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The p53 family orchestrates the regulation of metabolism: physiological regulation and implications for cancer therapy

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The p53 family of transcription factors is essential to counteract tumour formation and progression. Although previously this was exclusively associated with the ability of the p53 family to induce cell cycle arrest and apoptosis, an increasing number of reports have now indisputably demonstrated that the tumour suppressive functions of the p53 family members also rely on their ability to control and regulate cellular metabolism and maintain cellular oxidative homeostasis. Here, we review how each p53 family member, including p63 and p73, controls metabolic pathways in physiological conditions, and how these mechanisms could be exploited to provide anticancer therapeutic opportunities.

The p53 (*TP53*) gene is the most frequently mutated gene in human cancers (Kandoth *et al*, 2013), and has consequently captivated the attention of the cancer research community and is one of the most studied and best characterised tumour suppressor genes. This interest has been nourished by the phenotypes shown by numerous mouse models, including p53 knockout mice, that spontaneously develop tumours (Donehower *et al*, 1992; Jacks *et al*, 1994), as well as mice carrying somatic p53 mutations, that phenocopy Li–Fraumeni syndrome (Lang *et al*, 2004; Olive *et al*, 2004), a condition predisposing to early onset of several tumour types.

Initial efforts made to unveil the mechanisms utilised by p53 to mediate tumour suppression highlighted its ability to be induced by a variety of intrinsic and extrinsic stimuli, such as DNA damage, oncogene activation, ribosomal stress, hypoxia, heat shock, and others. In turn, p53 activates the expression of a large network of genes involved in many cellular processes including cell cycle control and programmed cell death. During the past decade, however, our knowledge of the p53 transcriptome became more comprehensive because of the ease of conducting genome-wide analyses. These analyses further indicated that p53 is a master regulator of many other biological processes, such as autophagy, differentiation, and tumour microenvironment remodelling (Bieging *et al*, 2014). The importance of these additional mechanisms in mediating p53 tumour suppression was recently underlined by various mouse models demonstrating that p53 tumour suppressive activities are maintained even when its regulation of cell cycle and programmed cell death are impaired (Brady *et al*, 2011; Li *et al*, 2012; Timofeev *et al*, 2013; Valente *et al*, 2013). Notably, one of these mouse models showed that lack of p53 classical responses (i.e., cell cycle arrest, apoptosis, and senescence) does not affect its capacity to control the expression of metabolism-related genes, through which p53 regulates glucose uptake and catabolism, and inhibits the production of reactive oxygen species (ROS; Li *et al*, 2012). However, when additional mutations abolishing p53 regulation of metabolism-related genes are introduced, p53 antitumour functions are restrained (Wang *et al*, 2016), thereby indicating that metabolic control by p53 is crucial to drive tumour suppression. These results are in line with the numerous connections established over the years between metabolism-related stressors (such as imbalanced nucleotide pools or nutrient deprivation) and p53 classical responses (Linke *et al*, 1996; Agarwal *et al*, 1998; Hastak *et al*, 2008) that indicate that the various p53-regulated processes are not compartmentalised, and instead they can synergistically promote each other to ultimately maintain cellular homeostasis and counteract tumour formation and progression (Bieging *et al*, 2014).

In performing its tumour suppressive activities, p53 acts in concert with the other members of its family, p63 and p73. In

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response to genotoxic stress, both proteins are recruited to the promoters of some p53 target genes and are essential for the proper induction of genes involved in apoptosis by p53 (Flores *et al*, 2002), a property relying on the high homology of the DNA-binding domains of these three transcription factors. In addition to cooperating in the regulation of the same set of genes, each p53 family member has its own transcriptional repertoire, whose distinctiveness is ascribed, at least in part, to the structural differences of these proteins (Botchkarev and Flores, 2014). In particular, both the p63 (*TP63*) and the p73 (*TP73*) genes encode two sets of abundantly expressed isoforms: full-length isoforms (called TAp63 and TAp73) having a transactivation domain similar to that present in p53 (known as TA1), and N-terminal truncated isoforms (ΔNp63 and ΔNp73) that are devoid of that domain and instead present an alternative and shorter transactivation domain (known as TA2) (Duijf *et al*, 2002; Orzol *et al*, 2015). Compared with the amino terminal truncated isoforms of p53 (ΔN40, ΔN133, and ΔN160), whose specific activities are still under investigation (Joruiz and Bourdon, 2016), the different functions fulfilled by the many p63 and p73 isoforms have been elucidated by the isoform-specific knockout mouse models generated over the past decade. These mouse models have revealed that both TAp63 and TAp73 are potent tumour suppressor genes: lack of either gene leads to spontaneous development of tumours in mice (Tomasini *et al*, 2008; Su *et al*, 2010). Intriguingly, their tumour suppressive activities are associated with the ability of these proteins to control lipid and glucose metabolism and mitochondrial function, respectively (Rufini *et al*, 2012; Su *et al*, 2012). On the other hand, Δ*Np63* and Δ*Np73* knockout mice have developmental defects in the epidermis and limbs, and in the nervous system, respectively (Wilhelm *et al*, 2010; Chakravarti *et al*, 2014; Restelli *et al*, 2014). Both proteins act as dominant negative by binding to the other members of the family and inhibiting their functions. A detailed mechanism underlying the oncogenic properties of ΔNp63 and ΔNp73 was recently connected with their ability to regulate metabolic reprogramming in tumours (Venkatanarayan *et al*, 2015).

Given the numerous links between the p53 family members and metabolic pathways, here we review the physiological roles of these transcription factors in controlling cellular metabolism and discuss how these connections reverberate through tumour initiation and progression, thus providing opportunities that can be exploited for cancer treatment.

THE P53 FAMILY AND CARBOHYDRATE METABOLISM

Glucose is one of the primary energy sources for both normal and cancer cells and the p53 family controls its metabolism at multiple levels (Figure 1). First, both p53 and TAp63 regulate the balance of glucose uptake via the many glucose transporters present on the cytoplasmic membrane. In the case of high intracellular levels of glucose, p53 directly represses the expression of *GLUT-1* and *GLUT-4* (Schwartzenberg-Bar-Yoseph *et al*, 2004), and it decreases expression of *GLUT-3* by antagonising the NF-κB pathway (Kawauchi *et al*, 2008). On the contrary, when intracellular levels of glucose are low, TAp63 promotes glucose uptake, even though the involved glucose transporters are not currently defined (Su *et al*, 2012). Once internalised, glucose is catabolised through glycolysis, whose first step is mediated by hexokinase II, encoded by the p53 transcriptional target gene *HK2* (Mathupala *et al*, 1997). The substrate of hexokinase II activity, glucose-6-phospate (G6P) can fuel two alternative pathways: glycolysis and the pentose phosphate pathway (PPP). In human and mouse cell lines, both in physiological conditions and in response to oxidative stress, p53 inhibits subsequent steps of the glycolysis pathway through its transcriptional target genes, *TIGAR* (Bensaad *et al*, 2006) and *miR-34a* (Kim *et al*, 2013), thereby shunting G6P towards the PPP. This pathway generates several metabolites, including precursors of nucleotides and aromatic amino acids, and allows for the production of reducing equivalents in the form of NADPH that in turn supports p53 regulation of the cellular oxidative homeostasis (Bensaad *et al*, 2006). *TIGAR* promotes the PPP and the formation of NAPDH through the elimination of ROS as demonstrated in *TIGAR* −/− mice that, although developmentally normal, are characterised by defects in ROS scavenging capacity and reduced tissue regeneration potential (Cheung *et al*, 2013).

The PPP flux is also enhanced by TAp73 through the induction of *glucose-6-phosphate dehydrogenase* (*G6PD*), the first and rate-limiting enzyme of the PPP (Jiang *et al*, 2013b). In human cancer cell lines, instead, p53 inhibits the PPP pathway by secluding G6PD (Jiang *et al*, 2011), thus depleting cells of antioxidants and leading to excessive oxidative stress and cell death. Independently of p53, both TAp63 and TAp73 can achieve the same effect through the induction of *IAPP* (Venkatanarayan *et al*, 2015); its gene product amylin is an inhibitor of hexokinase II preventing G6P formation and utilisation for the PPP. The relevance of amylin's tumour suppressive and preventive activity was demonstrated by its synthetic analogue pramlintide, an FDA approved antidiabetic drug that leads to tumour regression in *p53* −/− mice (Venkatanarayan *et al*, 2015, 2016).

The involvement of the p53 family in carbohydrate metabolism is also crucial during the final steps of glycolysis (Figure 1). The by-product of this pathway, lactate, is generally expelled by cells through the monocarboxylate transporter 1 (MCT1), whose expression is repressed by p53 in hypoxic conditions (Boidot *et al*, 2012). The subsequent accumulation of lactate prevents glycolysis to further take place and forces its precursor pyruvate to feed the tricarboxylic acid (TCA) cycle, an event additionally promoted by p53 that sustains the conversion of pyruvate into acetyl-CoA (Contractor and Harris, 2012). Concurrently, p53 inhibits pyruvate recycling by the TCA cycle through the repression of the two malic enzymes *ME1* and *ME2* (Jiang *et al*, 2013a) and provides additional fuel for this pathway by inducing *GSL2* (Hu *et al*, 2010; Suzuki *et al*, 2010), thus overall increasing the TCA cycle rate. Mass spectrometry experiments performed upon overexpression of *TAp73* suggested that it supports the TCA cycle by increasing the levels of several enzymes involved in this pathway (D'Alessandro *et al*, 2013). However, further investigation is needed to unveil the connections of the TCA cycle with TAp73 at physiological levels, as well as with the other members of the p53 family.

Overall, the p53 family members, and in particular p53 and TAp63, cooperate in regulating intracellular glucose levels by balancing glucose uptake accordingly, and promote the diversion of glucose metabolites towards PPP by acting on different steps of the glycolytic pathway.

LIPID METABOLISM CONTROL BY THE P53 FAMILY

Lipids have the highest caloric content among the biological macromolecules and represent the best energetic storage for cells; therefore, both fatty acid catabolism and anabolism are tightly regulated and kept in check by the p53 family. Synthesis of fatty acids is restricted to specialised tissues, including adipose tissue, liver, and lactating mammary glands. Both p53 and TAp63 concur in inhibiting this process as highlighted by the proclivity of their respective knockout mouse models to become obese (Su *et al*, 2012; Wang *et al*, 2013). In the case of p53, the counteraction of lipid biogenesis is mainly achieved in the adipocytes through the

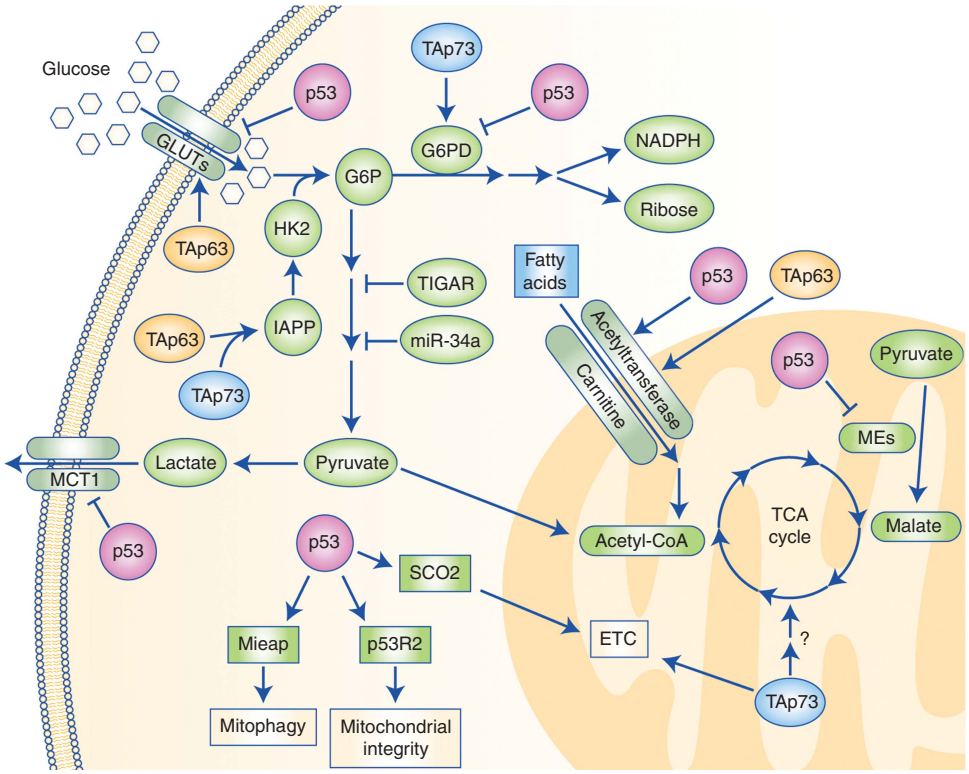

Figure 1. Crosstalk between the p53 family members and metabolic pathways. The p53 (pink) and its family members, TAp63 (orange) and TAp73 (blue), control glucose uptake and inhibit glycolysis while enhancing fatty acid oxidation and favouring mitochondrial maintenance and activity.

repression of the master regulator of fatty acid synthesis, *SREBP1*, that in turn cannot trigger the expression of several enzymes involved in this pathway, including *acetyl-CoA carboxylase* (*ACC*), *ATP citrate lyase* (*ACLY*), and *fatty acid synthase* (*FASN*) (Yahagi *et al*, 2003). TAp63 also controls downregulation of FASN and of other lipogenic enzymes through the concerted transcriptional activation of *AMPKα2*, *LKB1* (also known as *STK11*), and *SIRT1* (Su *et al*, 2012). This TAp63-mediated inhibition of lipid anabolism can be supported by metformin, a drug widely used to treat type II diabetes and reported to increase TAp63 levels in order to accomplish its antidiabetic effects (Su *et al*, 2012). A contribution opposite to p53 and TAp63 is provided by ΔNp63, whose induction of *FASN* in head and neck squamous cell carcinomas is required for ΔNp63-dependent prosurvival activities (Sabbisetti *et al*, 2009).

Mevalonate (MVA) is another important lipogenic pathway that allows for the synthesis of cholesterol. Many of the enzymes involved in the MVA pathway are induced by p53 that in this way can control both membrane permeability and the synthesis of cholesterol-derived hormones (Laezza *et al*, 2015). In tumours harbouring p53 mutations, these proteins interact with SREBP1 thus hijacking the MVA pathway and promoting the mutant p53-associated aggressiveness of several breast cancers (Freed-Pastor *et al*, 2012). This phenomenon can be counteracted by the utilisation of clinically available HMG-CoA reductase inhibitors, such as simvastatin (Freed-Pastor *et al*, 2012), that could represent a valid therapeutic opportunity to treat mutant p53-addicted tumours. As many of the gain-of-function properties of mutant p53 rely on its ability to inhibit TAp63 and TAp73 (Walerych *et al*, 2012), it would be interesting to investigate whether these two p53 family members may also affect the MVA pathway.

Lipid anabolism needs to be coordinated and compensated by fatty acid oxidation (FAO) that enables lipid stored energy to be utilised. In opposition to the limited number of tissues where *de novo* fatty acid biosynthesis takes place, this mitochondrial catabolic pathway occurs in all the cells of the body apart from red blood cells and neurons. The FAO mediates the degradation of fatty acids into two-carbon moieties that – once channelled into acetyl-CoA – may fuel the TCA cycle. The first step of FAO, that is the translocation of the fatty acids into the mitochondria, is performed by carnitine acetyltransferases, induced by both p53 (Sanchez-Macedo *et al*, 2013) and TAp63 (Su *et al*, 2012; Figure 1). In general, both p53 family members cooperate in reducing lipid synthesis and promoting lipid degradation, thus counteracting predisposition to obesity and tumour formation (Su *et al*, 2013). The other member of the family, p73, is also implicated in the regulation of lipid metabolism. The p73 knockout mice show abnormal lipid accumulation in the liver because of impaired triglyceride hydrolysis, with *in vitro* data pointing at an involvement of TAp73 in such a process (He *et al*, 2013, 2015). It would be interesting to assess the *in vivo* role of each p73 isoform, namely TAp73 and ΔNp73, in lipid metabolism in the respective isoform-specific knockout mice, even though a possible lack of evidence could be in line with some of the distinctive functions of these isoforms compared with the rest of their family (Napoli and Flores, 2016).

THE P53 FAMILY DICTATES MITOCHONDRIAL ACTIVITIES AND ROS PRODUCTION

The coordinated regulation of glycolysis and FAO by p53 and TAp63 causes the channelling of both pathways in the synthesis of acetyl-CoA, thus promoting the TCA cycle and the production of NADH and $FADH_2$. These reducing agents are then exploited by the oxidative phosphorylation (OXPHOS) in the mitochondria to

complete cellular respiration. The integration of these pathways allows the most efficient generation of ATP molecules per amount of glucose. In cancer cells, however, such a concerted action does not always occur and glucose may be entirely processed into lactate through glycolysis even in normoxic conditions. This was one of the earliest metabolic features of cancer cells to be discovered and is now known as Warburg effect (Warburg, 1925).

In addition, p53 sustains OXPHOS by inducing the expression of enzymes of the mitochondrial electron transport chain, including *cytochrome c oxidase 2* (*SCO2*; Matoba *et al*, 2006) and the *mitochondrial encoded cytochrome c oxidase 1* (*MT-CO1*) (Okamura *et al*, 1999). The latter observation is in agreement with the broader activity of p53 in mitochondrial maintenance. Indeed, p53 can localise to the mitochondria (Marchenko *et al*, 2000), where it controls mitochondrial genomic integrity through its interaction with mitochondrial DNA polymerase γ (Achanta *et al*, 2005). Furthermore, p53 regulates mitochondrial DNA copy number and mitochondrial mass through the induction of the *p53-controlled ribonucleotide reductase* (*p53R2*; Bourdon *et al*, 2007), and it is required for the proper removal of damaged mitochondria (i.e., mitophagy) via the upregulation of the mitochondria-eating protein (*Mieap*; Kitamura *et al*, 2011).

Although p53 and TAp63 promote OXPHOS at multiple levels, the support by TAp73 mainly relies on its ability to induce the expression of *cytochrome c oxidase 4 isoform 1* (*Cox4i1*; Flores and Lozano, 2012; Rufini *et al*, 2012; Figure 1). As reported for the other family members (Su *et al*, 2009, 2012; Vigneron and Vousden, 2010), altered mitochondrial functions due to loss of *TAp73* decrease oxygen consumption and ATP production by the mitochondria that in turn are associated with increased oxidative damage and senescence *in vitro*, and premature ageing *in vivo* (Rufini *et al*, 2012). All these effects are attributable to the increased levels of ROS, whose intracellular amounts are strictly regulated by all the p53 family members. p53 has been reported to both reduce and increase ROS levels, and this Janus effect is associated with different cellular conditions. In physiological conditions as well as under minor metabolic stress, p53 participates in reducing ROS levels through multiple approaches, including: (1) maintenance of mitochondrial integrity (Park *et al*, 2016); (2) induction of *TIGAR* that stimulates NADPH production by the PPP pathway (Bensaad *et al*, 2006); (3) promotion of GSH synthesis after serine depravation (Maddocks *et al*, 2013); (4) upregulation of several antioxidant factors, such as *aldehyde dehydrogenase 4* (*ALDH4*; Yoon *et al*, 2004), *sestrin-1* and *-2* (*SESN1* and *SESN2*) (Budanov and Karin, 2008), and *tumour protein p53 inducible nuclear protein 1* (*TP53INP1*; Cano *et al*, 2009); and (5) repression of pro-oxidant genes like *cyclooxygenase 2* (*COX2*; Subbaramaiah *et al*, 1999) and *nitric oxide synthase* (*NOS*; Ambs *et al*, 1998). However, in the case of severe damage, p53 increases ROS levels to eliminate the damaged cells through both induction of pro-oxidative genes (Zhuang *et al*, 2012) and inhibition of antioxidant genes, including *G6PD* (Jiang *et al*, 2011), *ME1* and *ME2* (Jiang *et al*, 2013a), and *manganese superoxide dismutase* (*SOD2*; Zhao *et al*, 2005). These p53-dependent augmented ROS levels can be further increased by the p53-mediated repression of *PGC-1α* and *PGC-1β*, two transcription factors required for mitochondrial biogenesis, in response to irreparable damage such as telomere shortening (Sahin *et al*, 2011). In *p53*-deficient or -mutated cancer cells, both TAp63 and TAp73 can substitute for p53 pro-oxidative functions by upregulating *IAPP* (Venkatanarayan *et al*, 2015) that inhibits hexokinase 2 and G6P formation to hinder PPP flux and the production of antioxidant equivalents. Hence, in physiological condition, p53, TAp63, and TAp73 cooperate in keeping ROS production under control, but, in line with their functions as tumour suppressors, these transcription factors can also exploit ROS to eliminate any overly damaged or cancerous cell.

CALORIC RESTRICTION, LONGER LIFESPAN, AND THE P53 FAMILY

A constantly growing body of compelling evidence obtained in multiple organisms clearly shows a correlation between restrained metabolism (i.e., caloric restriction) and increased lifespan (Ruetenik and Barrientos, 2015). Reduced availability of nutrients, such as glucose and amino acids, primarily triggers autophagy, a catabolic mechanism allowing protein recycle and degradation of damaged organelles (Napoli and Flores, 2013). This biological process can be activated by p53, TAp63, and TAp73 as stress response (Kenzelmann Broz *et al*, 2013), and it is essential to counteract ageing and age-related diseases (Martinez-Lopez *et al*, 2015). In line with this, one of the proposed physiological functions of p53 is to delay ageing. Indeed, transgenic mice expressing multiple copies of *p53* under its endogenous promoter – therefore maintaining its normal regulation – are characterised by increased lifespan (Matheu *et al*, 2007). On the contrary, any alterations of the p53 physiological activity, either its inhibition through mutations (as in p53 S18A) or its stable hyperactivation possibly because of the expression of C-terminal fragments, correlate with reduced longevity, osteoporosis, and other signs of accelerated ageing (Tyner *et al*, 2002; Armata *et al*, 2007). The protective role in ageing of physiological p53 levels could be attributed to the multiple connections between p53 and the two nutrient sensors and autophagy modulators, mTOR and Sirt1 (Tucci, 2012; Napoli and Flores, 2013). Both factors are crucial regulators of ageing. The mTOR is the hub on which nutrient levels and growth factor signalling pathways converge to block autophagy; therefore, either pharmacological or mutational inhibition of the mTOR pathway can increase longevity in a variety of *in vivo* models, ranging from yeast to mice (Johnson *et al*, 2013). Sirt1 can function as an indirect sensor of the cellular oxidative state and it activates autophagy in response to oxidative stress detected as high $NAD+$ levels. Although the relevance of Sirt1 in expanding lifespan may vary according to the considered animal model and could be concealed by the presence of other sirtuins having redundant function (Ramis *et al*, 2015), *Sirt1*-overexpressing mice show reduced incidence of age-related metabolic disorders such as diabetes and liver steatosis (Banks *et al*, 2008). Intriguingly, *Sirt1* is a direct TAp63 target gene (Su *et al*, 2012) and *TAp63* $-/-$ mice, which have low *Sirt1* levels, are characterised both by impaired glucose and lipid metabolism (Su *et al*, 2012) and by premature ageing and reduced lifespan (Su *et al*, 2009). Similar reduced lifespan is observed in *TAp73* $-/-$ mice and, also in this case, the defect is associated with metabolic dysfunctions (Rufini *et al*, 2012).

Taken together, these *in vivo* mouse models underline the crucial connections between metabolic pathways, ageing, and the tumour suppressive members of the p53 family.

TARGETING METABOLIC PATHWAYS AS ANTICANCER STRATEGY

The numerous connections interweaving the p53 family members with the above-discussed metabolic pathways are present in both normal and cancer cells. As a consequence, several compounds able to interfere with either glucose or lipid metabolism have been demonstrated to sustain the tumour suppressive activities of p53, TAp63, and TAp73 (Figure 2). One of the best-investigated examples is metformin. For more than a decade, reports have been accumulating regarding the antineoplastic properties of this drug that is primarily used for its antidiabetic efficacy (Aldea *et al*, 2014). Intriguingly, part of this anticancer effect can be attributed to the capability of metformin to increase the levels of TAp63, in turn promoting the TAp63-mediated induction of genes crucial for

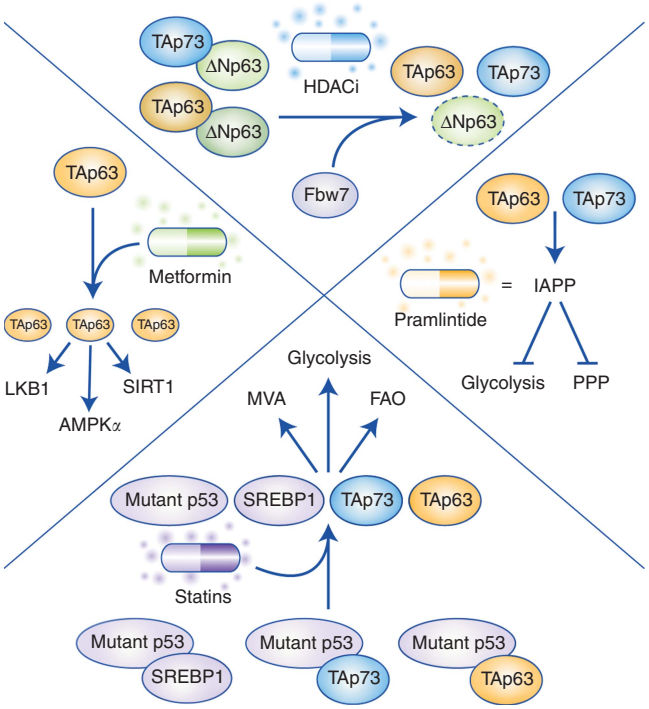

Figure 2. The FDA-approved drugs that enhance p53 family tumour suppression through metabolic reprogramming. The FDA-approved compounds promote the transcriptional activity of TAp63 (orange) and TAp73 (blue), ultimately supporting the p53 family-mediated tumour suppression through transcriptional regulation of metabolic reprogramming.

both metabolic regulation and tumour suppression, such as *AMPKα2*, *LKB1*, and *SIRT1* (Su *et al*, 2012). Another promising anticancer strategy is represented by the usage of statins (Matusewicz *et al*, 2015) that have been proved to limit the oncogenic properties of mutant p53 (Freed-Pastor *et al*, 2012). Given that one of the main features of mutant p53 is to sequester TAp63 and TAp73, it can be hypothesised that part of the tumour suppressive activities associated with statins might be achieved by unleashing these two transcription factors. In addition to inhibition by mutant p53, TAp63 and TAp73 can also be bound and blocked by ΔNp63 and ΔNp73 (Orzol *et al*, 2015). It has recently been demonstrated that ΔNp63 can be targeted by HDAC inhibitors (HDACi) that efficaciously reduce the levels of ΔNp63 through Fbw7 (Napoli *et al*, 2016). As tumour regression associated with loss of *ΔNp63* is also accompanied by metabolic reprogramming (Venkatanarayan *et al*, 2015), it would be interesting to verify whether the therapeutic activity of HDACi may partially rely on alterations in metabolism caused by the reactivation of TAp63 and TAp73. Once these two transcription factors are released from the inhibition of a dominant negative member of the family (namely mutant p53, ΔNp63, or ΔNp73), they induce the expression of *IAPP*, whose synthetic analogue, pramlintide, was proven to act as a potent anticancer drug in preclinical models (Venkatanarayan *et al*, 2015, 2016).

Taken together, these different classes of molecules (metformin, statins, HDACi, and pramlintide) indicate that perturbing the p53 family to achieve metabolic reprogramming can be an effective strategy to counteract tumour formation and progression. Hence, we deem that this evidence should prompt the investigation of additional compounds that have more specificity in targeting the p53 family-dependent metabolic regulation, thus providing anti-cancer therapies with additional tools.

CONCLUSIONS

During the past decade, the complex network connecting the p53 family and metabolic pathways has constantly expanded, thereby capturing the attention of the p53/p63/p73 field. Indeed, the tumour suppressive activities of p53, TAp63 and TAp73 do not exclusively rely on their cytostatic and cytotoxic effects, but they are also intertwined with their fundamental roles in governing cellular metabolism (Tomasini *et al*, 2008; Su *et al*, 2010, 2012; Li *et al*, 2012; Rufini *et al*, 2012). In general, these transcription factors cooperate in supervising glucose and lipid metabolism, mitochondrial functions, as well as ROS production. Many of these activities can also be mimicked by the usage of antidiabetic drugs, such as metformin and pramlintide, whose anticancer efficacy in patients needs to be assessed. Further investigation is also required to determine a possible role of the p53 isoforms in metabolism, as well as to unveil other metabolic pathways potentially regulated by the dominant negative isoforms, ΔNp63 and ΔNp73, and the rest of the family, in addition to what has been reported for glycolysis, synthesis of fatty acids, and ROS production (Sabbisetti *et al*, 2009; Venkatanarayan *et al*, 2015). These future characterisations will improve our comprehension of the metabolic regulation by the p53 family as a whole, and may allow the discovery of novel anticancer tools.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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