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Researchers find link between DNA damage and immune response

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Researchers offer the first evidence that DNA damage can lead to the regulation of inflammatory responses, the body's reaction to injury. The proteins involved in the regulation help protect the body from infection.

The study, performed by scientists at the National Institute of Environmental Health Sciences (NIEHS), which is part of the National Institutes of Health, is one of the first studies to come out of the recently established NIEHS Clinical Research Unit (CRU).

Appearing in the March 31 issue of *PLoS Genetics*, the research suggests that an injury to chromosomes alters the expression of a family of genes known as Toll-like receptors (TLRs). TLRs are proteins that play a role in the immune system by defending the body from infection. Following damage, the TLRs interact with the tumor suppressor gene p53 to regulate the amount of inflammation. The NIEHS investigators also establish that the integration of p53 and inflammation only occurs in primates.

Healthy volunteers with informed consent donated their blood cells for the study. The scientists separated white blood cells from the samples and exposed the cells to anti-cancer agents to activate p53. They then examined the expression of TLR genes. The team detected large variations among individuals, but found that p53 generally led to the activation of several TLR genes in patients' cells. They also found that TLR activation could be prevented by adding the p53 inhibitor pifithrin.

"We would not have found this connection if we only worked with rat or mice cells," said Michael Resnick, Ph.D., principal investigator in the Laboratory of Molecular Genetics (LMG) and corresponding author on the paper. "We needed to have human samples, so our collaboration with the CRU was crucial for these experiments."

Stavros Garantziotis, M.D., a principal investigator in the Laboratory of Respiratory Biology (LRB) and the medical director for the CRU, is a co-author on the article. He said that the publication had two main findings: humans evolved an inflammatory response when subjected to DNA damage, and the variation in TLR activity among humans suggests that some people are more prone to inflammation following DNA damage, for example, after receiving cancer therapy.

"Physicians don't have this information now, but understanding who would likely benefit from anti-inflammatory treatment after chemotherapy would greatly increase a doctor's ability to help his or her patient in the future," Garantziotis continued.

As a physician and co-author of the publication, LRB principal investigator Michael Fessler, M.D., went a step further in his explanation of how stimulating the human immune system could treat infection, and autoimmune and environmental diseases.

"The immune system very likely plays a role, not only in all inflammatory diseases that afflict humans, but also in cancer," Fessler concluded. "Because of the new connection discussed in our paper, we may have a new means to manipulate the responses that affect those diseases."

Now, the researchers are taking advantage of another NIEHS translational program, the Environmental Polymorphisms Registry (EPR), an ongoing study to collect DNA samples from nearly 20,000

North Carolinians. The EPR study will allow scientists to look for genes linked to disease. The study is a collaborative effort between NIEHS and the General Clinical Research Center at the University of North Carolina at Chapel Hill.

Daniel Menendez, Ph.D., and Maria Shatz, Ph.D., are two LMG scientists who share first authorship on the paper. Menendez added that the EPR work will permit researchers to further examine the association between p53 and inflammation. "In related studies, we are looking at individuals who have genetic alterations in the way they might respond to p53 activation," he said. "We will try to determine if their cells behave differently, and if these subjects have changes in their inflammatory response, or an increased risk for certain inflammatory diseases."

More information: Menendez D, Shatz M, Azzam K, Garantziotis S, Fessler MB, Resnick MA. 2011. The Toll-like receptor gene family is integrated into human DNA damage and p53 networks. PLoS Genet [Online 31 March 2011].

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