

Mutant p53 exerts oncogenic functions by modulating cancer cell metabolism

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The metabolic function of p53 is important for its oncosuppressive function. Mutant p53 (mutp53) with gain of oncogenic function can regulate cell metabolism. Our recent study revealed a novel transcription-independent mechanism for a gain-of-function mutp53 that directly inhibits activation of adenosine monophosphate-activated protein kinase (AMPK) to promote cancer cell metabolism.

As one of the most frequent genetic alterations in all cancer types, mutation of *TP53* can result in loss of the oncosuppressive functions of wild-type p53 (wtp53). Some p53 mutants also have a dominant-negative effect and can bind and inhibit the function of remaining wtp53. Moreover, p53 mutations can invoke activities different from those resulting from a simple loss of wtp53 oncosuppressive function. Many of these mutants actually acquire oncogenic properties that enable them to promote invasion, metastasis, genomic instability, cancer inflammation, cancer cell proliferation, and survival. However, how gain-of-function (GOF) p53 mutants acquire these properties remains a mystery that has attracted much attention from researchers in recent years.

Role of p53 in Tumor Suppression

Once activated, wtp53 mostly functions as a transcription factor that targets many downstream genes involved in various processes including cell cycle arrest, apoptosis, senescence, DNA repair, and metabolism. However, it is unclear which of these functions is the

most important in the oncosuppressive role of p53 under physiological conditions. Regulation of cell cycle arrest, apoptosis, and senescence have been widely accepted as the major functions contributing to the oncosuppressive role of p53, but recent studies with animal models have challenged this paradigm. For example, p53 efficiently suppresses tumor development in the complete absence of its cell cycle inhibitory and proapoptotic effectors p21, Puma, and Noxa. Moreover, mice expressing p53 with mutations at 3 acetylation sites (K117, K161, and K162) that abolish p53-mediated cell cycle arrest, apoptosis, and senescence are not prone to early onset spontaneous tumorigenesis, suggesting that these functions are dispensable for the p53 oncosuppressive activity in mice. More importantly, the acetylation site-mutated p53 retained the ability to inhibit glucose uptake, glycolysis, and reactive oxygen species production by regulating the metabolic p53 target genes *GLS2* and *TIGAR*, strongly suggesting that p53-mediated cell metabolism plays an important role in p53 oncosuppressive function (for a review see ref.¹).

As a tumor suppressor, p53 can regulate several aspects of cell metabolism and thereby counteract many of the metabolic alterations associated with cancer development and progression. For example, p53 generally dampens aerobic glycolysis and the pentose phosphate pathway and promotes mitochondrial respiration through multiple mechanisms. p53 also functions as a negative regulator of lipid synthesis by enhancing fatty acid oxidation and inhibiting fatty acid synthesis.²

Keywords: mutant p53, p53 mutation, AMPK, metabolism, gain of function, p53

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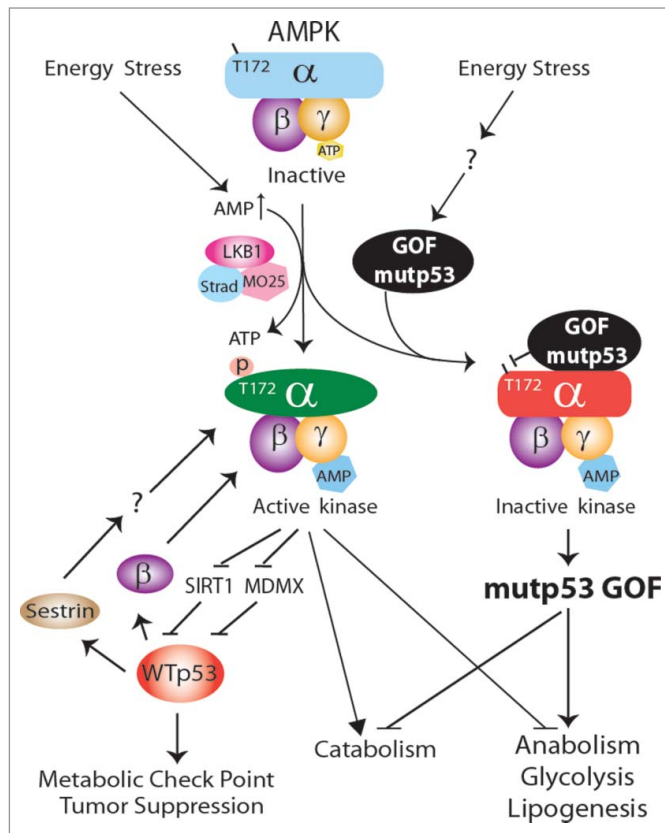


Figure 1. Gain-of-function mutant p53 inhibits adenosine monophosphate-activated protein kinase (AMPK) activation in head and neck squamous cell carcinoma. The wild-type p53 protein functions indirectly both upstream and downstream of AMPK. The gain-of-function mutant p53 functions directly upstream of AMPK and inhibits its activation, impairing the metabolic checkpoint and increasing anabolic tumor growth and progression.

Mutp53 Gain of Function and Cancer Metabolism

In contrast to wtp53, mutp53 that has gained oncogenic function promotes glycolysis by targeting RhoA/ROCK/GLUT-1, and lipid synthesis by targeting SREBPs and Pla2g16.^{1,3} Thus, GOF mutp53 may be actively involved in the regulation of cancer metabolism, which is important for the oncogenic function of GOF mutp53.

As the master regulator of cellular energy homeostasis, adenosine monophosphate-activated protein kinase (AMPK) senses the cellular energy status and regulates the balance between anabolism and catabolism. Once activated, AMPK targets many downstream metabolic enzymes and transcription factors or cofactors to regulate cell metabolism and gene expression.⁴ Although stimulation of AMPK often leads to the phosphorylation and activation of p53, it is unclear whether p53 is a

direct target of AMPK.⁴ AMPK was, however, recently shown to activate p53 indirectly through the phosphorylation and inactivation of MDMX⁵ and the p53 deacetylase SIRT1.⁶ Activated p53 can, in turn, increase AMPK activity through transcriptional activation of the gene encoding the β subunit of AMPK⁷ and sestrin,⁸ providing a positive feedback effect on AMPK function (Fig. 1). In contrast, we recently showed that GOF mutp53 directly inhibits AMPK activation to promote glycolysis and lipid synthesis in head and neck squamous cell carcinoma cells,⁹ providing the latest evidence that GOF mutp53 regulates cancer cell metabolism in an opposing manner to wtp53.

As the cellular energy sensor, AMPK acts as a tumor suppressor or an oncogene depending on the context.¹⁰ Earlier work with a variety of cell lines with different genetic backgrounds (e.g., wtp53 *versus*

mutp53) yielded seemingly inconsistent results. Given that p53 functions both upstream and downstream of AMPK and that GOF mutp53 inhibits AMPK (Fig. 1), we believe that p53 status plays an important role in determining the outcome of AMPK function as an oncogene or a tumor suppressor in different contexts.

Most of the proposed mechanisms for GOF mutp53 suggest that it functions as a transcriptional coactivator or a corepressor (or both) that interacts with many transcription factors or cofactors (e.g., p63, p73, Sp1, NF- κ B, NF-Y, VDR, ETS, SREBP) to modulate gene expression.¹¹ Our results, however, suggest that cytoplasmic inhibition of AMPK under metabolic stress is also important in the tumor-promoting function of GOF mutp53,⁹ indicating a novel transcription-independent mechanism for GOF mutp53 function. Consistent with this proposal, a recent study showed that a predominantly cytoplasmic localized p53 mutant (p53 ψ) gains oncogenic function to induce a metastatic program in a transcription-independent manner.¹² Finally, given that AMPK can target many transcription factors and cofactors,⁴ we expect that GOF mutp53 can also regulate gene expression indirectly via AMPK.

Conclusion

Although our results suggest that AMPK inhibition is an important mechanism in the tumor-promoting function of GOF mutp53, several questions—such as which signals control the mutp53–AMPK interaction and mutp53 cytoplasmic localization—remain to be answered.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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