

P53 mutations and cancer: a tight linkage

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Comment on: Yogev O, Barker K, Sikka A, *et al.* p53 Loss in MYC-Driven Neuroblastoma Leads to Metabolic Adaptations Supporting Radioresistance. *Cancer Res* 2016;76:3025-35.

Abstract: P53 is often mutated in solid tumors, in fact, somatic changes involving the gene encoding for p53 (TP53) have been discovered in more than 50% of human malignancies and several data confirmed that p53 mutations represent an early event in cancerogenesis. Main p53 functions consist in cell cycle arrest, DNA repair, senescence and apoptosis induction in response to mutagenic stimuli, and, to exert those functions, p53 acts as transcriptional factor. Recent data have highlighted another very important role of p53, consisting in regulate cell metabolism and cell response to oxidative stress. Majority of tumor suppressor genes, such as adenomatous polyposis coli (APC), retinoblastoma-associated protein (RB) and Von-Hippel-Lindau (VHL) are inactivated by deletion or early truncation mutations in tumors, resulting in the decreased or loss of expression of their proteins. Differently, most p53 mutations in human cancer are missense mutations, which result in the production of full-length mutant p53 proteins. It has been reported that mutant p53 proteins and wild type p53 proteins often regulate same cellular biological processes with opposite effects. So, mutant p53 has been reported to supply the cancer cells of glucose and nutrients, and, to avoid reactive oxygen species (ROS) mediated damage during oxidative stress. These last features are able to render tumor cells resistant to ionizing radiations and chemotherapy. A future therapeutic approach in tumors bearing p53 mutations may be to deplete cancer cells of their energy reserves and antioxidants.

Keywords: p53; Myc; transcriptional factor; cell cycle; metabolism

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Well-known P53 functions

P53 is often mutated in solid tumors, in fact, somatic changes involving the gene encoding for p53 (TP53) have been discovered in more than 50% of human malignancies. P53 is a transcription factor able to regulate several intracellular pathways involved in cell survival, DNA-repair, apoptosis and senescence. P53 is also known as “the guardian of genome”, being able to preserve DNA integrity in response to a number of stimuli, such as ionising radiations, genotoxic insults and oxidative stress (1-3).

In normal and un-stressed conditions, p53 is inactivated by its negative regulators, such as murine double minutes2 (Mdm2) and phosphatase and Tensin homolog (PTEN).

Mdm2 is an E3 ubiquitin ligase which favors the p53 degradation via proteasome. In stressed conditions, such as, the presence of genotoxic stimuli, p53 is stabilized by several post-translational covalent modifications which are mediated by another important enzyme named PML (promyelocytic leukemia). As result, it can accumulate and form tetramers with other p53 subunits which exert their function as transcription factors. P53 mainly promotes cell cycle arrest, DNA repair and, if the damage is abnormally wide, apoptosis. The function of p53 is to avoid DNA changes accumulation which can lead to cancerogenesis (4-6).

Cell cycle arrest and senescence are mainly mediated by a p53 downstream effector named p21 (encoded by the gene WAF). P21 acts inhibiting the hetero-dimers

formed by cyclins/Cdk, thus arresting cell-cycle progression and favoring the cell entrance in G₀ phase (senescence). Moreover, while cell cycle is arrested, p53 promotes DNA repair, mainly activating GADD45 (Growth Arrest and DNA Damage) and P53R2 (p53 inducible ribonucleotide reductase) genes. As result, DNA damage is repaired, avoiding mutations accumulation and their perpetration to descendent cells during mitosis. In response to severe or sustained stress signals causing irreparable DNA changes, p53 usually induces genes involved in apoptosis, namely PUMA (p53 upregulated modulator of apoptosis), Bax, Fas, PIG3 and Killer/DR5 (3,7-9).

Peculiar P53 functions

Recent studies have demonstrated that in addition to cell cycle arrest, senescence induction, DNA repair and apoptosis, p53 is able to exert additive functions, such as regulation of energy metabolism and anti-oxidant defense. Metabolic changes are a hallmark of tumor cells, in fact, cells rapid growth and division requires energy and precursor for macromolecule biosynthesis. To meet these aims, tumor cells often display changes in metabolism and p53 is the main responsible of these changes (10,11).

P53 has been discovered to regulate glycolysis, pentose phosphate pathway (PPP), mitochondrial oxidative phosphorylation, lipids and nucleotides metabolism and, importantly, the cell response to oxidative stress. Unlike the majority of cells, which depend on oxidative phosphorylation to provide energy, tumor cells mainly utilize glycolysis even in presence of sufficient oxygenation. This phenomenon (glycolysis in aerobic conditions) is named Warburg effect. Wild type P53 upregulates oxidative phosphorylation and down-regulates glycolysis inducing its target genes, such as SCO2 (synthesis of cytochrome oxidase 2) and GLS2 (mitochondrial glutaminase), which promote mitochondrial oxidative phosphorylation, and TIGAR (TP53 inducible glycolysis and apoptosis) which inhibit glycolysis (12). Moreover, P53 blocks the intracellular glucose uptake inhibiting the expression of GLUT1 and GLUT4 (glucose transporter) and also reduces the activity of the enzyme glucose-6-phosphate dehydrogenase (G6PD), which has an important role in initiate the PPP. The PPP is an alternative pathway to glycolysis and is often employed by tumor cells (13).

Tumor cells strongly needs of fatty acids (FAs) synthesis with the aim to perform rapid cell membrane production and intracellular signaling transduction. Wild type P53

has been reported to stimulate β -oxidation of FAs in mitochondria and to arrest FAs biosynthesis acting on FASN (fatty acids synthase) and ACLY (ATP citrate lyase), thus blocking the formation of new phosphor-lipid membrane to support the rapid growth and division of tumor cells (14).

Oxidative stress often leads to DNA-damage and apoptosis through the ROS (reactive oxygen species) production, and wild type p53 is the main controller of intracellular ROS level. Specifically, p53 regulates the level of NRF2 (nuclear factor erythroid-related factor 2) through p21 up-regulation. NRF2 is linked by p21 and translocated into nucleus allowing its transactivator function upon a number of genes which encodes for anti-oxidant enzymes, such as NQO1 (NADH-quinone oxidoreductase 1). In response to mild stress, p53 up-regulates NRF2 through p21, and NRF2, once translocated into nucleus, induces the synthesis of anti-oxidant enzymes. When the stress is severe, p53 inhibits NRF2 allowing the ROS accumulation and apoptosis induction (15).

TP53 mutations and cancer

Majority of tumor suppressor genes, such as APC (adenomatous polyposis coli), RB (retinoblastoma-associated protein) and VHL (Von-Hippel-Lindau) are inactivated by deletion or early truncation mutations in tumors, resulting in the decreased or loss of expression of their proteins. On the other hand, most p53 mutations in human cancer are missense mutations, which result in the production of full-length mutant p53 proteins. In fact, only 10-15% of TP53 mutations are defined as “disruptive mutations”, namely those leading to a inactive or truncated protein, while the remaining 85-90% often lead to the synthesis of functioning proteins. Missense mutations are often clustered in the 4–9 exons of the TP53 gene, which correspond to a particular sequence of the gene, representing the p53 DNA-binding-domain. As a consequence, missense p53 mutations are able to modify its ordinary function of transcriptional factor (16). Interestingly, several studies have demonstrated that many mutant p53 proteins, not only lose their tumor suppression functions, but also gain new oncogenic functions. This phenomenon is termed “the gain of function of mutant p53”. More specifically, mutant p53 interacts with proteins that normally partner with wild type p53. This new association deprive them of their anticancer activities and in place, they are corrupted to act as cancerogenesis promoters (17).

An example is given by the p53-PML interaction. PML stabilizes and activates wild type p53 only in presence

of stressed conditions, while, when p53 is mutated its association with PML is constitutive. Mutant p53-PML stabilized interaction leads p53 to aberrantly transcribe its targets. The major consequences of gain of functions mutant p53 affect the metabolism and the response to oxidative stress of cancer cells. Rapid cell proliferation strongly needs of a ready supply of energy and basic macromolecules, so mutant p53 proteins have been reported to facilitate the supply of cancer cells.

Proper repair of damaged DNA, not only requires DNA-repair enzymes, but also the availability of nucleotides, and, mutant p53 constitutively activates the ribonucleotide reductase (RRM2) to facilitate the conversion of ribonucleoside diphosphate to deoxy-ribonucleoside diphosphate, which is an essential step for DNA synthesis. In a similar manner, mutant p53 is able to modify the lipids metabolism in a way that encourages rapid cell proliferation and intracellular signaling. In fact, mutant p53 engages the SREBPs (sterol regulatory element-binding protein) and leads to FAs synthesis, β -oxidation arrest and cholesterol synthesis, favoring so, the generation of a robust supply of lipids for cell membranes formation (18).

The strongest effect of mutant p53 on the metabolism regards the glucose. Mutant p53 constitutively stimulates glycolysis acting in various ways. First of all, it up-regulates GLUT1 and GLUT 4 favoring the rapid uptake of glucose in tumor cells, moreover, mutant p53 stimulated genes involved in glycolysis activation such as TIGAR, and finally it stimulates the PPP acting on G6PD (13). The final result is a wide supply of glucose which can be consumed in order to produce energy also in aerobic conditions (Warburg effect).

Lately, an additive and very important mutant p53 function has been documented. Rapid cell proliferation produces high levels of ROS, which may dampen cell membranes, proteic structures and DNA inducing apoptosis. Mutant p53, as previously seen, can constitutively stimulate genes involved in antioxidant cell response. The greater response to the activation of these genes is the synthesis of molecules able to neutralize ROS, such as glutathione (19). Yogev *et al.* demonstrated that in MYC-driven neuroblastoma, the acquisition of p53 mutations can greatly worsen the prognosis of patients affected, and this feature can be mainly due to metabolic changes in tumor cells. In fact, Synergistic effect of Myc protein and mutant p53 strongly up-regulates the GSH (Glutathione S transferase) family, such as Gsta1 and Gstp1, resulting in an increased intracellular pool of glutathione. This

characteristic not only preserves tumor cells from oxidative-stress-induced damage, but also favors the resistance to ionising radiations. Up-regulation of GSH strongly predisposes to chemo and radioresistance and not only in Myc-driven neuroblastoma, but also in other solid tumors and it can be due to p53 missense mutations (20).

Conclusions

It has long been speculated that the main mechanism through which mutant p53 leads to cancerogenesis involves its impaired capability to arrest cell cycle, promote DNA repair and apoptosis in response to oncogenic stimuli. Nevertheless, p53 also regulates cell metabolism and oxidative status in response to stress. Mutant P53 is able to provide the cancer cells of energy supplies and antioxidants, thus favoring their proliferation and resistance to chemotherapeutics drugs and ionizing radiations. A possible new approach to the p53-driven tumors may be to deplete cancer cells of their energy reserves and antioxidants.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. *Nature* 2000;408:307-10.
2. Olivier M, Hussain SP, Caron de Fromental C, et al. TP53 mutation spectra and load: a tool for generating hypotheses on the etiology of cancer. *IARC Sci Publ* 2004;(157):247-70.
3. Perri F, Pacelli R, Della Vittoria Scarpati G, et al. Radioresistance in head and neck squamous cell carcinoma: Biological bases and therapeutic implications. *Head Neck* 2015;37:763-70.
4. Rokudai S, Laptenko O, Arnal SM, et al. MOZ increases p53 acetylation and premature senescence through its complex formation with PML. *Proc Natl Acad Sci U S A* 2013;110:3895-900.
5. de Stanchina E, Querido E, Narita M, et al. PML is a direct p53 target that modulates p53 effector functions. *Mol Cell* 2004;13:523-35.

6. Freeman DJ, Li AG, Wei G, Li HH, et al. PTEN tumor suppressor regulates p53 protein levels and activity through phosphatase-dependent and -independent mechanisms. *Cancer Cell* 2003;3:117-30.
7. Haupt S, Raghu D, Haupt Y. Mutant p53 Drives Cancer by Subverting Multiple Tumor Suppression Pathways. *Front Oncol* 2016;6:12.
8. Harris SL, Levine AJ. The p53 pathway: positive and negative feedback loops. *Oncogene* 2005;24:2899-908.
9. Jeffers JR, Parganas E, Lee Y, et al. Puma is an essential mediator of p53-dependent and -independent apoptotic pathways. *Cancer Cell* 2003;4:321-8.
10. Bensaad K, Tsuruta A, Selak MA, et al. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell* 2006;126:107-20.
11. Zhang C, Lin M, Wu R, et al. Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect. *Proc Natl Acad Sci U S A* 2011;108:16259-64.
12. Wang YC, Lee HS, Chen SK, et al. Analysis of K-ras gene mutations in lung carcinomas: correlation with gender, histological subtypes, and clinical outcome. *J Cancer Res Clin Oncol* 1998;124:517-22.
13. Jiang P, Du W, Wang X, et al. p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. *Nat Cell Biol* 2011;13:310-6.
14. Freed-Pastor WA, Mizuno H, Zhao X, et al. Mutant p53 disrupts mammary tissue architecture via the mevalonate pathway. *Cell* 2012;148:244-58.
15. Kalo E, Kogan-Sakin I, Solomon H, et al. Mutant p53R273H attenuates the expression of phase 2 detoxifying enzymes and promotes the survival of cells with high levels of reactive oxygen species. *J Cell Sci* 2012;125:5578-86.
16. Liu J, Zhang C, Feng Z. Tumor suppressor p53 and its gain-of-function mutants in cancer. *Acta Biochim Biophys Sin (Shanghai)* 2014;46:170-9.
17. Muller PA, Vousden KH. p53 mutations in cancer. *Nat Cell Biol* 2013;15:2-8.
18. Liu J, Zhang C, Hu W, et al. Tumor suppressor p53 and its mutants in cancer metabolism. *Cancer Lett* 2015;356:197-203.
19. Traverso N, Ricciarelli R, Nitti M, et al. Role of glutathione in cancer progression and chemoresistance. *Oxid Med Cell Longev* 2013;2013:972913.
20. Yogev O, Barker K, Sikka A, et al. p53 Loss in MYC-Driven Neuroblastoma Leads to Metabolic Adaptations Supporting Radioresistance. *Cancer Res* 2016;76:3025-35.

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