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The Role of ErbB Receptors in Endometrial Cancer

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1. Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract. Overall, about 2% to 3% of women develop EC during their lifetime [Jemal et al., 2006]. EC is a malignancy that occurs primarily in postmenopausal women.

Based on clinical and pathological features, EC is classified into 2 types [Bokhman, 1983]. Type I EC, represents the majority of sporadic EC cases (70-80%), is usually well differentiated and endometrioid in histology. Type II EC, represents the minority of sporadic EC cases (10-20%), is poorly differentiated and usually papillary serous or clear cell in histology [Bokhman, 1983; Lax, 2004; Doll et al., 2008].

The Epidermal Growth Factor system (EGF system) is present in human organs and play important role in embryogenesis and postnatal development [Casalini et al., 2004; Uberall et al., 2008].

Dysregulation of the EGF signaling network is implicated in various disorders [Marmor et al., 2004; Uberall et al., 2008]. In cancer, the EGF system contributes in proliferation, transformation, angiogenesis, migration and invasion [Holbro et al., 2003].

2. Epidermal growth factor system

2.1 Receptors and ligands

The EGF system is present in human organs and play important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development [Casalini et al., 2004; Uberall et al., 2008].

The EGF system has four receptors: epidermal growth factor receptor (EGFR) (also known as ErbB-1, HER1), ErbB-2 (also called HER2, Neu), ErbB-3 (also called HER3) and ErbB-4 (also called HER4)] [Holbro et al., 2003; Yarden, 2001a; Yarden & Sliwkowski, 2001b].

ErbB receptors belong to subclass I of the superfamily of Receptor Tyrosine Kinases (RTKs) [Holbro et al., 2003; Uberall et al., 2008]. 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 [Riese et al., 2007; Yarden, 2001a; Yarden & Sliwkowski, 2001b]. They catalyze the transfer of the γ phosphate of ATP to hydroxyl groups of tyrosines in target proteins [Hunter, 1998]. ErbB-3 lacks intrinsic tyrosine kinase activity [Mass, 2004].

The extracellular region of ErbB receptors has 4 subdomains (I-IV). Subdomains I and III (also called L1 and L2) are important for ligand binding. Subdomain II (also called S1) is important for dimerization between two receptors [Ogiso et al., 2002].

The EGF system has numerous ligands. According to their affinity for one or more ErbB receptors, they divided into three groups:

1. The first group includes ligands with binding specificity for EGFR: EGF, transforming growth factor-a (TGF-a) and amphiregulin (AR) [Yarden, 2001a; Yarden & Sliwkowski, 2001b; Holbro et al., 2003; Normanno et al., 2003;].
2. The second group includes ligands with dual binding specificity for EGFR and ErbB4: betacellulin (BTC), heparin-binding growth factor (HB-EGF) and epiregulin (EPR) [Yarden, 2001a; Yarden & Sliwkowski, 2001b; Holbro et al., 2003; Normanno et al., 2003;].
3. The third group includes 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) [Zhang et al., 1997; Harari et al., 1999; Yarden, 2001a; Yarden & Sliwkowski, 2001b; Holbro et al., 2003; Normanno et al., 2003].

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 [Alroy & Yarden, 1997; Yarden, 2001a; Yarden & Sliwkowski, 2001b ; Holbro et al., 2003]. No direct ligand for ErbB-2 has been described [Holbro et al., 2003].

2.2 ErbB receptors homodimerization and heterodimerization

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

1. The closed conformation (inactive), has intramolecular interactions between subdomains II and IV [Ferguson et al., 2003; Dawson et al., 2005; Riese et al., 2007].
2. The 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 [Ferguson et al., 2003; Dawson et al., 2005; Riese et al., 2007].

In the absence of ligand binding, the extracellular region of EGFR, ErbB-3 and ErbB-4 has equilibrium between closed and open conformation [Ferguson et al., 2003; Dawson et al., 2005; Ozcan et al., 2006; Riese et al., 2007]. This equilibrium favours the closed conformation [Ozcan et al., 2006; Riese et al., 2007].

Ligand binding stabilizes extracellular region in the open conformation and leads to the formation of both homodimeric and heterodimeric ErbB receptor complexes [Olayioye et al., 2000; Dawson et al., 2005; Ozcan et al., 2006; Riese et al., 2007]. The dimeric formation triggers receptor activation by an allosteric mechanism [Zhang et al., 2006]. That leads to intracellular kinase activation and initiation of downstream signaling pathways [Qian et al., 1994; Olayioye et al., 2000; Yarden & Sliwkowski, 2001b].

The extracellular region of ErbB-2 has a conformation not suitable for ligand binding [Garrett et al., 2003]. However, this conformation allows extension of the receptor dimerization arm in subdomain II [Burgess et al., 2003; Garrett et al., 2003; Riese et al., 2007]. This suggests that ErbB-2 is capable for ligand independent dimerization and signaling [Riese et al., 2007]. ErbB-2 heterodimerizes with other ErbB receptors and it is their preferred heterodimerization partner [Hynes & Stern, 1994; Graus-Porta et al., 1997; Olayioye et al.,

2000; Yarden & Sliwkowski, 2001b; Garrett et al., 2003]. At elevated expression levels ErbB-2 homodimerizes [Garrett et al., 2003].
ErbB-3 lacks intrinsic tyrosine kinase activity and therefore can initiate signaling only in association with another ErbB receptor, usually ErbB-2 [Mass, 2004].
Although both homodimerization and heterodimerization result in activation of the EGF system network, heterodimers are more potent and mitogenic [Marmor et al., 2004]. ErbB-2 and ErbB-3 heterodimer is the most transforming and mitogenic receptor complex and increases cell motility on stimulation with a ligand [Alimandi et al., 1995; Wallasch et al., 1995; Yarden & Sliwkowski, 2001].
The dimerization of ErbB receptors represents the fundamental mechanism that drives transformation [Zhang et al., 2007].

2.3 ErbB receptors signaling

Dimerization of ErbB receptors leads to intracellular kinase activation [Olayioye et al., 2000; Qian et al., 1994; Yarden & Sliwkowski, 2001b]. As a result, a number of tyrosine residues in the COOH-terminal portion of ErbB receptors become phosphorylated [Burgess et al., 2003; Holbro et al., 2003; Zhang et al., 2007]. These phosphorylated tyrosine residues function as docking sites for cytoplasmic proteins containing Src homology 2 (SH2) and phosphotyrosine binding (PTB) domains [Songyang et al., 1993; Marmor et al., 2004; Yarden & Sliwkowski, 2001b; Zhang et al., 2007]. Recruitment of proteins initiates intracellular signaling via several pathways:

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

The Ras / Raf / mitogen-activated protein kinase (MAPK) pathway regulates cell proliferation and survival [Scaltriti & Baselga, 2006]. 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 [Lowenstein et al., 1992; Batzer et al., 1994].
This interaction results in conformational modification of Sos, leading to recruitment of Ras-GDP and subsequent Ras activation (Ras-GTP) [Hallberg et al., 1994]. Ras-GTP activates Raf-1 and, through intermediate steps, phosphorylates MAPK-1 and MAPK-2 [Hallberg et al., 1994; Liebmann, 2001]. Activated MAPKs phosphorylate and regulate specific intranuclear transcription factors involved in cell migration and proliferation [Hill & Treisman, 1995; Scaltriti & Baselga, 2006 Gaestel, 2006].

2.3.2 Phosphatidylinositol 3-kinase (PI3K) / Akt pathway

The Phosphatidylinositol 3-kinase (PI3K) / Akt pathway regulates cell growth, apoptosis, tumor invasion, migration and resistance to chemotherapy [Vivanco & Sawyers, 2002; Shaw & Cantley, 2006].
PI3K is a dimeric enzyme that composed of a regulatory p85 subunit and a catalytic p110 subunit [Vivanco & Sawyers, 2002]. 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 [Yu et al, 1998a; Yu et al., 1998b]. The catalytic p110 subunit, catalyze the phosphorylation of phosphatidylinositol 4, 5 diphosphate at the 3' position [Vivanco & Sawyers, 2002]. Phosphatidylinositol 3, 4, 5 triphosphate, phosphorylates and activates the protein serine/threonine kinase Akt [Stokoe et al., 1997; Vivanco & Sawyers, 2002].

ErbB receptor specific docking sites for p85 subunit are present on ErbB-3 and absent on EGFR [Carpenter et al., 1993; Yarden & Sliwkowski, 2001b]. EGFR dependent PI3K activation occurs through dimerization of EGFR with ErbB-3 or through the docking protein Gab-1 [Mattoon et al., 2004; Scaltriti & Baselga, 2006].

2.3.3 Signal transducers and activators of transcription (STAT) pathway

Signal transducers and activators of transcription (STAT) pathway regulates oncogenesis and tumor progression [Bromberg, 2002].

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 [Haura et al., 2005; Yu et al., 2004; Zhong et al., 1994]. Constitutive activation of STAT proteins (especially STAT-3 and STAT-5) is present in various primary cancers [Bromberg, 2002; Haura et al., 2005].

EGFR regulate STAT pathway through a Janus kinase (JAK) or a JAK independent mechanism [Kloth et al., 2003; Andl et al., 2004]. Augmented activity of EGFR and ErbB-2, promote persistent STAT-3 activation and subsequently induce oncogenesis and tumor progression [Bromberg, 2002].

2.3.4 Src kinase pathway

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

Src is a member of a 10 gene 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 [Yeatman, 2004; Summy & Gallick, 2006;].

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 [Jorissen et al., 2003; Leu & Maa, 2003].

2.3.5 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) [Chattopadhyay et al., 1999; Patterson et al., 2005].

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 [Schönwasser et al., 1998; McClellan et al., 1999].

3. ErbB receptors and cancer

3.1 The role of epidermal growth factor system in carcinogenesis

Dysregulation of the EGF system signaling network is implicated in cancer, diabetes, autoimmune, inflammatory, cardiovascular and nervous system disorders [Marmor et al., 2004; Uberall et al., 2008].

Loss of control of the cell functions mediated by the EGF system signaling network is a hallmark of oncogenesis, in which the balance between cell proliferation and differentiation is disturbed. Several types of human cancers associated with dysregulation of the EGF system signaling network [Uberall et al., 2008].

The EGF system signaling network in cancer becomes hyperactivated with a range of mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation) [Marmor et al., 2004; Salomon et al, 1995; Yarden & Sliwkowski, 2001b]. It is also contributes in proliferation, transformation, angiogenesis, migration and invasion [Holbro et al., 2003].

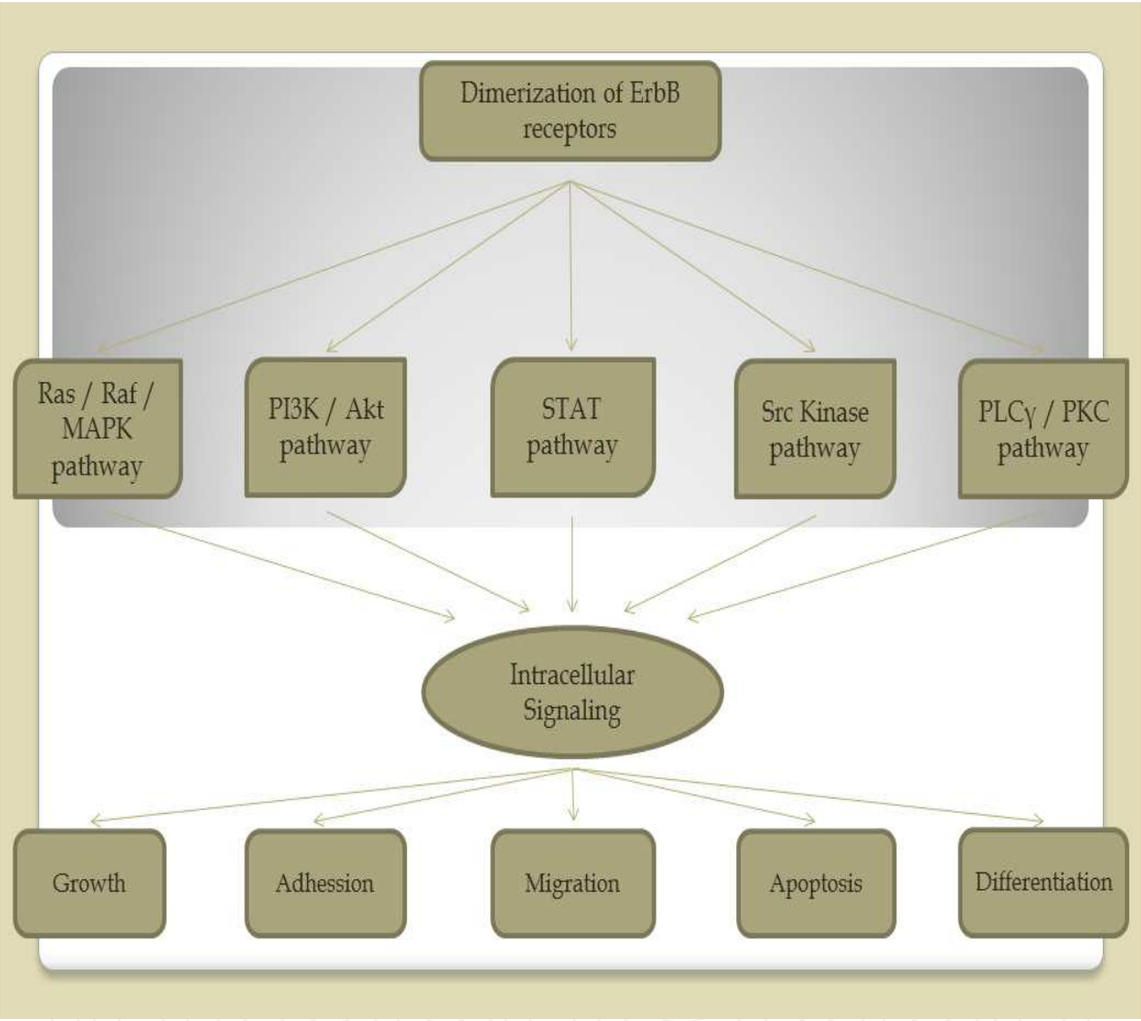

Fig. 1. ErbB receptors signalling.

3.2 Expression of ErbB receptors in cancer

Overexpression and structural alterations of EGFR are frequent in head, neck, esophageal, breast, lung, gastric, liver, kidney, colorectal, prostate, bladder and ovarian cancer [Moscatello et al., 1995; Yarden & Sliwkowski, 2001b; Uberall et al., 2008]. They associated with higher grade, disease progression, poor survival and resistance to radiotherapy and chemotherapy [Yarden & Sliwkowski, 2001b; Lurje & Lenz, 2009].

Overexpression of ErbB-2 is frequent in head, neck, breast, lung, pancreatic, esophageal, liver, colorectal, prostate, bladder, ovarian, endometrial and cervical cancer [Odicino et al.; Ross & Fletcher, 1998; Yarden & Sliwkowski, 2001b; Uberall et al., 2008]. It is an indicator of

a more aggressive clinical behavior [Ross & Fletcher, 1998; Yarden & Sliwkowski, 2001b; Odicino et al., 2008].

Overexpression of ErbB-3 is frequent in head, neck, breast, gastric, liver, colorectal, prostate and ovarian cancer [Yarden & Sliwkowski, 2001b; Uberall et al., 2008]. Although ErbB-3 overexpression related with ErbB-2 positivity and lymph node involvement, a definitive relationship with survival has not been established [Lemoine et al., 1992; Gasparini et al., 1994; Bièche et al., 2003].

Overexpression of ErbB-4 is frequent in head, neck, lung and liver cancer [Yarden & Sliwkowski, 2001b; Uberall et al., 2008]. It is related with favorable prognosis in breast and bladder cancer [Suo et al., 2002; Memon et al., 2004; Barnes et al., 2005].

4. ErbB receptors and endometrial cancer

4.1 Endometrial cancer classification

EC is the most common malignancy of the female genital tract. Overall, about 2% to 3% of women develop EC during their lifetime [Jemal et al., 2006]. EC is a malignancy that occurs primarily in postmenopausal women. Based on clinical and pathological features, EC is classified into 2 types [Bokhman, 1983]:

1. Type I EC, represents the majority of sporadic EC cases (70-80%). It is usually well differentiated and endometrioid in histology [Bokhman, 1983; Lax, 2004 Doll et al., 2008]. It is estrogen-related, usually arises from endometrial hyperplasia, has less aggressive clinical course and favorable prognosis [Bokhman, 1983; Sherman et al., 1997; Doll et al., 2008]. Type I EC overexpress genes hormonally regulated during the menstrual cycle and involved in endometrial homeostasis (MGB2, LTF, END1, MMP11) [Moreno-Bueno et al., 2003; Risinger et al., 2003]. It is also associated with defects in DNA mismatch repair, microsatelite instability MLH1/MSH6 and specific mutations in PTEN, K-ras and β-catenin genes [Basil et al., 2000; Lax et al., 2000; Lax, 2004; Hecht & Mutter, 2006; Bansal et al., 2009].
2. Type II EC, represents the minority of sporadic EC cases (10-20%). It is poorly differentiated and usually papillary serous or clear cell in histology [Bokhman, 1983; Lax, 2004 Doll et al., 2008]. It is not estrogen-related, arises from atrophic endometrium, has aggressive clinical course and propensity for early spread and poor prognosis [Bokhman, 1983; Abeler & Kjorstad, 1991; Goff et al, 1994].

Type II EC overexpress genes involved in the regulation of the mitotic spindle checkpoint and associated with aneuploidy and aggressive clinical behavior (STK15, BUB1, CCNB2) [Moreno-Bueno et al., 2003; Risinger et al., 2003 Hecht & Mutter, 2006]. It is also associated with mutations in p53 gene, inactivation of p16, ErbB-2 amplification/overexpression and decreased expression of E-cadherin [Hetzel et al., 1992; Tashiro et al. 1997; Lax et al., 2000; Holcomb et al., 2002; Lax, 2004; Santin et al., 2005; Hecht & Mutter, 2006; Grushko et al., 2008; Bansal et al., 2009].

4.2 Expression and clinical significance of ErbB receptors in endometrial cancer

Due to the inactive status of postmenopausal endometrium, it is expectable to find significantly higher expression of the 4 ErbB receptors in EC tissue [Ejskjaer et al., 2007].

EGFR, in endometrium, is localized to the basal part of surface epithelial cells, only in stromal cells, or both to epithelial and stromal cells [Bigsby et al., 1992; Wang et al., 1994; Imai et al., 1995; Möller et al., 2001; Ejskjaer et al., 2005]. It is primarily located to the cell membrane but also to the cytoplasm [Nyholm et al., 1993; Reinartz et al., 1994; Khalifa et al., 1994; Niikura et al., 1996; Ejskjaer et al., 2007].

In unselected patients with EC, it has been reported EGFR expression in 43–67% of cases [Reinartz et al., 1994; Khalifa et al., 1994; Scambia et al, 1994; Niikura et al., 1996; Androutsopoulos et al., 2006; Adonakis et al., 2008]. In patients with type I EC, it has been reported EGFR expression in 46% of cases. In patients with type II EC, it has been reported EGFR expression in 34% of cases [Konecny et al., 2009].
Although the clinical significance of EGFR has not been studied well in EC, it may have a dual role. EGFR overexpression did not affect disease progression in type I EC, although affects disease progression in type II EC. EGFR overexpression in type II EC associated with high grade and adverse clinical outcome [Konecny et al., 2009].
ErbB-2, in endometrium, is localized baso-laterally in the glands and surface epithelial cells [Bigsby et al., 1992; Wang et al., 1994; Miturski et al., 1998; Ejskjaer et al., 2005]. It is located to the cell membrane [Reinartz et al., 1994; Khalifa et al., 1994; Ejskjaer et al., 2007; Odicino et al., 2008].
In unselected patients with EC, ErbB-2 amplification/overexpression represents a rare event. 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 [Morrison et al., 2006; Konecny et al., 2009].
Although, ErbB-2 amplification/overexpression is more common in patients with type II EC, the exact frequency remains controversial. 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 [Santin et al., 2005; Morrison et al., 2006; Slomovitz et al., 2008; Grushko et al., 2008; Konecny et al., 2009;]. 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 [Morrison et al., 2006; Grushko et al., 2008; Konecny et al., 2009]. ErbB-2 overexpression especially in type II EC, is an indicator of a highly aggressive disease and a poor overall survival [Lukes et al., 1992; Santin et al., 2005; Morrison et al., 2006; Odicino et al., 2008].
ErbB-3, in endometrium, is localized to surface epithelial cells [Prigent et al., 1992; Srinivasan et al., 1999 Ejskjaer et al., 2005]. It is located to the cytoplasm, with membrane staining in a minority of samples [Srinivasan et al., 1999; Ejskjaer et al., 2007].
The clinical significance of ErbB-3 has not been studied well in EC [Srinivasan et al., 1999; Androutsopoulos et al., 2006; Ejskjaer et al., 2007; Adonakis et al., 2008].
ErbB-4, in endometrium, is localized to epithelial and stromal cells [Srinivasan et al., 1999; Chobotova et al., 2005; Ejskjaer et al., 2005]. It is located to the cytoplasm, with membrane staining in a minority of samples [Srinivasan et al., 1999; Ejskjaer et al., 2007;].
The clinical significance of ErbB-4 has not been studied well in EC [Srinivasan et al., 1999; Androutsopoulos et al., 2006; Ejskjaer et al., 2007; Adonakis et al., 2008].

4.3 Endometrial cancer and ErbB-targeted therapies

EGFR and ErbB-2 as targets for cancer therapy have been investigated for over 20 years. Two major classes of ErbB-targeted therapies have been developed.

4.3.1 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.
2. Anti-ErbB-2 MoAb (trastuzumab) binds to the extracellular domain of ErbB-2 and interferes with ligand independent receptor activation, but the exact mechanism of action is still subject of ongoing debate [Baselga & Arteaga, 2005; Lurje & Lenz, 2009].

3. There is a new class of Anti-ErbB MoAb (pertuzumab) that prevent receptor heterodimerization [Baselga & Arteaga, 2005].

4.3.2 ErbB-specific tyrosine kinase inhibitors (TKIs)

TKI block the binding of adenosine triphosphate to the intracellular domain of EGFR (gefitinib, erlotinib) or EGFR and ErbB-2 (lapatinib) and blocks ErbB activity and subsequent intracellular signaling [Baselga & Arteaga, 2005; Lurje & Lenz, 2009].

4.3.3 Effectiveness of ErbB-targeted therapies

Overall response rate to these drugs is modest, unless they are associated with chemotherapy or radiotherapy [Baselga & Arteaga, 2005]. ErbB-targeted therapies have not been clinically tested in type II EC [Konecny et al., 2009]. Preclinical data suggest that ErbB-targeted therapies may be clinically active in well-defined subgroups of type II EC patients with EGFR and ErbB-2 overexpression [Villella et al., 2006; Jewell et al., 2006; Konecny et al., 2008; Santin et al., 2008; Vandenput et al., 2009; El-Sahwi et al., 2010;].

The role of ErbB-targeted therapies in EC should be further investigated in clinical trials to evaluate their therapeutic efficacy [Odicino et al., 2008; Oza et al., 2008; Santin et al., 2008; Konecny et al., 2009; Fleming et al., 2010; Santin, 2010]. Also, further studies into the molecular pathways of EC development and progression, will increase our knowledge of this disease and will lead to the discovery of new generation molecules with higher therapeutic efficacy.

5. Conclusion

Additional studies into the molecular pathways of EC development and progression, will increase our knowledge of this disease and will lead to the discovery of new generation molecules with higher therapeutic efficacy.

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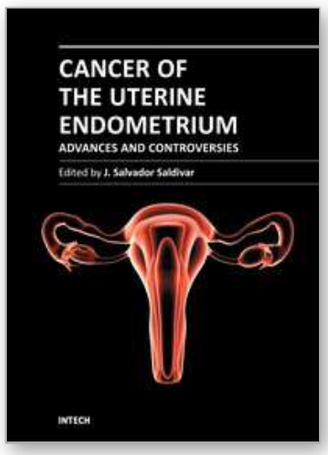

Cancer of the Uterine Endometrium - Advances and Controversies
Edited by Dr J.S. Saldivar

ISBN 978-953-51-0142-0
Hard cover, 182 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

The book Cancer of the Uterine Endometrium - Advances and Controversies brings together an international collaboration of authors who share their contributions for the management of endometrial carcinoma. The scope of the text is not basic, but rather aims to provide a comprehensive and updated source of advances in the diagnosis and therapeutic strategies in this field of gynecologic cancer. Each section in the book attempts to provide the most relevant evidence-based information in the biology and genetics, modern imaging, surgery and staging, and therapies for endometrial cancer. It is hoped that future editions will bring additional authors to contribute to this endeavor. To this end, it is our patients who will benefit from this work.

How to reference
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Adonakis Georgios and Androutsopoulos Georgios (2012). The Role of ErbB Receptors in Endometrial Cancer, Cancer of the Uterine Endometrium - Advances and Controversies, Dr J.S. Saldivar (Ed.), ISBN: 978-953-51-0142-0, InTech, Available from: http://www.intechopen.com/books/cancer-of-the-uterine-endometrium-advances-and-controversies/the-role-of-epidermal-growth-factor-system-in-endometrial-cancer

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