Medical Xpress

Colorectal cancer research reveals promising targetable pathway for prevention and treatment

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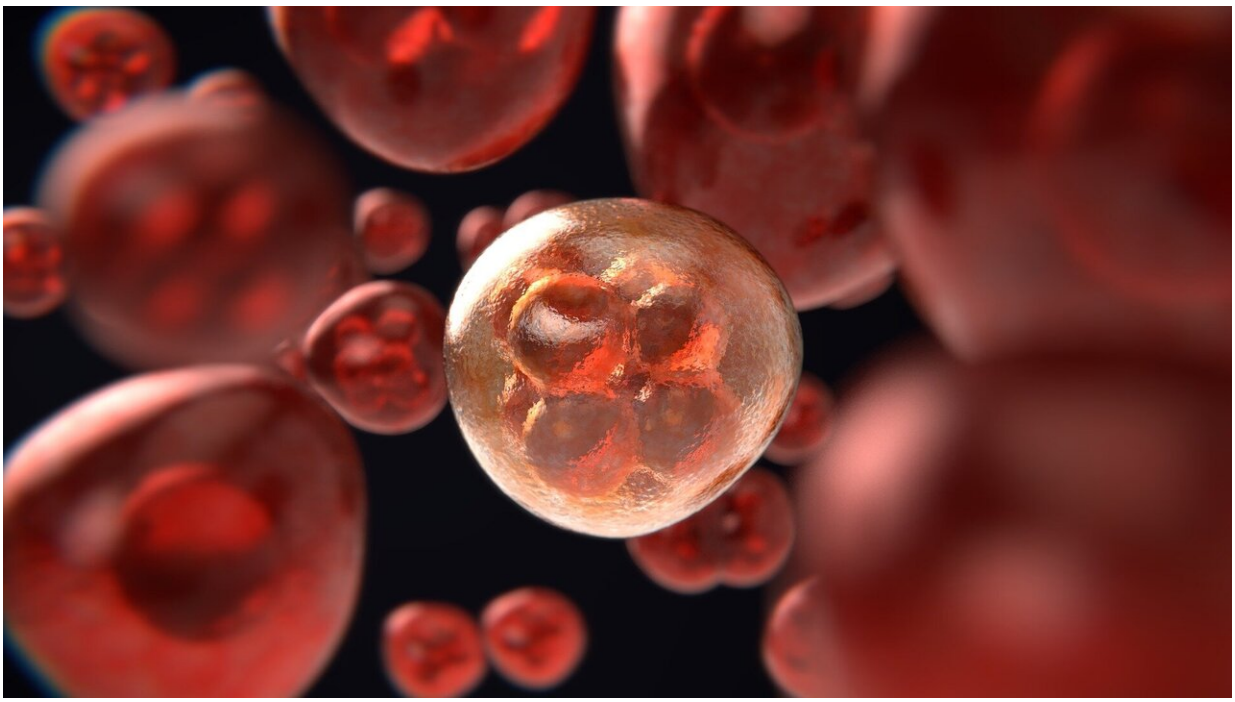

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An MUSC Hollings Cancer Center study sheds light on better ways to prevent and treat colorectal cancer, which often is found at advanced stages when it's much harder to treat.

MUSC Hollings Cancer Center director and researcher Raymond DuBois, M.D., Ph.D., discovered the connection between a series of pathways, actions among molecules that lead to a change in the cell, which showed how cancer cells and the immune system interact. This work, published online on Feb. 2 in *Cancer Prevention Research,* provides strong evidence for a new therapeutic approach to aid the immune system in fighting cancer.

Colorectal cancer (CRC) is one of the most common types of cancer and the second leading cause of cancer deaths. CRC cases have been increasing in young people across the U.S., but researchers are not quite sure why. "The rise in CRC cases in younger individuals is an area of concern for South Carolina and Hollings. In general, this region has a large number of sedentary individuals with high rates of obesity and smokers, which are known to promote cancer," said DuBois, who is also a Distinguished University Professor in MUSC's College of Medicine.

DuBois said that the low five-year survival rate is unacceptable for CRC patients with stage 4 (advanced) disease. Despite promising improvements in cancer treatments, immunotherapies, which help the immune system to fight cancer, such as checkpoint inhibitors, have had disappointing clinical results in many solid tumors, including CRC.

To find more effective options for patients, scientists have studied several molecular pathways to find new drug targets. However, much of this research is done with late-stage CRC, when there is already metastasis, or spread of the disease. "Looking at cancer and immune cell interactions in the early stages of cancer development may provide more answers for the field. Currently, there is very little understanding of what is going on in the immune system in the premalignant stage," said DuBois.

Last summer, DuBois published data that identified how a certain gene

mutation, or change, allows tumors to evade detection by the immune system in CRC patients. This new publication builds upon that foundation and adds pieces to the "big-picture" puzzle that will ultimately lead to better solutions for cancer patients.

Piecing together immune evasion in CRC

Cancer cells can thrive in a person's body when they hide from the immune system. The immune system is designed to kill and remove mutated cells: cytotoxic CD8+ T-cells kill the cancerous cells, and phagocytic macrophages clean up cellular debris. However, cancer often outsmarts the intricate immune system mechanisms. In a journey through signaling pathways, DuBois and colleagues pieced together the mechanism underlying immune evasion in early CRC.

"The mechanisms of how PD-1 is regulated in CD8+ T-cells and macrophages in the tumor environment is still mostly unclear," said DuBois. Using mouse models of CRC and complex genetic techniques, DuBois' team and his collaborator Jessica Lang, Ph.D., at the University of Wisconsin-Madison, identified that the EP4-PI3K-NFκB-PD-1 pathway was responsible for CRC immune evasion.

First, the researchers found a novel role of the prostaglandin PGE_2 in tumor immune evasion. Prostaglandins are hormone-like fatty molecules that are released early in response to inflammation. PGE_2 is the most abundant prostaglandin found in human cancers, including CRC. Additionally, high levels are associated with a poor prognosis.

"We discovered that the inflammatory mediator PGE_2 turns on PD-1 expression by a series of intermediary pathways. The result is that the CD8+ T-cells and macrophages do not effectively attack the developing cancer cells," said DuBois.

Identifying a new cancer treatment target

Next, the research team identified that blocking the molecule EP4 could "free" the immune system and restore the cancer-fighting functions. "In a mouse model of CRC, we found that blocking EP4 with a new class of receptor inhibitor restored the CD8+ T-cell cytotoxicity," said DuBois. He explained that interrupting the pathway through EP4 reduced the levels of PD-1 on both CD8+ T-cells and macrophages, which increased the immune cells' cancer-fighting functions in the intestines.

In CRC and other cancers, high levels of specific molecules, such as PD-1, are associated with worse survival. However, the biological reason was previously not apparent. "Our data shows that the proof of concept is there, and the negative PD-1 effect can be reversed," said DuBois. In the future, there may be several options for the use of EP4 inhibitors, including combining them with checkpoint inhibitors in patients with more advanced cancers.

Since the data shows that blocking EP4 is potentially effective as an early treatment for CRC, the research team plans to further these findings by looking at subsets of the pathways and performing studies in metastatic disease. They also plan to look at the role of this pathway and inhibitor in other cancers.

Cancer prevention

While the current study focused on understanding the pathway for cancer treatment, the EP4 inhibitor could also be pursued as a cancer prevention agent. "People who have a very high risk for cancer are put on aspirin since it has been shown to delay cancer. The problem is that aspirin can be bad for the GI system. If EP4 receptor pathways work as we saw in our research, then perhaps this approach could be used instead

of aspirin," said DuBois.

Cancer prevention is a central theme at Hollings, where, as director, DuBois creates the vision for the center's future. "We are really interested in growing our cancer prevention team. This includes cancer screening. Drs. (Marvella) Ford and (Gerard) Silvestri play lead roles with that work. Finding a pan-cancer blood test with proper sensitivity and specificity would be amazing."

Hollings' current goals are also in line with the recently announced Cancer Moonshot initiative, which aims to reduce the death rate from cancer by at least 50% over the next 25 years.

The current CRC screening guidelines recommend testing beginning at 45 years of age. "Patients can choose colonoscopy, CT colonography or stool tests," DuBois explained. "Any test is better than no test, especially since CRC is now affecting younger individuals." Hollings researchers Marvella Ford, Ph.D., and Kristin Wallace, Ph.D., are studying this troubling finding.

As MUSC works to change what is possible in cancer prevention and treatment, leaders have launched the community health research program In Our DNA SC. In partnership with Helix, a leading population genomics company, the program aims to enroll 100,000 participants in genetic testing to develop a secure genetic and research database. DuBois said this sequencing would help us to find those most at risk for developing cancer.

More information: Jie Wei et al, The COX-2-PGE2 pathway promotes tumor evasion in colorectal adenomas, *Cancer Prevention Research* (2022). DOI: 10.1158/1940-6207.CAPR-21-0572