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REVIEW

Estrogen receptors in gastric cancer: Advances and perspectives

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Abstract

Worldwide, gastric cancer is one of the most common malignancies with high mortality. Various aspects of the development and progression of gastric cancer continue to be extensively investigated in order to further our understanding and provide more effective means for the prevention, diagnosis, and treatment of the disease. Estrogen receptors (ERs) are steroid hormone receptors that regulate cellular activities in many physiological and pathological processes in different tissues. There are two distinct forms of ERs, namely ERα and ERβ, 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 role of ERs in gastric cancer, the possible mechanisms underlying these roles, and the clinical relevance of deregulated ERs in gastric cancer patients. To date, inconsistent associations of different ERs with gastric cancer have been reported. These inconsistencies may be caused by variations in *in vitro* cell models and clinical samples, including assay conditions and protocols with regard to different forms of ERs. Given the potential 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, to determine the specific roles and interactions that these individual ER isoforms play under specific conditions in the development and/or progression of gastric cancer, and to elucidate precisely these mechanisms. In this review, we summarize the achievements from early ER studies in gastric cancer to the most up-to-date discoveries, with an effort to provide a comprehensive understanding of the role of ERs roles in gastric cancer and its possible mechanisms. Furthermore, we propose directions for future investigations.

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

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 that ERs play in gastric cancer and the clinical relevance of deregulated ERs in gastric cancer patients. This review focuses on the current understanding 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 worldwide, with an estimated 723100 deaths and 951600 new cases in 2012[1]. Currently, tremendous efforts are being made to investigate the cellular and molecular mechanisms leading to the development and progression of gastric cancer, with the hope of improving the prevention, early diagnosis, and precise and personalized treatment of this cancer.

Estrogens are a class of steroids that was initially found to regulate the development and growth of the human reproductive system. Estrogens exert their influence on specific cells *via* activation of their cognate receptors (estrogen receptors, ERs). Estrogens/ERs have also been 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]. ERα and ERβ are members of a superfamily of nuclear receptors that can transduce extracellular signals into transcriptional responses and possess distinct protein structural characteristics, tissue distributions, and functions[4,5]. In certain ligands, cell-types, and promoter contexts, ERα and ERβ have different activities[6].

As illustrated in Figure 1, ERs share conserved domains for ligand binding, DNA binding, transcription activation (AF-1 and AF-2), and nuclear translocation (NLS). Based on their molecular weights, three isoforms for ERα have been identified, designated as ERα66, ERα46, and ERα36[7]. ERα66 functions as a ligand-dependent transcription factor that modulates gene expression by binding to estrogen response elements (EREs) in the transcriptional regulatory region in genomic DNA[5]. Despite lacking the AF-1 activation domain, ERα46 can still bind to EREs and form heterodimers with ERα66[8,9]. The subcellular localization and activation of the Src/phosphoinositide 3 kinase (PI3K)/AKT pathway upon estrogen-signaling also indicate possible roles for ERα46 in non-genomic estrogen signaling[10-12]. For ERα36, both activation domains (AF-1 and AF-2) are absent, but it retains the ability to dimerize, translocate to the nucleus, and bind DNA, with an even broader ligand-binding spectrum, and it may mediate rapid estrogen signaling[7,13]. Five alternatively spliced isoforms for ERβ have been identified (ERβ1-ERβ5). ERβ 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.

Expression of ERs has 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 ERs in gastric cancer will surely provide us additional 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 the role of ERs in gastric cancer and its possible mechanisms. Furthermore, we propose directions for future investigations.

EXPRESSION AND FUNCTIONAL INVESTIGATIONS ON ESTROGEN RECEPTORS IN GASTRIC CANCER

ERα66 (ERα)

Most of the literatures use terms "ER" or "ERα" when actually referring to the specific isoform ERα66, as it was the first identified isoform. Early investigation on ER expression in gastric cancer was initiated by the observation that there was an association between breast cancer and gastrointestinal cancer but no correlation between ER expression and gastric cancer[27]. The ER positive rate in gastric carcinoma was not significantly different between male and female cases[27,28], but the incidence of poorly differentiated adenocarcinoma was significantly higher than that of well differentiated adenocarcinoma[28]. Later studies showed a correlation between ER status and 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 the mRNA level, the ERα expression between gastric cancer tissues and matched normal tissues was not significantly different, but ERα-positive expression was correlated with poorer overall survival[15].

However, results from established cell lines were

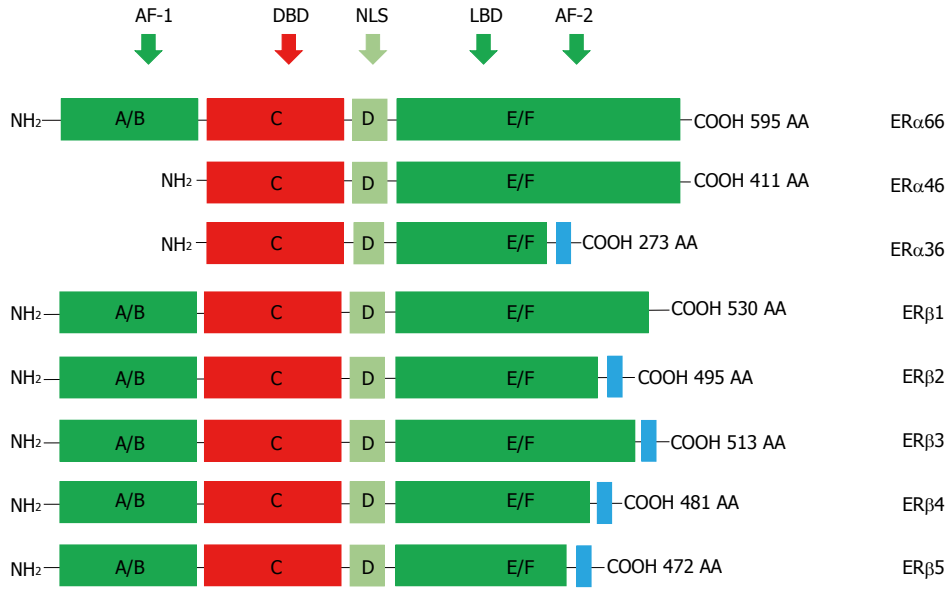

Figure 1 Protein structure of estrogen receptors. Two different forms of ER are encoded by two distinct genes located in chromosomes 6 and 14 and produce two proteins with 595 and 530 amino acids in full length, respectively. Six evolutionary conserved domains, namely A-F, are shared by different ERs. For ERα isoforms, compared to the full length ERα66, ERα46 lacks AF-1 domain (A/M), ERα36 lacks AF-1 and partial AF-2 domains but is equipped an extra different C-terminal. For alternatively-spliced ERβ 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; ERs: Estrogen receptors; AA: Amino acid.

inconsistent. More cell lines showed ERα expression by real-time polymerase chain reaction (RT-PCR) than that by western blotting[31,32], which may be due to differences in the sensitivity between the assays. ERα overexpression significantly inhibited cell growth and proliferation, promoted cell apoptosis, and blocked cell entry into the G_1/G_0 phase. In addition, ERα reduced the motility and invasion of gastric cancer cells. Overexpression of ERα decreased β-catenin expression, suggesting that ERα overexpression inhibited cell growth and cancer progression in gastric cancer by attenuating the expression of β-catenin[33].

ERα36

Although no work has been reported on ERα46 in gastric cancer to date, some studies have investigated the clinical significance and functions of ERα36 in gastric cancer. ERα36 is highly expressed in human gastric cancer, and its expression is correlated with lymph node metastasis, suggesting its use 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 levels were expressed in tumor specimens than in paired normal tissues. ERα36 protein was mainly expressed on the plasma membrane and in the cytoplasm of the established gastric cancer cells[34].

ERβ

Regarding the clinical relevance of ERβ with gastric cancer, the ERβ-positive group was associated with lower tumor stage, negative perineural invasion, Lauren's intestinal type, and free of recurrence. Presence of ERβ in gastric cancer could have a protective effect against the invasiveness of gastric cancer[32], similar to the function of ERβ in inhibiting proliferation, invasion, and tumor formation of breast cancer cells[35-37]. In multivariate analysis, the absence of ERβ was a significant independent prognostic factor that was 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 ERβ, and they may only be partly involved in gastric carcinogenesis. These data suggest that their clinicopathological and prognostic significance in gastric cancer may be limited[38].

For the transcription variants of ERβ in gastric cancer tissues, higher ERβ5 mRNA level was correlated with pTNM stage of the tumor, and lymph node metastasis was increased compared to their matched normal tissues. In contrast, levels of ERβ1 and β2 were not correlated with lymph node metastasis, gender, age, tumor size, tumor grade, or pTNM stage[39] (Table 1).

MECHANISMS FOR THE FUNCTION OF ERS IN GASTRIC CANCER

Current knowledge on the mechanisms underlying the function of ERs 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

Table 1 Summary of the association between estrogen receptor isoforms and gastric cancer

Estrogen receptors	Isoform	Association with gastric cancer
ERα	ERα66	No significant correlation between ERα66 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]
	ERα46	No reported result has been up to date
	ERα36	Expressed highly in gastric cancer[34]
		Expression correlated with lymph node metastasis[34]
		Expressed in plasma membrane and cytoplasm of gastric cancer[34]
ERβ	ERβ1	Associated with low tumor grades[32]
	ERβ2	Presence could have protective effect against invasion[32]
	ERβ3	Absence of ERβ a significant independent prognostic factor for poor OS[15]
	ERβ4	ERβ5 is associated with PTNM stage[39]
	ERβ5	

ER: Estrogen receptor; OS: Overall survival.

genomic and non-genomic pathways[40]. As illustrated in Figure 2, in the genomic pathway, estrogen-bound ERs translocate into the nucleus, bind to estrogen response elements (EREs) in genomic DNA, and regulate the expression of downstream genes. In the non-genomic pathway, ERs interact with some other signaling molecules in several pathways, such as the PI3K/Akt or mitogen activated protein kinase (MAPK) signaling pathway. ERα and ERβ play different roles in both genomic and non-genomic pathways, where ERβ 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 because of the special characteristics of this newly identified isoform. In established gastric cancer cells, ERα36 protein is mainly expressed on the plasma membrane and in the cytoplasm. Dysregulation of multiple signaling pathways involved in cell proliferation, metastasis, and invasion in relation to ERα36 has been described in gastric cancer[42,43].

ERα36 and glucose regulated protein 94

ERα36 is linked to glucose regulated protein (GRP) 94, 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 was involved in the malignant growth of gastric carcinoma cells[34,44]. The Akt signaling pathway is responsible in ERα36-mediated estrogen signaling *via* GPR-94 in gastric cancer[46]. ERα36 and GRP94 are highly expressed in gastric cancer. With knockdown of ERα36 in gastric cancer SGC-7901 cells, expression of GRP-94 and phosphorylation of Akt (Ser-473-Akt) were reduced significantly. Clinically, GRP94 expression level was significantly correlated with gender, tumor stage, and lymph node metastasis. It is known that estrogen induces the expression of GRPs, which suggests 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 cell proliferation by activating the membrane-initiated c-Src signaling pathway. C-Src in breast cancer cells has been reported to serve as a switch through the signal transducer and activator of transcription (STAT) 5/epidermal growth factor receptor (EGFR) pathway in ERα36 mediated biphasic estrogen signaling[47]. It has been reported that ERα36 also interacts physically with Src/Shc/EGFR complex[48]. As seen from these observations, c-Src functions in breast cancer in a similar manner as it does in ERα36-positive gastric cancer[44]. Revealed by the E_2-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 Tyr416 is phosphorylated and it negatively regulated when Tyr416 is dephosphorylated[50,51]. The phosphorylation status of c-Src-Tyr416 and c-Src-Tyr527 depends on the concentration of estrogen and serves to switch on and off non-genomic estrogen signaling[44]. E_2-ERα36 regulates phosphorylation of c-Src-Tyr 416 and Tyr 527; as a result, gastric cancer growth is promoted, further indicating that E_2-ERα36-c-Src is important for proliferation of gastric cancer cells. C-Src and ERα36 are known to interact in the presence of $E_2β$, while PP2 does not affect this interaction. However, PP2 inhibits the activation of c-Src.

ERα36 and cyclin D1

ERα36 upregulates cyclin D1 (CD1) when activating the c-Src signaling pathway, which leads to the proliferation of gastric cancer cells[34]. In ERα36 up-regulated

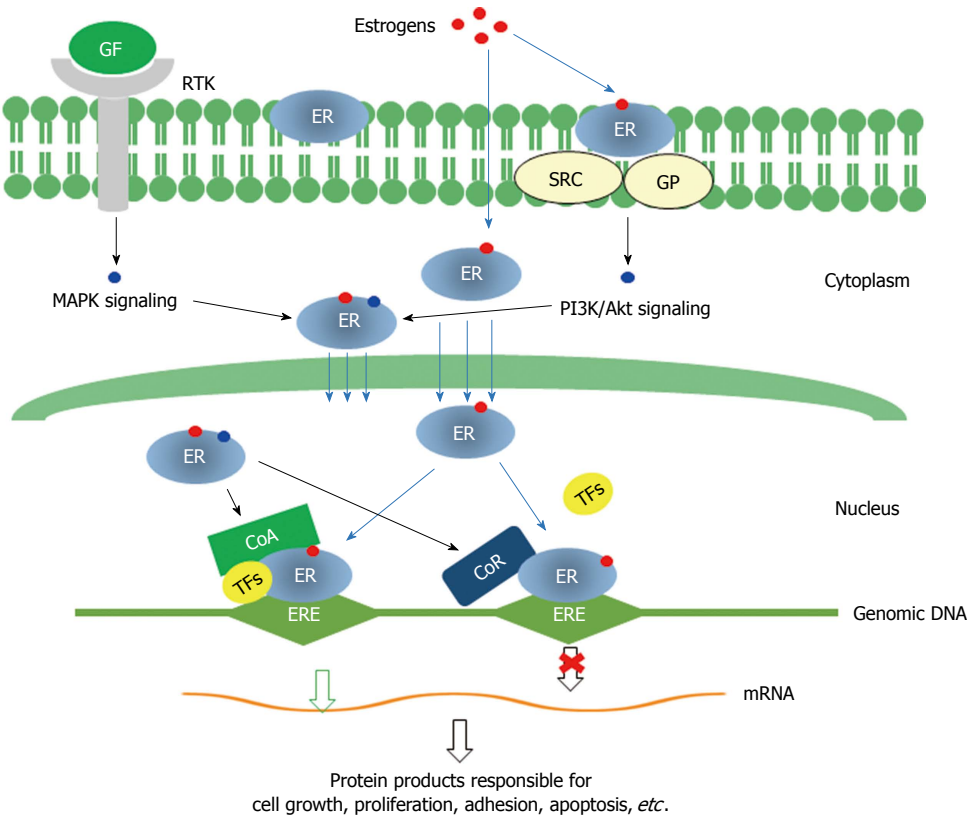

Figure 2 Molecular mechanisms for the functions of estrogen receptors. Genomic pathway: Estrogen binding leads to dimerization of ERs, then ERs translocate into nucleus and interact with transcriptional co-activators and/or co-repressor and bind to genomic DNA at specific sequences known as estrogen 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; MAPK: Mitogen activated protein kinase; PI3K: Phosphoinositide 3 kinase; ERs: Estrogen receptors.

cells, $E_2\beta$ induces c-Src-Tyr416 phosphorylation[46]. In contrast, $E_2\beta$ was unable to induce c-Src-Tyr527 phosphorylation in cells where ERα36 was knocked down. The level of CDI expression was increased by C-Src-Tyr416 phosphorylation in ERα36 up-regulated SGC7901 cells, and cell proliferation was promoted; 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 were reported to be a result of CDI overexpression, including gastric cancer. A gender difference in methyl-nitro-nitroso-guanidine (MNNG)-induced rat gastric carcinogenesis showed CD1/cdk4 expression[53]. To support these observations further, in tumors in nude mice, the xenograft with up-regulated ERα36 showed a 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 a 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 cases 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 α and β receptors is as yet clinically unclear. Moreover, the positive rate for ER expression in gastric cancer differs from study to study, with ERβ expressed more abundantly than ERα and different patterns in subtypes of gastric cancer. Although some studies showed that aberrant expression of ERα and ERβ mRNAs in tumors is associated with liver metastasis and lymph node metastasis, other have shown that there was no association between expression of ERβ and any clinical variables[57]. Furthermore, the mechanism of carcinogenesis linked to ERβ is unclear, and the use of estrogen for the therapeutic purposes may increase the risk for other cancers (breast or ovarian cancer);

the side effects of estrogen are also problematic[15,39,57]. The fractional agonist activity of tamoxifen through ERα in some circumstances can be entirely abolished upon co-expression of ERβ[15]. One possible role of ERβ is to moderate ERα transcriptional activity, and thus the relative expression level of the two isoforms might be a key factor for determining cellular responses to agonists and antagonists. Aromatase expression has been reported in gastric cancer cells recently, and with a short incubation period, gastric cancer can produce estradiol[58].

Notably, the role of estrogen in the stimulation of the growth of gastric cancer cells is associated with the concentration of estrogen[59]. A physiologically low concentration of estrogen was found 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 relationship between concentration of estrogen and its function 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. Some of the inconsistencies may be caused by the variations in these studies, such as *in vitro* gastric cancer cell models, clinical samples, and 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 the role of ERs in gastric cancer. Given the potential of deregulated ERs as diagnostic/prognostic markers or therapeutic targets for gastric cancer, it will be important to identify/confirm the specific roles that each isoform of these ERs (including their tissue-specific ligands) plays under specific conditions in the development and/or progression of gastric cancer, to determine the interactions of these isoforms, and to elucidate the mechanisms at all levels, including molecular, cellular, tissue/organ, and individual. This will provide 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 are being identified and studied in breast cancer, extensive investigation of ER in gastric cancer will surely provide us more knowledge on the development and progression of gastric cancer, and, therefore, will also provide us additional means to combat gastric cancer.

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