Published in final edited form as:

Curr Opin Oncol. 2012 January ; 24(1): 76–82. doi:10.1097/CCO.0b013e32834de1d8.

p53: exercise capacity and metabolism

Ping-yuan Wang, Jie Zhuang, and Paul M. Hwang

Center for Molecular Medicine, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Purpose of review—There is an inverse relationship between cancer incidence and cardiorespiratory fitness in large population studies. Mechanistic insights into these observations may strengthen the rationale for encouraging exercise fitness in the clinics for cancer prevention and may promote the development of new preventive strategies.

Recent findings—Studying the multi-faceted activities of p53, a critical tumor suppressor gene, has revealed various cellular pathways necessary for adapting to environmental stresses. Genetic connections are being made between p53 and an increasing number of metabolic activities such as oxidative phosphorylation, glycolysis and fatty acid oxidation. *In vivo* mouse models show that p53 plays an important role in determining both basal aerobic exercise capacity and its improvement by training.

Summary—The genetic pathways by which p53 regulates metabolism and exercise may help explain significant epidemiologic observations connecting cardiorespiratory fitness and cancer. Further understanding of these molecular pathways through human translational studies may promote the development of new cancer preventive strategies.

Keywords

p53; mitochondria; aerobic exercise; metabolism; cancer

Introduction

TP53 (*p53*), encoding the p53 protein, is unequivocally one of the most important genes in the human genome that determines the natural history and outcome of cancer. However, from an evolutionary perspective the presence of p53-like genetic sequences in unicellular protists and amoeba suggests that the regulation of cell proliferation in multicellular organisms may not have been the original function of p53 [1]. The observation that p53 is a critical tumor suppressor in human can be reconciled with a broader view of *p53* as a gene that is necessary for adapting to environmental stresses. As an example, the role of p53 in promoting mitochondrial respiration initially appeared to be unrelated to its main function of maintaining genomic stability [2]. However, when it is appreciated that the major evolutionary driving force proposed by the symbiotic theory of the mitochondrion is to

protect the host cell from the oxidative toxicity of oxygen, an essential factor for inducing genomic instability, then p53 regulation of mitochondrial oxygen consumption fits with its well accepted role in preventing DNA damage and cancer [3-5]. Because mitochondrial respiration is integrated with bioenergetic capacity by coupling to oxidative phosphorylation, this could serve as one possible mechanism underlying the striking correlation between cardiorespiratory fitness and cancer-free survival [6,7]. Experimentally, mice deficient in p53 show significant decreases in aerobic metabolism and exercise capacity [2,8,9]. It should be noted that the effect of p53 in species other than mouse remains to be seen as, for example, basal metabolism is markedly different between mouse and human. Furthermore, the isoforms of p53 and its homolog genes, p63 and p73, are known to modulate apoptosis through the mitochondria but their role in regulating metabolism remains unclear. In contrast, as there is growing evidence that p53 directly regulates a variety of metabolic activities in addition to respiration, we specifically focus on reviewing some recent findings in the field that may help us understand the multi-faceted nature of p53 with potential translational applications for cancer prevention.

Aerobic exercise and cancer

Accumulating data show that aerobic exercise reduces the incidence of multiple kinds of cancer in addition to its well established role in preventing diabetes and cardiovascular diseases [6,7,10-13]. More recent studies confirm that aerobic exercise capacity is a predictor of all-cause mortality in a graded manner over a 20-year follow up period even in the older age range of 65 to 92 years [14]. Interestingly, there is a trend of even greater risk reduction of all-cause mortality risk by aerobic exercise but not strength training in the over 65 versus the 45-65 year-old age group [15]. These data further underscore the benefits of cardiorespiratory fitness beyond preventing heart disease that applies to all age, gender and race groups.

Aerobic exercise is rhythmical physical activity of moderate intensity that promotes oxygen consumption, such as swimming, bicycling or long-distance running [16]. Aerobic exercise capacity can be measured by performing a metabolic stress test during which the maximal amount of oxygen consumption (VO_{2max}) by the mitochondria is quantified [17]. It is well established that exercise training increases mitochondrial volume and function by promoting the expression of proteins involved in glucose and fatty acid oxidation [18]. Mechanistically, exercise induces transcription of PGC-1 α , the master regulator of mitochondrial biogenesis, in skeletal muscle through the p38 MAPK pathway [19]. The improvement in mitochondrial respiration by either pharmacologic treatment or exercise training reduces oxidative stress and may contribute to the prevention of cancer and aging [4,20,21]. In contrast, post-mitotic senescent cells have decreased mitochondrial number and activity along with the appearance of “giant” mitochondria that produce high levels of reactive oxygen species (ROS) [22].

Carbohydrates and lipids serve as the two major sources of energy for physical activity, and their use is determined not only by availability but also by the type of activity [23]. Muscle glycogen can serve as fuel for glycolysis during high intensity anaerobic activities like sprinting [24,25] while fatty acids provide energy for longer duration and lower intensity aerobic activities like jogging [26]. The adaptations of muscle to aerobic exercise include

increased mitochondrial fatty acid β -oxidation and fatty acid transport proteins, resulting in less lactate production at a given level of exercise intensity in trained compared to untrained individuals [27,28]. The higher capacity for fatty acid oxidation with exercise training would be expected to prevent the accumulation of cellular lipids and lipid peroxides that can induce endoplasmic reticulum stress, mitochondrial damage and insulin resistance which are all associated with increased risk of cancer [29-32]. In addition, aerobic exercise reduces plasma insulin and IGF-1 levels, both of which can promote cancer cell survival and growth via the phosphoinositide 3-kinase/Akt pathway [33,34]. Regular exercise lowers mortality in prostate cancer patients, and in parallel, it has been observed that exercise plasma stimulates p53 expression in prostate cancer cells [35,36]. Finally, moderate-intensity treadmill exercise has been shown to reduce intestinal polyp burden by modulating multiple cellular signaling pathways related to polyposis in the *Apc^{Min/+}* mouse cancer model [37,38].

p53 promotes mitochondrial biogenesis and aerobic exercise capacity

Recent studies show that p53 is essential for regulating mitochondrial function. p53 promotes mitochondrial biogenesis by regulating the expression of genes that are components or assembly factors of the electron transport chain, such as *Cytochrome c Oxidase subunit I (MTCO1)* [39], *Synthesis of Cytochrome c Oxidase (SCO2)* [2], *Apoptosis Inducing Factor (AIF)* [40], *Ferredoxin Reductase (FDXR)* [41], *Mitochondrial Transcriptional Factor A (TFAM)* [9] and *Ribonucleotide Reductase M2 (RRM2B, p53R2)* [42]. Consistent with these findings, *p53*^{-/-} mice, which develop cancers at an early age, have decreased aerobic exercise capacity [2,8,9]. This phenotype has been associated with decreased skeletal muscle respiratory capacity and lower mitochondrial DNA (mtDNA) content specifically in the oxidative skeletal muscle fibers [8,9].

Skeletal muscle mass and fiber types significantly contribute to aerobic exercise capacity [18,43]. The slow twitch (type I, red) and the fast twitch (type II, white) are the two major fiber types of skeletal muscle. The fast twitch fibers are further comprised of type IIa, type IIb and IIc/x fiber types [44]. The type I fibers contain more than twice the amount of mitochondria as compared to the type IIb fibers and are thus referred to as oxidative fibers well-suited for performing endurance exercise. The type IIa fibers have oxidative capacity that is similar to type I fibers while the type IIb and IIc/x fibers are glycolytic and poor in oxidative capacity [45] [46]. Compared to sedentary individuals, who have roughly equal amounts of type I and type II fibers in their skeletal muscle, exercise trained individuals have a higher fraction of type I fiber [18]. Furthermore, type IIb and IIc/x fibers can be transformed into the more oxidative type IIa fibers by endurance exercise [47]. Interestingly, p53 appears to play a pivotal role in determining not only basal aerobic exercise capacity but also the adaptive processes necessary for improving aerobic exercise capacity with training [9]. It is known that p53 plays an important role in regulating muscle cell differentiation but whether p53 affects muscle fiber type switching or remodeling with exercise remains to be clarified [48,49].

p53 regulates mitochondrial genomic DNA

Associated with its essential role in improving aerobic exercise capacity, p53 plays a critical role in maintaining mitochondrial genomic DNA (mtDNA) integrity by directly binding to mtDNA or by modulating other proteins involved in mtDNA homeostasis such as p53R2, DNA polymerase γ (POL γ), TFAM and mitochondrial single-stranded DNA-binding (SSB) protein [7,42,50,51]. A somatic cell can contain hundreds of mitochondria, each of which has multiple copies of the 16.5 kb circular DNA within its matrix that are subject to oxidative damage. The damaged mtDNA inherited through the stochastic nature of replicative segregation may contribute to metabolic and age-related diseases such as diabetes and cancer [49,52,53]. The failure to repair mtDNA mutations due to defective p53 may result in disruption of mitochondrial respiration and redox homeostasis which in turn may contribute to tumorigenesis as mitochondria appear to confer metastatic capacity to cancer cells [54].

p53 regulates mitochondrial metabolism through multiple cellular pathways

In addition to regulating mitochondrial biogenesis, p53 also modulates non-mitochondrial genes that promote substrate/fuel supply to mitochondria for aerobic metabolism. Glutaminase 2 (GLS2) has recently been identified as a novel metabolic target of p53 [55,56]. GLS2 catalyzes the hydrolysis of glutamine to glutamate, which can be further converted into α -ketoglutarate, an important substrate for the tricarboxylic acid (TCA) cycle. Thus, p53-induced expression of GLS2 can increase mitochondrial respiration which consumes oxygen, the essential factor for ROS formation. Notably, glutamate, the product of GLS, also serves as substrate for the synthesis of glutathione that scavenges ROS and protects against oxidative stress.

Upon exposure to glucose starvation as a metabolic stress, p53 stimulates fatty acid oxidation by inducing the expression of guanidinoacetate methyltransferase (GAMT) that catalyzes creatine synthesis and subsequently activates AMPK [57]. This observation also fits with prior work showing that AMPK mediates the survival of glucose-deprived cells through p53 and that it can increase fatty acid oxidation [58,59].

Tumor suppressive activities of p53-regulated non-mitochondrial metabolism

p53 inhibits glycolysis

As cancer cells often display increased glycolytic activity known as the “Warburg effect”, the coordinate promotion of aerobic metabolism and inhibition of anaerobic metabolism by p53 through several different mechanisms appears to be consistent with its role as a tumor suppressor even in non-cell cycle related pathways. While wild-type p53 activity suppresses glycolysis, an earlier study showed that mutated p53, frequently overexpressed in cancer cells, can activate the expression of the *Hexokinase 2 (HK2)* gene which promotes glycolysis [60]. A subsequent study has shown that depleting HK2 restores oxidative metabolism in glioblastoma multiforme cancer cells [61]. p53 also transactivates the expression of *TIGAR* which decreases phosphofructokinase 1 (PFK1) activity and

destablizes phosphoglycerate mutase (PGM), both of which are important enzymes of the glycolytic pathway [62,63]. Furthermore, p53 prevents the uptake of glucose, the essential substrate for glycolysis, by reducing the levels of three different glucose transporters (GLUT1, GLUT3 and GLUT4) through various signaling pathways [64,65]. Consistent with its role in inhibiting cellular glucose uptake, p53 can inhibit insulin receptor (INSR) expression which is overexpressed when p53 is inactivated in cancer [66]. Carbohydrate responsive element-binding protein (ChREBP), another key promoter of glucose metabolism, is repressed by p53 and this regulation may keep in check the glycolytic and biosynthetic processes promoting the growth of cancer cells [67,68].

p53 inhibits anabolic metabolism

Various lines of evidence point to the importance of metabolism in cancer [69,70]. Therefore, in retrospect, it is not unexpected that p53 regulates various metabolic pathways including mitochondrial function, fatty acid oxidation, glycolysis, glutaminolysis and insulin signaling. The inefficient production of ATP by glycolysis may result in the need for more nutrient uptake to meet the bioenergetic requirements of proliferating cancer cells. The associated production of intermediate metabolites by increased glycolysis when p53 is dysfunctional may also provide substrates for the biosynthesis of lipids, proteins and nucleotides required for cellular proliferation. Indeed, there is evidence that mutant p53 may facilitate cell immortalization through increased PGM levels and anabolic activities [62]. A recent study has shown that via transient protein-protein interaction, p53 inhibits glucose-6-phosphate dehydrogenase (G6PD), an enzyme that catalyzes the first step of the pentose phosphate pathway (PPP) [71]. Thus, in p53-deficient cells, PPP flux would be increased with higher glucose consumption and elevated NADPH levels required for biosynthetic metabolism to support cancer cell proliferation.

p53 regulates cellular redox homeostasis

In addition to regulating metabolism, p53 plays a dual role in cellular redox homeostasis. p53 induced by high levels of cellular stress can activate prooxidant genes to promote apoptosis and necrosis [72,73]. In contrast, lower levels of p53 appear to regulate various genes involved in protecting against oxidative stress, such as sestrins (SESN) [74], glutathione peroxidase 1 (GPX-1) [75], TIGAR [63] and ALDH4 [76] and glutaminase 2 (GLS2) [55]. Although it is often believed that increased mitochondrial respiration leads to more ROS production, a well-controlled study has clearly demonstrated that active flies produce less mitochondrial H₂O₂ than inactive flies *in vivo* [77]. *In vitro* studies using isolated mitochondria also reveal that less functional mitochondria produce more ROS [78]. Thus, the promotion of mitochondrial biogenesis by aerobic exercise training may serve to protect against oxidative stress, aging and cancer.

A recent report has provided experimental data in support of the hypothesis that protection from oxygen toxicity constituted part of the evolutionary driving force for the symbiotic theory of the mitochondrion [4]. In the absence of respiration and active electron transfer to oxygen, isogenic human cells demonstrated a marked increase in the levels of intracellular reducing potential (NAD(P)H) which can contribute electrons to elevated levels of intracellular oxygen in the absence of its consumption to form ROS and cause oxidative

DNA damage. Others have also shown that increased levels of NADH caused by defective mitochondrial respiration inactivate PTEN, a tumor suppressor and transcriptional target of p53. The loss of PTEN mediated inhibition of the PI 3-kinase/Akt pathway may promote cancer cell survival and proliferation [79]. Taken together, p53 promotion of aerobic exercise capacity may also play an important role in preventing cancer by regulating redox homeostasis.

p53 bridges the DNA-damage response pathway to cell metabolism

Ataxiatelangiectasia (A-T) syndrome is an autosomal recessive cancer predisposition disorder caused by mutations of the *ATM* kinase gene. In response to DNA damage, ATM phosphorylates human p53 at Ser-15, and this activity appears to play a significant role in regulating glucose homeostasis [80]. Abolishing phosphorylation of p53 at Ser-18 in mice, equivalent to human p53 Ser-15, causes glucose intolerance and insulin resistance which can be reversed by treatment with the antioxidant N-acetylcysteine. To underscore the involvement of DNA damage-response pathway in regulating metabolism, a recent study demonstrated that failure of DNA repair in the *ATM*^{+/-} mice leads to mitochondrial dysfunction in association with hyperlipidemia, metabolic syndrome and atherosclerosis [81]. This study further showed that ATM deficiency impairs p53 activity and results in defective mitochondria with increased ROS production and mtDNA damage in various tissues enriched in mitochondria such as pancreas, liver, kidney and skeletal muscle.

Conclusion

We have reviewed recent basic science literature showing that aerobic exercise not only prevents cardiovascular diseases but also cancer. Consistent with its role as a tumor suppressor, p53 promotes mitochondrial function and aerobic metabolism while inhibiting glycolysis and anaerobic metabolism through multiple pathways as summarized in Table 1, thereby antagonizing a common metabolic phenotype of cancer cells. As part of its well known role in regulating cellular redox homeostasis, p53 facilitates mitochondrial respiration to prevent oxidative stress and DNA damage, and it also plays a role in relaying DNA damage signals to modulate cell metabolism. p53 augmentation of respiration, which is coupled to oxidative phosphorylation, may contribute to increased aerobic exercise capacity and its improvement with training. While this phenomenon can be observed in mouse models, its translational significance in humans remains unclear. Nonetheless, tumor suppressor p53 promotes aerobic metabolism through more than one genetic pathway making a strong case for prescribing exercise to patients not only for cardiovascular health but also for cancer prevention.

Acknowledgments

We wish to thank Cory U. Lago and other members of the laboratory for helpful discussions and assistance. This work was supported by the intramural program of National Heart, Lung and Blood Institute (NHLBI).

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Lu WJ, Amatruda JF, Abrams JM. p53 ancestry: gazing through an evolutionary lens. *Nat Rev Cancer*. 2009; 9:758–762. [PubMed: 19776745]
2. Matoba S, Kang JG, Patino WD, Wragg A, Boehm M, Gavrilova O, Hurley PJ, Bunz F, Hwang PM. p53 regulates mitochondrial respiration. *Science*. 2006; 312:1650–1653. [PubMed: 16728594]
3. Margulis, L. *Symbiosis in Cell Evolution*. 2. New York: W.H. Freeman and Company; 1993.
- 4•. Sung HJ, Ma W, Wang Py, Hynes J, O'Riordan TC, Combs CA, McCoy JP, Bunz F, Kang JG, Hwang PM. Mitochondrial respiration protects against oxygen-associated DNA damage. *Nat Commun*. 2010; 1:1–8. This research article demonstrates an important function of the mitochondria in preventing oxygen-dependent DNA damage. [PubMed: 20975674]
5. Sung HJ, Ma W, Starost MF, Lago CU, Lim PK, Sack MN, Kang JG, Wang PY, Hwang PM. Ambient oxygen promotes tumorigenesis. *PLoS One*. 2011; 6:e19785. [PubMed: 21589870]
6. Rogers CJ, Colbert LH, Greiner JW, Perkins SN, Hursting SD. Physical activity and cancer prevention : pathways and targets for intervention. *Sports Med*. 2008; 38:271–296. [PubMed: 18348589]
7. Lago CU, Sung HJ, Ma W, Wang PY, Hwang PM. p53, Aerobic Metabolism and Cancer. *Antioxid Redox Signal*. 2010 Epub ahead of print.
8. Saleem A, Adhihetty PJ, Hood DA. Role of p53 in mitochondrial biogenesis and apoptosis in skeletal muscle. *Physiol Genomics*. 2009; 37:58–66. [PubMed: 19106183]
9. Park JY, Wang PY, Matsumoto T, Sung HJ, Ma W, Choi JW, Anderson SA, Leary SC, Balaban RS, Kang JG, et al. p53 improves aerobic exercise capacity and augments skeletal muscle mitochondrial DNA content. *Circ Res*. 2009; 105:705–712. 711 p following 712. [PubMed: 19696408]
10. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. *N Engl J Med*. 1997; 336:1269–1275. [PubMed: 9113929]
11. Newton RU, Galvao DA. Exercise in prevention and management of cancer. *Curr Treat Options Oncol*. 2008; 9:135–146. [PubMed: 18704691]
12. Kokkinos P, Myers J, Kokkinos JP, Pittaras A, Narayan P, Manolis A, Karasik P, Greenberg M, Papademetriou V, Singh S. Exercise capacity and mortality in black and white men. *Circulation*. 2008; 117:614–622. [PubMed: 18212278]
13. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a metaanalysis. *Jama*. 2009; 301:2024–2035. [PubMed: 19454641]
14. Kokkinos P, Myers J, Faselis C, Panagiotakos DB, Doumas M, Pittaras A, Manolis A, Kokkinos JP, Karasik P, Greenberg M, et al. Exercise capacity and mortality in older men: a 20-year follow-up study. *Circulation*. 2010; 122:790–797. [PubMed: 20697029]
- 15•. Schoenborn CA, Stommel M. Adherence to the 2008 adult physical activity guidelines and mortality risk. *Am J Prev Med*. 2011; 40:514–521. This comprehensive study shows that adherence to the 2008 Physical Activity Guidelines is associated with reduced all-cause mortality risks among U.S. adults. Aerobic exercise, but not strength training, remarkably reduces mortality risks among adults of all ages with at least one chronic conditionxs. [PubMed: 21496750]
16. Pollock ML, Gaesser GA, Butcher JD, Despres JP, Dishman RK, Franklin BA, Garber CE. ACSM Position Stand: The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Medicine & Science in Sports & Exercise*. 1998; 30:975–991. [PubMed: 9624661]
17. Brooks, GA.; Fahey, TD.; Baldwin, KM. *Exercise Physiology: Human Bioenergetics and Its Applications*. 4. New York: McGraw-Hill; 2005.
18. Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J Appl Physiol*. 1984; 56:831–838. [PubMed: 6373687]

19. Akimoto T, Pohnert SC, Li P, Zhang M, Gumbs C, Rosenberg PB, Williams RS, Yan Z. Exercise stimulates Pgc-1alpha transcription in skeletal muscle through activation of the p38 MAPK pathway. *J Biol Chem.* 2005; 280:19587–19593. [PubMed: 15767263]
20. Hagen TM, Liu J, Lykkesfeldt J, Wehr CM, Ingersoll RT, Vinarsky V, Bartholomew JC, Ames BN. Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. *Proc Natl Acad Sci U S A.* 2002; 99:1870–1875. [PubMed: 11854487]
21. Murphy MP, Holmgren A, Larsson NG, Halliwell B, Chang CJ, Kalyanaraman B, Rhee SG, Thornalley PJ, Partridge L, Gems D, et al. Unraveling the biological roles of reactive oxygen species. *Cell Metab.* 2011; 13:361–366. [PubMed: 21459321]
22. Gdynia G, Keith M, Kopitz J, Bergmann M, Fassl A, Weber AN, George J, Kees T, Zentgraf HW, Wiestler OD, et al. Danger signaling protein HMGB1 induces a distinct form of cell death accompanied by formation of giant mitochondria. *Cancer Res.* 2010; 70:8558–8568. [PubMed: 20959471]
23. Sahlin K. Control of lipid oxidation at the mitochondrial level. *Appl Physiol Nutr Metab.* 2009; 34:382–388. [PubMed: 19448703]
24. Balsom PD, Wood K, Olsson P, Ekblom B. Carbohydrate intake and multiple sprint sports: with special reference to football (soccer). *Int J Sports Med.* 1999; 20:48–52. [PubMed: 10090462]
25. Esbjornsson-Liljedahl M, Sundberg CJ, Norman B, Jansson E. Metabolic response in type I and type II muscle fibers during a 30-s cycle sprint in men and women. *J Appl Physiol.* 1999; 87:1326–1332. [PubMed: 10517759]
26. Kiens B. Skeletal muscle lipid metabolism in exercise and insulin resistance. *Physiol Rev.* 2006; 86:205–243. [PubMed: 16371598]
27. Raney MA, Turcotte LP. Regulation of contraction-induced FA uptake and oxidation by AMPK and ERK1/2 is intensity dependent in rodent muscle. *Am J Physiol Endocrinol Metab.* 2006; 291:E1220–E1227. [PubMed: 16835401]
28. Talanian JL, Holloway GP, Snook LA, Heigenhauser GJ, Bonen A, Spriet LL. Exercise training increases sarcolemmal and mitochondrial fatty acid transport proteins in human skeletal muscle. *Am J Physiol Endocrinol Metab.* 2010; 299:E180–E188. [PubMed: 20484014]
29. Colgan SM, Hashimi AA, Austin RC. Endoplasmic reticulum stress and lipid dysregulation. *Expert Rev Mol Med.* 2011; 13:e4. [PubMed: 21288373]
30. Schrauwen P, Hesselink MK. Oxidative capacity, lipotoxicity, and mitochondrial damage in type 2 diabetes. *Diabetes.* 2004; 53:1412–1417. [PubMed: 15161742]
31. Bosch M, Mari M, Herms A, Fernandez A, Fajardo A, Kassan A, Giralt A, Colell A, Balgoma D, Barbero E, et al. Caveolin-1 deficiency causes cholesterol-dependent mitochondrial dysfunction and apoptotic susceptibility. *Curr Biol.* 2011; 21:681–686. [PubMed: 21497090]
32. Zhang Y, Daquinag A, Traktuev DO, Amaya-Manzanares F, Simmons PJ, March KL, Pasqualini R, Arap W, Kolonin MG. White adipose tissue cells are recruited by experimental tumors and promote cancer progression in mouse models. *Cancer Res.* 2009; 69:5259–5266. [PubMed: 19491274]
33. Barnard RJ, Ngo TH, Leung PS, Aronson WJ, Golding LA. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. *Prostate.* 2003; 56:201–206. [PubMed: 12772189]
34. Ngo TH, Barnard RJ, Leung PS, Cohen P, Aronson WJ. Insulin-like growth factor I (IGF-I) and IGF binding protein-1 modulate prostate cancer cell growth and apoptosis: possible mediators for the effects of diet and exercise on cancer cell survival. *Endocrinology.* 2003; 144:2319–2324. [PubMed: 12746292]
35. Leung PS, Aronson WJ, Ngo TH, Golding LA, Barnard RJ. Exercise alters the IGF axis in vivo and increases p53 protein in prostate tumor cells in vitro. *J Appl Physiol.* 2004; 96:450–454. [PubMed: 14715676]
36. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J Clin Oncol.* 2011; 29:726–732. [PubMed: 21205749]

37. Colbert LH, Mai V, Tooze JA, Perkins SN, Berrigan D, Hursting SD. Negative energy balance induced by voluntary wheel running inhibits polyp development in APCMin mice. *Carcinogenesis*. 2006; 27:2103–2107. [PubMed: 16699175]
38. Baltgalvis KA, Berger FG, Pena MM, Davis JM, Carson JA. Effect of exercise on biological pathways in ApcMin/+ mouse intestinal polyps. *J Appl Physiol*. 2008; 104:1137–1143. [PubMed: 18239078]
39. Okamura S, Ng CC, Koyama K, Takei Y, Arakawa H, Monden M, Nakamura Y. Identification of seven genes regulated by wild-type p53 in a colon cancer cell line carrying a well-controlled wild-type p53 expression system. *Oncol Res*. 1999; 11:281–285. [PubMed: 10691030]
40. Stambolsky P, Weisz L, Shats I, Klein Y, Goldfinger N, Oren M, Rotter V. Regulation of AIF expression by p53. *Cell Death Differ*. 2006; 13:2140–2149. [PubMed: 16729031]
41. Hwang PM, Bunz F, Yu J, Rago C, Chan TA, Murphy MP, Kelso GF, Smith RA, Kinzler KW, Vogelstein B. Ferredoxin reductase affects p53-dependent, 5-fluorouracil-induced apoptosis in colorectal cancer cells. *Nat Med*. 2001; 7:1111–1117. [PubMed: 11590433]
42. Bourdon A, Minai L, Serre V, Jais JP, Sarzi E, Aubert S, Chretien D, de Lonlay P, Paquis-Flucklinger V, Arakawa H, et al. Mutation of RRM2B, encoding p53-controlled ribonucleotide reductase (p53R2), causes severe mitochondrial DNA depletion. *Nat Genet*. 2007; 39:776–780. [PubMed: 17486094]
43. Segerstrom AB, Holmback AM, Hansson O, Elgzyri T, Eriksson KF, Ringsberg K, Groop L, Wollmer P, Thorsson O. Relation between cycling exercise capacity, fiber-type composition, and lower extremity muscle strength and muscle endurance. *J Strength Cond Res*. 2011; 25:16–22. [PubMed: 21150672]
44. Scott W, Stevens J, Binder-Macleod SA. Human skeletal muscle fiber type classifications. *Phys Ther*. 2001; 81:1810–1816. [PubMed: 11694174]
45. Prince FP, Hikida RS, Hagerman FC, Staron RS, Allen WH. A morphometric analysis of human muscle fibers with relation to fiber types and adaptations to exercise. *J Neurol Sci*. 1981; 49:165–179. [PubMed: 7217980]
46. Delp MD, Duan C. Composition and size of type I, IIA, IID/X, and IIB fibers and citrate synthase activity of rat muscle. *J Appl Physiol*. 1996; 80:261–270. [PubMed: 8847313]
47. Fitzsimons DP, Diffie GM, Herrick RE, Baldwin KM. Effects of endurance exercise on isomyosin patterns in fast- and slow-twitch skeletal muscles. *J Appl Physiol*. 1990; 68:1950–1955. [PubMed: 2141832]
48. Parker SB, Eichele G, Zhang P, Rawls A, Sands AT, Bradley A, Olson EN, Harper JW, Elledge SJ. p53-independent expression of p21Cip1 in muscle and other terminally differentiating cells. *Science*. 1995; 267:1024–1027. [PubMed: 7863329]
49. Molchadsky A, Shats I, Goldfinger N, Pevsner-Fischer M, Olson M, Rinon A, Tzahor E, Lozano G, Zipori D, Sarig R, et al. p53 plays a role in mesenchymal differentiation programs, in a cell fate dependent manner. *PLoS ONE*. 2008; 3:e3707. [PubMed: 19002260]
50. Achanta G, Sasaki R, Feng L, Carew JS, Lu W, Pelicano H, Keating MJ, Huang P. Novel role of p53 in maintaining mitochondrial genetic stability through interaction with DNA Pol gamma. *Embo J*. 2005; 24:3482–3492. [PubMed: 16163384]
51. Wong TS, Rajagopalan S, Townsley FM, Freund SM, Petrovich M, Loakes D, Fersht AR. Physical and functional interactions between human mitochondrial single-stranded DNA-binding protein and tumour suppressor p53. *Nucleic Acids Res*. 2008
52. Petros JA, Baumann AK, Ruiz-Pesini E, Amin MB, Sun CQ, Hall J, Lim S, Issa MM, Flanders WD, Hosseini SH, et al. mtDNA mutations increase tumorigenicity in prostate cancer. *Proc Natl Acad Sci U S A*. 2005; 102:719–724. [PubMed: 15647368]
53. Verma M, Naviaux RK, Tanaka M, Kumar D, Franceschi C, Singh KK. Meeting report: mitochondrial DNA and cancer epidemiology. *Cancer Res*. 2007; 67:437–439. [PubMed: 17213255]
54. Ishikawa K, Takenaga K, Akimoto M, Koshikawa N, Yamaguchi A, Imanishi H, Nakada K, Honma Y, Hayashi J. ROS-generating mitochondrial DNA mutations can regulate tumor cell metastasis. *Science*. 2008; 320:661–664. [PubMed: 18388260]

55. Hu W, Zhang C, Wu R, Sun Y, Levine A, Feng Z. Glutaminase 2, a novel p53 target gene regulating energy metabolism and antioxidant function. *Proc Natl Acad Sci U S A*. 2010; 107:7455–7460. [PubMed: 20378837]
56. Suzuki S, Tanaka T, Poyurovsky MV, Nagano H, Mayama T, Ohkubo S, Lokshin M, Hosokawa H, Nakayama T, Suzuki Y, et al. Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. *Proc Natl Acad Sci U S A*. 2010; 107:7461–7466. [PubMed: 20351271]
57. Ide T, Brown-Endres L, Chu K, Ongusaha PP, Ohtsuka T, El-Deiry WS, Aaronson SA, Lee SW. GAMT, a p53-inducible modulator of apoptosis, is critical for the adaptive response to nutrient stress. *Mol Cell*. 2009; 36:379–392. [PubMed: 19917247]
58. Hardie DG, Pan DA. Regulation of fatty acid synthesis and oxidation by the AMP- activated protein kinase. *Biochem Soc Trans*. 2002; 30:1064–1070. [PubMed: 12440973]
59. Jones RG, Plas DR, Kubek S, Buzzai M, Mu J, Xu Y, Birnbaum MJ, Thompson CB. AMP-activated protein kinase induces a p53-dependent metabolic checkpoint. *Mol Cell*. 2005; 18:283–293. [PubMed: 15866171]
60. Mathupala SP, Heese C, Pedersen PL. Glucose catabolism in cancer cells. The type II hexokinase promoter contains functionally active response elements for the tumor suppressor p53. *J Biol Chem*. 1997; 272:22776–22780. [PubMed: 9278438]
61. Wolf A, Agnihotri S, Micallef J, Mukherjee J, Sabha N, Cairns R, Hawkins C, Guha A. Hexokinase 2 is a key mediator of aerobic glycolysis and promotes tumor growth in human glioblastoma multiforme. *J Exp Med*. 2011; 208:313–326. [PubMed: 21242296]
62. Kondoh H, Leonart ME, Gil J, Wang J, Degan P, Peters G, Martinez D, Carnero A, Beach D. Glycolytic enzymes can modulate cellular life span. *Cancer Res*. 2005; 65:177–185. [PubMed: 15665293]
63. Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K, Bartrons R, Gottlieb E, Vousden KH. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell*. 2006; 126:107–120. [PubMed: 16839880]
64. Schwartzberg-Bar-Yoseph F, Armoni M, Karnieli E. The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression. *Cancer Res*. 2004; 64:2627–2633. [PubMed: 15059920]
65. Kawauchi K, Araki K, Tobiume K, Tanaka N. p53 regulates glucose metabolism through an IKK-NF-kappaB pathway and inhibits cell transformation. *Nat Cell Biol*. 2008; 10:611–618. [PubMed: 18391940]
66. Webster NJ, Resnik JL, Reichart DB, Strauss B, Haas M, Seely BL. Repression of the insulin receptor promoter by the tumor suppressor gene product p53: a possible mechanism for receptor overexpression in breast cancer. *Cancer Res*. 1996; 56:2781–2788. [PubMed: 8665514]
67. Tong X, Zhao F, Mancuso A, Gruber JJ, Thompson CB. The glucose-responsive transcription factor ChREBP contributes to glucose-dependent anabolic synthesis and cell proliferation. *Proc Natl Acad Sci U S A*. 2009; 106:21660–21665. [PubMed: 19995986]
68. Maddocks OD, Vousden KH. Metabolic regulation by p53. *J Mol Med*. 2011; 89:237–245. [PubMed: 21340684]
69. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*. 2009; 324:1029–1033. [PubMed: 19460998]
70. Locasale JW, Cantley LC. Altered metabolism in cancer. *BMC Biol*. 2010; 8:88. [PubMed: 20598111]
71. Jiang P, Du W, Wang X, Mancuso A, Gao X, Wu M, Yang X. p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. *Nat Cell Biol*. 2011; 13:310–316. [PubMed: 21336310]
72. Polyak K, Xia Y, Zweier JL, Kinzler KW, Vogelstein B. A model for p53-induced apoptosis. *Nature*. 1997; 389:300–305. [PubMed: 9305847]
73. Tu HC, Ren D, Wang GX, Chen DY, Westergard TD, Kim H, Sasagawa S, Hsieh JJ, Cheng EH. The p53-cathepsin axis cooperates with ROS to activate programmed necrotic death upon DNA damage. *Proc Natl Acad Sci U S A*. 2009; 106:1093–1098. [PubMed: 19144918]

74. Budanov AV, Sablina AA, Feinstein E, Koonin EV, Chumakov PM. Regeneration of peroxiredoxins by p53-regulated sestrins, homologs of bacterial AhpD. *Science*. 2004; 304:596–600. [PubMed: 15105503]
75. Sablina AA, Budanov AV, Ilyinskaya GV, Agapova LS, Kravchenko JE, Chumakov PM. The antioxidant function of the p53 tumor suppressor. *Nat Med*. 2005; 11:1306–1313. [PubMed: 16286925]
76. Yoon KA, Nakamura Y, Arakawa H. Identification of ALDH4 as a p53-inducible gene and its protective role in cellular stresses. *J Hum Genet*. 2004; 49:134–140. [PubMed: 14986171]
- 77•. Cocheme HM, Quin C, McQuaker SJ, Cabreiro F, Logan A, Prime TA, Abakumova I, Patel JV, Fearnley IM, James AM, et al. Measurement of H₂O₂ within living *Drosophila* during aging using a ratiometric mass spectrometry probe targeted to the mitochondrial matrix. *Cell Metab*. 2011; 13:340–350. Using a new technique to measure mitochondrial ROS in vivo, this paper shows that more mitochondrial ROS is produced in the aged state while physical activity reduces it. [PubMed: 21356523]
78. Murphy MP. How mitochondria produce reactive oxygen species. *Biochem J*. 2009; 417:1–13. [PubMed: 19061483]
79. Pelicano H, Xu RH, Du M, Feng L, Sasaki R, Carew JS, Hu Y, Ramdas L, Hu L, Keating MJ, et al. Mitochondrial respiration defects in cancer cells cause activation of Akt survival pathway through a redox-mediated mechanism. *J Cell Biol*. 2006; 175:913–923. [PubMed: 17158952]
80. Armata HL, Golebiowski D, Jung DY, Ko HJ, Kim JK, Sluss HK. Requirement of the ATM/p53 tumor suppressor pathway for glucose homeostasis. *Mol Cell Biol*. 2010; 30:5787–5794. [PubMed: 20956556]
81. Mercer JR, Cheng KK, Figg N, Gorenne I, Mahmoudi M, Griffin J, Vidal-Puig A, Logan A, Murphy MP, Bennett M. DNA Damage Links Mitochondrial Dysfunction to Atherosclerosis and the Metabolic Syndrome. *Circ Res*. 2010 Epub ahead of print.

Key points

- Higher aerobic exercise capacity is associated with a lower risk of cancer incidence.
- Tumor suppressor p53 promotes mitochondrial function and increases aerobic exercise capacity.
- p53 inhibits glycolysis while promoting aerobic metabolism.
- p53 regulates redox homeostasis and relays oxidative DNA-damage signals to cell metabolism.

Table 1
p53-regulated targets involved in modulating cell metabolism

	Gene	Metabolic function	p53 effect	Ref.
Mitochondrial genes	SCO2	Copper chaperone essential for complex IV assembly	+	2
	TFAM	Essential for mtDNA transcription and maintenance	+	9
	MTCO1	Cytochrome c oxidase subunit 1 (respiratory complex IV)	+	39
	AIF	Flavoprotein regulating complex I assembly	+	40
	FDXR	Essential for mitochondrial iron homeostasis and hemebiogenesis	+	41
	p53R2	Regulates dNTP and mtDNA homeostasis	+	42
	POL-γ	mtDNA repair and replication	+	50
Non-mitochondrial genes	GLS2	Glutaminolytic enzyme that provides substrate for OXPHOS and glutathione synthesis	+	55,56
	GAMT	Stimulates creatine synthesis and fatty acid oxidation	+	57
	HK2	Glycolytic enzyme	–	60,61
	PGM	Glycolytic enzyme	–	62
	TIGAR	Inhibits glycolysis and ROS production	+	63
	GLUT1	Glucose transporter involved in glycolysis	–	64
	GLUT4	Glucose transporter involved in glycolysis	–	64
	IKK/NF-κB	Increases GLUT3 expression and glycolysis	–	65
	INSR	Receptor for insulin signaling and glucose uptake	–	66
	ChREBP	Promotes aerobic glycolysis and anabolic metabolism	–	67,68
	G6PD	Enzyme in the pentose phosphate pathway that provides NADPH for biosynthetic processes	–	71
	PTEN	Inhibits Akt and glycolysis	–	79

The positive or negative effect of p53 on the listed metabolic function is denoted by + or – symbol, respectively.