International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Review Article.

Emerging Roles of G Protein- Coupled Estrogen Receptor 1 (GPER) in Obesity, Asthma, Diabetes, and Cancer: Molecular Mechanisms and Therapeutic Implications

Sandhya Suresh[1*], Siddharaj Singh Sisodia[2]

[1]M.Pharm (Pharmacology), Research Scholar, B. N. College of Pharmacy, Udaipur, Rajasthan, India.
[2]PhD (Pharmacology), Professor, B. N. College of Pharmacy, Udaipur, Rajasthan, India.

ABSTRACT

The G protein-coupled estrogen receptor 1 (GPER1) has gained recognition as a pivotal component of estrogen signalling, functioning independently from traditional nuclear estrogen receptors. GPER1 demonstrates a strong binding affinity for 17β-estradiol (E2) and can be activated by a range of estrogenic agents such as tamoxifen, genistein, bisphenol A, and atrazine. Its signalling mechanisms are multifaceted, involving Gα_s and Gα_i/o subunits, which initiate diverse downstream pathways including cyclic AMP (cAMP) generation, PI3K/Akt activation, and intracellular calcium flux. These signalling outcomes are highly context-dependent, varying with cell type and receptor environment. The development of pharmacological agents such as the GPER agonists G-1 and 5408-0877, as well as the antagonist G15, has facilitated deeper exploration of GPER's biological functions, though concerns remain regarding the specificity of these compounds.

GPER1 manifests itself in several forms of cancer, including breast, ovarian, endometrial, and testicular cancer. GPER activation frequently enhances migration and proliferation of tumor cells, and elevated GPER expression is inter linked to poor clinical outcomes, notably in breast and gynaecological cancers. Notably, tamoxifen—traditionally used as an anti-estrogen therapy—acts as an antagonist of GPER, potentially driving proliferation in GPER-positive tumours, including ERα-negative breast cancers.

Beyond oncology, GPER1 is essential for Homeostasis of glucose and metabolic control. Studies in GPER knockout mice reveal sex-specific impairments in insulin secretion and glucose tolerance, with estrogenic the modulation of pancreatic β-cell activity by estrogen and survival appearing to be GPER-dependent. These effects are mediated through both cAMP/PKA and PLC/IP3 mechanism, as PI3K/Akt and EGFR signalling cascades. GPER also protects β-cells from glucolipotoxicity and Oxidative stress and promotes islet cell proliferation, implying a potential role in the healing process of diabetes.

Collectively, GPER1 represents a multifunctional ER have in cancer progression, metabolic regulation, and endocrine function. Its dualistic signalling nature and tissue-specific actions highlight the intricacy of signaling by estrogen and underscore necessity of additional study to clarify its therapeutic potential and risks in hormone-sensitive conditions.

Keywords: G-proteins, GPER1, Diabetes, Obesity, Asthma, Cancer.

***Correspondence to:**

Sandhya Suresh,
M.Pharm (Pharmacology), Research Scholar, B. N. College of Pharmacy, Udaipur, Rajasthan, India.
Email: sandhyasuresh110@gmail.com

Article History:

Received: 28-04-2025, **Revised:** 02-06-2025, **Accepted:** 27-06-2025

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2025.11.4.001	

1. INTRODUCTION

1.1 GPCR 30/G-PROTEIN-COUPLED OESTROGEN RECEPTOR 1

GPER1, formerly known as GPR30, is a membrane-bound receptor capable of mediating estrogenic responses through its high affinity for 17β-estradiol (E2).[1,2] Multiple knockout mouse models have been developed to study GPER1's function relative to other estrogen receptors.[3] The selective GPER1 agonist G-1 exhibits strong binding and is widely used to investigate GPER1 signaling. Other ligands include 5408-0877, which mimics G-1 activity, and the antagonist G15, though G15 has been less frequently employed in studies. These agents-G-1, 5408-0877, and G15—are the main pharmacological tools for probing GPER1, although their specificity remains under evaluation.[4]

GPER1 exhibits unusual signalling by coupling both to Gα_s proteins, which increase cAMP, and Gα_i/o proteins, which attenuate it. This dual coupling was demonstrated in MDA-MB-231 breast cancer cells engineered to express GPER1, where E2 stimulated both cAMP production and pertussis toxin (PTX)-

sensitive ERK1/2 activation.[5] This dual behaviour—sometimes activating, sometimes inhibiting—has been further observed across different cell types. For instance, in vascular smooth muscle cells, E2-induced apoptosis required GPER1-mediated PI3K activation and PKA inhibition, both PTX-sensitive 6. Similarly, in SkBr3 cells, E2 triggered GPER1-dependent, PTX-sensitive c-Fos upregulation, correlating with earlier findings of cAMP generation in these cells.[6]

While most G protein-coupled receptors (GPCRs) bind one type of G protein, GPER1 can engage both Gα_s and Gα_i/o, a property shared only by select receptors like β-adrenergic receptors, which switch coupling depending on the ligand. Whether GPER1 similarly switches coupling is still unclear. GPER1 also mediates rises in cytosolic Ca^{2+}, a response that is PTX-sensitive and independent of phospholipase C (PLC), implicating Gα_i/o involvement rather than classical Gα_q signalling. This calcium signalling also varies by ERα status: in ERα-positive MCF-7 cells, GPER1 activation leads to a sustained IP_3 receptor–dependent Ca^{2+} increase; in ERα-negative SkBr3 cells, the response is brief and ryanodine receptor–mediated.[7]

Beyond calcium signalling, GPER1 activation leads to PI3K and PTX-sensitive Src activation, initiating phosphorylation cascades involving Akt and SHC. Akt phosphorylation is linked to anti-apoptotic and cardioprotective effects, while SHC phosphorylation promotes cleavage of heparin-binding EGF, likely via metalloproteinases, resulting in EGF receptor transactivation. However, the positioning of PI3K/Akt in GPER1 signalling remains debated. Some studies suggest PI3K/Akt acts downstream of the PTX-sensitive Src/SHC/EGF/ERK1/2 axis, while others, such as Revankar et al. (2005), found this activation to be PTX-insensitive, challenging the involvement of Gα_i/o proteins.[8]

1.2 ESTROGEN RECEPTORS

Estrogen functions through three main receptors: ERα, ERβ, and GPER. The classical nuclear receptors, ERα and ERβ, act as ligand-activated transcription factors. [9,10] Their tissue distribution varies; ERα is abundant in the uterus, bone, and luminal breast epithelial cells, whereas ERβ dominates in the lung, colon, and breast stromal myoepithelial cells.[11,12] Both receptors influence gene expression by binding DNA directly or interacting with other transcription regulators, often resulting in reduced gene expression levels.[13] Besides their genomic effects, which take minutes to hours, ERα and ERβ can also mediate rapid, non-genomic responses occurring within seconds to minutes. These include triggering kinase cascades and mobilizing intracellular calcium (Ca^{2+}).[14] This rapid signalling likely involves membrane-associated palmitoylated receptor forms or splice variants, rather than the nuclear receptors responsible for gene transcription.[15]

GPER, a G-protein-coupled receptor identified in the late 1990s, facilitates rapid non-genomic estrogen signalling. Upon activation, GPER initiates several downstream effects, including cAMP synthesis, intracellular Ca^{2+} release, and activation of kinases like MAPK and PI3K.[16] Interestingly, GPER activates PI3K and MAPK indirectly by transactivating the epidermal growth factor receptor (EGFR), via cleavage of membrane-bound HB-EGF, even though GPER is mainly localized in the endoplasmic reticulum and EGFR in the plasma membrane.[17] GPER is found in low levels at the plasma membrane and also within the nucleus, ER, and Golgi apparatus.[18] Some studies suggest nuclear GPER may act in transcriptional regulation, potentially in tandem with EGFR, though this role is not fully confirmed.[19] GPER influences gene expression through transcription factors like CREB, albeit regulating fewer genes than ERα and Erβ.[20] Notably, GPER activation increases c-fos expression in thyroid, endometrial, and GPER-positive breast cancer cells, while also upregulating genes such as Bcl-2 and CCN2.[21,22]

1.3 GPER-RELATED SIGNALLING PATHWAY

I. Nuclear factor-Kappa B (NF-κB) Signalling Pathway

Epithelial-mesenchymal transition (EMT) in epithelial cells can worsen mastitis. GPER1 activation has been shown to suppress EMT in goat mammary epithelial cells by inhibiting the NF-κB signalling pathway, thereby slowing mastitis progression. Additionally, Okamoto et al. reported that the GPER agonist G-1 reduces lipopolysaccharide (LPS)-induced IL-6 overexpression in mouse macrophages via NF-κB inhibition, highlighting estrogen's anti-inflammatory effects.

II. Hippo Signalling Pathway

As reported by Zhou et al. (Xie et al., 2021), GPER expression is significantly higher in breast invasive ductal carcinoma cells than in adjacent normal tissue. GPER's downstream signalling is closely linked to the Hippo/YAP/TAZ pathway, which plays a key role in breast cancer development. Deng et al. found that Bisphenol S activates YAP in triple-negative breast cancer cells, promoting its nuclear accumulation and gene activation. Blocking GPER reduces Bisphenol S-induced activation of the Hippo/YAP pathway.

III. Mitogen-Activated Protein Kinase Signalling Pathway

Triclosan has been found to mimic estrogen by activating GPER, leading to increased expression of miR-144 and disruption of neuro-related genes, contributing to neurodevelopmental toxicity through protein kinase C signalling. In estrogen receptor-positive (ER+) breast cancer cells, GPER activation also stimulates the MAPK/ERK pathway, elevating TRIM2 levels. This, in turn, suppresses BIM expression in tamoxifen-resistant cells, suggesting a potential therapeutic target for overcoming drug resistance in ER+ breast cancer.[23]

IV. Phosphatidylinositol 3-kinase (PI3K)/Akt Signalling Pathway

In SKBR-3 breast cancer cells lacking nuclear estrogen receptors but expressing GPER, cryptotanshinone—a compound from the Chinese herb Danshen—was found to inhibit PI3K and phosphorylated AKT by blocking GPER-mediated PI3K/AKT signalling. In MCF-7 cells, cryptotanshinone also downregulated this pathway and induced apoptosis through GPER activation.[24,25]

V. The Signaling Pathway of Extracellular Signal-Regulated Kinase (ERK)

In hepatocellular carcinoma (HCC), SMMC-7721 and HCCLM3 cell lines show high GPER expression. Qiu et al. (2021) found that GPER-positive HCC patients—mostly female, HBV surface antigen-negative—had smaller tumours, lower serum AFP, and longer survival than GPER-negative cases. GPER agonist G1 activated EGFR/AKT and EGFR/ERK pathways in HCC cells. Additionally, in a trinitrobenzene sulfonic acid-induced mouse model of Crohn's disease, GPER activation reduced mortality and C-reactive protein via ERK signalling regulation.

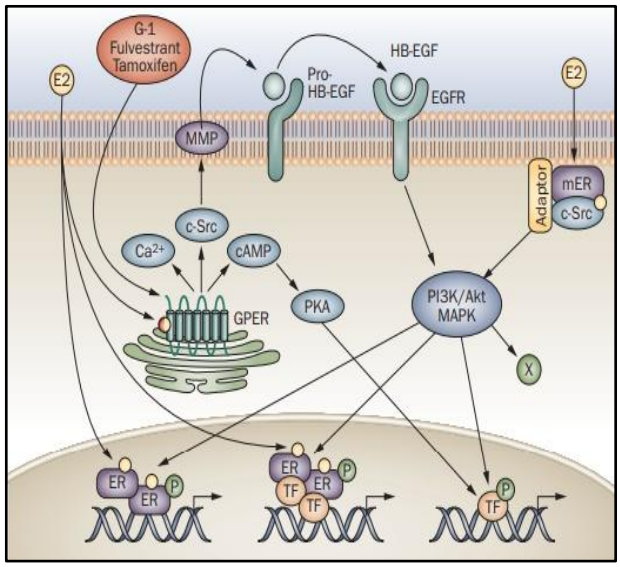

Figure 1 : Nongenomic and genomic estrogen signalling pathways.[7]

1.4 ESTROGEN THERAPY AND OBESITY

Estrogen signalling plays a key role in obesity development among menopausal women, who are three times more likely to develop obesity and metabolic syndrome than premenopausal women.[26] Hormone replacement therapy (HRT) using estrogen/progestin has been shown to reduce insulin, fasting glucose, and visceral fat levels. Estrogens also help lower cardiovascular risks, such as total cholesterol and LDL, which typically rise during menopause.[27]

Clinical outcomes vary based on estrogen type and delivery method. A WHI study reported that combination therapy (0.625 mg conjugated equine estrogens + 2.5 mg medroxyprogesterone acetate) or estrogen-only therapy led to reduced body fat in the first three years, with no further loss by year six, as per DXA body composition scans.[28] Estradiol (E2), the primary active estrogen, is available in oral and transdermal forms. Transdermal delivery offers more stable serum levels and avoids first-pass liver metabolism, reducing hepatic side effects compared to oral HRT.[29]

1.4.1 Estrogens in the Regulation of Metabolic Inflammation

Lipid-overloaded adipocytes undergo ER stress and mitochondrial dysfunction, leading to hypoxia, fibrosis, and cell death. This triggers the expression of pro-inflammatory genes, attracting immune cells that further impair adipocyte function via inflammatory mediators. Obesity is marked by chronic low-grade inflammation, or metaflammation, contributing to cardiometabolic disorders.

In lean individuals, M2 macrophages in adipose tissue release anti-inflammatory signals. In obesity, however, adipocytes secrete higher levels of IL-6 and TNFα, attracting M1 macrophages that sustain inflammation and promote cell death. Estrogen's immunomodulatory effects in adipose tissue depend on its concentration, receptor subtype, and immune cell type. Evidence suggests estrogen can suppress pro-inflammatory signals.

Macrophages lacking ERα show impaired phagocytosis and increased IL-1β, IL-6, and IFN-γ secretion. ERα-deficient myeloid cells in mice lead to elevated insulin, leptin, and PAI-1, resulting in insulin resistance and accelerated atherosclerosis—partly due to estradiol's regulation of Tgm2. Both male and female αERKO mice show increased adiposity and inflammation. In βERKO mice, ERα knockdown induces fibrosis, while ERβ remains functional. ArKO mice show increased M1 macrophages and inflammation, whereas aromatase overexpression reduces it—an effect not replicated by 17β-E2. In obese human adipose tissue, ER gene expression inversely correlates with IL-1β and IL-6. Estradiol also suppresses LPS/IFN-γ-induced activation of M2 macrophages.[30-33]

1.4.2 Estrogens as Anti-Obesity Agents

Female mice gain less weight than males on a high-fat diet due to lower caloric intake and higher physical activity. They also store fat subcutaneously, which is less harmful than visceral fat.[34] Estrogen receptors, especially ERα, are widely distributed, with ERβ mainly in the hypothalamus, lungs, and reproductive tract. 17β-estradiol (E2) enhances fat breakdown, reduces fat synthesis, and supports energy regulation via leptin signalling.[35] E2 also modulates inflammation—amplifying it during acute stress for immune defence, but suppressing it chronically to prevent tissue damage—contributing to lower inflammation-related disease risk in females.[36]

1.5 GPER FUNCTIONS IN DIABETES AND GLUCOSE HOMEOSTASIS

GPER plays a vital role in regulating glucose metabolism. Female GPER knockout (KO) mice show impaired glucose tolerance, reduced insulin secretion, and higher glucose levels than wild types, while male KO mice show minimal changes. STZ-treated female KO mice also had lower β-cell mass and insulin content.[37] GPER KO mice display age-related insulin resistance with elevated inflammatory markers and lipids, despite normal fasting glucose.[38] GPER deletion blunts E2's effects on glucose regulation, confirming its role in E2-mediated homeostasis.[39] GPER also supports β-cell function and survival by enhancing insulin release and activating protective signalling pathways.[40]

1.5.1 Mechanism of GPER Signalling in DM: The Potential Role of Epigenetic Modifications

Epigenetic mechanisms, including miRNA regulation, may mediate GPER's role in diabetes. E2 enhances miR-30b-5p expression via GPER, yet this miRNA is reduced in T2DM and nephropathy. BPA exposure activates GPER, suppressing miR-338 and PDX-1, impairing insulin secretion. Diabetes-related GPER modulation could affect β-cell survival and function. Though GPER epigenetic dysregulation is unconfirmed, other estrogen receptors like ERα and ERβ show epigenetic alterations in diabetes. Genistein, a phytoestrogen, increases GPER and ERβ expression, promotes β-cell survival, and may offer epigenetic benefits. Further studies are needed to explore GPER's direct epigenetic involvement in diabetic conditions.[41,42]

1.5.2 Therapeutics implantation

Though ERα and ERβ have been widely studied, GPER's metabolic role remains less understood. STX, a GPER activator, modulates hypothalamic neuron activity and limits weight gain in ovariectomized animals. GPER KO mice exhibit increased visceral fat and body weight, more prominently in females. However, some studies report no significant weight difference, while others note increased fat mass and adipocyte size in KO mice on low-fat diets. These inconsistencies suggest GPER's role in metabolism varies with sex, diet, and genetics. Understanding its exact contribution may support GPER-targeted therapies for obesity and metabolic disorders.[43]

1.6 GPCER IN CANCER

17β-estradiol is vital for breast development and plays a significant role in breast cancer progression. It drives tumour initiation, growth, and metastasis via estrogen signalling. Therapies like tamoxifen, aromatase inhibitors, fulvestrant, and raloxifene aim to disrupt this signalling. However, agents such as tamoxifen and fulvestrant also activate GPER, complicating treatment outcomes. In MCF-7 cells, estradiol deprivation increases GPER levels, while tamoxifen promotes proliferation via GPER-EGF signalling.[44,45]

GPER is expressed in about 50% of breast cancers, regardless of ER status, and is linked to larger tumors and metastasis. In tamoxifen-treated patients, high GPER expression correlates with poor survival, suggesting reduced treatment efficacy. Beyond breast cancer, GPER is also found in endometrial, ovarian, thyroid, lung, prostate, testicular, and brain tumours. GPER activation by estradiol or agents like genistein and bisphenol A can promote proliferation. Notably, genistein enhances acid ceramidase expression, facilitating MCF-7 cell growth. In ovarian and endometrial cancers, higher GPER levels associate with worse outcomes.[46]

1.6.1 Mechanism

GPER signalling can support or suppress tumour growth depending on the tissue type. In ER-positive breast tumours, GPER may induce endocrine resistance. Conversely, G-1-mediated GPER activation inhibits melanoma growth and improves PD-1 immunotherapy. In breast cancer fibroblasts, GPER induces pro-tumorigenic factors like VEGF and CTGF, enhancing migration and angiogenesis. It also exerts anti-inflammatory effects in immune cells by suppressing cytokines (IL-1β, TNF-α, IFN-γ), potentially aiding cancer prevention and autoimmune therapy. GPER reduces adipokine secretion and adiposity, which may indirectly impair tumour progression by limiting nutrient supply.[47]

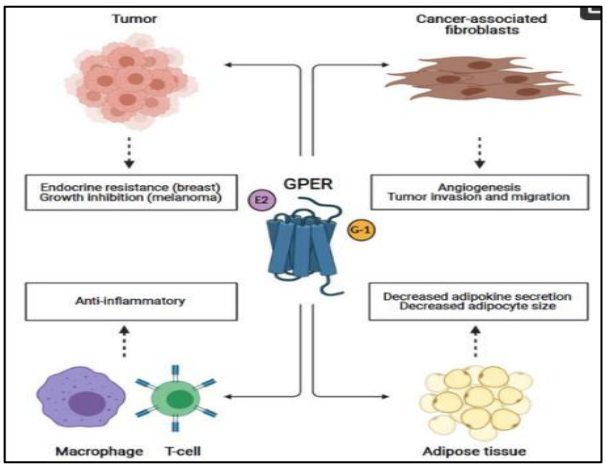

Figure 2: Impacts of G protein coupled estrogen receptor signalling in multiple tissue types that affect carcinogenesis.[47]

1.6.2 Therapeutics

GPER's expression in various cancers suggests diagnostic and therapeutic potential. In multiple cell lines, G-1 activates proliferation, though it suppresses growth in some (e.g., melanoma, prostate). In prostate cancer models, G-1 inhibits only castration-resistant types. Discrepancies in G-1 effects may stem from dosage or tumour biology. High GPER expression is associated with poor outcomes in breast, ovarian, and endometrial cancers. Tamoxifen-treated metastases often show higher GPER levels than primary tumours. In ER-/GPER+ cancers, tamoxifen is less effective than aromatase inhibitors. GPER knockout mice exhibit reduced tumour size and metastasis, confirming its tumour-promoting role.[48,49]

1.7 G PROTEINS IN ASTHMA

G proteins, through GPCRs, play a key role in asthma by regulating airway smooth muscle tone, inflammation, and immune response. Receptors like β2-adrenergic, muscarinic, and histamine couple with G proteins (Gs, Gi, Gq/11, G12/13), triggering signalling cascades essential to airway physiology and asthma pathogenesis.

1.7.1 Estrogen Receptors in Asthma

Estrogen receptors ERα and ERβ influence asthma via genomic actions (gene expression) and non-genomic effects (rapid signalling). These mechanisms affect muscle tone, inflammation, and mucus production, with GPCR interactions contributing to sex-based differences in asthma severity.

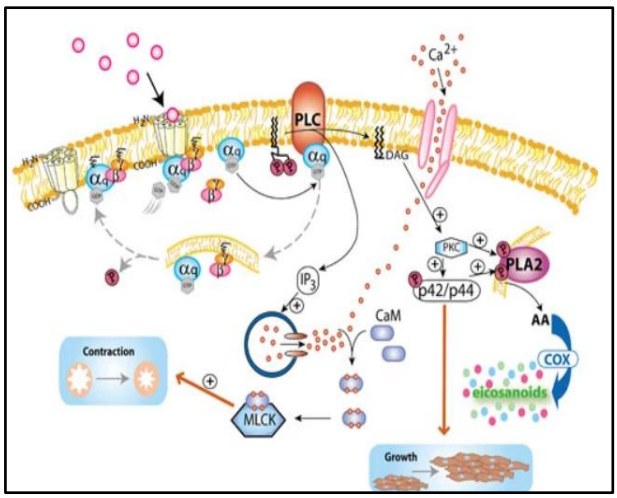

Figure 3: GP-coupled receptor signalling in airway smooth muscle.[53]

1.8 INTERACTION BETWEEN G PROTEINS AND ER

In asthma, estrogen receptors (ERs) and G protein-coupled receptors (GPCRs) demonstrate cross-talk, affecting each other's signalling. ERs influence GPCR expression and function, while GPCR pathways modulate ER activity. This interaction is particularly important in airway tissues where inflammation, immune responses, and smooth muscle tone are regulated. Estrogen and GPCR signalling contribute to sex-based differences in asthma severity and prevalence.

1.8.1 Mechanism

The integration of GPCR and ER signalling pathways governs cellular behaviour in asthma. GPCRs regulate calcium levels and muscle tone, while ERs contribute both genomic and non-genomic effects. Together, they coordinate immune and inflammatory responses that shape disease outcomes.

1.8.1.1 Function of G protein signalling in airway physiology

Regulation of smooth muscle tone by GPCRs

GPCRs regulate airway smooth muscle tone via G proteins. Gαq triggers Ca^{2+} release through PLCβ and IP3, activating MLCK and

contracting muscle. Gα12/13 activate RhoA, enhancing calcium sensitivity and contraction. In contrast, Gαs activation (via β2-agonists like albuterol) increases cAMP and PKA activity, inhibiting MLCK and relaxing muscle. Drugs like theophylline prolong relaxation by preventing cAMP degradation. These pathways highlight both contractile and relaxant roles of G proteins in airway physiology.[50-52]

1.8.2 Therapeutics

1.8.2.1 Protein signalling: A potential new target of antiallergy therapy

While GPCR-targeted drugs like β-agonists have advanced allergy treatment, long-term use leads to receptor and Gαs protein downregulation, reducing efficacy. Emerging research highlights the need to explore downstream G protein signalling as a therapeutic target. Regulator of G protein Signalling (RGS) proteins, key modulators of this pathway, bind Gα subunits (Gαi, Gαq, Gαs), accelerating GTP hydrolysis to GDP, thus deactivating downstream signalling. This ability to quickly terminate signalling presents RGS proteins as potential drug targets for restoring GPCR function and managing allergic inflammation effectively.[53]

1.8.2.2 RGS proteins

RGS proteins, over 20 in mammals, regulate GPCR cascades by dampening G protein signals. They promote GTP hydrolysis on Gα subunits, reducing activation lifespan and signal transmission. RGS proteins also block G proteins from interacting with effectors, independently of GAP activity. RGS1, RGS2, RGS3, RGS14, and RGS16 are expressed in immune cells and influence responses like chemotaxis and cytokine signalling. Expression is modulated by antigen and cytokine signals, indicating feedback control. RGS2–/– mice show impaired T-cell function and antiviral responses, suggesting vital roles for RGS proteins in immune regulation and inflammation.[54-56]

CONCLUSION

In conclusion, GPER1, a non-classical estrogen receptor, plays a multifaceted role in mediating estrogenic signals via its interaction with G proteins such as Gα_s and Gα_i/o. This receptor has gained attention for its involvement in essential physiological processes, including glucose homeostasis, β-cell survival, fat metabolism, and cancer progression. Its high-affinity binding to 17β-estradiol enables the activation of intracellular pathways such as cAMP generation, calcium mobilization, and PI3K/Akt signalling. Selective pharmacological agents like G-1, G15, and 5408-0877 have provided insights into it signalling mechanisms, although further studies are necessary to clarify their receptor specificity and tissue-specific effects.

In metabolic regulation, particularly in diabetes and obesity, GPER1 has shown a protective role. Studies on knockout models highlight its contribution to insulin secretion and preservation of β-cell function, especially in females. These effects point to a sex-specific metabolic advantage mediated by estrogen signalling through GPER1. Moreover, its activation holds potential therapeutic benefits for improving insulin sensitivity and combating metabolic disorders.

In cancer biology, GPER1 influences the progression of estrogen-responsive malignancies such as breast, ovarian, and endometrial cancers. Interestingly, drugs like tamoxifen and fulvestrant, designed to block classical estrogen receptors, may paradoxically activate GPER1 and inadvertently promote tumour growth in certain contexts.

Overall, GPER1 serves as a crucial link between endocrine signalling, metabolic regulation, and tumour biology. With ongoing research, selective targeting of GPER1 could offer innovative strategies for managing both metabolic and hormone-driven cancers, particularly where classical estrogen receptor pathways are absent or compromised.

REFERENCES

1. Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER. A transmembrane intracellular estrogen receptor mediates rapid cell signaling. Science. 2005;307(5715):1625-30.

2. Thomas P, Alyea R, Pang Y, Peyton C, Dong J, Berg AH. Conserved estrogen binding and signaling functions of the G protein-coupled estrogen receptor 1 (GPER) in mammals and fish. Steroids. 2010;75(8-9):595-602.

3. Wang J, Weng J, Cai Y, Penland R, Liu M, Ittmann M. The prostate-specific G-protein coupled receptors PSGR and PSGR2 are prostate cancer biomarkers that are complementary to α-methylacyl-CoA racemase. Prostate. 2006;66(8):847-57.

4. Mårtensson UE, Salehi SA, Windahl S, Gomez MF, Swärd K, Daszkiewicz-Nilsson J, Leeb-Lundberg LF. Deletion of the G protein-coupled receptor 30 impairs glucose tolerance, reduces bone growth, increases blood pressure, and eliminates estradiol-stimulated insulin release in female mice. Endocrinology. 2009;150(2):687-98.

5. Bologa CG, Revankar CM, Young SM, Edwards BS, Arterburn JB, Kiselyov AS, Prossnitz ER. Virtual and biomolecular screening converge on a selective agonist for GPR30. Nat Chem Biol. 2006;2(4):207-12.

6. Martin B, De Maturana RL, Brenneman R, Walent T, Mattson MP, Maudsley S. Class II G protein-coupled receptors and their ligands in neuronal function and protection. Neuromolecular Med. 2005;7:3-36.

7. Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER. A transmembrane intracellular estrogen receptor mediates rapid cell signaling. Science. 2005;307(5715):1625-30.

8. Terasawa E, Noel SD, Keen KL. Rapid action of oestrogen in luteinising hormone-releasing hormone neurones: the role of GPR30. J Neuroendocrinol. 2009;21(4):316-21.

9. King WJ, Greene GL. Monoclonal antibodies localize oestrogen receptor in nuclei of target cells. Nature.1984;307(5953):745-7.

10. Dahlman-Wright K, Cavailles V, Fuqua SA, Jordan VC, Katzenellenbogen JA, Korach KS, Gustafsson JÅ. International union of pharmacology. LXIV. Estrogen receptors. Pharmacol Rev. 2006;58(4):773-81.

11. Ruggiero RJ, Likis FE. Estrogen: physiology, pharmacology, and formulations for replacement therapy. J Midwifery Womens Health. 2002;47(3):130-8.

12. Nilsson S, Gustafsson JÅ. Estrogen receptors: therapies targeted to receptor subtypes. Clin Pharmacol Ther. 2011;89(1):44-55.

13. Frasor J, Stossi F, Danes JM, Komm B, Lyttle CR, Katzenellenbogen BS. Selective estrogen receptor modulators: discrimination of agonistic versus antagonistic activities by gene expression profiling in breast cancer cells. Cancer Res. 2004;64(4):1522-33.

14. Banerjee S, Chambliss KL, Mineo C, Shaul PW. Recent insights into non-nuclear actions of estrogen receptor alpha. Steroids. 2014;81:64-9.
15. Chambliss KL, Wu Q, Oltmann S, Konaniah ES, Umetani M, Korach KS, Shaul PW. Non-nuclear estrogen receptor α signaling promotes cardiovascular protection but not uterine or breast cancer growth in mice. J Clin Invest. 2010;120(7):2319-30.
16. Russo J, Russo IH. The role of estrogen in the initiation of breast cancer. J Steroid Biochem Mol Biol. 2006;102(1-5):89-96.
17. Filardo EJ, Quinn JA, Bland KI, Frackelton AR Jr. Estrogen-induced activation of Erk-1 and Erk-2 requires the G protein-coupled receptor homolog, GPR30, and occurs via trans-activation of the epidermal growth factor receptor through release of HB-EGF. Mol Endocrinol. 2000;14(10):1649-60.
18. Filardo E, Quinn J, Pang Y, Graeber C, Shaw S, Dong J, Thomas P. Activation of the novel estrogen receptor G protein-coupled receptor 30 (GPR30) at the plasma membrane. Endocrinology. 2007;148(7):3236-45.
19. Madeo A, Maggiolini M. Nuclear alternate estrogen receptor GPR30 mediates 17β-estradiol–induced gene expression and migration in breast cancer–associated fibroblasts. Cancer Res. 2010;70(14):6036-46.
20. Prossnitz ER, Maggiolini M. Mechanisms of estrogen signaling and gene expression via GPR30. Mol Cell Endocrinol. 2009;308(1-2):32-8.
21. Vivacqua A, Bonofiglio D, Recchia AG, Musti AM, Picard D, Andò S et al. The G protein-coupled receptor GPR30 mediates the proliferative effects induced by 17β-estradiol and hydroxytamoxifen in endometrial cancer cells. Mol Endocrinol. 2006;20(3):631-46.
22. Stauffer SR, Coletta CJ, Tedesco R, Nishiguchi G, Carlson K, Sun J et al. Pyrazole ligands: structure−affinity/activity relationships and estrogen receptor-α-selective agonists. J Med Chem. 2000;43(26):4934-47.
23. Diao W, Qian Q, Sheng G, He A, Yan J, Dahlgren RA, Wang H. Triclosan targets miR-144 abnormal expression to induce neurodevelopmental toxicity mediated by activating PKC/MAPK signaling pathway. J Hazard Mater. 2022;431:128560.
24. Okamoto M, Suzuki T, Mizukami Y, Ikeda T. The membrane-type estrogen receptor G-protein-coupled estrogen receptor suppresses lipopolysaccharide-induced interleukin 6 via inhibition of nuclear factor-kappa B pathway in murine macrophage cells. Anim Sci J. 2017;88(11):1870-9.
25. Shi D, Li H, Zhang Z, He Y, Chen M, Sun L, Zhao P. Cryptotanshinone inhibits proliferation and induces apoptosis of breast cancer MCF-7 cells via GPER mediated PI3K/AKT signaling pathway. PLoS One. 2022;17(1):e0262389.
26. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev. 2009;30(4):293-342.
27. Pickar JH, Thorneycroft I, Whitehead M. Effects of hormone replacement therapy on the endometrium and lipid parameters: a review of randomized clinical trials, 1985 to 1995. Am J Obstet Gynecol. 1998;178(5):1087-99.
28. Kenny AM, Kleppinger A, Wang Y, Prestwood KM. Effects of ultra-low-dose estrogen therapy on muscle and physical function in older women. J Am Geriatr Soc. 2005;53(11):1973-7.
29. Chu MC, Cosper P, Nakhuda GS, Lobo RA. A comparison of oral and transdermal short-term estrogen therapy in postmenopausal women with metabolic syndrome. Fertil Steril. 2006;86(6):1669-75.
30. Varghese M, Griffin C, Singer K. The role of sex and sex hormones in regulating obesity-induced inflammation. In: Sex and Gender Factors Affecting Metabolic Homeostasis, Diabetes and Obesity. 2017. p. 65-86.
31. Ribas V, Drew BG, Le JA, Soleymani T, Daraei P, Sitz D, et al. Myeloid-specific estrogen receptor α deficiency impairs metabolic homeostasis and accelerates atherosclerotic lesion development. Proc Natl Acad Sci U S A. 2011;108(39):16457-62.
32. Davis KE, Neinast MD, Sun K, Skiles WM, Bills JD, Zehr JA, et al. The sexually dimorphic role of adipose and adipocyte estrogen receptors in modulating adipose tissue expansion, inflammation, and fibrosis. Mol Metab. 2013;2(3):227-42.
33. Toniolo A, Fadini GP, Tedesco S, Cappellari R, Vegeto E, Maggi A, et al. Alternative activation of human macrophages is rescued by estrogen treatment in vitro and impaired by menopausal status. J Clin Endocrinol Metab. 2015;100(1):E50-8.
34. Hong J, Stubbins RE, Smith RR, Harvey AE, Núñez NP. Differential susceptibility to obesity between male, female and ovariectomized female mice. Nutr J. 2009;8:1-5.
35. Clegg DJ, Brown LM, Woods SC, Benoit SC. Gonadal hormones determine sensitivity to central leptin and insulin. Diabetes. 2006;55(4):978-87.
36. Couse JF, Lindzey J, Grandien KAJ, Gustafsson JA, Korach KS. Tissue distribution and quantitative analysis of estrogen receptor-α (ERα) and estrogen receptor-β (ERβ) messenger ribonucleic acid in the wild-type and ERα-knockout mouse. Endocrinology. 1997;138(11):4613-21.
37. Liu S, Mauvais-Jarvis F. Rapid, nongenomic estrogen actions protect pancreatic islet survival. Islets. 2009;1(3):273-5.
38. Sharma G, Prossnitz ER. Mechanisms of estradiol-induced insulin secretion by the G protein-coupled estrogen receptor GPR30/GPER in pancreatic β-cells. Endocrinology. 2013;152(8):3030-9.
39. Gilliam-Davis S, Cohen JA, Lindsey SH, Yamaleyeva L, Chappell M. The estrogen receptor GPR30 is renoprotective in diabetic hypertensive female rats. Hypertension. 2010;56(5 Suppl):E56.
40. Balhuizen A, Kumar R, Amisten S, Lundquist I, Salehi A. Activation of G protein-coupled receptor 30 modulates hormone secretion and counteracts cytokine-induced apoptosis in pancreatic islets of female mice. Mol Cell Endocrinol. 2010;320(1-2):16-24.
41. Chevalier N, Bouskine A, Fenichel P. Bisphenol A promotes testicular seminoma cell proliferation through GPER/GPR30. Journal name not provided—please add source for full citation.
42. Knabl J, Hiden U, Hüttenbrenner R, Riedel C, Hutter S, Kirn V, et al. GDM alters expression of placental estrogen receptor α in a cell type and gender-specific manner. Reprod Sci. 2015;22(12):1488-95.
43. Rae JM, Johnson MD. What does an orphan G-protein-coupled receptor have to do with estrogen? Breast Cancer Res. 2005;7:1-2.
44. Bagnato A, Loizidou M, Pflug BR, Curwen J, Growcott J. Role of the endothelin axis and its antagonists in the treatment of cancer. Br J Pharmacol. 2011;163(2):220-33.
45. Chae SS, Paik JH, Furneaux H, Hla T. Requirement for sphingosine 1–phosphate receptor-1 in tumor angiogenesis

demonstrated by in vivo RNA interference. J Clin Invest. 2004;114(8):1082-9.
46. Takuwa Y, Du W, Qi X, Okamoto Y, Takuwa N, Yoshioka K. Roles of sphingosine-1-phosphate signaling in angiogenesis. World J Biol Chem. 2010;1(10):298.
47. Gutkind JS. Regulation of mitogen-activated protein kinase signaling networks by G protein-coupled receptors. Sci STKE. 2000;2000(40):re1.
48. Tang J, Li Z, Lu L, Cho CH. β-Adrenergic system, a backstage manipulator regulating tumour progression and drug target in cancer therapy. Semin Cancer Biol. 2013;23(6):533-42.
49. Su LD, Peng JM, Ge YB. Formyl peptide receptor 2 mediated chemotherapeutics drug resistance in colon cancer cells. Eur Rev Med Pharmacol Sci. 2018;22(1).
50. Hákonarson H, Grunstein MM. Regulation of second messengers associated with airway smooth muscle contraction and relaxation. Am J Respir Crit Care Med. 1998;158(Suppl 2):S115-22.
51. Chiba Y, Misawa M. Increased expression of G12 and G13 proteins in bronchial smooth muscle of airway hyperresponsive rats. Inflamm Res. 2001;50:333-6.
52. Niewoehner DE, Duane ST, McGowan T, Montgomery MR. Mechanisms of airway smooth muscle response to isoproterenol and theophylline. J Appl Physiol. 1979;47(2):330-6.
53. Finney PA, Belvisi MG, Donnelly LE, Chuang TT, Mak JC, Scorer C, et al. Albuterol-induced downregulation of Gsα accounts for pulmonary β2-adrenoceptor desensitization in vivo. J Clin Invest. 2000;106(1):125-35.
54. Hepler JR, Berman DM, Gilman AG, Kozasa T. RGS4 and GAIP are GTPase-activating proteins for Gqα and block activation of phospholipase Cβ by γ-thio-GTP-Gqα. Proc Natl Acad Sci U S A. 1997;94(2):428-32.
55. Reif K, Cyster JG. RGS molecule expression in murine B lymphocytes and ability to down-regulate chemotaxis to lymphoid chemokines. J Immunol. 2000;164(9):4720-9.
56. Druey KM, Blumer KJ, Kang VH, Kehrl JH. Inhibition of G-protein-mediated MAP kinase activation by a new mammalian gene family. Nature. 1996;379(6567):742-6.

Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Sandhya Suresh, Siddharaj Singh Sisodia. Emerging Roles of G Protein- Coupled Estrogen Receptor 1 (GPER) in Obesity, Asthma, Diabetes, and Cancer: Molecular Mechanisms and Therapeutic Implications. Int J Med Res Prof. 2025 July; 11(4): 1-7. DOI:10.21276/ijmrp.2025.11.4.001