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REVIEW

G protein-coupled receptor 30 in tumor development

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Abstract Estrogen plays several important physiological and pathological functions in not only reproductive system but many other systems as well. Its transcriptional activation has been traditionally described as being mediated by classic nuclear estrogen receptors (ERs). It is however established recently that a novel functional estrogen transmembrane receptor, G protein-coupled receptor 30 (GPR30), modulates both rapid non-genomic events and genomic transcriptional events of estrogen. It has been demonstrated that GPR30 promotes the progress of estrogen-related tumors through mitogen-activated protein kinase (MAPK) signaling pathways. Effects mediated by GPR30 are maintained when classic ERs are absent or blocked. In addition, GPR30 is involved in drug resistance, which is often occurring during cancer treatments. All these new findings strongly imply that GPR30 may be an important therapeutic target for estrogen-related tumors. Simultaneously blocking both GPR30 and classic ERs may be a better strategy for the treatment of estrogen-related tumors.

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Introduction

Estrogen is an important hormone in humans, especially in women. It not only contributes to the development and function of female mammary and reproductive system, but also plays a vital role in regulations of skeletal growth and maintenance [1], cardiovascular function [2], central nervous system function [3] and immune reaction [4]. Correspondingly, the disorder of estrogen leads to a number of pathological conditions in above systems, such as endometrial, mammary and skeletal diseases, even tumors. Since its important roles in physiological and pathological conditions of so many systems, estrogen has been an important research topic for several decades. After years of study, the effects of estrogen are believed to be mediated by two well-established nuclear estrogen receptors (ERs), ERα and ERβ. ERα was firstly described in 1973 [5]; and much later after that, ERβ was identified in 1996 [6]. ERα and ERβ are encoded by separate genes, ESR1 and ESR2, respectively, but both genes are homologous in the DNA-binding domain (97% amino acid similarity) and ligand-binding domain (60% amino acid similarity) [7]. A clear difference of these two ERs was demonstrated in their tissue distributions [8, 9], which suggested that ERα and ERβ might have different physiological functions. Now, it has been evidenced that the activity of ERβ is opposed to that of ERα in many systems [10–16]. For example, in breast cancer cells, ERα is the receptor responsible for 17β-estradiol (E2)-induced proliferative effect, whereas activation of ERβ inhibits this effect by ERα activation [11]. In uterus, E2 induces proliferation of both epithelial and stromal cells through ERα,

which is the predominant ER in the mature organ, whereas in the immature uterus, ERα and ERβ are at comparable expression levels in both epithelium and stroma, and ERβ mediates predominately the action of E2 as a suppressor of cell proliferation against activation of ERα by E2 [13]. So in these cells or tissues, the ratio of ERα and ERβ determines the effect of E2.

ERs are mainly functional as ligand-dependent transcription factors through directly binding to estrogen response elements (ERMs) in the promoter regions of target genes, and subsequently recruiting additional transcriptional co-regulators, resulting in the regulation of target protein products, which reflect biological actions of estrogen [17]. It is called classic or genomic signaling pathway, which usually takes hours to days to produce effects on cells. Indeed many estrogen responses occur in such a time frame. There are, however, some rapid biochemical responses to estrogen stimulation which occur in seconds to minutes, such as the increase in intracellular free calcium ($[Ca^{2+}]_i$) and the activation of multiple intracellular kinases including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), protein kinase A (PKA), protein kinase C (PKC), etc. [10]. These rapid events are regarded as non-genomic effects of estrogen. There is evidence to link ERs to these rapid events associated with membrane bound receptor-mediated effects [18, 19]. In addition to ERs, recent studies have confirmed that these rapid effects are mediated by a novel transmembrane ER, G protein-coupled receptor 30 (GPR30), also known as G protein-coupled estrogen receptor (GPER) [18–22]. GPR30 is also reported to mediate genomic signaling pathways of estrogen [23]. It is known that ERs play important roles in the initiation and progression of estrogen-related cancers, such as breast cancer, endometrial cancer, ovarian cancer, adrenocortical cancer, prostate cancer, colorectal cancer, liver cancer, lung cancer and so on [10], and some related therapeutic targets are already used in clinical application or under investigation. It therefore raises a question: what is the relationship between the novel receptor GPR30 and cancers? In this review, we will summarize properties of GPR30 in relation to the development of estrogen-related cancers.

Discovery of GPR30

GPR30 was identified in different cells by four laboratories during 1996–1998 [24–27]. Since its ligand was unknown at that time, it was named after its significant homology to G protein-coupled receptor (GPCR) super-family. Furthermore, this receptor was found to be associated with local ER expression in breast cancer cell lines [26]. Later in 2000, Filardo et al. found that estrogen rapidly activated extracellular signal-regulated kinase (Erk)-1 and Erk-2 in two breast cancer cell lines, MCF-7 (ERα+/ERβ+/GPR30+) and SKBR3 (ERα−/ERβ−/GPR30+), with the cell line SKBR3 expressing non-ERs. These findings demonstrated that estrogen might be a potential ligand for GPR30 [28]. This view was further confirmed by the observation that estrogen did not active Erk-1/-2 in a breast cancer cell line MDA-MB-231 (ERα-/ERβ+/GPR30−) without GPR30 expression, whereas Erk-1/-2 was activated by estrogen after GPR30 transfection into the cells [28]. Therefore, GPR30 is necessary for the activation of Erk-1/-2 by estrogen.

So far, GPR30 has been detected in numerous human tissues or cell lines, such as heart, liver, lung, intestine, ovary, brain, breast, uterus, placenta, prostate, subcutaneous adipose, visceral adipose, arteries and vessels [20, 24–26, 29–33].

Structure and subcellular localization of GPR30

GPR30 is a member of GPCR super-family, and its gene is mapped to chromosome 7p22.3 [34]. There are four alternate transcriptional splicing variants encoding the same protein which is comprised of 375 amino acids, and contains seven transmembrane spanning segments [35].

Although, classic GPCR is described as a cell membrane protein which binds its ligand at cell surface, it has been confirmed the existence of intracellular-located GPCR when the ligand is permeable or endogenously produced [36]. Estrogen is a cell permeable hormone, which makes an intracellular localization of GPR30 possible. However, the subcellular location of GPR30 is still an object of controversy. In 2005, Thomas et al. reported that GPR30 on plasma membranes had a high affinity, limited capacity, and displaceable single binding site specific for estrogen [20]. Another two research groups also observed membrane located GPR30 in hippocampus CA2 pyramidal neuronal cells in rat brain [37] and in GPR30 transfected HEK-293 cells [38]. Almost simultaneously, a distinct observation was reported by Revankar et al. [39]. Using the green fluorescent protein (GFP) and some cellular organelle markers, they demonstrated the unique localization of functional GPR30 in endoplasmic reticulum of COS7 monkey kidney fibroblast cells [40]. The endoplasmic reticulum location of GPR30 was supported by other studies using the hamster neonatal ovary cells [41], rat hippocampus neurons [42], HEK-293 cells, MDA-MB-231 cells, and HEC50 cells [43]. Based on these reports, it is possible that the subcellular location of GPR30 may be regulated according to functional requirement of different cells, or both plasma membrane and endoplasmic reticulum

GPR30s are involved in estrogen action. If both sites are involved, proportionally different distribution of GPR30 in plasma and endoplasmic reticulum membranes may produce different biological functions required by cell types and/or cell conditions. If so, how is the distribution regulated and what's the functional link of certain proportional distribution? Further studies are needed to clarify these questions.

GPR30 ligands

Estrogen binds to GPR30 with a high affinity of a reported Kd 2.7 nM [20] or 6 nM [22], through which alternative estrogen signaling pathways are activated. GPR30-specific compound 1 (G-1), which was identified using virtual and bio-molecular screening in 2006 [44], is a specific synthetic agonist of GPR30. ICI 182,780 [19, 20], tamoxifen [19], and 4-hydroxytamoxifen (OHT) [45–47] are also found to bind GPR30 and mimic estrogen effects. The chemical structures of these compounds are shown in Fig. 1.

In addition, it is reported that varieties of environmental estrogens can bind GPR30, such as genistein, bisphenol A, zearalonone, nonylphenol, kepone, p, p′-DDT,2,2′,5′,-PCB-4-OH and o,p′-DDE. However, their binding affinities are much lower than estrogen [48]. Other two isoforms of estrogen, estrone and estriol, also have very low binding affinities to GPR30, with a relative binding affinity (RBA) less than 0.1% of that by E2 [20].

As the isomer of E2, 17α-estrogen cannot bind GPR30 at all, neither can other steroid hormones at μM concentration levels, such as progesterone, glucocorticoid, and testosterone [20]. Binding specificity of GPR30 is similar to that observed of the classical ERs [8, 49]. The affinities of GPR30 to different ligands are shown in Table 1.

GPR30 signaling pathways

GPR30 is capable of mediating both genomic and non-genomic responses induced by estrogen. Signaling pathways employed by GPR30 activation have not been fully elucidated yet. According to existing literatures, possible signaling systems have been summarized in Fig. 2. Briefly, ligands, for example, estrogen [50], tamoxifen [51], ICI 182,780 [52], and G-1 [44] may cross plasma membrane, and bind to GPR30, which is predominantly expressed on the membrane of endoplasmic reticulum, and activate heterotrimeric G proteins, which then activate Src and adenylyl cyclase (AC) resulting in intracellular cAMP production. Src is involved in matrix metalloproteinases (MMP) activation, which cleave pro-heparan-bound epidermal growth factor (pro-HB-EGF) and release free HB-EGF. The latter activates EGF receptor (EGFR), leading to multiple downstream events; for example, activation of phospholipase C (PLC), PI3K, and MAPK. Activated PLC produces inositol triphosphate (IP3), which further binds to IP3 receptor and leads to intracellular

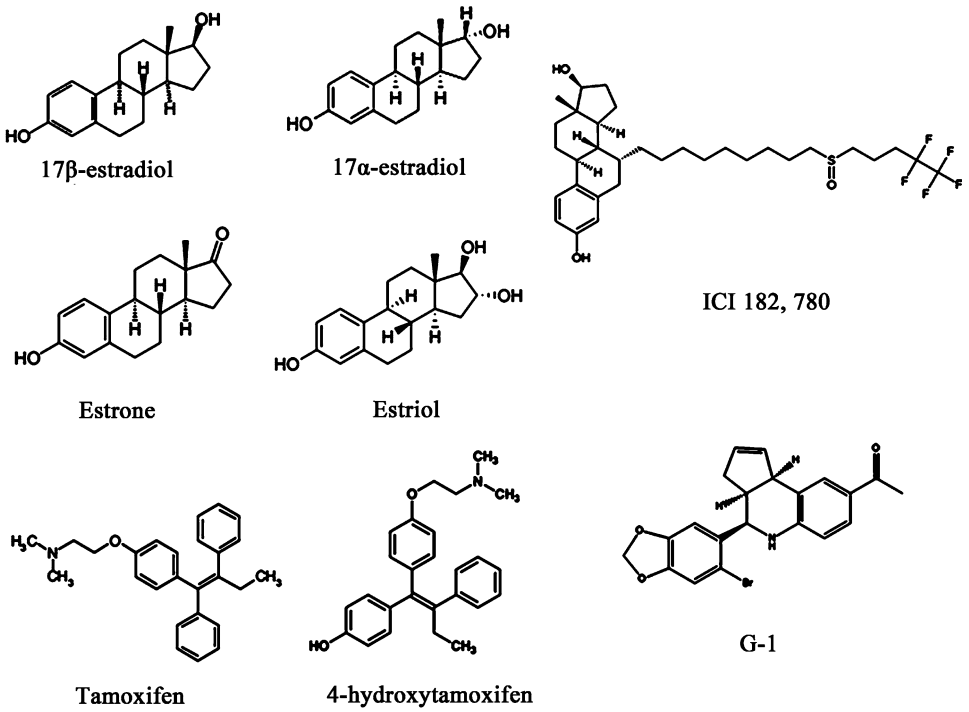

Fig. 1 Chemical structures of estrogens including E2, 17α-estradiol, estrone and estriol, representative selective estrogen receptor modulators (SERMs, are a class of chemicals that acts on the estrogen receptors to mimic or block estrogen effects) and GPR30-specific compound 1(G-1)

Table 1 The affinity of GPR30 ligand

GPR30 Ligands	Affinity (Kd)
E2	2.7 nM [20], 6 nM [22]
G-1	11 nM [22]
ICI 182,780	~10% that of E2 [20]
Tamoxifen	~10% that of E2 [20]
OHT	[a][45–47]
Genistein	IC_{50} 133 nM (~13% that of E2) [48]
Bisphenol A	2–3% that of E2 [48]
Zearalonone	2–3% that of E2 [48]
Nonylphenol	2–3% that of E2 [48]
Kepone	0.25–1.3% that of E2 [48]
p,p′-DDT	0.25–1.3% that of E2 [48]
2,2′,5′,-PCB-4-OH	0.25–1.3% that of E2 [48]
o,p′-DDE	0.25–1.3% that of E2 [48]
Estrone	0.1% that of E2 [20]
Estriol	0.1% that of E2 [20]
17α-estrogen	[b][20]
Progesterone	[b][20]
Glucocorticoid	[b][20]
Testosterone	[b][20]

[a] The ligand can bind with GPR30, but no exact figure was found

[b] The ligand cannot bind with GPR30 at all

calcium mobilization. The downstream signal of PI3K is AKT pathway. Main biological consequence of AKT activation is closely related to cancer cell growth; catalogued loosely into three aspects: survival, proliferation (increased cell number) and growth (increased cell size) [53]. The activation of MAPK and PI3K results in activation of numerous cytosolic pathways and nuclear proteins, which further regulate transcription factors such as serum response factor and members of the E26 transformation-specific (ETS) family by direct phosphorylation [54, 55]. In summary, the activation of GPR30 signaling pathways often leads to tumor promotion.

GPR30 in tumors

GPR30 expression in tumor tissues and cell lines

GPR30 gene expression has been detected in at least four kinds of human tumor specimens or cell lines (Table 2), including breast cancer [20, 26, 28, 30, 34, 47, 56–58], endometrial cancer [29, 45, 49, 59], ovarian cancer [21, 60, 61], thyroid cancer [46], and a rat pheochromocytoma cell line PC-12 [62]. In human breast cancer, GPR30 expression is decreased on both mRNA [56] and protein levels [30] compared with that in normal tissues, and its expression level is positively correlated with ERα [56]. But in human endometrial cancer, GPR30 expression is up-regulated on both mRNA and protein levels compared with that in normal tissues [29]. There is a growing body of evidence supporting that GPR30 is strongly associated with cancer proliferation [21, 23, 28, 29, 45–47, 61, 63, 64], migration [47, 60], invasion [29], metastasis [30, 58], differentiation [29], prognosis [30, 59], and drug resistance [65, 66]. These functional links are summarized in Table 3.

GPR30 promotes cancer cell proliferation

Uncontrolled cell proliferation is a hallmark of cancers [67]. In almost all instances, deregulated cell proliferation and suppressed cell death provide the underlying mechanism for neoplastic process of cancers [68]. A number of in vitro studies have demonstrated that activation of GPR30 stimulates cell proliferation in breast cancer, endometrial cancer, ovarian cancer and thyroid cancer, through EGFR-MAPK signaling pathway.

In breast cancer cell line SKBR3, Filardo et al. demonstrated that estrogen activated Erk-1/-2 via activation of EGFR by production of HB-EGF [28]. Another study also reported that the activation of GPR30 signaling by estrogen or OHT promoted cell proliferation in ERs (−) human breast cancer cells via induction of connective tissue growth factor (CTGF) [47]. Tectoridin, known as a phytoestrogen, a natural compound isolated from plants and structurally similar to animal estrogen, does not bind to ERα. However, tectoridin exerts estrogenic effects, such as induction of cell proliferation in breast cancer cell line MCF-7, via activation of GPR30 and downstream MAPK signaling pathways [64]. In addition, it has been reported that there is an enhancement of EGF production by activation of GRP30, which leads to an estrogen-induced proliferation of ERs (−) breast cancer cells [34]. In this study, EGF induced GPR30 protein expression through rapid Erk phosphorylation and c-fos (a proto-oncogene) induction [34].

In endometrial cancer, He et al. [29] demonstrated that estrogen and G-1 promoted cell proliferation in two endometrial cancer cell lines, KLE (ER−) and RL95-2 (ER+), through activation of GPR30 and MAPK signaling pathway.

In ovarian cancer cell line BG-1, GPR30 mediated growth response to estrogen and G-1 via EGFR-MAPK signaling pathways. Unlike other tumor types, this action required the co-expression of ERα [21]. Atrazine, which is one of the most common pesticide contaminants, stimulated proliferation of ovarian cancer cells via induction of Erk phosphorylation and expression of estrogen target genes through GPR30-EGFR transduction pathway with the involvement of ERα [61].

In thyroid cancer cell line WRO, GPR30 was reported to be responsible for estrogen, genistein and OHT-induced

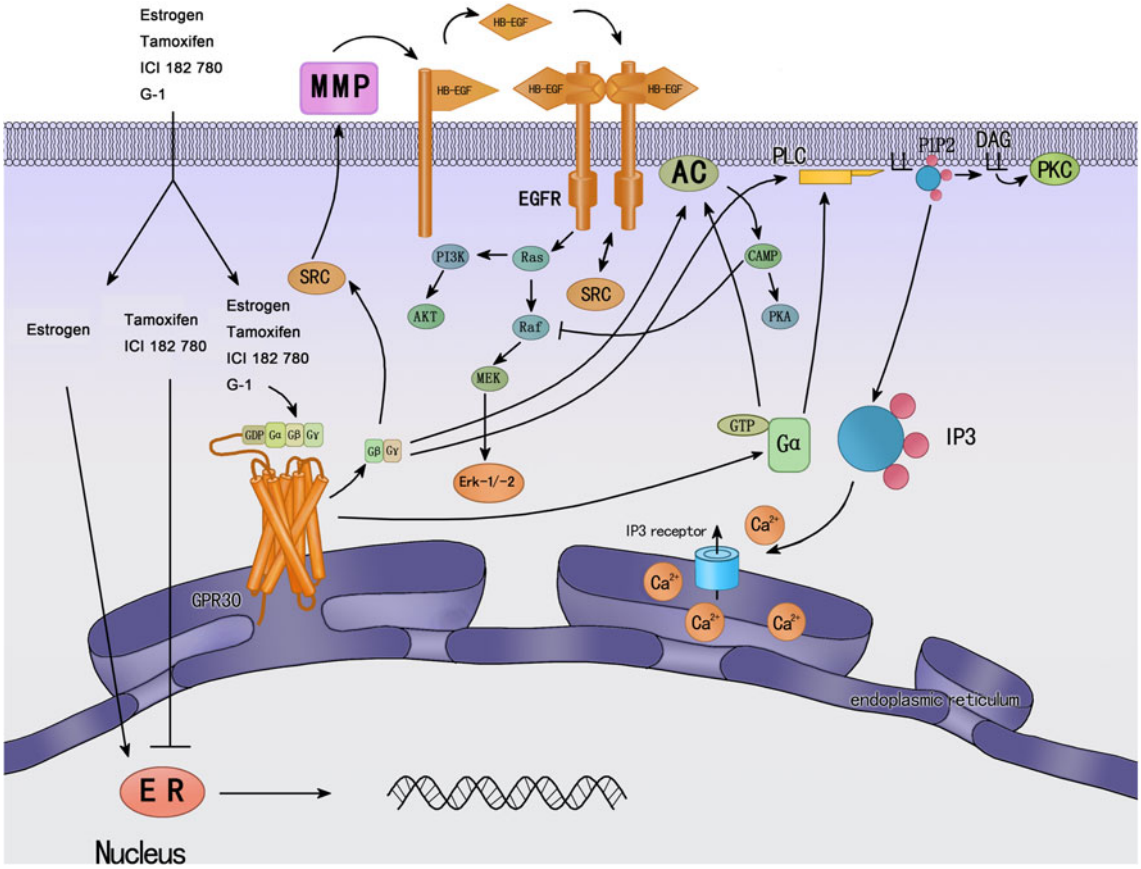

Fig. 2 Cellular signaling mechanisms of GPR30 and classic nuclear estrogen receptors (ERs) (↓ activate; ⊥ inhibit). ERs are widely accepted as mainly mediating gene transcriptional regulation. Tamoxifen is ER antagonist in some tissue, such as breast cancer, while has agonistic effects in other tissues, such as endometrium. ICI 182, 780 was reported as a pure ER antagonist. After GPR30 was discovered as a novel estrogen receptor, many subsequent studies indicated that GPR30 was found predominantly in the endoplasmic reticulum; and estrogen, tamoxifen, ICI 182, 780 and G-1 can bind GPR30, and then activate multiple cellular effectors, such as mitogen-activated protein kinases (MAPK), phosphoinositide 3-kinase (PI3K) and phospholipase C (PLC), and other rapid cellular processes. Most of them are mediated by trans-activation of epidermal growth factor receptor (EGFR). The consequences of GPR30 signaling pathways often lead to tumor promotion. This figure was modified from Prossnitz's reviews [17, 82]

Table 2 Estrogen receptors in human cancer cell lines

Human cancer cell lines	ERα	ERβ	GPR30
Breast cancer cell lines			
MCF-7	+ [28, 77]	+ [28, 77]	+ [28, 78]
MDA-MB-231	− [28, 79]	+ [28, 79]	− [28]
SKBR3	− [28, 79]	− [28, 79]	+ [28]
T47D	+ [66, 79, 80]	+ [66, 79, 80]	+ [66]
MDA-MB-468	− [66]	+ [66]	+ [66]
Endometrial cancer cell lines			
KLE	− [81]	− [81]	+ [29]
RL95-2	+ [78]	+ [78]	+ [29, 78]
Ishikawa	+ [80]	+ [80]	+ [45]
HEC-1A	− [77, 78]	+ [77, 78]	+ [45, 78]
Ovarian cancer cell line			
BG-1	+ [80]	+ [80]	+[21]
Thyroid cancer cell line			
WRO	+ [46]	− [46]	+ [46]

Table 3 The effect of GPR30 in cancers

Cancer type	Breast cancer	Endometrial cancer	Ovarian cancer	Thyroid cancer
Proliferation	↑[23, 28, 47, 63, 64]	↑[29, 45]	↑[21, 61]	↑[46]
Migration	↑[47]	/	↓[60]	/
Invasion	/	↑[29]	/	/
Metastasis	↑[30, 58]	/	/	/
Differentiation	/	↑,[b][29]	/	/
Prognosis	↓,[a][30]	↓,[a][59]	/	/
Drug resistance	↑[65, 66]	/	/	/

↑ GPR30 mediates the stimulatory effect, ↓ GPR30 mediates the inhibitory effect, [a] GPR30 is associated with poor survival, / no related data has been reported, [b] GPR30 overexpression is associated with high grade cancer

increase in cell proliferation via MAPK pathway [46]. Therefore, it is concluded that GPR30 activation promotes cell proliferation of many cancer cell types.

GPR30 is associated with cell migration, invasion and metastasis

Cell migration is a highly integrated multistep process, and plays a central role in the development and maintenance of multicellular organisms. For example, both embryonic morphogenesis and tissue repairing after injuries require an orchestrated movement of cells to specific locations [69]. Cancer cell migration may lead to invasion (instruction on and destruction of adjacent tissues) and sometimes metastasis (travel to other location in the body directly or via blood or lymph circulation), enabling cancer cells to spread from the primary cancer mass and colonize new terrain in the body [70]. Metastases are the cause of 90% of human cancer death [71]. It is reported that the activation of GPR30 signaling by estrogen or OHT promotes cell migration via induction of CTGF in ER(−) breast cancer cells [47]. GPR30 also mediates cell migration of ovarian cancer cells [61]. As we mentioned before, atrazine stimulated the proliferation through GPR30-EGFR transduction pathway [61], and EGF in ovarian cancer cells also stimulated cell migration [60]. In addition, He et al. indicated that in endometrial cancer cell lines KLE and RL95-2, estrogen and G-1 increased MMP production and promoted cell invasion through acting on GPR30 [29].

GPR30 is a novel indicator for poor survival

As discussed above, activation of GPR30 influences the growth and progression of breast cancer cells. It is further supported by the clinical study [30]. Immunohistochemistry analysis of 361 breast carcinomas and 12 normal breast tissues from reduction mammoplasty patients were performed. All 12 normal tissues displayed a strong cytoplasmic GPR30 staining pattern, without nuclear staining, whereas both ER and progesterone receptor (PR) were positively shown in the nucleus. However, the expression level of those three receptors varied in tumor tissues: among the 40 cases of ductal carcinoma in situ, 42% were GPR30 (+), whereas 63 and 45% were ER (+) or PR (+), respectively; among 321 cases of invasive ductal carcinoma, 62% were GPR30 (+), 62% were ER (+), and 40% were PR (+). GPR30 was found to be strongly associated with ER ($P < 0.05$), where 43% of invasive tumors expressed both ER and GRP30 [30]. But unlike ER which varied inversely with HER-2/neu (human epidermal growth factor receptor 2, a protein giving higher aggressiveness in breast cancer) [30, 72], GPR30 was positively associated with HER-2/neu, tumor size and distant metastases [30]. These results suggest that GPR30 may be used as a clinic predictor for poor survival in breast cancer. In addition, it is interesting that in above study [30] around half of classic ER (−) breast tumors retained GPR30 expression, which suggests that these tumors (GPR30+/ER−) may remain responsiveness to estrogen through GPR30 signaling pathways. In this proportion of breast cancer patients (GPR30+/ER−), anti-estrogen treatment targeting GPR30 may be an option. For patients with both ER (+) and GPR30 (+), anti-estrogen therapy targeting both ER and GPR30 may show a higher efficiency than single receptor targeting regime.

In endometrial cancer, GPR30 is also considered as a novel indicator of poor survival, as its high level expression is correlated with a more deteriorated cancer outcome. Smith et al. [59] performed immunohistochemical analysis to investigate expressions of GPR30, ER, PR, EGFR and Ki-67 (a proliferation marker) in 47 endometrial cancer patients. The results showed that GPR30 expression was positively correlated with EGFR expression but negatively correlated with PR expression, and GPR30 overexpression occurred more frequently in tumors with extensive myometrial invasion, higher pathological grade, more aggressive histological subtypes, and is correlated with poorer survival [59]. Similar result was reported by He et al. [29], who investigated 50 cases of endometrial carcinoma and 30 cases of non-cancer specimens. They found that GPR30 expression was up-regulated in cancers compared with non-cancer controls, and GPR30 overexpression was

positively correlated with high pathological grade of endometrial carcinoma. They also found that GPR 30 signaling was involved in the development of endometrial carcinoma by promoting proliferation and enhancing invasion [29].

In summary, in these two common estrogen-related cancers, breast cancer and endometrial cancer, GPR30 is clearly associated with tumor growth and metastasis development, and may serve as an indicator of poor survival.

GPR30 is a potential therapeutic target

Breast cancer is the most common malignancy (23% of all cancers) occurring in female and is a major health burden worldwide [73]. Estrogen stimulates the progression of breast cancer in approximately two-thirds of patients who are ER (+) [74, 75]. Some selective estrogen receptor modulators (SERMs) such as tamoxifen have been clinically used to antagonize the binding of estrogen to its classic ERs, which is an effective therapeutic strategy in attenuating the growth of ER (+) breast cancers. However, there are around 25% of ER (+) breast cancer patients who do not respond to anti-estrogen therapy [76]. It implies that blockade of classic ERs alone may not be enough to completely abolish estrogen-induced breast cancer cell growth, since estrogen may promote cell growth through other receptor besides classic ERs. Such hypothesis is further supported by the discovery of GPR30 as the third specific ER with different structure and function to ERα and ERβ. GPR30 has a high binding affinity to not only estrogen, but also some SERMs, such as tamoxifen and ICI 182,780. Estrogen and SERMs stimulate GPR30 action without any antagonist effects [20]. These important findings provide a new possible mechanism for the progression of estrogen-related cancers, and raise a new potential target for anti-estrogen therapy. Antagonist to both GPR30 and classic ERs may serve to achieve a better treatment outcome.

Drug resistance is a major problem in cancer treatment. Two recent studies have demonstrated that GPR30 might be associated with such resistance. Kleuser and colleagues reported that estrogen and ICI 182,780 disrupted the signaling network and function of transforming growth factor (TGF)-β through GPR30-MAPK signaling pathway. Down-regulation of TGF-β signaling was believed to be responsible for resistance to anti-estrogen treatments in breast cancer [65]. In addition, bisphenol A-related chemotherapy resistance was associated with GPR30, as in both breast cancer cell line T47D (ER+/GPR30+) and MDA-MB-468 (ER-/GPR30+), and bisphenol A at environmentally relevant doses was found to reduce the efficacy of chemotherapeutic agents, such as doxorubicin, cisplatin, and vinblastine, through activation of GPR30 [66].

It is still not clear about the mechanism underlying the effect of GPR30 in estrogen-related cancer therapy, and there is no drug specifically blocking GPR30 action yet. It would be clearly important to clarify whether GPR30 is essential for certain cancer development and whether GPR30 is responsible for anti-estrogen therapy and chemotherapy resistance in these cancers.

GPR30 targeted genes

It is reported that c-fos and CTGF are two GPR30 targeted genes. GPR30 has been demonstrated to increase c-fos expression induced by estrogen via EGFR-MAPK signaling pathways in breast cancer [23], endometrial cancer [45], ovarian caner [21], and thyroid cancer [46]. This effect is independent of ERα. In ovarian cancer, it requires, however, the co-expression of ERα [21]. Pandey et al. studied the alterations in gene expression elicited by GPR30 signaling pathways. The results showed that in ERs (−) human breast cancer cells, estrogen or OHT-induced activation of GPR30 evoked a transcriptional factor network, and CTGF appeared to be a target of these transcriptional factors [47]. The underlying mechanisms of GPR30 activation-induced effects on gene expression remain unclear so far.

Conclusions

Although the role of GPR30 in estrogen-related tumor initiation and progression has just recently begun to emerge, a rapid progress has been achieved. It has been demonstrated that GPR30 not only activates estrogen-induced rapid non-genomic signaling pathways, but also regulates certain gene transcriptions. Besides the specific GPR30 agonist G-1, some well-known SERMs (tamoxifen and ICI 182,780) and environmental estrogens are also able to bind to GPR30 and activate downstream signaling pathways, which regulate cell proliferation, invasion, metastasis, and c-fos and CTGF expression. GPR30 mediated effects are independent of classic ERs expression in most cancers, except in ovarian cancer where co-expression of ERα is required. The mechanisms of GPR30 activation and downstream signaling systems still need further investigations. In conclusion, existing experimental evidences suggest that GPR30 should be included in anti-estrogen treatment of estrogen-related tumors and GPR30 may also serve as a valuable predictor of cancer development in some estrogen-related cancers. More bench top and clinic researches are warranted for its roles in estrogen-related cancers.

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