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Epiregulin: Roles in Normal Physiology and Cancer

David J. Riese II^{a,*} and Richard L Cullum^b

David J. Riese: driesee@auburn.edu; Richard L Cullum: rlc0029@auburn.edu

^aDepartment of Drug Discovery and Development, Harrison School of Pharmacy, 2316 Walker Building, Auburn University, Auburn, AL 36849 USA, Tel: 334-844-8358

^bDepartment of Chemical Engineering, Ginn College of Engineering, Auburn University, Auburn, AL 36849 USA, Tel: 334-844-8293

Abstract

Epiregulin is a 46-amino acid protein that belongs to the Epidermal Growth Factor (EGF) family of peptide hormones. Epiregulin binds to the EGF receptor (EGFR/ErbB1) and ErbB4 (HER4) and can stimulate signaling of ErbB2 (HER2/Neu) and ErbB3 (HER3) through ligand-induced heterodimerization with a cognate receptor. Epiregulin possesses a range of functions in both normal physiologic states as well as in pathologic conditions. Epiregulin contributes to inflammation, wound healing, tissue repair, and oocyte maturation by regulating angiogenesis and vascular remodeling and by stimulating cell proliferation. Deregulated epiregulin activity appears to contribute to the progression of a number of different malignancies, including cancers of the bladder, stomach, colon, breast, lung, head and neck, and liver. Therefore, epiregulin and the elements of the EGF/ErbB signaling network that lie downstream of epiregulin appear to be good targets for therapeutic intervention.

Keywords

Epiregulin; EGF/ErbB receptors; Oocyte maturation; Inflammation; Tumor Progression; Epithelial cell proliferation

1. Introduction

Epiregulin is a member of the epidermal growth factor (EGF) family of peptide growth factors. Like the other members of the EGF family, epiregulin is initially expressed as a transmembrane proform in which the mature, soluble form is contained within the extracellular region of the preform (Figure 1). EGF family precursors are cleaved by a disintegrin and metalloproteinase (ADAM) enzyme to release a mature form of approximately 50 amino acids. The mature growth factors bind to members of the EGF

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*Correspondence to: Harrison School of Pharmacy, 2316 Walker Building, Auburn University, Auburn, AL 36849 USA, Tel: 334-844-8358, FAX: 334-844-8353, driesee@auburn.edu.

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Receptor (ErbB) family of receptor tyrosine kinases. This family consists of EGF receptor (EGFR/ErbB1), ErbB2 (HER2/Neu), ErbB3 (HER3), and ErbB4 (HER4). A liganded ErbB receptor can either homodimerize with an identical member of the ErbB family or can heterodimerize with a different member of the ErbB family. Receptor dimerization enables tyrosine phosphorylation of one receptor monomer by the other. This cross-phosphorylation creates binding sites for effector proteins that possess phosphotyrosine binding motifs (SH2 or PTB), thereby enabling the receptors to couple to numerous signaling cascades, most notably the Raf/Ras/MAP kinase (Erk) signaling pathway, the phospholipase C gamma pathway, and the PI3 kinase/Akt signaling pathway [1–9]. The network of EGF family hormones and ErbB family receptors regulates the proliferation, differentiation, and function of numerous tissues in humans and deregulated signaling of this network is a hallmark of several different human malignancies. Thus, here we will review the cloning and basic pharmacology of epiregulin, as well as the roles that epiregulin plays in inflammation, wound healing, normal physiology, and human malignancies.

2. Cloning of Epiregulin and Basic Epiregulin Pharmacology

Epiregulin was purified from the conditioned medium of a transformed NIH 3T3 mouse fibroblast cell line on the basis of its ability to induce morphological changes in the HeLa cervical cancer cell line [10]. The 46-amino acid sequence of this purified protein has homology to other members of the Epidermal Growth Factor (EGF) family of peptide hormones. Therefore, it is not surprising that epiregulin binds to EGFR and ErbB4 [10, 11], stimulates EGFR and ErbB4 tyrosine phosphorylation [11–13], stimulates cognate receptor heterodimerization with ErbB2 or ErbB3 [12, 13], and stimulates ErbB receptor coupling to cell proliferation and DNA synthesis [12, 14]. The binding of epiregulin to EGFR and ErbB4 makes epiregulin resemble the EGF family members betacellulin and heparin-binding EGF-like growth factor (HB-EGF), both of which bind EGFR and ErbB4 [15, 16], and the EGF family member neuregulin-2beta, which binds EGFR, ErbB3, and ErbB4 (Table 1) [7, 17].

The amino acid sequence of purified mouse epiregulin was used to synthesize degenerate oligonucleotides which were used to clone the epiregulin cDNA from the transformed NIH 3T3 cell line used as the source for the epiregulin protein. The full-length epiregulin cDNA encodes a 162-amino acid transmembrane precursor that is then cleaved to release the 46-amino acid mature peptide [18]. This mouse cDNA sequence was used to identify the human epiregulin cDNA sequence and the human and mouse epiregulin genes. The human epiregulin gene is located on chromosome 4, adjacent to the genes encoding the EGF family hormones amphiregulin and betacellulin [19]. The mouse epiregulin gene is located on chromosome 5, adjacent to the genes encoding amphiregulin and betacellulin [20]. Epiregulin null mice exhibit no overt developmental defects [20].

Phe44 of mature human epiregulin corresponds to a hydrophobic amino acid residue essential for EGF family hormones to bind with high affinity to ErbB4, including Tyr45 of neuregulin-1beta, Phe45 of neuregulin-2beta, and Val44 of betacellulin (Table 2) [12, 21–24]. Glu42 of epiregulin corresponds to a Gln or Glu residue critical for the activity of efficacious ErbB4 ligands, including Gln43 of neuregulin-1beta, Gln43 of neuregulin-2beta,

and Glu42 of betacellulin (Table 2) [5, 7, 12, 15, 21, 22, 24–26]. Thus, it appears that epiregulin and other high-affinity ErbB4 ligands share a common binding site on ErbB4 and that epiregulin and other efficacious ErbB4 ligands stimulate ErbB4 signaling in essentially the same manner. In a variety of model systems, epiregulin is a more efficacious stimulus of cell proliferation and DNA synthesis than is EGF, perhaps due to prolonged EGFR tyrosine phosphorylation and MAP kinase activity, reduced ligand-induced EGFR down-regulation, and increased receptor recycling. These are common mechanisms by which EGFR ligands display differences in efficacy (intrinsic activity) [7, 13, 26–28].

3. The Roles of Epiregulin in Inflammation, Wound-Healing and Normal Physiology

3.1. Angiogenesis, vascular remodeling, and inflammation

A wealth of functional data indicates that epiregulin plays important roles in angiogenesis and vascular remodeling, particularly during inflammation. Several G-protein-coupled receptor agonists involved in inflammatory processes, including angiotensin II, endothelin-1, and α -thrombin, stimulate cleavage of the transmembrane epiregulin proform and release of the mature form of epiregulin (Figure 1). The mature epiregulin molecule then binds EGFR and stimulates its tyrosine phosphorylation and coupling to effectors and biological responses [29, 30]. Similarly, Factor Xa stimulates expression and release of mature epiregulin by VSMCs [31]. Epiregulin expression by VSMCs is accompanied by VSMC dedifferentiation, suggesting that epiregulin regulates vascular remodeling, such as during atherosclerosis [32]. The membrane-bound chemokine CX₃CL1 (fractalkine) is expressed by coronary artery smooth muscle cells (CASMCs), where it mediates chemotaxis toward the source of fractalkine and stimulates MAP kinase and Akt/PI3K signaling in CASMCs and CASMC proliferation. These effects are accompanied by epiregulin transcription and release by CASMCs and these effects are blocked by epiregulin neutralizing antibodies or an EGFR tyrosine kinase inhibitor [33]. Intermittent hypoxia, such as that associated with obstructive sleep apnea, induces angiogenic effects, including the proliferation of VSMCs. This VSMC proliferation is associated with increased epiregulin expression and EGFR-ErbB2 crosstalk. Furthermore, an ErbB2 antagonist blocks the stimulation of VSMC proliferation by intermittent hypoxia [34].

3.2. Liver repair and regeneration

There is some evidence that epiregulin plays a role in liver repair and regeneration. Treating primary rat hepatocytes with epiregulin stimulates transcription of the EGF family hormones of TGF α and HB-EGF, which in turn stimulates epiregulin transcription via an autocrine signaling loop [27]. However, epiregulin null mice do not exhibit altered liver regeneration [20]. Indeed, amphiregulin, but not epiregulin, is involved in protecting the liver from damage by a Fas-agonist antibody [35]. Consequently, the role that epiregulin plays in liver repair or regeneration appears to be limited.

3.3 Skin inflammation and cutaneous wound healing

Expression and functional data suggest that epiregulin plays a role in skin inflammation and cutaneous wound healing. Epiregulin expression is detected in peripheral blood macrophages [14] and normal keratinocytes [36]. IL-1 α causes less down-regulation of IL-18 expression in epiregulin-null keratinocytes than in normal keratinocytes [37]. Epiregulin-null macrophages exhibit lower production of proinflammatory cytokines in response to Toll-like receptor (TLR) agonists than normal macrophages [37]. Epiregulin-null macrophages and dendritic cells exhibit lower expression of IL-6 upon peptidoglycan stimulation than do normal macrophages and dendritic cells [38]. Thus, it is reasonable to predict that epiregulin-null mice exhibit reduced skin inflammation than normal mice. Surprisingly, however, epiregulin-null mice develop chronic dermatitis [37]. Cutaneous excisional wound inflammation and healing is associated with increased expression of epiregulin and genes associated with angiogenesis, including angiomin and VEGF-B, suggesting that epiregulin contributes to cutaneous excisional wound healing by promoting angiogenesis [39].

3.4 Ovarian follicle formation and oocyte development

Early studies of epiregulin function focused on the roles that epiregulin plays in ovarian follicle formation and oocyte development and these topics remain areas of intense interest. Epiregulin expression is detected in ovarian granulosa cells during ovarian follicle formation and oocyte development [40]. Follicle stimulating hormone (FSH) induces this expression, in part by the binding of Sp1 and Sp3 transcription factors to two CT boxes found in the epiregulin promoter [41]. Luteinizing hormone (LH) also induces epiregulin expression in the ovulatory follicle [19, 42], in part by stimulating increased intracellular cAMP [19, 43]. A combination of LH and FSH induces cleavage of the transmembrane amphiregulin and epiregulin proforms in porcine cumulus oocyte complexes and inhibition of this cleavage suppresses the effects of LH and FSH on oocyte maturation [44].

Interestingly, neither epiregulin null mice [20] nor amphiregulin null mice [45] exhibit reduced litter size. However, epiregulin null mice and amphiregulin null mice display delayed or reduced oocyte maturation and cumulus expansion [46].

3.5 Other reproductive processes

Epiregulin may play other roles in reproductive processes. Epiregulin expression is detected in the placenta [14] and is detected in the uterus at the site of blastocyst implantation [47]. The cytokine leukemia inhibitor factor (LIF) appears to regulate this expression, as the absence of LIF correlates with reduced epiregulin expression in the uterus during blastocyst expression [48]. However, as noted before, epiregulin null mice do not exhibit reduced litter size [20].

3.6. Airway epithelial differentiation, proliferation, and inflammation

Epiregulin appears to regulate the proliferation and differentiation of airway epithelial cells, particularly under pathological conditions. Normal human lung fibroblasts express epiregulin and induce cocultures of human airway epithelial cells to differentiate via a paracrine/juxtacrine EGFR signaling mechanism [49]. Epiregulin transcription can be

stimulated by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, through aryl hydrocarbon receptor binding to a dioxin-responsive element upstream of the epiregulin transcriptional start site [50]. Taken together, it appears plausible that the differentiation program of human airway epithelial cells is altered by exposure to airborne polycyclic aromatic hydrocarbons through stimulation of epiregulin expression and EGFR signaling.

Human airway epithelial cells exposed to compressive stress in a model of asthmatic bronchoconstriction exhibit increased epiregulin expression. This stimulates EGFR signaling and further epiregulin transcription via an autocrine signaling loop [51]. Infection of bronchial epithelial cells with rhinovirus (RV16 serotype) causes increased epiregulin expression and EGFR signaling, leading to IL-8 and ICAM-1 expression by these cells [52]. Similarly, infection of bronchial epithelial cells with *M. pneumoniae* induces IL-8 production, apparently through increased epiregulin expression and EGFR signaling [53]. Because IL-8 production by bronchial epithelial cells contributes to the inflammation and tissue remodeling associated with bacterial pneumonia, asthma and chronic obstructive pulmonary disease (COPD), targeting the EGFR signaling network may provide some relief from these disorders without affecting antimicrobial responses mediated by pathogen recognition receptors such as TLR3 [52, 53]. This idea should be considered with some skepticism, as polymorphisms in the epiregulin gene (which presumably affect epiregulin expression and/or function) are associated with increased susceptibility to *M. tuberculosis* infections, particularly infections of the Beijing lineage of *M. tuberculosis* [54].

3.7. Rheumatoid arthritis

The general principle that epiregulin stimulates cell proliferation during inflammation appears to apply to the pathogenesis of rheumatoid arthritis. This autoimmune disease is characterized by hyperproliferation of fibroblast-like synoviocytes (FLSs) in the synovial tissue, resulting in joint destruction. FLS hyperproliferation is accompanied by elevated expression of epiregulin, amphiregulin, and other pro-inflammatory cytokines and growth factors. An aryl hydrocarbon receptor antagonist abrogates the elevated expression of epiregulin and amphiregulin and diminishes the invasive phenotype of rheumatoid arthritis FLSs [55], suggesting that epiregulin and/or amphiregulin stimulation of EGFR signaling contributes to the pathogenesis of rheumatoid arthritis.

3.8. Corneal wound healing

The roles that epiregulin plays during inflammation and wound healing are also evident in the cornea. Epiregulin expression in the limbal basal epithelial cells of the mouse eye is greater than expression in the adjacent corneal basal epithelial cells [56]. However, epiregulin expression is detected in cultured human corneal epithelial cells (HCECs) and in human corneal epithelial samples obtained from cadavers. In HCECs, ectopic epiregulin stimulates EGFR tyrosine phosphorylation, expression of endogenous epiregulin, and cell proliferation [57]. Consequently, it has been proposed that increased epiregulin expression and EGFR signaling contribute to healing of corneal wounds. Indeed, a single injury to the cornea causes greater corneal opacity and greater corneal infiltration by polymorphonuclear cells in epiregulin-null mice than in normal mice. Likewise, epiregulin-null mice also exhibit defects in the responses to repetitive corneal injuries [58].

3.9 Intestinal epithelial proliferation and inflammation

As noted earlier, epiregulin stimulates the proliferation of epithelial cells in a number of different contexts. Another example is the stimulation of intestinal epithelial cell proliferation by epiregulin. Glucagon-like peptide-2 (GLP-2) is a peptide hormone secreted by enteroendocrine cells in response to nutrient ingestion. GLP-2 stimulates cell proliferation that leads to expansion of the mucosal epithelium. GLP-2 administration in mice *in vivo* stimulates expression of epiregulin and other EGF family hormones, crypt cell proliferation, and bowel growth [59]. All of these effects are inhibited by the pan-ErbB tyrosine kinase inhibitor CI-1033, suggesting that GLP-2 stimulates an autocrine loop of EGFR signaling that is coupled to proliferation of intestinal epithelial cells [59]. The pro-inflammatory cytokines interleukin-1 β and tumor necrosis factor alpha induce epiregulin transcription and release by human colonic subepithelial myofibroblasts (SEMFs), resulting in increased proliferation of these cells [60]. Similarly, in mice given 2.5% dextran sodium sulfate in a model of acute colitis and healing, the intestinal mucosa display elevated epiregulin and amphiregulin expression [61], suggesting that these growth factors and EGFR signaling mediate intestinal wound healing and protection from inflammatory bowel disorders [62].

4. The Roles of Epiregulin in Cancer

4.1. Bladder cancer

There is circumstantial evidence suggesting that epiregulin plays an important role in bladder cancer progression and aggressiveness. Epiregulin expression is elevated in bladder cancer samples [63]. Moreover, the frequency and amount of epiregulin overexpression positively correlates with metastatic potential in bladder cancer cases [64]. In bladder cancer cells, insulin induces maturation (cleavage) of the proform of the EGF family hormone HB-EGF, leading to EGFR tyrosine phosphorylation and EGFR coupling to increased endogenous expression of amphiregulin and epiregulin, further increases in EGFR signaling, and cell proliferation [65]. In bladder cancer cells, insulin also directly stimulates transcription of the epiregulin gene via a 200 bp domain upstream of the epiregulin transcriptional start site. This domain contains potential binding sites for the transcription factors Sp1, AP1, and NF- κ B [66]. Indeed, Sp1, NF- κ B, and AP2 regulate epiregulin gene expression [41, 67, 68]. Insulin-induced cell proliferation is abrogated by an EGFR tyrosine kinase inhibitor, indicating that the EGFR autocrine signaling loop is required for insulin-induced cell proliferation [65].

4.2. Gastric cancer

The role that epiregulin appears to play in gastric cancer exemplifies a relatively novel mechanism of cancer progression. Epiregulin and other EGF family members are expressed in the TMK1 and MKN-45 human gastric tumor cell lines [69]. Similarly, a large percentage of gastrointestinal stromal tumor (GIST) samples display expression of epiregulin, other EGF family members, ErbB family receptors, and ADAM17 (which is responsible for cleavage of EGF family member proforms) [70]. This elevated expression of epiregulin and other EGF family members may be the consequence of prostaglandin E2 (PGE₂) action on the EP4 PGE₂ receptor in transgenic mouse models of gastric cancer and gastric epithelial

cells [71]. However, there are also reports that amphiregulin or epiregulin stimulate PGE₂ production by stimulating cyclooxygenase 2 expression [72]. Either of these mechanisms may account for the suppression of gastric tumor growth *in vivo* and for the inhibition of gastric tumor cell line proliferation *in vitro* by COX-2 inhibitors [73, 74].

4.3. Colorectal cancer

The roles that epiregulin appears to play in colorectal cancer illustrate the concept of “oncogene addiction” and sensitivity to targeted cancer chemotherapeutics [75, 76]. The role that epiregulin appears to play in colorectal cancer may also explain how dietary factors contribute to colon cancer risk. Epiregulin and other EGF family members are expressed in the SW1116 and HT-29 human colon tumor cell lines [69]. However, epiregulin null mice exhibit unaltered susceptibility to intestinal tumorigenesis when crossed against the Apc^{Min} transgenic model of intestinal tumors [20]. In contrast, endogenous expression of epiregulin and/or amphiregulin in colorectal tumor samples or xenografts correlates with responsiveness to the anti-EGFR monoclonal antibody cetuximab [77–81], suggesting that epiregulin or amphiregulin expression establishes an autocrine EGFR signaling loop within colorectal tumor cells that is responsible for EGFR-dependency [77, 78]. Epiregulin may be involved in the paracrine regulation of colitis-associated neoplasms by the tumor stroma, as epiregulin expression and shedding by intestinal fibroblasts stimulate proliferation of adjacent intestinal epithelial cells and stimulate their development into tumor cells [82]. Transcriptional profiling of 160 colorectal tumor specimens reveals that a change in transcription of 10 genes can be used to predict liver metastasis by colorectal tumors with 86% accuracy in a small population of colorectal tumor test samples. Increased epiregulin expression and increased amphiregulin expression are among the 10 changes in gene expression that collectively predict liver metastasis by colorectal tumors [83]. Finally, haem, the iron-porphyrin pigment of red meat, induces colonic epithelial hyperproliferation in mice. This effect is accompanied by increased expression of COX-2, amphiregulin, and epiregulin [84]. These data may account for the linkage between red meat consumption and colorectal cancer as well as the effects of COX-2 inhibitors and EGFR antagonists on colorectal cancer [85].

4.4. Breast cancer

The linkage between epiregulin and breast cancer progression is currently weak but deserving of additional investigation. Analyses of the expression of all four ErbB family receptors and most of the EGF family hormones in a panel of 100 human breast tumor samples indicate that epiregulin expression is weakly associated ($P=0.23$) with poorer overall survival [86]. In a small panel of human breast tumor samples, overexpression of the transcription factor HOX89 is associated with high tumor grade. Because HOX89 induces expression of amphiregulin, epiregulin, and neuregulins, these EGF family hormones may mediate the effect of HOX89 on tumor behavior [87]. The LM2-4175 subclone of the MDA-MB-231 human breast tumor cell line exhibits a much greater tendency to metastasize to the lung than the parental MDA-MB-231 cells. Relative to the parental MDA-MB-231 cells, the LM2-4175 cells exhibit elevated expression of epiregulin, COX-2, matrix metalloprotease 1 (MMP1) and matrix metalloprotease 2 (MMP2) [88, 89]. Individually silencing any one of these genes markedly reduces the ability of the LM2-4175 cells to metastasize to the lung

and simultaneously silencing all four genes almost completely abrogates the ability of the LM2-475 cells to metastasize to the lung [88, 89]. Analogous gene silencing studies indicate that epiregulin contributes to tumor cell-mediated angiogenesis and tumor cell extravasation [88, 89]. The expression of epiregulin in multiple human tumor cell lines (including breast tumor cell lines) is inhibited by the transcription factor AP-2 [68]. Moreover, silencing AP-2 in these cells causes increased cell proliferation, increased growth in semisolid medium, and increased tumorigenicity in xenograft assays [68]. At least some of these phenotypes are the consequence of increased epiregulin expression [68]. Epiregulin may also contribute to breast tumor progression via a paracrine mechanism, as tumor-associated monocytes express epiregulin in response to growth factors expressed by tumor cells [90].

4.5. Lung cancer

Linkages between epiregulin and lung cancer progression continue to emerge. In non-small cell lung carcinoma (NSCLC) samples, epiregulin expression is associated with nodal metastasis and a shorter duration of survival [91]. Similarly, the invasiveness (through matrigel) of NSCLC cell lines that harbor activating mutations in EGFR is reduced by silencing epiregulin or by treatment with neutralizing anti-epiregulin antibodies [91]. The polycyclic aromatic hydrocarbon (PAH) benzo[a]pyrene (B[a]P), a constituent of cigarette smoke, induces epiregulin expression and proliferation by the A549 lung adenocarcinoma cell line [92]. As noted elsewhere, the liganded aryl hydrocarbon receptor stimulates epiregulin gene transcription in a variety of contexts, including head and neck squamous cell carcinoma (HNSCC) cell lines [50, 93]. Therefore, it is possible that B[a]P stimulates lung epithelial cell proliferation and malignant growth transformation in part by stimulating epiregulin expression and EGFR signaling. Indeed, B[a]P stimulation of A549 proliferation is blocked by an EGFR tyrosine kinase inhibitor [92] and epiregulin expression in select HNSCC cell lines is inhibited by an aryl hydrocarbon receptor antagonist [93]. Activating mutations in the K-ras gene in NSCLC tumor samples are associated with increased epiregulin expression. This appears to be functionally significant, as silencing epiregulin expression inhibits proliferation and stimulates apoptosis of NSCLC cell lines that possess K-ras activating mutations and elevated epiregulin expression [94].

4.6. Head and neck cancers

Epiregulin appears to play a role in oncogene addiction and targeted chemotherapeutic drug sensitivity in head and neck tumors. Epiregulin expression is much greater in oral squamous cell carcinoma (SCC) specimens than in normal gingivae or oral epithelial dysplasias [95]. Indeed, larger SCC tumors exhibit greater epiregulin expression than smaller tumors and stage III/IV SCC tumors exhibit greater epiregulin expression than stage I/II SCC tumors [95], thereby indicating that epiregulin expression is associated with more aggressive SCCs and poorer clinical outcomes. Finally, epiregulin or amphiregulin expression in human head and neck tumor cell lines and xenografts is also correlated with responsiveness to cetuximab [80, 96].

4.7. Liver cancer

Epiregulin appears to contribute to hepatocellular carcinoma progression, particularly in those tumors arising from increased translocation of intestinal bacteria to the liver in patients

suffering from chronic liver disease. The HepG2 human hepatoma cell line exhibits elevated N-ras signaling. Silencing N-ras in HepG2 cells results in elevated epiregulin expression. Simultaneously silencing N-ras and epiregulin suppresses HepG2 cell proliferation, MAPK signaling, and Akt/PI3K signaling to a much greater extent than silencing N-ras or epiregulin individually [97]. This suggests that the increase in epiregulin expression in response to N-ras silencing in HepG2 cells is a compensatory mechanism evolved to maintain MAPK and/or Akt/PI3K signaling in these cells and that targeting these pathways may be effective in treating hepatocellular carcinomas [97]. Increased translocation of intestinal bacteria to the liver is observed in patients with chronic liver disease. Lipopolysaccharide (LPS) synthesized by these bacteria initiates inflammatory responses mediated by the toll-like receptor 4 (TLR4), resulting in increased expression of epiregulin and hyperproliferation of the non-bone marrow-derived liver cells [98]. This hyperproliferation contributes to hepatocarcinogenesis, suggesting that targeting the gut flora [99] or the EGFR pathway [98] may be effective in treating some forms of hepatocellular carcinoma.

4.8. Other cancers

Finally, a limited number of reports suggest that epiregulin is involved in other human malignancies. Epiregulin expression is elevated in androgen-independent prostate cancer cell lines [47], malignant fibrous histiocytoma samples [100], and pancreatic tumor cell lines and pancreatic tumor samples [101]. Similarly, the expression of epiregulin, neuregulins, and all four ErbB receptors can be detected at varying frequencies in neoplastic Schwann cells within schwannoma tumor specimens [102].

5. Conclusion

Epiregulin is expressed in a wide range of adult tissues. Consequently, it is not surprising that epiregulin plays a significant role in the maintenance and function of a wide range of adult tissues, both under physiological conditions and in pathologic states. These roles, however, are mainly focused on a few fundamental properties of epiregulin. (1) Epiregulin is a mitogen for several types of tissues. (2) Epiregulin stimulates inflammation, either directly or through neovascularization, vascular remodeling, or release of inflammatory cytokines. (3) Epiregulin regulates the differentiation of several tissue types. Naturally, then, increased expression or activity of epiregulin appears to contribute to the progression of several different human malignancies, including cancers of the bladder, stomach, colon, breast, lung, head and neck, and liver. Therefore, the epiregulin signaling pathway(s) appear to be suitable targets for therapeutics that could be used to treat a variety of pathologic conditions.

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Abbreviations

ADAM	A disintegrin and metalloproteinase
B[a]P	Benzo[a]pyrene
CASMC	Coronary artery smooth muscle cell
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase 2
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
FLS	Fibroblast-like synoviocyte
FSH	Follicle-stimulating hormone
GIST	Gastrointestinal stromal tumor
GLP	Glucagon-like peptide
HB-EGF	Heparin-binding EGF-like growth factor
HCEC	Human corneal epithelial cell
HNSCC	Head and neck squamous cell carcinoma
IL	Interleukin
LH	Luteinizing hormone
LIF	Leukemia inhibitor factor
LPS	Lipopolysaccharide
MAP kinase	Mitogen-activated protein kinase
MMP	Matrix metalloprotease
NSCLC	Non-small cell lung carcinoma
PAH	Polycyclic aromatic hydrocarbon
PGE₂	Prostaglandin E2
PI3 kinase	Phosphatidylinositide 3-kinase
PTB	Phosphotyrosine binding
SCC	Squamous cell carcinoma
SEMF	Subepithelial myofibroblasts
SH2	Src homology domain 2
TGFalpha	Transforming growth factor alpha
TLR	Toll-like receptor
VSMC	Vascular smooth muscle cell

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Highlights

- Epiregulin is a member of the EGF family of peptide growth factors
- Epiregulin regulates ovarian follicle formation and oocyte development
- Epiregulin stimulates inflammatory responses and epithelial cell proliferation
- Epiregulin contributes to the progression of many different kinds of tumors

Figure 1. Regulation of tumor cell behavior by the epiregulin/EGF receptor signaling pathway is depicted.

Table 1

Growth Factor	Receptor Binding			
	EGFR	ErbB2	ErbB3	ErbB4
EGF	+	–	–	–
Epiregulin	+	–	–	+
Betacellulin	+	–	–	+
HB-EGF	+	–	–	+
Neuregulin 1beta	–	–	+	+
Neuregulin 2beta	+	–	+	+

The pattern of ErbB receptor binding for selected EGF family hormones is shown.

Table 2

a.

1					2					3					4					5				
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QVITKCSSDMNGYCLHGGCIYLVDM SQNYCRCEVGYTGVRC <u>E</u> H <u>F</u> L																								

b.

Growth Factor	ErbB4		Select Amino Acids
	Affinity	Efficacy	
Epiregulin	+	+	Cys <u>Glu</u> His <u>Phe</u>
EGF	-	-	Cys <u>Gln</u> Tyr <u>Arg</u>
Betacellulin	+	+	Cys <u>Glu</u> Arg Val
Neuregulin-1beta	+	+	Cys <u>Gln</u> Asn <u>Tyr</u>
Neuregulin-2beta	+	+	Cys <u>Gln</u> <u>Gln</u> <u>Phe</u>

^aThe amino acid sequence of the EGF homology domain of the mature form of human epiregulin is indicated. b. The relative affinity of selected EGF family hormones for ErbB4 and their relative efficacy (intrinsic activity) at ErbB4 is indicated. The amino acid sequence for a portion of each of these hormones is indicated. Amino acid residues that regulate ligand affinity for ErbB4 and ligand efficacy at ErbB4 and that are discussed in the text are underlined.