Review

Tumor suppressor p53 and metabolism

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p53 plays a key role in tumor suppression. The tumor suppressive function of p53 has long been attributed to its ability to induce apoptosis, cell cycle arrest, and senescence in cells. However, recent studies suggest that other functions of p53 also contribute to its role as a tumor suppressor, such as its function in metabolic regulation. p53 regulates various metabolic pathways to maintain the metabolic homeostasis of cells and adapt cells to stress. In addition, recent studies have also shown that gain-of-function (GOF) mutant p53 proteins drive metabolic reprogramming in cancer cells, contributing to cancer progression. Further understanding of p53 and its GOF mutants in metabolism will provide new opportunities for cancer therapy.

Tumor suppressor p53

Metabolic reprogramming is a hall marker of cancer cells, which plays a pivotal role in cancer progression by providing energy and a wide variety of substrates for biosynthesis to support the rapid proliferation and survival of cancer cells (Cairns et al., 2011; Pavlova and Thompson, 2016; Wolpaw and Dang, 2018). Activation of oncogenes and/or inactivation of tumor suppressors drive metabolic reprogramming in cancer cells (Cairns et al., 2011; Pavlova and Thompson, 2016; Wolpaw and Dang, 2018). Tumor suppressor p53 has been reported to play an important role in metabolic regulation in cells (Vousden and Prives, 2009; Liu et al., 2013; Muller and Vousden, 2013; Gurpinar and Vousden, 2015; Kruiswijk et al., 2015).

As a key tumor suppressor, p53 is the most commonly mutated gene in human cancers; p53 is mutated in >50% of all human cancers (Olivier et al., 2004; Vousden and Prives, 2009; Muller and Vousden, 2013). p53 knockout (p53$^{-/-}$) mice are extremely susceptible to early tumor development (Donehower et al., 1992; Jacks et al., 1994). To maintain its proper function in tumor suppression, p53 is tightly regulated through different

mechanisms in cells, including ubiquitination and degradation of p53 by different E3 ubiquitin ligases such as MDM2 (Vousden and Prives, 2009; Wade et al., 2013; Zhao et al., 2014; Tavana and Gu, 2017; Zhou et al., 2017). As a transcription factor, p53 regulates the expression of its target genes whose products are involved in many important biological processes, including apoptosis (e.g. Puma, Noxa), cell cycle arrest, and senescence (e.g. p21) (Levine et al., 2006b; Levine and Oren, 2009; Vousden and Prives, 2009). For a long time, apoptosis, cell cycle arrest, and senescence were widely believed to mediate the main function of p53 in tumor suppression. However, this concept has been challenged by recent studies, especially studies from mouse models. For instance, p53$^{3KR/3KR}$ mice carrying lysine (K) to arginine (R) mutations at three acetylation sites of p53 (K117R+K161R+K162R) display impaired p53 function in apoptosis, cell cycle arrest, and senescence but are not prone to early tumor development, unlike p53$^{-/-}$ mice (Li et al., 2012). Interestingly, p53$^{3KR/3KR}$ mice retain the ability to transactivate p53 target genes involved in metabolic regulation (Li et al., 2012). Similarly, mice deficient for Puma, Noxa, and p21, three well-known p53 target genes involved in the induction of apoptosis, cell cycle arrest, and senescence, do not develop tumors at early ages (Valente et al., 2013). These studies suggest that additional functions of p53, such as its function in metabolic regulation, may contribute to the tumor suppressive function of p53. In this review, we summarize recent advances in the research of p53 and its gain-of-function (GOF) mutants in metabolic regulation.

p53 and glucose metabolism

Enhanced glycolysis is the most well-characterized metabolic change in cancer cells. Majority of cancer cells display dramatically increased glucose uptake and lactate production compared with normal cells, which was first observed by Otto Warburg almost 100 years ago and named the Warburg effect (Warburg et al., 1927). Recent studies have shown that p53 plays an important role in regulating glucose metabolism in cells (Figure 1). Glucose transporters (GLUTs) facilitate the transport of glucose across the cellular plasma membrane, which is the first rate-limiting event in glucose metabolism. p53 was reported to directly repress the transcription of GLUT1 and GLUT4 to reduce glucose uptake (Schwartzenberg-Bar-Yoseph et al., 2004). p53 also represses GLUT3 expression through downregulation of the activity of NF-κB, which transcriptionally upregulates GLUT3 expression in cells (Kawauchi et al., 2008). In addition to downregulating the levels of the above-mentioned GLUTs, p53 inhibits the translocation of GLUT1 to the cellular plasma membrane to suppress glucose uptake (Zhang et al., 2014). One important mechanism by which p53 inhibits GLUT1 translocation to the plasma membrane is through transcriptional

activation of its target RRAD, which binds to p65 of the NF-κB and inhibits NF-κB activity to suppress GLUT1 translocation (Zhang et al., 2014). p53 also regulates glucose metabolism through direct or indirect regulation of the expression of several key enzymes involved in glucose metabolism. For instance, p53 downregulates protein levels of hexokinase 2 (HK2) through reducing HK2 mRNA stability (Wang et al., 2014) and downregulates protein levels of phosphoglycerate mutase 1 (PGAM1) via an unclear mechanism, leading to the suppression of glycolysis (Kondoh et al., 2005). p53 transcriptionally induces expression of PARK2, which encodes E3 ubiquitin ligase Parkin (Zhang et al., 2011; Viotti et al., 2014). Parkin directly binds to transcription factor HIF-1α to ubiquitinate and degrade HIF-1α (Liu et al., 2017). It is known that HIF-1α transcriptionally activates some key genes involved in glycolysis, such as GLUT1 and LDHA, to promote glycolysis (Semenza, 2010). Thus, p53 represses glycolysis through transcriptional activation of Parkin (Zhang et al., 2011; Liu et al., 2018). p53 transcriptionally induces TIGAR to reduce intracellular levels of fructose-2,6-bisphosphate, which stimulates glycolysis, and thereby suppresses glycolysis (Bensaad et al., 2006). p53 also transcriptionally represses
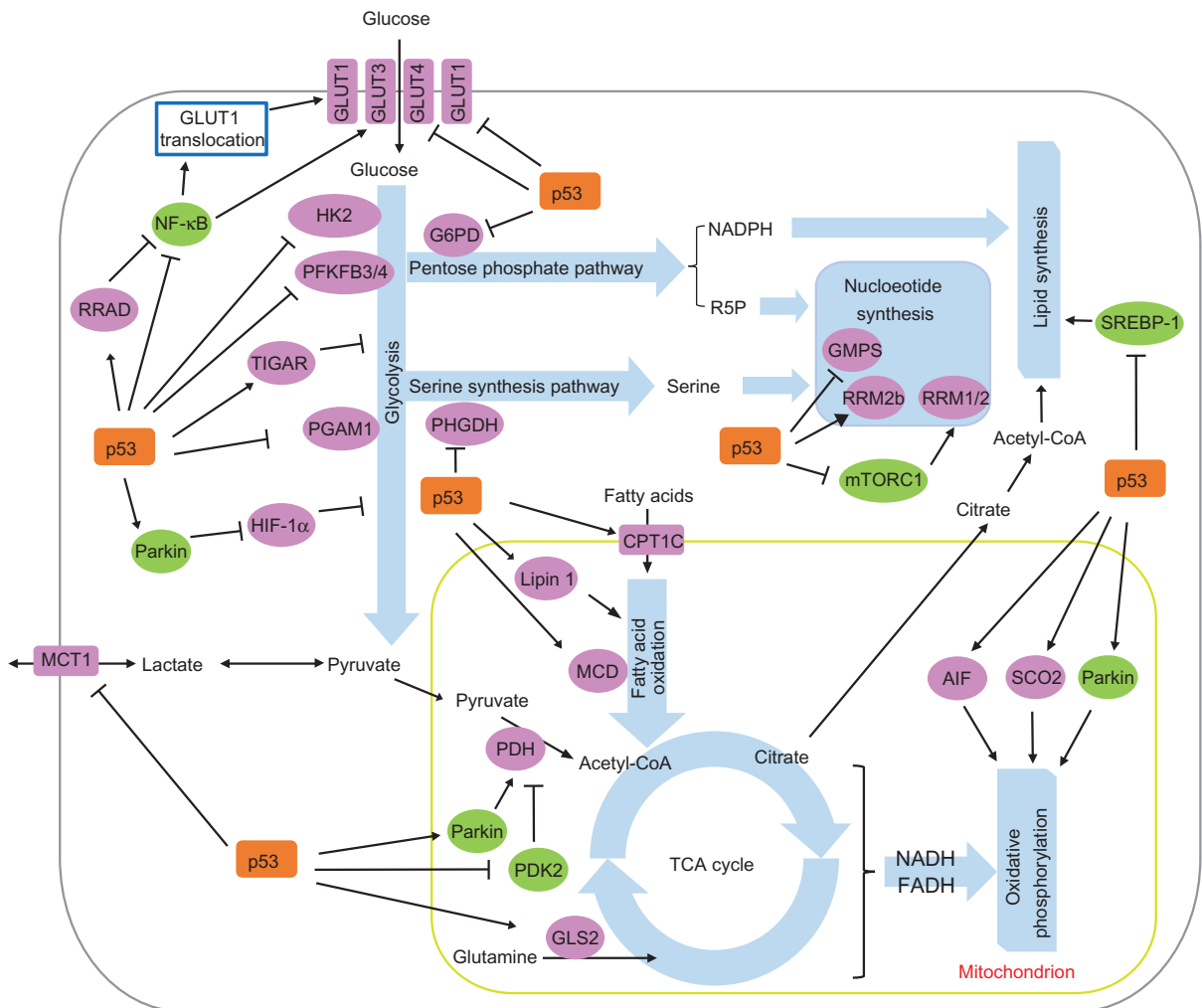

Figure 1 The regulation of metabolism by p53. p53 regulates glycolysis, oxidative phosphorylation, lipid metabolism, the PPP, serine synthesis, and nucleotide synthesis in cells. →, promote; ⊣, inhibit.

PFKFB3 and PFKFB4, which reduce intracellular levels of fructose-2,6-bisphosphate, leading to the inhibition of glycolysis (Franklin et al., 2016; Ros et al., 2017). p53 inhibits the pentose phosphate pathway (PPP) to suppress glucose consumption through direct binding to glucose-6-phosphate dehydrogenase (G6PD), the first and rate-limiting enzyme of the PPP, and preventing the formation of active G6PD dimers (Jiang et al., 2011). In addition, p53 suppresses the transcription of monocarboxylate transporter 1 (MCT1) to inhibit the transportation of glycolytic product lactate into and out of cancer cells (Boidot et al., 2012). Elevated expression of MCT1 in p53-deficient cancer cells adapts these cells to metabolic needs by facilitating lactate export or import depending on the glucose availability (Boidot et al., 2012) (Figure 1).

p53 has also been reported to suppress glycolysis through regulation of other signaling pathways involved in glycolysis. For instance, activation of the PI3K/AKT signaling drives glycolysis in cancer cells (Feng and Levine, 2010; Cairns et al., 2011; Ward and Thompson, 2012). PTEN is a critical negative regulator of the PI3K/AKT signaling; PTEN hydrolyzes PIP_3, which binds to and activates AKT, to negatively regulate AKT activity (Janku et al., 2018). Parkin positively regulates PTEN to suppress the PI3K/AKT signaling; Parkin deficiency leads to the downregulation of PTEN protein levels through S-nitrosylation and ubiquitination, leading to the activation of PI3K/AKT signaling in cells (Gupta et al., 2017). p53 negatively regulates the PI3K/AKT signaling through transcriptional induction of PTEN and Parkin, which in turn inhibits glycolysis (Stambolic et al., 2001; Feng et al., 2007; Zhang et al., 2011; Viotti et al., 2014; Liu et al., 2018). Similarly, mTORC1 activation plays an important role in promoting glycolysis. p53 transcriptionally induces several genes that negatively regulates mTORC1 activity, including AMPKβ, PTEN, and TSC1/2 (Feng et al., 2005, 2007; Levine et al., 2006a). p53 was also reported to transcriptionally induce Sestrin 1/2 to activate AMPK, which negatively regulates mTORC1 activity, leading to the inhibition of glycolysis in cells (Budanov and Karin, 2008).

p53, oxidative phosphorylation, and mitochondrial metabolism

Recent studies show that p53 plays an important role in the maintenance of the mitochondrial oxidative phosphorylation machinery (Figure 1). p53 induces SCO2 expression to maintain cytochrome c oxidase complex, and thereby enhances mitochondrial oxidative phosphorylation (Matoba et al., 2006). p53 transcriptionally induces the expression of AIF to maintain the integrity of mitochondrial complex I in the mitochondrial electron transport chain (Stambolsky et al., 2006). p53 represses the transcription of pyruvate dehydrogenase kinase 2 (PDK2), which is a negative regulator of pyruvate dehydrogenase (PDH) that converts pyruvate to acetyl-CoA, a primary substrate for the tricarboxylic acid (TCA) cycle (Contractor and Harris, 2012). Thus, the inhibition of PDK2 by p53 activates PDH to reduce the conversion of pyruvate to lactate and increase the conversion of pyruvate to acetyl-CoA, which in turn promotes mitochondrial oxidative phosphorylation (Contractor and Harris, 2012). p53

also promotes mitochondrial oxidative phosphorylation through upregulation of its target Parkin (Zhang et al., 2011). One mechanism is through the upregulation of PDH activity; Parkin increases the protein expression of pyruvate dehydrogenase E1α1 (PDHA1), which is a critical component of the PDH complex, to facilitate the conversion of pyruvate into acetyl-CoA (Zhang et al., 2011). In addition, p53-mediated transcriptional activation of mitochondrial glutaminase 2 (GLS2), which catalyzes the hydrolysis of glutamine to glutamate, promotes mitochondrial oxidative phosphorylation, and enhances glutathione (GSH) synthesis to reduce levels of reactive oxygen species (ROS) in cells (Hu et al., 2010; Suzuki et al., 2010) (Figure 1).

p53 and lipid metabolism

Lipids are essential constituents of all biological membranes, important substrates for energy metabolism, and are used for post-translational modifications in cells. Increased *de novo* lipid synthesis is another important metabolic change in many cancers; whereas most normal tissues preferentially use circulating lipids, many cancer cells display a high rate of *de novo* lipid synthesis (Menendez and Lupu, 2007; Currie et al., 2013; Rohrig and Schulze, 2016). Overexpression and/or activation of enzymes involved in lipid synthesis, such as ACLY and FASN, promotes tumor progression (Bauer et al., 2005; Hatzivassiliou et al., 2005; Currie et al., 2013; Rohrig and Schulze, 2016; Zhang et al., 2016). p53 regulates lipid metabolism through different mechanisms (Figure 1). SREBP1/2 are transcription factors that regulate expression of a group of genes involved in lipid metabolism. Specifically, SREBP-1 regulates the expression of enzymes in fatty acid synthesis, and SREBP-2 regulates expression of enzymes in the mevalonate pathway. p53 was reported to directly bind to the promoter region of SREBP-1 and transcriptionally repress the expression of SREBP-1 (Yahagi et al., 2003). As mentioned above, p53 inhibits the PPP by binding to G6PD, leading to decreased production of NADPH, which is required for lipid synthesis (Jiang et al., 2011). Thus, inhibition of the PPP by p53 contributes to p53 function in suppression of lipid synthesis. Compared with p53$^{-/-}$ mice, p53$^{+/+}$ mice displayed decreased lipid accumulation in the liver (Jiang et al., 2011). In addition to the inhibition of fatty acid synthesis, p53 enhances fatty acid oxidation in cells. p53 transcriptionally induces the phosphatidate phosphatase Lipin 1 and the carnitine palmitoyltransferase CPT1C, two important enzymes involved in fatty acid oxidation, leading to increased fatty acid oxidation in cells (Assaily et al., 2011; Sanchez-Macedo et al., 2013). p53 was also reported to transcriptionally induce malonyl-CoA decarboxylase (MCD), which catalyzes the conversion of malonyl-CoA to acetyl-CoA, to promote fatty acid oxidation and prevent lipid accumulation in cells (Liu et al., 2014c).

p53, serine metabolism, and nucleotide metabolism

Serine is required for a number of biosynthetic and signaling pathways, including synthesis of other amino acids (e.g. glycine and cysteine), nucleotides, glutathione, and phospholipids (Amelio et al., 2014; Mattaini et al., 2016). Serine metabolism is

frequently dysregulated in cancers (Amelio et al., 2014; Mattaini et al., 2016). PHGDH is a key enzyme that catalyzes the first and rate-limiting step of the serine synthesis pathway from 3-phosphoglycerate to phospho-hydroxypyruvate. PHGDH is frequently overexpressed in several types of cancers, including breast cancer, melanomas, and lung cancer, which plays a critical role in promoting tumorigenesis through activating the serine synthesis pathway (Possemato et al., 2011; Mattaini et al., 2016; Mullarky et al., 2016). Recently, p53 was reported to transcriptionally repress PHGDH expression to inhibit *de novo* serine biosynthesis in melanoma cells (Ou et al., 2015) (Figure 1). Further, serine starvation dramatically enhances p53-mediated cell death in response to Nutlin-3, a small molecule MDM2 antagonist that stabilizes p53, in melanoma cells (Ou et al., 2015). Interestingly, another recent study reported that upon serine starvation, p53 activates p21 to induce cell cycle arrest, promoting cell survival in colorectal cancer cells. This is achieved through channeling depleted serine stores to glutathione synthesis to preserve cellular anti-oxidant capacity in $p53^{+/+}$ colorectal cancer cells. In contrast, $p53^{-/-}$ colorectal cancer cells fail to complete the response to serine starvation, resulting in reduced viability and impaired proliferation (Maddocks et al., 2013). The mechanism accounting for the observed different roles of p53 in regulating cell fates in response to serine starvation is currently unclear, which could be due to the context- and cell type-specific p53 response.

Rapidly proliferating cancer cells are highly dependent on nucleotide biosynthesis to support DNA replication and RNA production (Aird and Zhang, 2015; Lane and Fan, 2015; Pavlova and Thompson, 2016). p53 is an important regulator of nucleotide metabolism in cells (Figure 1). p53 transcriptionally represses GMP synthetase (GMPS), a key enzyme of the *de novo* purine synthesis pathway, to inhibit the purine synthesis and cell proliferation (Holzer et al., 2017). p53 plays a critical role in negative regulation of mTORC1 activity (Feng et al., 2005, 2010; Feng and Levine, 2010). Through inhibiting mTORC1, p53 inhibits the ribonucleotide reductase subunits 1 and 2 (RRM1/2), which catalyze conversion of ribonucleotides to deoxyribonucleotides, an essential step for the nucleotide synthesis (He et al., 2017). Furthermore, p53 inhibits the PPP and decreases the production of ribose-5-phosphate (R5P), an important precursor for nucleotide synthesis, which contributes to p53 function in suppression of nucleotide synthesis (Jiang et al., 2011).

Interestingly, p53 can promote nucleotide synthesis in response to DNA damage to facilitate DNA repair in cells. For instance, p53 transcriptionally induces RRM2b in response to DNA damage, and thereby activates nucleotide synthesis to facilitate DNA repair (Link et al., 2008). p53 induces TIGAR expression and suppresses PFKFB3 expression in response to DNA damage, which in turn switches glycolysis to the PPP and thus promotes nucleotide synthesis to facilitate DNA repair in cells (Bensaad et al., 2006; Franklin et al., 2016). The bidirectional roles of p53 in nucleotide synthesis suggest that p53 may suppress nucleotide synthesis under the normal condition to negatively regulate cell proliferation, whereas temporarily increase the nucleotide synthesis in response to DNA damage to facilitate DNA repair in cells.

p53, iron metabolism, and ferroptosis

Iron is essential for a variety of important cellular processes, including oxygen transport, energy production, and DNA synthesis, and is also required for the regulation of cell growth, inflammation, and cell death (Lawen and Lane, 2013; Gozzelino and Arosio, 2016). On the other hand, iron overload is associated with increased cancer risk. For instance, patients with hereditary hemochromatosis characterized by iron accumulation are prone to hepatocellular carcinoma (HCC) and colorectal cancer (Elmberg et al., 2003; Gozzelino and Arosio, 2016). High dietary iron intake is associated with an increased risk of cancers, including HCC, colorectal cancer, and breast cancer (Fonseca-Nunes et al., 2014; Gozzelino and Arosio, 2016). Emerging studies show that p53 is important for maintaining iron homeostasis in cells, contributing to its function in tumor suppression. A recent study reported that excess dietary iron causes significant elevation of serum iron levels in $p53^{-/-}$ but not $p53^{+/+}$ mice, and further, p53 maintains iron homeostasis through transcriptionally inducing iron-sulfur cluster assembly enzyme (ISCU), which encodes a scaffold protein important for Fe-S cluster biogenesis (Funauchi et al., 2015). Recently, p53 was reported to regulate iron metabolism through ferredoxin reductase (FDXR) (Zhang et al., 2017). FDXR, which transfers electron from NADPH to cytochrome P450 via ferredoxin in mitochondria, is a direct p53 target (Hwang et al., 2001). FDXR plays an essential role in maintaining mitochondrial iron homeostasis, and p53 is required for FDXR-mediated iron metabolism (Zhang et al., 2017). $FDXR^{+/-}$ mice are prone to spontaneous HCC and other tumors. Interestingly, FDXR deficiency suppresses p53 mRNA translation. These results suggest that FDXR–p53 loop is critical for tumor suppression via regulation of iron homeostasis (Zhang et al., 2017). In addition to tumor suppression, iron deprivation is also used as a defense mechanism against infection. p53 was reported to transcriptionally induces hepcidin, an iron-regulatory protein that is upregulated in response to increased iron or inflammatory stimuli (Weizer-Stern et al., 2007). Hepcidin reduces serum iron and induces iron sequestration in the reticuloendothelial macrophages, which is a hallmark of anemia of inflammation (Weizer-Stern et al., 2007). Thus, in addition to tumor suppression, p53 may enhance cellular anti-infection function via regulation of iron metabolism.

Interestingly, iron metabolism was also reported to regulate p53; iron excess downregulates p53 protein levels and function (Shen et al., 2014). The iron polyporphyrin heme directly binds to p53 to interfere with p53–DNA interactions and promote nuclear export and degradation of p53. Further, iron deprivation activates p53 and preferentially suppresses tumorigenesis of cancer cells expressing wild-type (wt) p53 (Shen et al., 2014).

Ferroptosis is an iron-mediated caspase-independent pathway of cell death that requires the accumulation of ROS and lipid peroxides. Emerging evidence suggests that ferroptosis is a

critical function of tumor suppression by p53 (Wang et al., 2016; Gnanapradeepan et al., 2018). FDXR was reported to be involved in p53-mediated ferroptosis through its regulation of iron, although its precise role in ferroptosis needs further investigation (Zhang et al., 2017). p53 was recently reported to induce ferroptosis through its negative regulation of SLC7A11, a component of the cystine/glutamate antiporter (Jiang et al., 2015). SLC7A11 is frequently overexpressed in human cancers, and its overexpression inhibits ROS-induced ferroptosis. p53 transcriptionally represses SLC7A11, leading to decreased cystine import, which in turn leads to reduced glutathione production and increased ROS in cells (Jiang et al., 2015). Interestingly, in p53$^{3KR/3KR}$ mice that do not develop early tumors, the 3KR mutant p53 (K117R+K161R+K162R) retains the function to repress SLC7A11 expression (Jiang et al., 2015). In contrast, p53$^{4KR/4KR}$ mice, which contain an additional K to R mutation at lysine 98 of p53 in addition to the 3KR mutations, develop early tumors. Notably, the 4KR mutant p53 loses the function to repress SLC7A11 expression (Jiang et al., 2015). These results suggest that p53-mediated ferroptosis contributes to the tumor suppressive function of p53. The single nucleotide polymorphism (SNP) at codon 47 of p53 (P/S 47) is the second most common SNP of p53 after codon 72 SNP (R/P 72) in human populations (Li et al., 2005; Basu and Murphy, 2016). Like P72 SNP, S47 SNP impairs p53 function in tumor suppression (Dumont et al., 2003; Basu and Murphy, 2016; Jennis et al., 2016; Zhao et al., 2018). Mice expressing human S47 are prone to spontaneous tumors (Jennis et al., 2016). Compared with wt p53, S47 has nearly indistinguishable transcriptional activity towards majority of p53 target genes but shows impaired transcriptional activity towards GLS2 and SCO2, two p53 target genes involved in metabolic regulation. Notably, cells expressing S47 are markedly resistant to ferroptosis induced by Erastin and RSL3, suggesting that ferroptosis contributes to p53 function in tumor suppression (Jennis et al., 2016). The potential contribution of p53-mediated ferroptosis to tumor suppression is further supported by following observations. p53 target GLS2 was reported to be essential for ferroptosis; knockdown of GLS2 greatly abolishes ferroptosis in cells (Gao et al., 2015). GLS2 is frequently downregulated in human HCC, and plays a critical role in tumor suppression in HCC (Hu et al., 2010; Suzuki et al., 2010; Zhang et al., 2014; Liu et al., 2014b). Spermidine/spermine N1-acetyltransferase 1 (SAT1) is another recently identified p53 target involved in ferroptosis, which catalyzes the acetylation of spermidine and spermine (Ou et al., 2016). SAT1 overexpression sensitizes cells to ferroptosis in response to ROS-induced stress in a p53-dependent manner, and also suppresses growth of xenograft tumors in mice (Ou et al., 2016).

Interestingly, p53 was also reported to negatively regulate ferroptosis in some cells. For instance, p53 inhibits ferroptosis in colorectal cancer cells through binding to dipeptidyl-peptidase-4 (DPP4), which positively regulates ferroptosis (Xie et al., 2017). The binding of p53 to DPP4 sequesters DPP4 in a nuclear enzymatic inactive pool, leading to ferroptosis inhibition (Xie et al., 2017). MDM2 antagonist Nutlin-3 delays the onset of ferroptosis

in some cells in a p53-dependent manner to promote cell survival under metabolic stress, such as cystine deprivation (Tarangelo et al., 2018). Further, this p53-delayed onset of ferroptosis is p21 dependent, although its mechanism is unclear (Tarangelo et al., 2018). Again, the dual functions of p53 in regulation of ferroptosis suggest that this regulation could be highly cell-type, stress, and context dependent.

GOF mutant p53 in metabolism

p53 is the most frequently mutated gene in human cancers. The majority of p53 mutations in human cancers are missense mutations, including several 'hotspot' mutations that account for ~30% of p53 mutations (e.g. R175, R245, R248, R273, and R282), which express full-length mutant p53 proteins in cancer cells (Olivier et al., 2004; Freed-Pastor and Prives, 2012; Muller and Vousden, 2013). Mutant p53 proteins often stabilize and accumulate to high levels in cancer cells through different mechanisms, including inhibition of E3 ubiquitin ligases MDM2 and ChIP (Terzian et al., 2008; Freed-Pastor et al., 2012; Muller and Vousden, 2013; Zheng et al., 2013; Yue et al., 2015, 2017). Many tumor-associated mutant p53 proteins, including above-mentioned 'hotspot' mutants, display different GOF activities to promote tumorigenesis independent of wt p53 function, including promoting proliferation, survival, angiogenesis, migration, and metastasis of cancer cells (Blandino et al., 2012; Freed-Pastor et al., 2012; Muller and Vousden, 2013; Liu et al., 2014a; Liao et al., 2017; Yue et al., 2017). Mice expressing different 'hotspot' mutant p53 have been reported to develop more malignant and/or earlier tumors compared with p53$^{-/-}$ mice (Lang et al., 2004; Olive et al., 2004; Hanel et al., 2013). Recently, mutant p53 has been reported to promote metabolic reprogramming in cancer cells as a novel GOF to promote tumorigenesis (Freed-Pastor and Prives, 2012; Freed-Pastor et al., 2012; Zhang et al., 2013; Gurpinar and Vousden, 2015) (Figure 2).

In contrast to the function of wt p53 to suppress glycolysis, GOF mutant p53 activates glycolysis in cancer cells to promote proliferation and growth of cancer cells (Zhang et al., 2013). Mutant p53 promotes GLUT1 translocation through activation of
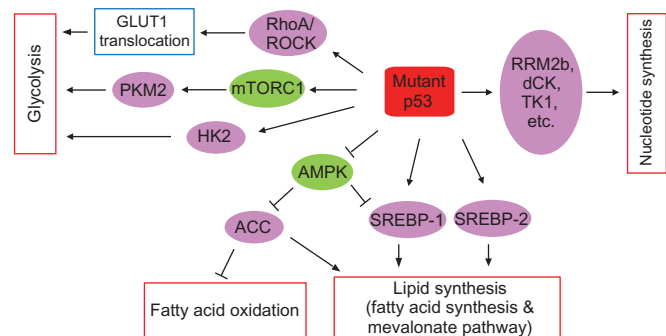

Figure 2 The regulation of metabolism by GOF mutant p53. GOF mutant p53 regulates glycolysis, lipid metabolism, and nucleotide synthesis in cells.

small GTPase RhoA and its downstream kinase ROCK, which plays a critical role in promoting vesicle trafficking of GLUTs (Zhang et al., 2013). Inhibition of the RhoA/ROCK/GLUT1 axis abolishes the function of mutant p53 in promoting glycolysis, and greatly inhibits GOF of mutant p53 in promoting tumorigenesis (Zhang et al., 2013). In addition, mutant p53 was reported to promote glycolysis through inducing the expression of glycolytic enzyme HK2 and enhancing mTORC1-mediated phosphorylation of glycolytic enzyme PKM2 (Mathupala et al., 1997; Dando et al., 2016) (Figure 2).

Mutant p53 was also reported to promote lipid synthesis. Mutant p53 binds and activates transcription factor SREBP1/2, and induces the expression of a set of genes in the mevalonate pathway and fatty acid synthesis pathway regulated by SREBP1/2 to promote tumorigenesis (Freed-Pastor et al., 2012). Inhibition of the mevalonate pathway compromises GOF of mutant p53 in tumorigenesis (Freed-Pastor et al., 2012). Interestingly, inhibition of the mevalonate pathway leads to the downregulation of GOF mutant p53 protein levels in cancer cells through inducing CHIP-mediated nuclear export, ubiquitination, and degradation of mutant p53 (Parrales et al., 2016). AMPK has been known to inhibit lipid synthesis and enhance fatty acid oxidation through phosphorylation of SREBP1/2 and acetyl-CoA carboxylase (ACC) to inhibit their activities (Hardie and Pan, 2002; Li et al., 2011). Mutant p53 was further reported to bind to AMPKα to inhibit AMPK activity, thereby enhancing lipid synthesis to promote tumorigenesis (Zhou et al., 2014) (Figure 2).

Mutant p53 was also reported to promote nucleotide synthesis through cooperating with transcription factor ETS2 to transcriptionally activate multiple nucleotide metabolism genes, including RRM2b, dCK, and TK1 (Kollareddy et al., 2015). Knockdown of mutant p53 in cancer cells reduces expression of these genes and depletes nucleotide pools, leading to comprised tumorigenecity of cancer cells, suggesting that mutant p53 upregulates nucleotide biosynthesis to promote tumorigenesis (Kollareddy et al., 2015) (Figure 2). Collectively, these studies indicate that promoting metabolic reprogramming in cancer cells is a critical mechanism contributing to mutant p53 GOF in tumorigenesis.

Conclusion and perspective

Recently, significant advances have been made in understanding the role of p53 and its GOF mutants in metabolism. While wt p53 usually represses glycolysis and the synthesis of lipids and nucleotides, GOF mutant p53 was reported to promote glycolysis and the synthesis of lipids and nucleotides in cancer cells. Further, while the regulation of metabolism by wt p53 often contributes to the tumor suppressive function of wt p53, the regulation of metabolism by mutant p53 often contributes to their oncogenic GOF in tumorigenesis. It is also worth noting that the mechanisms by which wt p53 and mutant p53 regulate the same metabolic pathways are very different. These findings have significantly increased our understanding of the role and mechanism of p53 in metabolic regulation and tumor suppression. However, currently, the roles and mechanisms of p53 and its GOF mutants in metabolic regulation and their contributions to tumor suppression or progression are far from clear. Obviously, many questions remain to be addressed and many more studies are needed in future. These remaining questions include: (i) whether p53 (both wt and mutant forms) regulates metabolism differently in different types of cells and tissues, in response to different types of stress signals, and under the basal non-stress conditions and the stress conditions; (ii) whether different mutant p53 proteins exert different effects on metabolism; (iii) which functions of wt p53 in regulation of different metabolic pathways contribute to its role as a tumor suppressor, and whether some of these functions of wt p53 in metabolic regulation especially in response to metabolic stress contribute to survival and therapeutic resistance of cancer cells; (iv) whether p53 (both wt and mutant forms) alters metabolism in the tumor microenvironment in addition to tumor cells to impact tumor progression and therapies. In addition to its role in tumor suppression, p53 has been demonstrated to be involved in many important biological processes and diseases, such as reproduction, metabolic diseases, aging, and neurodegenerative diseases (Hu et al., 2007, 2009; Vousden and Lane, 2007; Levine and Oren, 2009; Levine et al., 2011; Chang et al., 2012; Checler and Alves da Costa, 2014; Kung and Murphy, 2016; Moyer et al., 2017). It remains unclear whether and how the function of p53 in metabolic regulation contributes to these biological processes and diseases in addition to cancer. Finally, it will be of interest and importance to study whether restoration of some of wt p53 functions in metabolic regulation and/or blocking some of mutant p53 GOF activities in metabolism in cancer cells can be exploited as novel and effective strategies for cancer treatment. Future studies on these important questions are expected to shed further light on the roles and mechanisms of p53 and its GOF mutants in metabolic regulation, leading to new opportunities for therapies for cancer and other diseases.

Conflict of interest: none declared.

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