

Unexpected protein partnership has implications for cancer treatment

By Pamela Kidron

NIEHS scientists have identified two unlikely partners that may alter tumor growth by working together in response to cancer drugs to increase inflammation. Researchers from the Laboratory of Respiratory Biology (LRB) published the [study](http://www.ncbi.nlm.nih.gov/pubmed/24737129) (<http://www.ncbi.nlm.nih.gov/pubmed/24737129>) in the journal *Cancer Research*.

These partners, located in a type of immune cell called a macrophage, 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 LRB.

Proteins thought to have opposing roles

Both p53 and NF-kappaB have been studied in modern cancer research, but they were generally 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.

Researchers exposed immune cells from the blood and lungs of healthy volunteers at the NIEHS Clinical Research Unit to p53-activating chemotherapeutic drugs and then measured inflammatory response. They 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.

Implications for both cancer and lung disease

Currently, most cancer therapies related to the p53 tumor suppression process are directed at activating the p53 protein. This study has clinical applications not only for cancer, but also for smoking-related lung disease, as smoking also activates p53. 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.

Citation: Lowe JM, Menendez D, Bushel PR, Shatz M, Kirk EL, Troester MA, Garantziotis S, Fessler MB, Resnick MA.

(<http://www.ncbi.nlm.nih.gov/pubmed/24737129>)

2014. p53 and NF-kappaB coregulate proinflammatory gene responses in human macrophages. *Cancer Res.* 74(8):2182-2192.

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"The novelty of our study is that we show, in response to drugs used to treat cancer patients, p53 and NF-kappaB work together to promote inflammatory responses in cells central to the immune system," noted Lowe. (Photo courtesy of Steve McCaw)



"This effort continues our extensive work on the human tumor suppressor p53, which is altered in over half of human cancers," said Michael Resnick, Ph.D., lead researcher and head of the NIEHS Chromosome Stability Group. (Photo courtesy of Steve McCaw)

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