Transfected SARS-CoV-2 spike DNA suppresses cancer cell response to chemotherapy

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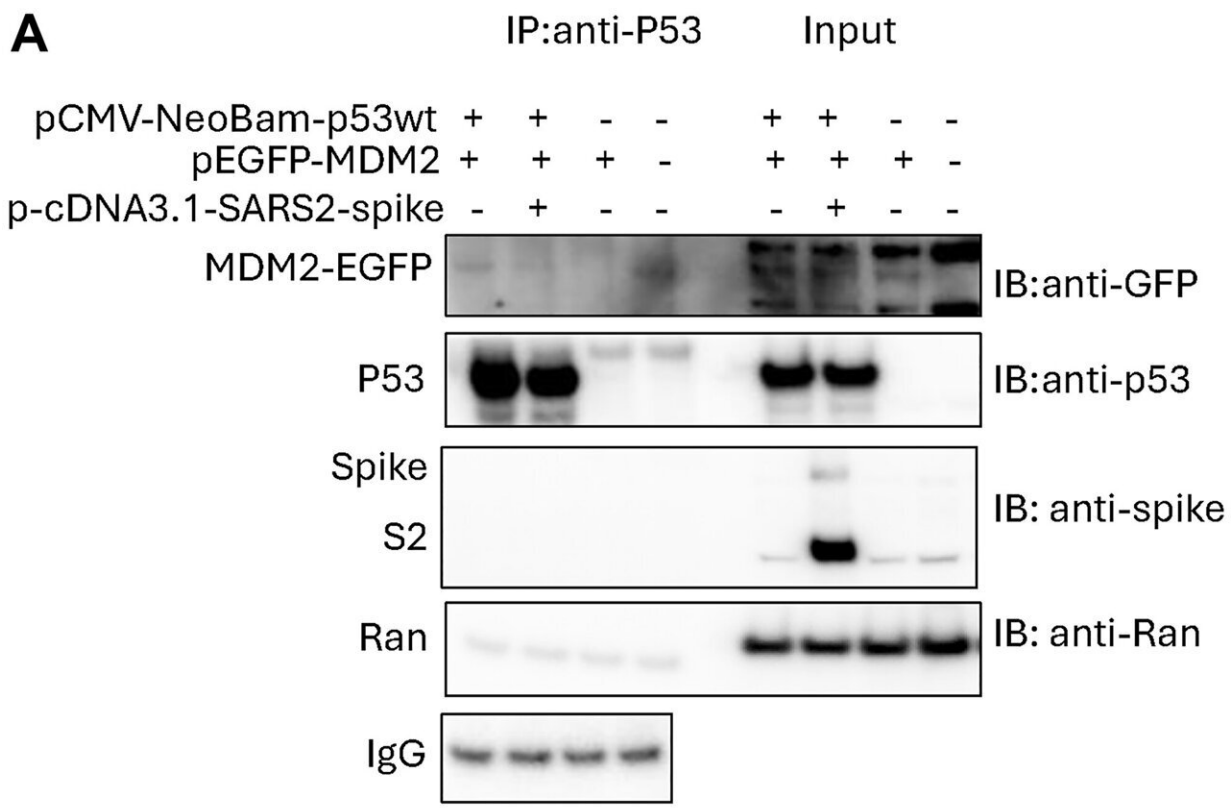

Reduced interaction between p53 and MDM2 following SARS-CoV-2 spike protein overexpression in cancer cells. Credit: *Oncotarget* (2024). DOI: 10.18632/oncotarget.28582

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19 infection has led to worsened outcomes for patients with cancer. SARS-CoV-2 spike protein mediates host cell infection and cell-cell fusion that causes stabilization of tumor suppressor p53 protein. In-silico analysis previously suggested that SARS-CoV-2 spike interacts with p53 directly but this putative interaction has not been demonstrated in cells.

In this new study, researchers Shengliang Zhang and Wafik S. El-Deiry from Brown University and Lifespan Health System examined the interaction between SARS-CoV-2 spike, p53 and MDM2 (E3 ligase, which mediates p53 degradation) in cancer cells using an immunoprecipitation assay.

The paper is published in *Oncotarget* and titled "Transfected SARS-CoV-2 spike DNA for mammalian cell expression inhibits p53 activation of p21(WAF1), TRAIL Death Receptor DR5 and MDM2 proteins in cancer cells and increases cancer cell viability after chemotherapy exposure."

"We observed that SARS-CoV-2 spike protein interrupts p53-MDM2 protein interaction but did not detect SARS-CoV-2 spike bound with p53 protein in the cancer cells," write the authors

The researchers further observed that SARS-CoV-2 spike suppresses p53 transcriptional activity in cancer cells including after nutlin exposure of wild-type p53-, spike-expressing tumor cells and inhibits chemotherapy-induced p53 gene activation of p21(WAF1), TRAIL Death Receptor DR5 and MDM2.

The suppressive effect of SARS-CoV-2 spike on p53-dependent gene activation provides a potential molecular mechanism by which SARS-CoV-2 infection may impact tumorigenesis, tumor progression and

chemotherapy sensitivity. In fact, cisplatin-treated tumor cells expressing spike were found to have increased cell viability as compared to control cells.

Further observations on γ-H2AX expression in spike-expressing cells treated with cisplatin may indicate altered DNA damage sensing in the DNA damage response pathway. The preliminary observations reported here warrant further studies to unravel the impact of SARS-CoV-2 and its various encoded proteins including spike on pathways of tumorigenesis and response to cancer therapeutics. More efforts should be directed at studying the effects of the SARS-CoV-2 spike and other viral proteins on host DNA damage sensing, response and repair mechanisms.

The researchers say, "A goal would be to understand the structural basis for maximal anti-viral immunity while minimizing suppression of host defenses including the p53 DNA damage response and tumor suppression pathway.

"Such directions are relevant and important including not only in the context of viral infection and mRNA vaccines in general but also for patients with cancer who may be receiving cytotoxic or other cancer treatments."

More information: Shengliang Zhang et al, Transfected SARS-CoV-2 spike DNA for mammalian cell expression inhibits p53 activation of p21(WAF1), TRAIL Death Receptor DR5 and MDM2 proteins in cancer cells and increases cancer cell viability after chemotherapy exposure, *Oncotarget* (2024). DOI: 10.18632/oncotarget.28582