CELL DEATH AND AUTOPHAGY

p53 in survival, death and metabolic health: a lifeguard with a licence to kill

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Abstract | The function of p53 as a tumour suppressor has been attributed to its ability to promote cell death or permanently inhibit cell proliferation. However, in recent years, it has become clear that p53 can also contribute to cell survival. p53 regulates various metabolic pathways, helping to balance glycolysis and oxidative phosphorylation, limiting the production of reactive oxygen species, and contributing to the ability of cells to adapt to and survive mild metabolic stresses. Although these activities may be integrated into the tumour suppressive functions of p53, deregulation of some elements of the p53-induced response might also provide tumours with a survival advantage.

Despite 35 years of intense research into the regulation and functions of the tumour suppressor protein p53, new and surprising observations are still being made. The best-understood function of p53 is as a transcription factor that can either activate or repress the expression of a large number of genes and microRNAs[1–3]. Additional transcriptionally independent activities of p53 are mediated by its direct interactions with cytoplasmic proteins, such as apoptotic effectors or metabolic enzymes[4]. Although not absolutely required for normal growth and development, p53 has an important role in determining the response of cells to numerous types of stress — such as DNA damage, hypoxia and nutrient fluctuation — by both supporting cell survival and promoting cell death[5,6]. In this Review, we consider the role of p53 in these life and death decisions. We summarize the different ways in which p53 activity can result in a permanent inhibition of cell proliferation, through the induction of cell death, senescence and differentiation. We then consider the various mechanisms through which p53 can support cell survival, with an emphasis on our more recent understanding of the role of p53 in enabling metabolic adaptation. Finally, we discuss how the final response to p53 activation — be it cell survival or cell death — can be regulated.

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Regulation of p53

A p53 response can be activated by many different stress signals, including genotoxic stress, oncogene activation, ribosomal stress and a lack of oxygen or other nutrients. These stress signals lead to the activation of p53 through numerous mechanisms, which we can only briefly summarize here. The expression of p53 can be modulated by changes in transcription, translation and mRNA splicing events[7], which have recently been shown to give rise to several p53 isoforms that exhibit different activities[8]. p53 is also subject to a wide range of post-translational modifications, including phosphorylation, modification with ubiquitin and other ubiquitin-like proteins, acetylation, methylation, glycosylation, farnesylation, hydroxylation, ADP ribosylation and PIN1-mediated prolyl isomerization[9,10]. These post-translational modifications — in concert with the interaction of p53 with a wide variety of protein-binding partners — help to regulate the subcellular localization, stability and conformation of p53, ultimately controlling both its transcriptional and transcriptionally independent functions. The regulation of protein stability is one of the central mechanisms through which p53 function is controlled, with a key role for the ubiquitin ligase MDM2, which both targets p53 for degradation and directly inhibits p53 activity by binding to the transcriptional activation domain[11,12]. Under conditions of cellular homeostasis, MDM2 functions in combination with its binding partner MDMX (also known as MDM4) to keep p53 activity under control[13]. Importantly, p53 transcriptionally activates several of its own regulators, including MDM2, allowing for efficient feedback control to limit the p53 response. Therefore, many levels of p53 regulation coordinate the duration and type of response to different forms of stress.

Functions of p53 in health and disease

Although best known for its activity as a tumour suppressor, p53 can help to control a diverse range of cellular processes and diseases. From its ancestral role in protecting

Box 1 | **Apoptosis**

In response to intracellular (intrinsic) and extracellular (extrinsic) stimuli, cells can undergo a caspase-dependent form of programmed cell death called apoptosis. The extrinsic apoptotic pathway is initiated by the binding of death ligands such as FAS ligand or TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) to their respective receptors, leading to cell death through the activation of caspase 8. The intrinsic apoptotic cascade leads to mitochondrial outer membrane permeabilization (MOMP), which releases cytochrome *c* into the cytoplasm. This in turn activates the caspase cascade that leads to cell death. MOMP is regulated by the BCL-2 family of proteins, including the pro-apoptotic factors BCL-2-associated X protein (BAX) and BCL-2 homologous antagonist/killer (BAK) that are required for forming pores in the mitochondrial membrane. This activity is regulated by anti-apoptotic multidomain proteins such as BCL-2 and BCL-X_L, which bind to BAX and BAK to render them inactive. One group of BH3-only proteins (the sensitizers) indirectly induce apoptosis by binding to anti-apoptotic proteins to release BAX and BAK. A second group of BH3-only proteins (the activators) directly activate the MOMP-inducing functions of BAX and BAK; these activators are in turn negatively controlled by the anti-apoptotic proteins[157].

DNA in the germ line, p53 has evolved to contribute to the regulation of almost every facet of cell behaviour, including proliferation, growth, DNA repair, cell death, cell survival, senescence, differentiation, stem cell reprogramming, metabolism and motility. Unsurprisingly, these functions of p53 have broad effects on many aspects of health and disease. For example, the ability of p53 to induce cell death and regulate redox stress may help to limit cancer progression, but these functions of p53 have also been implicated in the development of obesity, diabetes, ischaemia, ribosomal syndromes and various neurodegenerative diseases[14]. A slight elevation or deregulation of p53 activity results in early ageing and developmental disorders[15,16], whereas the metabolic functions of p53 can help to sustain stamina during exercise[17]. The ability of p53 to limit stem cell renewal[18] can suppress tumour development but may also promote other pathologies, including ageing. p53 can have a role in restraining cell migration[19] and angiogenesis[20], regulating immune responses[21] and mediating non-cell-autonomous interactions between stressed cells and surrounding tissue[22,23]. Although each of these activities would limit tumour development, they are likely to have additional, as yet unidentified, roles in health and disease.

Taken together, the bewildering array of cellular responses to p53 is reflected by the many mechanisms through which p53 functions. Our ability to predict the outcome of p53 activation is further confounded by the observation that many responses are both positively and negatively controlled by p53. For example, p53 can decrease or increase oxidative stress, promote or inhibit autophagy, drive cell death or help cell survival (see below). Integrating some of the known functions of p53 into an overall model can help to provide a framework to rationalize p53 function. Although some aspects of this model remain speculative, the emerging theme is that p53 has a pivotal role in maintaining organismal fitness and fidelity through two broad mechanisms: first, by supporting the adaptation and repair of cells under conditions of stress and damage, and second, by driving the elimination of cells that cannot be repaired or cells in which the stress does not resolve.

BCL-2 family proteins
A group of proteins characterized by the presence of one or more BCL-2 homology (BH) domains that regulate mitochondrial outer membrane permeabilization through both pro-apoptotic and anti-apoptotic family members.

BH3-only proteins
A subclass of BCL-2 family proteins that only contain a BCL-2 homology 3 (BH3) domain.

Hitting the brakes on proliferation

The ability of p53 to prevent cell proliferation underlies the best-established model of how p53 functions to suppress tumour development. Induction of an irreversible exit from the cell cycle or activation of cell death is clearly an efficient way to eliminate nascent cancer cells and block tumour progression. Reactivation of this function of p53 in existing cancers is also a promising therapeutic goal.

p53 in cell death: apoptosis, necrosis and more? Among the first biological functions described for wild-type p53 was its ability to induce apoptosis in transformed cells[24,25] (BOX 1). p53 transcriptionally activates the expression of several pro-apoptotic BCL-2 family proteins — including BCL-2-associated X protein (BAX), NOXA (also known as PMAIP1) and p53 upregulated modulator of apoptosis (PUMA; also known as BBC3)[26,27] — and directly interacts with various pro-apoptotic and anti-apoptotic proteins in the cytoplasm and at the mitochondrial membrane[4,28]. In this context, p53 can function as both a sensitizer and an activator of apoptosis[26] (BOX 1). Interestingly, the transcriptional and cytoplasmic functions of p53 are closely intertwined, as revealed by elegant studies showing that PUMA (a transcriptional target of p53) can bind to the anti-apoptotic protein BCL-X_L and release p53, which can then function as a direct activator of apoptosis[29,30]. Both the transcriptional and the cytoplasmic apoptotic activities of p53 depend on its DNA-binding domain; thus, tumour-associated mutations — which generally affect this region of p53 — fully inactivate its apoptotic function[29]. Many other transcriptional targets of p53 also have a role in promoting apoptosis, including mediators of the extrinsic apoptotic pathway such as the death receptors (DRs) FAS, DR4 (also known as TNFRSF10A) and DR5 (also known as TNFRSF10B)[31]. p53 also activates the expression of the adenosine receptor ADORA2B — a cell death-priming receptor that sensitizes cells to apoptosis through the intrinsic apoptotic pathway (BOX 1) — in response to increased extracellular levels of adenosine that are induced by hypoxia (a condition found in solid tumours) or chemotherapy[32].

In addition to apoptosis, several mechanisms of regulated necrosis have been described, including necroptosis, parthanatos, pyroptosis and ferroptosis[33]. p53 has been implicated in the promotion of some of these non-apoptotic forms of cell death, although the full extent of these activities of p53 remain unclear. In cells that lack BAX and BCL-2 homologous antagonist/killer (BAK), the p53-induced transcription of the lysosomal protease cathepsin Q in response to DNA-damaging agents is required for necrotic cell death[34]. Even in apoptosis-proficient models, p53-mediated necrosis can contribute to cell death. For example, oxidative stress during ischaemic–reperfusion injury drives the accumulation of p53 in the mitochondrial matrix[35]. Under these conditions, rather than regulating BH3-only proteins, mitochondrial p53 interacts with cyclophilin D (CYPD; also known as PPID), which causes opening of the mitochondrial permeability transition

pore to induce CYPD-mediated regulated necrosis[35]. Furthermore, p53 activates the DNA repair protein poly(ADP-ribose) polymerase 1 (PARP1) in response to reactive oxygen species (ROS)-induced DNA damage. Although this might contribute to the repair of damaged DNA, hyperactivated PARP1 can cause NAD^+ and ATP depletion and, subsequently, a form of necrotic cell death called parthanatos[36,37]. Podoptosis (which is a p53 overactivation-related cell death) is another mechanism by which p53 can promote cell death, albeit through as yet unidentified signalling pathways[38]. Finally, a recent study has described a role for p53 in sensitizing cells to ferroptosis, through the downregulation of the cystine/glutamate transporter SLC7A11 (REF 176).

Finally, p53 can regulate autophagy, a process that generally contributes to cell survival (see below) but that, under some conditions, can lead to cell death. Indeed, p53-induced autophagy can contribute to the induction of p53-dependent apoptosis[39]. Thus, p53 can promote cell death through multiple pathways.

p53 in senescence and differentiation. In addition to killing cells, the permanent inhibition of proliferation is also promoted by p53 through the induction of senescence and differentiation, which are processes that prevent further replication but leave a surviving, functioning cell. p53-induced senescence can be detected in response to oncogene activation or telomere dysfunction[40,41] and is dependent on the p53-mediated transcriptional activation of p21, which is a cyclin-dependent kinase (CDK) inhibitor that halts the cell cycle in the G_1 phase[42]. Prolonged p21-mediated cell cycle arrest leads to upregulation of the CDK inhibitor $p16^{INK4A}$ and the subsequent activation of the RB transcriptional regulator, which promotes a transcriptional programme that activates senescence[43]. However, p21 is not required for senescence in all settings, and p53 can also induce and maintain senescence through the transcriptional activation of plasminogen activator inhibitor 1 (PAI1; also known as SERPINE1)[44], which represses growth factor signalling through the PI3K pathway. Activation of senescence not only halts cell proliferation but also triggers the release of a set of secreted factors (known as the 'senescence-associated secretory phenotype')[45]. These factors can signal the clearance of senescent cells by the immune system but may also promote tumorigenesis by inducing growth and invasion[43]. The effect of senescence on tumour progression is therefore not easy to predict. Furthermore, p53 activation in surrounding stromal cells can also contribute to the fate of the tumour. In stellate cells of the liver stroma, p53-mediated senescence is required for the activation of a secretory programme that induces tumour-clearing properties in surrounding macrophages, whereas p53-deficient stellate cells recruit macrophages that stimulate tumorigenesis[23].

Although a role for p53 in the differentiation of both haematopoietic cells and several cell lines was described some time ago[46], interest in this function of p53 has recently increased. p53 has now been shown to have a role in rendering cells resistant to reprogramming and inhibiting pluripotent characteristics during cancer stem cell and induced pluripotent stem cell formation[18]. Several activities of p53 help to block reprogramming, including the induction of p21 and PUMA[47]. p53 can also repress the expression of nestin (a stem cell marker) in differentiated cells, thereby limiting cell plasticity and inhibiting tumorigenesis in response to oncogenic stress[48]. This work supports the hypothesis that p53-mediated tumour suppression is in part dependent on its capacity to maintain a differentiated cell fate.

Keeping the wheels rolling

The induction of cell death or senescence removes the proliferative capacity from damaged and potentially dangerous cells, providing a strong defence against the acquisition of cancer or defective germ cells. However, p53-activating stress signals are highly diverse, ranging from acute DNA damage to transient nutrient depletion, and it is clear that not all cells subject to p53-inducing stress are permanently eliminated. Indeed, cells that are exposed to non-genotoxic and transient stress — such as nutrient deprivation, which affects many cells during the lifetime of an organism — show effective adaptation and survival responses. Even normal cell proliferation generates signals that activate p53 (REF. 49), which must be restrained to allow cell cycle progression. In short, the induction of p53 does not necessarily lead to cell death or senescence but might even contribute to the adaptation and survival of cells to certain stress conditions. These functions reflect the ability of p53 to establish a temporary pause in cell cycle progression and contribute to DNA repair, the maintenance of energy levels and the control of redox balance.

p53 and the repair of genotoxic damage. The ability of p53 to help to repair cells has been shown most clearly following DNA damage, where p53-activated cell cycle arrest can suspend cell cycle progression, allowing DNA lesions to be repaired. The main transcriptional target of p53 involved in establishing this process is *CDKN1A* (encoding p21), which can induce a temporary cell cycle arrest in addition to its contribution to senescence described above[50–52]. Indeed, the reversibility of the p53 response is key to allowing cells that have successfully repaired any damage to resume proliferation. Furthermore, p53 can contribute to the activation of many DNA repair pathways[53]. As mentioned above, p53 activates PARP1 in response to moderate DNA damage, which contributes to the detection and repair of single-stranded DNA breaks. p53 is also important in maintaining genome stability, at least in part by helping to regulate centrosome duplication[54,55]. Therefore, p53 can both eliminate irreparably damaged cells through the induction of cell death while supporting the repair and survival of cells that have sustained moderate degrees of DNA damage.

Watching the fuel gauge: p53 and metabolic health. Although severe or sustained metabolic insult can promote p53-dependent cell death, we are increasingly appreciating a more subtle role of p53 in maintaining metabolic homeostasis and allowing cells to adapt to

Box 2 | **Energy metabolism**

Cellular nutrients are taken up and metabolized to produce energy and building blocks to support cell growth and cell proliferation[158]. Glucose is a key nutrient used for both the synthesis of macromolecules (such as lipids, proteins and DNA) and the generation of energy, which is conserved as ATP. Glucose is oxidized in the glycolytic pathway to pyruvate (in the cytoplasm), which enters the tricarboxylic acid cycle in the mitochondria where it is further oxidized. This produces NADH and $FADH_2$, which carry electrons to the electron transport chain, in which ATP is produced through oxidative phosphorylation (OXPHOS)[159]. When glucose is completely oxidized, a total of approximately 36 ATP molecules are produced per molecule of glucose; two of these ATPs are acquired from glycolysis itself and the rest from OXPHOS. Cancer cells increase their glucose uptake and glycolytic rate while decreasing OXPHOS in aerobic conditions, a process known as the Warburg effect[158]. This enables more glycolytic intermediates to be used for the biosynthesis of lipids, proteins and DNA and helps to limit the production of reactive oxygen species.

In addition to glucose, amino acids support cell survival and cell growth, as they are used for protein synthesis and are important sources of carbon and nitrogen for lipid and nucleic acid synthesis. Some non-essential amino acids such as serine become 'conditionally essential' in rapidly proliferating cells as demand outweighs their biosynthesis[89,160–162, 163]. Fatty acids, which can be produced *de novo* or taken up from the extracellular environment, are also important sources of energy. When glucose levels are depleted, cells switch their metabolism to fatty acid oxidation as a source for ATP production. Fatty acids are also important signalling molecules and are the main building blocks of lipids used for cell membrane biosynthesis.

and survive transient metabolic stress[56]. These protective functions of p53 can not only help to prevent damage and thereby limit cancer development, but also provide unexpected and counterintuitive mechanisms through which p53-related activities might contribute to tumorigenesis[14].

Activation of p53 in response to nutrient stress. Numerous mechanisms induce p53 in response to nutrient stress. AMP-activated protein kinase (AMPK) is an important nutrient sensor that stabilizes and activates p53 through several means, including the phosphorylation and acetylation of p53 (REFS 57,58), and the phosphorylation (and thus inhibition) of MDMX[59,58]. The nucleocytoplasmic enzyme malate dehydrogenase (MDH1) also stabilizes p53 by directly binding to it upon glucose starvation, inducing cell cycle arrest[60].

Perturbations in ribosome biogenesis in response to nutrient deprivation result in the direct binding of ribosomal proteins to MDM2, inhibiting MDM2 activity and thus stabilizing p53 (REF. 61). This pathway is distinct from those that result in the inhibition of MDM2 in response to DNA damage, and it can be selectively disrupted by a mutation in the gene encoding MDM2 that prevents ribosomal protein binding. Mice carrying this *Mdm2* mutation respond normally to DNA damage but fail to maintain liver homeostasis when starved[62], possibly reflecting a role for p53 in the promotion of fatty acid oxidation (FAO) under low-nutrient conditions (see below).

A lack of folate — a water-soluble vitamin and an essential nutrient for normal cell metabolism and proliferation — can also induce p53 activity. However, under these conditions, the activation of p53 was associated with the *de novo* synthesis of ceramide and apoptosis, rather than enhanced cell survival[63]. The essential amino acid methionine and its metabolite *S*-adenosylmethionine (SAM) are important components of DNA and protein methylation and are crucial for cell proliferation. Depriving pluripotent stem cells of methionine leads to cell cycle arrest and apoptosis, which are partly induced by p53 (REF. 64).

Bioenergy versus biomass: a role for p53. A key metabolic function of p53 is to regulate energy metabolism by lowering rates of glycolysis and augmenting mitochondrial respiration (BOX 2; FIG. 1). p53 downregulates the first step of glycolysis (that is, cellular glucose uptake) by directly supressing the transcription of glucose transporter type 1 (GLUT1; also known as SLC2A1) and GLUT4 (also known as SLC2A4)[65], and by inhibiting nuclear factor-κB (NF-κB), which activates GLUT3 (also known as SLC2A3)[66]. TIGAR (*TP53*-inducible glycolysis and apoptosis regulator), which is encoded by a p53-inducible gene, has a fructose bisphosphatase activity similar to that shown by the bifunctional enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK2/FBPase 2). This enables TIGAR to hydrolyse — and thus lower the levels of — fructose-2,6,-bisphosphate, which is an allosteric activator of phosphofructokinase 1 (PFK1), the enzyme that catalyses the rate-limiting step in glycolysis[67,68] (FIG. 1). p53 can also downregulate the expression of another glycolytic enzyme, phosphoglycerate mutase (PGM)[69] and, through the activation of miR-34a, p53 can indirectly repress the expression of several glycolytic enzymes[70]. The net result of p53 activation is therefore to limit the glucose flux to pyruvate, which is the end product of glycolysis. Pyruvate can be converted into either lactate or acetyl-coenzyme A (CoA) in reactions that are catalysed by lactate dehydrogenase (LDH) and pyruvate dehydrogenase (PDH), respectively. p53 inhibits the expression of mitochondrial PDH kinase 2 (PDK2) — a negative regulator of PDH[71] — resulting in increased PDH activity. This promotes the conversion of pyruvate into acetyl-CoA, which can enter the tricarboxylic acid cycle (TCA cycle) and enhance mitochondrial respiration (FIG. 1). Similarly, p53 can activate the expression of parkin (*PARK2*)[72], the Parkinson disease-associated gene that augments the expression of PDHA1, an important subunit of PDH.

In addition to limiting glycolysis and diverting pyruvate towards the TCA cycle, p53 can enhance mitochondrial function and respiration through several other mechanisms. The gene encoding the mitochondrial protein glutaminase 2 (GLS2) is a transcriptional target of p53. GLS2 catalyses the hydrolysis of glutamine to produce glutamate, which can be further catabolized to the TCA cycle intermediate α-ketoglutarate and ammonia, thereby supporting mitochondrial respiration and ATP production[73,74] (FIG. 1). p53 activates the expression of synthesis of cytochrome *c* oxidase 2 (SCO2), a positive regulator of mitochondrial cytochrome *c* oxidase (COX) assembly, which is crucial for the normal functioning of the electron transport chain and oxidative phosphorylation (OXPHOS)[75]. Basal p53 levels maintain the expression of mitochondrial apoptosis-induced factor (AIF), which is required to maintain the electron transport chain.

Ceramide
A lipid comprising sphingosine and a fatty acyl chain that is concentrated in cell membranes. In addition to a structural role, ceramide has various signalling functions, including the ability to induce apoptosis.

Glycolysis
A cytoplasmic metabolic pathway that converts glucose into pyruvate through a range of enzymatic reactions.

Tricarboxylic acid cycle
(TCA cycle). A mitochondrial cycle that utilizes metabolites derived from sugar, protein and fat to provide anabolic intermediates and the reducing agents NADH and $FADH_2$ for ATP production through oxidative phosphorylation.

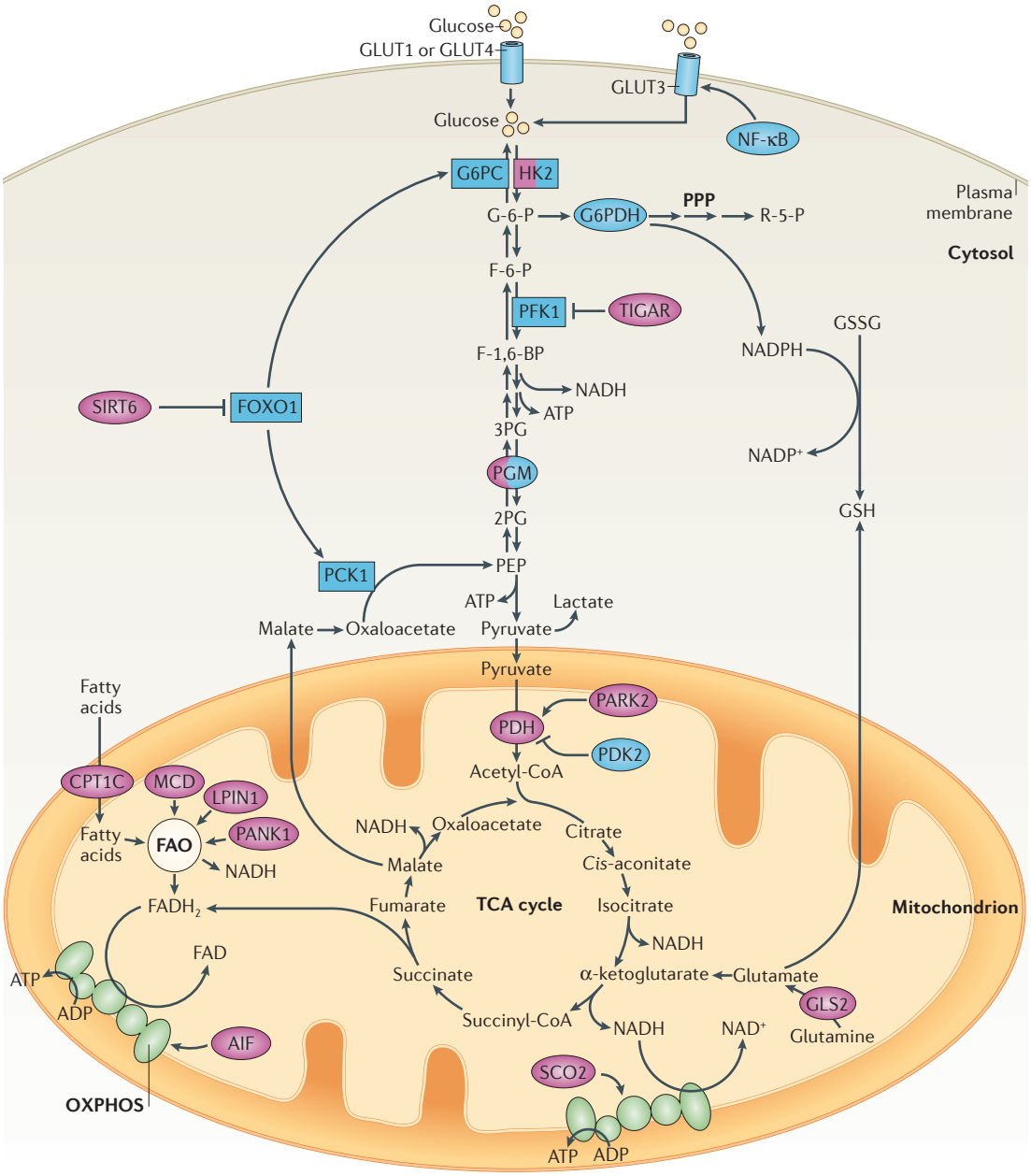

Figure 1 | **p53 regulates metabolism by restricting glycolysis and enhancing oxidative phosphorylation.** p53 regulates metabolic pathways by modulating the transcription or activity of metabolic enzymes and by regulating signalling pathways that affect metabolic control. Proteins depicted in blue are downregulated by p53, whereas proteins depicted in pink are upregulated by p53. The figure demonstrates how p53 limits the glycolytic rate by inhibiting the uptake of glucose (by glucose transporter type 1 (GLUT1), GLUT4, and GLUT3) and its downstream oxidation to pyruvate (by phosphofructokinase 1 (PFK1) and phosphoglycerate mutase (PGM)) through direct or indirect inhibition of enzymes that are important for glycolysis. The pentose phosphate pathway (PPP) — a side arm of glycolysis — can be inhibited by p53 through its binding to glucose-6-phosphate (G-6-P) dehydrogenase (G6PDH). p53 activates sirtuin 6 (SIRT6), which inhibits gluconeogenesis by preventing the activation of glucose-6-phosphatase (G6PC) and phosphoenolpyruvate carboxykinase (PCK1) through forkhead box protein O1 (FOXO1). Furthermore, p53 promotes mitochondrial respiration by activating proteins that are important for fatty acid uptake (such as carnitine palmitoyltransferase 1C (CPT1C)) and fatty acid oxidation (FAO; such as malonyl-coenzyme A decarboxylase (MCD), lipin 1 (LPIN1) and pantothenate kinase 1 (PANK1)) in the mitochondria. The conversion of pyruvate to acetyl-coenzyme A (CoA) — through enhanced pyruvate dehydrogenase (PDH) activity resulting from parkin (PARK2) activation and PDH kinase 2 (PDK2) inhibition — and the conversion of glutamine to glutamate (by glutaminase 2 (GLS2)) is increased to enhance the tricarboxylic acid (TCA) cycle, while apoptosis-inducing factor (AIF) and synthesis of cytochrome *c* oxidase 2 (SCO2) are activated to promote oxidative phosphorylation (OXPHOS). In specific cases, p53 can increase hexokinase 2 (HK2) and PGM to enhance glycolysis. p53 regulates many proteins that can influence metabolism; only examples are depicted here. F-1,6-BP, fructose-1,6-bisphosphate; F-6-P, fructose-6-phosphate; GSH, reduced glutathione; GSSG, oxidized glutathione; NF-κB, nuclear factor-κB; PEP, phosphoenolpyruvate; PG, phosphoglycerate; R-5-P, ribose-5-phosphate.

However, under conditions of severe stress and mitochondrial damage, AIF is released from the mitochondria and can translocate to the nucleus, where it has a role in apoptosis by triggering DNA fragmentation[76,77]. p53 also supports the maintenance of mitochondrial mass and DNA[78]. In summary, the expression of p53 balances glucose metabolism to favour energy production through OXPHOS, a situation that is seen in quiescent tissues such as brain and heart tissues. Of note, loss of p53 tips this balance towards glycolysis and away from OXPHOS — a metabolic profile (also known as the Warburg effect or aerobic glycolysis) that is seen in highly proliferating normal and cancer cells.

The roles of p53 in limiting glycolysis and enhancing OXPHOS are most likely to reflect the functions of p53 that do not depend on acute damage activation but that help to maintain homeostasis under conditions of mild or transient metabolic stress. In mice, complete loss of p53 diminishes exercise capacity, a response that is linked to decreased mitochondrial synthesis and mitochondrial respiration[17,79,80]. However, the effect of p53 on glucose metabolism is likely to be highly context dependent[81], with p53 reported to promote glycolysis by activating PGM (in the muscle)[82]. Furthermore, hexokinase 2 (HK2) — which catalyses the first step in glycolysis (FIG. 1) — is expressed from a p53-responsive promoter[83], and this activity may cooperate with the p53-induced activity of TIGAR to promote the use of an alternative pathway for glucose metabolism: the pentose phosphate pathway (PPP) (FIG. 1). Although this pathway is a major source of NADPH, which supports antioxidant capacity (see below), it also provides ribose sugars for nucleotide synthesis, which could be important to support the DNA repair activity of p53. In what is becoming a recurring theme for p53 responses, there is evidence that p53 can also promote the opposite effect and directly inhibit the PPP by binding to and inactivating glucose-6-phosphate dehydrogenase (G6PDH), which catalyses the first step in this pathway[84].

The glycolytic pathway can also flow in reverse to produce glucose from pyruvate, a process known as gluconeogenesis. p53 has been reported to both inhibit and activate gluconeogenesis[85–87], and the regulation of glucose levels by p53 is likely to be context and tissue dependent. A recent study showed that p53 suppresses gluconeogenesis by activating the deacetylase sirtuin 6 (SIRT6). SIRT6 promotes the deacetylation and subsequent nuclear exclusion of the transcription factor forkhead box protein O1 (FOXO1), which, when in the nucleus, activates the expression of genes encoding the gluconeogenesis rate-limiting enzymes phosphoenolpyruvate carboxykinase (PCK1; also known as PEPCK1) and glucose-6-phosphatase (G6PC)[88] (FIG. 1). As gluconeogenesis and glycolysis generate similar intermediates, inhibition of either pathway could limit the availability of anabolic precursors for cell growth.

While glucose is a key nutrient, amino acids also support cell survival and cell growth, and p53 helps cells to survive serine and glutamine starvation by inducing a p21-mediated transient cell cycle arrest[89,90]. Rapidly proliferating cells have high demands for serine, which can be synthesized *de novo* or taken up from the extracellular environment. Serine is used for protein synthesis and for the production of anabolic intermediates, including sphingolipids, nucleotides, NADPH and glutathione (GSH)[91–94]. In response to serine deprivation, pyruvate kinase M2 (PKM2) activity is decreased, which facilitates the diversion of glycolytic flux into the *de novo* serine synthesis pathway[95]. To compensate for the decrease in energy production that results from a decrease in glycolytic flux, there is an increase in the rate of OXPHOS, which leads to an increase in the production of ROS. Intriguingly, to ensure the successful cellular adaptation to serine depletion, the p21-mediated transient cell cycle arrest induced by p53 and the accompanying inhibition of nucleotide synthesis allow the sustained generation of GSH to combat this increase in oxidative stress[89]. Under normal conditions, these changes are reversed when the *de novo* pathway restores sufficient serine levels. However, cells that lack p53 continue nucleotide synthesis and undergo oxidative stress and, ultimately, cell death. In this context, the retention of p53 can be beneficial for cancer cells by supporting their survival under serine-deficient conditions. Although this may seem to reflect a useful vulnerability of p53-deficient tumour cells, unfortunately there are other p53-independent mechanisms to deal with serine starvation, such as upregulating the expression of enzymes in the *de novo* serine synthesis pathway[91]. These changes make even p53-defective cancer cells much less vulnerable to fluctuations in exogenous serine availability.

p53 provides further assistance to starving cells through the promotion of FAO. p53 activates the expression of carnitine palmitoyltransferase 1C (CPT1C), which facilitates the transport of fatty acids into the mitochondria[96] (FIG. 1) and positively regulates malonyl-CoA decarboxylase (MCD; also known as MLYCD) (see below)[62] and lipin 1 (LPIN1) in response to nutrient deprivation. LPIN1 translocates to the nucleus under nutrient stress conditions to function as a transcriptional co-activator and regulate the transcription of genes involved in FAO[97]. Pantothenate kinase 1 (PANK1) — which is essential in CoA biosynthesis — is also a p53 target[87]. CoA is crucial for many metabolic processes, including β-oxidation, the main FAO pathway. The ability of p53 to increase FAO helps to sustain ATP levels by supporting OXPHOS through the generation of $FADH_2$ and NADH, and so promotes cell survival during metabolic stress[87,96]. Cancer cells, and other highly proliferative cells, often show a shift towards higher fatty acid uptake and synthesis to support the increased demand for membrane biosynthesis[98] and, as seen in the regulation of glycolysis, p53 would oppose this effect by promoting FAO.

Overall, many of the metabolic functions of p53 seem to relate to the ability of cells to cope with and survive nutrient fluctuation. Cells have evolved sophisticated mechanisms for sensing and responding to changes in nutrient levels, and the induction of p53 during nutrient depletion has several beneficial outcomes. p53 can help to preserve energy by activating cell cycle arrest and inhibiting cell growth, while promoting catabolic

Pentose phosphate pathway (PPP). A pathway that produces ribose sugars and NADPH from glucose and that is important for redox balance and anabolism.

Box 3 | **Autophagy**

A key response to nutrient depletion is the induction of autophagy, a process that can generate metabolic intermediates to help cells to survive starvation and remove unwanted or damaged organelles. To do this, a double-membrane-bound structure called the autophagosome is formed, which engulfs a portion of the cytosol including proteins and organelles. The autophagosome then fuses with a lysosome, and its cargo is degraded and recycled[164]. Autophagy can be general — when random cytosolic components are degraded to obtain metabolites to fuel growth and survival — or selective, when cargo receptors form a bridge between the microtubule-associated protein light chain 3 (LC3) in the autophagosomal membrane and specific macromolecules or organelles that need to be cleared[165]. In normal cells, autophagy is mainly a pro-survival mechanism that ensures cellular homeostasis, protecting cells from the accumulation of damaged mitochondria and the accompanying reactive oxygen species (ROS) burden and, when necessary, providing an alternative source of fuel to maintain ATP levels[166]. However, autophagy can also function as a cell death effector through various mechanisms that are only partially understood[167].

The functions of autophagy are reflected in its ability to both promote and suppress tumorigenesis. On the one hand, autophagy-deficient mice develop benign liver tumours[168], and BCL-2-interacting myosin/moesin-like coiled-coil protein 1 (BECLIN1)-induced autophagy suppresses tumorigenesis[169,170]. On the other hand, tumours with activated RAS require autophagy for tumour progression[171,172]. Taken together, it seems plausible that autophagy may inhibit the early stages of cancer development (by preventing ROS, DNA damage and inflammation) but help to support the later stages of tumour progression (by maintaining metabolism and survival).

responses such as FAO and autophagy (see below). Together, these activities help to coordinate a reduction in energy demand with the mobilization of alternative energy sources. Of course, key to the utility of such survival responses is the reversibility of both p53 activity and proliferative arrest[99]. The metabolic shift associated with loss of wild-type p53 — as seen in most cancers — results in an enhanced anabolic capacity that may be useful to support cancer cell proliferation but may also leave cancers less able to cope with nutrient fluctuations.

Autophagy: eating up and cleaning up. Autophagy is emerging as a key process in the control of tumour development (BOX 3), and there are increasing links between autophagy and p53. Autophagy can restrain p53 activity by preventing activating signals such as oxidative stress and DNA damage, and possibly also by directly degrading p53 (REF. 100). Conversely, p53 can activate the expression of a large set of target genes that are involved in the autophagic programme, including DNA-damage-regulated autophagy modulator 1 (*DRAM1*), UNC-51-like autophagy-activating kinase 1 (*ULK1*) and cathepsin D[39,101,102], and there is evidence that p53-induced autophagy has a role in tumour suppression[103]. Indeed, the autophagic machinery can even influence the choice of response to p53. One autophagy protein, ATG7, binds to p53 and promotes cell cycle arrest and cell survival through p21 activation in response to nutrient starvation[104]. In this case, loss of ATG7 switches the p53 response from cell cycle arrest to apoptosis.

The interplay between autophagy and p53 suggests a negative-feedback loop in which p53 induces autophagy, which then limits p53 activation. However, the complexity of this relationship makes it difficult to predict the outcome of perturbations of the systems. Will inhibition of the autophagic response promote tumour development (by removing an important arm of the p53-induced tumour suppressive response) or inhibit cancer progression (by allowing full activation of the apoptotic and metabolic tumour suppressor activities of p53)? Studies in mouse models of pancreatic and lung cancer have begun to address this question but highlight the context dependence of any answers. For example, loss of autophagy promotes the initial stages of RAS-driven tumorigenesis, leading to the formation of more premalignant lesions, but strongly inhibits further progression of these tumours[105,106]; in the case of lung cancer, this leads to the development of mostly benign oncocytomas[107]. This restraint on the progression of autophagy-defective tumours is partly due to the activation of p53, as deleting *Trp53* (encoding mouse p53) reinstated their rapid progression[105,106]. Perplexingly, however, in a very similar model of pancreatic cancer, loss of p53 did not restore the progression of the lesions[108]. In the pancreatic model, *Trp53* was deleted through loss of heterozygosity during the course of tumour development, rather than by homozygous deletion of *Trp53* during embryogenesis[106], suggesting that the timing and mechanism of p53 loss may determine outcome.

To complicate matters further, there are additional mechanisms by which p53 can indirectly promote autophagy, for example, by inhibiting mTOR and the PI3K–AKT pathway[109,110], and further evidence suggests that p53 can also limit or inhibit autophagy. Indeed, various antioxidant functions of p53 can lead to a decrease in autophagy[67], and transcriptionally independent functions of p53 can also inhibit autophagy[111], in part, through the direct interaction between p53 and the autophagy-stimulating protein RB1CC1 (REF. 112). The balance between autophagy and apoptosis may also be regulated by the binding of p53 to high-mobility group protein B1 (HMGB1), an interaction that limits both the pro-autophagic activity of HMGB1 and the cytosolic apoptotic activity of p53 (REF. 113). Understanding the complex relationship between p53-induced apoptosis and autophagy will be important to guide therapeutic options that are based on the modulation of these responses.

Redox homeostasis: playing with fire. Another important but complex relationship has evolved around p53 and the control of ROS (BOX 4), with evidence that ROS induces p53, while p53 promotes antioxidant activity under normal conditions and pro-oxidant activity under severe oxidative stress[114] (FIG. 2). p53 controls the expression of numerous metabolic enzymes that regulate ROS, including several that can control the production of NADPH. For example, TIGAR, which can limit glycolysis, enhances the antioxidant capacity of the cell by promoting the PPP and so increasing NADPH levels[67,115–117]. The biosynthesis of GSH itself can also be increased by p53 through the transcriptional activation of the gene encoding GLS2, which can help to provide a source of intermediates for the TCA cycle

Oncocytomas
Usually benign tumours composed of oncocytes with granular, eosinophilic cytoplasm.

Box 4 | **Reactive oxygen species**

Intracellular reactive oxygen species (ROS) can be generated through several pathways, but the main source of ROS is the mitochondria, with increased oxidative phosphorylation (OXPHOS) leading to the increased production of ROS[173].
ROS signalling regulates numerous cellular processes with varying outcomes.
Basal levels of ROS are essential for many cellular signalling processes and promote cell proliferation, cell growth and cell survival. By contrast, persistently excessive levels of ROS can lead to oxidative damage and cell death[174]. Cancer progression is associated with increased oxidative stress, and enhanced ROS levels can encourage tumorigenesis by promoting proliferative signalling, angiogenesis, metastasis and genetic damage. However, to avoid cell death induced by excess levels of ROS, cancer cells upregulate antioxidant defences, including NADPH production, the main reducing agent for the regeneration of glutathione, which is the most abundant intracellular antioxidant.
This complex balance between the cancer-promoting and cancer-limiting activities of ROS is underscored by the complex responses of tumours to antioxidant therapies, which have been described to both help and hinder cancer progression[175].

(as mentioned above) and also generate glutamate, one of the amino acids of the glutathione (GSH) tripeptide. As already discussed, p53 also maintains GSH levels under conditions of serinestarvation[89]. p53-mediated expression of CPT1C may have functions in addition to the regulation of FAO (as outlined above), potentially also regulating ROS levels and cell survival[118]. Other antioxidant functions of p53 include the positive regulation of sestrins, GSH peroxidase 1 (GPX1), aldehyde dehydrogenase 4 (ALDH4) and NFE2-related factor 2 (NRF2; also known as NFE2L2)[119], as well as the more general ability of p53 to maintain mitochondrial health[78] and thus limit the production of ROS. It is interesting to speculate that the antioxidant functions of p53 are necessary to support the increased OXPHOS (a major ROS-generating system) seen in p53-expressing cells. Conversely, maybe the switch from OXPHOS to glycolysis in p53-deficient cells is partly driven by a requirement to limit ROS levels in the absence of p53 antioxidant functions.

By contrast, conditions that promote apoptosis and senescence are associated with strong pro-oxidant functions of p53 (REFS 120–123). ROS-producing proteins that are induced by p53 during apoptotic events include p53-induced gene 3 protein (PIG3; also known as TP53I3), PIG6 (a proline oxidase), BAX and PUMA[124,125], and p53 may also function in some situations to limit mitophagy, leading to the retention of damaged, ROS-generating mitochondria[78]. As mentioned above, p53 can lower NADPH production by inactivating glucose-6-phosphate dehydrogenase (G6PDH)[84] and inhibiting the expression of malic enzyme 1 (ME1) and ME2 (REF. 126). The inhibition of malic enzymes activates p53 in a feed-forward manner through the activation of AMPK and by diminishing the levels of MDM2. The ability of p53 to limit and promote ROS therefore closely parallels its dual activities in controlling cell death and cell survival (FIG. 2).

Glutathione (GSH) tripeptide
Consists of cysteine, glutamate and glycine and functions as an important intracellular antioxidant.

Mitophagy
A selective form of autophagy that targets the mitochondria; it is generally thought to help to maintain cell health by removing damaged mitochondria.

Choosing which p53 response to use

Given the multiple possible consequences of p53 activation, how the cellular outcome of p53 induction is determined is a key question. This is a complex topic, and some recent reviews provide excellent overviews of the processes underlying life or death decisions by p53 (REFS 5,6,127). Broadly, the cell type and environment, as well as the nature, severity and duration of the stress stimulus, all influence the consequence of p53 activation. The different outcomes are determined by changes in p53 itself (such as the regulation of protein stability and activity by post-translational modifications), by p53-independent factors that modulate p53 activity (such as alterations in the availability of its response elements in target promoters or interacting proteins (for example, other transcriptional cofactors)) and by p53-independent activities that cooperate with the responses to p53 (such as the overall level of pro-apoptotic proteins). Most simply, the ability of p53 to drive the expression of apoptotic genes might correspond to the induction of cell death, whereas p53-induced cell cycle arrest (and especially p53-induced increase in the expression of p21) would be linked to cell survival. Importantly, a failure to induce p21 is often associated with a switch to cell death. However, as discussed above, p53 can both promote or inhibit responses such as ROS production, glycolysis, NADPH production and autophagy with profound implications for the final outcome of p53 activation. Further complication is introduced by the fact that many of these responses (such as ROS production and autophagy) can themselves have opposing effects on cell death, cell survival and cell proliferation.

To try to make sense of this complexity, a model has emerged in which p53 functions as a rheostat, helping to maintain homeostasis under basal or low-stress conditions while also eliminating irreparably damaged or stressed cells[128] (FIG. 3). Both of these response modes would help to prevent the progression of malignancy, but each poses a hazard. On the one hand, the inappropriate activation of the death response may result in tissue degeneration; indeed, p53-dependent cell death has been associated with undesirable pathologies such as diabetes, neurodegenerative disease, reperfusion injury and even ageing. On the other hand, the inappropriate activation of survival pathways that evolved to protect normal cells may also shield cancer cells from elimination, and the overexpression of p53 target genes, including *TIGAR* and *CPT1C*, has been linked with tumour progression[129]. However, more encouragingly for the use of p53 activation in cancer treatment, oncogenic transformation seems to sensitize at least some cells to p53-induced apoptosis or senescence[130], possibly by triggering high-intensity stress associated with unrestrained mitogenic signalling or DNA damage[131].

Although it is clear that p53 can trigger different responses, the exact molecular mechanisms underlying these decisions are multilayered, complex and only partially understood. In general, the outcome of p53 activation reflects both differential activities of p53 itself and context-dependent events that contribute to the final response independently of changes in p53 activity. Most simply, differences in the level, dynamics or persistence of p53 activation can change the response by altering the selection of downstream target genes

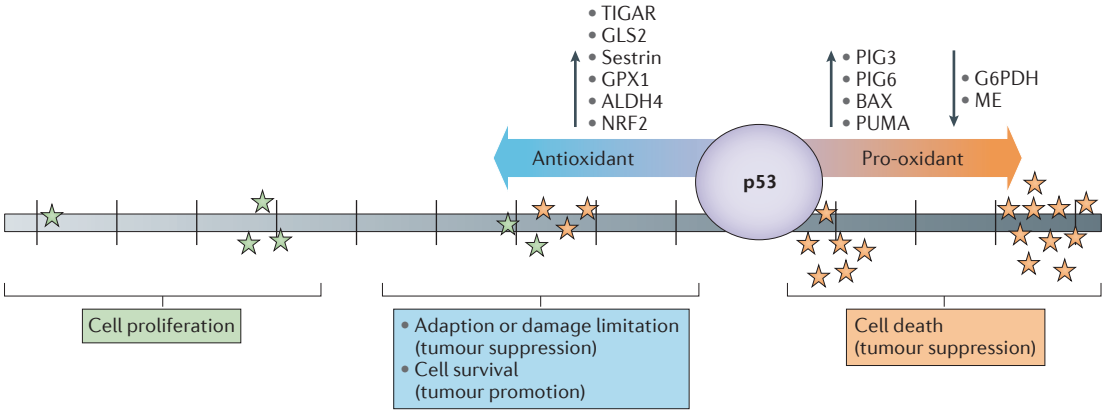

Figure 2 | **p53 regulates cellular redox homeostasis.** Basal levels of reactive oxygen species (ROS; green stars) are essential for many cellular signalling processes and promote normal cell proliferation, cell growth and cell survival. However, excessive levels of ROS (orange stars) can lead to the induction of adaptive responses and, ultimately, damage that can contribute to the acquisition of oncogenic mutations and cell death. p53 can activate an antioxidant or a pro-oxidant response by upregulating (↑) or downregulating (↓) the expression or activity of many proteins, examples of which are depicted in this figure. The antioxidant activity of p53 protects cells from the accumulation of damage and helps to prevent tumour development. However, this activity may also protect tumour cells from excessive levels of ROS and cell death, thereby promoting cell survival and tumour development. Conversely, by promoting the production of ROS in response to oncogenic changes, p53 can induce cell death and eliminate incipient cancer cells. ALDH4, aldehyde dehydrogenase 4; BAX, BCL-2-associated X protein; G6PDH, glucose-6-phosphate dehydrogenase; GLS2, glutaminase 2; GPX1, glutathione peroxidase 1; ME, malic enzyme; NRF2, NFE2-related factor 2; PIG, p53-induced gene; PUMA, p53 upregulated modulator of apoptosis; TIGAR, *TP53*-inducible glycolysis and apoptosis regulator.

of p53 (REFS 132–134). The conformation of the p53 protein can also have a role in the selection of target genes[135], and the DNA-binding cooperativity of p53 is more important for the activation of apoptotic genes than the activation of cell cycle-arrest target genes[136]. Furthermore, the two transactivation domains of p53 (TAD1 and TAD2) seem to be responsible for the regulation of certain subgroups of target genes, with TAD1 required specifically for the control of proteins that are involved in cell cycle arrest and apoptosis, whereas both transactivation domains can independently promote the induction of proteins that promote senescence[137].

The sequence, context and availability of p53 response elements can regulate the output to p53 activity, as does the core promoter composition[138]. The induction and availability of numerous p53-interacting cofactors can also help to determine which subset of p53-inducible genes is activated, and thereby which response ensues[139]. Key to the control of p53 transcriptional activity — and thus the outcome to p53 induction — is the modulation of the number, type and combination of post-translational modifications on p53 (REF. 127), which determine the affinity for certain response elements or interacting partners and favour the transactivation of a specific subset of target genes. Given that up to 40 residues on p53 are subject to multiple post-translational modifications, the number of combinations and permutations of p53 modifications is high. It is not possible to do justice here to the many studies that are unravelling the role of transcriptional and post-transcriptional regulation of p53 target gene expression, although several excellent reviews are available[10,140,141]. One intriguing observation is the importance of lysine modification in controlling the p53 response; the mutation of three lysine residues in mouse p53 (Lys117, Lys161 and Lys162, equivalent to Lys120, Lys164 and Lys165 in human p53, respectively) completely abrogated its ability to induce cell cycle arrest, senescence and apoptosis without affecting its antioxidant and metabolic functions[142]. Intriguingly, this mutant has recently been shown to also retain the ability to induce ferroptosis in response to increased ROS[176].

The overall state of the cell, which is controlled by factors independent of p53, will also influence the outcome to p53 activation. For example, the overall propensity of the cell to undergo apoptosis is partly determined by the pattern of pro-apoptotic and anti-apoptotic protein expression. Cells that are 'primed for death' (REF. 143) selectively undergo apoptosis in response to p53 without requiring any differences in the activity of p53 compared with cells that do not die[144]. Similarly, inhibition of ATM and MET kinases can switch the p53 response from cell cycle arrest to apoptosis without changing the induction of p53 target genes[145].

Identifying how the outcome of p53 signalling is regulated, and predicting the consequences of p53 activation, will be crucial for our ability to harness p53 as a target for cancer therapy. Although it was generally thought that cancer inhibition resulted from the canonical p53 responses of apoptosis and/or senescence, surprising recent observations have shown that these are not required for tumour suppression[137,142,146,147]. This raises the question of, which, if any, specific function of p53 is essential for preventing tumorigenesis? As yet, there are no definitive answers, although the activities that we have considered in this Review — such as the induction of alternative cell death pathways or various cell survival functions of p53, including DNA damage

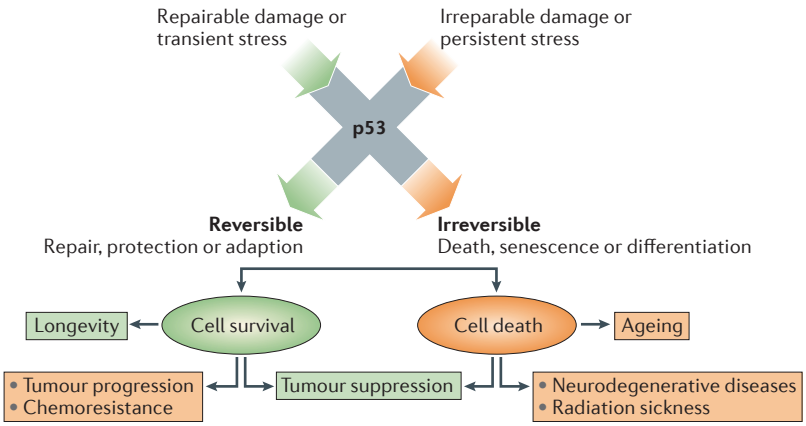

Figure 3 | **p53 as an integrator of cellular stress.** p53 functions to integrate signals from different types of cellular stress and subsequently promotes the appropriate biological response, which can lead to cell survival or cell death. In the case of repairable damage or transient stress, a reversible process is activated that allows for damage repair and/or adaptation in response to the change in environment. However, when the stress stimulus is persistent and irreparable, the affected cell is permanently removed from the pool of proliferating cells through cell death, senescence or the induction of terminal differentiation. Although both responses can promote tumour suppression, uncoupled or deregulated survival functions can contribute to tumour progression and chemoresistance. Conversely, inappropriate activation of the cell death response can contribute to ischaemia, neurodegenerative disease or radiation sickness. p53-mediated stress responses may also have a role in promoting longevity as well as contributing to ageing, by regulating stem cell renewal and oxidative stress.

repair, the maintenance of genomic stability and the regulation of metabolism — could all have a role. Both the lysine-mutant and transactivation-domain-mutant mice described above, each of which lack the p53-mediated responses of cell cycle arrest and apoptosis, retain protection from tumour development[137,142]. Importantly, this is not a curiosity limited to one tumour type; further analysis has shown that the ability to induce expression of p21, PUMA and NOXA, the key mediators of p53-induced cell cycle arrest and apoptosis, was not necessary for p53 to limit tumour development in a diverse range of tissue types[147]. Furthermore, mice that lack the genes encoding p21, PUMA and NOXA retain tumour suppressor activity, along with the ability to upregulate a suite of DNA repair genes[146].

Despite these intriguing observations, other studies suggest that it would be premature to discard apoptosis as an important or useful 'weapon' with which to fight cancer. The analysis of p53 mutants that are defective in their assembly into tetramers that are required for cooperative DNA binding, has indicated that apoptosis can be important for preventing oncogene-induced cancer development[148]. Furthermore, reactivation of p53 in various cancer models leads to regression of the tumour, which is associated with the induction of apoptosis or senescence[149–151]. These observations can be reconciled in a model in which the protective functions of p53 serve to prevent cancer development, whereas the ability of p53 to eliminate cells helps in the resolution of existing tumours (FIG. 3). In terms of our discussion on the choice of response, it is worth considering that developed tumours are subject to severe and persistent stress driven by oncogene activation, loss of normal environment and continual oscillations in nutrient and oxygen availability.

Concluding remarks

When p53 was originally identified as a tumour suppressor that was defective in most cancers and capable of killing tumour cells in culture, p53 reactivation was hailed as an obvious goal to halt tumour progression. However, as novel functions for p53 that are important in inhibiting tumorigenesis and also in maintaining cellular homeostasis have been uncovered, the use of p53 as a therapeutic target has become more complicated. Not only are many aspects of its function still unclear, but its ability to regulate the same cellular processes both positively and negatively, in different cellular contexts, makes it difficult to predict the consequences of p53 activation. Even if the p53 response itself can be accurately determined, the consequences of each response are also confusingly variable. For example, p53 may enhance or limit the production of ROS, and an increase in ROS levels can both hinder or accelerate tumour development. Indeed, both ROS limitation and ROS induction have been proposed for cancer therapy[152]. Similarly, autophagy can be induced or inhibited by p53, and autophagy can both contribute to or limit tumour development.

However, a concept that is becoming clear is that the functions of p53 that help normal cells to overcome and survive genotoxic or metabolic stress can also be usurped by cancer cells — so that under some conditions, retention of wild-type p53 or deregulation of the mediators of p53 survival activities can be advantageous for tumour development. Of interest in this context are recent studies in *Drosophila melanogaster* showing that, although the presence or absence of p53 did not affect the viability of cells with deregulated Myc that were grown in the same culture, the situation changed when the dysregualted-Myc cells were mixed with wild-type cells. Under these conditions, p53 was required for the Myc-expressing cells to display a super-competitor phenotype, enabling them to kill the surrounding wild-type cells and increase their own proliferation[153]. It seems possible that p53 has a similar role in nascent cancer cells: increasing their fitness at the expense of surrounding normal tissue. However, it is worth noting that mouse haematopoietic stem cells with lower levels of p53 outcompete their neighbours upon radiation treatment[154]. Taken together, however, it is possible that activation of p53 is not necessarily beneficial during cancer treatment, a concern that is reflected in preclinical and clinical data showing that for some tumours the retention of wild-type p53 is associated with a poor response to certain chemotherapies[155,156].

As a final complication, although the activation of p53 to treat cancer may be generally advantageous, as we have discussed, several other less desirable pathologies are also associated with p53 activity. How or whether these might become manifest during p53 inducing therapies is not known. As p53 biology continues to surprise, the question of how to efficiently harness the modulation of p53 activities for therapeutic benefit remains tantalizingly unanswered.

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Competing interests statement
The authors declare no competing interests.