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**Estrogen receptors in gastric cancer: advances and perspectives**

Rahman MS *et al*. Estrogen receptors in gc

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**Abstract**

Gastric cancer is one of the most common malignancies worldwide with high mortality. Extensive investigations are being conducted in various aspects of the development and progression of gastric cancer in order to furnish us with better understanding and more effective means in prevention, diagnosis and therapy of the disease. Estrogen receptors (ERs) are steroid hormone receptors that regulate cellular activities in many physiological and pathological processes of different tissues. There are two distinct forms of ERs, namely ER alpha (ERα) and ER beta (ER), with several alternative-splicing isoforms for each. They show distinct tissue distribution patterns and exert different biological functions. Dysregulation of ERs has been found to be associated closely with many diseases including cancer. A number of studies have been conducted to investigate the roles ERs play in gastric cancer, the possible mechanisms for these roles, and the clinical relevance of deregulated ERs in gastric cancer patients. Inconsistent associations of different ERs with gastric cancer have been reported up to date. The inconsistence may be caused by the variables in *in vitro* cell models and clinical samples, including assay conditions and protocols with regard to different forms of the ERs. Expecting the potentials of the deregulated ERs as diagnostic/prognostic markers or therapeutic targets for gastric cancer, it will be important to identify/confirm the association of each ER isoform with gastric cancer, the specific roles and interactions of these individual ER isoforms play under specific conditions in the development and/or progression of gastric cancer, and to elucidate the precise mechanisms. In this review we summarize the achievements from early ERs studies in gastric cancer to the most up-to-date discoveries with an effort to provide a comprehensive understanding of ERs’ roles and possible mechanisms in gastric cancer, and propose directions for future investigations.

**Key words:** Gastric cancer; Estrogen receptor; Isoform; Carcinogenesis; Mechanism; Genomic pathway; Non-genomic pathway

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**Core tip:** Gastric cancer is one of the common malignancies worldwide with high mortality. Estrogen receptors (ERs) are steroid hormone receptors that regulate cellular activities in many physiological and pathological processes of different tissues. Dysregulation of ERs is associated with many diseases including gastric cancer. Studies have been conducted to investigate the roles and possible mechanisms that ERs play in gastric cancer and the clinical relevance of deregulated ERs in gastric cancer patients. This review focuses on the current understandings of ERs in gastric cancer and proposes directions for future investigations.

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**INTRODUCTION**

Gastric cancer is one of the most common types of cancer and one of the leading causes of cancer-related deaths world-wide, with an estimated 723100 deaths and 951600 new cases in 2012[1]. Currently tremendous efforts are being made to investigate various cellular and molecular mechanisms leading to the development and progression of gastric cancer, hoping to improve the prevention, early diagnosis and precise and personalized treatment with approaches based on the new findings.

Estrogens are a class of steroids that was initially found to regulate the development and growth of human reproductive system. Estrogens exert their influences on specific cells *via* their receptors (estrogen receptors, ERs). Estrogens/ERs are now also found to be involved in other physiological/pathological processes of cardiovascular, skeletal and neuroendocrine systems[2]. ERα and ERβ were first cloned from human breast cancer MCF-7 cells and from rat prostate in 1986 and 1996 respectively[3]. ER and ER are members of a superfamily of nuclear receptor that can transduce extracellular signals into transcriptional response, with distinct protein structural characteristics, tissue distributions and functions[4,5]. In certain ligands, cell-types, and promoter contextsER and ER have different activities[6].

As illustrated in Figure 1, ERs share conserved domains for ligand binding (LBD), DNA binding (DBD), transcription activation (AF1 and AF2) and nuclear translocation (NLS). Three isoforms for ERhave been identified, designated as ER66, ER46 and ER36 respectively based on their protein molecular weights[7]. ER66 functions as a ligand-dependent transcription factor that modulates the gene expression by binding to estrogen response elements (EREs) in the transcriptional regulatory region in genomic DNA[5]. Despite lacking of the AF-1 activation domain, ER46 can still bind to EREs and form heterodimers with ER66[8,9]. The subcellular localization and activation of Src/PI3k/AKT pathways upon estrogen-signaling also indicate possible roles for ER46 in non-genomic estrogen signaling[10-12]. For ER36, both activation domains (AF-1 and AF-2) are absent, but it retains the ability of dimerization, nuclear translocation and DNA binding, with an even broader ligand-binding spectrum and may mediates rapid estrogen signaling[7,13]. Five alternatively spliced isoforms for ER have been identified (ER1-ER5). ER appears to have a weaker corresponding AF-1 domain and its transcriptional activation function depends more on the AF-2 domain rather than AF-1 domain.

Expressions of ERs have been well documented in a variety of human tumors, including gastric cancer[14-24]. Hormonal therapy targeting ERs for the treatment of breast cancer has played a remarkable role[25,26]. Investigation on the roles and mechanisms of these ERs in gastric cancer will surely provide us more means for the management of the disease.

In this review we summarize the achievements from early ERs studies in gastric cancer to the most up-to-date discoveries with an effort to provide a comprehensive understanding of ERs’ roles and possible mechanisms in gastric cancer, and propose directions for future investigations.

**EXPRESSIONAL AND FUNCTIONAL INVESTIGATIONS ON ESTROGEN RECEPTORS IN GASTRIC CANCER**

***ER66 (ER)***

Most of the literatures use terms “ER” or “ER” when actually referring to the specific isoform ER66 as it is the major and first identified isoform. Early investigation on ER expression in gastric cancer was initiated by the observation of the association between breast cancer and gastrointestinal cancer, but no correlation between ER expression and gastric cancer was found[27]. The ER positive rate in gastric carcinoma was not significantly different between male and female cases[27,28], but the incidence in poorly differentiated adenocarcinoma being significantly higher than that of well differentiated adenocarcinoma[28]. Later studies further showed the correlation of ER status to tumor grades in gastric cancer[29,30], and ER expression was found to be associated with diffuse type gastric cancer and shorter disease free survival[31]. At mRNA level, the ERexpression between gastric cancer tissues and matched normal tissues had no statistically significant difference, but ER-positive expression correlated with poorer overall survival[15].

However, some investigations showed inconsistent results in established cell lines. More cell lines showed ER expression by RT-PCR than that by Western blotting[31,32], which may be due to the differences of sensitivity between the assays. ER overexpression significantly inhibited cell growth and proliferation, promoted cell apoptosis, blocked cell entry into the G1/G0 phase. In addition, ER reduced the motility and invasion of gastric cancer cells. Over expression of ER  decreases -catenin expression, this phenomena may partly explain this expression level. By suppressing -catenin, ERα overexpression effectively inhibited cell growth and cancer progression in gastric cancer[33].

***ERα36***

Although no work has been reported on ERα46 in gastric cancer up to date, there are some studies investigated the clinical significance and functions of ERα36 in gastric cancer. ERα36 is found to be highly expressed in human gastric cancer, and such expression is correlated with lymph node metastasis and may be used as a predictive marker for lymph node metastasis of gastric cancer[34]. Both mRNA and protein of ERα36 were detected in the established gastric cancer cell lines examined. Higher ERα36 mRNA level were expressed in tumor specimens examined compared to the paired normal tissues. ERα36 protein was mainly expressed on the plasma membrane and in the cytoplasm of the established gastric cancer cells[34].

***ER***

For the clinical relevance of ERwith gastric cancer, ER-positive group was associated with lower tumor stage, negative perineural invasion, and Lauren’s intestinal type and free of recurrence. Presence of ER in gastric cancer could have a protective effect against invasiveness of gastric cancer[32], similar to the functions of ER in inhibiting proliferation, invasion and tumor formation of breast cancer cells[35-37]. In multivariate analysis, the absence of ER was a significant independent prognostic factor which associated with poor overall survival[15].

A more recent study, however, showed that although ERs are present in both gastric tumors and normal tissues, their expression levels were extremely low except for the predominance of ER, and they may only be partly involved in gastric carcinogenesis but their clinicopathological and prognostic significance in gastric cancer appears to be limited[38].

For the transcription variants of ER in gastric cancer tissues, higher ER5 mRNA level was correlated with pTNM stage of the tumor, the lymph node metastasis compared to their matched normal tissues while ER1 and 2 were not correlated with lymph node metastasis, gender, age, tumor size, tumor grade and pTNM stage[39] (Table 1).

**MECHANISMS FOR ERS’ FUNCTIONS IN GASTRIC CANCER**

Current knowledge on the mechanisms for ERs’ functions in cancer mainly comes from investigations in breast cancer, which may be extendable to other cancers including gastric cancer. Estrogens exert their functions *via* ERs through both genomic and non-genomic ways[40]. As illustrated in Figure 2, in the genomic way, estrogen-bound ERs translocate into the nucleus and bind to estrogen response elements (EREs) in genomic DNA and regulate the expression of downstream genes. In the non-genomic way, ERs interact with some other signaling molecules in several pathways such as PI3K/Akt or MAPK signaling pathways. ERα and ERα play different roles in both genomic and non-genomic ways, where ER functions as a transdominant inhibitor/competitor of ERα transcriptional activity at sub-saturating hormone levels[41].

Recently more investigations were conducted on ERα36-related mechanisms in gastric cancer due to the special characteristics of this newly identified type of isoform. In established gastric cancer cells, ERα36 protein mainly expressed on the plasma membrane and in the cytoplasm. The dysregulation of multiple signaling pathways in relation to ERα36 involved in cell proliferation, metastasis and invasion has been described in gastric cancer[42,43].

***ERα36 and GRP94***

ERα36 is linked to GRP94 as its expression level is positively associated with lymph node metastasis and GRP94 expression levels[34,44,45]. Higher expression of ERα36 in human gastric cancer is involved in the malignant growth of gastric carcinoma cells[34,44]. AKt signaling pathway is responsible in ERα36-mediated estrogen signaling *via* GPR-94 in gastric cancer[46]. ERα36 and GRP94 have high expression in gastric cancer. With knockdown of ERα36 in gastric cancer SGC-7901 cells, the expression of GRP-94 and phosphorylated Akt (Ser-473-Akt) level reduced significantly. Clinically the GRP94 expression level is significantly correlated with gender, tumor stage, lymph node metastasis. It is known that estrogen induces the expression of GRPs, which proposed that GRP94 may have some role in gastric carcinogenesis through ERα36-mediated estrogen signaling.

***ERα36 and c-Src***

C-Src also takes part in ERα36-mediated regulation of gastric cancer cells proliferation by activating the membrane‑initiated c‑Src signaling pathways. C‑Src in breast cancer cells, is also reported to serve as a switch through STAT5/EGFR pathway in ERα36 mediated biphasic estrogen signaling[47]. It is reported that ERα36 also interact physically with Src/Shc/EGFR complex[48]. As seen from these observations, in breast cancer c‑Src also functions in similar manner as it does in ERα36-positive gastric cancer[44]. Revealed by E2-ERα36-c-Src pathway, c‑Src transduces signals that are responsible for adhesion, growth, differentiation and invasion of gastric cancer cells[49]. An important mechanism of c‑Src tyrosine kinase activity monitoring is comprised of its phosphorylation status control. C‑Src protein has two major phosphorylation sites, Tyr416 and Tyr527. The activity of c-Src is positively regulated when Tyr-416 is phosphorylated, and it is negatively regulated when Tyr-416 is dephosphorylated[50,51]. The phosphorylation status of c‑Src‑Tyr416 and c‑Src‑Tyr527 depends on concentration of estrogen; and serves to switch on and off non‑genomic estrogen signaling[44]. E2‑ERα36 regulates phosphorylation of c‑Src‑Tyr‑416 and Tyr‑527; as a result gastric cancer growth is promoted, which further indicates that E2‑ERα36‑c‑Src is impor­tant for proliferation of gastric cancer cells. C‑Src and ERα36 are known to interact in the presence of E2, while PP2 doesn’t effect this interaction. However, PP2 inhibits activation of c-Src.

***ERα36 and cyclin D1***

ERα36 upregulates cyclin D1 (CD1) when activating c-Src signaling pathway which leads to the proliferation of gastric cancer cells[34]. In ERα36 up-regulated cells E2 induces c‑Src‑Tyr416 phosphorylation[46]. Whereas E2 is unable to induce c‑Src‑Tyr527 phosphorylation in cells knocked down by ERα36. The level of CDI expression is increased by C‑Src‑Tyr416 phosphoryla­tion in ERα36 up-regulated SGC7901 cells and promoted cell proliferation, while in ERα36-knockdown SGC7901 cells the opposite occurred. A noteworthy regulatory factor for cell cycle progression is CDI, it mediates the transition from G1 to S, which in turn results in DNA synthesis and cell cycle progression[52]. Various carcinomas are reported to be result of CDI overexpression, including gastric cancer. A gender difference in [Methyl-nitro-nitroso-guanidine](http://en.wikipedia.org/wiki/Methylnitronitrosoguanidine) (MNNG) ‑induced rat gastric carcinogenesis showed CD1/cdk4 expression[53]. To support these observations further, nude mice tumor, the xenograft with up-regulated ERα36 showed the positive correlation between CD1 and ERα36[46].

**OTHER ASPECTS OF ERs IN GASTRIC CANCER**

ERα is expressed in 20-30% of human gastric cancers[15]. Epidemiological studies indicate the predominance of gastric cancer in males globally, with the ratio to female as 2:1[54,55]. Antiestrogen and tamoxifen agents have been shown to induce tumor progression and enhance the overall chances of gastric adenocarcinoma[56]. These findings indicate a connection between pathogenesis of gastric cancer and estrogen signaling. Hormone therapy may be a useful strategy for the treatment of gastric cancer in case of hormone-dependent tumor growth[32].

While the clinicopathological and prognostic relevance of ERs in gastric cancer appears to be significant[16,43], the interaction between the two receptors  and  is yet clinically unclear. Moreover, the positive rate for ER expression in gastric cancer differs from study to study, with ER expressed more abundantly than ERα and showed different patterns by subtypes of gastric cancer. Inconsistent results also arouse from different studies; some studies showed that aberrant expression of ERα and ER mRNAs in tumors is associated to liver metastasis and lymph node metastasis, while some other studies showed that there was no association between expression of ER and any of the clinical variables[57]. Furthermore, the mechanism of carcinogenesis linked to ER is unclear, and the use of estrogen for the therapeutic purpose may increase the risk of other cancers (breast or ovarian cancer), and the side effects of estrogen are also problematic[15,39,57]. The fractional agonist activity of tamoxifen evident through ERα in some circumstances can be entirely abolished upon co-expression of ER[15]. One possible role of ER is to moderate ERα transcriptional activity, and thus the relative expression level of the two isoforms might be a key factor of cellular responses to agonists and antagonists. Aromatase expression has been reported in gastric cancer cells recently, and in short incubation period gastric cancer can produce estradiol[58].

Noticeably, the function of estrogen that stimulates the growth of gastric cancer cells is associated with the concen­tration of estrogen[59]. A physiologically low concentration of estrogen is recognized to stimulate the expression of ERα36 and growth of gastric cancer cells, while high concentrations of estrogen repressed the expression of ERα36 and the growth of gastric cancer cells. This association in concentration of estrogen and its functions may explain the predominance of gastric cancer in males[60].

**PERSPECTIVES**

Many studies have been conducted on the expression and association of different isoforms of ERs with gastric cancer with various conclusions up to date. Some of the inconsistencies may be caused by the variables in these studies such as *in vitro* gastric cancer cell models, clinical samples, assay protocols, with regard to different isoforms of the ERs. Detailed investigations regarding individual isoforms using specific assay protocols (such as specific primer pairs for reverse transcription polymerase chain reaction, antibodies against specific epitopes for each individual isoforms) will no doubt reveal more insight into ERs’ involvement in gastric cancer. Expecting the potentials of the deregulated ERs as diagnostic/prognostic markers or therapeutic targets for gastric cancer, it will be important to identify/confirm the specific roles of each isoform of these ERs (including their tissue-specific ligands) play under specific conditions in the development and/or progression of gastric cancer, interactions of these isoforms and to elucidate the mechanisms at all levels including molecular, cellular, tissue/organ and individual. This will give us a systematic understanding of ERs and provide the basis for developing preventive, diagnostic and therapeutic approaches with precise targets in ER-related gastric cancer. Furthermore, as new isoforms of ER being identified and studied in breast cancer, extensive investigations of ER in gastric cancer will sure to provide us more knowledge of the development and progression of gastric cancer, and therefore will also provide us more means in the dealing with gastric cancer.

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**Table 1 Summary of association of estrogen receptor isoforms with gastric cancer**

|  |  |  |
| --- | --- | --- |
| **Estrogen receptors** | **Isoform** | **Association with gastric cancer** |
| ER | ERa66 | No significant correlation between ER66 and gastric cancer is found[27]No positive significant difference in both male and female[27,28]Incidence higher in poorly differentiated adenocarcinoma[28]Association with diffused type Gastric cancer is found[31]Associated with poor overall survival[31]. |
| ERa46 | No reported result has been up to date. |
| ERa36 | Expressed highly in Gastric cancer[34].Expression correlated with lymph node metastasis[34].Expressed in plasma membrane and cytoplasm of Gastric cancer[34] |
| ER | ER1ER2ER3ER4ERb5 | Associated with low tumor grades[32].Presence could have protective effect against invasion[32].Absence of ER a significant independent prognostic factor for poor OS[15]. |
| ER5 is associated with PTNM stage[39]. |



**Figure 1 protein structure of estrogen receptors.** Two different forms of ER are encoded by two distinct genes located in chromosomes 6 and 14 and produce two proteins with 595 and 530 amino acids in full length respectively. Six evolutionary conserved domains, namely A-F, are shared by different ERs. For ER isoforms, compared to the full length ER66, ER46 lacks AF-1 domain (A/M), ER36 lacks AF-1 and partial AF-2 domains but equipped an extra different C-terminal. For alternatively-spliced ER isoforms, they differ mainly at their C-terminals. AF-1: Transcriptional activation factor-1; DBD: DNA-binding domain; NLS: Nuclear localization signals; LBD: Ligand binding domain; AF-2: Transcriptional activation factor-2.



**Figure 2 Molecular mechanisms for estrogen receptors’ functions.** Genomic pathway: Estrogen binding leads to dimerization of ERs, then ERs translocate into nucleus and interact with transcriptional co-activators and/or co-repressor, and bind to genomic DNA at specific sequences known as estrogen response elements (EREs) to activate or repress the transcription of specific genes. Non-genomic signaling pathway: Membrane ERs interact with SRC/G protein and activate PI3K/Akt signaling. Both MAPK signaling initiated by binding of growth factors to receptor tyrosine kinases and PI3K/Akt signaling can modify cytosolic ERs, which may interact with other transcription factors and modulate the transcription of specific genes. GF: Growth factor; RTK: Receptor tyrosine kinase; GP: G proteins; CoA: Transcription co-activator; CoR: Transcription co-receptor; TFs: Transcription factors; ERE: Estrogen response element.