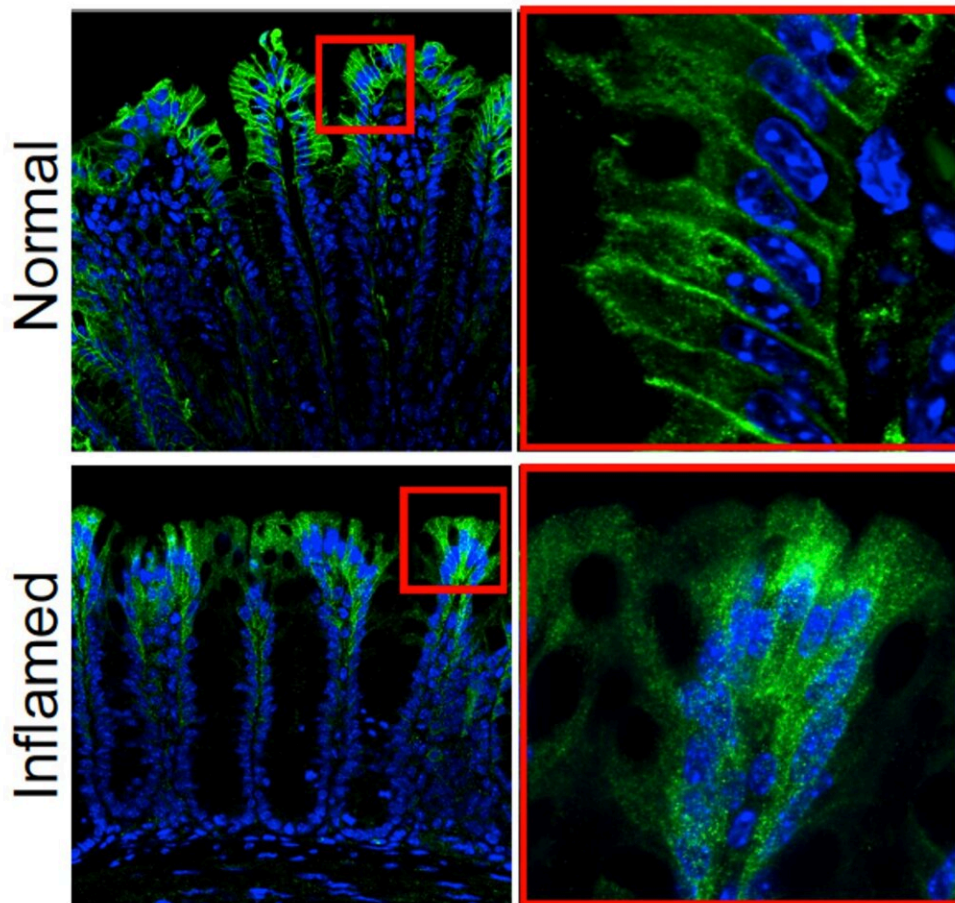


Scientists reveal mechanism for colon pain and inflammation

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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 PAR₂—on [nerve cells](#), it produces [pain](#). PAR₂ 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 PAR₂ 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 PAR₂'s location in the gut, the researchers created a [mouse model](#) in which the gene for PAR₂ is fused to a green fluorescent protein. When a cell expresses PAR₂, it lights up green, allowing the researchers to precisely locate where the receptor is positioned. They

found that PAR₂ 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 PAR₂ in healthy mice versus mice with colitis. In healthy mice, PAR₂ 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 PAR₂ 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 PAR₂ induces inflammation in the colon.

If PAR₂ 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 PAR₂ 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 PAR₂—and specifically, PAR₂ in endosomes—may be a useful target in treating pain in [inflammatory bowel disease](#).

"This could be achieved through blocking PAR₂ from entering cells, as we did in this study by inhibiting dynamin-2," said Bunnett. "It could also mean getting drugs that activate PAR₂ 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](https://doi.org/10.1073/pnas.2112059119).

Provided by New York University

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