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Review

Molecular biology, expression and clinical significance of ErbB receptors in endometrial cancer

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Abstract

The epidermal growth factor system (EGF system) is present in human organs and play important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development. It has 4 receptors (EGFR, ErbB - 2, ErbB - 3 and ErbB - 4) and numerous ligands. Dysregulation of the epidermal growth factor system 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). Endometrial cancer occurs primarily in postmenopausal women. Due to the inactive status of postmenopausal endometrium, it is expectable to find significantly higher expression of the 4 ErbB receptors in endometrial cancer tissue. EGFR overexpression in type I endometrial cancer, did not affect disease progression. However EGFR overexpression in type II endometrial cancer, associated with high grade 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 clinical significance of ErbB receptors in endometrial cancer should be further investigated in future clinical trials. Moreover additional studies into the molecular pathways of endometrial cancer development and progression, will increase our knowledge and lead to the discovery of new generation molecules with higher therapeutic efficacy.

Key words: endometrial cancer; epidermal growth factor system; ErbB receptors; molecular biology; expression; clinical significance

The epidermal growth factor system (EGF system) is present in human organs and play important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development[1-3].

Dysregulation of the EGF signaling network is implicated in various disorders[1-4]. Especially in cancer, the EGF system contributes in proliferation, transformation, angiogenesis, migration and invasion[2,3,5].

Endometrial cancer (EC) is the most common malignancy of the female genital tract and occurs primarily in postmenopausal women[6]. Due to the inactive status of postmenopausal endometrium, it is expectable to find significantly higher expression of the EGF system in EC tissue[2,3,7].

Molecular biology of the EGF system

Receptors and ligands

The EGF system is present in human organs and

play important role during embryogenesis and postnatal development[1-3].

The EGF system has 4 receptors: epidermal growth factor receptor (EGFR) (also known as ErbB - 1, HER1), ErbB - 2 (also known as HER2, Neu), ErbB - 3 (also known as HER3) and ErbB - 4 (also known as HER4)[1,3,5,8].

ErbB receptors belong to subclass I of the superfamily of Receptor Tyrosine Kinases (RTKs)[1,5]. 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[8,9]. They catalyze the transfer of the γ phosphate of ATP to hydroxyl groups of tyrosines in target proteins[9].

Moreover, EGF system has numerous ligands[2,3,8]. According to their affinity for one or more ErbB receptors, they are divided into three groups:

Ligands with binding specificity for EGFR: EGF, transforming growth factor - a (TGF - a) and amphiregulin (AR)[5,8].

Ligands with dual binding specificity for EGFR and ErbB4: betacellulin (BTC), heparin-binding growth factor (HB - EGF) and epiregulin (EPR)[5,8].

Ligands with binding specificity for ErbB - 3 and ErbB - 4: neuregulins (NRGs) or heregulins (HRGs). They are 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)[5,8].

Receptors activation

The extracellular region of EGFR, ErbB - 3 and ErbB - 4 has two distinct conformations:

Closed conformation (inactive) which has intramolecular interactions between subdomains II and IV[9,10].

Open conformation (active), where subdomains I and III form a ligand - binding pocket that permits interactions between a single ligand and subdomains I and III[9,10].

In the absence of ligand binding, the extracellular region of EGFR, ErbB - 3 and ErbB - 4 has equilibrium between closed and open conformation[9-11]. This equilibrium favours the closed conformation[9-11].

Ligand binding stabilizes extracellular region in the open conformation and leads to the formation of both homodimeric and heterodimeric ErbB receptor complexes[9-12]. The dimeric formation triggers receptor activation by an allosteric mechanism[10,12] which leads to intracellular kinase activation and initiation of downstream signaling pathways[8,12].

The extracellular region of ErbB - 2 has a conformation not suitable for ligand binding[13]. However, this conformation allows extension of the receptor dimerization arm in subdomain II[9,13]. This suggests that ErbB - 2 is capable for ligand independent dimerization and signaling[9]. ErbB - 2 heterodimerizes with other ErbB receptors and it is their preferred heterodimerization partner[8,12,13]. At elevated expression levels ErbB - 2 homodimerizes[13].

ErbB - 3 lacks intrinsic tyrosine kinase activity and therefore can initiate signaling only in association with another ErbB receptor, usually ErbB - 2[2,3,8]. ErbB - 2 and ErbB - 3 heterodimer is the most transforming and mitogenic receptor complex and increases cell motility on stimulation with a ligand[8].

The dimerization of ErbB receptors represents the fundamental mechanism that drives transformation[2,3,8].

Signaling pathways

Dimerization of ErbB receptors leads to intracellular kinase activation[8,12]. Subsequently, a number of tyrosine residues in the COOH - terminal portion of ErbB receptors become phosphorylated[5,13]. These phosphorylated tyrosine residues function as docking sites for cytoplasmic proteins containing Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains[4,8]. Recruitment of proteins initiates intracellular signaling via several pathways:

Ras / Raf / mitogen - activated protein kinase (MAPK) pathway

The Ras / Raf / mitogen - activated protein kinase (MAPK) pathway regulates cell proliferation and

survival[14]. Following ErbB phosphorylation, the complex of Grb2 and Sos adaptor proteins binds directly or indirectly (through Shc adaptor protein) to specific intracellular ErbB docking sites[14].

This interaction results in conformational modification of Sos, leading to recruitment of Ras - GDP and subsequent Ras activation (Ras - GTP)[15]. Ras-GTP activates Raf - 1 and, through intermediate steps, phosphorylates MAPK - 1 and MAPK - 2[15]. Activated MAPKs phosphorylate and regulate specific intranuclear transcription factors involved in cell migration and proliferation[14].

Phosphatidylinositol 3 - kinase (PI3K)/Akt pathway

The Phosphatidylinositol 3 - kinase (PI3K)/ Akt pathway regulates cell growth, apoptosis, tumor invasion, migration and resistance to chemotherapy[16].

PI3K is a dimeric enzyme that composed of a regulatory p85 subunit and a catalytic p110 subunit[16]. The regulatory p85 subunit, is responsible of the anchorage to ErbB receptor specific docking sites, through interaction of its Src homology domain 2 (SH2) with phosphotyrosine residues[16]. The catalytic p110 subunit, catalyzes the phosphorylation of phosphatidylinositol 4, 5 diphosphate at the 3' position[16]. Phosphatidylinositol 3, 4, 5 triphosphate, phosphorylates and activates the protein serine/threonine kinase Akt[16].

ErbB receptor specific docking sites for p85 subunit are present on ErbB - 3 and absent on EGFR[8]. EGFR dependent PI3K activation occurs through dimerization of EGFR with ErbB - 3 or through the docking protein Gab - 1[14].

Signal transducers and activators of transcription (STAT) pathway

Signal transducers and activators of transcription (STAT) pathway regulates oncogenesis and tumor progression[17].

STAT proteins interact with phosphotyrosine residues via their Src homology domain 2 (SH2) and, on dimerization, translocate to the nucleus and induce the expression of specific target genes[18]. Constitutive activation of STAT proteins (especially STAT - 3 and STAT - 5) is present in various primary cancers[17,18].

EGFR regulate STAT pathway through a Janus kinase (JAK) or a JAK independent mechanism[17]. Augmented activity of EGFR and ErbB - 2, promotes persistent STAT - 3 activation and subsequently induces oncogenesis and tumor progression[17].

Src Kinase pathway

The Src kinase pathway regulates cell proliferation, migration, adhesion, angiogenesis, and immune function[19].

Src is a member of a 10 genes family (FYN, YES, BLK, FRK, FGR, HCK, LCK, LYN, SRMS) of non - RTKs. It is located in the cytoplasm and cross - connected with other signaling pathways, such as PI3K and STAT pathway[19].

Although Src functions independently, it may interact with RTKs such as EGFR. The interaction between Src and EGFR may enhance ErbB signaling and may be involved in resistance to EGFR targeted therapy[13].

Phospholipase Cγ / protein kinase C pathway

Phospholipase Cγ (PLCγ) interacts directly with activated EGFR and ErbB - 2 and hydrolyses phosphatidylinositol 4, 5 diphosphate to inositol 1, 3, 5 triphosphate (IP3) and 1, 2 diacylglycerol (DAG)[20].

IP3 is important for intracellular calcium release. DAG is cofactor in protein kinase C (PKC) activation. Activated PKC activates MAPK and c - Jun NH2 - terminal kinase[21].

Dysregulation and carcinogenesis

Dysregulation of the EGF system signaling network is implicated in cancer, diabetes, autoimmune, inflammatory, cardiovascular and nervous system disorders[1,4].

Loss of control of the cell functions mediated by the EGF system signaling network is a hallmark in oncogenesis[2,3]. Several types of human cancers are associated with dysregulation of the EGF system signaling network[1].

Especially in cancer, the EGF system signaling network becomes hyperactivated with a range of mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation)[2,4,8]. It also contributes in proliferation, transformation, angiogenesis, migration and invasion[5].

Expression of ErbB receptors in endometrial cancer

EC is the most common malignancy of the female genital tract and occurs primarily in postmenopausal women[6]. Overall, 2.64% of women develop EC during their lifetime[6]. Based on clinical and pathological features, sporadic EC is classified into 2 types[22,23].

Type I EC, represents the majority of sporadic EC cases (70 - 80%)[22,23]. It is usually well differentiated and endometrioid in histology[22,23]. It is estrogen - related and usually arises from endometrial hyperplasia[22,23]. It has less aggressive clinical course and favorable prognosis[22,23].

Type II EC, represents the minority of sporadic EC cases (10 - 20%)[22,23]. It is poorly differentiated and usually papillary serous or clear cell in histology[22,23]. It is not estrogen - related and arises from atrophic endometrium[22]. It has aggressive clinical course and propensity for early spread and poor prognosis[22].

Due to the inactive status of postmenopausal endometrium, it is expectable to find significantly higher expression of the 4 ErbB receptors in EC tissue[2,3,7].

EGFR localized to the basal part of surface epithelial cells, only in stromal cells, or both to epithelial and stromal cells of endometrium[2,3,24-27]. It is primarily located to the cell membrane but also located to the cytoplasm[2,3,7 25-29].

In unselected patients with EC, it has been reported EGFR expression in 43 - 67% of cases[2,3,25,26, 28,31]. In patients with type I EC, it has been reported EGFR expression in 46% of cases[2,3]. In patients with type II EC, it has been reported EGFR expression in 34 - 50% of cases[2,3,27,30,32].

ErbB-2 is localized baso - laterally in the glands and surface epithelial cells of endometrium[2,3,24-27]. It is located to the cell membrane[2,3,7,25-29,33].

In unselected patients with EC, ErbB - 2 amplification/overexpression represents a rare event[31]. 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[30,34]. Although ErbB - 2 amplification/overexpression is more common in patients with type II EC, the exact frequency remains controversial[2,3,27,30]. Moreover, there are racial differences regarding ErbB - 2 overexpression in patients with type II EC[3,35]. ErbB - 2 overexpression is more common in Black race patients with type II EC[35].

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[2, 3,27,30,34, 36]. 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[2,3,27,30,34,36].

ErbB - 3 is localized to surface epithelial cells of endometrium[2,3,24-27,37]. It is located in the cytoplasm, with membrane staining in a minority of samples[2,3,7,25-27,37].

ErbB - 4 is localized at epithelial and stromal cells of endometrium[2,3,24-27,37]. It is located in the cytoplasm, with membrane staining in a minority of samples[2, 3,7,25-27,37].

Clinical significance of ErbB receptors in endometrial cancer

Overexpression and structural alterations of EGFR in various cancers are associated with higher grade, disease progression, poor survival and resistance to radiotherapy and chemotherapy[8]. Although the clinical significance of EGFR has not been studied well in EC, it may have a dual role[2,3,30]. EGFR overexpression did not affect disease progression in type I EC, although affects disease progression in type II EC[30]. EGFR overexpression in type II EC is associated with high grade disease and adverse clinical outcome[2, 3,27,30,32].

Overexpression of ErbB - 2 in various cancers is an indicator of a more aggressive clinical behavior[8,33]. ErbB - 2 overexpression especially in type II EC, is an indicator of a highly aggressive disease with poor overall survival[2,3,27,32-34,38].

Overexpression of ErbB - 3 in various cancers is related with ErbB - 2 positivity and lymph node involvement[39,40]. However, a definitive relationship with survival has not been established[39,40]. The clinical significance of ErbB - 3 has not been studied well in EC[2,3,7,25-27,32,37].

Overexpression of ErbB - 4 is related with favorable prognosis in breast and bladder cancer[41]. The clinical significance of ErbB - 4 has not been studied well in EC [2,3,7, 25-27,32,37].

It is obvious that the clinical significance of ErbB receptors in EC should be further investigated in future clinical trials[2,3,27, 30,33,42-47]. 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[2,3,27].

Conflict of interest

All authors declare no conflict of interest.

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