosphate-bound energy storage and transmission. The reversible phosphorylation of creatine by creatine kinase with ATP/ADP provides a high-energy phosphate buffering system.[29] This system is essential in cells and tissues with high and fluctuating energy demands. Creatine is synthesized in a two-step mechanism by two enzymes: AGAT (arginine:glycine amidinotransferase) and GAMT (guanidinoacetate methyltransferase). AGAT, primarily expressed in the kidney and pancreas, catalyzes the first biosynthetic step of creatine by taking glycine and arginine to produce ornithine and GAA (guanidinoacetate). Subsequently, GAA enters the blood stream to reach the liver where it is methylated by GAMT to yield creatine. Creatine is then exported back into the blood stream to be taken up by tissues requiring creatine, such as muscle, brain and heart, through active creatine transporters. Loss of GAMT causes a creatine deficiency syndrome, first described in 1994, that is characterized by developmental delay, mental retardation, neurological and motor dysfunction.[30-34] Aside from the more commonly known function and disorders of creatine metabolism, other roles of creatine metabolism exist. Since creatine

metabolism is intimately connected with ATP homeostasis and tumor cells have high demand for ATP, the role of creatine metabolism in cancer cells is conceivable and may be of importance. In fact, the association between creatine metabolism and cancer has long been reported in the literature.[35-42] However, when levels of creatine content and creatine kinase activity were examined in malignant cells and tumor-bearing animals, the results are somewhat inconsistent. Some reports show increased creatine content and elevated creatine kinase activity in various human carcinoma tissues,[35,36,38,42] while some show downregulation of the creatine kinase system in malignant tissues and tumor-bearing mice.[37,39,41,43] It is possible that the specific role of creatine shuttle in cancer is tissue and isoform specific, as several tissue-related isoforms of creatine kinase exist: muscle, mitochondrial and brain creatine kinase.

In connection with p53 and creatine metabolic pathway, mouse p53 has been reported to repress the expression of rat brain creatine kinase but activate the rat muscle creatine kinase gene, although it is unclear of how p53 and creatine kinase function in cell metabolism.[44] Recently, GAMT was identified as a novel p53 target, demonstrating another metabolic pathway, namely creatine metabolism, by which p53 can control to adapt to metabolic stress.[45] Overexpression of p53 or inducing p53 by etoposide treatment leads to an increase in creatine level that is reduced upon ablation of GAMT. Moreover, depletion of creatine by treating cells with creatine circuit inhibitor produces less etoposide-mediated apoptosis. In response to glucose deprivation, GAMT is induced in a p53-dependent manner, and levels of GAMT and creatine are increased in several tissues of nutrient-deprived p53 wild-type mice while remaining unchanged in the same tissues of p53 null mice. GAMT ablation also reduces glucose depletion-induced apoptosis, demonstrating that GAMT is not only involved in p53-dependent apoptosis in response to genotoxic stress but is important for apoptosis induced by nutrient starvation. It is well established that increased level of reactive oxygen species (ROS) can initiate apoptotic pathway.[46,47] Therefore, etoposide treated cells result in an increase in intracellular ROS level that is inhibited by creatine circuit inhibitor, and creatine treated cells produced an increase in intracellular ROS level. These findings suggest a new role for GAMT and creatine metabolism in p53-dependent apoptosis. Since some reports have also shown anticancer effects of creatine by leading to the increased formation of nitric oxide,[48] emerging possibility implicates that p53-creatine metabolic pathway might function as tumor suppressing mechanism, although further examinations are required.

Altered Lipid Metabolism in Cancer Cells

Although the Warburg effect has been recognized for 90 years, alterations in lipid metabolism are less well appreciated. Several studies reveal that many tumors have high rates of de novo fatty acid biosynthesis regardless of the concentration of extra cellular lipids, which primarily reflects dietary fats.[49-51] Fatty acid synthase (FASN) and the enzymatic activity of ATP citrate lyase are increased to support the synthesis of fatty acids.[52] FASN is a lipogenic enzyme which catalyzes the de novo synthesis of long-chain fatty acids from acetyl-CoA, malonyl-CoA and NADPH precursors and is overexpressed in several human cancers.[53] It is reported that PI3K/Akt pathway stimulates fatty acid synthesis via activation of ATP citrate lyase and inhibition of fatty acid oxidation (FAO) via reduced expression of CPT1 (carnitine palmitoyltransferase 1). CPT1, which catalyzes the transport of long-chain fatty acids into mitochondria for FAO, is recently reported to be decreased in human cancer specimens.[54] Furthermore, mouse mammary carcinoma models and human primary breast cancer often show diminished expression of DecR1 (2,4-dienoyl-coenzyme A reductase), another enzyme involved in FAO. More importantly as well, ectopic expression of DecR1 reduced tumor growth and decreased de novo fatty acid synthesis,[55] providing the therapeutic potential of targeting tumor cell fatty acid synthesis.

The tumor microenvironment is spatially and temporally heterogeneous, containing region of low oxygen and low glucose. When glucose is not available, FAO is reported to be the first alternate pathway used by most tissues to generate energy.[56,57] Our results show that increased FAO ensues and that this requires p53 and GAMT in response to glucose deprivation.[45] Further examinations reveal that creatine increases phosphorylation of AMPK and ACC (acetyl-CoA carboxylase), indicating that FAO has been switched on. Moreover, similar evidence came from the observation that increased FAO in liver occurs upon starvation of wild-type but not p53 deficient animals, and p53 deficient animals have generally lower levels of liver FAO than their wild-type counterparts, indicating p53 in energy maintenance by FAO pathway. FAO connects to Krebs cycle by converting Acyl-CoA to Acetyl-CoA and contributes to maintaining oxidative phosphorylation, and increased FAO can inhibit glycolysis.[58] Thus, p53-GAMT regulation of FAO may function to keep the balance between glycolytic and respiratory pathway to oppose the metabolic shift (Warburg effect) in tumorigenic state (**Fig. 1**).

Concluding Remarks

In summary, p53 can communicate with creatine biosynthetic and FAO pathways through its target gene GAMT to regulate energy metabolism. It still remains a challenge to understand when and how each of the p53 metabolic target genes or outcomes is all coordinated. Metabolic changes are emerging as key contributors to malignant progression and most cancer cells show the characteristic increase in aerobic glycolysis known as the Warburg effect. Better understanding of p53 and its targets in energy metabolism may hold the key to effective therapeutic approaches against cancer and metabolism-related diseases.

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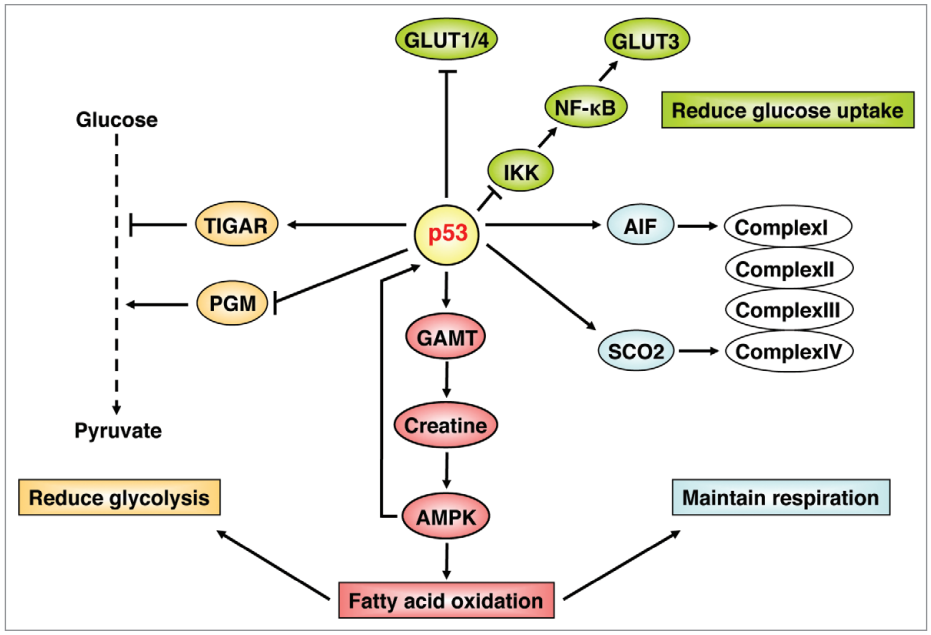

Figure 1. Regulation of energy metabolism by p53. Several functions of p53 slow the flux through the glycolytic pathway and promote oxidative phosphorylation, thereby opposing the metabolic shift (Warburg effect) by which cancer cells often use glycolysis for energy production. p53-GAMT regulation of FAO also joins this network as a balancer between glycolytic and respiratory pathway. GLUT, glucose transporter; IKK, IκB kinase; NFκB, nuclear factor-κB; TIGAR, TP53-induced glycolysis and apoptosis regulator; PGM, phosphoglycerate mutase; AIF, apoptosis-inducing factor; SCO2, synthesis of cytochrome oxidase 2; GAMT, guanidinoacetate methyltransferase; AMPK, AMP-activated protein kinase.

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