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**Media contacts:**

Eileen Leahy  
Elsevier  
+1 732 238 3628  
[ajpmedia@elsevier.com](mailto:ajpmedia@elsevier.com)

Chhavi Chauhan, PhD  
Director of Scientific Outreach  
*The American Journal of Pathology*  
+1 240 283 9724  
[cchauhan@asip.org](mailto:cchauhan@asip.org)

**New study identifies potential therapeutic target for colonic disorders**

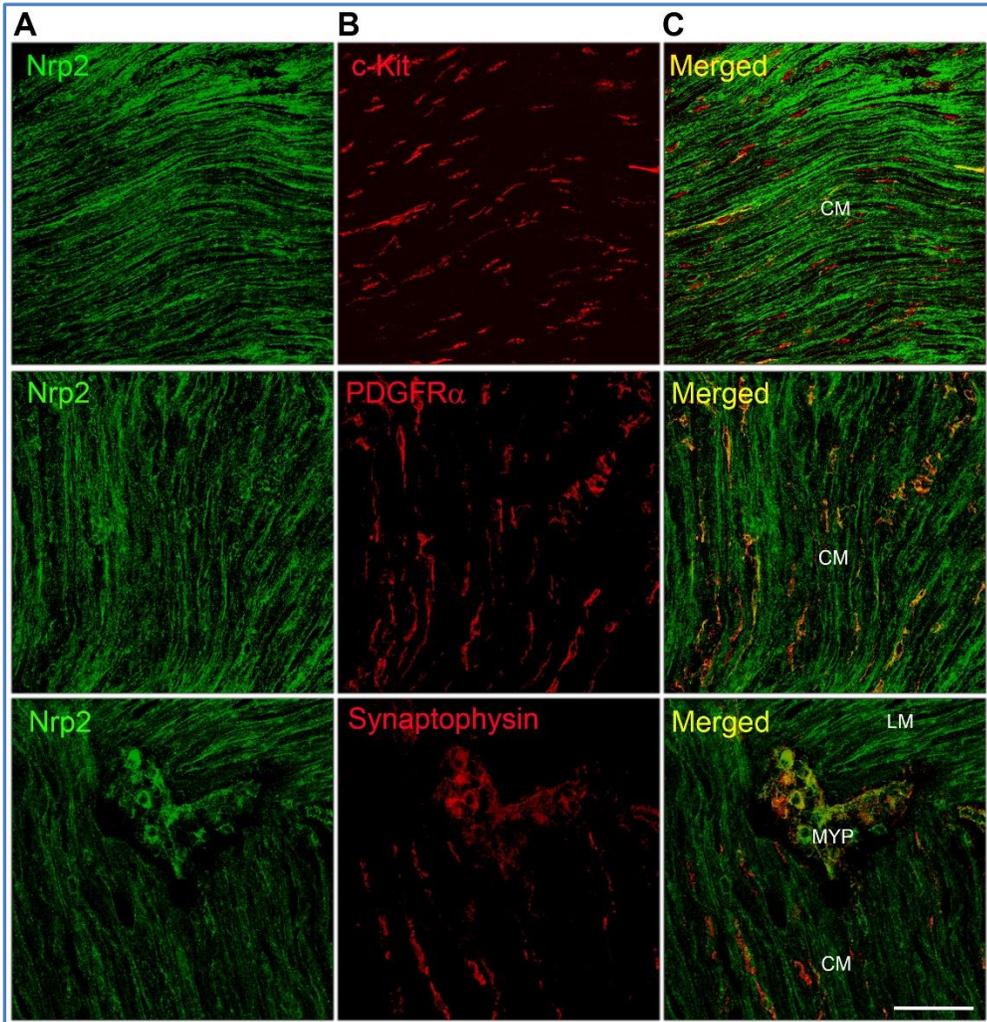
*Inhibiting neuropilin 2 in smooth muscle of mice enhances contraction and motility of the distal colon, investigators report in The American Journal of Pathology*

**Philadelphia, October 11, 2022** – Colonic motility disorders, especially problems associated with constipation and diarrhea, are common in adults and children, greatly impacting quality of life. A [new study](#) in [The American Journal of Pathology](#), published by Elsevier, identifies neuropilin 2 (NRP2) as a novel regulator of distal colonic smooth muscle motility. Its ability to regulate cytoskeletal tone and restrain abnormal smooth muscle contraction may provide opportunities in the future to inhibit or activate signaling and thereby regulate smooth muscle activity in patients suffering from colonic motility disorders.

“Normal visceral smooth muscle activity is central to the function of many body systems including the gastrointestinal and urinary tracts, but it is much less studied than vascular smooth muscle,” explained co-lead investigator Maryrose P. Sullivan, PhD, Department of Surgery, Harvard Medical School; and Division of Urology, VA Boston Healthcare System, Boston, MA, USA. “Earlier studies by our group that showed robust expression of *Nrp2* in smooth muscle of the colon prompted us to understand its functional significance in contraction and colonic motility.”

The investigators found extensive NRP2 expression in the distal colon that was especially prominent in circular and longitudinal smooth muscles in both humans and mouse models. They used genetically modified mice to determine the impact of *Nrp2* deletion on contractility of the colon. Having demonstrated extensive expression of *Nrp2* in smooth muscle of the gastrointestinal tract, they determined the functional consequences of *Nrp2* gene deletion *in vitro* and motility analysis in intact mice. Their findings showed colonic tissues displayed increased

evoked contraction in mice with global or smooth muscle-specific deletion of Nrp2. Mice with inducible, smooth muscle-specific Nrp2 deletion also showed an increase in colonic motility.



Caption: Neuropilin 2 (Nrp2, green) is prominently distributed in longitudinal and circular colonic smooth muscle. Colocalization, shown in the merged images, indicates Nrp2 is also expressed in interstitial cells of Cajal, marked by type III receptor tyrosine kinase cancer biomarker (c-Kit), platelet-derived growth factor receptor alpha (PDGFR $\alpha$ )-positive cells and neural structures marked by synaptophysin. MYP, myenteric plexus. CM, circular muscle; LM, longitudinal muscle (Credit: Vivian Cristofaro and Maryrose Sullivan).

“We were intrigued by the emergence of functional changes as early as a week after deletion of Nrp2,” said co-lead investigator Rosalyn M. Adam, PhD, Urological Diseases Research Center, Boston Children’s Hospital; and Department of Surgery, Harvard Medical School, Boston, MA, USA. “The relatively rapid detection of differences in contractile behavior of colonic muscle argues against major structural changes to the tissue, but rather suggests changes in cellular signaling. Delineating the signaling networks regulated by Nrp2 in smooth muscle is a major focus of our ongoing research.”

Dr. Sullivan and Dr. Adam observed that their study provides an important addition to understanding mechanisms of regulation of visceral smooth muscle and suggests that Nrp2 may be an actionable target in diseases characterized by abnormal smooth muscle contraction.

“Although studies in patients are many years away, ongoing studies in our group are focused on development of small molecule inhibitors designed to inhibit Nrp2. These efforts may provide opportunities in the future to inhibit signaling via Nrp2 and regulate smooth muscle activity in patients. This is particularly relevant for diseases in which visceral smooth muscle is impaired, since effective pharmacotherapy for these conditions is not currently available,” they noted.

Alterations in colonic motility can result from a variety of conditions, including congenital anomalies such as Hirschsprung disease, diabetes, inflammation, infection, gut dysbiosis, and nerve damage secondary to spinal injury. Furthermore, changes in the magnitude and/or coordination of contractile activity throughout the gastrointestinal tract can lead to dysfunctional motility with ensuing disturbances in intestinal flora, inflammation, and nutrient absorption, often with serious health consequences.

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### Notes for editors

The article is “Neuropilin 2 Is a Novel Regulator of Distal Colon Contractility,” by George Lambrinos, Vivian Cristofaro, Kristine Pelton, Alexander Bigger-Allen, Claire Doyle, Evalynn Vasquez, Diane R. Bielenberg, Maryrose P. Sullivan, and Rosalyn M. Adam (<https://doi.org/10.1016/j.ajpath.2022.07.013>). It appears online in advance of *The American Journal of Pathology*, volume 192, issue 11 (November 2022), published by [Elsevier](#).

Full text of the article is available to credentialed journalists upon request. Contact Eileen Leahy at +1 732 238 3628 or [ajpmedia@elsevier.com](mailto:ajpmedia@elsevier.com) to request a PDF of the article. To request an interview with the authors please contact the Media Relations Group, Boston Children’s Hospital, at [media.relations@childrens.harvard.edu](mailto:media.relations@childrens.harvard.edu).

### About *The American Journal of Pathology*

[The American Journal of Pathology](#), official journal of the [American Society for Investigative Pathology](#), published by Elsevier, seeks high-quality original research reports, reviews, and commentaries related to the molecular and cellular basis of disease. The editors will consider basic, translational, and clinical investigations that directly address mechanisms of pathogenesis or provide a foundation for future mechanistic inquiries. Examples of such foundational investigations include data mining, identification of biomarkers, molecular pathology, and discovery research. High priority is given to studies of human disease and relevant experimental models using molecular, cellular, and organismal approaches. <https://ajp.amjpathol.org>

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