Genetic modifier affects colon tumor formation

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(Medical Xpress)—Unexpected results from an ongoing experiment in the lab of Kristi Neufeld, co-leader of the Cancer Biology Program at the University of Kansas Cancer Center, led to a potentially important discovery that could have an effect on how cancer researchers test anti-cancer therapies in mice as well as possibly prevent colon cancer in people.

Neufeld, associate professor in the Department of Molecular Biosciences, studies the adenomatous polyposis coli protein, which protects against colon cancer. Many of her experiments involve testing mice with APC mutations, which cause colon cancer, and seeing if any new drug compounds will work against the mutations.

While doing one of these experiments a few years ago, Neufeld's team discovered that some mice weren't developing colon tumors like mice with APC mutations normally do. The mice with fewer tumors could not be used to test drugs; however, Maged Zeineldin, a postdoctoral fellow working in Neufeld's lab, didn't want to let the research go to waste. They further explored the cause of this unexpected tumor decrease and reported their results in the August issue of *Genetics*.

Neufeld's lab discovered why these strains of mice were developing fewer tumors—they had a quirk in a genetic modifier called Pla2g2a that turned out to be protecting them from tumors. They suspected that outbred nude mice, which are commonly used to grow tumors from human cancer cells for anti-tumor drug testing, would also have

alterations in Pla2g2a that can affect tumor growth.

"We're thinking maybe this variation could affect other tumorigenicity studies as well," Neufeld said. "If you're injecting a nude mouse with a human colon cancer cell and you don't know whether the Pla2g2a alteration is there or not, it could potentially change the outcome of the experiment."

Neufeld now will screen her mice for this Pla2g2a polymorphism and hopes to make other cancer researchers, especially those who test new drug therapies, aware of how genetic modifiers alter the results of an experiment.

"We think this is really important because if someone injects cancer cells, grows a tumor and then injects a compound to see if it treats the cancer, you don't know if what you're seeing is a result of the actual test compound or if it was affected by the differences in genes in these outbred nude mice," she said.

Though this work was a side project from her concentration on the APC protein, Neufeld hopes to collaborate with another lab to determine whether this genetic modifier is something that would have a similar effect in humans. Would the overexpression of Pla2g2a prevent tumors from forming in a human colon? Would it be as simple as infecting the gut with bacteria that expresses the Pla2g2a alteration?

Though the answers to those questions are likely many years away, discoveries like this could potentially aid in preventing cancer or screening for a modifier that could affect whether someone is at risk for colon cancer. Perhaps doctors will someday screen for the absence or presence of the Pla2g2a alteration like they do for the BRCA or HER2 genes, but first researchers would have to see if the Pla2g2a alteration helps to prevent tumors like it did in the mice, according to Neufeld.

"We would want to figure out if simply expressing the Pla2g2a would be enough in humans to have the same protective properties," Neufeld said. "We were just trying to salvage something from our original experiment, but it turned out to be a lot more interesting. I think the lesson is that if you have the time, sometimes following through on things that don't make sense really pays off."

She noted seeing large variability in results has likely happened before in numerous cancer experiments, but researchers often see these mice as outliers and remove them from the experiment all together rather than try to determine the potential effect of genetic modifiers on this variability.

Genetic modifiers are changes in a gene which result in the modification of another gene's function. For example, if a person's hair color is the A allele (one variant of a gene) and the shade of a person's hair is controlled by the C allele, the C allele doesn't mask the effect of the A allele but rather just changes how it's expressed. A person could have light brown hair or dark brown hair, depending on whether the dominant or recessive allele is expressed. In the case of Plag2ga, the mice either have two sensitive or resistant alleles, or one of each.

To confirm that the Pla2g2a modifier did indeed play a role in whether the outbred nude mice formed colon tumors, Neufeld's team injected mice with colon cancer cells to see if tumors would form and screened them for the Pla2g2a alteration.

"What we found is that the formation of tumors correlated with the presence or absence of these resistant alleles," Neufeld said. "Mice with resistant alleles (the Pla2g2a alteration) had fewer tumors than the ones with the sensitive alleles."

This is only one change in one genetic modifier—there are hundreds of

others that have yet to be identified that could be affecting cancer research experiments and influence prevention and treatment options in the future.

"There are so many genetic modifiers. Any change to these modifiers can affect many other things, therefore, many gene alterations could potentially have an effect on cancer," Neufeld said. "Even in the case of Pla2g2a, it's not clear why it protects against these tumors. It's still something we have to figure out."

Provided by University of Kansas