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Reply. We read with a considerable attention the comments of Lees et al, relative to potential side effects that might occur in the digestive tract while manipulating the Hedgehog (Hh) signaling pathway. Considering these statements, we would like to underline some parallel issues, with likely consequences on cancer therapeutic strategy.

There is first a crucial need of more fundamental studies to reasonably understand the scope of Hh and PPARβ actions in the gastrointestinal (GI) tract, particularly with respect to the risk of cancer development. The correspondence by Lees et al indeed underscores how Hh inhibition is on the one hand proposed to potentially treat a variety of cancer, including colon cancer, while on the other hand potentially promoting colon carcinogenesis.[1] Similar discrepancies are observed concerning the role of PPARβ in the appearance and growth of cancer in the GI tract, with evidence either for protumorigenic[2–6] or antitumorigenic activity.[7–9] The PPARβ-mediated down-regulation of Ihh expression, which favors Paneth cell maturation, might also be negatively considered because of the presence of Paneth cells in familial adenomatous polyposis dysplasia, as well as in the corresponding mouse model.[10,11] In contrast, it might also be interpreted as one mechanism by which activated PPARβ favors cell differentiation and may protect from GI tumorigenesis.

The second and related issue is that both Hh and PPARβ pathways are active in a broad range of tissues and organs. For each tissue, within the GI tract and outside this organ, they might trigger different responses depending on other interfering pathways that are also active (eg, Wnt, Notch, Akt). For both pathways, the use of systemic agents are presently considered, in cancer, tissue repair and inflammation for Hh, and to treat metabolic disorders for PPARβ.[12] As highlighted in the correspondence by Lees et al, it seems indeed very important to raise a word of caution, proposing a careful and recurrent examination of the GI tract response to these drugs, when given in a non–GI-related pathology. Alternately, manipulating either Hh or PPARβ signaling in the context of tumor, regardless of its localization, should rather be considered in the context of site-specific drug delivery systems, such as with antibody–drug conjugates specifically targeting epitopes present at the cancer cell surface (reviewed Schrama et al[13]).

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Correction

Mori Y, Cai K, Cheng Y, Wang S, Paun B, Hamilton JP, Jin Z, Sato F, Berki AT, Kan T, Ito T, Mantzur C, Abraham JM, Meltzer SJ. A genome-wide search identifies epigenetic silencing of *Somatostatin, Tachykinin-1,* and 5 other genes in colon cancer. Gastroenterology 2006;131:797–808.

The third paragraph in the Results section should have read as follows:

In support of our approach, 6 of these genes had been reported to undergo promoter hypermethylation and mRNA down-regulation in human cancers in the literature: RUNX3, HLTF/SMARCA3, RAB32, AKAP12, CAV1, and RRAD/REM3. RUNX3, HLTF/SMARCA3, and RAB32 were hypermethylated in primary colon cancers, whereas AKAP12, CAV1, and RRAD/REM3 were hypermethylated in non-colonic cancers.[6,8–10,12,13]

Answer to the Clinical Challenges and Images in GI Question: Image 1 (page 1379): *Yersinia enterocolitica* Mesenteric Adenitis and Terminal Ileitis

The presentation and clinical studies supported a differential diagnosis of malignancy, Crohn's disease, as well as infectious mesenteric adenitis. Histological findings from colonic biopsies revealed severe acute colitis with neutrophils infiltrations, acute ulceration, and necrosis. Stool cultures yielded growth of *Yersinia enterocolitica.* The patient was treated with antibiotics based on sensitivity test. His symptoms resolved promptly with medical therapy alone. Twenty-four days later, follow-up colonoscopy showed complete healing of the ulcer. The patient recovered completely and was discharged without surgery. Two months later, abdominal CT showed a clear regression of enlarged mass. Retrospectively, the CT findings were compatible with mesenteric adenitis.

Infection with *Y enterocolitica* is usually a benign, self-limited disorder characterized by fever, diarrhea, abdominal pain, mesenteric adenitis, erythema nodosum, or other immunologic manifestations. Emergency intestinal resections have been performed in some patients, however, and some have died of fulminant disease. *Yersinia* septicemia can occur during acute infection, particularly infants and those with impaired immune defenses or iron-overload states.[1,2] *Y enterocolitica* usually invades *via* Peyer's patches, causing microabscesses, and ulceration of the overlying epithelium. The organism commonly involves the terminal ileum and can invade mesenteric nodes.[3] Mesenteric adenities, which is the most common clinical manifestation, causes a pseudoappendicular syndrome. However, there have been very few reports of *Yersinia* infection presenting as an abdominal mass.[4] Although rare, as in our case, it can present with an abdominal mass caused by pathologic enlargement of one or more of the mesenteric lymph nodes in the ileocecal region. *Yersinia* infection should be considered in patients with a right lower abdominal mass.

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