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Review

The G Protein-Coupled Estrogen Receptor GPER in the Development and Progression of Cancer

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Abstract: The high incidence of cancer and the prevalence of chemoresistance are serious problems worldwide, underscoring the urgency of novel research focused on understanding the underlying mechanisms and finding new therapeutic targets. Recently, the G protein-coupled estrogen receptor (GPER) has received increasing attention, and it has been studied in various models, including physiological and pathological conditions, using appropriate pharmacological and molecular biological strategies. Numerous studies indicate that GPER plays an important role in cancer progression and resistance. This review focuses on the structure of GPER, the diversity of its ligands and GPER-activated signaling pathways, the role of GPER in cancer progression, and mechanisms of chemoresistance, with special emphasis on different cancer types and the tumor microenvironment. GPER was evidenced to exhibit conformational plasticity and different ligand binding modes. Therefore, GPER-mediated effects can be triggered by estrogens or various estrogen mimetics, including synthesized compounds, licensed drugs, or exogenous environmental compounds. We found multiple reports evidencing that GPER is differentially expressed in healthy tissues and tumors and plays a protumor role in breast, ovarian, lung, thyroid, and endometrial cancers. Additionally, there are several studies that indicate that GPER expression in cells of the tumor microenvironment may also contribute to cancer progression. Among the major mechanisms of GPER-mediated chemoresistance are the epithelial-mesenchymal transition, the overexpression of multidrug resistance pumps, and autophagy regulation.

Keywords: GPER; cancer; chemoresistance; tumor microenvironment; GPER ligands; estrogen mimetics

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1. Introduction

Estrogens play an important role in the proliferation, differentiation, and cell growth of multiple tissues, particularly those dependent on hormones. Disrupted regulation of these hormones and their receptors has been linked to multiple diseases [1]. The physiological role of estrogens has been studied for several decades, with a conventional understanding that they only exert their effects through nuclear estrogen receptors α (ER-α) and β (ER-β). It was not until the 1990s that a G-protein-coupled receptor (GPCR) concomitantly expressed with ER-α was first described [2]. This receptor, a member of the seven transmembrane receptor (7TMR) family, is now known as the G protein-coupled estrogen receptor (GPER, GPER1, or GPR30).

GPER can mediate both immediate cell signaling and transcription-related events [3,4]. Its expression has been reported either alone or co-expressed with nuclear ERs, where it mediates opposite responses to those of ER-α. Remarkably, in tissues devoid of nuclear ERs, GPER can replicate the same effects as nuclear ER, despite disparities in the mechanisms of action between nuclear and membrane receptors. For example, in SKBr3 breast cancer

cells that do not express the nuclear ER receptor, GPER has been shown to inhibit cell proliferation, an effect typically caused in cells expressing nuclear ERs by traditional ligands such as E2 [5]. Nevertheless, the activation of GPER demonstrates an antiproliferative effect—an outcome contrasting with the impact of ER-α activation [6,7]. The type of response largely depends on multiple factors, such as cell type, the profile of estrogen receptors present, and their expression levels. This panorama is represented by traditional ER ligand, tamoxifen (TAM), which acts as an agonist of GPER but is an ER-α antagonist.

GPER has been demonstrated to play a pivotal role in various physiological and pathological processes across the immune, cardiovascular, endocrine, nervous, and reproductive systems [3,4]. Consequently, GPER is now recognized as a novel therapeutic target or prognostic marker in a range of pathologies, including cancer [8–12]. Here, we aim to provide a comprehensive summary of the current understanding of GPER's role in various cancer types. To better understand the diversity of GPER's modulatory effects, this review incorporates a separate chapter dedicated to GPER structure, highlighting its structural plasticity and its capacity to bind various ligands. Within the chapter addressing GPER's role in human cancers, each cancer type will be examined individually, with a focus on the differential expression of GPER in tumor cells versus healthy tissues, its subcellular localization, the biological effect of its expression or absence, activation or inhibition, as well as its implications in chemoresistance and metastatic processes. Particular attention will be paid to the role of GPER in the tumor microenvironment.

2. GPER Characteristics

2.1. GPER Structure and Binding Modes

GPER belongs to the class A (rhodopsin-like) GPCR family, and its complete amino acid sequence is known (Figure 1). It consists of 375 amino acids, corresponding to a molecular weight of 42 kDa. Due to the different levels of glycosylation present in the receptor, dimerization, and interaction with other membrane proteins, diverse molecular weights of 59, 80, and 124 kDa have been reported [13]. Although the crystallographic structure of the receptor is not available, in silico assays confirm the homology of GPER with other GPCRs, such as the chemokine receptor CXCR4 [14,15] and the β-adrenergic receptor [16]. These two protein structures are mainly used as templates for the design of molecular docking assays. For example, for the active form of the receptor, Arnatt and colleagues used the crystal structure of the β2 adrenergic receptor-Gs protein complex as a template, while for the inactive form, they used the receptor without the G protein [16].

Computational studies indicate that GPER has a ligand-binding site consisting of 73 amino acid residues [17], with a volume of 457 $Å^3$ [18]. Molecular dynamics simulations revealed that a distinctive feature of GPER is the ability to undergo various structural changes, allowing it to bind multiple ligands [18]. Moreover, the same ligand can be recognized at different binding positions according to the structural conformations of GPER. For instance, two alternative binding modes overlapping each other have been observed for the G-1 agonist within the active state of the GPER receptor. In the active state, these different binding modes correspond to two distinct orientations that the ligand can adopt when binding to GPER. In contrast, only one binding mode was described for docking GPER antagonists, G-15 and G-36, in the inactive state [16]. Furthermore, GPER possesses additional cavities to accommodate ligands larger than estradiol (E2), such as TAM and fulvestrant, which fit better than smaller E2 [18]. In the next chapter, we will describe in detail the variety of GPER ligands and their effects.

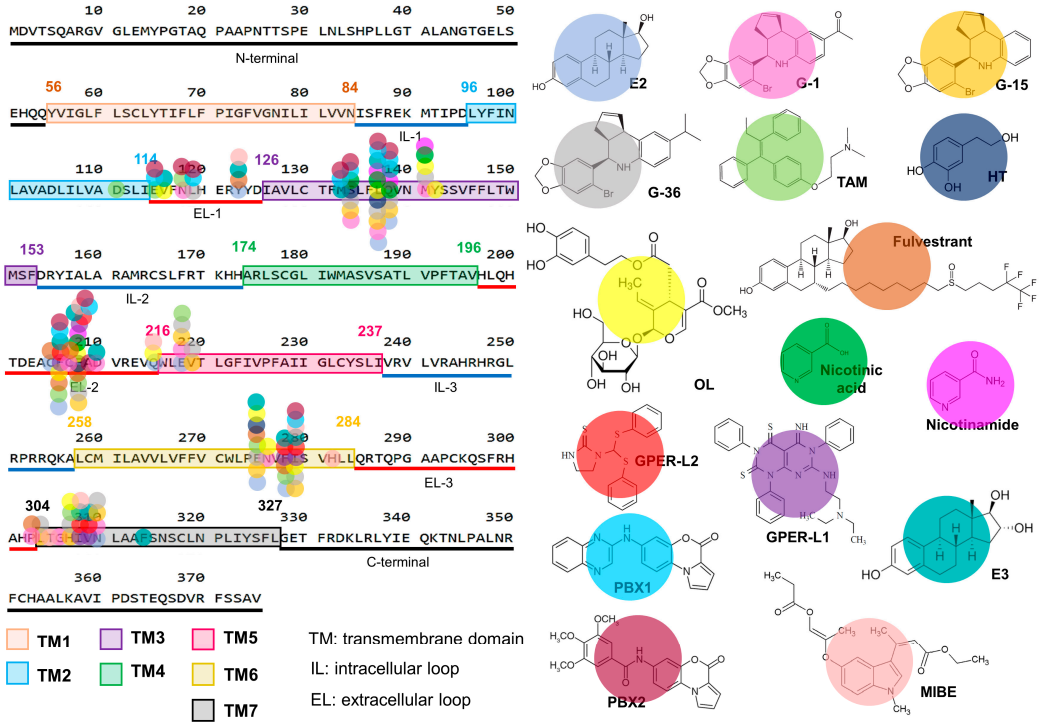


Figure 1. Sites of interaction with ligands in the amino acid sequence of GPER. The amino acid sequence corresponding to GPER was obtained from the Uniprot database (accession number: Q6FHU6). Transmembrane domains (TM1–7) are marked in different colors. The amino-terminal (N-terminal), carboxyl-terminal (C-terminal), and intra- and extracellular loops are indicated. The chemical structures of some known GPER ligands are presented in the right panel. Each ligand is assigned a specific circle that appears at the corresponding interaction site on the GPER amino acid sequence in the left panel.

2.2. GPER Ligands

According to previous studies, ligand molecules that effectively bind to GPER must possess certain chemical properties, such as the presence of aliphatic chains, which promote the affinity of the ligand for the receptor and the stability of the receptor binding site, favoring more interactions [19]. Conversely, in vitro assays have demonstrated that a larger number of hydrophilic groups in the compound impedes an adequate ligand interaction with the GPER receptor binding site [19], reducing its effectiveness [20].

To date, a large number of molecules capable of interacting with GPER have been described, which is likely due to GPER conformational plasticity. The most studied ligands include the endogenous E2 and the first reported synthetic ligands, the agonist G-1 and the antagonists G-15 and G-36 [21–23]. The mentioned compounds are considered to be canonical ligands because they were traditionally considered to be able to interact with the receptor.

Recently, there has been a growing discovery of compounds from diverse sources and with different characteristics that can interact with GPER, serving as either agonists or antagonists. These newly described compounds are often classified as “non-canonical” ligands. The name is given because previously they were not classified as classical ligands, although the effects of canonical and non-canonical ligands may overlap to some extent.

In the following sections, we describe how representative canonical and non-canonical ligands interact with the GPER receptor. We will exclusively present results where the interaction with GPER has been verified through molecular biology strategies, in silico assays, ligand binding assays, or the application of anti-GPER antibodies, ensuring the reliability and confirmation of the reported findings.

2.2.1. Canonical GPER Ligands

The selective GPER agonist G-1 has a high affinity for GPER. In competitive ligand-binding assays carried out in COS7 cells transfected with GPER, ER-α, or ER-β conjugated to GFP, G-1 was reported to have a Kd = 11 nM for GPER and minimal binding to nuclear receptors ER-α/ER-β (Ki > 10 μM). Furthermore, in GPER-GFP-transfected COS7 cells, G-1 caused a slow calcium intracellular mobilization (compared to E2) but of the same magnitude with an EC50 of 2 nM [21].

G-1 has three oxygen atoms capable of forming hydrogen bonds as acceptors. The first acceptor is located in the oxygen of the acetophenone group and interacts with Asn276 [16,17,24], Cys207 [18], and Asn118 [15,16]. The hydrogen bond formed by this oxygen and Asn276 has been strongly associated with the agonist effect of G-1, where the loss of the acetyl radical or the increase in the steric volume of the compound can lead to a decrease in activity [25]; the interaction stabilizes the active state of the receptor [16]. Furthermore, interaction with the amino group of Cys207 produces structural changes in the disulfide bridge with Cys130, resulting in a conformational change in the cytoplasmic region of the transmembrane domain (TM) 3, reaching the intracellular loop 2 (IL2), which is attributed to GPER agonist properties [18].

The other two acceptors correspond to the oxygens of the 1,3-benzodioxol ring, which interacts with Asp210 [17], Gln134 [15], and Asn118 [16]. Furthermore, the nitrogen atom of the amine group is capable of forming a hydrogen bond as a donor with Glu218, Ser144, Asn310, and Ser134 [14–17], and the bromine atom maintains hydrophobic interactions with the receptor [16–18] at Leu137, Met141, Gly306, Pro303, and Asn310.

The G-1 agonist is capable of interacting with the GPER receptor in the two binding modes described above [16,18]. In binding mode I, the acetyl group of the ligand is oriented towards the extracellular domain of the binding site, and the average ligand-receptor interaction gives a binding free energy (ΔG) of approximately −8.2 kcal/mol, while when it binds in mode II, the acetyl group is oriented inward, between TM 5 and 6, obtaining a ΔG of approximately −9.5 kcal/mol. Although both binding modes activate the receptor upon interaction, mode II is thermodynamically more favorable, being up to five times more favored than mode I [16,18]. In comparison, the ΔG for GPER natural ligand E2 is −9.5 kcal/mol in binding mode I and ranges from −8 to −9.5 kcal/mol in binding mode II [16].

Although all the chemical characteristics of G-1 support its high affinity and selectivity for GPER, several biological effects have been reported in cancer models where G-1 acts independently of GPER (often referred to as off-target effects). Notably, many of these effects were also independent of the nuclear ERs, but through a truncated isoform of ER-α (ER-α66) called ER-α36 [26]. There are several independent reports indicating that G-1 is capable of modifying the structure of the cytoskeleton, particularly microtubules, in various cancers, including breast [27], ovarian cancer [28], glioma [29], and acute lymphoblastic T cell leukemia (T-ALL) [30]. The effect was likely independent of GPER. In vitro tubulin polymerization assays have shown that G-1 alters the structure of microtubules and prevents their correct assembly through direct interaction at the same site as colchicine [27]. As a result, G-1 caused cell cycle arrest, decreased cell growth, and subsequent apoptosis [27–30]. GPER-dependent and GPER-independent effects caused by G-1 have been reviewed previously [30].

Regarding G-15 and G-36, both antagonists have similar binding free energies to G-1 [18]. In SKBR3 cells, they limited the E2 and G-1-mediated calcium mobilization through GPER, with IC50s of 190 nM and 112 nM for G-15 and G-36, respectively.

These synthetic antagonists can effectively interact with GPER in their inactive state. While both compounds demonstrate selectivity for GPER, the isopropyl group present in G-36 provides a more specific antagonist profile compared to G-15. This is due to steric hindrance, resulting in less nonspecific binding to nuclear receptors [23].

Molecular docking assays showed that the isopropyl group of G-36 is oriented towards Met141, strengthening the theory that the amino acid Cys207 is necessary for the activation of the receptor [18]. Furthermore, aromatic groups of G-36 form π-π stacking interactions with

Phe208 and His307 [16], as well as hydrogen bonds with Asn310, Glu275 [16], Gln218 [17], Ser134, and Gln138 [15]. Other interactions with Leu137, Leu304, Ile279, and Val219 were also reported [17]. The interactions presented by G-15 were similar to those of G-36, except for the interaction with Met141 and Leu119 due to the absence of the isopropyl group [16–18].

Similar to G-1, E2 is capable of interacting with the GPER receptor in both binding modes. In binding mode I, E2 forms hydrogen bonds with Glu275, Cys205, Tyr123, and Asn310, in addition to interactions with the aromatic residues Phe206, Phe278, and Tyr123. In mode II, E2 makes hydrogen bond interactions with Glu218, Gln215, and Gln138 and hydrophobic interactions with Leu137 [18].

The residues that are part of the binding pocket and with which E2, G-1, G-15, and G-36 interact are presented in Figure 1.

While G-36 demonstrates superior antagonist properties due to its chemical characteristics, G-15 remains the most extensively documented antagonist in studies assessing the effects of G-1 or E2 through GPER. Moreover, little attention has been directed towards the effects of G-15 itself in certain cell lines, which do not consistently align with the outcomes observed from silencing GPER using molecular biology strategies. In human breast [31], gastric [32], and oral [33] cancer cell lines, G-15 (2.5–20 µM) decreased cell viability. In the HL-60 cell line, G-15 (10 µM) induced *c-fos* upregulation [34], which is one of the signaling pathways activated by GPER (described in Section 2.3); this effect was inhibited by pharmacological inhibition of extracellular-signal-regulated kinase (ERK) and phosphatidylinositol 3-kinase (PI3K). Interestingly, G-15 at a lower concentration (1 µM) increased cell viability in ovarian cancer cell lines Caov4 and Caov3, and this effect was not reproduced by GPER knockdown [35]. Furthermore, GPER silencing in Caov3 decreased basal p-ERK expression, while G-15 did not reproduce such an effect [35].

2.2.2. Non-Canonical GPER Ligands

The biological effects caused by some non-canonical ligands in human cancer cell lines are summarized in Figure 2 and Table 1.

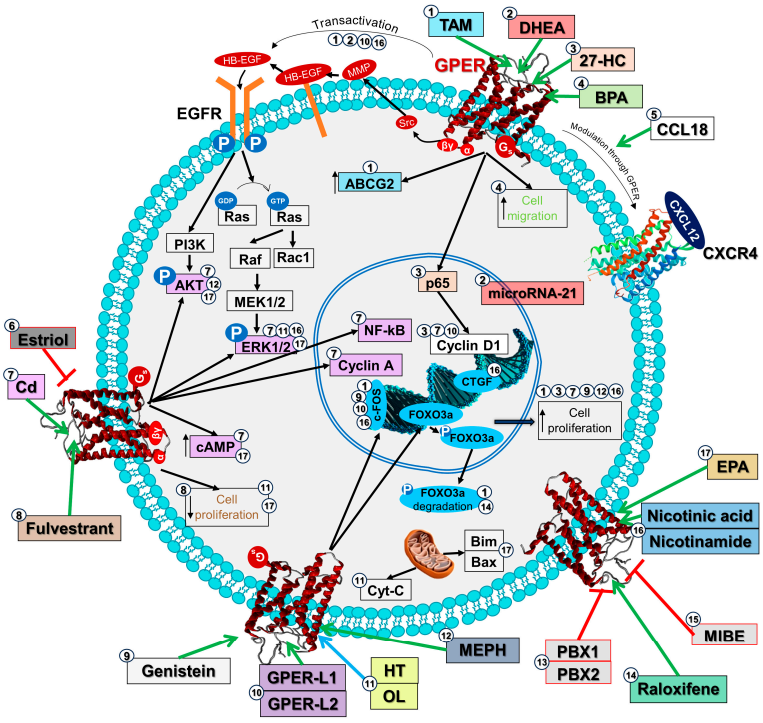


Figure 2. Biological effects and activation pathways of non-canonical GPER ligands. Agonists are connected to GPER by a green arrow, while antagonists' inhibition are indicated by a red. Each ligand is assigned a number that appears in the corresponding signaling pathway activated by that ligand, as well as in the box with the biological effect into which those pathways are translated.

Table 1. Non-canonical GPER ligands.

Ligand	Model	Biological Effect	Reference
4-OHTAM	MDA-MB-435 and HCC1806 (triple-negative breast cancer) cell lines	Increased cell numbers, caused transactivation of EGFR and *c-fos* expression through GPER [a]	[36]
	WRO, FRO, and ARO (thyroid cancer) cell lines	Increased cell proliferation and *c-fos* expression through GPER [a]	[37]
	RL95-2 and HEC-1A (endometrial adenocarcinoma) cell lines	Increased cell growth, cyclin D1 expression, and EGFR transactivation through GPER [a]	[38]
	Ishikawa and RL95-2 (endometrial adenocarcinoma) cell lines	Induced cell migration and increased phosphorylated FAK levels through GPER [a]	[39]
27-HC	MDA-MB-231 (breast cancer) cell line	Increased cell proliferation and induced p65 nuclear translocation through GPER [a,c]	[40]
BPA	MDA-MB-231 (breast cancer) cell lines	Increased the migration of MDA-MB-231 cells through GPER [a]	[41]
Cadmium	WRO and FRO (thyroid cancer) cell ines	Induced cell proliferation, migration, invasion, ERK and AKT activation, nuclear NF-kB, secretion of IL-8, and cyclin A and D1 expression through GPER [a]	[42]
	SKBR3 (breast cancer) cell line	Induced cell proliferation, stimulation of cAMP production, and ERK signaling pathway through GPER [d]	[43]
CCL18	Primary pre-B ALL samples; Nalm-6 (ALL) cell line	Through interaction with GPER [b] increased its expression Modulator of CXCR4-dependent responses	[44]
DHEA	HepG2 (hepatocellular carcinoma) cell line	Induced microRNA-21 transcription and EGFR transactivation through GPER [a]	[45]
EPA	ES2 and SKOV3 (ovarian cancer) cell lines	Decreased cell proliferation, induced cell apoptosis, increased p-AKT, p-ERK, pro-apoptotic Bim and Bax proteins, PKA activity, and cAMP expression through GPER [a]	[46]
ERα17p	MDA-MB-231 (breast cancer) cell lines	Decreased cell proliferation through GPER [e,f]	[47,48]
Estriol	SKBR3 (breast cancer) cell line	GPER [c,e] antagonist. Avoid GPER [a] activation (with G-1 and 4-OHTAM) effects: c-fos, p-ERKand CTGF expression, cell proliferation	[49]
Fulvestrant	MCF-7 (breast cancer) cell line	Decreased cell proliferation through GPER [a]	[50]
Genistein	WRO, FRO, and ARO (thyroid cancer) cell lines	Increased cell proliferation and c-fos expression through GPER [a]	[37]
GPER-L1 GPER-L2	SKBR3 (breast cancer) and Ishikawa (endometrial cancer) cell lines	Increased cell growth, caused cyclin D1 protein induction and p-ERK and c-fos expression through GPER [a,e]	[51]
HT	SKBR3 (breast cancer) cell line	GPER [c,e] inverse agonist. Decreased cell viability, increased p-ERK1/2 levels and Cyt-c cytosolic release through GPER [a].	[52]
MEHP	HeLa and SiHa (cervical cancer) cell lines	Increased cell proliferation and p-AKT and nuclear localization through GPER [a]	[53]
MIBE	SKBR3 (breast cancer) cell line	GPER [c,e] antagonist. Avoid GPER activation (with E2) effects: EGFR transactivation, cell proliferation, c-fos, and CTGF expression	[54]
Nicotinic acid Nicotinamide	SKBR3 (breast cancer) cell line and CAFs from breast cancer patients	Increased cell growth, migration, p-ERK1/2, c-fos and CTGF expression through GPER [a,c,e] in cells that do not express nicotinic acid receptor	[55]

Table 1. *Cont.*

Ligand	Model	Biological Effect	Reference
OL	SKBR3 (breast cancer) cell line	GPER [c,e] inverse agonist. Decreased cell viability, increased p-ERK1/2 levels, and Cyt-c cytosolic release through GPER [a].	[52]
PBX1 PBX2	SKBR3 (breast cancer) cell line and CAFs from breast cancer patients	GPER [c,e] antagonist. Avoid GPER activation (with E2 and G-1) effects: cell growth, EGFR transactivation, p-ERK, *c-fos*, and *CTGF* expression	[56]
PLMI	MDA-MB-231 (breast cancer) cell lines	Decreased cell proliferation through GPER [e,f]	[47,48]
Raloxifene	MCF-7 (breast cancer) cell line	Induced FOXO3a inactivation through GPER [a]	[57]
TAM	MCF-7 (breast cancer) cell line	Induced FOXO3a inactivation through GPER [a]	[57]
	MCF-7 (breast cancer) wild-type and TAM-resistant cell lines	Increased cell proliferation and caused transactivation of EGFR through GPER [a] Increased GPER translocation to the cell surface	[58]
	TAM-resistant MCF-7 (breast cancer) cell line	Caused ABCG2 upregulation, increased p-ERK and p-AKT levels, and caused EGFR transactivation through GPER [a]	[59]
	HEC-1A (endometrial adenocarcinoma) cell line	Increased cell proliferation through GPER [a]	[60]
	TAM-resistant MCF-7 (breast cancer) cell line	Induced β1-integrin expression through GPER [a] and EGFR	[61]

[a] Interaction was confirmed by GPER silencing. [b] Interaction was confirmed by antibodies against GPER that abolished ligand binding. [c] Interaction was confirmed by ligand binding assays. [d] Interaction was confirmed in cells that expressed an interfering mutant of GPER. [e] Interaction was confirmed by molecular docking assays. [f] Interaction was confirmed by the GPER knockout. 27-HC: 27-hydroxycholesterol; 4-OHTAM: 4-hydroxytamoxifen; AKT: also known as protein kinase B (PKB); ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; BPA: bisphenol A; CAFs: cancer-associated fibroblast; cAMP: cyclic adenosine monophosphate; CTGF: connective tissue growth factor; Cyt-c: cytochrome c; DHEA: dehydroepiandrosterone; E2: 17β-estradiol; EGFR: epidermal growth factor receptor; EPA: eicosapentaenoic acid; ERα17p: ER-α-derived peptide PLMIKRSKKNSLALSLT; ERK: extracellular signal regulated kinase; FAK: focal adhesion kinase; HT: hydroxytyrosol; MEHP: mono-2-ethyhexyl phthalate; PLMI: ERα17p-derived peptide; TAM: tamoxifen.

The most studied non-canonical GPER modulator is TAM, classically used as an ER-α antagonist in the treatment of breast cancer positive for ER-α. TAM is also a GPER agonist, which in its most metabolically active form (4-OHTAM) was shown to be capable of transactivating the epidermal growth factor (EGF) receptor (EGFR), leading to increased expression of c-fos [36,38], cyclin D1 [38], and focal adhesion kinase (FAK) [39], as well as increased cell growth [36–38] and migration [39]. Similar, TAM increased cell proliferation [58,60], caused EGFR transactivation [58,59,61], and GPER translocation to the cell surface [58], as well as induced ATP binding cassette subfamily G member 2 (ABCG2), p-ERK and p-AKT (also known as protein kinase B) upregulation [59], and FOXO3a inactivation. The same effect on FOXO3a inactivation was replicated by raloxifene [57]. These pathways activated by TAM (mainly EGFR transactivation, ABCG2 upregulation, and GPER translocation to the plasma membrane) are mainly associated with TAM resistance in breast cancer.

Molecular docking assays demonstrated that TAM makes hydrogen bonds with the amine moiety of Glu275 and Asp111, and the aromatic groups of TAM form π-π interactions with Phe206, Phe208, Phe278 [18], and His307 in addition to ionic interactions with Glu218 [15]. 4-OHTAM formed hydrogen bonds with Glu115 and Asn118 [15].

Fulvestrant (also known as ICI 182,780) is an anti-estrogen drug that, similar to TAM, acts as an antagonist of ERs but functions as a GPER agonist [3]. Fulvestrant was shown to decrease the proliferation of breast cancer MCF-7 cells, with the specific interaction confirmed through GPER silencing [50]. Molecular docking assays showed that fulvestrant forms hydrogen bonds with Cys205, Pro303, Cys207, Tyr123, and Glu275, as well as interactions with Phe206, Phe208, and Phe278 [18].

Some endogenous metabolites were shown to interact with GPER. For example, the precursor hormone dehydroepiandrosterone (DHEA) is capable of transactivating EGFR

through the GPER-EGFR-ERK-c-Jun pathway, activating the transcription factor activating protein 1 (AP-1) and inducing the hepatic cancer-associated microRNA-21 [45].

Recently, an abundant cholesterol metabolite, 27-hydroxycholesterol (27-HC), was shown to interact with GPER as an agonist, increase the proliferation of MDA-MB-231 cells, induce p-ERK, and induce the nuclear translocation of p65. The specific interaction with GPER was confirmed by ligand binding assays, GPER knockdown for cell proliferation and p65 assays, and G-15 for p-ERK evaluation [40].

GPER appears to be able to act as a fatty acid receptor since eicosapentaenoic acid (EPA), through GPER, increased the levels of p-AKT, p-ERK, the pro-apoptotic Bim and Bax proteins, PKA activity, and cAMP expression, decreased cell proliferation, and induced apoptotic cell death in ovarian cancer cell lines [46].

Estriol (E3), a derivative of E2 and a natural activator of ERs, was also shown to be a natural antagonist of GPER, as it efficiently inhibited the expression of c-fos, p-ERK, and connective tissue growth factor (CTGF), as well as cell proliferation induced by G-1 and 4-OHTAM in the ER-negative SKBR3 breast cancer cells. Molecular docking assays showed that E3 accommodates in the ligand binding pocket by interacting with Val116, Met133, Leu137, Phe206, Phe208, Phe278, Ile279, Ile308, Val309, and Phe314 through Van der Waals forces and forming hydrogen bonds with Tyr123, Gln138, Asp210, and Glu275 [49].

Homeostatic chemokine C-C motif chemokine ligand 18 (CCL18) is considered an important regulator of cell homing and migration, and its expression is up-regulated in different pathophysiologic conditions, including inflammation and cancer [62]. Although a specific CCL18 receptor has not yet been identified, some reports suggest that GPER is likely able to bind it, triggering signals distinct from those induced by its interaction with E2 [44,63]. In a model of pre-B ALL, CCL18 was shown to attenuate CXCL12-induced activation of leukemic Nalm-6 cells, as evaluated by calcium mobilization, chemotaxis, proliferation, and pseudo-emperipolesis [44]. Importantly, direct interactions of CCL18 with specific CXCL12 receptor CXCR4 were excluded, but anti-GPER antibodies abolished observed CCL18 effects. CCL18 did not cause changes in CXCR4 but in GPER expression. CCL18 interaction with GPER prevented the increase in intracellular calcium produced by the interaction of GPER with its specific agonists G-1 or E2 [44].

The phenolic compound of natural origin, oleuropein, and its metabolite, hydroxytyrosol, were shown to act as GPER inverse agonists in ER-negative and GPER-positive SKBR3 cells. Both phenols reduced cell growth and viability, increased p-ERK1/2 levels, and increased the release of cytochrome c (Cyt-c) from mitochondria to cytosol. The cytotoxic effect was abolished by GPER silencing. Ligand-binding experiments and in silico simulations also evidenced that oleuropein and hydroxytyrosol are able to bind GPER. Oleuropein forms hydrogen bonds with Tyr142, Gln216, Glu275, Asn276 and His307 and maintains hydrophobic interactions with Val116, Leu137, Met141, Phe206, Phe208, and Ile279. HT interacted with Ser134 and Glu275 through hydrogen bonds, hydrophobic interactions with Leu137, and π-π stacking with Phe208 [52].

Genistein is an isoflavone derived from soy that has been identified as a possible anticancer agent by inducing cell death and reducing metastasis [64]; however, little has been proven about its mechanisms of action through GPER. In this regard, Vivacqua and co-authors [37] demonstrated that in thyroid cancer cell lines, genistein increased cell proliferation and c-fos expression through GPER.

Different exogenous environmental substances were also shown to interact with GPER and trigger cellular responses. Bisphenol A (BPA), a synthetic plasticizer used in the production of polycarbonate domestic containers, was reported to exert endocrine disruptor actions binding to both nuclear ERs and GPER and has been attributed the ability to generate chemoresistance in several hormone-related cancers [65]. BPA was reported to increase levels of phosphorylated FAK, protein tyrosine kinase (Src), and ERK levels and reduce MDA-MB-231 migration and invasion without affecting cell viability, but the specific effect of BPA on GPER was confirmed only in the migration assay [41]. Like BPA, phthalates are used in the production of household plastics. Mono-2-ethyhexyl phthalate

(MEHP) through GPER increased proliferation in cervical cancer cell lines (HeLa and SiHa), p-AKT expression, and its nuclear localization [53].

Another endocrine disruptor, cadmium (Cd), has been shown to modify the expression of hormone receptors and be involved in the development of metabolic diseases [66,67]. Cd appears to have agonistic effects on GPER, as demonstrated in thyroid and breast cancer cell lines [42,43]. In GPER-positive thyroid cancer cell lines, WRO and FRO Cd stimulated the activation of the GPER/ERK and AKT/NF-KB pathways, the secretion of interleukin 8 (IL-8), and the expression of cyclins A and D1, which in turn induce proliferation, migration, and invasion of tumor cells [42]. The involvement of GPER was confirmed by experiments in which Cd-induced effects were suppressed either by specific GPER inhibitors or by GPER knockdown. Similarly, Cd induced proliferation in the breast cancer cell line SKBR3 through activation of cyclic AMP (cAMP) production and triggering the ERK signaling cascade [43]. The effect was likely GPER-dependent since it was significantly attenuated in SKBR3 cells stably expressing the GPER interfering mutant [43].

Nicotinic acid (niacin) and its amide form, nicotinamide, were able to activate classical GPER pathways, including increased p-ERK1/2, c-fos, and CTGF expression, as well as increased cell growth in the SKBR3 breast cancer cell line and in cancer-associated fibroblasts (CAFs). The specific action through GPER was confirmed by GPER silencing, ligand binding assays, and molecular docking assays; furthermore, SKBR3 cells do not express any isoforms (GPR109A and GPR109B) of the nicotinic acid receptor. Molecular docking showed that nicotinic acid makes two hydrogen bonds with Ser134 and one with Gln138, as well as interactions with Leu137, Met141, Met309, and Phe208; nicotinamide interacts with the same amino acid residues except for one of the hydrogen bonds with Ser134 [55].

Two newly synthesized GPER agonists, GPER-L1 and GPER-L2, were demonstrated to specifically activate the receptor, causing induction of cyclin D1, p-ERK, and c-fos expression, which ultimately results in increased SKBR3 and Ishikawa cell growth. Both agonists interacted through π-π stacking with Phe206 and Phe208 and formed hydrophobic interactions with Phe278, Ile279, Ile308, and Val309 [51]. The same authors also synthesized a potent GPER antagonist, MIBE, whose effect was verified by inhibiting the signaling pathways activated by E2 in the ER-negative SKBR3 cell line; namely, MIBE prevented EGFR transactivation, cell proliferation, c-fos, and CTGF expression. Amino acid moieties Tyr123, Gln215, and His282 formed hydrogen bonds with MIBE, in addition to Van der Waals interactions with Phe208, Ile279, Thr305, and Ile308, and π-π stacking interactions with Phe208 [54].

Other synthetic GPER-specific antagonists PBX1 and PBX2 have been shown to prevent cell growth, EGFR transactivation, p-ERK, *c-fos*, and *CTGF* expression caused by G-1 and E2 in breast cancer cells and CAFs. Molecular docking assays showed that PBX1 forms hydrogen bonds with Glu115, Ser134, and Gln138 and hydrophobic interactions with Leu119, Met133, Leu137, Phe206, Phe208, and Ile279. PBX2 retains the interaction with the same amino acids, adding a hydrogen bond with Asn118 and a hydrophobic contact with Ala209 [56].

Peptide ERα17p is a derivative of the ERα receptor, whose amino acid sequence corresponds to the Pro295–Thr311 region. ERα17p has been shown to act as an inverse agonist of GPER [48]. This peptide decreased the proliferation of MDA-MB-231 cells through GPER. The same biological effect was caused by the N-terminal short synthetic tetrapeptide, formed by Pro295-Leu296-Met297-Ile298 (PLMI) of ERα17p, which is accommodated within the extracellular GPER ligand-binding site and shares some structural similarities with the GPER antagonist PBX1 [47,48]. The N-terminal Pro295 of ERα17p and PLMI forms a hydrogen bond with either the Gln138 or Ala209, hydrophobic interactions with Pro192, and the C-terminal Ile298 points towards Ile279 [68].

Collectively, the data presented here demonstrate that GPER can accommodate various ligands of different chemical compositions and origins, encompassing both endogenous

metabolites and exogenous compounds. These ligands have the potential to significantly impact a range of physiological and pathophysiological processes.

Furthermore, this underscores the importance of assessing the effects of both canonical and non-canonical GPER ligands using appropriate molecular biology strategies. Additionally, the use of specific antagonists is crucial to preventing misinterpretation.

2.3. GPER Signaling Pathways in Cancer Cells

The mechanisms of action described for the GPER receptor are very diverse. It is known that GPER is coupled to a G_s protein and that activation of the receptor causes the $\beta\gamma$ dimer to transactivate EGFR by releasing heparin-bound EGF (HB-EGF) from the cell membrane, in a manner dependent on extracellular matrix metalloproteinases (MMP) and Src [69,70]. Activation of EGFR can trigger various signaling cascades, including: (1) the RAS/RAF-MEK-ERK MAPK pathway related to cell proliferation and differentiation; (2) the PI3K-AKT/PKB-mTOR pathway that regulates proliferation and metabolism; (3) the PLC-γ1-PKC pathway regulated signal transduction pathways; (4) the JNK/C-Jun pathway involved in apoptosis, inflammation, and metabolism; and (5) the JAK-STAT pathway related to signal transduction [71–74].

The GPER-dependent regulation of ERK 1/2 occurs through stimulation of adenylate cyclase (AC) and an increase in cAMP, which in turn produces the inactivation of Raf-1 [75]. In some models, GPER activation stimulated IL-8 secretion through activation of the AKT and ERK pathways and nuclear NF-kB translocation [42,76].

One of the most reported effects of GPER-dependent ERK 1/2 activation in cancer cells is the induction of *c-fos* expression [36,37,49,51,55,56,77–79]. This proto-oncogene encodes a DNA-binding protein domain and dimerizes with c-Jun to form the transcription factor AP-1, which regulates genes involved in metastasis, proliferation, differentiation, and survival [80,81].

Another GPER-induced response is FOXO3a inactivation [57]. FOXO3a is a member of the forkhead box (FOX) transcription factor family and is traditionally considered to mediate the expression of target genes involved in apoptosis, proliferation, cell cycle progression, survival, and DNA damage. FOXO3a is phosphorylated through the PI3K-AKT and ERK pathways, which cause its subsequent translocation into the cytoplasm and degradation [82,83].

Furthermore, it has been discussed that GPER is capable of signaling through G_i and G_q proteins [4].

Various alternative mechanisms have also been described. In a seminoma-like TCam-2 cell line, GPER activation with E2 induced the expression of ER-α36, a truncated form of ER-α, and the effect was diminished with GPER silencing. The signaling cascade was through GPER-cAMP/PKA-CREB, where GPER activation was necessary for rapid induction of ER-α36 expression but not to maintain its elevated levels. ER-α36 was required for EGFR expression since ER-α36 silencing prevented E2-induced EGFR expression [84]. In breast cancer SKBR3 cells, GPER knockdown reduced mRNA and protein levels of ER-α36, while induced expression of GPER caused endogenous ER-α36 expression [26]. Indeed, it was determined by proximity ligand assay that E2 treatment slightly induced physical interaction between ER-α36 and GPER in SKBR3 cells, and lipopolysaccharide (LPS) stimulation caused a higher ER-α36-GPER interaction. This treatment was shown to induce nuclear GPER translocation, its co-localization with NF-kB, and the possible formation of an ER-α36-GPER-NF-kB complex, inhibiting NFκB-mediated inflammation [85].

2.4. GPER Signaling Pathways in Cancer Chemorresistance

One of the greatest challenges in cancer treatment is the resistance to chemotherapy that can be developed in a cancer cell population. This section discusses the different chemoresistance mechanisms that can be mediated by GPER (Figure 3).

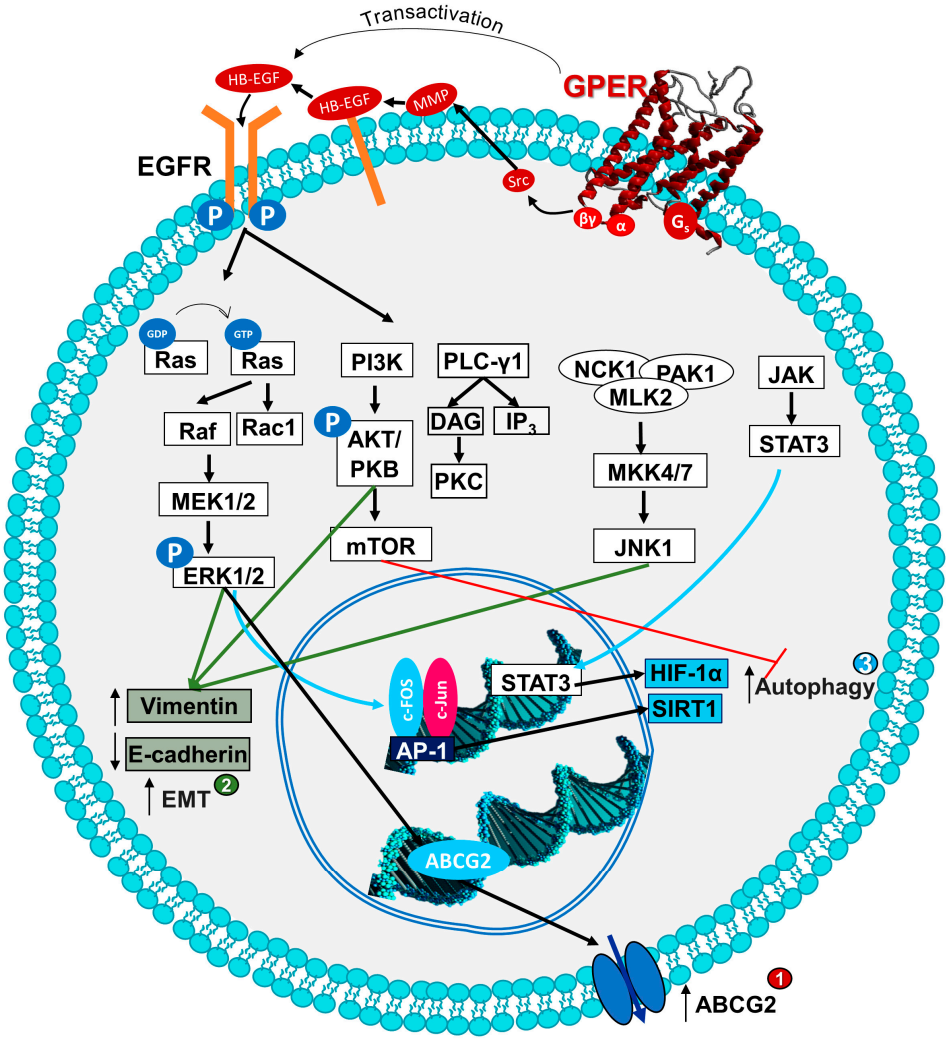


Figure 3. GPER-activated pathways related to chemoresistance. The different pathways are assigned different numbers and colors: (1) upregulation of ATP binding cassette subfamily G member 2 (ABCG2; black arrows), (2) favoring the epithelial–mesenchymal transition (EMT; green arrows), and (3) induction of autophagy (blue arrows). Autophagy inhibition by mTOR is indicated in red.

Yu and colleagues described a model of TAM-resistant breast cancer cells in which GPER activation by TAM induced EGFR transactivation and activation of the ERK 1/2 pathway, leading to an overexpression of ABCG2 and its AKT-dependent localization in the membrane, causing the extrusion of the chemotherapeutic agent doxorubicin [59].

It is well known that the epithelial–mesenchymal transition (EMT) in cancers is highly associated with metastasis and chemoresistance since the cancer cell acquires phenotypic characteristics that allow it to migrate and invade other tissues [86]. In breast and gastric cancer cell lines, GPER was shown to be involved in cisplatin resistance by promoting EMT [32,87,88]. Notably, GPER knockdown increased E-cadherin levels, indicative of an epithelial phenotype, and, conversely, decreased vimentin levels, characteristic of a mesenchymal phenotype [31,32,88]. This decrease in E-cadherin could occur due to the action of metalloproteinases that degrade adhesion proteins through EGFR and its kinase pathways [89]. On the other hand, in pancreatic [90] and cervical cancer cell lines [91], GPER activation inhibited EMT.

Autophagy is a third mechanism that appears to be mediated by GPER-induced transactivation of EGFR and the subsequent activation of kinase pathways. A correlation in expression of GPER and pro-apoptotic hypoxia-inducible factor (HIF-1α) has been reported [92], likely through the Janus kinase/signal transduction and transcription activation

3 (JAK/STAT3) pathway, where STAT3 at the nuclear level favors the expression of pro-autophagic genes, including HIF-1α [93]. Furthermore, GPER-dependent activation of the ERK/*c-fos*/AP-1 pathway has been reported to induce the expression of NAD-dependent sirtuin-1 deacetylase (SIRT1) through GPER [94], which is required for the induction of autophagy [95]. Finally, the PI3K-AKT/PKB-mammalian target of the rapamycin (mTOR) pathway is known to inhibit autophagy.

3. Role of GPER in Human Cancer

3.1. In Silico Studies of Different Cancer Types

Several authors have conducted in silico analysis of information available in databases to reveal the involvement of GPER in the progression of various cancers. For this purpose, most of them used the cancer genome atlas (TCGA) [29,90,96–99], gene expression omnibus (GEO) [97–99], European genome-phenome archive (EGA) [97], and oncomine [92,99] databases for GPER mRNA expression and human protein atlas [97] for GPER protein expression, as well as specific databases for breast (METABRIC) [96], stomach (TCGA-STAD) [99], and colon [100] cancer. The association between GPER mRNA expression and cancer prognosis was determined by Kaplan-Meier survival analysis [29,88,90,96,97,99–101].

Higher GPER expression was reported in lung adenocarcinomas compared with normal lung tissues; furthermore, large tumors expressed a higher level of GPER than small tumors, and GPER expression (mRNA) was correlated with NOTCH1 gene expression [92].

In contrast, lower GPER expression has been demonstrated in breast, liver, lung, stomach, uterine, kidney, thyroid, gastric, and colorectal cancers compared to their healthy counterparts [90,97–100]. Regarding survival rates and GPER expression, there are reports of both positive and negative correlations.

High GPER expression was associated with a good prognosis in female glioblastoma (GBM) patients, despite the fact that GPER expression was similar between males and females [29]. However, ER-negative breast cancer patients with high GPER expression had a shorter disease-free interval [96].

Patients with colorectal cancer who exhibit high GPER expression tend to have poorer outcomes [100]. Similarly, high GPER expression was associated with poor relapse-free survival in colorectal cancer stages 3–4, in the female population [101]. For thyroid cancer, low GPER expression was associated with metastatic lymph nodes and the B-Raf proto-oncogene (BRAF) mutation [98].

Decreased GPER in gastric cancer was associated with poor overall survival, progression-free survival, and post-progression survival [97], while high expression was associated with better overall and disease-free survival, especially in female patients [99]. Contrary to this, other authors reported that tumors with increased GPER expression had worse overall survival [88].

In conclusion, the role of GPER in cancer progression seems to be largely dependent on its expression level, site of localization, and cancer type, as shown in Figure 4 and Table 2.

In subsequent sections, we will take a closer look at experimental rather than in silico data obtained in various types of cancer.

It should be noted that for this review, we only considered those experimental works that were carried out in human models where the involvement of GPER as a mediator of biological effects was proven by receptor silencing or molecular biology strategies diminishing GPER expression.

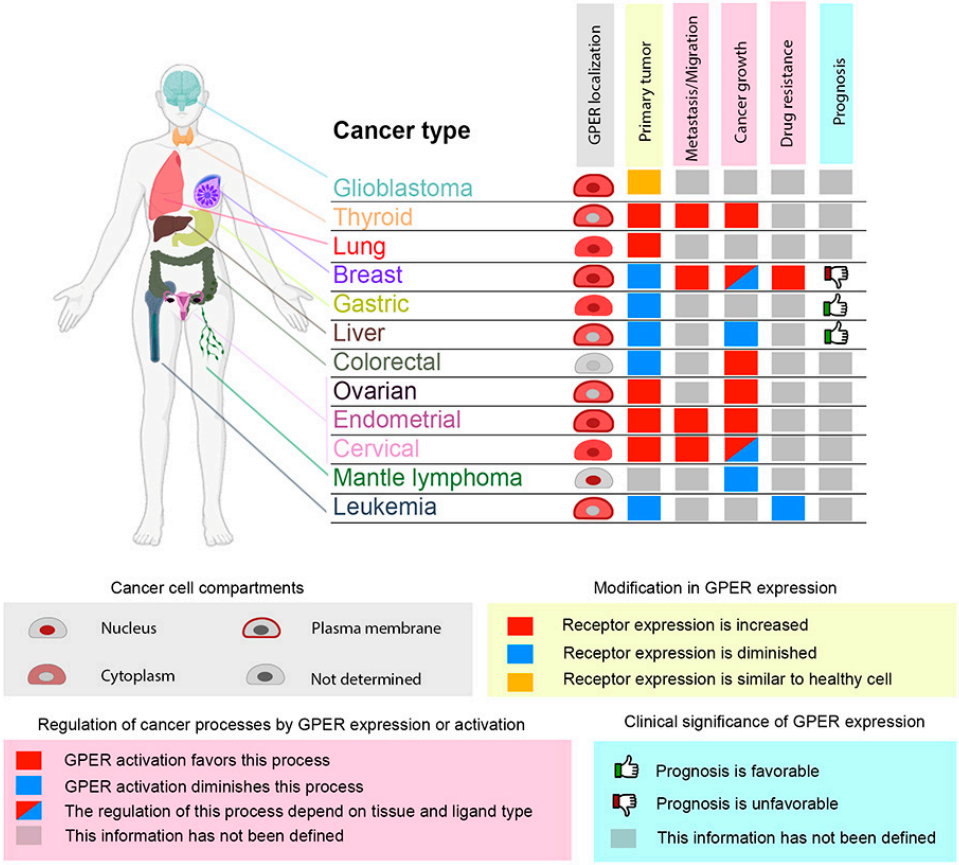


Figure 4. Role of GPER in different cancer types. For enhanced comprehension, attending to the figure code located in the lower section of the figure is strongly recommended. The "Localization" column (grey) provides a simplified depiction of cellular compartments (nucleus, plasma membrane, or cytosol), with red color highlighting confirmed GPER expression in the corresponding model (consult Table 2 for further information). In the "Primary tumor" column (yellow), GPER expression is examined for each specific cancer type. Columns highlighted in red delineate cancerous processes influenced by GPER expression or GPER activation by ligands. The blue column denotes the overall significance of GPER expression concerning the prognosis of the respective cancer type.

Table 2. GPER expression and associated function.

Type of Cancer	Model	Localization	Role in Cancer	Reference
Breast cancer (BC)	Tissue samples from early-stage invasive BC	Nucleus Cytoplasm	High nuclear GPER expression was associated with smaller tumors and a lower tumor grade Low cytoplasmic GPER expression was associated with adverse survival in BC patients treated with endocrine therapy	[102]
	Primary invasive breast carcinoma samples Normal breast tissues T47D and MCF7 cell lines	Nucleus Cytoplasm	Cytoplasmic GPER expression was associated with better OS, a low tumor stage, and a luminal A/B subtype Nuclear GPER expression was associated with poorly differentiated carcinomas and triple-negative subtype	[103]
	Tissue samples from ductal carcinoma and a normal breast	Cytoplasm	GPER expression was associated with tumor size and metastases	[104]
	Tissue samples from tamoxifen-treated primary BC	Plasma membrane Cytoplasm Perinuclear	Plasma membrane GPER expression was associated with a poorer prognosis	[105]

Table 2. *Cont.*

Type of Cancer	Model	Localization	Role in Cancer	Reference
	Tissue samples from tamoxifen-treated primary invasive BC or without tamoxifen treatment	Plasma membrane Cytoplasm Nucleus	GPER expression was associated with a shorter RFS in patients treated with tamoxifen and a favorable RFS in patients without tamoxifen treatment GPER expression is correlated with EGFR expression	[106]
	Tissue samples from tamoxifen-treated BC (metastatic BC and primary tumors)	Plasma membrane Cytoplasm	GPER expression is correlated with EGFR expression Higher GPER expression in metastatic cancer compared to primary tumor	[107]
	Tissue samples from recurred BC and primary tumors	Cytoplasm	Higher GPER expression in recurred tumors compared to primary tumors, where GPER expression had an inverse correlation with pro-apoptotic Bim protein	[108]
	Tissue samples from BC	Cytoplasm	GPER and CXCR1 expression in advanced stages of BC.	[109]
	Tissue samples from triple-negative BC	Cytoplasm	Higher GPER expression is correlated with necrosis in the cancer nest, increased metastatic events, mesenchymal-like subtypes, and worse DMFS	[110]
	Tissue samples from tamoxifen-treated BC (metastatic BC and primary tumors) Tamoxifen resistant MCF-7 cell line	N.D.	Higher GPER expression in metastatic cancer compared to primary tumors. GPR30 expression is correlated with ABCG2 expression GPER activation * (with G-1) caused ABCG2 upregulation, increased p-ERK and p-AKT levels, and caused EGFR transactivation	[59]
	BC stem cells and non-BC stem cells from patient-derived xenografts	N.D.	Higher GPER expression in BC stem cells compared to non-BC stem cells GPER silencing reduced cell growth in BC stem cells	[111]
	SKBR3 cell line	N.D.	GPER activation * (with G-1, E2) caused cell proliferation	[112]
	SKBR3 and BT-20 cell lines	N.D.	GPER activation * (with E2) increased p-ERK and p-AKT levels, migration, and IL-8 secretion	[76]
	MDA-MB-435 and HCC1806 cell lines	N.D.	GPER activation * (with E2) increased cell number, *c-fos* expression, and EGFR transactivation	[36]
	SKBR3 and MDA-MB-231 cell lines	N.D.	GPER activation * (with G-1) decreased cell viability	[6]
	MDA-MB-435 and MDA-MB-231 cell lines	N.D.	GPER activation * (with G-1) decreased cell viability, caused cell death, and caused cell cycle arrest	[7]
	MCF-7 cell line	N.D.	GPER activation * (with E2, G-1) induced FOXO3a inactivation	[57]
	MCF-7, MDA-MB-231, and Bcap-37 cell lines	N.D.	GPER inhibition * (or G-15 treatment) increased doxorubicin sensitivity and avoid doxorubicin-induced EMT	[31]
	MDA-MB-231 and HCC1806 cell lines	N.D.	GPER inhibition * decreased cell invasion and sensitized cells to tamoxifen	[113]

Table 2. *Cont.*

Type of Cancer	Model	Localization	Role in Cancer	Reference
	SKBR3 cell line and CAFs	N.D.	GPER activation * (with G-1, E2) increased *c-fos* and FASN expression through EGFR transactivation	[77]
	SKBR3 cell line	N.D.	GPER activation ** (with E2) induced cell proliferation, stimulation of cAMP production, and the ERK signaling pathway	[43]
	SKBR3 cell line and CAFs	N.D.	GPER activation * (with G-1, E2) increased cell proliferation, *c-fos* expression, and downregulated microRNA-338-3p	[78]
Cervical cancer (CC)	Tissue samples from CC tumors, healthy tissue, and precursor lesions	Cytoplasm Nucleus	Higher cytoplasmic and nuclear GPER expression in cervical cancer compared to healthy tissue	[114]
	HeLa, SiHa, C-33A and CaSki cell lines Tissue samples from normal cervical epithelial cells	N.D.	GPER activation * (with G-1) decreased cell viability, caused cell cycle arrest, and caused EGFR transactivation	[115]
	HeLa, SiHa, and C-33A cell lines	N.D.	GPER inhibition * increased stem cell properties and invasive behavior; enhanced EMT	[91]
	Surgical specimens from cervical adenocarcinoma patients HCA1 cell line	N.D.	Co-expression of GPER and claudin-1 is correlated with a poor prognosis GPER activation * (with G-1) increased claudin-1 expression	[116]
Colorectal cancer (CRC)	Tissue samples from CRC tumors and adjacent normal tissues	N.D.	Lower GPER expression in CRC compared to normal tissues Low GPER expression was associated with a poorer survival rate	[117]
	HT-29, DLD-1, and HCT116 cell lines	N.D.	GPER activation * (with G-1, E2) decreased ATM; under normoxic conditions, decreased cell proliferation, migration, VEGFA, and HIF1-α expression; and increased them in a hypoxic environment	[101]
	LoVo cell line	N.D.	GPER activation * (with G-1, E2) increased *c-fos* and FASN expression through EGFR transactivation	[77]
	HCT116 cell line Tissue samples from CRC tumors and matched normal tissues	N.D.	GPER activation * (with G-1, E2) induced cell proliferation GPER expression is correlated with CTGF expression	[100]
Endometrial cancer (EC)	Endometrial tissues from patients with BC treated or not with tamoxifen	Nucleus Cytoplasm	GPER expression is correlated with the time of tamoxifen treatment and the development of an endometrial abnormality Mostly expressed in abnormal endometrial tissue of patients treated with tamoxifen	[60]
	Endometrial tissues from patients with BC treated or not with tamoxifen	Plasma membrane Cytoplasm	Higher GPER in expression EC tissue of patients treated with tamoxifen, which had a worse prognosis	[38]

Table 2. *Cont.*

Type of Cancer	Model	Localization	Role in Cancer	Reference
	Tissue samples from uterine EC KLE and RL95-2 cell lines	Plasma membrane Cytoplasm	Higher GPER expression in uterine EC compared to normal tissues GPER inhibition * decreased cell growth. GPER activation * (with E2, G-1) increased cell viability	[118]
	Tissue samples from the uterine EC	Subcellular	GPER expression correlated with EGFR expression but negatively with PR GPER overexpression was associated with poorer survival	[119]
	Hec50 cell line	Cytoplasm	GPER activation * (with E2)-induced PI3K activation	[120]
	Tissue samples from EC tumors Ishikawa and RL95-2 cell lines	N.D.	GPER expression is correlated with pFAK expression GPER activation * (with E2 and G-1) induced cell migration and increased pFAK levels	[39]
	Tissue samples from endometrial adenocarcinoma tumors and normal endometrium HEC-1A, HEC-1B, and RL95-2 cell lines	N.D.	Lower GPER expression in endometrial adenocarcinoma compared to normal tissues. GPER expression was associated with PR and PTEN expression G-1 decreased cell viability without effect on the GPER-negative cell line	[121]
Gastric cancer (GC)	Tissue samples from GC tumors and adjacent normal gastric HGC-27, MGC-803, SGC-7901, and GES-1 cell lines	Nucleus Cytoplasm	Lower GPER expression in GC compared to normal tissues and cells Low GPER mRNA levels predict a poor prognosis	[99]
	Tissue samples from GC tumors and normal gastric AGS, SNU-216, NCI-N87, SNU-620, SNU-638, SNU-668, NUGC-3, and MKN-74 cell lines	N.D.	Lower GPER expression in GC compared to normal tissues GPER activation * (with G-1) in highly GPER-expressive cell lines decreases cell viability. Without effect in the GPER-low cell line	[122]
	AGS and BGC-823 cell lines	N.D.	GPER induces cisplatin resistance by promoting EMT GPER activation * (with G-1) reduced cisplatin sensitivity. GPER inhibition * (or G-15 treatment) increased cisplatin sensitivity	[32]
	AGS and MGC-803 cell lines	N.D.	GPER inhibition * decreased cell viability, proliferation, migration, invasion, EMT, cyclin D1, CDK4, p-PI3K, p-AKT, p-mTOR, MMP2, and MMP9 levels. Contrary effects with GPER overexpression	[88]
Glioma	U87, LN229, T98, and U251 cell lines	Cytoplasm Plasma membrane	Lower GPER (only mRNA) expression between glioma tissue and human astrocytes	[123]
	LN229 and U251 cell lines	Plasma membrane Cytoplasm Around the nucleus	N.D.	[29]
	U87 and T98G cell lines	N.D.	Without differences in GPER expression between glioma tissue and glial cells	[124]

Table 2. *Cont.*

Type of Cancer	Model	Localization	Role in Cancer	Reference
Hepatocellular carcinoma (HCC)	Tissue samples from HCC tumors and adjacent normal tissues	Cytoplasm Plasma membrane	Lower GPER expression in HCC compared to normal tissues	[125]
	Tissue samples from HCC tumors, cirrhotic livers and normal liver	Cytoplasm	Higher GPER expression in HCC and cirrhotic livers compared to normal liver	[126]
	Tissue samples from HCC tumors and paired normal tissues HCCLM3 cell line	Cytoplasm	Lower GPER expression in HCC compared to normal tissues. GPER expression is correlated with better OS. Co-expression of GPER and p-ERK predicted an improved prognosis GPER activation * (with G-1) increased p-ERK levels and caused cell cycle arrest and apoptosis	[127]
	HepG2 cell line	N.D.	GPER activation * (with G-1, E2) increased *c-fos* and FASN expression through EGFR transactivation	[77]
	HepG2 cell line	N.D.	GPER activation * (with G-1) induced microRNA-21 transcription	[45]
Leukemia	Primary pre-B ALL samples; Nalm-6 cell line	Plasma membrane	Expressed in primary cells from pre-B ALL but not from common ALL	[44]
	Primary AML samples and bone marrow mononuclear cells from healthy donors NB4, U937, KG1a, THP-1, and OCI-AML2 cell lines	Plasma membrane	Low GPER expression in B-ALL blast compared to bone marrow mononuclear cells from healthy donors GPER activation * (with G-1) induced apoptosis and enhanced the efficacy of venetoclax	[128]
	Jurkat, CCRF-CEM, and Molt-3 cell lines	Plasma membrane	Low GPER expression in T-ALL blasts compared to $CD4^+$ lymphocytes	[30] [129]
	HL-60 cell line	Plasma membrane Cytoplasm	N.D.	[34]
	Primary AML samples: MOLM14, U937, HL60, and THP-1 cell lines	N.D.	N.D.	[130]
Lung cancer (LC)	Tissue samples from NSCLC and benign pulmonary lesions	Cytoplasm Nucleus	Higher GPER expression in NSCLC compared to benign pulmonary tissue Higher cytoplasmic GPER expression was associated with higher stages and poorer differentiation. Cytoplasmic GPER is correlated with ER-β	[131]
	Tissue samples from NSCLC	Cytoplasm Nucleus	Co-expression of cytoplasmic and nuclear GPER expression was associated with a poor prognosis. Nuclear GPER is correlated with ER-β	[132]
	Tissue samples from LC tumors and adjacent normal tissues A549, H23, H1299, H1792, H1395, H1435, H1793, H1944, H2073 (LC), and HPL1D, HBEC2-E, HBEC2-KT, and HBEC3-KT (epithelial lung) cell lines	N.D.	Higher GPER expression in LC compared to normal tissues Higher GPER expression in LC cell lines compared to epithelial lung cell lines	[13]
	A549 and H1299 cell lines	N.D.	GPER inhibition * decreased cell growth, NOTCH1, HIF-1α, and CXCR4 mRNA levels; Contrary effects with GPER overexpression	[92]

Table 2. *Cont.*

Type of Cancer	Model	Localization	Role in Cancer	Reference
Mantle cell lymphoma (MCL)	MCL samples Jeko-1, Mino, Rec-1, and Granta-519 cell lines	Nucleus	GPER activation * (with G-1) caused cell death and enhanced the antiproliferative effect of ibrutinib GPER inhibition * increased cell proliferation	[133]
	MCL samples Rec-1, Granta-519, Mino, Jeko-1, Hbl-2, Nceb-1, Upn-1, Upn-2, L128 and Z138C cell lines	Nucleus	GPER inhibition * decreased p-p42/44 (ERK1/2), p-AKT, and cyclin D1 levels. GPER inhibition (with G-36) reduced cell proliferation and potentiated the effects of paclitaxel. Cell lines with low GPER expression did not respond to G-36	[134]
Ovarian cancer (OC)	Primary epithelial OC samples Low malignant potential tumors	Cytoplasm	Higher GPER expression in OC compared to borderline malignancies Co-expression of GPER-EGFR was associated with a poorer PFS	[135]
	Epithelial OC samples Low malignant potential tumors	Nucleus	Greater frequency of high GPER in OC compared to low-malignant ovarian tumors. GPER is preferably expressed in high-risk OC. High GPER expression was associated with poorer survival	[136]
	Epithelial OC samples	Cytoplasm	GPER expression is correlated with FSHR and LHCGR. High GPER was associated with better OS in FSHR/LHCGR negative patients.	[137]
	Ovarian granulosa cell tumor samples	Cytoplasm	Higher GPER expression in well-differentiated carcinomas compared to poorly differentiated carcinomas High GPER was associated with a poorer outcome in newly-diagnosed ovarian granulosa cell tumors	[138]
	Epithelial OC samples	Cytoplasm	Cytoplasmic GPER is correlated with Dkk2 expression. Patients with high co-expression of GPER and Dkk2 had better OS	[139]
	Primary epithelial OC samples SKOV3 cell line	Cytoplasm Nucleus	Nuclear GPER expression was an independent negative prognostic factor for OS	[140]
	Epithelial OC samples Caov3 and Caov4 cell lines	Cytoplasm Plasma membrane	Co-expression with H3K4me3 correlates with a favorable prognosis GPER activation * (with G-1) attenuated cell proliferation/migration and increased H3K4me3 and p-ERK1/2 levels	[35]
	OC, low-malignant tumors, and benign ovarian tumors samples SKOV3 and OVCAR3 cell lines	N.D.	Lower GPER expression in OC compared to benign and low-malignant ovarian tumors. GPER expression was associated with favorable DFS	[141]
	OVCAR5 cell line	N.D.	GPER activation * (with E2, G-1) increased cell migration, invasion, MMP-9 expression, and activity.	[142]
	BG-1 and 2008 cell lines	N.D.	Contrary effects with GPER inhibition * GPER activation * (with G-1, E2) causes cell proliferation	[112]
	SKOV3 cell line	N.D.	GPER inhibition * decreased cell number, migration, invasion, c-fos, and cyclin D1 expression	[79]

Table 2. *Cont.*

Type of Cancer	Model	Localization	Role in Cancer	Reference
Prostate cancer	PC-3 cell line	N.D.	GPER activation * (with G-1) decreased cell growth, increased p-ERK and p21 levels	[143]
Renal cell carcinoma	ACHN, OS-RC-2, and SW839 cell lines	N.D.	GPER activation * (with G-1) increased cell migration and invasion	[144]
Thyroid cancer	Tissues samples from papillary thyroid carcinoma (PTC), nodular hyperplasia, and normal thyroid	Cytoplasm Plasma membrane	GPER expression correlated with EGFR and CXCR1 expression; expression of these receptors correlated with lymph node metastasis. Higher GPER, EGFR, and CXCR1 expression in PTC compared to nodular hyperplasia and normal thyroid tissues	[145]
	Tissue samples from malignant follicular thyroid carcinoma (FTC), benign follicular thyroid adenoma (FTA), and normal thyroid	Cytoplasm Plasma membrane	Higher GPER expression in malignant FTC compared to benign FTA, without significant differences between FTA and normal thyroid tissues. GPER expression is correlated with EGFR and CXCR1 expression in malignant FTC	[87]
	Tissues samples from PTC, follicular variant of PTC, and adjacent non-malignant tissues	Cytoplasm	Lower GPER (mRNA) expression in PTC compared to non-malignant tissues, without differences in protein expression. Lower GPER (mRNA) expression in classical PTC compared to the follicular variant of PTC	[98]
Uveal melanoma	Omm1.3 and 92.1 cell lines	N.D.	GPER inhibition * induced cell growth and downregulation of p53	[146]

* Its activation/inhibition was confirmed by GPER silencing. ** Its activation/inhibition was confirmed in cells that expressed an interfering mutant of GPER. N.D.: not determined; 4-OHTAM: 4-hydroxytamoxifen; ABCG2: ATP binding cassette subfamily G member 2; KT: also known as protein kinase B (PKB); ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; ATM: ataxia-telangiectasia mutated; BC: breast cancer; CAFs: cancer-associated fibroblast; CC: cervical cancer; CDK4: cyclin dependent kinase 4; CRC: colorectal cancer; CTGF: connective tissue growth factor; DFS: disease-free survival; DMFS: distant metastasis-free survival; E2: 17β-estradiol; EC: endometrial cancer; EGFR: epidermal growth factor receptor; EMT: epithelial-mesenchymal transition; FAK: focal adhesion kinase; FASN: fatty acid synthase; FSHR: follicle stimulating hormone receptor; FTA: follicular thyroid adenoma; FTC: follicular thyroid carcinoma; GC: gastric cancer; GBM: glioblastoma; HCC: hepatocellular carcinoma; HIF-1α: hypoxia-inducible factor; LHCGR: luteinizing hormone receptor; MCL: mantle cell lymphoma; MMP: matrix metalloproteinases; NSCLC: non-small cell lung cancer; OC: ovarian cancer; OS: overall survival; PDAC: pancreatic ductal adenocarcinoma; PFS: progression-free survival; PI3K: phosphatidyl inositol 3-kinase; PR: progesterone receptor; PTC: papillary thyroid carcinoma; PTEN: phosphatase and tensin homolog; RFS: relapse-free survival.

3.2. Breast Cancer

In studies of metastatic tissues derived from patients with breast cancer, an overexpression of GPER has been found relative to primary breast cancer tissues [59,107,108]. This elevated expression counteracts what was reported in silico analysis of RNA-seq data from breast invasive carcinoma [90]. Greater GPER expression has been reported in breast cancer stem cells (BCSCs) compared to non-BCSCs, with GPER silencing significantly reducing stemness features [111].

High GPER expression has been correlated with a worse prognosis in patients treated with TAM [105,106] or those who did not receive it [110]. Additionally, GPER has been found to be co-expressed with EGFR [106,107], ABCG2 [59], and the chemokine receptor CXCR1 [109], and has shown an inverse correlation with the pro-apoptotic Bim protein [108].

In tissue samples from primary, invasive, or metastatic breast tumors treated with TAM, exclusive GPER localization in the plasma membrane was reported [105–107]. Cytoplasmic GPER expression was found in all subtypes of breast cancer [102–110], while a nuclear

pattern was reported in invasive breast cancer [102,103,106]. Finally, in breast cancer tissue samples from TAM-treated patients, GPER was possibly expressed in the endoplasmic reticulum [105]. This variation in GPER localization can be explained by the retrograde transport of the receptor, whereby in the absence of an agonist, GPER is endocytosed and accumulates at the perinuclear level to avoid chronic signaling through the receptor [147]. Remarkably, GPER expression in the plasma membrane was associated with a worse prognosis in TAM-treated patients [105].

In tumors derived from early stage invasive breast cancer patients, high nuclear expression has been associated with smaller tumors and a lower tumor grade without association with survival, while in patients treated with endocrine therapy, low cytoplasmic expression was associated with adverse survival [102]. In primary invasive breast carcinomas, nuclear GPER expression was associated with poorly differentiated and triple-negative subtypes, whereas cytoplasmic expression was associated with low tumor stage, luminal A and B subtypes, and better overall survival [103].

Activation of GPER produced transactivation of EGFR in different breast cancer cell lines (MDA-MB-435, HCC1806, SKBR3, tamoxifen-resistant MCF-7) and CAFs [36,59,77].

Similarly, GPER activation in SKBR3, BT-20, TAM-resistant MCF-7 cell lines, and CAFs produced increases in p-ERK [43,51,52,55,59,76] and p-AKT levels [59,76], which is also a manifestation of EGFR transactivation.

In addition, GPER activation caused ABCG2 upregulation in TAM-resistant MCF-7 cell line [59]. GPER-dependent secretion of IL-8, which binds to CXCR1, an active regulator for cancer metastasis, has been described in SKBR3 and BT-20 cell lines [76]. GPER also caused FOXO3a inactivation in the MCF-7 cell line [57], fatty acid synthase (FASN) expression [77], and downregulation of microRNA-338-3p [78] in the SKBR3 cell line and CAFs.

Increased *c-fos* levels through GPER activation have been reported in SKBR3, CAFs, MDA-MB-435, and HCC1806 cell lines [36,51,77,78], which may be accompanied by connective tissue growth factor (CTGF) expression [55]. It is worth mentioning that, although MDA-MB-435 is widely used to study breast cancer, its characteristics are more consistent with a melanoma cell line [148].

GPER-dependent activation of these signaling pathways induced cell proliferation/cell growth [36,40,43,49,51,55,58,78,112] and migration [41,76]. These effects have been reported both in cell lines that express ER-α (for example, MCF-7) and in those that do not express it (for example, SKBR3). However, some authors report that GPER activation induces a decrement in cell proliferation [6,7,50].

In summary, most experimental studies suggest that GPER expression in breast cancer tumors predicts a higher risk of metastasis, favors chemoresistance, and is an indicator of a worse prognosis for patients.

3.3. Cervical Cancer

Contrary to breast tumors, GPER appears to have a tumor-suppressive role in cervical cancer. Notably, GPER had an inhibitory effect on the stem cell properties of HeLa and SiHa cell lines, which was demonstrated through GPER silencing that increased colony formation and its size. GPER knockdown in the HeLa cell line also increased its invasive behavior (increased tumor sphere formation), *SERPINE1* and PAI-1 (human plasminogen activator inhibitor-1, gene product of *SERPINE1*) expression, and produced morphological changes (larger filopodia) related to EMT [91].

Although GPER was predominantly expressed in the cytoplasm in cervical tumors, it was also present in the nucleus. In comparison with cervical precursor lesions, GPER expression is higher in cervical cancer tumors [114].

In cervical adenocarcinomas, the co-expression of GPER with claudin-1, a protein related to proliferation, migration, and invasion, is correlated with a poor prognosis [116]. In addition, GPER activation by G-1 in HeLa, SiHa, C-33A, CaSki, and HCA1 cell lines transactivated EGFR, decreased cell viability, caused cell cycle arrest [115], and increased claudin-1 expression [116]. Although other GPER-dependent cytotoxic effects have been

reported in cervical cancer cell lines, the involvement of GPER was only tested using G-15 [114].

3.4. Colorectal Cancer

Tumor samples from colorectal cancer patients expressed lower GPER levels at protein and mRNA levels compared to adjacent non-cancerous mucosa tissues, without differences between age and sex [117]. These data correlate with the in silico assay reported by Gilligan and co-authors, but not with colorectal cancer samples from postmenopausal female and age-matched male patients, where a correlation in the expression of GPER and CTGF was reported [100].

GPER expression significantly decreases with advancing stage and lymph node metastasis in colorectal cancer patients. This explains why patients whose tumors express lower levels of GPER present poorer survival rates, while higher expression correlates with a favorable prognosis [117].

Data on the biological effects of GPER obtained using cell lines are not very clear, which may depend on the cell line or the culture conditions used. Under normoxic conditions, GPER activation decreased cell proliferation and migration of HT-29 and DLD-1 cell lines and decreased vascular endothelial growth factor A (VEGFA) and hypoxia-inducible factor (HIF1-α) expression in HT-29, DLD-1, and HCT116 cell lines, while in hypoxia, E2 increased cell growth, VEGFA, and HIF1-α expression [101]. Similarly, GPER knockdown under normoxic conditions increased cell migration in HT-29 cells but decreased it in DLD-1 cells. In a hypoxic environment, GPER silencing decreased cell migration in both cell lines. In the HT-29 cell line, E2 decreased ataxia-telangiectasia mutated (ATM) mRNA and protein expression, which is necessary for DNA reparation, in both cultured conditions.

In HCT116 cells, treatment with E2 or G-1 induced cell proliferation through GPER, which was inhibited by GPER or CTGF knockdown [100]. However, GPER activation in the LoVo cell line increased *c-fos* and FASN expression through EGFR transactivation, favoring cell proliferation [77].

Likewise, pharmacological inhibition (with G-15) or activation (with G-1) of GPER in HCT-116 xenograft models seems to have a similar effect on reducing tumor growth [100,117].

All these data seem to indicate that GPER expression could be used as an indicator of good prognosis, although its participation in cell proliferation is not entirely clear and must be evaluated in different cell lines with different levels of GPER expression.

3.5. Endometrial Cancer

GPER has been shown to be expressed in both normal endometrial tissues and endometrial cancer [118,119,121]. However, data on the levels of GPER expression in endometrial carcinoma tumors compared to non-cancerous uterine tissues are highly controversial. Early immunohistochemistry- and PCR-based studies performed with tissue samples obtained from patients reported high GPER expression in endometrioid adenocarcinomas in comparison to normal endometrium [118,119]. No correlation was found between GPER and ER-α expression [118]. GPER overexpression was more often observed in high-grade tumors, advanced stage tumours, and high-risk subtypes and was associated with poorer survival [119]. However, later reports from independent groups did not confirm these findings. Contrary to this, Skrzypczak and colleagues reported that endometrial adenocarcinoma showed lower GPER mRNA expression than normal endometrium tissue [121]. Moreover, loss of GPER expression among ER-α-positive patients has been reported to be associated with disease progression, poor prognosis, and reduced 5-year survival, with loss of GPER and ER-α more commonly in metastatic lesions [149].

One of the adverse effects of TAM use in ER-α-positive breast cancer patients was the higher incidence of endometrial hyperplasia and polyps, with abnormal endometrial tissue demonstrating higher GPER expression compared to the healthy endometrium of asymptomatic patients [60]. Moreover, higher endometrial GPER expression predicted earlier development of tamoxifen-induced pathologies. The authors suggest that GPER

plays an important role in tamoxifen-induced endometrial abnormalities. In this context, endometrial cancer tissues from breast cancer patients treated with TAM were reported to have a higher stage and pathological grade, more lymph node metastases, and a worse prognosis [38].

In primary endometrial cancer as well as in abnormal endometrial cancer tissues obtained from breast cancer patients treated with TAM, GPER expression was detected in both the plasma membrane and the cytoplasm [38,118,119]. In abnormal endometrial tissues derived from breast cancer patients treated with TAM, GPER expression was reported in both the nucleus and cytoplasm [60].

An important finding was the positive correlation between the expression of GPER and EGFR [119], as well as between GPER and pFAK expression, particularly pronounced in endometrial cancers with low levels of ER-α [39]. Additionally, GPER expression at the RNA level was associated with the endometrial tumor suppressor PTEN but not ER-α [121]. Regarding the association between GPER and the progesterone receptor (PR) in endometrial cancer, the data are contradictory: both positive and negative correlations were reported [119,121].

GPER-signaling has been explored in endometrial cell lines. Natural ligand E2, through GPER, activated PI3K in Hec50 cells [120], while both E2 and 4-OHTAM increased pFAK levels in Ishikawa and RL95-2 cell lines [39]. Similarly, GPER activation with non-canonical agonists GPER-L1 and GPER-L2 increased cyclin D1, p-ERK, and *c-fos* expression in Ishikawa cells [51], while 4-OHTAM increased cyclin D1 expression and EGFR transactivation in RL95-2 and HEC-1A cells [38]. The activation of GPER-dependent signaling pathways leads to an increase in cell viability and migration, which has been demonstrated in various cell models, including cell lines KLE [118], Ishikawa [39,51], RL95-2 [38,39,118], and HEC-1A [38,60]. Skrzypczak and colleagues obtained conflicting results: in their experiments, the synthetic agonist G-1 reduced the viability of GPER-expressing HEC-1A and RL95-2 cells but not GPER-negative HEC-1B cells, whereas the natural agonist E2 did not cause any changes in the viability any of the cell lines [121].

In summary, although there is a large amount of experimental and clinical data on the role of GPER in endometrial cancer, the data are conflicting. Inconsistency in the analysis of histological sections by immunological methods may be a consequence of differences in the protocol or the storage time of samples and antibodies. In order to draw correct conclusions, a thorough comparative analysis of published works is necessary.

3.6. Gastric Cancer

Lower expression of GPER has been reported in gastric cancer tumors compared to normal tissues [99,122]. Subcellular localization of the protein in the nucleus and cytoplasm has been reported [99]. Low levels of GPER mRNA have been observed as a predictor of poor prognosis [99].

As previously noted in Section 2.4, the EMT is one of the resistance mechanisms mediated by GPER. In this regard, GPER has been reported to promote EMT, as GPER silencing reduced the mesenchymal phenotype (reduction in vimentin and N-cadherin expression) and increased epithelial phenotype (E-cadherin) in AGS, BGC-823, and MGC-803 cell lines [32,88]. Accordingly, G-1 reduced cisplatin sensitivity in a GPER-dependent manner, whereas the selective GPER antagonist G-15 or GPER knockdown, conversely, increased cisplatin sensitivity in AGS and BGC-823 cells [32].

GPER knockdown in AGS and MGC-803 cell lines decreased cyclin D1, cyclin dependent kinase 4 (CDK4), MMP2, MMP9, and phosphorylated forms of PI3K, AKT, and mTOR levels. Inactivation of these signaling pathways caused a decrease in cell viability, proliferation, migration, and invasion, while overexpression of GPER led to the opposite effects [88].

In most gastric cancer models, treatment with E2 or G-1 either increased or did not produce any effect on GPER expression [122]. However, G-1 reduced GPER expression and cell viability in the high-GPER-expressing cell lines AGS and SNU-216 and, in contrast,

had no effect on NCI-N87 cells expressing low levels of GPER, indicating that GPER overexpression is required for G-1 to reduce the viability of gastric tumor cells [122].

Thus, several reports suggest that the presence of GPER appears to be associated with a favorable prognosis. However, it must be taken into account that in tumors expressing GPER, activation of the receptor can either promote cell proliferation [88] or inhibit it [122], depending on the level of GPER. It is also important to consider the possible involvement of GPER in chemoresistance, as has been shown in the particular case of cisplatin resistance [32].

3.7. Hepatocellular Carcinoma

Data on GPER expression in hepatocarcinoma are controversial, as there have been reports of both lower [125,127] and higher [126] GPER expression compared to normal adjacent tissues. Lower GPER expression was also observed in cirrhotic livers in comparison to healthy livers [126]. Although the GPER protein was predominantly present in the cytoplasm of hepatocellular carcinoma [125–127], it was also found in the plasma membrane [125]. In this type of cancer, GPER expression was likely to correlate with better overall survival, and co-expression of GPER and phosphorylated ERK was predictive of a good prognosis [127].

In the HepG2 cell line, activation of GPER with E2 or G-1 increased *c-fos* and FASN expression through EGFR transactivation, with FASN overexpression favoring cell proliferation [77]. In the same cell line, GPER activation caused transcription of cancer-associated microRNA-21 [45,150].

Similarly, G-1 in the HCCLM3 cell line was able to activate the GPER-mediated ERK signaling pathway, increasing the levels of p-EGFR, p-AKT, and p-ERK, and finally causing cell cycle arrest and apoptosis [127]. Moreover, given that GPER and p-ERK co-expression is a predictor of improved prognosis in patients with hepatocellular carcinoma, GPER-mediated activation of the ERK signaling pathway may be considered to play a protective role.

3.8. Leukemia and Lymphoma

Little is known about the involvement of GPER in the pathogenesis of leukemia and lymphoma. To the best of our knowledge, there are no clinical studies on the significance and prognostic value of GPER expression.

GPER expression has been reported in lymphoblasts derived from patients with pre-B acute lymphoblastic leukemia (ALL), but not in common ALL lymphoblasts [44]. Pre-B ALL derives from a more mature lineage than common ALL, which may explain why pre-B ALL lymphoblasts express GPER like mature B cells [151]. However, hematopoietic stem cells also express GPER [152], so the role of GPER in normal hematopoiesis is not known with certainty.

Leukemic blasts from acute myeloid leukemia (AML) patients expressed a lower level of GPER compared to peripheral blood mononuclear cells from healthy patients [128]. Similarly, leukemic cell lines from T-ALL showed lower GPER compared to $CD4^+$ T-lymphocytes extracted from the peripheral blood of healthy donors [129]. The expression of GPER was reported mainly in the plasma membrane, both in samples from patients with B-ALL [44], AML [128], T-ALL cell lines [30], and AML cell lines [34], where GPER expression was also observed in the cytoplasm.

In terms of biological effects, GPER seems to play a tumor suppressive role, as its activation with G-1 (1 μM, 24h) induced apoptosis in the AML OCI-AML2 cell line and improved the efficacy of the chemotherapeutic venetoclax [128]. However, treatment with G-1 during a prolonged period (1.25 μM for 72 h) decreased cell viability in the AML MOLM14 cell line in a GPER-independent manner, which was confirmed by GPER knockdown [130].

Little is known about the subcellular localization of GPER in healthy lymphoid tissues and malignancies. GPER was found at the nuclear level in mantle cell lymphoma (MCL) tumor tissues and cell lines [133,134]. It is important to mention that the expression or

absence of expression of GPER in MCL samples does not correlate with a better or worse prognosis, since no significant differences in overall or event-free survival were found in patients with GPER-positive or -negative tumors [134].

G-1 induced apoptotic and necrotic cell death (apoptosis and necrosis) in MCL Jeko-1, Mino, and Rec-1 cell lines in a GPER-dependent manner, while GPER knockdown increased cell proliferation of Jeko-1 cells without inducing or decreasing the number of dead cells [133]. In Mino and Granta cell lines, GPER silencing or treatment with the GPER antagonist G-36 decreased p-ERK, p-AKT, and cyclin D1 levels. Additionally, G-36 reduced cell proliferation only in cell lines that expressed GPER and had a synergistic effect with paclitaxel, decreasing Mino and Granta cell proliferation [134]. Controversially, G-36 did not decrease Mino cell proliferation at higher concentrations and treatment times [133].

3.9. Lung Cancer

In patient-derived lung tumor samples, GPER expression has been shown to be higher compared to benign pulmonary tissue [13,131]. Similarly, NSCLC cell lines had a higher GPER expression compared to normal lung bronchial epithelial cell lines [13].

Regarding the subcellular localization of GPER, in non-small cell lung cancer (NSCLC) samples (including lung adenocarcinoma and squamous cell carcinoma), it was expressed in both the cytoplasm and nucleus [131,132]. A correlation was found in the expression of GPER and ER-β [131,132]. Moreover, higher cytoplasmic expression of GPER was associated with higher tumor stages with less cell differentiation [131]. Concurrent cytoplasmic and nuclear expression of GPER has been shown to be associated with poor prognosis (worse disease-free survival), higher stage, lymph node metastasis, and EGFR expression [131].

Finally, GPER knockdown in the A549 cell line decreased cell growth and mRNA levels; of NOTCH1, HIF-1α, and CXCR4, while overexpression of GPER in the H1299 cell line caused the opposite effects [92].

3.10. Ovarian Cancer

As with other types of cancer, reports of GPER expression in ovarian tumors compared with non-tumor tissues are inconsistent. Fujiwara and colleagues have reported higher GPER expression in ovarian cancer compared to non-tumor tissue [135]. GPER expression was characteristic of high-risk ovarian tumors associated with poor survival [136,138]. Although both nuclear and cytoplasmic GPER expression were associated with poor overall survival, regardless of tumor stage or grade, it was nuclear GPER that was predictive of a worse prognosis [140].

Other histological reports mentioned that GPER was expressed at lower levels in ovarian cancer compared to benign and low-malignant ovarian tumors, but its lower expression was associated with favorable disease-free survival [141]. Additionally, GPER was found to be more expressed in well-differentiated compared to poorly differentiated carcinomas, and in ovarian cancer tumors negative for follicle-stimulating (FSH) hormone receptor (FSHR) and luteinizing (LH) hormone receptor (LHCGR), high GPER expression was associated with better overall survival [137]. On the other hand, Kolkova and colleagues reported that GPER was expressed at similar levels in benign and malignant ovarian tumors and borderline tissue, and when comparing patients with GPER-positive or GPER-negative tumors, no differences were found in histological grade, type, clinical stage, or overall survival [153].

In ovarian tumors, GPER protein was reported to be expressed in the cytoplasm [35,135,137–140], nucleus [136,140], and plasma membrane [35], and was co-expressed with EGFR, FSHR, LHCGR, Wnt pathway modulator dickkopf 2 (Dkk2), and histone H3 lysine 4 trimethylation (H3K4me3).

The co-expression of GPER and EGFR was associated with worse progression-free survival [135]. Regarding GPER co-expression with FSHR and LHCGR, treatment with FSH and LH enhanced GPER expression in the ovarian cancer cell line OVCAR3, and

the addition of these two hormones prevented the antiproliferative effect of G-1 and 4-OHTAM only in FSHR/LHCGR-positive cell lines [137]. On the other hand, Dkk2, which is an antagonist of Wnt signaling, a pathway associated with cancer [154], was found to be downregulated in ovarian cancer [155]. This appears to be why patients with high co-expression of GPER-Dkk2 had better overall survival [139]. Also, GPER-H3K4me3 co-expression predicted a favorable prognosis [35], likely because H3K4me3 is an epigenetic regulator associated with greater enhancer activity in tumor suppressor genes [156].

In BG-1 and 2008 cell lines, G-1 or E2 induced cell proliferation through GPER [107]. Similarly, both agonists activated GPER and increased cell migration, invasion, activity of MMP-9, and its expression in the OVCAR5 cell line [142]. Knockdown of GPER caused the opposite effects, in addition to decreasing c-fos and cyclin D1 expression [79]. Opposite effects were reported in ES2, SKOV3, Caov3, and Caov4 cell lines, where GPER activation caused attenuated cell proliferation [35,46], induced apoptosis, and increased expression of pro-apoptotic proteins Bim-Bax, p-AKT, cAMP [46], p-ERK [35,46], and H3K4me3 levels [35]. This could be supported by the results of Heublein and co-authors [137], where it was shown that Caov3 does not express FHS and LH receptors, and G-1 or 4-OHTAM are capable of reducing the proliferation of these cells; however, SKOV3 does express hormone receptors.

3.11. Thyroid Cancer

Papillary and follicular thyroid carcinoma are the main types of thyroid cancer. Results regarding the comparative expression of GPER in thyroid cancer versus normal tissue vary. For example, higher GPER expression was observed in papillary thyroid cancer compared to nodular hyperplasia and normal thyroid [145], as well as in follicular thyroid cancer, which showed high levels of GPER compared to benign follicular adenoma thyroid gland and normal thyroid gland [87]. However, another study of histological specimens of papillary thyroid carcinoma found that GPER mRNA was less expressed in tumor tissue compared to adjacent benign tissues, but no difference in protein expression was found [98].

In thyroid cancer, GPER protein has been reported to be expressed in the cytoplasm [87,98,145] and plasma membrane [87,145]. In papillary thyroid carcinoma tissues, GPER expression was correlated with EGFR and CXCR1 expression, where the co-expression of 2 receptors (for example, GPER and EGFR) as well as the co-expression of the 3 receptors correlated with lymph node metastasis [145]. Similarly, in follicular thyroid carcinoma tissues, the concomitant high expression of all three receptors was associated with the occurrence of follicular thyroid carcinoma [87].

In WRO, FRO, and ARO cell lines, activation of GPER activation with no canonical ligands increased cell proliferation [37,42], migration, invasion, ERK and AKT activation, nuclear NF-kB, secretion of IL-8, and expression of cyclin A, cyclin D1 [42], and c-fos [37].

3.12. Other Cancers

To our knowledge, no histological studies have been reported on the expression levels of GPER present in tissues derived from glioma or other cancers of the central nervous system, prostate, renal, and melanoma cancers. In glioma, GPER was expressed in U87, LN229, T98, and U251 cell lines. In U87, LN229, and U251 cell lines, GPER was found in the cytoplasm and plasmatic membrane [29,123]. Additionally, GPER mRNA expression was lower in glioma cell lines than in human astrocytes [123], without differences in protein expression comparing glioma cells with human astrocytes or glial cells [123,124].

In the prostate cancer cell line (PC-3), GPER activation decreased cell growth and increased p-ERK and p21 levels [143]. Similar to ACHN, OS-RC-2 and SW839 cell lines from renal cell carcinoma showed that G-1 through GPER increased cell migration and invasion [144]. As well as the GPER knockdown in uveal melanoma, Omm1.3 and 92.1 cell lines induced the opposite effects of activation: increased cell growth and downregulation of p53 [146]. Given that this review focuses on studies performed in human models,

the studies reporting a role for GPER in mouse models of melanoma or glioma were not considered.

4. Role of GPER in the Tumor Microenvironment

The pivotal role of GPR30/GPER has been studied in the carcinogenesis of various cancer types; however, its influence extends beyond cancer cells and impacts multiple components of the tumor microenvironment (TME) to indirectly boost or limit cancer progression.

In the first place, GPER overexpression but no ER-α expression has been associated with the ability of stem-like stromal cells to differentiate into CAFs [157]. These altered fibroblasts are essential in the tumor microenvironment as they are actively involved in promoting tumor growth, invasion, and metastasis.

Growing evidence has indicated that cancer cells are able to recruit multiple cellular components to transform the TME and support cancer progression. Such components of the TME include CAFs, immune cells (mostly macrophages and lymphocytes), stromal cells, adipocytes, and endothelial cells. It has been demonstrated that the migration of CAFs to the TME of breast cancer tumors relies on GPER stimulation [158]. In this model, the administration of E2 or G-1 promoted the activation of proliferation genes, which was attributed to GPER stimulation since the corresponding Western blot analysis demonstrated that CAFs expressed only GPER but not ER-α or ER-β receptors.

The importance of GPER expressed in CAFs in tumor development is highlighted by the observation that GPER is expressed in CAFs from the primary tumoral sites, but its levels are higher in metastatic tumor fibroblasts. In these CAFs, the agonism of GPER, either by TAM (10 nM) or G-1 (1 μM), induces transient intracellular calcium mobilization and consequent CAF activation [159]. Importantly, these activated CAFs contributed to tumor progression by promoting autophagy-inducing agent release, which stimulated autophagy in cancer cells and allowed them to escape the cytotoxic effects of anticancer drugs [159]. Moreover, GPER was shown to regulate the secretome of CAFs, as GPER-silenced CAFs failed to produce and release IL6, a proinflammatory cytokine necessary for the activation of macrophages and the prostate cancer invasion [160].

Interestingly, absolute cytoplasmic GPER expression was observed in CAFs of tumor samples from TAM-resistant breast cancer patients, in contrast to TAM-sensible cases with a combined nuclear/cytoplasmic GPER [161]. Accordingly, cytoplasmic GPER expression in CAFs has been suggested as a predictable factor in the worse prognosis. This data was consistent with experiments performed in vitro with breast cancer cell lines co-cultured with CAFs, demonstrating that tumor cells induced the translocation of GPER from the nucleus to the cytosol in CAFs. Cytoplasmic GPER was able to trigger GPER/cAMP/PKA/CREB signaling and aerobic glycolysis switching in CAFs. Glycolytic CAFs provided additional pyruvate and lactate for tumor cells, leading to increased mitochondrial activity and resistance to several anticancer drugs, including TAM, herceptin, and epirubicine. These findings provide important evidence for the mutual relationship between cancer cells and their niches and the ability of cancer cells to modulate the niches for their needs ("host–parasite relationship"), as well as the role of GPER in these processes.

The importance of adipose tissue in cancer cell protection and tumor progression has been extensively reviewed [162]. Among the cells found in the TME, adipocytes largely contribute to cancer cell survival, proliferation, metastasis, and drug resistance. Interestingly, mice with GPER knockouts do not accumulate adipose tissue even on a high fat diet [163]. This was attributed to the reduced adipogenic differentiation potential of the preadipocyte cells. Correspondingly, GPER stimulation with G-1 enhanced adipogenic differentiation. This is of particular interest in the context of the TME; however, the implications of such findings in the context of cancer progression must be evaluated.

Other non-cellular components of the TME, such as nutrient levels, are able to regulate GPER expression in cancer cells. The work by Rasoulpoor and colleagues demonstrated that under normoxic conditions, a low glucose microenvironment (5 mM) promoted a 3-fold increase in GPER expression in breast cancer cells, whereas under high glucose

conditions, GPER levels were reduced [164]. Moreover, an oxygen restrictive microenvironment (hypoxic) under normal glucose levels resulted in a substantial (40-fold) GPER overexpression. The results varied depending on the breast cancer cell line evaluated, the ER expression patterns, and the time. Therefore, the influence of nutrients on GPER expression must be carefully evaluated for each cancer type.

Finally, the TME is able to house multiple immune cells. In this context, the presence of GPER has been observed in multiple immune cells, such as T and B lymphocytes, monocytes and macrophages, eosinophils, and neutrophils [151]. Immune cells in the tumor microenvironment undoubtedly have the potential to modulate disease progression, but we do not yet have evidence that GPER is involved in this process, and this topic remains to be explored.

5. Conclusions

In this review, we found that GPER is present at different levels in many healthy tissues and malignancies. However, the correlation of GPER expression levels between malignant and normal tissue varied significantly depending on the tumor type. GPER appears to be highly expressed and likely to play a protumor role in breast, ovarian, lung, thyroid, and endometrial cancers, whereas its expression in gastric, liver, colorectal, and leukemia cancers is lower compared to normal tissues. The expression level of GPER and its subcellular distribution can be used as a prognostic factor in many types of cancer. However, pharmacological modulation of GPER signaling as an anticancer treatment should be used with caution to avoid unwanted effects. It should be noted that many small molecules designed as specific GPER ligands, agonists, or antagonists are cell-permeable and can cause various "off-target" effects. GPER has been reported to be responsible for chemoresistance in many cancers through mechanisms related to EMT, ABCG2 activation, and autophagy.

Moreover, GPER is likely involved in the development and maintenance of key components of the TME, such as CAFs or adipocytes. These components, in turn, create a protective niche ("sanctuary") for cancer cells.

It is important to note that, due to the conformational plasticity of GPER, there are a large number of molecules capable of interacting with this receptor. These include endogenous molecules such as hormones and their metabolites, some drugs (TAM), as well as various exogenous compounds. These molecules can then modulate GPER signaling, which in some cases can cause malignant transformation, accelerate cancer progression, or induce chemoresistance. This should be considered in the clinic, especially when using hormonal treatment. It is strongly recommended to avoid the use of household chemicals and plastics with potential effects as endocrine disruptors.

An important observation is that there are many published results that appear contradictory, which could be attributed to differences in experimental conditions, drug concentrations, and types of assessment methods. Therefore, we encourage our colleagues to take all these factors into account when comparing the results of independent groups and drawing conclusions.

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