

G protein-coupled estrogen receptor in GtoPdb v.2023.1

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Abstract

The G protein-coupled estrogen receptor (GPER, **nomenclature as agreed by the NC-IUPHAR Subcommittee on the G protein-coupled estrogen receptor [26]**) was identified following observations of estrogen-evoked **cyclic AMP** signalling in breast cancer cells [2], which mirrored the differential expression of an orphan 7-transmembrane receptor GPR30 [6]. There are observations of both cell-surface and intracellular expression of the GPER receptor [29, 34]. Selective agonist/ antagonists for GPER have been characterized [26]. Antagonists of the nuclear estrogen receptor, such as **fulvestrant** [11], **tamoxifen** [29, 34] and **raloxifene** [25], as well as the flavonoid 'phytoestrogens' **genistein** and **quercetin** [18], are agonists of GPER. Reviews of GPER pharmacology have been published [26]. The roles of GPER in (patho)physiological systems throughout the body (cardiovascular, metabolic, endocrine, immune, reproductive) and in cancer have also been reviewed [26, 27, 20, 17, 9]. The GPER-selective agonist G-1 is currently in Phase I/II clinical trials for cancer (NCT04130516).

Contents

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Database links

[G protein-coupled estrogen receptor](#)

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=22>

[Introduction to G protein-coupled estrogen receptor](#)

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=22>

Receptors

[GPER](#)

References

1. Albanito L, Madeo A, Lappano R, Vivacqua A, Rago V, Carpino A, Oprea TI, Prossnitz ER, Musti AM and Andò S *et al.* (2007) G protein-coupled receptor 30 (GPR30) mediates gene expression changes and growth response to 17beta-estradiol and selective GPR30 ligand G-1 in ovarian cancer cells. *Cancer Res* **67**: 1859-66 [PMID:17308128]
2. Aronica SM, Kraus WL and Katzenellenbogen BS. (1994) Estrogen action via the cAMP signaling pathway: stimulation of adenylate cyclase and cAMP-regulated gene transcription. *Proc Natl Acad Sci USA* **91**: 8517-21 [PMID:8078914]
3. Bologa CG, Revankar CM, Young SM, Edwards BS, Arterburn JB, Kiselyov AS, Parker MA, Tkachenko SE, Savchuck NP and Sklar LA *et al.* (2006) Virtual and biomolecular screening converge on a selective agonist for GPR30. *Nat Chem Biol* **2**: 207-12 [PMID:16520733]
4. Bonini JA, Anderson SM and Steiner DF. (1997) Molecular cloning and tissue expression of a novel orphan G protein-coupled receptor from rat lung. *Biochem Biophys Res Commun* **234**: 190-3 [PMID:9168987]
5. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
6. Carmeci C, Thompson DA, Ring HZ, Francke U and Weigel RJ. (1997) Identification of a gene (GPR30) with homology to the G-protein-coupled receptor superfamily associated with estrogen receptor expression in breast cancer. *Genomics* **45**: 607-17 [PMID:9367686]
7. Dennis MK, Burai R, Ramesh C, Petrie WK, Alcon SN, Nayak TK, Bologa CG, Leitao A, Brailoiu E and Deliu E *et al.* (2009) In vivo effects of a GPR30 antagonist. *Nat Chem Biol* **5**: 421-7 [PMID:19430488]
8. Dennis MK, Field AS, Burai R, Ramesh C, Petrie WK, Bologa CG, Oprea TI, Yamaguchi Y, Hayashi S and Sklar LA *et al.* (2011) Identification of a GPER/GPR30 antagonist with improved estrogen receptor counterselectivity. *J Steroid Biochem Mol Biol* **127**: 358-66 [PMID:21782022]
9. Filardo EJ. (2018) A role for G-protein coupled estrogen receptor (GPER) in estrogen-induced carcinogenesis: Dysregulated glandular homeostasis, survival and metastasis. *J Steroid Biochem Mol Biol* **176**: 38-48 [PMID:28595943]
10. Filardo EJ, Graeber CT, Quinn JA, Resnick MB, Giri D, DeLellis RA, Steinhoff MM and Sabo E. (2006) Distribution of GPR30, a seven membrane-spanning estrogen receptor, in primary breast cancer and its association with clinicopathologic determinants of tumor progression. *Clin Cancer Res* **12**: 6359-66 [PMID:17085646]
11. Filardo EJ, Quinn JA, Bland KI and Frackelton Jr AR. (2000) 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* **14**: 1649-60 [PMID:11043579]
12. Filardo EJ, Quinn JA, Frackelton Jr AR and Bland KI. (2002) Estrogen action via the G protein-coupled receptor, GPR30: stimulation of adenylyl cyclase and cAMP-mediated attenuation of the epidermal growth factor receptor-to-MAPK signaling axis. *Mol Endocrinol* **16**: 70-84 [PMID:11773440]
13. Gaudet HM, Cheng SB, Christensen EM and Filardo EJ. (2015) The G-protein coupled estrogen receptor, GPER: The inside and inside-out story. *Mol Cell Endocrinol* **418 Pt 3**: 207-19 [PMID:26190834]
14. Isensee J, Meoli L, Zazzu V, Nabzdyk C, Witt H, Soewarto D, Effertz K, Fuchs H, Gailus-Durner V and Busch D *et al.* (2009) Expression pattern of G protein-coupled receptor 30 in LacZ reporter mice. *Endocrinology* **150**: 1722-30 [PMID:19095739]
15. Kanda N and Watanabe S. (2003) 17beta-estradiol inhibits oxidative stress-induced apoptosis in keratinocytes by promoting Bcl-2 expression. *J Invest Dermatol* **121**: 1500-9 [PMID:14675202]
16. Koganti S, Snyder R, Gumaste U, Karamyan VT and Thekkumkara T. (2014) 2-methoxyestradiol binding of GPR30 down-regulates angiotensin AT(1) receptor. *Eur J Pharmacol* **723**: 131-40 [PMID:24262995]
17. Lappano R and Maggiolini M. (2018) GPER is involved in the functional liaison between breast tumor cells and cancer-associated fibroblasts (CAFs). *J Steroid Biochem Mol Biol* **176**: 49-56 [PMID:28249728]
18. Maggiolini M, Vivacqua A, Fasanella G, Recchia AG, Sisci D, Pezzi V, Montanaro D, Musti AM, Picard D and Andò S. (2004) The G protein-coupled receptor GPR30 mediates c-fos up-regulation by 17beta-estradiol and phytoestrogens in breast cancer cells. *J Biol Chem* **279**: 27008-16 [PMID:15090535]

19. Manavathi B and Kumar R. (2006) Steering estrogen signals from the plasma membrane to the nucleus: two sides of the coin. *J Cell Physiol* **207**: 594-604 [PMID:16270355]
20. Meyer MR and Barton M. (2018) GPER blockers as Nox downregulators: A new drug class to target chronic non-communicable diseases. *J Steroid Biochem Mol Biol* **176**: 82-87 [PMID:28343901]
21. Meyer MR, Fredette NC, Daniel C, Sharma G, Amann K, Arterburn JB, Barton M and Prossnitz ER. (2016) Obligatory role for GPER in cardiovascular aging and disease. *Sci Signal* **9**: ra105 [PMID:27803283]
22. Mårtensson UE, Salehi SA, Windahl S, Gomez MF, Swärd K, Daszkiewicz-Nilsson J, Wendt A, Andersson N, Hellstrand P and Grände PO *et al.* (2009) 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* **150**: 687-98 [PMID:18845638]
23. O'Dowd BF, Nguyen T, Marchese A, Cheng R, Lynch KR, Heng HH, Kolakowski Jr LF and George SR. (1998) Discovery of three novel G-protein-coupled receptor genes. *Genomics* **47**: 310-3 [PMID:9479505]
24. Owman C, Blay P, Nilsson C and Lolait SJ. (1996) Cloning of human cDNA encoding a novel heptahelix receptor expressed in Burkitt's lymphoma and widely distributed in brain and peripheral tissues. *Biochem Biophys Res Commun* **228**: 285-92 [PMID:8920907]
25. Petrie WK, Dennis MK, Hu C, Dai D, Arterburn JB, Smith HO, Hathaway HJ and Prossnitz ER. (2013) G protein-coupled estrogen receptor-selective ligands modulate endometrial tumor growth. *Obstet Gynecol Int* **2013**: 472720 [PMID:24379833]
26. Prossnitz ER and Arterburn JB. (2015) International Union of Basic and Clinical Pharmacology. XCVII. G Protein-Coupled Estrogen Receptor and Its Pharmacologic Modulators. *Pharmacol Rev* **67**: 505-40 [PMID:26023144]
27. Prossnitz ER and Hathaway HJ. (2015) What have we learned about GPER function in physiology and disease from knockout mice? *J Steroid Biochem Mol Biol* **153**: 114-26 [PMID:26189910]
28. Quinn JA, Graeber CT, Frackelton Jr AR, Kim M, Schwarzbauer JE and Filardo EJ. (2009) Coordinate regulation of estrogen-mediated fibronectin matrix assembly and epidermal growth factor receptor transactivation by the G protein-coupled receptor, GPR30. *Mol Endocrinol* **23**: 1052-64 [PMID:19342448]
29. Revankar CM, Cimino DF, Sklar LA, Arterburn JB and Prossnitz ER. (2005) A transmembrane intracellular estrogen receptor mediates rapid cell signaling. *Science* **307**: 1625-30 [PMID:15705806]
30. Sharma G, Hu C, Brigman JL, Zhu G, Hathaway HJ and Prossnitz ER. (2013) GPER deficiency in male mice results in insulin resistance, dyslipidemia, and a proinflammatory state. *Endocrinology* **154**: 4136-45 [PMID:23970785]
31. Smith HO, Arias-Pulido H, Kuo DY, Howard T, Qualls CR, Lee SJ, Verschraegen CF, Hathaway HJ, Joste NE and Prossnitz ER. (2009) GPR30 predicts poor survival for ovarian cancer. *Gynecol Oncol* **114**: 465-71 [PMID:19501895]
32. Southern C, Cook JM, Neetoo-Isseljee Z, Taylor DL, Kettleborough CA, Merritt A, Bassoni DL, Raab WJ, Quinn E and Wehrman TS *et al.* (2013) Screening β -Arrestin Recruitment for the Identification of Natural Ligands for Orphan G-Protein-Coupled Receptors. *J Biomol Screen* **18**: 599-609 [PMID:23396314]
33. Terasawa E, Noel SD and Keen KL. (2009) Rapid action of oestrogen in luteinising hormone-releasing hormone neurones: the role of GPR30. *J Neuroendocrinol* **21**: 316-21 [PMID:19207808]
34. Thomas P, Pang Y, Filardo EJ and Dong J. (2005) Identity of an estrogen membrane receptor coupled to a G protein in human breast cancer cells. *Endocrinology* **146**: 624-32 [PMID:15539556]
35. Wang C, Dehghani B, Magrisso IJ, Rick EA, Bonhomme E, Cody DB, Elenich LA, Subramanian S, Murphy SJ and Kelly MJ *et al.* (2008) GPR30 contributes to estrogen-induced thymic atrophy. *Mol Endocrinol* **22**: 636-48 [PMID:18063692]
36. Windahl SH, Andersson N, Chagin AS, Mårtensson UE, Carlsten H, Olde B, Swanson C, Movérare-Skrtic S, Sävendahl L and Lagerquist MK *et al.* (2009) The role of the G protein-coupled receptor GPR30 in the effects of estrogen in ovariectomized mice. *Am J Physiol Endocrinol Metab* **296**: E490-6 [PMID:19088255]
37. Zekas E and Prossnitz ER. (2015) Estrogen-mediated inactivation of FOXO3a by the G protein-coupled estrogen receptor GPER. *BMC Cancer* **15**: 702 [PMID:26470790]