Oral drug reduces formation of precancerous polyps in the colon, researchers find

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An oral biologic medication has successfully treated chronic, precancerous inflammation in the intestine, according to results of an animal study authored by an MD/PhD student in the University at Buffalo School of Medicine and Biomedical Sciences.

The study is featured on the cover of the current issue of *Cancer Research*; it was published online ahead of print in September. The journal's editors characterized the study's findings as "striking."

Inflammatory cells in the colon, or polyps, are very common after the age of 50. The average 60-year-old has an estimated 25 percent chance of having polyps. Most polyps are benign, but some will develop into colon cancer. For that reason, the standard treatment for polyps is to remove them.

"Our most important finding is that disease-promoting inflammatory cells in the mouse intestine can be targeted by oral formulations of purified cellular proteins, rendering the inflammatory cells less able to cause disease," says first author Allen Chung, an MD/PhD student in the UB medical school's Medical Scientist Training Program.

According to the paper, this is one of the first times an oral biologic has been used successfully to change the natural history of a genetic disease; in this case, a mutation that puts individuals at very high risk for colon cancer.

Oral biologics are drugs based on biological molecules derived from natural substances from humans, animals or microorganisms. Oral biologics have an obvious advantage over other biologics, which must be injected or otherwise administered.

But even though it was administered orally, the drug used in the study did not deliver its pharmaceutical payload until it reached the intestinal surface.

"We found that high pharmacologic levels of the bioactive drug of interest can be achieved at the intestinal surface without systemic circulation of the drug," Chung explains, so the drug can be administered without the threat of potential toxicities associated with exposure to kidney, liver and brain tissue.

Using animal models of precancerous polyps in the bowel, Chung and his team determined that certain types of immune cells within a chronically inflamed intestine can become rewired, causing them—paradoxically—to contribute to disease development rather than protect against it.

The researchers went on to reprogram these immune cells, making them lose their pathogenic potential.

They did it by delivering immuno-modulatory compounds—specifically, the bioactive protein interleukin-10—into the inflamed intestine, which reduced both the speed and severity of polyp formation. Interleukin-10 was administered as a whole recombinant protein encapsulated within polymer micro-particles, a process originally developed by some of Chung's collaborators at Brown University.

This, in turn, significantly benefited the mice, relieving symptoms including anemia, enlarged spleen and weight loss, and lengthening their

lifespan.

"Site-specific oral therapy for intestinal disorders is a promising avenue of research," says Chung, whose findings formed the basis for his doctoral thesis at UB.

Chung became interested in exploring the relationship between inflammation and polyp formation as a PhD candidate in UB's Department of Microbiology and Immunology. He began investigating how immunologic activity in the intestine may contribute to the development of precancerous polyps—or polyposis—within the bowel.

"It has long been known that inflammation within the colon increases the risk of developing colon cancer," says Chung. Rates of colon cancer are much higher in individuals with inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, than in the overall population, he notes.

"There are also genetic mutations that predispose individuals to develop colon cancer in early adulthood—and these individuals have been found to develop intestinal inflammation even before the appearance of their neoplastic disease," he says.

Chung and his co-author and doctoral mentor Nejat Egilmez, PhD, formerly of UB and now at the University of Louisville, have applied for patent protection on the research.

"We are now involved in studies which hope to determine whether some of the immunologic phenomenon we observed in our mouse models are representative of intestinal disease in human patients who harbor genetic mutations which predispose them to develop colon cancer," says Chung.

Provided by University at Buffalo