

Targeting a Binding Protein in Mutated p53 Could Yield New Cancer Treatment Strategies

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New Brunswick, N.J. – Research by Rutgers Cancer Institute of New Jersey investigators shows the targeting of a binding protein of mutant p53 known as Rac1 could lead to new therapeutic strategies for patients whose cancer carries mutations in the p53 gene. Rutgers Cancer Institute resident research members **Wenwei Hu, PhD** and **Zhaohui Feng, MD, PhD**, who are associate professors of radiation oncology at Rutgers Robert Wood Johnson Medical School, are the senior authors of the work to be published in the September 22, 2017, online issue of *Genes & Development* (doi: 10.1101/gad.301564.117). Drs. Hu and Feng are also members of the Cancer Institute's Genomic Instability and Cancer Genetics Program. They share more about the work.

Q: Why is this topic important to explore?

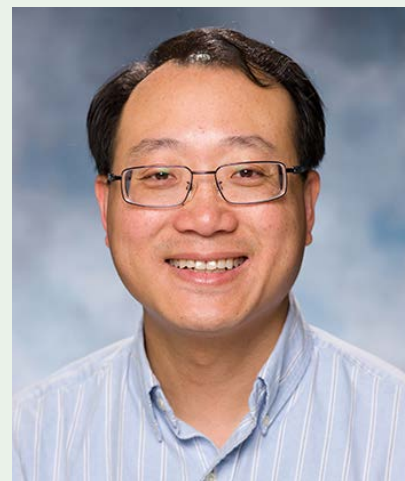
This study focuses on tumor suppressor p53, which in its wild type form plays a critical role in preventing tumor formation. The p53 gene is the most commonly mutated gene in human tumors; more than half of all human tumors harbor mutant p53. In addition to loss of tumor suppressive functions of wild type p53, tumor-associated mutant p53 proteins often exhibit oncogenic activities to promote tumor malignant progression, termed as mutant p53 gain-of-function (GOF). Clinical studies have shown that GOF mutant p53 is frequently associated with more aggressive cancer, poorer therapeutic response and worse prognosis. Therefore, GOF mutant p53 has become an attractive target for cancer therapy. However, the mechanism of mutant p53 to exert its GOFs is not well-understood, which hinders the development of efficient strategies targeting tumors containing mutant p53. This study investigates the mechanism of mutant p53 GOF which is an important research topic.

Q: How was this study structured and what did you learn?

In this study, we screened for mutant p53 specific interacting proteins in human cancer cell lines expressing wild type p53 or mutant p53. Through this approach, we identified Rac1 as a mutant p53 specific binding protein. Rac1 regulates many important cellular functions. Rac1 signaling is frequently activated in various cancers to promote cancer development and progression. We found that the interaction of mutant p53 with Rac1 promotes Rac1 activation. We further identified the mechanism by which mutant p53 promotes Rac1 activation. Rac1 stays active through SUMOylation, a type of protein modification. Removing SUMOylation modification (de-SUMOylation) from Rac1 by a protein called SENP1 inactivates Rac1. Results from this study showed that the mutant p53-Rac1 interaction blocks SENP1 to bind to and de-SUMOylate Rac1, which in turn keeps Rac1 in an active state. In clinical



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human tumor samples, mutant p53 expression is associated with enhanced Rac1 activity. Importantly, we found that that activation of Rac1 by mutant p53 contributes to mutant p53 GOF in cancer. Targeting Rac1 signaling greatly inhibits mutant p53 GOF in promoting tumor growth and metastasis.

Q: What is the implication of these findings and potential applications to future cancer treatment and other diseases?

These results reveal that activation of Rac1 is an unidentified and critical mechanism for mutant p53 GOF in tumorigenesis. These results suggest that targeting Rac1 and its signaling is a potential therapeutic strategy for cancer with mutant p53.

Along with Drs. Hu and Feng, the other authors on the research are Xuetian Yue, Cen Zhang, Yuhao Zhao, Juan Liu, Alan W. Lin, Victor M. Tan and Justin M. Drake of Rutgers Cancer Institute and Rutgers Robert Wood Johnson Medical School; Lianxin Liu, The First Affiliated Hospital of Harbin Medical University, China; and Michael N. Boateng and Jun Li, Rutgers Cancer Institute and Rutgers Robert Wood Johnson Medical School.

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