Researchers link common variant of p53 tumor suppressor gene to increased inflammatory responses

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New findings by Fox Chase Cancer Center researchers link a common variant of the powerful anticancer gene p53 to increased inflammatory responses following DNA damage. The results may help explain why African Americans, who more frequently possess this variant, tend to be more susceptible to certain kinds of inflammation-related diseases and cancers, such as type II diabetes and colorectal cancer.

Maureen Murphy, PhD, associate professor at Fox Chase, published the findings in the March issue of the journal *Molecular and Cellular Biology*, and will present the results at the AACR 102nd Annual Meeting 2011 on Monday, April 4.

Murphy and her colleagues studied the DNA variation, or polymorphism , located at amino acid 72, or codon 72, in the p53 gene—human beings can have either the proline or arginine amino acid at this location. The proline variant is more common in African Americans and other human populations originating from regions near the equator. The arginine and proline variants were known to affect p53's anticancer functions at the cellular level, but their role in living organisms had not been explored.

To find out how the polymorphisms influence p53's activity, the researchers genetically engineered mice to express either the proline or the arginine variant. In animals with the proline variant, DNA-damaging radiation triggered an increase in programmed cell death along with

enhanced activation of inflammation genes.

"This study provides the first evidence that p53 and its polymorphisms play a role in inflammation," says Murphy. "Now we need to look at these variants and the risk of cancers associated with inflammation".

Tracing precisely how the proline variant increases activation of inflammation genes, the researchers found that the proline form of the gene interacts more with a DNA-binding protein complex called NF-kB, which regulates the immune response to infection and cellular stress. Consistently, Murphy and her colleagues found that mice with the proline variant responded more strongly to the challenge of DNA damage than did mice with the arginine variant.

Murphy suggests that the proline version may be more common in individuals living near the equator because it may help people fight the greater number of immune challenges presented by viruses and bacteria that thrive in the warmer temperatures near the equator.

Next, Murphy and her team will study whether the codon 72 polymorphisms influence animals' susceptibility to inflammation-associated cancers, such as colitis-associated colorectal cancer, prostate cancer, stomach cancer induced by Helicobacter pylori infection, and liver cancer caused by the hepatitis B virus.

Murphy notes that p53 mutations are seen in the majority of human cancers, a fact that lends particular significance to the research being pursued in her lab.

"The p53 tumor suppressor gene is the most important cancer-related gene," she says. "It responds to DNA damage and other stress by halting the cell cycle, helping to repair DNA. But, when the damage is too severe, or when the earliest pre-cancerous lesion forms, p53 initiates

programmed cell death of that pre-cancerous cell."

This area of investigation was new for Murphy, who relied on guidance from colleagues with different scientific backgrounds to make rapid headway in her studies. Noting Fox Chase's collaborative environment, she says that "it wasn't so painful making the transition into making mouse models. I could not have done this research anyplace else."

Provided by Fox Chase Cancer Center