

JULY 06, 2007

When Tissue Repair Backfires

A new molecular link between inflammation and cancer, discovered through experiments with mice, has revealed how the body's natural repair response to tissue injury can actually spur tumor growth.

Howard Hughes Medical Institute investigator Ruslan Medzhitov and colleague Seth Rakoff-Nahoum have found that a protein involved in repairing damaged tissue in the intestine also drives the growth of intestinal tumors. The scientists, both at the Yale University School of Medicine, reported their findings in the July 6, 2007, issue of the journal *Science*. They said the new study will help scientists understand, and perhaps ultimately control, the tissue repair pathway that feeds tumor growth.

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— **Ruslan M. Medzhitov**

Medzhitov and Rakoff-Nahoum explored the function of a protein called Myd88, which participates in a molecular signaling pathway that launches tissue repair in the intestine. Myd88 receives its activating signal from a set of key immune-system regulators called Toll-like receptors.

It has long been speculated that the tissue-repair response may be involved in tumorigenesis, because tumor growth can be viewed as an unregulated state of tissue repair, said Medzhitov. So we hypothesized that induction of the tissue repair response by Toll-like receptors may contribute to tumorigenesis.

In their experiments, the researchers used mice that have a mutation in a gene called adenomatous polyposis coli (APC), which in humans is associated with the vast majority of both inherited and sporadic colorectal cancers. Like humans, mice with the mutant gene develop abnormal intestinal growths and tumors. To test the role of Myd88 in tumor development, the researchers engineered these mice to also lack a functioning gene for the Myd88 protein.

The resulting double-mutant mice developed fewer intestinal growths and tumors than mice who were missing only APC. Detailed comparisons of the two mouse strains revealed that both strains formed about the same number of pre-cancerous structures called microadenomas, but without Myd88, many of those microadenomas never progressed to tumors. This told the researchers that Myd88 contributes to tumor growth and progression, rather than the early initiation of cancer. This idea was further supported by genetic studies of the intestinal tumors, which showed that Myd88 activates a number of genes known to be involved in both tissue repair and tumor development, including some key modifier genes known to be critical for tumorigenesis in both humans and mice.

These findings suggest to us that perhaps the Myd88 pathway controls tumorigenesis by controlling the induction of the tissue repair response, said Medzhitov. In normal tissues, once the tissue repair response is induced it replenishes the damaged tissue and then stops. But in the case of oncogenic mutations, the tissue-repair response is induced because initial tumor growth is sensed as damage to tissue. This turns into a vicious cycle, in which tissue repair generates cells that contribute to tumor mass, but that is perceived as even greater tissue damage, which provides even more cell mass to the growing tumor.

The researchers further confirmed the role of Myd88 in cancer growth with an entirely different model of intestinal tumor formation. They found that when mice were given the cancer-causing chemical azoxymethane, fewer tumors formed when Myd88 was missing.

While they have identified Myd88 as an important trigger of the tissue-repair response, Medzhitov said that future studies in his laboratory will seek to identify the molecular signal that switches off that response once tissue is repaired. If we could identify this negative signal, it might lead to a therapeutic application in which tumor growth could be inhibited by providing that signal, said Medzhitov. Future studies will also search for the signal the tumor uses to trigger the tissue-repair response. If we knew what that signal was, we could attempt to neutralize it, and that could also potentially help to inhibit or block tumor growth, by blocking this tumor tissue-repair program, he said.