cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

New Immune Role for Axin1 in Colon Cancer Suppression

Epithelial cells lining the intestine continually renew, with nearly complete replacement occurring at least weekly.[1] The intestine can absorb nutrients and water because of precisely regulated cellular proliferation, differentiation, and death, all of which maintain the proper balance of stem and differentiated cells. Several signaling pathways are involved in intestinal homeostasis and Wnt signaling plays a key role. In cells not encountering a Wnt ligand, tumor-suppressor protein adenomatous polyposis coli (APC) and Axin form a scaffold that brings β-catenin in proximity with other proteins that mark β-catenin for proteasome-mediated destruction. Inactivating *APC* mutations are observed in approximately 80% of all colorectal cancers (CRCs). Mutations in genes that encode Axin1 and Axin2 are observed less often (3%–6%) and mutations in *CTNNB1* (encoding β-catenin) that render β-catenin resistant to destruction are found in approximately 6% of CRCs, thus indicating a critical role for Wnt signaling in colon tissue maintenance.[2] By comparison, 27% of liver cancers show mutations in *CTNNB1,* 8% in *Axin1* and 3% in *APC*.[3] It remains unexplained why tumors originating in these 2 tissues appear to dysregulate the same signaling pathway using mutations in different signal components. Furthermore, although the 2 Axin proteins, Axin1 and Axin2, appear to have divergent properties in a colon cancer cell line with *APC* mutations,[4] distinctions in colon tissue are not understood. Why would a cell have multiple scaffolding proteins—are the activities of the Axins and APC completely redundant? Why would inactivating mutations in both *APC* alleles be prevalent in CRC, when Wnt signal activation with a single *CTNNB1* mutation to stabilize β-catenin would seem simpler? Do the Axins and APC each have tumor-suppressing roles beyond serving as scaffolds for the β-catenin destruction complex in the context of Wnt signaling?

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Sanson et al[5] start to address these challenging questions using mouse models to distinguish the roles of Axin1, Axin2, and APC. By using an estrogen-inducible Cre that is driven by the *Villin* promoter, Axin1 was eliminated from intestinal-lining cells of young mice. Intestinal homeostasis in these Axin1-knockout mice appeared to be minimally affected by Axin1 elimination, aside from a slight increase in apoptosis resulting from temporary Cre toxicity. Furthermore, there was no increase in Wnt signaling observed in the Axin1-knockout mice, indicating system redundancy. In contrast, mice with knockout of both Axin1 and Axin2, or only a knockout of APC, showed comparable phenotypes including Wnt signal activation, defective liver metabolic zonation, and lethality within a week. Thus, the 2 Axins possess overlapping functions as Wnt signal antagonists. However, the Axins and APC have distinct roles in Wnt signaling such that elimination of either component compromises Wnt regulation.

To identify unique functions of Axin1, Sanson et al[5] initiated colonic tumors in mice using the mutagen azoxymethane (AOM), and then promoted tumorigenesis with the colon irritant dextran sodium sulfate (DSS).[5] Indeed, treated Axin1-knockout mice developed more adenocarcinomas than treated wild-type mice, indicating that Axin2 could not compensate for Axin1 in this tumor-suppressor context. Unexpectedly, the DSS-treated Axin1 knockout mice displayed less weight loss than treated wild-type mice (both with and without AOM), suggesting a novel proinflammatory role for Axin1. RNA sequencing analysis of tumors from AOM/DSS-treated Axin1 knockout mice showed a gene signature consistent with reduced numbers of proinflammatory T helper (Th1) 1 cells. This Axin1-dependent gene signature was recapitulated in colons of DSS-treated Axin1-knockout mice, along with a significant decrease in Th1 cell numbers as determined by flow cytometry. These results provide compelling evidence that Axin1 promotes development of a Th1 proinflammatory immune response. This proinflammatory role for Axin1 might contribute to the Wnt-independent tumor-suppressor functions of Axin1. Defining the mechanism by which Axin1 promotes this process will be crucial. Previous demonstration that Axin1 is capable of nucleocytoplasmic shuttling makes a more direct role for Axin1 in transcription of proinflammatory mediators such as interferon γ and STAT1 signal transducer and activator of transcription 1 possible.[6] In human colon cancers, the Axin1-deficient gene signature correlated with a small but significant decrease in disease-free survival.[5] Thus, colon cancers with an Axin1-proficient signature might respond favorably to combination therapy using Axin-stabilizing tankyrase inhibitors and immune checkpoint inhibitors.

Overall, the study provides compelling evidence that Axin1 and Axin2 have overlapping functions in Wnt signaling, but unique functions in tumor suppression.[5] Moreover, the investigators uncovered a proinflammatory role for Axin1, beyond that of a Wnt signal regulator. Although the mechanistic details of this emerging new Axin1 function remain to be determined, Wnt-independent roles for Axin1 and other tumor suppressors could serve as innovative platforms for future cancer therapies.

KRISTI L. NEUFELD
Department of Molecular Biosciences
University of Kansas
Lawrence, Kansas

References

1. Radtke F, Clevers H, Riccio O. From gut homeostasis to cancer. Curr Mol Med 2006;6:275–289.
2. Parker TW, Rudeen AJ, Neufeld KL. Oncogenic serine 45-deleted β-catenin remains susceptible to Wnt stimulation and APC regulation in human colonocytes. Cancers (Basel) 2020;12:2114.
3. Xu C, Xu Z, Zhang Y, et al. β-Catenin signaling in hepatocellular carcinoma. J Clin Invest 2022;132:e154515.
4. Thorvaldsen TE, Pedersen NM, Wenzel EM, et al. Differential roles of AXIN1 and AXIN2 in tankyrase inhibitor-induced formation of degradasomes and β-catenin degradation. PLoS One 2017;12:e0170508.
5. Sanson R, Lazzara SL, Cune D, et al. *Axin1* protects colon carcinogenesis by an immune-mediated effect. Cell Mol Gastroenterol Hepatol 2023;15:689–715.
6. Wiechens N, Heinle K, Englmeier L, et al. Nucleo-cytoplasmic shuttling of Axin, a negative regulator of the Wnt-beta-catenin pathway. J Biol Chem 2004; 279:5263–5267.

Correspondence
Address correspondence to: Kristi L. Neufeld, PhD, Department of Molecular Biosciences, University of Kansas, 7049 Haworth Hall, 1200 Sunnyside Avenue, Lawrence, Kansas 66045. e-mail: klneuf@ku.edu.

Conflicts of interest
The author discloses no conflicts.

Funding
Supported by National Institutes of Health grant R01 DK132320.

Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2022.11.011