First and foremost, the authors would like to thank the Managing Editor for considering our invited manuscript entitled "*G protein-coupled estrogen receptor in colon function, immune regulation and carcinogenesis*" to be published in *World Journal of Gastroenterology*. We thanks the Reviewers' for their valuable comments and suggestions on how to improve the manuscript. The manuscript has been rephrased and corrected accordingly and we hope that these improvements will recommends for further processing.

Responses to the Reviewers' comments:

Reviewer #1

This is a well-structured review. Some points should be revised for considering in WJG:

a) The entire manuscript should be revised for avoiding grammar and punctuation mistakes.

The entire manuscript was revised by each co-authors and grammar and punctuation mistakes were corrected.

b) I suggest information of specific ligands acting on the GPER (endogenous-exogenous ligands, natural and synthetic). are there differences among their effects on CRC?). Probably a table let one to analyze in brief this information.

There is evidence that GPER agonists, including 17β-estradiol, synthetic ligand G-1, fulvestrant (ICI 182.780), tamoxifen and bisphenol A, have the same effects, i.e., they are able to activate GPER and modulate GPER–downstream signaling pathways, regardless of their nature (natural, synthetic, endogenous or exogenous). For example Bustos et al. (2017) using HT-29 and DLD-1 colorectal cancer cells proved that both G-1, which is a synthetic, exogenous agonist of GPER and estrogen, i.e. 17β-estradiol, which is a natural, endogenous agonist of GPER reduce cell migration under normoxic condition (PMID: 29137421). However, it should be emphasized that the GPER ligands described differ in their affinity for GPER (reviewed by Prossnitz and Arterburn, PMID: 26023144). Direct evidence for the functionality of estrogen signaling by GPER in the colon are research findings indicating that the administration of G-1, a synthetic selective GPER agonist, has an adverse effect on colonic transit time in mice as compared to G-15, which is a synthetic selective GPER antagonist (the results described in the section "GPER modulates colonic motility").

As suggested by the reviewer, the table describing GPER ligands is included in the revised version of the manuscript.

(page: 4, line: 88 – 91): "GPER activity is not only stimulated by 17β-estradiol, but also by numerous xeno- and phyto-estrogens (e.g. bisphenols and genistein), clinically relevant anti-hormonal therapeutic agents (e.g. tamoxifen and fulvestrant) and synthetic GPER-selective ligands (e.g. G-1,) as summarized in Table 1."

(page: 8, line: 220 – 222): "In a murine model of pancreatic cancer, treatment with tamoxifen, which acts as a GPER agonist (see Table 1), reduced the percentage of tissue macrophages as well as the polarization of TAMs to the M2 phenotype."

(page: 9, line: 232 – 235): "Bisphenol A (BPA), a non-selective ER/GPER agonist (Table 1) induces proliferation, migration and invasion of laryngeal cancer cells, as a result of increased IL-6 mRNA expression, potentially via GPER activation."

(page: 12, line: 330 – 332): "Although BPA is classically thought to function through the nuclear estrogen receptors, particularly ERα, it also binds and activates GPER (Table 1)."

(page: 29, line: 854 – 855): “ Table 1 G protein-coupled estrogen receptor ligands”

Agonist	**Type**
Estrogen (17β-estradiol)	natural steroid
Bisphenol A	synthetic xenoestrogen
Genistein	natural phytoestrogen
Tamoxifen	synthetic therapeutic
Fulvestrant (ICI 182.780)	synthetic therapeutic
G-1	synthetic selective ligand
Antagonist	**Type**
G-15	synthetic selective ligand
G-36	synthetic selective ligand

c) I am in agreement about the conclusions, "...GPER appears to be an important estrogen receptor during neoplastic transformation of colon and tumor progression..." but the last sentence (...and (they) should be considered a potential therapeutic target in the future)is unclear. Authors should be clear about the putative strategy to treat CRC.

The second part of the sentence mentioned by the reviewer has been changed:

(page: 15, line: 432 – 435): “In conclusion, GPER appears to be an important mediator of estrogenic actions in both neoplastic transformation of the colon and tumor progression, effects that need to be considered in the application and development of therapeutic strategies.”

Reviewer #2

This review article summarizes the current state of knowledge regarding the role of G protein-coupled estrogen receptor (GPER) in colon function and colorectal cancer. My only comment is that the meaning of the table 1 is not clear. In this table, the processes modulated by GPER are related only to cancer in situ and metastasis. What were the criteria used to define cancer in situ in the colorectum? In the sections regarding the colorectal carcinogenesis the term "cancer in situ" is not expressed and should be clarified.

In our manuscript, we presented data from the studies performed on colorectal cancer cell lines (i.e. HCT-116, SW-480, HT-29, DLD-1) and colorectal cancer xenograft models as well as from experiments using colon samples obtained from patients with colorectal cancer. The results of the research on GPER involvement in neoplastic transformation assessed by cell proliferation and tumor growth, as well as the ability of cancer cells to migrate, we summarized in the table 1 (table 2 in revised version of the manuscript). We agree with the reviewer that the term cancer *in situ* is not fully applicable for describing the results of such experiments. In the revised version of the table, we have more precisely defined the characteristics of cancer cells.

(page: 30, line: 856 – 258): "Table 2 Processes modulated by G protein-coupled estrogen receptor and their importance in neoplastic transformation of the colon"

Features of cancer cells	**Process**	**Anti-tumorigenic**	**Pro-tumorigenic**	**Reference**
Proliferation and tumor growth	Apoptosis	yes	no	[72]
	Cell cycle	yes	no	[72]
	DNA repair	no	yes	[63]
	Endoplasmic reticulum stress	yes	no	[72]
	Estrogen metabolism	no	yes	[89, 90]
	Mitochondrial membrane polarity	yes	no	[72]
	Oxygen level	yes under normoxia	yes under hypoxia	[63]
Migration	Fatty acid metabolism	no	yes	[106]
	Oxygen level	yes under normoxia	yes under hypoxia	[63]