Cancer Prevention Research

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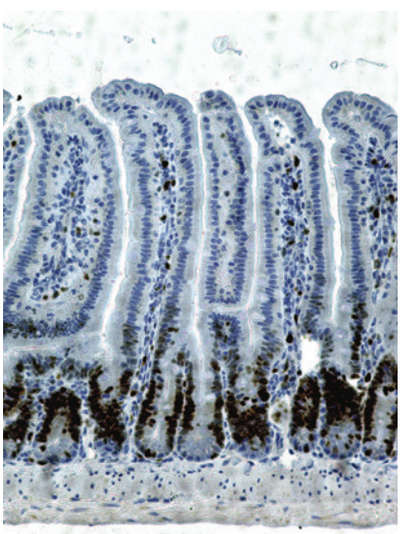
REVIEW

RESEARCH ARTICLES

ABOUT THE COVER

Colorectal cancer (CRC) is one of the most commonly diagnosed tumors, and has significant mortality due to the advanced stage when first detected. People diagnosed with familial adenomatous polyposis, Lynch syndrome, inflammatory bowel disease, and those with familial association or prior polypectomy have higher risk of developing CRC and would benefit from a chemoprevention strategy. Although there is a paucity of targets, mounting preclinical evidence supports the tumor suppressive potential of cGMP-elevating agents such as guanylyl-cyclase C (GCC) agonists and phosphodiesterase 5 (PDE5) inhibitors. Further development of these drugs for CRC prevention has been hampered by an incomplete understanding of the mechanism and a lack of information concerning the merits of each approach to cGMP elevation. A study by Sharman and colleagues (page 81) has tested the ability of two different cGMP-elevating drugs to prevent tumorigenesis in the intestine of Apc^{Min} mice: the PDE5 inhibitor sildenafil and the GCC agonist linaclotide. The results show that these drugs were equally effective at reducing polyp formation in this model, and they support that idea that suppressing proliferation in the non-neoplastic crypts is central to the inhibitory mechanism. The cover image shows Ki67 staining in the intestine of an Apc^{Min} mouse to identify the proliferative compartment, which is significantly reduced by both cGMP elevating drugs. The very low side-effect profile of the pediatric dose of sildenafil used in this study highlights PDE5 inhibitors for future clinical application for primary chemoprevention of CRC in populations predisposed to this disease.



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