Role of G Protein-Coupled Estrogen Receptor in Digestive System Carcinomas: A Minireview

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Abstract: Digestive system carcinomas are one of the leading causes of cancer-related deaths worldwide. G protein-coupled estrogen receptor (GPER), a novel estrogen receptor, has been recognized as an important mediator in numerous cancer types. Recently, the function and clinical significance of GPER in digestive system carcinomas has been a subject of interest. Increasing evidence has revealed that GPER plays an important role as a potential biomarker in digestive system carcinomas. This work summarizes the recent literature and focuses on the emerging functional role of GPER in digestive system carcinomas, including gastric cancer, hepatocellular carcinoma, pancreatic cancer, and colorectal cancer. The potential application of GPER in novel strategies for the diagnosis and treatment of digestive system carcinomas is discussed and highlighted.

Keywords: GPER, digestive system carcinomas, prognostic indicator, therapeutic target

Introduction

Digestive system carcinomas have a high incidence and mortality in developing and developed countries and they constitute a heavy burden globally.¹ Digestive tract cancers, such as gastric, esophageal, and liver cancers, are frequently diagnosed in China and are identified as the leading causes of cancer-related deaths.² Early diagnosis and treatment could remarkably improve the prognosis of patients with digestive system carcinomas. However, due to the lack of useful biomarkers, patients with digestive system carcinomas are often diagnosed at an advanced stage, which is highly refractory to most systemic therapies. Therefore, to improve prognosis, novel effective biomarkers for early diagnosis in patients with such cancers must be identified.

GPER, formerly named as G protein-coupled receptor 30 (GPR30), is a member of G protein-coupled receptors (GPCRs), which belongs to the 7-transmembrane spanning G protein-coupled receptor family and mediates the rapid cellular responses to estrogen, involving second messengers, kinases, and ion channels.^{3–7} GPER was identified and characterized from estrogen-induced activation of extracellular signal-regulated kinase (ERK) 1/2 in classical nuclear estrogen receptor alpha/beta (ER α/β)-negative breast cancer SKBR3 cells.⁸ The gene encoding GPER is located on the human chromosomal 7p22.3 region, and it consists of three exons. Only the third exon encodes a full-length 375 amino acid protein with seven membrane segments, and the relative molecular weight of the protein is approximately 42 kDa. The understanding of the function of GPER has made significant advances in the identification of GPER-selective agonists and antagonists and the

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use of GPER knockout mice.^{9–11} Studies have shown that GPER can be localized in the plasma membrane at the cell surface¹² and intracellular membranes, such as the endoplasmic reticulum and Golgi apparatus.⁵ The nuclear localization of GPER has also been observed.¹³ GPER translocation has been shown to have a significant effect on resistance to chemotherapy in breast cancer.¹⁴

The contribution of GPER has been described in many physiological systems, such as the reproductive, nervous, endocrine, immune, and cardiovascular systems.¹⁵ Several studies have demonstrated that GPER mediates biological effects in various malignant tumors, including cancers of organs in which estrogen acts directly, such as breast, endometrial, and ovarian cancers, as well as other estrogen-responsive organ cancers, such as lung, prostate, and adrenocortical cancers. Yu et al¹⁶ reported that GPER enhanced cell viability and motility in triple-negative breast cancer cells. Li et al¹⁷ found that autocrine motility factor/GPER/protein-serine-threonine kinase (AKT) signaling promotes endometrial cancer progression. Yan et al¹⁸ showed that GPER is involved in the proliferation, migration, and invasion of ovarian cancer cells. Conversely, GPER may act as a tumor suppressor in several cancer types, including lung cancer,¹⁹ prostate cancer,²⁰ and adrenocortical carcinoma.²¹ Due to the different research conditions and the complex interactions between multiple estrogen receptors, contradictory results have been reported regarding the subcellular localization of GPER and its function, being described as both proliferative and pro-apoptotic in breast cancer.²² Similarly, numerous studies have suggested that GPER has dual roles (antitumorigenic or protumorigenic) in the pathogenesis, progression, and metastasis of malignant tumors. The causes of this phenomenon remain to be investigated.

To date, the molecular mechanisms and clinical significance of GPER in digestive system carcinomas remain obscure. This review summarized the present state of knowledge about the role of GPER in digestive system carcinomas (Table 1), of which GPER may emerge as a novel potential prognostic indicator and therapeutic target.

GPER Ligands

There are five main types of GPER ligands: steroids (Table 2), selective estrogen receptor downregulators (SERDs)/selective estrogen receptor modulators (SERMs), phytoestrogens, synthetic estrogens, and synthetic compounds. Many studies have reported that the binding of estrogen (17 β -estradiol, E2) to

GPER exhibits high selectivity.^{4,15,23,24} In addition, other steroids, including estrone and 17 α -estradiol, exhibited very low affinities, whereas progesterone, cortisol, and testosterone did not bind to GPER.²³ Furthermore, estriol has been reported to act as a GPER antagonist.²⁵ Interestingly, among the therapeutic anti-estrogen agents, SERDs/SERMs, such as ICI 182780 (fulvestrant), tamoxifen, and raloxifene, were also shown to act as agonists of GPER as opposed to their antagonistic action towards ER α/β .^{8,23,26,27} Many synthetic estrogenic compounds, including pesticides, herbicides, and plasticizers (eg bisphenols, methoxychlor, alkylphenols, polychlorinated biphenyls, dioxins, and phthalates) have been demonstrated to activate GPER.^{28,29} Some phytoestrogens, such as quercetin, genistein, daidzein, resveratrol, oleuropein, and hydroxytyrosol, also bind to GPER.^{30–33} Studies clarifying the potential physiological and pathophysiological functions of GPER are substantially facilitated by extremely high GPER-selective compounds sharing the scaffold domain of a tetrahydro-3H-cyclopenta-[c]quinoline, such as G1, G15, and G36, which serve as useful probes to stimulate (G1) or antagonize (G15 and G36) GPER signaling.^{9,10,34} Recently, based on a computational screen, a new compound, 2-cyclohexyl-4-isopropyl-N-(4-methoxybenzyl) aniline (CIMBA) was designed and synthesized, which exhibits high selectivity and superior antagonism for GPER and reduces the formation of estrogen-induced cholesterol gallstones in female mice.³⁵

GPER ligands may serve as novel pharmacological agents for treating human diseases.³⁶ Recent preclinical studies have shown that chronic administration of G1 could restore fat, glucose, and lipid homeostasis in mouse models.³⁷ This observation indicates that chronic GPER signaling has potential implications for the role of GPER in cancer, as metabolic syndrome is an independent risk factor for cancer.³⁸ G1 is currently undergoing Phase I clinical trials for its antitumor properties.³⁹

Models explaining estrogen-induced carcinogenesis in breast and gynecological cancers have focused on the ER-dependent mechanisms of cellular proliferation and somatic mutations.⁴⁰ However, a protective effect of estrogen has been suggested to explain the male predominance in cancers of the digestive tract, such as esophageal, gastric, and liver cancers.^{41,42} Soy and soy-based foods have been used as basic traditional ingredients in the diets of the Asian population for thousands of years. Soy isoflavones such as daidzein and genistein are polyphenols with estrogenic properties.⁴³ Soy intake has received wide attention because of its potential role in reducing the risk of gastrointestinal cancer.^{44–46} Bisphenol A (BPA) and phthalates, classified as

Table I Summary of the Role of GPER in Various Digestive System Malignancies

Types	GPER Expression*	Function	Ligand	Signaling Pathways	Study Objects	Reference
GC	Down-regulated	Predict good prognosis	Non-specified	EMT	Bioinformatics Clinical samples In vitro	[76]
	Down-regulated	Increase cell death	G1	ER stress	Clinical In vitro In vivo	[77]
	Up-regulated	Predict poor prognosis	Non-specified	Non-specified	Bioinformatics	[78]
HCC	Non-specified	Regulate iron metabolism	E2; G1 ICI I82720	GPR30/BMP6	In vitro In vivo	[85]
	Non-specified	Antiviral	E2; G1; G15 tamoxifen	GPR30/MMP9	In vitro	[86]
	Non-specified	Mechanical reprogramming	Tamoxifen	GPER/RhoA/myosin	In vitro	[87]
	Non-specified	Inhibit proliferation; Stimulate apoptosis	E2; G1	GPER/ERK	In vitro	[88]
	Down-regulated	Regulate inflammatory responses	G1	Non-specified	Clinical samples In vitro In vivo	[69]
	Up-regulated	Promote tumor development	E2	GPER/PI3K/AKT/mTOR	Clinical samples In vivo	[89]
	Non-specified	Increase miR-21 transcription	DHEA; G1; G15 ICI I82720	GPER/ERK	In vitro	[90]
	Non-specified	Up-regulate FASN; Increase cell growth	E2; G1	GPER/ERK/c-fos/AP-1	In vitro	[92]
PDAC	Non-specified	Sensitize cells to chemotherapy	AXP107- I1 G1; G15	GPER/MAPK	Bioinformatics In vitro In vivo	[96]
	Non-specified	Inhibit mechanotransduction and invasion	G1 G15	GPER/PKA/RhoA/myosin2	Bioinformatics In vitro	[97]
	Non-specified	Induce tumor regression; Increase cell immunogenicity	G1	Non-specified	Clinical samples In vitro In vivo	[72]
	Non-specified	Reprogram the tumor Microenvironment; Increase apoptosis	Tamoxifen	GPER/HIF-1 α	In vitro In vivo	[99]
	Non-specified	Mechanically regulate the tumor microenvironment	Tamoxifen	GPER/RhoA	In vitro In vivo	[100]

(Continued)

Table 1 (Continued).

Types	GPER Expression*	Function	Ligand	Signaling Pathways	Study Objects	Reference
CRC	Down-regulated	Inhibit proliferation; Induce cell cycle arrest; Increase the mitochondrial related apoptosis	G1	GPER/ROS/ERK1/2 GPER/KK α /I κ B α /NF- κ B GPER/GSK-3 β /NF- κ B	Bioinformatics Clinical samples In vitro In vivo	[102]
	Up-regulated (hypoxia)	Induce cell migration and proliferation (hypoxia); Suppress cell migration and proliferation (normoxia)	E2	GPER/HIF-1 α GPER/VEGFA	Bioinformatics In vitro	[105]
	Non-specified	Hydrolyze E ₁ S	E2; G1 tamoxifen ICI I82780	GPER/STS	In vitro	[106]
	Up-regulated	Augment proliferation; Predict poor outcomes	E2; G1; G15	Non-specified	Bioinformatics In vitro In vivo	[107]
	Non-specified	Up-regulate FASN; Increase cell growth	E2; G1	GPER/ERK/c-fos/AP-1	In vitro	[92]

Note: *GPER expression levels in tumor tissues or cells compared to those in normal tissues and cells.

Abbreviations: AXPI07-11, a genistein analogue; CRC, colorectal cancer; DHEA, dehydroepiandrosterone; GC, gastric cancer; HCC, hepatocellular carcinoma; I κ B, inhibitor of nuclear factor- κ B; IKK, I κ B kinase; MAPK, mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; PDAC, pancreatic ductal adenocarcinoma; PKA, protein kinase A; ROS, reactive oxygen species; VEGFA, vascular endothelial growth factor A.

synthetic plasticizers, can exert endocrine disruption due to their weak estrogenic properties and increased risk of cancer.^{47,48} BPA exposure not only increases the risk of colon cancer, but also induces chemotherapy resistance,⁴⁹ which reflects its potential importance in digestive carcinomas. As such, a better understanding of the role of GPER in digestive system carcinomas may help to elucidate the potential mechanisms to improve prevention and management of the disease.

GPER-Activated Signaling Pathways

As a classical GPCR, GPER exhibits the hallmarks of a plasma membrane receptor that manifests its actions through G protein-dependent cell signaling.⁵⁰ GPER activation induces heterotrimeric G proteins, which then activate multiple downstream effectors, including adenylyl cyclase, resulting in cyclic adenosine monophosphate (cAMP)/protein kinase A/cAMP response element binding protein production, an increase in

Table 2 Summary of the Type of GPER Ligands

Steroid Hormones	SERDs/SERMs	Synthetic Estrogens	Phytoestrogens	Synthetic Compounds
17 β -estradiol	ICI182780	Bisphenols	Quercetin	G1
17 α -estradiol	Tamoxifen	Methoxychlor	Genistein	G15
Estrone	Raloxifene	Alkylphenols	Daidzein	G36
Estriol		Polychlorinated biphenyls	Resveratrol	CIMBA
		Dioxins	Oleuropein	
		Phthalates	Hydroxytyrosol	

Src-like nonreceptor tyrosine kinases (Src) and sphingosine kinase (SphK). The latter two signals induce the activation of matrix metalloproteinases (MMPs), which cleave pro-heparin-binding EGF-like growth factor (HB-EGF), liberating free HB-EGF, which in turn could transactivate epidermal growth factor receptors (EGFRs). EGFR activation appears to be involved in the activation of mitogen-activated protein kinases (MAPKs)/ERK pathway.^{51–54} EGFR activation also triggers phosphatidylinositol 3-kinases (PI3Ks)/AKT.⁵⁵ The additional downstream pathways reported to be activated by GPER include protein kinase C, calcium mobilization, and Hippo/Yes-associated protein signaling.^{56–58} The GPER-mediated signaling pathways are outlined in Figure 1.

GPER in Metabolic Syndrome, Clinical Targeted-Therapy, and the Immune System

Estrogen is an important modulator of metabolic disorders in both humans and animal models;⁵⁹ thus, it is expected that GPER plays a vital role in metabolic regulation. Similar to the pathological features of a patient with metabolic syndrome, GPER knockout mice show a phenotype marked by vascular disease,⁶⁰ impaired glucose tolerance,^{61,62} dyslipidemia,⁶² and obesity.⁶⁰ A large sample (38,940 cancer cases) meta-analysis showed that the presence of metabolic syndrome was associated with colorectal, liver, and stomach cancer in men and pancreatic cancer in women.⁶³ From the perspective of GPER-mediated energy metabolic coupling

Figure 1 Schematic diagram of the GPER signaling pathways. Once the binding of the agonist is generated, GPER can induce heterotrimeric G proteins, resulting in multiple downstream events, including AC/cAMP/PKA/CREB, Src, and SphK. MMP, activated by the latter two signals, may cleave pro-HB-EGF and liberate free HB-EGF, which in turn transactivates EGFR. Subsequently, EGFR activation appears to be involved in the activation of MAPK/ERK and PI3K/AKT pathways. Additionally, the additional signals activated by GPER include PLC/IP3/calcium mobilization, PKC, and Hippo/YAP signaling.

Abbreviations: AC, adenylyl cyclase; CREB, cAMP response element binding protein; IP3, inositol triphosphate; MAPK, mitogen-activated protein kinases; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; YAP, Yes-associated protein.

(EMC) in clinical targeted therapy, cytoplasmic GPER translocation in cancer-associated fibroblasts mediates the cAMP/PKA/CREB/glycolytic axis and confers breast tumor cells with Her-2-targeted therapy (herceptin) resistance.¹⁴ Moreover, inhibition of EGFR by gefitinib reduces the expression of GPER and subsequently prevents E2-induced cell growth in triple-negative breast cancer cells.⁶⁴

In the immune system, GPER is expressed in each population of immune cells, including peripheral B and T lymphocytes, monocytes, eosinophils, and neutrophils.⁶⁵ In addition, it regulates estrogenic effects on immune functions in humans and other species.^{66,67} The immunomodulatory effect of GPER has also been beneficial in immune-mediated diseases such as multiple sclerosis, liver fibrosis, and autoimmune encephalomyelitis by reducing the levels of inflammatory cytokines and upregulating programmed death-1 (PD-1) on CD4⁺ Foxp3⁺ regulatory T cells.^{68–70} Systematically administered G1 was well tolerated in mice and markedly increased the efficacy of immune checkpoint blockade in melanoma and pancreatic cancer.^{71,72}

GPER in Gastric Cancer (GC)

GC is the fourth most commonly diagnosed cancer among men and the fifth among women worldwide, with an estimated 951,600 new cases and 723,100 deaths in 2012.⁷³ In China, GC is the second leading cause of cancer-related deaths, with an estimated 498,000 deaths in 2015.² The GC rates are approximately twice as high in men as in women,⁷³ possibly due to the presence of estrogen in women. Gastrectomy and chemotherapy are currently the main therapeutic options for patients with GC.⁷⁴ The rate of early diagnosis of GC is dismal because it is symptom-free.⁷⁵ Most patients present with advanced stage (locally advanced or metastatic) GC and have a poor prognosis. Therefore, identifying novel diagnostic and prognostic biomarkers and investigating specific therapeutic targets for GC are urgently needed.

Tian et al⁷⁶ demonstrated that GPER mRNA and protein levels were downregulated in GC tissues and cells, and the decreased expression of GPER protein was an independent risk factor for poor prognosis in patients with GC. Furthermore, bioinformatics data showed that GPER DNA promoter methylation may be involved in the reduced expression of GPER in GC and that GPER may act as a tumor suppressor through the regulation of the epithelial–mesenchymal transition (EMT) pathway.⁷⁶ Another study similarly indicated that GPER mRNA

levels were significantly lower in GC tissues than in normal tissues, and a stage-dependent decrease was found in the GPER expression of GC on the basis of GPER fluorescence intensity in cancer stages I and II (45% and 30%) versus stages III and IV (25% and 20%, respectively).⁷⁷ The induction of pERK-dependent endoplasmic reticulum stress via GPER signaling may increase G1's chemotherapeutic effect in the GC cells.⁷⁷ However, by contrast, a bioinformatics screening for hub genes associated with GC by Zheng et al indicated that GPER was highly expressed in GC tissues and that the overexpression of GPER was associated with poor survival.⁷⁸

In conclusion, GPER is associated with GC prognosis. As a GPER agonist, G1 induced gastric cancer cell apoptosis. However, a study by Zheng et al provided inconsistent evidence.⁷⁸ The possible reason is that this study only carried out clip data and a bioinformatics analysis and lacked clinical data and in vitro or in vivo experimental validation. Furthermore, the database and research tools used in this study were different from those used in a previous study. To our knowledge, few studies have focused on the role of GPER in GC. More investigations are required to determine whether GPER can be a potential prognostic biomarker and therapeutic target for GC in the future.

GPER in Hepatocellular Carcinoma (HCC)

Primary liver cancer (PLC) is an aggressive malignancy with a generally poor prognosis, with an estimated 782,500 new cases and 745,500 deaths worldwide in 2012.⁷³ In China, PLC is the third leading cause of cancer-related deaths, with an estimated 422,100 deaths in 2015.² HCC, which represents approximately 90% of PLC, is generally caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and alcohol use.^{79,80} The HCC rates in men are usually 2–4 times higher than those in women, thus suggesting the vital role of sex hormones in HCC pathogenesis.^{81,82} A clinical study suggested a protective role of estrogen in HCC, as higher HCC morbidity and mortality were found in male patients.⁸³ However, the mechanisms involved in estrogen-mediated protection in HCC remain to be explored.

The role of GPER in HCC has been investigated in recent years. Hepcidin, a liver-derived iron regulatory protein, regulates iron absorption in the small intestine via internalization and degradation of ferroportin, an

exporter of iron.⁸⁴ E2 and ICI 182,720 increased hepcidin expression in HepG2 cells through a GPER/bone morphologic protein 6 (BMP6)-dependent mechanism, indicating that estrogen decreases iron absorption in the intestine.⁸⁵ This finding provides a new perspective for explaining the gender differences in iron storage in the body. Ulitzy et al⁸⁶ reported that GPER activation downregulated HCV entry and spread by promoting occludin cleavage through MMP-9, thus providing a new insight into a novel antiviral effect. Cortes et al⁸⁷ showed that tamoxifen mechanically deactivated hepatic stellate cells (HSCs), whose activation triggers and perpetuates liver fibrosis in HCC via the GPER/GTPase Ras homolog family member A (RhoA)/myosin axis. These results suggest that GPER-mediated estrogen signaling is an option for the mechanical reprogramming of HSCs in the tumor microenvironment. Shen et al⁸⁸ revealed that E2 and G1 antagonized the oncogenic actions of leptin in HepG2 cells by inhibiting cell proliferation and stimulating cell apoptosis, which was partly associated with increased ERK activation mediated by GPER. Wei et al⁶⁹ showed that GPER mRNA and protein levels were significantly lower in HCC tissues than in matched non-tumor tissues. Interestingly, modulating GPER expression did not affect the viability and proliferation of HCC cells in vitro.⁶⁹ Furthermore, GPER knockout in a diethylnitrosamine-induced mouse tumor model significantly facilitated liver tumorigenesis by promoting inflammation and fibrosis, thus revealing that GPER may inhibit HCC tumorigenesis by modulating inflammatory responses.⁶⁹ However, Chaturantabut et al⁸⁹ indicated that the activation of GPER promoted liver growth and tumor development via the PI3K/mammalian target of rapamycin signaling in zebrafish. They also found that human HCC samples had increased GPER expression levels compared to non-tumor tissues. Teng et al⁹⁰ suggested that a rapid increase in microRNA-21, an oncomiR in HCC, transcription stimulated by dehydroepiandrosterone in HepG2 cells involved GPER activation, which increased ERK1/2 and c-Src phosphorylation. Activation of lipid metabolism is present in many tumors. Fatty acid synthase (FASN) is necessary for cancer cell survival, growth, and migration.⁹¹ E2 and G1 upregulated FASN expression in HepG2 cells via GPER activation, which involved GPER/ERK/c-fos/activator protein 1 (AP-1) signaling.⁹²

In summary, GPER may play a crucial role in HCC, suggesting its potential as a therapeutic target. However, the results of current studies illustrate the complexity of

the role of GPER in HCC, including metabolism, anti-virus, microenvironment, immunity, tumor growth, and epigenetic regulation. Genetic variability has been discussed as a cause of HCC development.⁹³ Not surprisingly, GPER may have bilateral effects on HCC proliferation in different species. In populations with different genetic backgrounds, diets, or possibly environmental factors, the GPER expression in HCC tissues in different studies may vary significantly. Whether GPER contributes to gender differences in HCC requires further exploration, especially in large sample clinical studies that include complete prognostic data.

GPER in Pancreatic Cancer (PDAC)

PDAC is one of the deadliest cancers and is poorly responsive to current treatments. PDAC is projected to become the second leading cause of cancer-related deaths in the United States by 2030.⁹⁴ In 2015, an estimated 90,100 new cases of PDAC and 79,400 deaths were reported in China.² Thus, finding new therapeutic targets to inhibit PDAC is urgently needed.

Andersson et al⁹⁵ suggested that the use of hormone replacement therapy (HRT), in particular an estrogen-only regimen, was associated with a decreased risk of PDAC in women. A group revealed that high GPER expression in PDAC was indicative of improved survival, and a genistein analog sensitized PDAC patient-derived xenografts to chemotherapy through GPER activation.⁹⁶ Rice et al⁹⁷ also found that high GPER expression was associated with improved survival and lengthened relapse-free time in PDAC. Furthermore, GPER activation represses cell proliferation, mechanotransduction, cell contractility, EMT, and basement membrane invasion in cancer cells via RhoA.⁹⁷ Natale et al⁷² suggested that GPER activation in G1 decreased PDAC cell proliferation and increased tumor cell immunogenicity. In addition, G1 was well tolerated in mice, promoted tumor regression, enhanced the efficacy of programmed cell death protein-1 targeted immune therapy, and prolonged survival.⁷²

PDAC is associated with severe tissue fibrosis or desmoplasia, which provides a distinct microenvironment that regulates pancreatic tumor behavior, including its ability to progress and metastasize, as well as its resistance to drugs.⁹⁸ Therefore, tumor stroma is not a bystander in PDAC evolution, and targeting the stromal tissue may open up a promising option for PDAC therapy. Cortes et al⁹⁹ demonstrated that tamoxifen

regulated peri-tumoral stromal remodeling and the fibro-vascular tumor microenvironment in PDAC tissues via the GPER/hypoxia-inducible factor-1 alpha (HIF-1 α) axis. Another study by Cortes et al indicated that tamoxifen suppressed myofibroblastic differentiation of pancreatic stellate cells via GPER/RhoA signaling and lowered collagen deposition and macrophage infiltration in the tumor microenvironment.¹⁰⁰ These findings highlight the potential of GPER as an effective mechanoregulator of the tumor microenvironment in PDAC.

In summary, the current evidence suggests that GPER may be an important cancer suppressor in PDAC. G1 and tamoxifen may provide novel avenues for PDAC therapeutics. Clinical trials are needed to verify the clinical utility of GPER as a useful prognostic indicator and therapeutic target for PDAC.

GPER in Colorectal Cancer (CRC)

Colorectal cancer (CRC) is one of the most common cancer types worldwide.¹ In China, an estimated 376,300 (215,700 males; 160,600 females) new cases of CRC and 191,000 (111,100 males; 80,000 females) deaths were reported in 2015.² Although the incidence and mortality of women are lower than those of men, the role of estrogen in colorectal cancer remains controversial.¹⁰¹ Despite advances in multimodal therapies, the survival of patients with advanced CRC remains poor. Identifying reliable biomarkers is beneficial for improving the prognosis of CRC.

GPER expression in CRC tissues was significantly lower than that in matched adjacent normal tissues, and patients whose tumors expressed less GPER had a poor prognosis.¹⁰² In addition, GPER expression in CRC cells and clinical tissues is downregulated by DNA promoter methylation and histone H3 acetylation.¹⁰² The activation of GPER by G1 inhibits proliferation, induces cell cycle arrest, increases mitochondrial-related apoptosis, and elevates endoplasmic reticulum stress in CRC cells via multiple intracellular signaling pathways, including reactive oxygen species/ERK1/2, IkappaB kinase/inhibitor of nuclear factor- κ B (NF- κ B), and glycogen synthase kinase-3 β (GSK-3 β)/NF- κ B.¹⁰² ER β is the predominant estrogen receptor in normal colonic epithelium, and the decline in ER β expression paralleled the dedifferentiation of malignant colon cells.^{103,104} Estrogen may have a protective effect depending on the expression of ER β .¹⁰³ Although ER β is frequently lost in the hypoxic microenvironment as CRC malignancy progresses,

hypoxia induces the expression of GPER in CRC cells.¹⁰⁵ Bustos et al¹⁰⁵ found that E2 treatment, through the action of GPER, suppressed CRC cell migration and proliferation in normoxia but enhanced them in hypoxia. This finding was consistent with the repression or enhancement of HIF-1 α and vascular endothelial growth factor A expression under normoxic and hypoxic conditions, respectively. It appears that the interpretation of the role of E2 in CRC progression is complicated by the relative expression levels of estrogen receptor isoforms and the action of GPER under varying ambient oxygen tension. A cohort study showed that GPER expression was associated with poor relapse-free survival in female patients with stage 3 and 4 CRC, but not in male patients with matched stages.¹⁰⁵ Local estrogen may stimulate the development of CRC.⁷⁰ GPER stimulation, through E2 and G1, increased CRC steroid sulfatase (STS) activity, which could hydrolyze estrone sulfate (E₁S) and promote CRC cell proliferation, suggesting that HRT (primarily consisting of E₁S) may lead to undesired effects in patients with CRC.^{106,107} Tamoxifen and ICI 182780 also enhanced STS activity via GPER activation, indicating that these agents could play negative roles in CRC development and progression.¹⁰⁶ Additionally, GPER activation further upregulated FASN expression in colorectal LoVo cancer cells via ERK/c-fos/AP-1 signaling.⁹²

The precise role of GPER in CRC is currently ill-defined, which may result from variations in cell and animal models under different experimental conditions and protocols. On the other hand, the complex cross-talk between GPER and the genomic actions of estrogen may lead to ambiguous results. In addition, the role of GPER in CRC may change depending in part on the aerobic/anoxic conditions of the local tumor microenvironment. Even so, GPER is a significant mediator of CRC progression. Further studies are required to explore the factors influencing GPER exerting function in CRC.

Conclusion

Clinical and experimental data have shown that GPER signaling plays an important role in digestive system carcinomas. Taken together, GPER is involved in many cellular processes, including proliferation, apoptosis, migration, invasion, vascularization, inflammation, immunogenicity, microenvironment, cell cycle regulation, endoplasmic reticulum stress, EMT, estrogen metabolism, and fatty acid regulation in digestive system carcinomas. However, while being a well-established tumour suppressor in

pancreatic cancer, the role of GPER in other digestive system carcinomas is currently controversial. The possible reasons include the following: First, the role of GPER varies considerably at different stages of tumor development. Second, the biological effect of GPER is closely related to oxygen levels in cancer cells. Third, GPER may show diverse mechanisms in different research objects and conditions. Fourth, the complexity of the physiological effects of estrogen and potential cross-talk among various steroid receptors may affect the accurate interpretation of GPER. Differentiating the molecular and phenotypic subgroups of individuals may be essential to pinpoint the contributions of GPER in digestive system carcinomas. Further studies are needed to elucidate the relative molecular mechanisms and regulatory networks of GPER in digestive system carcinomas to develop prevention, diagnostic, and therapeutic strategies. Finally, the information related to the role of GPER in pancreatic cancer indicated that GPER may serve as an effective predictor and therapeutic target for this highly malignant disease.

Abbreviations

AKT, protein-serine-threonine kinase; AP-1, activator protein 1; BMP6, bone morphologic protein-6; cAMP, cyclic Adenosine monophosphate; CRC, colorectal cancer; EGFRs, epidermal growth factor receptors; EMC, energy metabolic coupling; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; ER, endoplasmic reticulum; ER α , estrogen receptor alpha; ER β , estrogen receptor beta; E₁S, estrone sulfate; FASN, fatty acid synthase; GC, gastric cancer; GPCRs, G protein-coupled receptors; GPER, G protein-coupled estrogen receptor; GPR30, G protein-coupled receptor 30; GSK-3 β , Glycogen Synthase Kinase-3 β ; GTP, guanosine triphosphate; HB-EGF, heparin-binding EGF-like growth factor; HCV, hepatitis C virus; HIF-1 α , hypoxia-inducible factor-1 alpha; HCC, hepatocellular carcinoma; HSCs, hepatic stellate cells; MMPs, matrix metalloproteinases; NF- κ B, nuclear transcription factor- κ B; PDAC, pancreatic ductal adenocarcinoma; PERK, protein kinase R-like ER kinase; PI3K, phosphatidylinositol 3-kinases; PLC, primary liver cancer; RhoA, GTPase Ras homolog family member A; SphK, sphingosine kinase; Src, Src-like nonreceptor tyrosine kinases; STS, steroid sulfatase.

Data Sharing Statement

The authors confirm that the data used to support the findings of this study are available from the corresponding author upon request.

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Disclosure

The authors declare no conflicts of interest.

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