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Role of G Protein-Coupled Estrogen Receptor in Cancer Progression

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Abstract

Cancer is the leading cause of mortality worldwide. In cancer progression, sex hormones and their receptors are thought to be major factors. Many studies have reported the effects of estrogen and estrogen receptors (ERs) in cancer development and progression. Among them, G protein-coupled estrogen receptor (GPER), a G protein-coupled receptor, has been identified as an estrogen membrane receptor unrelated to nuclear ER. The mechanism of GPER, including its biological action, function, and role, has been studied in various cancer types. In this review, we discuss the relation between GPER and estrogen or estrogen agonists/antagonists and cancer progression.

***Key words*:** GPER, Cancer progression, Estrogen, G1

INTRODUCTION

Understanding cancer progression, a major cause of mortality, plays an important role in clinical applications and extension of healthy life span. Cancer progression consists of multistage carcinogenesis and metastasis programs (1), which are caused through complex pathways including genetic and environmental factors. Among them, sex hormones and their receptors are attractive factors for promoting cancer progression. The effect of sex hormones and their receptors on cancer progression has been studied for a long time. Typically, breast cancer and prostate cancer (PC) are known to be related to sex hormone. However, the role of androgen receptor and estrogen receptors (ERs) are not sufficient to drive cancer progression. Recently, GPR30, also called G-protein coupled estrogen receptor (GPER), has been identified.

GPER is a G-protein coupled receptor, which are seven-transmembrane receptors (2) and also a type of ER (3); however, it does not have the same mechanism of action as typical nuclear receptors, such as ER α and β. GPER is well known to play a role of substituted ER in physiological function from the model of GPER knockout mice (4). GPER is a mediator of estrogen in nervous system (5,6), immune system (7), cardiovascular system (8,9), bone metabolism (10), glucose metabolism in pancreas (11), kidney function (12), reproductive system and cancer (13-16) (Table 1). Among them, this review focuses on the

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List of abbreviations: AR, androgen receptor; CAFs, cancer-associated fibroblasts; CRC, colorectal cancer; EC, endometrial cancer; EGFR, epithelial growth factor receptor; ER, estrogen receptor; ERK, extracellular-signal-regulated kinase; ERT, estrogen replacement therapy; FAS, fatty acid synthase; GnR, gonadotrophin receptor; GnRH, gonadotrophin releasing hormone; GPER, G protein-coupled estrogen receptor; HCC, hepatocellular carcinoma; IGF-I, insulin-like growth factor-I; KO, knockout; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NHERF1, Na^+/H^+ exchanger regulatory factor; PC, prostate cancer; PI3K, phosphoinositide 3-kinase; PR, progesterone receptor; TAZ, transcriptional coactivator with PDZ-binding domain; TF, transcriptional factor; TK, tyrosine kinases; TNBC, triple-negative breast cancer; YAP, yes-associated protein 1.

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Table 1. The role of GPER in physiology

System	Function	Reference
Nervous system	Release of neurotransmitter, neurogeneration	(5,6,14)
Immune system	Thymocyte apoptosis	(7)
Cardiovascular system	Regulation of vascular tone Protection from myocardial injury	(8,9,14)
Bone	Bone mineral density	(10,14-16)
Pancreas	Maintain the metabolic function of insulin	(11,14-16)
Kidney	Protection of hypertensive nephropathy	(12)

role of GPER in tumor progression.

GPER-ACTIVATED SIGNALING PATHWAYS

Estrogen binds to and activates GPER in plasma membrane (3). Tamoxifen, ICI 182,780, o, p′-dichlorodiphenyl dichloroethylene can also act as agonists of GPER (3). Furthermore, G1 has been identified as an agonist of GPER, and G15 has been found to be a GPER antagonist (17). Ligand-bound GPER induces a cascade response and triggers several pathways leading to cell proliferation, gene expression, cell growth, and tumor progression (Fig. 1). It activates adenylyl cyclase, cAMP, calcium mobilization, and mitogen-activated protein kinase (MAPK). Additionally, it relates to the phosphoinositide 3-kinase (PI3K)/Akt pathway, the Hippo/yes-associated protein 1 (YAP)/transcriptional coactivator with PDZ-binding domain (TAZ) pathway, and epithelial growth factor receptor (EGFR)/MARL transactivation (18-21). Activated GPER induces the release of calcium from the endoplasmic reticulum, which activates Src-like nonreceptor tyrosine kinases (TKs). TKs then promote matrix metalloproteinase (MMP) activation and EGFR activation (12). EGFR phosphorylation activates the STAT5 and MAPK/extracellular regulated kinase (ERK) pathways. These pathways are affected by ER-α36 expression, which is induced by GPER, and involved in cell proliferation in breast cancer (22). Activation of these pathways via GPER might contribute to progression in various cancers.

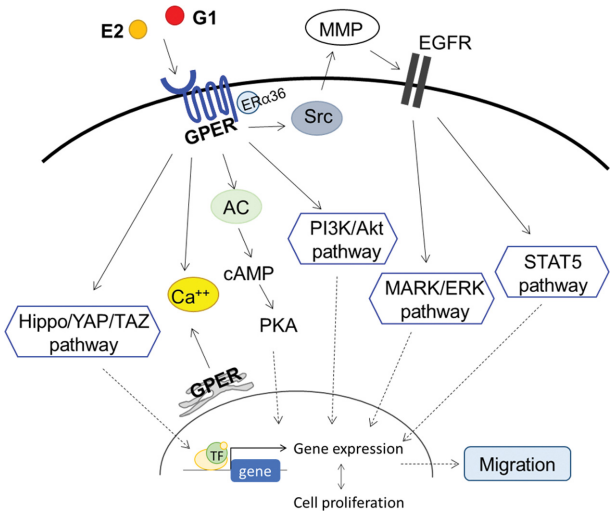

Fig. 1. Proposed mechanism of GPER in cancer cells. AC, adenylyl cyclase; PKA, protein kinase A; MMP, matrix metalloproteinase; EGFR, epithelial growth factor receptor; TF, transcriptional factor.

GPER IN BREAST CANCER

The role of GPER has been best studied in breast cancer, which is more prevalent in women than men. GPER is known to contribute to cancer cell proliferation, migration, and invasion in breast cancer (18). From cDNA library screening, the expression of GPER is shown in ER-positive breast cancer more than in ER-negative breast cancer (23). GPER signaling modulates miR-144 expression and stimulates cancer progression in the breast (24). GPER is highly expressed in triple negative breast cancer (TNBC), GPER/ERK signaling contributes to tumor progression in TNBC (25), and GPER knock-down reduces proliferation in TNBC. While GPER knockout mice do develop tumors, their histological grade and necrosis score are lower than those of control mice (26). Furthermore, an agonist of gonadotrophin releasing hormone (GnRH) receptor inhibits GPER signaling in ERα-negative breast cancer, and cancer cell proliferation is suppressed (27). Na^+/H^+ exchanger regulatory factor (NHERF1) is a tumor suppressor (28) related to GPER expression and stability in ER-positive breast cancer (18). NHERF1 overexpression inhibits GPER-mediated proliferation in MDA-MB-231 (TNBC) (Table 2) cells and in early stage of TNBC (29). However, absence of GPER does not affect early tumor

Table 2. Cancer cell lines used *in vitro* studies

Cancer	Cell lines
Breast cancer	MDA-MB-231 (triple negative breast cancer)
Ovarian cancer	OVCAR5, OVCAR-3, SKOV-3
Endometrial cancer	Hec50
Lung cancer	A549

initiation or proliferation (30). GPER inhibitors, such as estriol (31) and gefitinib (32), and inhibition of GPER expression by inhibition of growth hormone receptor (33) prevent the 17β-estradiol-induced growth of TNBC. Furthermore, knockdown of ER-α36, which is induced by GPER, reduces estrogen resistance, proliferation, migration and invasion in breast cancer (28).

As with breast cancer cells, the tumor microenvironment contributes to cancer progression. Unlike GPER, which is a membrane receptor, GPER p16L, caused by a single nucleotide polymorphism, localizes to the nucleus of cancer-associated fibroblasts (CAFs) and acts as a transcription factor. GPER p16L induces the secretion of paracrine factors, which promotes cancer cell migration. Indeed, coculture of MDA-MB-231 cells with CAFs treated with estrogen increases migration of the MDA-MB-231 cells (34,35).

GPER IN OVARIAN CANCER

A cohort study in the United States showed a correlation between estrogen replacement therapy and ovarian cancer (Table 2), but a meta-analysis found no such association (30,36). Similarly, the estrogen-binding role of GPER is controversial in ovarian cancer. GPER is expressed in both the nuclears and cytosol in ovarian cancer, and nuclear GPER is a predictive factor of poor survival in ovarian cancer (37,38). Furthermore, estrogen-activated GPER promotes cell proliferation, migration and invasion in ER-negative ovarian cancer (39), and high expression of GPER is correlated with tumor size and stage. High GPER is also associated with MMP9 expression (36), which induces invasion and migration in OVCAR5 cells (40). High GFER expression in ovarian cancer also induces lymph node metastasis, which decreases survival in ER-negative ovarian cancer patients. Moreover, GPER, independent of estrogen binding, promotes proliferation, migration and invasion in ER-positive SKOV-3 cells (41). Additionally, GnRH receptor agonist inhibits ERs signaling in GPER and ER-positive ovarian cancer cells (27). In contrast, high GPER expression predicts longer survival in gonadotrophin receptor (GnR)-negative patients (42,43). GPER expression is lower in ovarian cancer than in benign and low-malignant tumors (44), and GPER-positive ovarian cancer patients have a significantly higher 2-year disease-free survival than GPER-negative patients, indicating GPER acts as a tumor suppressor in ovarian cancer. G1, a GPER agonist, induces G2/M phase arrest and apoptosis through cyclin B1, Cdc2, and phosphorylated histone H3 in SKOV-3 and OVCAR-3 cells (44).

GPER IN ENDOMETRIAL CANCER

Endometrial cancer (EC) is one of the gynecologic cancers in which estrogen signaling causes proliferation. Therefore, estrogen-activated receptors affect EC progression, and ER-negative EC has a lower survival rate than ER-positive EC. GPER is present in EC, although expression differs depending on cell type and tumor grade (45). GPER is overexpressed in ER- and progesterone receptor (PR)-negative cancer and is associated with myometrial invasion and poor survival (46). GPER is overexpressed in ERα-negative Hec50 cells (Table 2), and GPER agonists enhance tumor growth in Hec50-derived xenografts (47). Tamoxifen, acting as a GPER agonist, increases tumor proliferation through cyclin D1, ERK, and EGFR (48). GPER mRNA levels are reduced in EC as compared to normal endometrial tissue (45). miRNA-424 suppresses E2F7 and E2F6 and inhibits cell proliferation and invasion via GPER in EC tissues (49,50). Additionally, progesterone receptor mRNA expression is related to GPER mRNA expression (45). Loss of GPER in ER-positive patients indicates poor prognosis and promotes tumor progression (51).

GPER IN LUNG CANCER

GPER expression is also high in lung cancer. GPER expression is high in human non-small cell lung cancer cell lines, other than A549 cells (Table 2), and normal lung bronchial epithelial cells (52). High GPER expression is associated with high ERβ expression in lung cancer (17). GPER signaling induces MMPs in human lung cancer cells (53). Metastasis is higher in cells with GPER expression than in large cell carcinoma, squamous cell carcinoma or adenocarcinoma (52), and lung metastasis is dramatically decreased in GPER knockout (KO) mice. GPER acts as a modulator of neoplastic transformation via PI3K/IKK/NF-γB signaling (54-56). Migration stimulation is induced by GPER-associated activation of insulin-like growth factor-I (IGF-I)/IGF-IR via ERK, p38, and Akt activation (57).

GPER IN COLORECTAL CANCER

GPER acts as a tumor suppressor in colorectal cancer (CRC). In CRC progression, the *GPER* promoter has increased methylation and histone H3 deacetylation, and GPER expression is negatively correlated with increased stage and lymph node metastasis. Additionally, higher GPER expression is associated with longer survival. However, treatment with G-1 inhibits tumor growth via ROS, ERK 1/2 activation, and GSK-3β activation/p65(NF-γB) suppression (58). Estrogen accelerates the proliferation of CRC because conjugated estrogen is activated by steroid sulfatase via GPER (56,59). Furthermore, GPER regulates the expression of fatty acid synthase, which induces CAFs and contributes to cancer progression (60). E2-activated GPER contributes to migration and proliferation in hypoxia-induced CRC cells (61), and hormone replacement therapy may be associated with CRC progression (59).

GPER IN ADRENOCORTICAL CARCINOMA

GPER agonists suppress adrenocortical carcinoma proliferation via cell cycle arrest, DNA damage, and apoptosis via ERK1/2 activation (62).

GPER IN PROSTATE CANCER

G1, a GPER agonist, inhibits the growth of PC cells and xenograft models via ERK1/2 and p21 activation (63-66). Furthermore, GPER expression is higher in castration-resistant PC cells than in androgen-sensitive PC cells, and G1 inhibits the growth of castration-resistant PC via necrosis (67). In contrast, high GPER levels in CAFs decrease ERα expression, which promotes the proliferation and migration of prostate stromal cells (68). PC is associated with testosterone, but older men have decreased testosterone level. Nevertheless, xeno-estrogens and poor diet increase aromatase activation, which causes estrogen levels to increase. This increased estrogen activates ERα and GPER activation, which promotes PC (69).

DISCUSSION

The role of GPER in tumor progression differs depending on tumor stage, site, and environment. GPER expression is high in ER-negative cancer, and estrogen signaling via GPER promotes cancer progression. However, high GPER expression increases survival in ovarian cancer, even though the levels are lower than those in normal cells. Moreover, a GPER selective agonist, G1, suppresses tumor proliferation in CRC, PC, and adrenocortical carcinoma. Thus, GPER expression and its activators (estrogen and G1) should be considered, along with ERα, ERβ, PR, and GnR, when examining cancer progression.

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CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

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