represents the largest of such population examined with regards to peppermint oil efficacy.

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Conflicts of interest
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Most current article

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Two Sides of the Same Coin: The Roles of Transforming Growth Factor-β in Colorectal Carcinogenesis

Dear Editors,

We read with great interest the article by Gu et al,[1] which investigated impaired transforming growth factor (TGF) beta signaling and its link with carcinoembryonic antigen-related cell adhesion molecule family and microbiome in colorectal carcinogenesis (CRC). The authors found that TGF-β signaling-deficient mice spontaneously developed adenomas and CRC with altered health microbiome in the gut. Moreover, the authors found that overexpression of carcinoembryonic antigen-related cell adhesion molecule promoted cell proliferation and colony formation via inhibition of TGF-β pathway activity. Intriguingly, the authors showed that the stemness of CRC was inversely correlated with the TGF-β pathway activity, which is different with the scenarios in breast cancer, liver cancer, gastric cancer, skin cancer, glioblastoma, and leukemia, showing that TGF-β is a positive regulator for cancer stem cell identity.[2] This finding further supports the notion that TGF-β can either work as tumor suppressor or inducer depending on different contexts (eg, TGF-β is a tumor suppressor in normal tissue and early cancer cells, whereas TGF-β frequently plays a protumorigenic role in advanced stages of cancer).[3] For example, TGF-β can promote epithelial-to-mesenchymal transition, cell proliferation, and metastasis, and suppress the immune response, which are critical for cancer progression. Furthermore, TGF-β maintains the self-renewal and pluripotency of human embryonic stem cells, and has been similarly implicated in promoting the stem cell-like characteristics of cancer stem cell by promoting their self-renewal and expression of stem cell factors. In other cell types, TGF-β signaling can induce cell cycle arrest by upregulating cyclin-dependent kinase inhibitors, induce apoptosis, regulate autophagy and suppress inflammation.[3] Considering this dual function of the pathway, cellular heterogeneity and dynamics of colorectal cancer stem cells,[4] it will be interesting to compare the activity and functionality of TGF-β signaling pathway in the cancer stem cells from primary and metastatic CRC.

The multitude, contrasting, and context-dependent function of TGF-β signaling pathway makes it also challenging to use as a target for therapeutic applications. Currently, monoclonal antibodies and inhibitors targeting TGF-β have been used in clinical trial (ClinicalTrials.gov Identifier: NCT01291784, NCT00043706, NCT02452008, NCT02581787) to treat myofibrosis, systemic sclerosis, metastatic prostate, and non-small cell lung cancer, respectively. Considering the difficulty of predicting the effects of all TGF-β blocking from the current strategies, especially the potential CRC risk inferred from the study by Gu et al, it might be important to monitor the gut microbiome and incidence of CRC in the patients during long-term follow-up. Moreover, because TGF-β is a critical regulator in the balancing of tolerance and response of the gut immune system,[5] the impact of anti-TGF-β therapy on the immune homeostasis of the gut should not be overlooked.

Mechanistically, the pleiotropic nature of TGF-β signaling pathway may largely rely on the interaction partners of Smad2/3 transcription factors and the functionality of Smad4 in the TGF-β pathway. For example, FoxH1, ID1, or other cofactors that can facilitate the activation of specific transcriptional programs to enhance the protumorigenic arm of TGF-β signaling (eg, up-regulation of stem cell factors and developmental plasticity of cancer stem cells, stimulation of epithelial-to-mesenchymal transition, cell migration, angiogenesis, chemoresistance, immune-suppressive functions etc) while removing its antitumorigenic arm (eg, induction of cell cycle arrest, apoptosis, autophagy, tissue inflammation, etc).[6] Thus, in the future, it will be vital to specifically manipulate the downstream signaling interaction partners/cofactors of

the TGF-β other than non-selective targeting of the whole TGF-β signaling pathway with its multiple branching signaling cascades and locus-specific functions of Smad2/3 with its transcriptional cofactors and epigenetic regulators. Moreover, by integrating the development of novel cell delivery approaches (eg, CELL-SELEX[7], engineered exosomes[8]), it will be possible to achieve cell-type–specific TGF-β targeting and provides long-term effectiveness and safety in clinical practice.

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Reply. We agree with the authors that the multitude, contrasting and context-dependent functions of transforming growth factor (TGF)-β pathway render the pathway challenging to manipulate for therapeutics, particularly the cancer therapy. Context-driven targeting of TGF-β signaling has been a strong focus of our work.[1] Targeting TGF-β in a subset of patients with hepatocellular carcinoma with high levels of TGF-β and alpha fetoprotein (AFP) increases overall survival by $>$21 months in AFP responders (defined as a $>$20% decrease in AFP from baseline) versus nonresponders.[2] Further insight in the dichotomous TGF-β tumor suppressor and tumor promoter functions in diverse settings have been provided from The Cancer Genome Atlas analyses of 9125 patients from 33 cancer types, as well as in vivo mouse models.[1,3] We observed genomic alterations (which included mutations, homozygous deletions or amplification) of the TGF-β pathway in 39% of the 9125 patient samples, the highest frequencies occurring in gastrointestinal (GI) cancers,[3] and colorectal cancers (CRC) display recurrent genetic aberrations at every level (ligands, receptors and SMADs).

More interestingly, a subset of CRCs with TGF-β pathway gene mutations are predominantly associated with mismatch repair deficiency (in whom the mutational burden is substantially increased), raised levels of immune-related genes (such as markers for cytotoxic T cells), IL6 levels, levels of vascular endothelial growth factor, compared with non-GI cancers, providing insight into targeting TGF-β signaling combined with anti-vascular endothelial growth factor/checkpoint blockade therapy for GI cancers.[3]

As the authors indicate, our recent study revealed that loss of tumor suppressor function of TGF-β pathway leads to CRC development which can also be attributed to gut microbiota.[4] For example, *Clostridiales* and *Fusobacterium* increase TGF-β1 expression levels, increasing the risk for CRC progression. Gut microbial species such as *Clostridium* induce $CD4^{+}FOXP3^{+}$ regulatory T-cell differentiation via TGF-β production, which in turn alters host immune response in cancer progression as well as cancer therapy.[5]

Another aspect is the effect of the gut microbiome on chemotherapy or immune therapy.[6,7] We observed that TGF-β deficient cells are more sensitive to 5-fluoracil (5-FU),[4] thus identifying specific chemoresponsive populations of CRC. For instance, patients with microsatellite stable CRC with SMAD4 loss (18q deletion) or patients with microsatellite instable CRC with inactivating mutations in TGFBR2 may benefit from DNA crosslinking chemotherapy.[4] However, some microsatellite instable tumors are non-responsive to 5-FU. This could be a reflection of microbial alterations (eg, *B vulgatus* and, to a lesser extent, *F nucleatum*) that we observed in our TGF-β–deficient mice which could have modulated the 5-FU response.[7,8] Thus, our data indicate that such therapies should include treatment strategies to maintain a healthy microbiome composition. Mechanistic insight—how CEACAMs become permissive for oncogenic bacteria to endocytose and inactivate, for example, TGFBR1 and its tumor suppressor function—will be important future steps. Combining genomic data and microbiome data, as well as clinical features of cancers are crucial toward defining the appropriate patient population for therapy in the context of TGF-β–driven targeting of CRC.[4]

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