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Molecular Mechanisms, Expression and Clinical Role of ErbB Receptors in Endometrial Cancer

Review Article

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Abstract

The epidermal growth factor system (EGF System) is present in various human organs. It has 4 receptors (EGFR, ErbB-2, ErbB-3 and ErbB-4) and numerous ligands. Especially in cancer, the epidermal growth factor system signaling network becomes hyperactivated with a variety of mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation).

ErbB receptors are trans-membrane glycoproteins. Dimerization of ErbB receptors leads to intracellular kinase activation and initiates intracellular signaling via several pathways.

Due to the inactive status of postmenopausal endometrium, we expect to find significantly higher expression of the 4 ErbB receptors in endometrial cancer tissue.

In unselected endometrial cancer patients, there is EGFR expression in 43-67% of cases. EGFR overexpression in patients with Type I endometrial cancer, did not affect disease progression. However EGFR overexpression in patients with Type II endometrial cancer, associated with high grade disease and adverse clinical outcome.

In unselected endometrial cancer patients, ErbB-2 amplification/overexpression represents a rare event. ErbB-2 overexpression especially in patients with Type II endometrial cancer, is an indicator of a highly aggressive disease with poor overall survival.

Recent years ErbB receptors (especially EGFR and ErbB-2) have a particular importance, as they are potential targets in endometrial cancer treatment.

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Introduction

The epidermal growth factor system (EGF system) is present in various human organs. It has an important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development [1, 2].

Dysregulation of the EGF system signaling network is involved in cancer, diabetes, autoimmune, inflammatory, cardiovascular and nervous system disorders [1, 3].

Especially in cancer, the EGF system signaling network becomes hyperactivated with a variety of mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation) [3, 4].

Furthermore, the EGF system in cancer contributes in proliferation, transformation, angiogenesis, migration and invasion [5]. Recent years the receptors of the EGF system, are potential targets in cancer treatment [6, 7].

Molecular Biology of ErbB Receptors

The EGF system has 4 receptors (EGFR, ErbB-2, ErbB-3 and ErbB-4) and numerous ligands [1, 4, 5].

ErbB receptors are trans-membrane glycoproteins and belong to the superfamily of Receptor Tyrosine Kinases (RTKs) [1, 5]. They have an extracellular region with two ligand-binding domains, an extracellular juxtamembrane region, a hydrophobic transmembrane domain and an intracellular domain with tyrosine kinase activity [4, 8]. They catalyze the transfer of the γ phosphate of ATP to the hydroxyl groups of tyrosines in target proteins [9].

The extracellular region of EGFR, ErbB-3 and ErbB-4 has 2 distinct conformations. The closed conformation of extracellular region is inactive. The open conformation of extracellular region, is active and permits interactions with a ligand. In the absence of ligand binding, there is an equilibrium between the 2 conformations that favors the closed conformation [8, 10-12].

Ligand binding stabilizes the extracellular region in the open conformation, leads to the formation of homodimeric and heterodimeric ErbB receptor complexes and activates ErbB receptors by an allosteric mechanism [8, 11-14]. That leads to intracellular kinase activation and initiation of downstream signaling pathways [4, 13, 15]. However, ErbB-3 has no intrinsic tyrosine kinase activity and initiates signaling only in association with another ErbB receptor, usually ErbB-2 [16].

The extracellular region of ErbB-2 has a conformation not suitable for ligand binding [17]. However, ErbB-2 is capable for ligand independent dimerization and signaling [8, 17]. ErbB-2 heterodimerizes with other ErbB receptors and is their preferred heterodimerization partner [4, 13, 17]. Moreover, at elevated expression levels ErbB-2 homodimerizes [17].

Signaling Pathways of ErbB Receptors

Dimerization of ErbB receptors leads to intracellular kinase activation [4, 13, 15]. Subsequently, a number of tyrosine residues in the COOH-terminal portion of ErbB receptors becomes phosphorylated [5, 17, 18]. That phosphorylated tyrosine residues function as docking sites for cytoplasmic proteins containing Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains [3, 4, 18]. Recruitment of protein initiates intracellular signaling via several pathways:

1. Ras/Raf/mitogen-activated protein kinase (MAPK) pathway (regulates cell proliferation and survival) [Figure 1] [19, 20].
2. Phosphatidylinositol 3-kinase (PI3K)/Akt pathway (regulates cell growth, apoptosis, tumor invasion, migration and resistance to chemotherapy) [Figure 1] [21, 22].
3. Signal transducers and activators of transcription (STAT) pathway (regulates oncogenesis and tumor progression) [Figure 1] [23].
4. Src Kinase pathway (regulates cell proliferation, migration, adhesion, angiogenesis and immune function) [Figure 1] [24, 25].
5. Phospholipase Cγ/protein kinase C pathway [Figure 1] [26, 27].

Expression of ErbB receptors in EC

Due to the inactive status of postmenopausal endometrium, we expect to find significantly higher expression of the 4 ErbB receptors in EC tissue [28].

EGFR localized to the basal part of surface epithelial cells, only in stromal cells, or both, of epithelial and stromal cells of endometrium [29-36]. It is primarily located in the cell membrane but also located in the cytoplasm [28, 32-40].

In unselected EC patients, there is EGFR expression in 43-67% of cases [32-34, 36, 38-43]. In patients with Type I EC, there is EGFR expression in 46% of cases [34]. In patients with Type II EC, there is EGFR expression in 34-50% of cases [34, 35, 42, 44, 45].

ErbB-2 localized base-laterally in the glands and surface epithelial cells of endometrium [6, 29, 46]. It is located to the cell membrane [8, 28, 32-36, 39, 47].

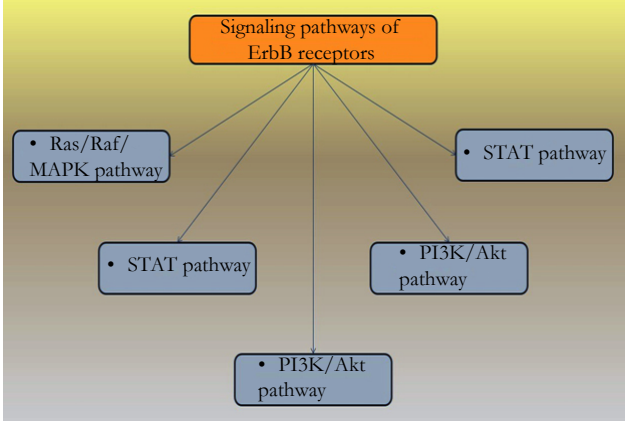
In unselected EC patients, ErbB-2 amplification/overexpression represents a rare event [43]. In patients with Type I EC, there is ErbB-2 receptor overexpression in 8% of cases and Erb-2 gene amplification in 1.4-3% of cases [42, 48]. Although ErbB-2 amplification/overexpression is ore common in patients with type II EC, the exact frequency remains controversial [34, 35, 42]. Moreover, there are racial differences regarding ErbB-2 overexpression in patients with type II EC [49]. ErbB-2 overexpression is more common in Black race patients with type II EC [49].

In patients with papillary serous EC, there is ErbB-2 receptor overexpression in 18%-80% of cases and ErbB-2 gene amplification in 17-47% of cases [34, 35, 42, 48, 50-52]. In patients with clear cell EC, there is ErbB-2 receptor overexpression in 33% of cases and ErbB-2 gene amplification in 16-50% of cases [34, 35, 42, 48, 51].

ErbB-3 localized to surface epithelial cells of endometrium [31-36, 53, 54]. It is located in the cytoplasm, with membrane staining in a minority of samples [28, 32-36, 54].

ErbB-4 localized to epithelial and stromal cells of endometrium [31-36, 54, 55]. It is located in the cytoplasm, with membrane

Figure 1. Signaling pathways of ErbB receptors [4, 13, 15, 19-27].



staining in a minority of samples [28, 32-36, 54].

Clinical role of ErbB receptors in EC

Recent years, the clinical role of ErbB receptors (especially EGFR and ErbB-2) in EC patients, have increasing popularity [35, 36, 42, 44, 45, 56-58].

EGFR may have a dual role in EC [42]. EGFR overexpression did not affect disease progression in patients with type I EC, although affects disease progression in Type II EC [42]. More specifically EGFR overexpression in patients with Type II EC, associated with high grade disease and adverse clinical outcome [34, 35, 42, 44, 45].

Moreover, ErbB-2 overexpression especially in patients with Type II EC, is an indicator of a highly aggressive disease with poor overall survival [34, 35, 44, 45, 47, 48, 50, 59, 60].

ErbB-3 overexpression in patients with EC, has an unclear clinical role and not well studied [28, 44, 45, 54, 61]. The clinical role of ErbB-4 in patients with EC, is poorly understood and not well studied [28, 32-35, 44, 45 ,54, 62]. It is obvious that ErbB receptors (especially EGFR and ErbB-2) in EC patients, are potential targets of molecular targeted therapies [35, 36, 42, 44, 45, 56, 58, 63]. Anti-ErbB MoAbs (cetuximab, panitumumab, trastuzumab, pertuzumab) may be an attractive treatment option, especially in EC patients with advanced, recurrent or metastatic disease and overexpression of EGFR and ErbB-2 [6, 7, 34-36, 44, 56, 64, 65].

However, a phase II study (NCT00392769) failed to demonstrate significant activity of cetuximab in unselected EC patients with advanced or recurrent disease [66, 67]. The clinical efficacy of trastuzumab in EC, has been reported in several case reports [64, 68-70]. However, a phase II study of Gynecologic Oncology Group (GOG-181B) failed to demonstrate significant activity of trastuzumab in unselected EC patients with advanced or recurrent disease and overexpression of ErbB-2 [71]. Moreover, an ongoing randomized phase II study (NCT01367002) evaluates the efficacy of carboplatin/paclitaxel with or without trastuzumab in selected EC patients (papillary serous) with advanced or recurrent disease and overexpression of ErbB-2 [72].

ErbB-specific TKIs (gefitinib, erlotinib, lapatinib, afatinib) may be another attractive treatment option in EC patients with advanced, recurrent or metastatic disease and overexpression of EGFR and ErbB-2 [34-36, 44, 45, 56, 73-75]. However, a phase II study of the Gynecologic Oncology Group (GOG-229C) failed to demonstrate significant activity of gefitinib in unselected EC patients with persistent or recurrent disease [75]. Also, a phase II study (NCIC IND-148) failed to demonstrate significant activity of erlotinib in unselected EC patients with advanced or metastatic disease [74].

Moreover, a phase II study of the Gynecologic Oncology Group (GOG-229D) failed to demonstrate significant activity of lapatinib in unselected EC patients with persistent or recurrent disease [73]. It is obvious that ErbB-targeted therapies have only modest effect in unselected EC patients [34, 35, 44, 45, 56, 58, 63, 76]. Further studies into the molecular pathways of EC, may increase our knowledge regarding ErbB receptors and ErbB-targeted therapies [34, 44]. Perhaps the clinical role of ErbB receptors is more important in type II EC patients [34, 35, 44, 45, 47, 48, 50, 59, 60]. Also, ErbB-targeted therapies may be more effective as adjuvant treatment in type II EC patients with EGFR and ErbB-2 over expression [35, 36, 42 ,44 ,56-58, 64, 68, 69, 71-81].

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Special Issue on

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