

p53 Regulation of Metabolic Pathways

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During the course of tumorigenesis, cells acquire a number of alterations that contribute to the acquisition of the malignant phenotype, allowing them to survive and flourish in increasingly hostile environments. Cancer cells can be characterized by perturbations in the control of cell proliferation and growth, resistance to death, and alterations in their interactions with the microenvironment. Underpinning many of these changes are shifts in metabolism that allow cancer cells to use alternative pathways for energy production and building the macromolecules necessary for growth, as well as regulating the generation of signaling molecules such as reactive oxygen species (ROS). In the past few years, it became clear that p53, the most studied, if not most important, tumor suppressor protein, can also directly control metabolic traits of cells.

Given the importance of metabolic reprogramming in tumor development, it is no surprise that many oncogenes and tumor suppressor genes have been shown to help control these pathways (DeBerardinis et al. 2008a; Tennant et al. 2009). In most cases, these effects are fairly clear—proteins that can promote cancer development drive the metabolic transformation associated with malignancies and tumor suppressor proteins oppose these effects. p53 plays a central and key role in preventing cancer development (Vousden and Prives 2009), but the regulation of metabolism by p53 is proving to be far from straightforward. Although the explanation for this complexity is not clear, there are several obvious and ultimately testable models. What is evident, however, is that the regulation of metabolic pathways is an important facet of p53 function that may provide us with some novel and

effective new therapeutic targets, for cancer and maybe also other diseases.

METABOLISM AND CANCER

The role of metabolic reprogramming in cancer development has been the subject of increasing investigation and speculation over recent years, with a number of excellent reviews that summarize the most recent developments in this area (DeBerardinis et al. 2008b; Hsu and Sabatini 2008; Kroemer and Pouyssegur 2008; Tennant et al. 2009). We therefore provide a brief overview of the metabolic changes involved in cancer, and then describe some of the roles of p53 in these pathways. Alterations in metabolism can have fundamental effects on almost every aspect of cell behavior, including the ability to help regulate proliferation, growth, and survival

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under conditions of variable nutrient and oxygen availability.

Regulation of Energy Production

It is almost impossible to address the metabolic changes in cancer without reference to the Warburg effect—the unusually high rate of glycolysis under aerobic conditions seen in virtually all cancer cells. Glycolysis, the breakdown of glucose to pyruvate in the cytosol, is an important energy-generating process in cells and the only alternative to oxidative phosphorylation for ATP production. Oxidative phosphorylation is a mitochondrial process in which ADP is phosphorylated to ATP as a direct consequence of oxidizing NADH and FADH₂ (Fig. 1).

Although oxidative phosphorylation produces larger amounts of ATP per molecule of glucose, glycolysis acts faster. As any sprinter knows, glycolysis is the quickest way to recycle rapidly phospho-hydrolyzed ATP to maintain

a favored bioenergetic ATP/ADP ratio on surges in energy demands. This is because of the fact that glycolysis is a highly regulated process that can be quickly stimulated by hundreds of folds. However, under physiological conditions, oxidative phosphorylation is the most efficient way to generate ATP either from glucose, fatty acids, or amino acids, and in most normal energy demanding tissues, it is the major generator of energy. Like any other rapidly proliferating cell, cancer cells grow (in size) and divide at a high rate, a process that requires a lot of energy. Surprisingly, many studies have suggested that in cancer cells, glycolysis plays a far more important role in ATP generation than it does in normal energy-demanding tissues or rapidly proliferating cells (such as embryonic cells) (Frezza and Gottlieb 2009).

The reasons for the increased glycolysis are not completely understood but many cancer cells seem to actively reduce oxidative phosphorylation, and there are strong indications that the cells come to depend on glycolysis. Glycolysis

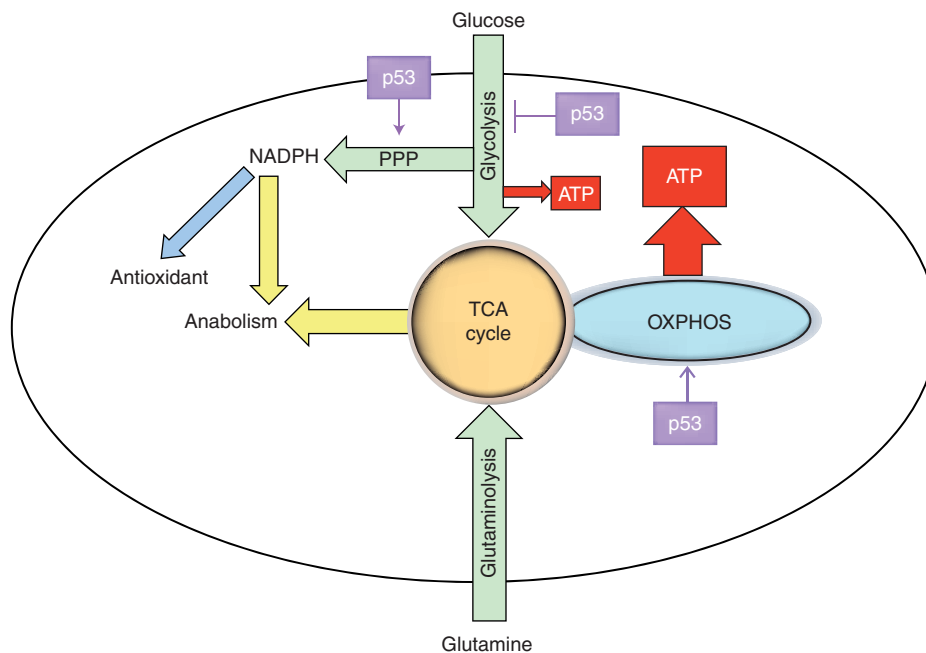


Figure 1. The main energy-generating metabolic pathways, and their regulation by p53. By promoting oxidative phosphorylation and inhibiting glycolysis, p53 might oppose the Warburg effect that is seen in many cancers. Promotion of the pentose phosphate pathway would also provide survival functions and may contribute to anabolic pathways necessary for damage repair.



is kept active by diverting its end product, pyruvate, into lactate. Diverting the fate of pyruvate from reducing to lactate in the cytosol to oxidizing to acetyl-CoA in the mitochondria inhibits glycolysis and increases oxidative phosphorylation in cancer cells and also slows tumor progression (Fantin et al. 2006). This, and the fact that several oncogenes, particularly Myc and Akt, directly stimulate glycolysis (DeBerardinis et al. 2008a; Tennant et al. 2009), shows that cancer cells also depend on increased glucose consumption for their survival and growth in vitro and in vivo. Furthermore, the hypoxia inducible factor (HIF) directly activates the expression of most glycolytic enzymes. HIF itself plays a crucial role in the pathology of cancer either in low oxygen (hypoxia) conditions observed in most tumors or when it is abnormally activated under normoxic conditions (pseudo-hypoxia). The importance of hypoxia in tumorigenesis may provide a partial explanation for the increased need for glycolysis-derived ATP because glycolysis is an oxygen-independent mechanism.

Providing the Building Blocks—Regulation of Anabolic Pathways

Of course, the rapid provision of excessive energy to support proliferation is only one of the challenges facing cancer cells. To proliferate, cells must first grow. The major part of the cell's growth normally occurs in the G1 phase of the cell cycle, before the commitment to division. This requires a dramatic increase in anabolic processes as cells need to double their protein and lipid content before doubling their DNA content in the S phase. The two major carbon sources of cancer cells are glucose and glutamine (DeBerardinis et al. 2008a). As discussed previously, the breakdown of glucose by glycolysis is an important bioenergetic process, but so is the breakdown of glutamine (glutaminolysis), a process that sustains the levels of Krebs-cycle intermediates (Fig. 1). In addition to their bioenergetic roles, intermediates of the glycolytic and glutaminolytic processes are important precursors for the synthesis of nonessential amino acids and lipids. Thus, the

increased uptake and metabolism of both glucose and glutamine observed in cancer cells serves two important metabolic purposes: energy production and anabolism (Fig. 1).

One important anabolic process that is supported by glucose and glutamine is fatty-acid biosynthesis. Krebs-cycle-derived citrate is the source for cytosolic acetyl-CoA, which is a precursor of fatty acids. Furthermore, NADPH is an important factor required in fatty-acid biosynthesis, where it is oxidized to NADP⁺. Maintaining a working NADPH/NADP⁺ ratio is important for sustaining lipid production and both glucose and glutamine metabolism contributes to retaining an anabolic ratio of NADPH/NADP⁺. The diversion of glucose metabolism from linear glycolysis into a bypass that goes through the pentose phosphate pathway (PPP) is an important source of NADPH (Fig. 1). Two other reactions that generate NADPH involve the Krebs-cycle intermediates malate and isocitrate. In the cytosol, malate is converted to pyruvate and isocitrate is converted to α -ketoglutarate by malic enzyme and isocitrate dehydrogenase-1, respectively, both enzymes that reduce NADP⁺ to NADPH. Considering the role of glutamine in sustaining the levels of Krebs-cycle intermediates, one can clearly see the importance of glutamine in these two reactions. Therefore, the consumption of glucose and glutamine by cancer cells not only provides energy and precursors for anabolic reactions, it also generates the accessory factors for the anabolic processes to take place.

Protection from a Hostile World

Adverse environmental and internal conditions and various developmental cues force normal cells to activate checkpoints that prevent expansion. However, metabolic transformation provides cancer cells with mechanisms that allow them to grow and proliferate unchecked. These include the ability to ignore signals that normally suppress growth under conditions of nutrient or oxygen starvation. Metabolic transformation can also provide the developing tumor cell with defenses against the alarm signals that trigger death or senescence in response to their aberrant growth behavior. Of particular

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importance to cancer cells is the role of reactive oxygen species (ROS). These are oxygen-derived active molecules (usually free radicals), which can play a dual role in controlling cell fate. On the one hand, ROS can contribute to cell proliferation and survival signaling pathways such as those mediated by receptor tyrosine kinase cascades (Chiarugi and Cirri 2003; Wu et al. 2008). On the other hand, high levels of ROS have a profound toxic effect on cells and can lead to apoptosis or necrosis. Therefore, the redox state of cells, which is defined by the ratio of reduced molecules to oxidized ones, critically regulates survival and death mechanisms. Of particular importance is the ratio between reduced to oxidized glutathione (GSH/GSSG). GSH is a major antioxidant in cells and is directly involved in enzymatic and nonenzymatic antioxidative reactions in which it donates an electron to reduce pro-oxidants to nontoxic molecules while itself being oxidized to a glutathione dimer—GSSG. Consequently, the rate of reduction of GSSG back to GSH is crucial for the protection from oxidative stress. This reaction, catalyzed by glutathione reductase, is dependent on NADPH. Therefore, as for the process of fatty-acid synthesis described previously, the redox state of cells is controlled by metabolism of glucose via the PPP and by glutaminolysis. It is important to mention that PPP appears to be the major pathway that controls the GSH/GSSG ratio by supporting NADPH production, and thus, the reduction of glutathione. Therefore, channeling glucose metabolism preferably towards glycolysis and avoiding the PPP could have catastrophic consequences on cell survival (Herrero-Mendez et al. 2009), while diverting more glucose through the PPP protects cells from oxidative stress (Bensaad et al. 2006).

Overall, changes in metabolism are essential to tumor progression; they enable cells to survive and to continue to grow and proliferate under conditions of adversity that would directly arrest or kill a normal cell. However, this strength comes at the price of tumor cell reliance on the lifeline provided by metabolic transformation. Interfering with this support mechanism by inactivating or blocking transformed

metabolic pathways may have a much more critical effect on the survival of tumor cells compared with their much more sedate and protected normal counterparts. This leads to the seductive idea that understanding these pathways may allow us to develop effective new cancer therapies. Because recent research has shown that p53 is a significant actor on the cell-metabolism stage, its role in metabolism and its potential as a target for therapy is considered next.

THE ROLE OF p53

By far, the best-understood functions of p53 are those that inhibit the proliferation of cells that are undergoing malignant transformation. There are numerous points in cancer progression at which p53 might play such a role—reflecting the ability of various forms of cancer-associated stress to induce p53 (Evan and Vousden 2001). Genotoxic damage, oncogene activation, telomere erosion, loss of stromal support, and nutrient and oxygen deprivation can all activate p53 (Horn and Vousden 2007), resulting in the induction of apoptotic cell death or senescence—two responses that irreversibly remove the cell from the proliferative population and therefore neutralize any potential danger of further malignant progression. But the ability of p53 to control tumor progression appears to have a more subtle side—and in addition to eliminating the stressed cell, p53 can also play a role in the protection and survival of cells exposed to modest stress levels (Kim et al. 2009) (Fig. 2). This rather more nurturing side of p53 is likely to reflect the exquisite sensitivity of the response, in which the presence of even a single DNA double-strand break in a cell can trigger p53 (Di Leonardo et al. 1994). This level of alacrity brings some challenges because many of our cells are frequently exposed to such modest damage—indeed, merely the process of living and breathing generates a certain level of p53-inducing stress, including the production of ROS from mitochondrial respiration. Simply eliminating all of these cells through p53-driven death or senescence is likely to become untenable for the organism. So, to cope with low, everyday levels of stress (which

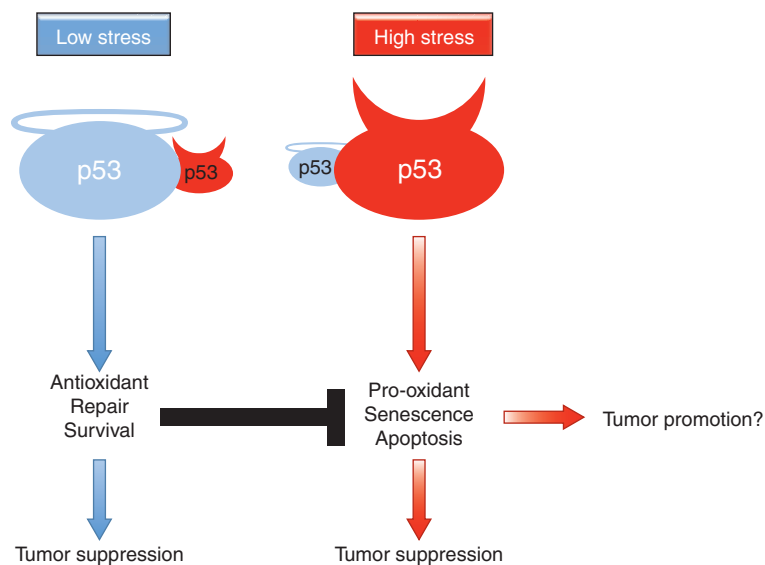


Figure 2. p53 drives different responses under conditions of low stress (where cell survival and repair is supported) and high stress (where the damaged cell is eliminated through death or senescence). However, the inappropriate maintenance of the low-stress functions may contribute to cancer cell survival and growth.

might nevertheless be extremely hazardous), p53 has developed a suite of responses that function to lower ROS levels, promote survival, and even participate in certain types of DNA repair processes. Although its ability to protect from oncogenic progression has led p53 to be dubbed the “molecular policeman” (Lane 1992), it seems as though p53 can play both good cop and bad cop. But within this duality of function for p53 also lies a weakness, in that the p53-driven responses designed to save modestly damaged cells might also contribute to tumor progression if inappropriately expressed in more severely compromised cells. We come back to this idea later.

p53 and the Regulation of Oxidative Phosphorylation

The use of oxidative phosphorylation by cells growing in the presence of oxygen is a hallmark of normal cells existing under normal conditions, and reflects the acquisition of a highly efficient energy-producing pathway. However, as described previously, it has become apparent that the use of glycolysis even under aerobic conditions may be advantageous to cancer cells,

and that a high glycolytic rate is important for the maintenance of the tumor. These observations are leading us to reconsider the effects of regulating glycolysis and oxidative phosphorylation—with the possibility that the promotion of the latter may decrease glycolysis and so act as a barrier to cancer progression. Viewed in this light, it is not surprising that p53 has been shown to play a role in promoting oxidative phosphorylation. Cells expressing p53 derive a much greater proportion of their ATP through oxidative phosphorylation than their counterparts lacking p53 (Ma et al. 2007), and p53 is important for the maintenance of mtDNA copy number and mitochondrial mass (Kulawiec et al. 2009; Lebedeva et al. 2009). Several functions of p53 may contribute to the maintenance of mitochondria and oxidative phosphorylation. These include the transcriptional activation of proteins, like synthesis of cytochrome c oxidase 2 (SCO2) (Matoba et al. 2006), subunit I of cytochrome c oxidase (Okamura et al. 1999), and p52R2, a subunit of ribonucleotide reductase (Bourdon et al. 2007), as well as the posttranscriptional regulation of the COXII subunit by p53 (Zhou et al. 2003). In addition to its nuclear functions, p53 has

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also been shown to be localized to mitochondria, where it can interact with the Bcl-2 family of proteins and VDAC (Ferecatu et al. 2009). Although this activity of p53 contributes to the induction of the apoptotic response, mitochondrial localization of basal p53 in unstressed cells raises the possibility that there may also be a direct contribution of p53 in the maintenance of mitochondrial health and activity.

p53 and the Regulation of Glycolysis

The counterpoint to the ability of p53 to support oxidative phosphorylation is the ability of p53 to modulate glycolysis (Fig. 1), although the details of this effect are somewhat complicated and likely to be highly tissue- and cell-type specific. Most straightforward are the functions of p53 that can contribute to the dampening of glycolysis. These include the down-regulation of expression of several glucose transporters—both through the direct transcriptional repression of genes encoding GLUT1 and GLUT4 (Schwartzberg-Bar-Yoseph et al. 2004) and by the indirect reduction of GLUT3 expression through the inhibition of IKK (Kawauchi et al. 2008). The ability of p53 to drive the ubiquitination and inactivation of the glycolytic enzyme phosphoglycerate mutase (PGM) (Kondoh et al. 2005) would further function to lower the glycolytic rate, as would the p53-dependent expression of TIGAR—a protein that functions as a fructose 2,6-bisphosphatase (FBPase) to lower fructose 2,6-bisphosphate levels and glycolytic rate (Bensaad et al. 2006; Li and Jogl 2009). At first glance, this ability of p53 to limit glycolysis seems completely consistent with its function as a tumor suppressor, because it would oppose the acquisition of the aerobic glycolysis seen in most cancers. However, this may be a simplistic view—and p53 activities that might even promote glycolysis have also been described. For example, both hexokinase-2 (HK2) and PGM are expressed from p53-inducible promoters (Mathupala et al. 1997; Ruiz-Lozano et al. 1999). As a further complication, it is possible that the importance of these functions may reflect not so much the overall flux through the glycolytic pathway,

but the activation and regulation of the PPP—the alternative route for the metabolism of glucose-6-phosphate. Clearly, an increase in HK2 activity in concert with a decrease in phosphofructokinase-1 (PFK1) activity (resulting from TIGAR expression) would promote the use of the PPP. Furthermore, inhibition of the PPP can result in an activation of p53 (Muniyappa et al. 2009), suggesting a feedback loop that may function to restore PPP activity through p53 and TIGAR. Although the importance of the activation of the PPP to p53's tumor suppressor activity is not yet clear, the current models suggest that this function is important to help cells survive and avoid or repair moderate levels of damage sustained under normal growth conditions or in response to mild stress (Vousden 2009) (Fig. 2).

p53 as an Antioxidant

Activities of p53 that promote the PPP highlight another important function of p53, which is to limit levels of oxidative stress (Sablina et al. 2005). p53-dependent activation of expression of genes like TIGAR (Bensaad et al. 2006), sestrins (Budanov et al. 2004), p53INP1 (Cano et al. 2009), and several others helps to lower intracellular ROS levels, providing a survival function and protecting cells from ROS-associated damage that could contribute to both cancer development and aging. An indirect activity of p53 in regulating oxidative stress has also been described, in which p21 (a direct transcriptional target of p53) functions to stabilize, and so enhance the activity of the transcriptional regulator Nrf2 (Chen et al. 2009). Nrf2 is a master regulator of a complex program of antioxidant gene expression (Jaiswal 2004) and this link to the p53/p21 pathway provides another important facet to the ROS-limiting functions for p53. The importance of these antioxidant and survival activities of p53 is clearly shown in mice lacking p53, in which higher levels of oxidative stress correlate with adverse pathologies. Most obviously, these include increased tumor susceptibility (Sablina et al. 2005), but it is also possible that loss of these functions of p53 could be contributing to other aspects of



health and disease, including accelerated aging (Vousden and Lane 2007; Matheu et al. 2008).

It is important to remember, however, that p53 has a dual role in the regulation of oxidative stress. Indeed, under conditions in which the response to p53 is apoptotic cell death, there is a clear pro-oxidant function for p53. Several p53 target genes that are important mediators of the apoptotic response drive increased ROS, including PUMA, NOXA, and PIG3. The ability of p53 to promote oxidative stress is strongly linked to the ability of p53 to kill cells (Liu et al. 2008)—although the induction of ROS by p53 is also likely to play a role in other growth inhibitory responses such as the induction of senescence. The real reason behind this somewhat bipolar behavior of p53 is not yet clear, but as suggested previously, these responses may reflect different roles of p53 depending on the extent or duration of cellular stress or damage. Put simply, p53 may help cells survive and repair damage that is mild or transient (including the background levels of stress associated with simply living) by activating survival, repair, and antioxidant responses. However, when damage is extensive or stress continues unabated (for example, following oncogene activation or persistent growth abnormalities associated with tumor progression), p53 switches to drive the elimination of the affected cell through pathways that include the activation of ROS (Vousden and Prives 2009) (Fig. 2). Intriguingly, in contrast to the antioxidant functions of p53 that may help to promote longevity, the pro-oxidant response of p53 might contribute to more rapid aging. The prediction would be that persistently high stress that results in a persistent induction of p53 would promote aging—precisely the phenotype described in mice engineered to express slightly elevated levels of p53 constitutively in all tissues (Matheu et al. 2008).

Finally, we should remember that ROS can also regulate p53 (Liu et al. 2008), so the role of p53 in limiting or enhancing ROS could form part of a feedback or feed-forward loop, depending on circumstances. A recent study has shown that oxidative stress in adipose tissue, linked to a high-calorie diet, leads to the induction of a p53-dependent acquisition of insulin depend-

ence (Minamino et al. 2009). Given the importance of p53 in regulating metabolism, this intriguing result may be the first of many linking p53 to diabetes.

p53 and Hypoxia

One of the most important drivers of metabolic reprogramming in cancer cells is the response to hypoxia, or the activation of a pseudo-hypoxic response under normoxic conditions (Kaelin 2008). The shortage of blood supply during the development of a solid tumor leads to a reduced oxygen tension that signals a stress response designed to help cells survive low oxygen while promoting the systems to bring blood and oxygen back to the tissue.

Although part of the response to HIF1 is the induction of angiogenesis to ameliorate the hypoxic environment, HIF1 also drives the expression of most of the components of glycolysis, and has been suggested to be a major driving force behind the Warburg effect. Interestingly, hypoxia has also been shown to activate p53, although the underlying mechanism remains obscure (Hammond and Giaccia 2005). Hypoxia can induce ROS and through this activate p53, although ROS-independent induction of p53 by hypoxia has also been described (Munniyappa et al. 2009). Although direct protein interactions have been shown to result in the stabilization of p53 (An et al. 1998; Chen et al. 2003) and inhibition of HIF1 (Blagosklonny et al. 1998), the observation that much more severe oxygen deprivation is required to induce p53 than HIF suggests a more complex relationship between the two responses (Hammond and Giaccia 2005). Furthermore, whereas HIF1 can enhance p53 activity and stability, the ability of HIF2 to control ROS has recently been associated with the negative regulation of p53 (Bertout et al. 2009).

Activation of p53 under conditions of low oxygen can drive a number of responses that might enhance tumor suppression. The antiangiogenic effects of p53 could function under hypoxic conditions to counteract the effects of HIF in driving neovascularization, although the observation that the maintenance of hypoxia

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correlates with more aggressive tumors and a poor response to therapy complicates the simple model that an enhanced blood supply benefits the cancer. The activation of p53 under hypoxic conditions can also directly target an apoptotic response, through both the transcriptional activation of genes like PUMA (Yu et al. 2003) or Fas (Liu et al. 2007), and the transcriptional repression of the miRNA-17-92 cluster (Yan et al. 2009), and so counter the survival functions of HIF.

As with the control of angiogenesis, HIF and p53 appear to have opposing effects on glycolysis, which is promoted by HIF-1 and dampened by p53 (Yeung et al. 2008). Of course, there is likely to be enormous cell and context dependency on the outcome of the response to hypoxia, and careful comparisons of the contribution of HIF and p53 may reveal different effects under different conditions. But the observation that mild hypoxia activates HIF, whereas a much more severe lack of oxygen is required to induce p53, suggests another explanation, that the HIF response is designed to help cells survive mild or transient reductions in oxygen, whereas the p53 response (which under these conditions leads to cell death) is harnessed only under much more severe circumstances. The Cockayne syndrome B protein (CSB) functions here—serving to dampen the activity of p53 in favor of HIF-1 function and so helps maintain cell survival under hypoxia (Filippi et al. 2008). Loss of CSB results in an overactivation of p53, which may account for the enhanced aging seen in Cockayne syndrome patients.

TUMOR SUPPRESSION AND PROMOTION BY p53-INDUCED PATHWAYS

There is abundant and compelling evidence to support the role of p53 as a tumor suppressor, including the high incidence of p53 mutations in many types of cancer, a large number of animal models showing enhancement of cancer development under almost all conditions following loss of p53, and the enormously increased cancer burden shown by individuals who inherit one mutant p53 allele. The reactivation of wild-type p53 function in cancers results in effective

tumor regression because of the cell death or senescence responses (depending on the tissue type) (Martins et al. 2006; Ventura et al. 2007; Xue et al. 2007), leading to great hope for the generation of p53-activating drugs for the treatment of human malignant disease. However, not all p53 activities are so easily reconciled with a prevention of cancer development and it is possible that some functions of p53 may be hijacked to help, rather than hinder, malignant progression.

In general, the abnormal behavior of cancer cells reflects the inappropriate manifestation of normal cell responses, which have been commandeered during the evolution of the cancer to promote malignant growth. Examples include the mis- or overactivation of components of signal transduction mechanisms that drive cell proliferation or cell survival, but further examples can be found within the metabolic pathways. HIF-1 mediated functions such as angiogenesis, survival, and glycolysis are essential during normal development or for cells transiently experiencing a dip in oxygen levels. However, when not properly regulated—as seen in patients with VHL in which the normal negative regulation of HIF is lost—these same activities can help tumor development. Similarly, certain functions of p53 that are important for normal growth, development, and tumor suppression might also be misused to help promote, rather than hinder, tumor development, and several of the metabolic functions of p53 could fall into this category. An example is the ability of p53 to limit ROS, which can function to limit tumor development but might also help tumor cells to survive and flourish. It would seem that to avoid this, the ability of p53 to regulate the antioxidant genes is tightly regulated, and that their expression may actually decrease under conditions of sustained stress, in which p53 starts to induce cell death (Sablina et al. 2005; Bensaad et al. 2006). Similarly, transcription of Nrf2, which drives a strong antioxidant program, is also inhibited by p53 under conditions of sustained stress and irreparable damage (Farianio et al. 2006; Chen et al. 2009). So, the ability to switch off some of these responses to p53 may be as important to tumor suppression as the ability to turn them on.



It seems that the induction of p53 can allow cells to tolerate a certain degree of stress, but that as the levels of damage and abnormalities build, a tipping point is reached in which elimination of the affected cell (by p53) becomes necessary. On the one hand, the first function of p53 ensures that cells are not too fragile, allowing them to endure some level of insult. The latter activity, on the other hand, prevents cells from becoming too hardy, because survival under conditions of persistent stress would greatly favor the development of cancer. It seems highly likely, then, that the misappropriation of p53's survival activities could be used by cancers, and that a defect in the ability to down-regulate these functions of p53 would have catastrophic consequences.

HARNESSING THE METABOLIC FUNCTIONS OF p53 FOR THERAPY

Although the contribution of metabolic reprogramming to the initiation of cancers still remains unclear, there is an obvious role for changes in metabolism in the maintenance of the malignant phenotype. Many studies have now shown that cancers become dependent on their abnormal metabolism, and are completely reliant on pathways such as glutaminolysis and glycolysis. These observations prompt a further analysis of the metabolic functions of p53, and how we might make use of these in cancer therapy. In keeping with the suggestion that p53 functions may, in some cases, be an advantage to cancer cells, studies have shown that the retention of wild-type p53 in breast cancers can predict poor prognosis and poor response to therapy (Bertheau et al. 2008). Intriguingly, p53 also helps tumors to survive treatment with Metformin, a drug that activates AMPK. Metformin is widely used in the treatment of diabetes (Buzzai et al. 2007) and was recently shown to lower the risk for cancer in diabetic patients (Jiralerspong et al. 2009; Libby et al. 2009). Similarly, expression of proteins like TIGAR or Sestrins might contribute to the success of cancer cells, and so may be targets for therapeutic intervention.

Finally, the metabolic activities of p53 may also be important in the regulation of other aspects of p53 behavior, in addition to cancer. Very recently, a role for p53 in the promotion of insulin resistance was described, suggesting that the proaging and prosenescence functions of p53 will also drive the development of diabetes. The ability of p53 to directly control several aspects of metabolism, including glycolysis and the mTOR pathway, suggests that there may be further functions for p53 in the regulation of other metabolic diseases, as well as aspects of aging and longevity.

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