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# Metabolic regulation of oxygen and redox homeostasis by p53: lessons from evolutionary biology?

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## Abstract

The genetic links between p53 and metabolic processes such as oxidative phosphorylation are being studied with increasing interest as cellular metabolism appears to play an important role in tumorigenesis. This review focuses on how p53 regulation of various metabolic genes may influence redox homeostasis as the genome is constantly susceptible to oxidative damage, a consequence of living in an aerobic environment. As p53-like genetic sequences are also found in life forms that may not necessarily benefit from tumor suppression, an evolutionary introduction is given in an attempt to understand why p53 might regulate a basic cellular activity such as metabolism. The presented epidemiologic and experimental data suggest that one reason may be for the homeostatic regulation of oxygen, the essential substrate for reactive oxygen species (ROS) generation.

### Keywords

p53; oxygen; oxidative stress; redox; antioxidant; metabolism; cancer; mitochondria; altitude

## Introduction

The challenges of studying the complex history of atmospheric molecular oxygen faced by geologists appear to extend to cancer biologists [1]. Oxygen has been shown both to promote and inhibit tumorigenesis, depending on various factors including its level and the experimental model [2–6]. Even the basic question of whether oxidative stress, fueled by molecular oxygen, is causally linked to aging and tumorigenesis is debated [7]. However, studying a fundamental principle such as that governing the evolution of aerobic life may provide useful lessons for advancing our understanding of cancer biology.

p53 is commonly referred to as one of the most important tumor suppressor genes and the “guardian of the genome” [8]. However, p53 gene-like sequences are also found in unicellular forms of life that would not be expected to benefit from its sophisticated tumor surveillance function [9]. Thus, it has been proposed that p53 may have provided basic adaptive functions for cell survival prior to its adoption for tumor suppression. One such primordial connection may be that between p53 and numerous metabolic functions including mitochondrial respiration [10–13]. Although the growing number of disparate cellular

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processes regulated by p53 may appear to be of unclear significance for its tumor suppressor function [14], examining them from an evolutionary perspective may provide important lessons about tumorigenesis.

With the rapid increase in atmospheric oxygen over the past half billion years, life is thought to have evolved from a relatively anoxic to an oxygen-rich environment [15]. Protection from oxygen toxicity, or oxidative stress, has thus been proposed as a driving evolutionary force underlying the symbiotic incorporation of the oxygen consuming purple bacteria that were the progenitors of mitochondria [16]. Notably, the mitochondrion is generally regarded as the major source of reactive oxygen species (ROS), but a critical review of the supporting data is not entirely convincing of this concept [17]. In fact, cells with defective respiration due to the disruption of a critical mitochondrial gene regulated by p53 actually display increased oxidative stress and genomic DNA damage [18]. If p53 regulation of metabolism represents an adaptive function, it could also be speculated that the other p53 family members, p63 and p73, may regulate some aspect of metabolism. Despite the well characterized role of p63 and p73 in apoptosis and development, their direct effect on metabolic pathways remains to be determined [19].

Based on the following review of epidemiologic and basic experimental data, the possibility arises that regulation of aerobic metabolism by p53 may contribute to oxygen and redox homeostasis for preventing oxidative DNA damage and maintaining genomic stability. p53 has been shown to have both pro-oxidant and antioxidant functions depending on its level, activity and context of induction; however, both activities are directed at tumor suppression [10, 13, 20, 21]. The antioxidant function of p53 at basal levels may protect against genomic DNA damage while the pro-oxidant effect at high p53 levels may induce apoptosis or senescence to eliminate cells with irreparable genomic DNA damage (Fig. 2). The pro-oxidant effects can be through both direct and indirect mechanisms as briefly summarized in this review. Because there is already extensive literature supporting the pro-oxidant function of p53, this review will mainly focus on the role of basal level p53-regulated metabolic pathways in redox homeostasis. A major objective of this review is to propose that p53 promotion of aerobic metabolism reduces oxidative stress which in turn may contribute to preventing DNA damage and genomic instability.

## Oxygen toxicity and tumorigenesis

The antioxidant mechanisms used by cells for protection from ROS have been extensively delineated, but less is known about how cells may actively decrease exposure to oxygen. Even in bioenergetically demanding tissues such as the heart, molecular oxygen has previously been thought to be non-limiting for mitochondrial respiration under normal physiologic conditions [22]. However, direct measurements show that oxygen concentrations vary significantly among tissue types suggesting that the levels of oxygen are dependent on its local delivery and utilization [23]. A recent paper measuring the oxidation state of mitochondria has revealed a significant oxygen concentration gradient from the site of delivery (capillary) to the site of utilization (core of skeletal muscle) [24]. As might be predicted from such an observation, it has also been shown that increased mitochondrial biogenesis decreases oxygen concentration in skeletal muscle, presumably by increasing its consumption, and supports the concept that modulation of mitochondrial activity has the potential to affect intracellular oxygen homeostasis [25].

While on one hand oxygen is necessary for cellular energy production by oxidative phosphorylation (OXPHOS), it can also serve as the substrate for the generation of ROS that causes oxidative DNA damage. In fact, oxygen has been shown to be a mutagen in bacteria and proposed to be toxic to humans [15, 26]. A large epidemiologic study supports the

concept that oxidative stress, as followed by exposure to ambient oxygen, may indeed be associated with tumorigenesis. Using data from 80 cities in the United States, the age-adjusted cancer mortality rates for a number of common cancers, including lung cancer, showed a significant negative relationship with increasing altitude even after adjusting for background radiation (Fig. 1A) [27]. Therefore, it has been proposed that changes in exposure to oxygen may be an important factor contributing to the striking inverse relationship between altitude and age-adjusted cancer mortality.

The epidemiologic observation that oxygen may be pro-tumorigenic has recently been supported by experimental data. Chronically lowering the ambient oxygen exposure of *p53*$^{-/-}$ mice, a well established model of accelerated *de novo* tumorigenesis, dramatically increased cancer-free survival (Fig. 1B) [18]. Lowering the exposure to oxygen was associated with an increase in the antioxidant capacity of blood and a concomitant decrease in oxidative DNA damage [6]. Furthermore, in the *APC*$^{Min/+}$ mouse model of intestinal polyposis, reduced oxygen exposure decreased the appearance of polyps which serve as a marker of genomic instability at the wild-type *APC* gene locus [6, 28]. It is notable that most of the polyps in the *APC*$^{Min/+}$ mouse model appear in the small intestine which is known to have a higher intraluminal oxygen tension compared to the large intestine [29, 30]. A recent publication has provided genetic evidence that increased mitochondrial ROS caused by mitochondrial transcription factor A (TFAM) haploinsufficiency is associated with increased polyp number and growth in the small intestine of *APC*$^{Min/+}$ mice [31]. Using human colon cancer cells, the genetic disruption of mitochondrial respiration altered intracellular oxygen homeostasis and markedly increased oxidative DNA damage which could be prevented by decreasing ambient oxygen [18]. Taken together, these data suggest the critical role that the mitochondria and oxygen homeostasis may play in tumorigenesis. We speculate that although most of the DNA damage caused by oxygen can be repaired by response proteins such as p53, they are unlikely to prevent all of the cumulative mutations over a life-time that manifest as the inverse relationship between cancer incidence and altitude (oxygen exposure).

## p53 and mitochondria are oxygen-responsive

It is well established that mammalian cells utilize hypoxia inducible factors (*HIF* genes) to sense and respond to alterations in cellular oxygen availability. Mitochondrial respiration has the potential to increase HIF-1α protein levels by at least two different mechanisms: 1) relative hypoxia caused by the consumption and redistribution of intracellular oxygen [32, 33]; and/or 2) ROS production associated with respiratory electron transfer under hypoxic conditions [34, 35]. Potentially as feedback under conditions of limiting oxygen, HIF-1α can inhibit respiration by transactivating the *PDK* gene and can decrease mitochondrial biogenesis by repressing the expression of *C-MYC*, an activator of PGC-1β transcription [36–38]. In contrast, increased oxygen exposure may stabilize p53 through multiple mechanisms and promote mitochondrial biogenesis. Among the possible scenarios, molecular oxygen could regulate p53 via redox sensitive proteins as discussed in the next section or it could serve as a substrate to increase ROS levels which damage DNA or activate signaling enzymes such as polo-like kinase 3 (PLK3) with resultant N-terminal phosphorylation and stabilization of p53 (Fig. 2) [18, 39]. As evidence of interaction between these two oxygen sensitive transcription factors, p53 has been shown to decrease HIF-1α level by inhibiting its translation through p53-induced microRNA-107 or by promoting its degradation by MDM2-mediated ubiquitination [40, 41]. In parallel, HIF-1α may prevent p53 degradation by inhibiting MDM2-mediated p53 ubiquitination under severe stress such as anoxia [42]. Such regulatory relationships between p53 and HIF-1α as well as other HIF members have been extensively studied and are reviewed in greater detail elsewhere [43–45].

## Redox regulation of p53

Although p53 stability and activity are regulated by a host of different posttranslational modifications [46], the primary structure of p53 confers redox sensitivity to its DNA binding and transactivating properties [47, 48]. The hydrophobic DNA binding domain of p53 has 10 cysteine amino acid residues, the majority of which are also present in the two well-studied p53 isoforms delta133p53 and delta40p53, both associated with oxidative stress and aging [48]. Cysteine residues 176, 238 and 242 of p53 are known to coordinate zinc and play a critical role in its DNA binding and transactivating activities [49]. Cysteine 124, 141 and 182 are sites of glutathionylation that may modulate p53 DNA binding and tetramerization [50, 51]. The formation of intramolecular disulfide bonds between cysteine pairs 275/277 and 135/141 both modulate DNA binding of p53 [52, 53]. In addition, ROS has been shown to induce p53 phosphorylation and activation [54], while reactive nitrogen species (RNS) can cause p53 nitration at critical tyrosine residues to disrupt its interaction with DNA [55, 56]. The specific redox modifications of p53 and its isoforms are extensive and have been expertly reviewed elsewhere [48].

Besides its structural modifications by cellular redox state, p53 also interacts with regulatory redox proteins (Fig. 2). As an enzyme that can both repair DNA and regulate the redox state of proteins, apurinic endonuclease/redox factor 1 (APE/REF1, APEX1) directly interacts with p53 to stimulate its DNA binding and transcriptional activity [57, 58]. The redox-dependent mechanism by which REF1 increases basal p53 activity involves the thioredoxin system without the N-terminal phosphorylation of p53 associated with DNA damage [59]. It has been shown that depleting thioredoxin reductase 1 (TXNRD1) increases the DNA binding capacity of p53 by sequestering oxidized thioredoxin in the cytoplasm and preventing its oxidation of p53 in the nucleus. NAD(P)H:quinoneoxidoreductase-1 (NQO1), another redox enzyme that is responsive to oxidative stress through nuclear factor erythroid 2-like 2 (NRF2, NFE2L2), physically interacts with p53 and inhibits its degradation [60]. The growing number of redox factors interacting with and regulating p53 points to an important of p53 in redox homeostasis.

## p53 can regulate redox homeostasis through the mitochondrion

Increasing evidence indicates a dual role for p53 in redox homeostasis that depends on its activity and expression level as well as the context of the cell (Figs. 3 and 4) [10, 13, 20, 21]. A genetic link between p53 and mitochondrial respiration was established by using isogenic human colon cancer cells with *p53* disruption and by the identification of synthesis of cytochrome c oxidase 2 (*SCO2*) as a transcriptional target of p53 required for complex IV assembly [61, 62]. It now appears that p53 promotes mitochondrial function through multiple pathways involving genes required for the assembly of other respiratory chain complexes, maintenance of the mitochondrial genome, regulation of mitochondrial dynamics, and metabolism (SCO2, cytochrome c oxidase subunit 1 (MTCO1), apoptosis-inducing factor (AIF), ferredoxin reductase (FDXR), PGC-1α, TFAM, p53-inducible ribonucleotide reductase (p53R2), DNA polymerase γ (POLG), mitochondrial glutaminase 2 (GLS2)) (Fig. 3) [12, 13, 63–65]. Although many of these metabolic pathways are transcriptionally regulated by p53, it is also evident that p53 can regulate metabolism by protein-protein interactions. For example, p53 can directly stabilize TFAM, interact with POLG, facilitate the translocation of p53R2 to the nucleus, and inactivate glucose-6-phosphate dehydrogenase (G6PD) at the protein level [66–69].

The substrates used for mitochondrial metabolism can play an important role in cellular redox homeostasis. p53-stimulated glutaminolysis via GLS2 lowers oxidative stress levels in association with increased mitochondrial respiration and glutathione production [70, 71].

Furthermore, compared to succinate, the oxidation of fatty acids promoted by p53 through its target gene guanidinoacetate methyltransferase (*GAMT*) produces less ROS due to low reverse electron transfer [72, 73]. ROS-activated ataxia telangiectasia mutated (ATM) can phosphorylate p53 at Ser-18 which increases fatty acid oxidation via the transactivation of the gene encoding phosphatidic acid phosphohydrolase (*LPIN1)* [74]. As fatty acid oxidation consumes more oxygen per ATP generated compared to glucose utilization and also provides NADPH needed for the biosynthesis of glutathione [75], the choice of substrate for mitochondrial respiration may be another level at which p53 may moderate oxidative stress.

As might be expected in a homeostatic relationship, mitochondrial function in turn influences p53 levels. Mitochondrial dysfunction has been shown to increase DNA damage [76], and the specific disruption of respiratory complex IV increases p53 protein levels as well as oxidative DNA damage in an oxygen dependent manner [18]. In contrast, the disruption of complex I has been shown to impair p53 stabilization suggesting that the interaction between the electron transport chain and p53 is likely to be rather complex [77]. Interestingly, it also appears that p53 can inhibit mitochondrial function and increase oxidative stress for eliminating cells with irreparable DNA damage (Fig. 4). p53 target genes, such as BCL-2 binding component 3 (*BBC3 or PUMA*) and BCL2-associated X protein (*BAX*), are upregulated in association with high ROS levels and cytochrome c release during p53-mediated apoptosis [13, 78]. Telomere shortening can promote premature aging by activating p53 [79]. A recent study has shown that p53 activation by telomerase deficiency can suppress PGC-13 expression thereby inhibiting mitochondrial biogenesis and increasing cellular stress and senescence [76, 80]. Consistent with this observation, p53 can also promote mitochondrial damage and oxidative stress via the regulation of $p66^{shc}$ [81, 82]. Furthermore, p53 transcriptionally regulates FDXR, a mitochondrial cytochrome P-450 NADPH reductase that mediates ROS generation during p53-dependent apoptosis [83] but is also essential for heme biogenesis and normal mitochondrial function [84, 85].

## p53 regulates oxidative stress via nonmitochondrial pathways

Adenoviral vector mediated overexpression studies first associated p53 with oxidative stress and resulted in the identification of a number of non-mitochondrial genes thought to have a pro-oxidant function (Fig. 4) [86, 87]. These genes include the pro-apoptotic galectin family member *LGALS7* (p53-induced gene 1, PIG1) and the NADPH-quinone oxidoreductase homolog *TP53I3* (PIG3), both of which have ROS generating capacity [88, 89]). In contrast, basal p53 expression levels were subsequently shown to have a striking antioxidant effect [78]. Depletion of p53 caused increased oxidative DNA damage and chromosomal instability while dietary supplementation with the antioxidant N-acetylcysteine (NAC) markedly delayed *de novo* tumorigenesis in *p53−/−* mice, suggesting that the antioxidant function of p53 plays an important role in tumor suppression [78]. p53-regulated sestrins (SESN), essential for regenerating peroxide-reducing peroxiredoxins (PRX), were implicated in this specific study [90, 91].

Consistent with the above findings, mouse and human cells lacking p53 show increased sensitivity to oxidative and nitrosative stress in association with decreased heme oxygenase-1 (HO-1), a p53-dependent antioxidant gene [92–94]. However, there are additional ROS detoxifying pathway genes directly regulated by p53 both in the cytosol, such as peroxisomal catalase (*CAT*) and tumor protein 53-induced nuclear protein 1 (*TP53INPI*), as well as in the mitochondria, such as glutathione peroxidase 1 (*GPX1*), manganese superoxide dismutase (*SOD2*) and aldehyde dehydrogenase 4 (*ALDH4*) [95–98]. The relative contributions and responses of these various enzymatic systems likely depend

on various factors including the type of oxidative stress, cell type and even the species of interest.

Glycolytic metabolism results in the generation of high energy reducing equivalents that can contribute to superoxide production. Consistent with an antioxidant role for p53, it is notable that p53 inhibits glycolysis through more than one regulatory pathway (Fig. 3). It can down-regulate glucose transporters (GLUT1 and GLUT4) thereby decreasing the availability of glucose for glycolysis [99]. The lactate produced during glycolysis to regenerate oxidized NAD by lactate dehydrogenase, an enzyme implicated in tumorigenicity [100], requires elimination by transport across the plasma membrane. p53 represses the expression of the monocarboxylate transporter gene (*MCT1*) that would decrease lactate efflux out of the cell and inhibit glycolysis [101]. p53 mutational status can also affect the activity of glycolytic enzymes such as hexokinase 2 (HK2) and phosphoglycerate mutase (PGM) [102, 103]. PGM is down-regulated by wild-type p53, and mutated p53 appears to facilitate cellular immortalization by increasing glycolysis [103].

p53 can modulate the activity of the key gylcolysis entry enzyme phosphofructokinase 1 (PFK1) by transactivating TP53-induced glycolysis and apoptosis regulator (*TIGAR*) which hydrolyzes the allosteric activator fructose-2,6-bisphosphate [104]. Notably, the decrease in glycolysis results in increased flux through the pentose phosphate pathway (PPP) which lowers apoptosis and ROS levels through increased glutathione synthesis. However, more recent data show that p53 can directly interact with and inactivate G6PD, the rate limiting enzyme of the PPP (Fig. 4) [69]. The biologic significance of these two seemingly opposing effects appears unclear but may also be reflective of the complexities surrounding the pro-oxidant and antioxidant effects of p53 depending on cellular context.

## Summary

The association between ambient oxygen exposure and tumorigenesis as revealed by both human epidemiologic studies and experimental mouse models suggests that life in an aerobic environment requires dynamic regulation of the cellular redox state. Delineating the specific effects of p53 on the redox state of the cell has been challenging because of its multi-faceted activities, however, a common emerging theme is that p53 plays an essential role in redox homeostasis. In the context of a normal cell under basal conditions, p53 regulates antioxidant enzymes and metabolism, such as promoting mitochondrial respiration while inhibiting glycolysis to reduce cellular ROS levels and prevent DNA damage. In senescent or DNA damaged cells, p53 induces pro-oxidant genes while suppressing mitochondrial respiration to increase oxidative stress and promote cell death. Together, the dual effect of p53 on redox homeostasis may significantly contribute to its overall function of maintaining genomic stability and tumor suppression.

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## Highlights

1. Human and animal data suggest that oxygen promotes tumorigenesis
2. Oxygen consumption by mitochondrial respiration affects redox homeostasis
3. p53 has both pro-oxidant and antioxidant activities via multiple pathways
4. p53 regulates mitochondrial respiration as part of its antioxidant function

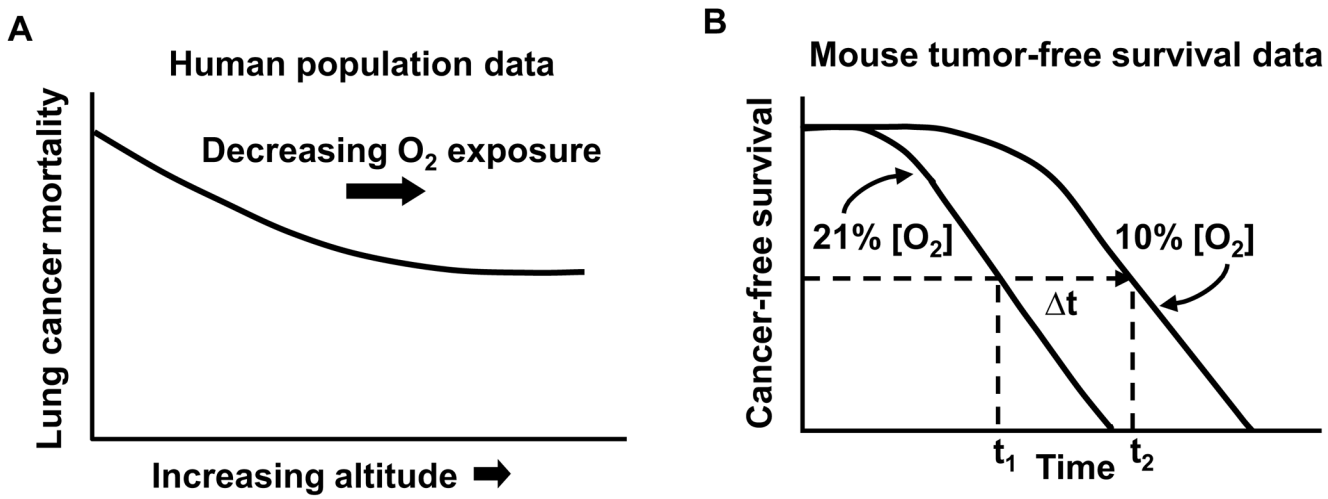


**Fig. 1.**

Relationship between cancer and oxygen exposure. A) A schematic representation of the inverse relationship between age-adjusted male lung cancer mortality and altitude (oxygen exposure). Figure adapted from [27] with publisher's permission. B) A schematic representation of the increase in cancer-free survival of *p53−/−* mice by chronic exposure to 10% oxygen versus 21% (room air) (difference in median cancer-free survival time, ~40–50%) [6].

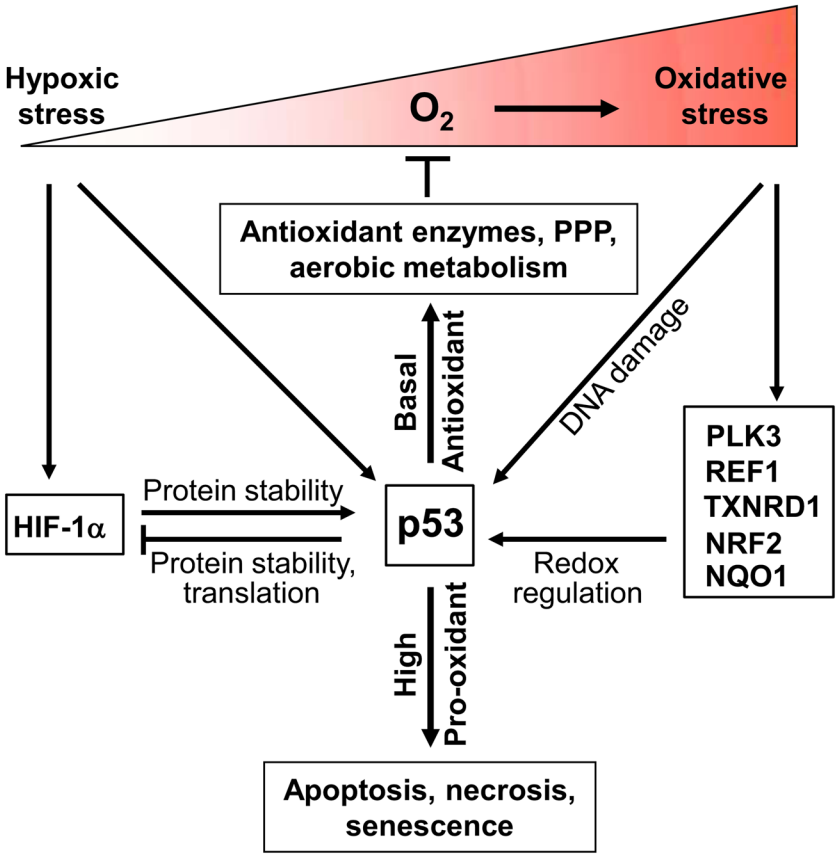


**Fig. 2.**

Redox regulation of p53 and its dual role in cellular redox homeostasis. Oxygen serves as the essential substrate for reactive oxygen species generation and oxidative stress. Varying intracellular oxygen availability can regulate p53 activity and protein level through a number of different mechanisms including oxidative DNA damage, various redox regulatory genes, severe hypoxic stress, and HIF-1α. Basal levels of p53 have antioxidant function that prevents oxidative damage while high levels of p53 are pro-oxidant and cause apoptosis, necrosis or senescence to eliminate cells with irreversible DNA damage.

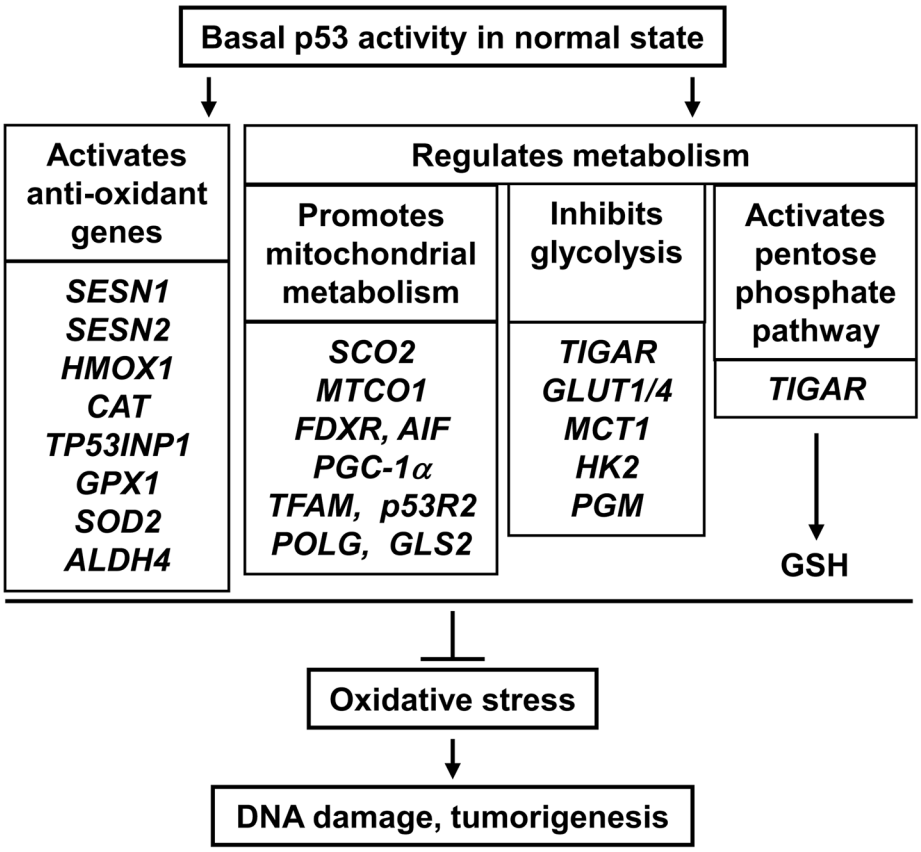


**Fig. 3.**

Basal levels of p53 under physiologic or normal states regulate multiple pathways to prevent oxidative DNA damage and tumorigenesis. p53 can counteract oxidative stress by inducing the expression of anti-oxidant enzymes and by increasing cellular antioxidant glutathione (GSH) biosynthesis through the pentose phosphate pathway. The promotion of aerobic metabolism by the concurrent stimulation of mitochondrial respiration and inhibition of glycolysis decreases the levels of ROS generating factors oxygen and high energy reducing equivalent (NADH), respectively.

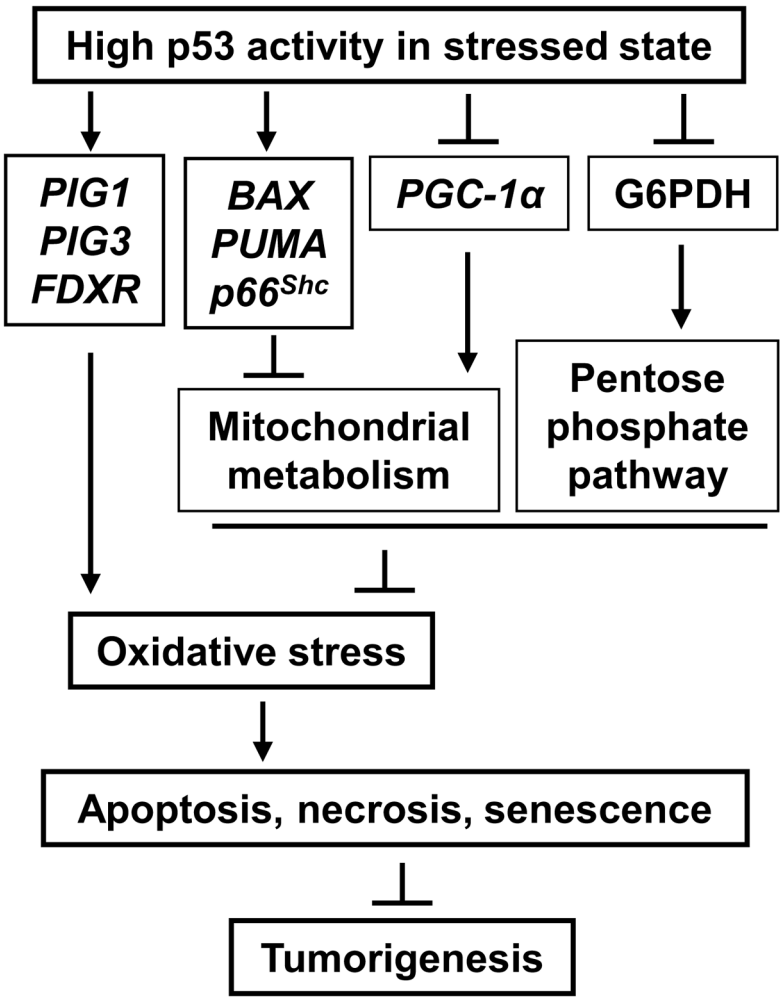


**Fig. 4.**

High levels of p53 caused by severe stress such as irreversible DNA damage increase oxidative stress to promote the elimination of damaged cells and prevent tumorigenesis. p53 can transactivate genes capable of generating ROS during apoptosis. In contrast to the antioxidant effects of p53 shown in Fig. 3, the inhibition of both mitochondrial metabolism and the pentose phosphate pathway may also contribute to increase cellular oxidative stress.