

ErbB Receptors and ErbB Targeted Therapies in Endometrial Cancer

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Abstract

The Epidermal Growth Factor system is present in human organs and plays an important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development. It has four receptors (EGFR, ErbB-2, ErbB-3 and ErbB-4) and numerous ligands. Dysregulation of the Epidermal Growth Factor signaling network is implicated in the pathogenesis of various disorders. Especially in cancer, the Epidermal Growth Factor system becomes hyperactivated with various mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation). EGFR overexpression may have a dual role in endometrial cancer. It seems that in type I endometrial cancer, EGFR overexpression did not affect disease progression. However in type II endometrial cancer, EGFR overexpression associated with high grade disease and adverse clinical outcome. Moreover ErbB-2 overexpression especially in type II endometrial cancer, is an indicator of a highly aggressive disease with poor overall survival. The potential role of ErbB receptors (especially EGFR and ErbB-2) as targets for cancer therapy has been investigated for over 20 years. There are 2 major classes of ErbB targeted therapies: anti-ErbB monoclonal antibodies (MoAbs) and ErbB-specific tyrosine kinase inhibitors (TKIs). ErbB targeted therapies have still shown modest effect in unselected endometrial cancer patients. However, they may be clinically active as adjuvant therapy in well-defined subgroups of type II endometrial cancer patients with EGFR and ErbB-2 overexpression.

Keywords

Endometrial Cancer, ErbB Receptors, ErbB Targeted Therapy

1. Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract and occurs primarily in

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postmenopausal women [1] [2]. Overall, about 2.64% of women develop EC during their lifetime [1].

The epidermal growth factor system (EGF system) is present in human organs and plays an important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development [3] [4].

Dysregulation of the EGF signaling network is implicated in various disorders [3] [5]. Especially in cancer, the EGF system contributes in proliferation, transformation, angiogenesis, migration and invasion [6].

2. Epidermal Growth Factor System

2.1. Receptors and Ligands

The EGF system is present in human organs and play important role during embryogenesis and postnatal development [3] [4]. It has 4 receptors: epidermal growth factor receptor (EGFR or ErbB-1), ErbB-2, ErbB-3 and ErbB-4 [3] [6] [7].

ErbB receptors belong to subclass I of the superfamily of Receptor Tyrosine Kinases (RTKs) [3] [6]. They are trans-membrane glycoproteins with an extracellular region containing two ligand-binding domains, an extracellular juxtamembrane region, a hydrophobic transmembrane domain and an intracellular domain with tyrosine kinase activity [7] [8]. ErbB receptors catalyze the transfer of the γ phosphate of ATP to hydroxyl groups of tyrosines in target proteins [9].

Moreover, EGF system has numerous ligands. According to their affinity for one or more ErbB receptors, the ligands divided into:

1) Ligands with binding specificity for EGFR: EGF, transforming growth factor- α (TGF- α) and amphiregulin (AR) [6] [7] [10].

2) Ligands with dual binding specificity for EGFR and ErbB-4: betacellulin (BTC), heparin-binding growth factor (HB-EGF) and epiregulin (EPR) [6] [7] [10].

3) Ligands with binding specificity for ErbB-3 and ErbB-4: neuregulins (NRGs) or heregulins (HRGs). They divided in two subgroups based on their ability to bind ErbB-3 and ErbB-4 (NRG-1 and NRG-2) or only ErbB-4 (NRG-3 and NRG-4) [6] [7] [10]-[12].

The ligands for ErbB receptors bind to the extracellular domain, resulting in receptor activation by homodimer and/or heterodimer formation and the subsequent transphosphorylation of tyrosine residues in the cytoplasmic region [6] [7] [13]. However, there is no direct ligand for ErbB-2 receptor [6].

2.2. Receptor Activation

The extracellular region of EGFR, ErbB-3 and ErbB-4 has two distinct conformations: the closed conformation (inactive) and the open conformation (active) [8] [14] [15].

In the absence of ligand binding, the extracellular region of EGFR, ErbB-3 and ErbB-4 has equilibrium between closed and open conformation [8] [14]-[16]. This equilibrium favours the closed conformation [8] [16].

Ligand binding stabilizes extracellular region in the open conformation and leads to the formation of both homodimeric and heterodimeric ErbB receptor complexes [8] [15]-[17]. The dimeric formation triggers receptor activation by an allosteric mechanism [18]. That leads to intracellular kinase activation and initiation of downstream signaling pathways [7] [17] [19].

The extracellular region of ErbB-2 has a conformation not suitable for ligand binding [20]. However, ErbB-2 is capable for ligand independent dimerization and signaling [8] [20]. At elevated expression levels ErbB-2 homodimerizes [20]. Moreover, ErbB-2 heterodimerizes with other ErbB receptors and it is their preferred heterodimerization partner [7] [17] [20]-[22].

ErbB-3 lacks intrinsic tyrosine kinase activity [23]. It can initiate signaling only in association with another ErbB receptor, usually ErbB-2 [23].

The dimerization of ErbB receptors represents the fundamental mechanism that drives transformation [24]. Although both homodimerization and heterodimerization result in activation of the EGF signaling network, heterodimers are more potent and mitogenic [5].

2.3. Intracellular Signaling

Dimerization of ErbB receptors leads to intracellular kinase activation [7] [17] [19]. As a result, a number of tyrosine residues in the COOH-terminal portion of ErbB receptors become phosphorylated [6] [20] [24]. These

phosphorylated tyrosine residues function as docking sites for cytoplasmic proteins containing Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains [5] [7] [24] [25]. Recruitment of proteins initiates intracellular signaling via several pathways:

- 1) Ras/Raf/mitogen-activated protein kinase (MAPK) pathway [26]-[30].
- 2) Phosphatidylinositol 3-kinase (PI3K)/Akt pathway [26] [31]-[34].
- 3) Signal transducers and activators of transcription (STAT) pathway [35]-[39].
- 4) Src Kinase pathway [40]-[43].
- 5) Phospholipase C γ /protein kinase C pathway [44]-[47].

2.4. Dysregulation and Oncogenesis

Dysregulation of the EGF signaling network is implicated in cancer, diabetes, autoimmune, inflammatory, cardiovascular and nervous system disorders [3] [5].

Loss of control of the cell functions mediated by the EGF signaling network is a hallmark of oncogenesis, in which the balance between cell proliferation and differentiation is disturbed. Several types of human cancer associated with dysregulation of the EGF signaling network [3].

In cancer, the EGF signaling network becomes hyperactivated with various mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation) [5] [7] [48]. Moreover contributes in proliferation, transformation, angiogenesis, migration and invasion [6].

3. Endometrial Cancer

3.1. Classification

EC is the most common malignancy of the female genital tract [1]. Based on clinical and pathological features, sporadic EC is classified into 2 types [49] [50].

1) Type I EC, represents the majority of sporadic EC cases (70% - 80%) [49] [50]. It is usually well differentiated and endometrioid in histology [49]-[51]. It is estrogen-related, usually arises from endometrial hyperplasia, has less aggressive clinical course and favorable prognosis [49] [50] [52].

2) Type II EC, represents the minority of sporadic EC cases (10% - 20%) [49] [50]. It is poorly differentiated and usually papillary serous or clear cell in histology [49]-[51]. It is not estrogen-related, arises from atrophic endometrium, has aggressive clinical course and propensity for early spread and poor prognosis [49] [53] [54].

3.2. Expression and Clinical Significance of ErbB Receptors

Due to the inactive status of postmenopausal endometrium, it is expectable to find significantly higher expression of the ErbB receptors in EC tissue [55].

In endometrium, EGFR localized to the basal part of surface epithelial cells, only in stromal cells, or both to epithelial and stromal cells [56]-[65]. It is primarily located to the cell membrane but also located to the cytoplasm [55] [61]-[69].

In unselected patients with EC, it has been reported EGFR expression in 43% - 67% of cases [61]-[63] [67]-[72]. In patients with type I EC, it has been reported EGFR expression in 46% of cases [63]. In patients with type II EC, it has been reported EGFR expression in 34% - 50% of cases [63] [64] [71].

EGFR over expression may have a dual role in EC [71]. It seems that in type I EC, EGFR overexpression did not affect disease progression [71]. However in type II endometrial cancer, EGFR overexpression associated with high grade disease and adverse clinical outcome [63] [64] [71].

In endometrium, ErbB-2 localized baso-laterally in the glands and surface epithelial cells [56] [57] [60]-[65] [73]. It is located to the cell membrane [55] [61]-[65] [67] [68] [74].

In unselected patients with EC, ErbB-2 amplification/overexpression represents a rare event [72]. In patients with type I EC, it has been reported ErbB-2 receptor overexpression in 8% of cases and ErbB-2 gene amplification in 1.4% - 3% of cases [71] [75]. Although ErbB-2 amplification/overexpression is more common in patients with type II EC, the exact frequency remains controversial [63] [64] [71]. However, there are racial differences regarding ErbB-2 overexpression in patients with type II EC [76]. ErbB-2 overexpression is more common in Black race patients with type II EC [65] [76].

In patients with papillary serous EC, it has been reported ErbB-2 receptor overexpression in 18% - 80% of cases and ErbB-2 gene amplification in 17% - 47% of cases [63] [64] [71] [75] [77]-[79]. In patients with clear cell EC, it has been reported ErbB-2 receptor overexpression in 33% of cases and ErbB-2 gene amplification in 16% - 50% of cases [63] [64] [71] [75] [78]. ErbB-2 overexpression especially in type II EC, is an indicator of a highly aggressive disease with poor overall survival [63] [64] [74] [75] [77] [80] [81].

In endometrium, ErbB-3 localized to surface epithelial cells [60]-[65] [82] [83]. It is located to the cytoplasm, with membrane staining in a minority of samples [55] [61]-[65] [83].

The clinical significance of ErbB-3 has not been studied well in EC [55] [61]-[65] [83].

In endometrium, ErbB-4 localized to epithelial and stromal cells [60]-[65] [83] [84]. It is located to the cytoplasm, with membrane staining in a minority of samples [55] [61]-[65] [83].

The clinical significance of ErbB-4 has not been studied well in EC [55] [61]-[65] [83].

4. ErbB Targeted Therapies

4.1. Classification

EGFR and ErbB-2 as targets for cancer therapy have been investigated for over 30 years [85]. There are 2 major classes of ErbB targeted therapies: [85] [86].

4.1.1. Anti-ErbB Monoclonal Antibodies (MoAbs)

1) Anti-EGFR MoAbs (cetuximab, panitumumab) bind to the extracellular domain of EGFR and prevent ligand binding and ligand dependent receptor activation [85] [86].

2) Anti-ErbB-2 MoAb (trastuzumab) binds to the extracellular domain of ErbB-2 and interferes with ligand independent receptor activation [85] [86]. However, the exact mechanism of action remains controversial [85] [86].

3) Anti-ErbB MoAb (pertuzumab) prevents receptor heterodimerization [85] [86].

4.1.2. ErbB-Specific Tyrosine Kinase Inhibitors (TKIs)

1) EGFR TKIs (gefitinib, erlotinib) block the binding of ATP to the intracellular domain of EGFR and prevent tyrosine kinase activity and subsequent intracellular signaling [85] [86].

2) EGFR and ErbB-2 TKI (lapatinib) block the binding of ATP to the intracellular domain of EGFR and ErbB-2 and prevents tyrosine kinase activity and subsequent intracellular signaling [85] [86].

4.2. Effectiveness in Unselected Endometrial Cancer Patients

4.2.1. Anti-ErbB Monoclonal Antibodies (MoAbs) in Endometrial Cancer

Anti-ErbB-2 MoAb (trastuzumab) may be an attractive and viable therapeutic option in patients with advanced, recurrent and/or metastatic EC overexpressing ErbB-2 [87].

Clinical responses to trastuzumab as single agent or in combination with chemotherapy have been reported in several case reports [87]-[90].

However a phase II study of trastuzumab as single agent in unselected patients with advanced or recurrent EC overexpressing ErbB-2, failed to demonstrate significant activity [91].

Moreover a phase II study of carboplatin/paclitaxel with or without trastuzumab in patients with advanced or recurrent type II EC (papillary serous) overexpressing ErbB-2, is currently underway (NCT01367002) [92].

4.2.2. ErbB-Specific Tyrosine Kinase Inhibitors (TKIs) in Endometrial Cancer

ErbB-specific TKIs (gefitinib, erlotinib, lapatinib) may be another viable therapeutic option in patients with advanced, recurrent and/or metastatic EC overexpressing EGFR and ErbB-2 [65] [93]-[95].

However a phase II study of gefitinib as single agent in unselected patients with persistent or recurrent EC overexpressing EGFR, demonstrate 4.1% complete response rate and 16.6% progression free survival \geq 6 months [93].

Also a phase II study of erlotinib as single agent in unselected patients with metastatic or recurrent EC, demonstrate 12.5% partial response rate [94].

Moreover a phase II study of lapatinib as single agent in unselected patients with persistent or recurrent EC,

demonstrate 3.3% partial response rate and 10% progression free survival ≥ 6 months [95].

4.3. Effectiveness in Well-Defined Subgroups of Endometrial Cancer Patients

Recent years, molecular targeted therapies have still shown modest effect in unselected EC patients [96]. Overall response rate to these drugs is modest, unless they are associated with chemotherapy or radiotherapy [85].

ErbB targeted therapies have not clinically tested in type II EC [71]. Perhaps they may be clinically active as adjuvant therapy in well-defined subgroups of type II EC patients with EGFR and ErbB-2 overexpression [64] [65] [71] [87]-[89] [97]-[104].

5. Conclusion

The role of ErbB targeted therapies in EC should be further investigated in clinical trials to evaluate their therapeutic efficacy [63]-[65] [71] [74] [87] [90]-[92] [94] [100] [101]. Moreover additional studies into the molecular pathways of EC development and progression, will increase our knowledge and lead to the discovery of new generation molecules with higher therapeutic efficacy [63]-[65].

Conflict of Interest

We declare that we have no conflict of interest.

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