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Unexpected protein partnership has implications for cancer treatment

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Scientists have identified two unlikely partners, in a type of immune cell called a macrophage, that work together, in response to cancer drugs, to increase inflammation in a way that may alter tumor growth. Researchers from the National Institutes of Health published the study in the journal *Cancer Research*.

These partners are the p53 protein that suppresses tumors and the nuclear factor-kappaB (NF-kappaB) protein that stimulates their growth. Blocking this partnership could help prevent inflammation from occurring in cancer patients undergoing chemotherapy.

"Since many chemotherapy drugs target p53 to fight cancer cells, our finding helps us better understand the inflammatory-based side effects often seen in patients undergoing chemotherapy, as well as roles for inflammation within tumors," said Julie Lowe, Ph.D., lead author on the paper and fellow in the Laboratory of Respiratory Biology at the National Institute of Environmental Health Sciences (NIEHS), part of NIH.

Both p53 and NF-kappaB have been studied in modern cancer research. But, until now, they have generally been viewed as having opposite effects on growth. This study is among the first to show a cooperative interaction between p53 and NF-kappaB in human immune cells, and to reveal unexpected roles of p53 in tumor-related macrophages.

The study described a new collaboration between two major pathways to

generate inflammation, said Michael Resnick, Ph.D., senior author and head of the NIEHS Chromosome Stability Group.

Inflammatory responses to exposures of p53-activating chemotherapeutic drugs were measured in immune cells from the blood and lungs of healthy volunteers at the NIEHS Clinical Research Unit. The researchers found that these drugs enhanced the expression of molecules that direct inflammation, an effect that required both p53 and NF-kappaB. The study also characterized a role for p53 in immune cells associated with tumors.

Currently, most cancer therapies related to the p53 tumor suppression process are directed at activating the p53 protein. However, this study has clinical applications not only for cancer, but also for smoking-related lung disease. In both cases, p53 is activated in immune cells through chemotherapy, radiation, or smoking. Modifying this pathway through inhibitors of p53 activation could decrease the inflammatory response, both in cancer treatment and in lung diseases, such as chronic obstructive pulmonary disease.

More information: Lowe JM, Menendez D, Bushel PR, Shatz M, Kirk EL, Troester MA, Garantziotis S, Fessler MB, Resnick MA. 2014. p53 and NF-kappaB co-regulate pro-inflammatory gene responses in human macrophages. *Cancer Res*; DOI: 10.1158/0008-5472.CAN-13-1070 [Online 15 April 2014].

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