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Scientists reveal mechanism for colon pain and inflammation

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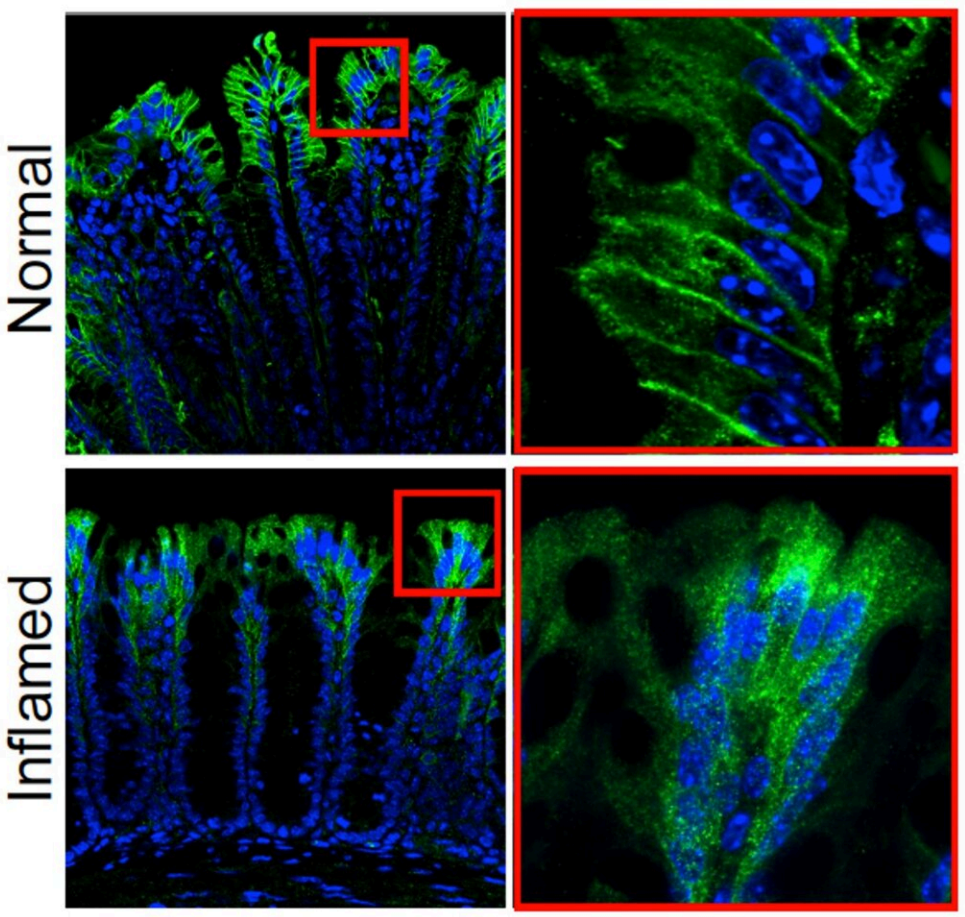

In normal tissue, PAR2—seen here in fluorescent green—is found on the surface of cells, but in inflamed tissue, it moves from the surface of cells to compartments within cells called endosomes. Credit: Bunnett Lab, NYU Dentistry

Researchers at the NYU Pain Research Center have identified a mechanism that underlies inflammation and pain in the colon, and demonstrated that blocking a key receptor from entering colon cells can inhibit inflammation and pain, uncovering a potential target for treating pain in inflammatory bowel disease.

Their study, published in the *Proceedings of the National Academy of Sciences* (*PNAS*), was conducted in mice with colitis, an inflammatory bowel disease marked by chronic and sometimes painful inflammation of the large intestine.

The digestive tract is home to a large number of proteases, or enzymes that break down proteins. These proteases come from a variety of sources, including the microbiome, inflammatory cells, or digestive enzymes in the intestines.

While proteases are important for digestion and help to degrade proteins in the gut, many also signal cells by activating specific receptors. When proteases activate one such receptor—protease-activated receptor-2, or PAR_2—on nerve cells, it produces pain. PAR_2 is part of a large family of receptors named G protein-coupled receptors, which regulate many processes in the body and are the target of one third of clinically used drugs.

Studies show that proteases and PAR_2 are involved in gastrointestinal diseases and pain, including inflammatory bowel disease, irritable bowel syndrome, and cancer. But until now, scientists have not fully understood the receptor's signaling mechanism and how it induces pain.

To pinpoint PAR_2's location in the gut, the researchers created a mouse model in which the gene for PAR_2 is fused to a green fluorescent protein. When a cell expresses PAR_2, it lights up green, allowing the researchers to precisely locate where the receptor is positioned. They

found that PAR_2 was very highly expressed in cells lining the small and large intestines, as well as the colon's nerve fibers.

The researchers then discovered a key difference in the location and behavior of PAR_2 in healthy mice versus mice with colitis. In healthy mice, PAR_2 was found on the surface of colon cells, but in mice with colitis, it shifted from the surface of cells to compartments within cells called endosomes. When the receptor moved into endosomes, it generated signals that cause inflammation and pain by disrupting the normal protective function of cells lining the colon.

"We identified not only where this receptor is in the digestive tract, but also how it signals inflammation and pain in the colon," said Nigel Bunnett, Ph.D., professor and chair of the Department of Molecular Pathobiology at NYU College of Dentistry and the study's senior author. "This more complete understanding of PAR_2 and its signaling mechanism could ultimately help us to better treat inflammatory and painful diseases of the colon."

Additional studies using human colon tissue confirmed that activating PAR_2 induces inflammation in the colon.

If PAR_2 moving from the surface of cells into endosomes leads to inflammation and pain, could blocking the receptor from entering cells limit inflammation and pain? To test this idea, the researchers prevented the movement of PAR_2 into cells by knocking down the expression of a protein called dynamin-2. Keeping the receptor out of cells did, in fact, inhibit signaling and significantly reduced pain and inflammation.

The findings suggest that PAR_2—and specifically, PAR_2 in endosomes—may be a useful target in treating pain in inflammatory bowel disease.

"This could be achieved through blocking PAR_2 from entering cells, as we did in this study by inhibiting dynamin-2," said Bunnett. "It could also mean getting drugs that activate PAR_2 not just to the surface of cells, but into the interior of cells using nanoparticles to reach the receptor in endosomes."

More information: Mice expressing fluorescent PAR reveal that endocytosis mediates colonic inflammation and pain, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2112059119.

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