# p53, Aerobic Metabolism, and Cancer

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## Abstract

p53 regulates the cell cycle and deoxyribonucleic acid (DNA) repair pathways as part of its unequivocally important function to maintain genomic stability. Intriguingly, recent studies show that p53 can also transactivate genes involved in coordinating the two major pathways of energy generation to promote aerobic metabolism, but how this serves to maintain genomic stability is less clear. In an attempt to understand the biology, this review presents human epidemiologic data on the inverse relationship between aerobic capacity and cancer incidence that appears to be mirrored by the impact of p53 on aerobic capacity in mouse models. The review summarizes mechanisms by which p53 regulates mitochondrial respiration and proposes how this might contribute to maintaining genomic stability. Although disparate in nature, the data taken together suggest that the promotion of aerobic metabolism by p53 serves as an important tumor suppressor activity and may provide insights for cancer prevention strategies in the future. *Antioxid. Redox Signal.* 15, 1739–1748.

## Introduction

THE LOSS OF P53 ACTIVITY in the majority of malignant human cancers is a testament to its critical role in maintaining genomic stability and preventing tumorigenesis, hence the reference to p53 as "guardian of the genome" (47, 52). Major advances in our understanding of p53 in cancer biology have been made by investigating its activities in regulating the cell cycle, senescence, apoptosis, and genomic stability (108). The involvement of p53 in functions as diverse as fecundity and metabolism continue to be uncovered (109). *p53* is a gene that evolved before the beginning of multicellular life (56); therefore, studying its function is likely to yield valuable information beyond that relevant for cancer biology.

The promotion of aerobic metabolism by 53 through the stimulation of mitochondrial respiration and the concurrent inhibition of glycolysis have attracted attention because the frequent inactivation of p53 in cancers would be predicted to contribute to the observed phenomenon of increased glycolysis (62, 110, 112, 122). Increased glycolysis, also known to be stimulated by a number of oncogenes, may be advantageous to proliferating cancer cells as it generates high energy reducing equivalents, tricarboxcylic acid cycle substrates, and other carbon-back bone intermediates needed for the biosynthesis of lipids, proteins, and nucleic acids (24, 43). Likely reflecting altered cellular demands, cancer cells show other changes in metabolism, such as a greater dependence on glutamine as a bioenergetic substrate, which p53 also appears to regulate (36, 99, 113).

Consistent with abundant biochemical and genetic data demonstrating mitochondrial dysfunction in cancer cells (18, 66, 111), p53, as a tumor suppressor, appears to counteract this and promotes respiration.

The impedance of electron transfer, caused by mutations in nuclear and mitochondrial genes encoding the respiratory chain complex genes, may result in increased reactive oxygen species (ROS) and genomic deoxyribonucleic acid (DNA) damage (111). A recent study has demonstrated the importance of the mitochondria even at later stages of cancer progression by transferring metastatic potential between cancer cell lines through the mitochondria (39). This review begins by summarizing epidemiologic data that show an inverse relationship between cancer and cardiorespiratory fitness (CRF), a phenotype that is strongly associated with mitochondrial biogenesis (114). In light of this human data, the marked decrease in exercise capacity of p53-deficient mice appears to take on additional significance (62, 76, 88), and the current state of knowledge on both the physiological and molecular aspects of p53 regulation of mitochondrial respiration is presented. The remarkable consistency with which p53 promotes aerobic metabolism suggests that this phenotype may be important for tumor suppression and that it may reveal insights useful for devising new preventive strategies.

## Cancer and CRF

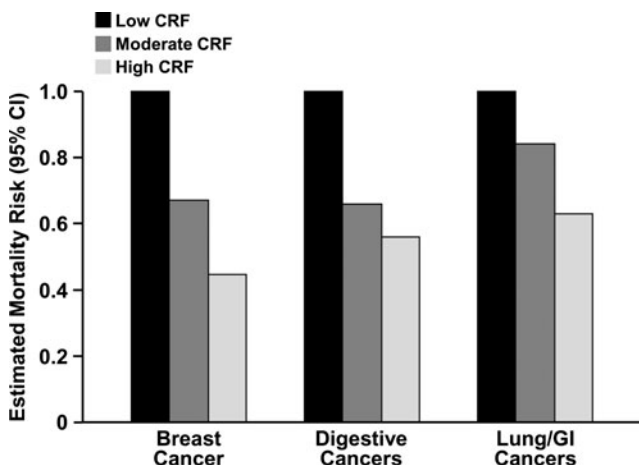Clues to the biological significance of the relationship between p53 and aerobic metabolism may be gleaned from the

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many clinical studies that have established the benefits of physical activity against cancer. Exercise can have cancer preventive effects, both before and after disease diagnosis (72), and therefore may affect both tumor initiation and progression (86). A number of comprehensive reviews have summarized evidence that supports this link between cancer prevention and physical activity in epidemiologic studies (29) and experimental models (35). To quantify physical activity and exercise habits, researchers have measured CRF (also termed aerobic endurance or aerobic fitness) by maximal exercise treadmill testing and resting heart rate (8, 12).

The strongest epidemiologic evidence for the protective effects of physical activity is seen in breast (67) and colon cancer (104). There is a dose-dependent relationship between CRF and estimated mortality risk from breast cancer (78), digestive cancer (79), and primarily lung and gastrointestinal cancers (49) (Fig. 1). In an evaluation of 29 case-controlled and 19 cohort epidemiologic studies, physical activity was associated with a 15%–20% decrease in the combined risk of pre- and postmenopausal breast cancer with stronger evidence for the latter. Conversely, 13%–14% of colon cancer incidence can be attributed to physical inactivity (34). Emerging evidence suggests that the risk of developing other types of cancers, such as that of the prostate (72), lung (49, 51), and gastrointestinal or digestive system (49, 79), may be decreased by physical activity as well.

The cancer-type-specific benefits of exercise further increase the complexity of the potential mechanisms and indicate a need for improved understanding of this phenomenon (31, 70). The beneficial effects of exercise are often attributed to factors such as lowered risk of chronic diseases, including mental illnesses, decreased osteoporosis and sarcopenia, and decreased obesity. The specific mechanisms by which exercise may inhibit cancer formation can be summarized using the multistep model of carcinogenesis (Fig. 2) (86). Such a model provides a framework for outlining the complex network of

cellular processes affected by exercise, some of which are better characterized than others.

The first step in the multistep carcinogenesis model is initiation involving carcinogen metabolism and detoxification processes. Exercise has been shown to enhance cytochrome P450 and other enzymes such as NAD(P)H:quinone oxido-reductase 1 (NQO1) for carcinogen handling by the body (82, 107). Although acute, high-intensity exercise may increase mitochondrial ROS production (93), moderate long-term physical activity reduces oxidative damage by increasing antioxidant enzymes (26, 71, 83). Another direct mechanism by which moderate exercise could affect cancer may be through enhancing DNA damage repair enzymes such as human 8-hydroxyguanine DNA-glycosylase (hOGG1) (83). Notably, p53 has been shown to interact with, or regulate, many of the components discussed above (4, 73) and with both nuclear and mitochondrial genomic DNA repair pathways (1, 17).

Exercise affects a heterogeneous set of physiological processes to suppress tumorigenesis that include boosting innate immunity (69, 117) and decreasing chronic inflammation linked to cancer (21, 44, 86). Transcription factors important for mediating inflammatory signals, such as nuclear factor κ-light-chain-enhancer of activated B cells (NFKB) and activator protein-1 (AP-1), have been shown to be reduced by regular exercise (81). Besides the immune system, exercise modulates a host of other processes involved in cancer progression, for example, by suppressing ROS-induced mutagenesis even after initiation and balancing cell proliferation and apoptosis (86). The relative importance of the specific mechanisms by which exercise decreases cancer likely depends on multiple factors, including the type of mutagen, tissue, and species. Despite these complexities, the important fact is that increased CRF has a striking effect in preventing human cancers.

## The Physiological Effects of p53 on CRF

Given the inverse relationship between CRF and cancer, the positive effect of p53 on exercise capacity is consistent with its role as a tumor suppressor (62). However, it was initially a surprising observation that mice deficient in p53 ($p53^{-/-}$) had markedly lower exercise capacity ($\sim 50\%$) in comparison to their wild-type ($p53^{+/+}$) littermates using a forced swimming test (62). Further confirming this observation, $p53^{-/-}$ mice ran only a fraction of the distance of $p53^{+/+}$ mice during an



FIG. 1. The inverse relationship between cardiorespiratory fitness (CRF) and cancer mortality. Estimated mortality risks (95% confidence interval [95% CI]) were extrapolated from multivariate hazard ratio (breast and digestive cancers) and relative risk values (primarily lung and gastrointestinal [GI] cancers) in primary epidemiological studies: breast cancer (78), digestive cancer (79), and primarily lung and GI cancers (49).



FIG. 2. Some of the proposed pathways by which exercise inhibits cancer are summarized using the multistep model of carcinogenesis (86). Such a model provides a useful framework for outlining the complex network of cellular processes affecting initiation and promotion/progression of cancer formation. The strength of evidence supporting the specific mechanisms is variable.

8-week period of voluntary wheel running (88). Although maximum exercise testing is considered to be the gold standard for assessing human CRF (30, 68), its interpretation can be complicated in mice because forced exercise testing can activate stress responses in mice (3), while voluntary wheel running can be affected by circadian and neuro-behavioral factors. Although most animal exercise tests have their limitations, the combination of voluntary wheel running, forced swimming, and treadmill exercise data has provided convincing evidence for a defect in the exercise capacity of $p53^{-/-}$ mice (76, 88).

The decreased exercise capacity of $p53^{-/-}$ mice was further revealed biochemically after submaximum exercise (76). The blood lactate level was increased approximately threefold in $p53^{-/-}$ mice compared to wild-type, suggesting a lower aerobic metabolic capacity, and this difference was magnified after a 5-week period of treadmill training. The maximum work capacity of $p53^{+/+}$ mice was significantly increased by training, whereas that of $p53^{-/-}$ mice was relatively unresponsive. There was further widening of the differences in aerobic capacity as monitored by both the lactate level and respiratory exchange ratio (RER, $CO_2$ production/$O_2$ consumption) during exercise, the latter being a parameter that is highly correlated to CRF in human subjects (85).

How p53 affects CRF warranted closer investigation, as the overt behavioral and morphometric features of $p53^{+/+}$ and $p53^{-/-}$ mice are similar. CRF is determined by a number of important physiological parameters such as cardiac, pulmonary, and skeletal muscle function. Compensatory augmentation of cardiac output, in response to increased circulatory demand, is a major physiological determinant of exercise capacity. By cardiac magnetic resonance imaging, the baseline left ventricular function and inotropic reserve, as elicited by dobutamine stimulation, showed no significant dependence on p53 (76). In addition, there was no gross difference in the motor coordination or skeletal muscle strength of $p53^{-/-}$ mice (76, 88). Consistent with this finding, both genotypes demonstrated equivalent levels of high intensity sprinting in which glycolytic muscle fibers play an important role (76). Other factors that could affect exercise capacity such as hemoglobin concentration and skeletal muscle capillary density were also similar.

The lack of a significant difference in these important physiological parameters between $p53^{-/-}$ and $p53^{+/+}$ mice indicated that the previous finding of p53-regulated mitochondrial respiration may contribute to the difference in aerobic exercise capacity (62). While muscle strength depends on short-term anaerobic energy generation, muscle endurance (or fatigue) is mainly determined by mitochondrial function and lactate disposition (25). $p53^{-/-}$ mice showed 50% greater fatigue than $p53^{+/+}$ mice by an *in situ* muscle stimulation experiment, and $p53^{-/-}$ intermyofibrillar mitochondria had lower state 3 respiration and higher respiration-induced ROS production (88). $p53^{-/-}$ skeletal muscle also has decreased levels of the respiratory chain complex succinate dehydrogenase enzyme activity and lower mitochondrial DNA (mtDNA) content, further suggesting a decrease in functional mitochondria (76). In summary, experiments examining exercise metabolism and skeletal muscle revealed that p53 may contribute to CRF by regulating mitochondrial function.

p53 may also regulate other physiological parameters that determine cardiovascular function. In addition to the adaptive changes in skeletal muscle, prolonged exercise induces balanced cardiac hypertrophy in humans, which increases ventricular stroke volume (cardiac output), thus increasing exercise capacity (90). A recent study demonstrated that the downregulation of hypoxia-inducible factor 1, alpha subunit by p53 during sustained pressure overload of the heart impairs angiogenesis and may cause maladaptive cardiac hypertrophy in mice (89). In this model, p53 apparently serves to decrease cardiac function under pathological states, whereas under physiological exercise training conditions, p53 appears to promote aerobic exercise capacity. Apart from the cardiovascular system, p53 has been shown to inhibit insulin-like growth factor signaling (53) that is associated with glycolytic metabolism. Thus, through this pathway as well, p53 would be predicted to promote oxidative metabolism.

## p53 Suppresses Anaerobic Metabolism

The phenotype of increased glycolysis observed in many cancer cells and the promotion of oxidative phosphorylation by p53 is intriguing as they represent the contrasting pathways of energy generation through anaerobic and aerobic metabolism, respectively. Even in primary human fibroblasts, the depletion of p53 increases glycolysis (15). Before addressing p53 and aerobic metabolism, the studies linking p53 to the regulation of anaerobic metabolism (glycolysis) are summarized (Fig. 3). The earliest studies showing that p53 can affect metabolism involved mutant p53 transactivating the hexokinase 2 (*HK2*) gene in hepatoma cells predictive of increased glycolysis in a p53 defective background (61). Subsequently, mutant p53 was shown to increase the activity of another glycolytic enzyme phosphoglycerate mutase (PGM) (45). In contrast, wild-type p53 was shown to interact with and transactivate *PGM* promoter constructs *in vitro* and in muscle cells, suggesting cell-type-specific effects of unclear significance (87). However, these initial metabolic studies collectively indicated that in the setting of defective p53 signaling, there is an increase in glycolytic metabolism.

More recently, the *TP53*-induced glycolysis and apoptosis regulator (*TIGAR*) gene has been shown to decrease the cellular levels of fructose-2,6-bisphosphate (F-2,6-$P_2$), a potent allosteric activator of the enzyme 6-phosphofructo-1-kinase (PFK-1) that serves as a control point of the glycolytic pathway (11). The expression of TIGAR not only decreases glycolytic activity by dephosphorylating F-2,6-$P_2$, but also reduces ROS levels and apoptosis by redirecting metabolites
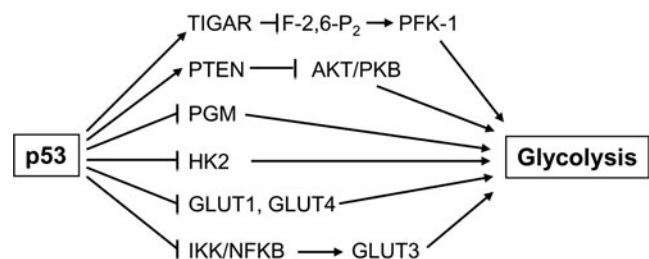


FIG. 3. **The suppression of anaerobic metabolism by p53 is mediated through multiple pathways.** Glycolysis is inhibited by decreasing metabolic substrate availability through downregulation of glucose transporters and by modulating key enzymes in the glycolytic pathway hexokinase 2 (HK2), 6-phosphofructo-1-kinase (PFK-1), and phosphoglycerate mutase (PGM).

into the pentose phosphate shunt and promoting glutathione production, further supporting an antioxidant role for p53 (11, 73). p53 may also regulate glycolysis by downregulating the plasma membrane glucose transporters 1 and 4 (GLUT1 and GLUT4) (91). In addition, loss of p53 activates IKK, which through the NFKB pathway increases GLUT3 and glucose availability for glycolysis (41). Taken together, these various studies show that wild-type p53 activity suppresses anaerobic metabolism.

### p53 Promotes Mitochondrial Function

The importance of p53 in regulating normal mitochondrial function was first suggested by its apparent requirement for the transition from anaerobic to aerobic metabolism in mouse embryo development (38). In the absence of p53, there was a marked decrease in cytochrome c oxidase (COX ) staining in association with lower ATP and mitochondrial 16S ribosomal RNA levels in day 8 mouse embryos (7–8 somite stage). Early studies focusing on p53-induced apoptosis clearly demonstrated that p53 regulates redox homeostasis, including the transactivation of a number of genes bearing homology to redox enzymes (40, 80). Since that time, significant progress has been made to advance our understanding of p53 redox biology (73) and emerging data show that p53 also regulates mitochondrial respiration through multiple pathways (Fig. 4).

The mechanisms by which p53 regulates respiration are being elucidated, but the underlying biology is less clear. The recent creation of a nonrespiring human cell line, through somatic cell homologous recombination, has demonstrated the critical role of respiration in regulating both intracellular oxygen and redox homeostasis, which are both important for preventing oxygen-associated genomic DNA damage (98). This observation reinforces the original concept underlying the symbiotic theory of the mitochondrion. Protection from oxygen toxicity, rather than the bioenergetic benefits of oxi-

dative phosphorylation, was proposed to be the evolutionary driving force for the incorporation of oxygen consuming proteobacteria into primordial anaerobic eukaryotes (59).

### Assembly of the respiratory chain complexes

The identification of ferrodoxin reductase, encoded by the p53-transactivated gene *FDXR*, was an early clue that p53 may regulate respiration as this mitochondrial NADPH P450 reductase is required for iron–sulfur protein and heme biogenesis, both essential for the function of respiratory complexes (37, 54). COX enzymatic activity was shown to be decreased in the p53-deficient human colon cancer HCT116 cell line in parallel with reduced COX II subunit protein level (122). However, the genetic mechanism by which p53 affected COX II subunit expression remained unclear, as its transcript levels were reported to be unchanged (122).

Through gene expression analysis, the synthesis of cytochrome c oxidase 2 (*SCO2*) gene was identified as a p53 transcriptional target gene (37, 62). Given its critical role in COX assembly as a copper delivery chaperone, SCO2 provided a defined genetic mechanism by which p53 directly regulated the eukaryotic center of oxygen consumption (62, 75). Like SCO2, mitochondrial flavoprotein apoptosis-inducing factor (AIF) also appeared to contribute to mitochondrial complex assembly, as its depletion results in reduced content and activity of respiratory chain complex I and increased glycolysis (105). The *AIF* gene was later found to have a p53 binding element that is responsive to basal levels of p53, further supporting a physiologic function (95). Thus, p53 appears to transcriptionally regulate at least three proteins that are involved in the assembly of respiratory complexes.

### Mitochondrial DNA

In analogy to its role in maintaining nuclear genomic integrity, p53 is also important for the mitochondrial genome. p53 can translocate into mitochondria and interact with DNA polymerase $\gamma$ and single-stranded DNA-binding (SSB) protein to regulate mtDNA repair, replication, and recombination (2, 7, 116) as well as directly bind to mtDNA to regulate nucleoid remodeling (5). It can also interact with mitochondrial transcription factor A (TFAM), essential for regulating both mtDNA transcription and replication (48), and modulate its binding to mtDNA (120). A recent study has shown that the interaction of TFAM with both the N-terminal transactivation and C-terminal regulatory domains of p53 has implications for the repair of damaged mtDNA (115). Besides TFAM, cytoplasmic p53-inducible ribonucleotide reductase 2 (p53R2) is essential for maintaining mtDNA through regulating deoxyribonucleotide (dNTP) homeostasis (33). In the skeletal muscle of both mice and humans, p53R2 mutations cause severe mtDNA depletion (13, 14).

The observation of higher mtDNA content in the skeletal muscle of $p53^{+/+}$ compared to $p53^{-/-}$ mice was consistent with the expected major role that skeletal muscle plays in determining exercise capacity. It was particularly notable that the relative difference in mtDNA content between the $p53^{+/+}$ and $p53^{-/-}$ mice was greater in the oxidative (soleus, plantaris) *versus* glycolytic (tibialis anterior, extensor digitorum longus) skeletal muscles, underscoring the observation that p53 promotes aerobic metabolism (76). The lower mtDNA content in $p53^{-/-}$ muscle correlated with reduced respiratory
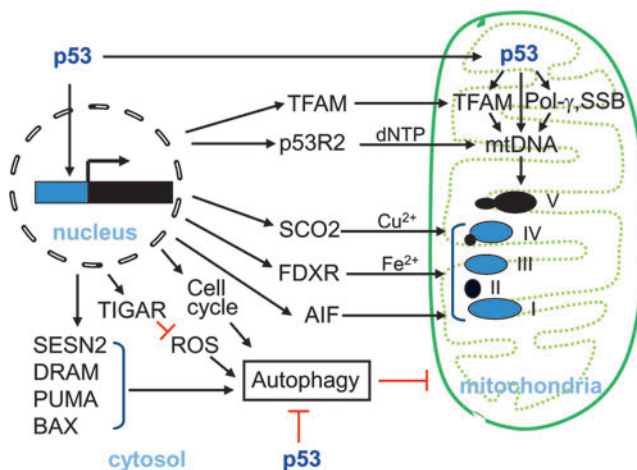


**FIG. 4.   The multiple pathways of mitochondrial regulation by p53.** These are: (1) assembly of the oxidative phosphorylation complexes; (2) mitochondrial deoxyribonucleic acid (mtDNA) repair, replication, and transcription through DNA polymerase $\gamma$, p53-inducible ribonucleotide reductase 2 (p53R2), and TF1M; and (3) autophagy for normal mitochondrial homeostasis. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

activity (76, 88). The maintenance of mtDNA by p53 is not limited to skeletal muscle, as it is also reduced in $p53^{-/-}$ mouse embryonic fibroblasts and p53-depleted human fibroblasts in association with reductions in TFAM and/or p53R2 (46, 50). Although the modulation of TFAM by p53 appears complex and may involve post-transcriptional mechanisms (50), the mouse *TFAM* gene also has p53 responsive elements (76). This may explain the augmentation of *TFAM* expression by p53 in mouse skeletal muscle with exercise (76). Whether p53 is also involved in the regulation of exercise-induced *TFAM* expression in humans remains to be seen (9).

### Mitochondrial autophagy

Autophagy is a membrane-trafficking process used to degrade cytosolic proteins and organelles and is important in regulating mitochondrial function. The selective degradation of dysfunctional mitochondria (mitophagy) is required for normal mitochondrial homeostasis as deletion of the critical autophagy gene *ATG7* in muscle results in the accumulation of abnormal mitochondria (42, 60). Intriguingly, like the anti- and pro-oxidant effects of p53, the regulation of autophagy by p53 also displays a dual nature (101, 109). In response to genotoxic stress, nuclear p53 induces autophagy by transactivating damage-regulated autophagy modulator (*DRAM*), a gene essential for both p53-triggered autophagy and apoptosis (22). In contrast, basal levels of cytoplasmic p53 suppress autophagy by inhibiting 5'adenosine monophosphate-activated protein kinase and activating mammalian target of rapamycin whereas the loss of p53 induces autophagy in both normal and cancer cells (28, 102).

Compared with the established role of p53-induced apoptosis in tumor suppression, the dual nature of p53-regulated autophagy on cancer is less clear. DRAM is downregulated in several human cancer cell lines, suggesting a tumor suppressor role for p53-regulated autophagy (22). A recent study showed that another p53 target gene, Sestrin 2 (*SESN2*), induces autophagy in cells with wild-type p53, whereas depletion of SESN2 or DRAM was equally efficient in preventing autophagy (57). Autophagy also shares pathways that promote apoptosis, further linking it to tumor suppression. p53 transactivated apoptotic genes, p53 upregulated

modulator of apoptosis (*PUMA*), and Bcl-2-associated X protein (*BAX*) can coordinately trigger autophagy that selectively degrades the mitochondria (119). Mitochondrial autophagy itself facilitates apoptosis-associated cytochrome c release and likewise the antiapoptotic protein Bcl-2 suppresses autophagy (121).

In contrast to its proautophagic function associated with apoptosis, p53 also suppresses autophagy and this may facilitate cell survival under conditions of physiologic stress. In addition to inhibiting glycolysis, p53-induced TIGAR decreases ROS production in response to nutrient starvation, thereby inhibiting autophagy (10). While SESN2 has been reported to promote autophagy, it remains to be seen whether other p53-regulated sestrin family members that are known to have antioxidant function have inhibitory activities on autophagy (73). Mitochondrial morphology and homeostasis are connected to the cell cycle and a "mitochondrial checkpoint" in the G1 phase has been proposed (65). Mitochondrial respiration is high in G1 and its dysfunction causes G1 arrest (58, 63). The depletion of p53 induces a periodic peak of autophagy at the G1 and S phases but not in the G2 or M phase (103). Thus, the antiautophagic function of p53 appears to be cell cycle specific and possibly related to variations in bioenergetic requirements during different phases of the cell cycle. In summary, p53-regulated autophagy may play an important role in modulating mitochondrial function to meet different cellular and physiologic requirements.

### Redox Regulation of p53

p53 activity is sensitive to the cellular redox state, suggesting its role as a mediator of redox homeostasis. p53 regulates mitochondrial respiration, which has a profound effect on the cellular redox state (98), and other accumulating evidence supports the role of p53 as a redox sensor (Fig. 5) (55). The presence of cellular reducing agents are required for the binding of p53 to its target DNA *in vitro* (32), whereas increased cellular oxidants such as copper inhibit its DNA-binding activity in mammalian cells (106). Depleting yeast thioredoxin reductase (TRR) causes accumulation of an oxidized, inactive form of p53 (77), whereas knocking down mammalian TRR does not affect p53 disulfide status but instead stabilizes p53 and increases its activity (92). The redox regulation of p53 is specifically dependent on an intact



**FIG. 5. p53 as a sensor and regulator of cellular redox homeostasis.** All 10 cysteine residues of human p53 are localized to the DNA binding domain. Cysteine residues numbered in red are those that have been shown to be important for regulating p53 activity and those coordinated with zinc have been shown to be protected from oxidation. (To see this illustration in color the reader is referred to the web version of this article at www.lieberonline.com/ars).
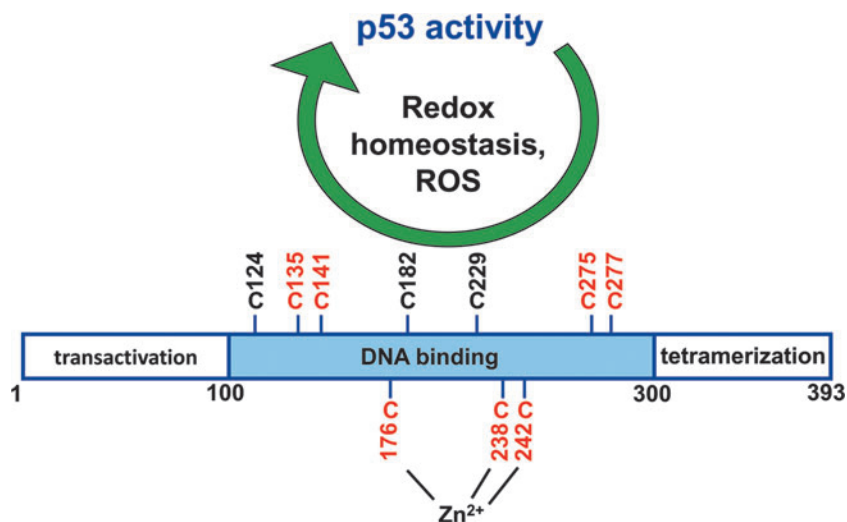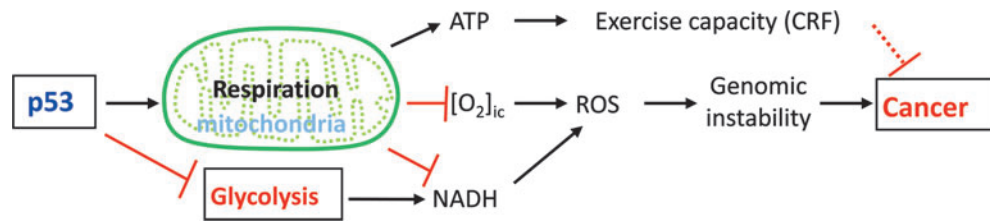
**FIG. 6. p53 promotion of mitochondrial functions improves CRF and decreases oxidative stress to prevent DNA damage.** Respiration consumes intracellular oxygen ($[O_2]_{ic}$) and NADH, both of which contribute to reactive oxygen species (ROS) generation and genomic instability. Concurrent inhibition of glycolysis decreases the generation of reducing equivalents (NADH) that serve as electron source to molecular oxygen. The pleiotropic nature of the mechanism by which CRF may contribute to tumor suppression is indicated by a *dashed line*. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars.)

thioredoxin system and genetically altering the ratio of oxidized to reduced glutathione does not affect p53 activity (64, 96). In mammalian cells, p53 also binds to apurinic (apyrimidinic) endonuclease/redox-factor1 (APE/REF-1). Depleting APE/REF-1 results in the degradation of p53 although its basal level does not change when both TRR and APE/REF-1 are depleted (92). Therefore, without apparently affecting its disulfide status, TRR and APE/REF-1 differentially regulate p53 basal and stress-induced levels, nuclear translocation, and DNA binding.

Human p53 contains 10 cysteine residues, all in the DNA-binding domain, and their redox state is critical for p53 function (Fig. 5). Three cysteine residues C176, C238, and C242 are tightly bound to zinc, which protects them from being oxidized, and their substitution by serine abolishes p53 activity (19, 96). Oxidation of the cysteine residues and formation of disulfide bonds inhibit p53 tetramerization and DNA binding activity (97). Other cysteine residues such as C135, C141, C275, and C277 have also been reported to be important for the selective modulation of p53 activity (16, 96). For example, intramolecular disulfide bond formation between C275 and C277 in response to DNA damage specifically prevents p53 binding to the promoter sequence of *GADD45* but not that of *p21* (16, 94). Similarly, using DNA-mediated charge transport to selectively oxidize DNA-bound proteins *in vitro* to simulate severe stress, oxidized p53 loses its ability to bind to the *GADD45* but not the *p21* promoter (6). The importance of these specific cysteine residues for p53 activity is further supported by the absence of the nonessential human p53 C229 in mouse and by the observation that the three additional cysteines in mouse p53 (C40, C293, and C308) are not required for activity (84). In summary, mitochondrial function is an important determinant of cellular redox state and, in turn, the sensitivity of p53 to cellular redox state points to a homeostatic relationship.

### Conclusions and Perspectives

In the context of the reviewed data, the capacity of p53 to regulate mitochondrial respiration and thereby promote aerobic metabolism are proposed to have a tumor suppressor function. As a gene that is represented in the earliest of unicellular life, its ancestral function has been proposed to extend beyond protection against tumor formation in the multicellular animal (56). Given its early evolutionary origin, its promotion of aerobic metabolism likely pertains to more basic functions such as adaptations for aerobic life. In support of

this notion, when mitochondrial respiration is ablated by the targeted disruption of both copies of the p53 target gene *SCO2*, the essential substrates for ROS generation (intracellular oxygen and reducing equivalents) are increased with resultant oxidative genomic DNA damage (Fig. 6) (98). Studying such primary biologic functions reveals at least one reason why p53 might promote aerobic metabolism, for genomic protection in an oxidative environment, and may provide more insights into cancer biology.

Recent work further underscores the important effect of metabolism on tumorigenesis. A specific mutation in the cytosolic enzyme isocitrate dehydrogenase 1 results in a gain of function that may contribute to cancer pathogenesis (23, 118) and the switching of pyruvate kinase enzyme isoforms improves cancer cell survival (20). In retrospect, the previous observations that mitochondrial enzymes succinate dehydrogenase and fumarate hydratase act as tumor suppressor genes (27) also presaged the finding that p53 promotes aerobic metabolism. The hope is that translating these basic principles to specific populations with genetic susceptibility to cancers, such as in Li-Fraumeni syndrome (74, 100), or to the general population may result in new strategies to prevent cancer and improve overall human health.

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### Abbreviations Used

95% CI = associated 95% confidence intervals
AIF = apoptosis-inducing factor
APE/REF-1 = apurinic (apurimidinic) endonuclease/redox-factor 1
BAX = Bcl-2-associated X protein
COX = cytochrome c oxidase
CRF = cardiorespiratory fitness
DNA = deoxyribonucleic acid
dNTP = deoxyribonucleotide
DRAM = damage-regulated autophagy modulator
F-2,6-P$_2$ = fructose-2,6-bisphosphate
FDXR = ferrodoxin reductase
GI = gastrointestinal
GLUT = glucose transporter
HK2 = hexokinase 2
IKK/NFKB = I$\kappa$B kinase/nuclear factor $\kappa$-light-chain-enhancer of activated B cells
mtDNA = mitochondrial DNA
NADH = reduced nicotinamide adenine dinucleotide
[O$_2$]$_{ic}$ = intracellular oxygen concentration
p53R2 = p53-inducible ribonucleotide reductase 2
PFK-1 = 6-phosphofructo-1-kinase
PGM = phosphoglycerate mutase
Pol-$\gamma$ = DNA polymerase $\gamma$
PTEN = phosphatase and tensin homolog
PUMA = p53 upregulated modulator of apoptosis
ROS = reactive oxygen species
SCO2 = synthesis of cytochrome c oxidase 2
SESN2 = sestrin 2
SSB = single-stranded DNA binding protein
TFAM = mitochondrial transcription factor A
TIGAR = *TP53*-induced glycolysis and apoptosis regulator
TRR = thioredoxin reductase