Colonic healing requires Wnt produced by epithelium as well as Tagln$^+$ and Acta2$^+$ stromal cells

Soumyashree Das, Qiang Feng, Iyshwarya Balasubramanian, Xiang Lin, Haoran Liu, Oscar Pellón-Cardenas, Shiyan Yu, Xiao Zhang, Yue Liu, Zhi Wei, Edward M. Bonder, Michael P. Verzi, Wei Hsu, Lanjing Zhang, Timothy C. Wang and Nan Gao
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Original submission

First decision letter

MS ID#: DEVELOP/2021/199587

MS TITLE: Colonic healing requires WNT produced by epithelium as well as Tagln+ and Acta2+ stromal cells

AUTHORS: Soumyashree Das, Qiang Feng, Iyshwarya Balasubramanian, Xiang Lin, Haoran Liu, Shiyan Yu, Xiao Zhang, Yue Liu, Zhi Wei, Edward M Bonder, Wei Hsu, Lanjing Zhang, Timothy C Wang, and Nan Gao

I have now received all the referees' reports on the above manuscript, and have reached a decision. The referees' comments are appended below, or you can access them online: please go to BenchPress and click on the 'Manuscripts with Decisions' queue in the Author Area.

As you will see, the referees express considerable interest in your work, but have some significant criticisms and recommend a substantial revision of your manuscript before we can consider publication. If you are able to revise the manuscript along the lines suggested, which may involve further experiments, I will be happy receive a revised version of the manuscript. Your revised paper will be re-reviewed by one or more of the original referees, and acceptance of your manuscript will depend on your addressing satisfactorily the reviewers' major concerns. Please also note that Development will normally permit only one round of major revision.

We are aware that you may be experiencing disruption to the normal running of your lab that make experimental revisions challenging. If it would be helpful, we encourage you to contact us to discuss your revision in greater detail. Please send us a point-by-point response indicating where you are able to address concerns raised (either experimentally or by changes to the text) and where you will not be able to do so within the normal timeframe of a revision. We will then provide further guidance. Please also note that we are happy to extend revision timeframes as necessary.

Please attend to all of the reviewers' comments and ensure that you clearly highlight all changes made in the revised manuscript. Please avoid using 'Tracked changes' in Word files as these are lost

in PDF conversion. I should be grateful if you would also provide a point-by-point response detailing how you have dealt with the points raised by the reviewers in the 'Response to Reviewers' box. If you do not agree with any of their criticisms or suggestions please explain clearly why this is so.

Reviewer 1

Advance summary and potential significance to field

While the role of Wnt signaling in crypts of the small intestine has been established 25 years and has been detailed to a great extent since, this is the first complete study of the same phenomena in colon crypts. The authors use a variety of complementary in vivo and in vitro approaches in a variety of genetic models. They thus define two (novel) stromal populations that sustain epithelial repair in colon. In particular the role of Wnt signals in the formation of Deep Crypt Secretory cells of the colon -proposed to be the equivalents of the small intestinal Paneth cells- is novel.

Comments for the author

The authors show here that a genetic block of epithelial Wnt production affects formation of colonic Reg4+ Deep Crypt Secretory Cells and limits colonic epithelial regeneration after chemical injury. Single cell RNA survey of intestinal stroma showed the majority of Wnt-producing cells wereconstrained to transgelin (Tagln+) and smooth muscle actin alpha 2 (Acta2+) expressing populations. Using Tagln-Cre and Acta2-CreERdrivers, Wnt production was attenuatedin these stromal populations. Blocking Wntproduction from either epithelium or Tagln+ and Acta2+ stromal cellsimpaired colonic epithelial healing following chemical-induced mucosalinjury. Aggregated Wnt blockage from epithelium and Tagln+ or Acta2+ stromal cells diminished ß-catenin nuclear accumulation and epithelial repair, leading to increased morbidity and mortality. These new results from two previously uncharacterized stromal cell sub-populations suggested thatcolonic recovery from mucosal-demolishing injury may depend on a combined contributionofWnt molecules collected from multiple sources at the regenerating niche.

Reviewer 2

Advance summary and potential significance to field

Colonic healing requires WNT produced by epithelium as well as Tagln+ and Acta2+ stromal cells. In this paper, Das S et al. demonstrated the regeneration promoting effect of Wnt producing epithelial and stromal cells in mouse colons. The paper was well-written, and their data supported the conclusion. There are several concerns before its publication as following.

Comments for the author

1. p6 This rescuing effect was only partially recapitulated by Wnt2b at the initial phase (Fig. 1l) This poor rescue effect of Wnt2b may have been due to the poor quality of recombinant Wnt2b. (I cannot read the detail methods because there were no supplementary files in the reviewer area). If the authors want to claim this they should use an alternative method, such as overexpression of Wnt2b. Of note Farin H et al. showed that Wnt2b overexpression substituted for Wnt3a (Farin H et al. Gastroenterology 2012).

2. The above paper also showed no canonical Wnt activity in Wnt4 and Wnt5a (Farin H et al. Gastroenterology 2012). Although Foxl1+ cells express these Wnt ligands, accumulating evidence suggested that Foxl1+ cells do not serve as canonical Wnt activators (McCarthy N et al. Cell Stem Cell 2020). The authors should cite this paper and reconsider the functional role of Foxl1+ cells. In Fig2c, CD81 expression should be included.

3. p12. Tagln-expressing cells were detected at the base of nascent crypt (Fig. 7C). The Tagln-expressing cells seem muscularis mucosae, and the expression was irrelevant to the ulceration. In general, quantification of nuclear beta-catenin is not sensitive to measure the Wnt activity. CD44

and cMyc are regulated by multiple growth factors other than Wnt. The authors should utilize a better surrogate marker, such as Axin2 mRNA expression.

4. A Diminished number of Reg4+ cells in Vil-Cre/Tagln-Cre/ Gpr177L/- colons is an interesting finding. However, the decrease was less evident in Vil-Cre/Acta2-CreER/ Gpr177L/- colons. The difference may be due to the timing of knockout and possibly they may need to delete Gpr177 from the neonatal stage for this phenotype. To determine this possibility, the authors should treat tamoxifen for a longer duration. Alternatively, the authors could see a similar phenotype in colon organoids using porcupine inhibitor treatment.

First revision

Author response to reviewers' comments

Point-by-Point Response to Reviewer's Comments:

Reviewer #1:

The authors show here that a genetic block of epithelial Wnt production affects formation of colonic Reg4+ Deep Crypt Secretory Cells and limits colonic epithelial regeneration after chemical injury. Single cell RNA survey of intestinal stroma showed the majority of Wnt-producing cells were constrained to transgelin (Tagln+) and smooth muscle actin alpha 2 (Acta2+) expressing populations. Using Tagln-Cre and Acta2- CreERdrivers, Wnt production was attenuated in these stromal populations. Blocking Wnt production from either epithelium or Tagln+ and Acta2+ stromal cells impaired colonic epithelial healing following chemical- induced mucosal injury. Aggregated Wnt blockage from epithelium and Tagln+ or Acta2+ stromal cells diminished ▫-catenin nuclear accumulation and epithelial repair, leading to increased morbidity and mortality. These new results from two previously uncharacterized stromal cell sub-populations suggested that colonic recovery from mucosal-demolishing injury may depend on a combined contribution of Wnt molecules collected from multiple sources at the regenerating niche.

Author's response: We thank reviewer 1's overall positive assessment of our study.

Reviewer #2:

1. p6 This rescuing effect was only partially recapitulated by Wnt2b at the initial phase (Fig. 1l) This poor rescue effect of Wnt2b may have been due to the poor quality of recombinant Wnt2b. (I cannot read the detail methods because there were no supplementary files in the reviewer area). If the authors want to claim this, they should use an alternative method, such as overexpression of Wnt2b. Of note, Farin H et al. showed that Wnt2b overexpression substituted for Wnt3a (Farin H et al. Gastroenterology 2012).

Author's response: We appreciate reviewer 2's comment on the results for Wnt2b rescue. As the rescuing effect was shown by Wnt3 in this experiment, which was used by us to demonstrate Wnt-dependent survival of Gpr177-deficient enteroids, we decided to remove the data of related to Wnt2b recombinant protein. This change does not change the conclusion of these experiments.

2. The above paper also showed no canonical Wnt activity in Wnt4 and Wnt5a (Farin H et al. Gastroenterology 2012). Although Foxl1+ cells express these Wnt ligands, accumulating evidence suggested that Foxl1+ cells do not serve as canonical Wnt activators (McCarthy N et al. Cell Stem Cell 2020). The authors should cite this paper and reconsider the functional role of Foxl1+ cells. In Fig2c, CD81 expression should be included.

Author's response: We thank the reviewer for raising this very important point. We have added new data related to CD81+ cells, with the expression of Grem1 in revised Figures 2B-D and Supplementary Figures 2A-B. We also cited McCarthy et al, and revised our interpretation and discussion about Foxl1+ cells.

3. p12. Tagln-expressing cells were detected at the base of nascent crypt (Fig. 7C). The Tagln-expressing cells seem muscularis mucosae, and the expression was irrelevant to the ulceration. In general, quantification of nuclear beta-catenin is not sensitive to measure the Wnt activity. CD44 and cMyc are regulated by multiple growth factors other than Wnt. The authors should utilize a better surrogate marker, such as Axin2 mRNA expression.

Author's response: Thanks for suggesting a surrogate marker, Axin2. We performed new immunohistochemistry for Axin2 in DSS-injured colons. We have now included these new results in Supplementary Fig 6C.

4. A Diminished number of Reg4+ cells in Vil-Cre/Tagln-Cre/ Gpr177L/- colons is an interesting finding.

However, the decrease was less evident in Vil-Cre/Acta2- CreER/ Gpr177L/- colons. The difference may be due to the timing of knockout, and possibly they may need to delete Gpr177 from the neonatal stage for this phenotype. To determine this possibility, the authors should treat tamoxifen for a longer duration. Alternatively, the authors could see a similar phenotype in colon organoids using porcupine inhibitor treatment.

Author's response: We now acknowledged, in the revised manuscript, the different degree of loss of Reg4+ cells in mice driven by Tagln-Cre versus Acta2-CreER. In the last 4 months, we have been continuously trying to perform the suggested "Wnt withdrawal" experiments using mouse colonoids. Unfortunately, the results from a limited number of experiments were inconsistent. Further experimentation was hampered by the continued back-order status of Corning Matrigel (Life Sciences # 356231). We sought assistance from Dr. Mike Verzi lab and tried a number of different brands of commercial Matrigel. However, the growth of colonoids in these non-Corning Matrigel was not successful. At this stage, we decided to turn in the revised manuscript to avoid further delay and will pursue the mechanistic study of regulation of Reg4 in future study.

Second decision letter

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I have now received all the referees reports on the above manuscript, and have reached a decision. The referees' comments are appended below, or you can access them online: please go to BenchPress and click on the 'Manuscripts with Decisions' queue in the Author Area.

The overall evaluation is positive and we would like to publish a revised manuscript in Development, provided that the referees' comments can be satisfactorily addressed. While we do not think additional experiments are necessary, one reviewer highlights some questions about possible roles of different Wnt ligands (canonical vs non-canonical) that could be clarified in your discussion. Please address this in the discussion of your revised manuscript and detail them in your point-by-point response. If you do not agree with any of their criticisms or suggestions explain clearly why this is so.

Reviewer 1

Advance summary and potential significance to field

While the role of Wnt signaling in crypts of the small intestine has been established 25 years and has been detailed to a great extent since, this is the first complete study of the same phenomena in colon crypts. The authors use a variety of complementary in vivo and in vitro approaches in a variety of genetic models. They thus define two (novel) stromal populations that sustain epithelial repair in colon. In particular the role of Wnt signals in the formation of Deep Crypt Secretory cells of the colon -proposed to be the equivalents of the small intestinal Paneth cells- is novel.

Comments for the author

The authors show that a genetic block of epithelial Wnt production in the mouse gut affects formation of colonic Reg4+ Deep Crypt Secretory Cells and limits colonic epithelial regeneration after chemical injury. As another novel finding, single cell RNA analysis of intestinal stroma revealed that transgelin (Tagln+) and smooth muscle actin alpha 2 (Acta2+) cells express Wnts. Blocking Wnt production in these stromal populations using Cre alleles driven by either of these two marker genes was then convincingly demonstrated. Blocking Wnt production from either epithelium or from the Tagln+ and Acta2+ stromal cells impaired colonic epithelial healing following chemical-induced mucosal injury. Combining the above Cre drivers for epithelial- and stromal cells enhanced these effects.

My points
-It is unexpected that the key Wnt drivers of small intestinal crypts, stromal Wnt2B and Paneth Cell-produced Wnt 3, don't appear to play a role in colon crypts. Wnt5a is generally seen as a non-canonical Wnt and is known to be produced by stromal cells located near the villus tip in small intestine and underneath the surface of the colonic epithelium, thus away from the stem cells.
It also is not expected to drive stem cells (given that it -in most systems- doesn't activate beta-catenin/Tcf-driven transcription). This is less clear for Wnt4. Can the authors provide experimental evidence (e.g. in organoid cultures)
if any of two indeed drive growth of crypt stem cells/progenitors?
-It has been notoriously difficult to stain for Wnt proteins. How convinced are the authors that the reagents do what they are supposed to do?
-A minor remark: The authors may want to refer to the first description of the role of Wnt signaling for crypt stem cells (Korinek et al 1998).

Reviewer 2

Advance summary and potential significance to field

The authors significantly improved the paper.
Axin2 immunohistochemistry seems non-specific. The community usually uses in situ hybridization.

Comments for the author

The authors significantly improved the paper.
Axin2 immunohistochemistry seems non-specific. The community usually uses in situ hybridization.

Second revision

Author response to reviewers' comments

Point-by-Point Response to the Reviewer's Comments

Reviewer #1

Advance Summary and Potential Significance to Field:

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Comments for the Author:
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Points
-It is unexpected that the key Wnt drivers of small intestinal crypts, stromal Wnt2B and Paneth Cell-produced Wnt 3, don't appear to play a role in colon crypts. Wnt5a is generally seen as a non-canonical Wnt and is known to be produced by stromal cells located near the villus tip in small intestine and underneath the surface of the colonic epithelium, thus away from the stem cells. It also is not expected to drive stem cells (given that it -in most systems- doesn't activate beta-catenin/Tcf-driven transcription). This is less clear for Wnt4. Can the authors provide experimental evidence (e.g. in organoid cultures) if any of two indeed drive growth of crypt stem cells/progenitors?

Author's response: We appreciate Reviewer 1's points, which are well taken by us. Regarding the growth-driving effects of various Wnts on intestinal stem cell renewal and enteroids, several literatures documented these results. Farin et al. and Valenta et al. showed that the addition of Wnt2b was sufficient to restore growth of $Wnt3^{\Delta/\Delta}$ enteroids and *Wls*-deficient enteroids (Farin et al., 2012; Valenta et al., 2016). Valenta also showed that Wnt5a treatment resulted in the growth of *Wls*-deficient crypts into small spheroids (Valenta et al., 2016). Kabiri et al. showed that stromal cells promoted survival and growth of *Porcn-deficient* enteroids and supported epithelial regeneration in IEC-specific *Porcn*-deficient mice post-radiation injury (Kabiri et al., 2014). Deleting *Porcn* in telocytes reduced epithelial proliferation in the small and large intestine (Shoshkes-Carmel et al., 2018). Further, mice with Wnt5a deleted in telocytes showed shortened intestines, an observation that was attributed to increased apoptosis in the neonatal mice (Kondo and Kaestner, 2021). Upon infection with rotavirus (RV), an enteric pathogen that affects differentiated cells, the number of CBCs expanded, and the proliferating cells migrated faster. While mice lacking epithelial Wnt (VillinCreERT;WLSf/f;R26mTmG) did not exhibit a similar response post-infection, suggesting the role of epithelial Wnts in inducing a regenerative response to infection (Zou et al., 2018). In et al. demonstrated a mosaic expression of Wnt2b in specific epithelial cells of human colonic crypts and undifferentiated colonoids. In response to E.coli-secreted cytotoxin EspP-induced injury to colonoids, there was an increase in Wnt2b-expressing cells (In et al., 2020). The infected colonoids failed to survive in the absence of epithelial Wnts when treated with a Porcupine inhibitor, suggesting the importance of epithelial Wnts for colonic regeneration in response to injury. Overall, we consider that the contribution of our study is a

delineation of the functional contribution of Wnts from two uncharacterized stromal populations (Tagln+ and SMA+) to the homeostasis of small and large intestines. Our data add to but does not oppose any of the existing literature.

-It has been notoriously difficult to stain for Wnt proteins. How convinced are the authors that the reagents do what they are supposed to do?

Author's response: We agree with the reviewer, and this was why we had rigorously tested these antibodies before our assays. Both antibodies used in our study have been extensively documented in previous literature [Wnt2b (Klaus et al., 2014; Li et al., 2021; Schwab et al., 2018) and Wnt5a (Feng et al., 2018; Hu et al., 2016; Yuan et al., 2018; Zhang et al., 2021)] for their usage in biochemical and immunohistochemistry assays. Examples are shown below for Wnt5A, where the study confirmed an increase of Wnt5A staining in tumor sections of mouse brains injected with TS453 cells-overexpressing WNT5A.

[We have removed a figure that was provided in confidence to the reviewers]

-A minor remark: The authors may want to refer to the first description of the role of Wnt signaling for crypt stem cells (Korinek et al. 1998).

Author's response: We thank the reviewer for the suggestion. We have accordingly cited Korinek et al. in our introduction.

Reviewer #2
Comments for the Author:
The authors significantly improved the paper.
Axin2 immunohistochemistry seems non-specific. The community usually uses in situ hybridization.

Author's response: We appreciate the reviewer's cautious note. We actually tested this antibody and compared the results to an independent study that tested this antibody on a paraffin-embedded mouse colon tissue: https://www.thermofisher.com/antibody/product/AXIN2-Antibody-clone-JM11-30-Recombinant-Monoclonal/MA5-32646. We thus felt the results included in the supplemental information of our paper might be a valid contribution to the community that intends to use this antibody for their research.

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Third decision letter

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ARTICLE TYPE: Research Article

I am happy to tell you that your manuscript has been accepted for publication in Development, pending our standard ethics checks.