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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Ulcerative Colitis–Associated Carcinoma: Epithelial SMAD4-Mediated Signaling Is a Key Guardian

Patients affected by long-lasting and relapsing intestinal inflammation such as ulcerative colitis are at high risk of progressing to colitis-associated cancer (CAC).[1] CAC is a multifactorial disease and involves genetic predisposition, environmental triggers, dysbiosis, as well as an impaired immune system. Chronic inflammation also causes DNA damage and genomic mutations in the epithelium as a result of its requirement to go through numerous regenerative cycles. The sporadic colorectal cancer adenoma–carcinoma sequence involves sequential mutations of key tumor-suppressor genes or oncogenes such as *APC*, *KRAS*, and *TP53*,[2] whereas colitis-associated colorectal cancer instead follows a multistep process called inflammation dysplasia sequence, with *TP53* mutations being an early detrimental genetic event.[1]

Transforming growth factor β (TGFβ) superfamily proteins regulate a variety of cellular functions as well as pathologic processes. TGFβ superfamily members include TGFβ, activins, and bone morphogenetic proteins (BMPs), among others. TGFβ superfamily ligands signal through serine/threonine kinase–receptor subtypes I and II, where the type I receptor is activated upon ligand binding and then associates with the type II receptor. This activated receptor complex leads to the transphosphorylation of the receptor-associated SMAD (R-SMAD) proteins, which include SMAD1, 5, and 8 for the BMPs, and SMAD 2 and 3 for the activins and TGFβ. These phosphorylated R-SMADs associate with SMAD4, a shared partner of the TGFβ superfamily. This SMAD trimer complex (phosphorylated R-Smads-SMAD4)s then translocates to the nucleus where it activates transcription of specific target genes. Over the years, impairments of the TGFβ superfamily signaling pathway in inflammatory bowel disease (IBD) pathogenesis and wound healing process have been studied in experimental models as well as in patients.[3–5] However, the relationship between CAC and specific elements of the TGFβ superfamily signaling, such as the SMADs effectors, has not been studied extensively, with one study investigating the specific role of SMAD7 in lamina propria mononuclear cells as a protective role for CAC in murine models.[6] To date, there has been limited attention directed toward the role played by SMAD effectors within the epithelial compartment in CAC pathogenesis.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Means et al[7] used a conditional knockout mouse model with an intestinal epithelial deletion of *SMAD4* to characterize the homeostatic role of this important TGFβ superfamily intracellular effector during experimental colitis. The investigators showed that mice with epithelial deletion of *Smad4* presented macroscopic invasive adenocarcinomas of the distal colon and rectum, 3 months after the completion of 3 rounds of treatment with the colonic irritant dextran sulfate sodium. Surprisingly, chronic dextran sulfate sodium treatment alone was sufficient to drive carcinogenesis in mutant mice and the histopathologic analysis of the tumors showed a strong similarity from those derived from human CAC. Lesions found in mice with epithelial deletion of *Smad4* followed the inflammation dysplasia sequence[1] because the WNT/β–catenin pathway was not up-regulated and tumors appeared flat or slightly elevated at the mucosal surface with extensive invasion of glands into the submucosa and muscularis mucosa. The development of CAC in these mutant mice was shown to be an early event because colonic carcinomas invading the submucosa already were observed after 2 months in some mice. By using RNA sequencing analysis, Means et al[7] showed a strong inflammatory signature after loss of epithelial *Smad4*, with deregulated expression of numerous chemokines and cytokines as well as their receptors. From the group of deregulated molecules, C-C motif chemokine 20 (CCL20) was of particular interest because it is known to play a role in IBD as well as in colon cancer. Means et al[7] then used elegant in vitro studies involving conditionally immortalized $Smad4^{fl/fl}$ cell lines as well as rectal cancer–derived human tumoroids to confirm the central role played by SMAD4 in repression of *CCL20* gene expression in colonic epithelial cells. In addition, they explored mechanisms by which epithelial colonic TGFβ/BMP signaling, through the SMAD4 intracellular effector, interacts with cytokine and chemokine expression. Again using in vitro models, Means et al[7] showed that TGFβ signaling, as well as BMP signaling, could block the induction of CCL20 in a cell-autonomous manner when used as a prophylactic treatment or after an inflammatory trigger such as tumor necrosis factor, interleukin 1β, or lipopolysaccharides.

This study by Means et al[7] provides new insight into the importance of the TGFβ/BMP signaling pathways within the colonic epithelium and its relevance regarding gastrointestinal pathologies such as IBD and CAC. As Means et al[7] showed, loss of *Smad4* in the colonic epithelium implicates an important deregulation of cytokine and chemokine expression, thus leading to an increase of professional immune cell infiltration in the colonic submucosa, inevitably modifying the subepithelial microenvironment. How this dysfunctional

microenvironment impacts the development of CAC in the long run will need to be investigated in future studies and could lead to translational insight involving regulation of these morphogenetic pathways for the treatment of the disease.

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References

1. Low D, Mino-Kenudson M, Mizoguchi E. Recent advancement in understanding colitis-associated tumorigenesis. Inflamm Bowel Dis 2014;20:2115–2123.
2. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759–767.
3. Allaire JM, Darsigny M, Marcoux SS, Roy SA, Schmouth JF, Umans L, Zwijsen A, Boudreau F, Perreault N. Loss of Smad5 leads to the disassembly of the apical junctional complex and increased susceptibility to experimental colitis. Am J Physiol Gastrointest Liver Physiol 2011;300:G586–G597.
4. Ihara S, Hirata Y, Koike K. TGF-beta in inflammatory bowel disease: a key regulator of immune cells, epithelium, and the intestinal microbiota. J Gastroenterol 2017;52:777–787.
5. Sedda S, Marafini I, Dinallo V, Di Fusco D, Monteleone G. The TGF-beta/Smad system in IBD pathogenesis. Inflamm Bowel Dis 2015;21:2921–2925.
6. Chandrasinghe P, Cereser B, Moorghen M, Al Bakir I, Tabassum N, Hart A, Stebbing J, Warusavitarne J. Role of SMAD proteins in colitis-associated cancer: from known to the unknown. Oncogene 2018;37:1–7.
7. Means AL, Freeman TJ, Zhu J, Woodbury LG, Marincola-Smith P, Wu C, Meyer AR, Weaver CJ, Padmanabhan C, An H, Zi J, Wessinger BC, Chaturvedi R, Brown TD, Deane NG, Coffey RJ, Wilson KT, Smith JJ, Sawyers CL, Goldenring JR, Novitskiy SV, Washington MK, Shi C, Beauchamp RD. Epithelial Smad4 deletion up-regulates inflammation and promotes inflammation-associated cancer. Cell Mol Gastroenterol Hepatol 2018;6:257–276.

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