The Role of EREG/EGFR Pathway in Tumor Progression

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Aberrant activation of the epidermal growth factor receptor (EGFR/ERBB1) by erythroblastic leukemia viral oncogene homolog (ERBB) ligands contributes to various tumor malignancies, including lung cancer and colorectal cancer (CRC). Epiregulin (EREG) is one of the EGFR ligands and is low expressed in most normal tissues. Elevated EREG in various cancers mainly activates EGFR signaling pathways and promotes cancer progression.

epidermal growth factor receptor (EGFR) epiregulin (EREG) tumor microenvironment

1. Introduction

Erythroblastic Leukemia Viral Oncogene Homolog Signaling

The expression of the erythroblastic leukemia viral oncogene homolog (ERBB) family is closely linked to tumor progression through the constitutive activation of downstream signaling, such as the epidermal growth factor (EGF) receptor (EGFR) pathway or through a somatic mutation; ERBB expression is enhanced during tumor microenvironment (TME) formation, cancer progression, and drug-resistance [1]. The ERBB family comprises transmembrane receptor tyrosine kinases, including the ERBB1/ EGFR)/HER (human EGF receptor) 1, ERBB2/HER2/Neu, ERBB3/HER3, and ERBB4/HER4 [2]. Activated ERBB mediates various signaling pathways including the RAS (rat sarcoma)/RAF (rapidly accelerated fibrosarcoma), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT (a serine/threonine protein kinase), phospholipase C (PLC)-γ1, and signal transducer and activator of transcription (STAT) pathways [3]. Several ligands can bind to EGFR, including EGF, epigen, transforming growth factor (TGF)-α, amphiregulin (AREG), epiregulin (EREG), betacellulin (BTC), and heparin-binding EGF (HB-EGF) (**Figure 1**). The simplified representation of these ligands with distinct functional domains are shown in **Figure 1**. The transmembrane EGFR ligands comprise an N-terminal signal peptide, pro-peptide region, the EGF-lik short juxtamembrane stalk, a hydrophobic transmembrane domain, and a cytoplasmic domain (**Figure 1**A). Neuregulins (NRGs) are a family containing the EGF-like domain proteins; they play an essential role in the development of the adult brain [4] and various cancers [5][6][7]. The most studied NRGs, such as the *NRG1* gene, produce six different types and 33 spliced isoforms, due to different transcriptional initiation sites and alternative splicing [4]. NRG proteins mainly contain EGF-like and transmembrane domains; however, the type-specific N-terminal region (type I, II, and IV-VI NRG1), an immunoglobulin-like domain, and the glycosylation site are dependent on the isoform [8][9]. Additionally, the identity of the overall protein sequence in these ligands is low [10] and a conserved EGF module including six cysteines is arranged as three disulfide bridges (**Figure 1**B). The spacing of EGF-motif in seven EGFR ligands can be represented as in the cysteines pattern CX_7CX_{4-}

$_5CX_{10}CXCX_8C$ (X can be any amino acid). Notably, recent studies demonstrated that the N57 residue of EREG is pivotal for the interaction with the domains I and III of EGFR [11]. EGF is unique in that there are nine EGF motifs, although only the one adjacent to the cell membrane has the function of the EGFR binding domain (**Figure 1**C). EREG and HB-EGF contain an additional heparin-binding domain. The functional EGF module is located within approximately 25 residues of the transmembrane domain. The presence and spacing of additional specific residues further distinguishes EGFR ligands from NRGs containing EGF modules at the structural level, and defines high-affinity binding to EGFR [12]. Moreover, NRG1 and 2 selectively bind to ERBB3 (**Figure 1**D). Ligands such as BTC, HB-EGF, EREG, and NRG1-4 interact with the ERBB4. ERBB ligands bind to the extracellular domain of ERBB1, ERBB3, and ERBB4 receptors to form active homodimers or heterodimers. However, ligands do not directly bind to ERBB2 in the ligand-activated state, favoring homodimerization. In addition, ERBB2 proteins can be activated through interaction with other ERBBs. G-protein-coupled receptors (GPCRs) stimulate specific metalloproteinases, such as disintegrin and metalloproteinase (ADAM) family members, resulting in EGFR pro-ligand cleavage and transactive EGFR downstream cascade [13] (**Figure 1**E). Ectodomain shedding arises in diverse physiological responses, and the cleavage efficiency is mainly determined by the specific sequence in the cleavage site and the length of the membrane-proximal domain [14]. Soluble ligands bind to receptors, activating intracellular signaling on the original cell, neighboring cells, and distant cells through autocrine, paracrine (or juxtacrine), and endocrine pathways, respectively [12]. EGFR-medaited signaling pathways can be activated by binding to soluble ligands or membrane-anchored ligands by the juxtacrine pathway. In addition to the actions of soluble ligands, the free cytoplasmic tail (CT) of these ligands (e.g., pro-AREG CT) are required for basolateral sorting [15] and pro-HBE-GF CT can directly regulate gene expression [16]. The efficacy and specificity of intracellular signaling pathways are regulated by specific ligands, receptor dimerization, and interacting proteins that bind to the phosphorylated domains of ERBB [17].

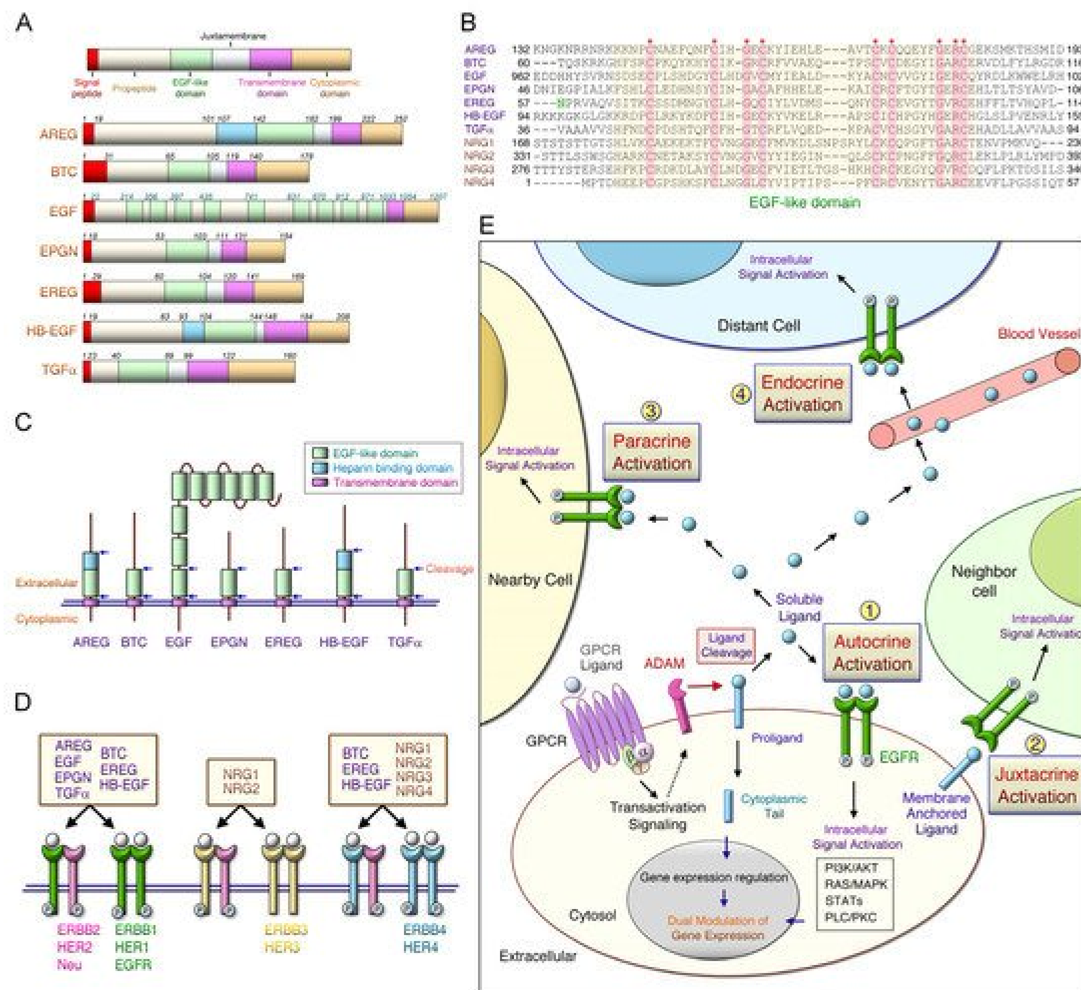

Figure 1. Protein domains, corresponding receptors of ERBB ligands and the possible activation pathways. (**A**) Erythroblastic leukemia viral oncogene homolog (ERBB) ligands include a signal peptide, a propeptide region, an epidermal growth factor (EGF)-like domain, a juxtamembrane, a transmembrane, and a cytoplasmic tail. Schematic representation of the membrane-anchored precursor form of the seven human EGF receptor (EGFR) ligands: EGF, transforming growth factor-a (TGFA), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin (AREG), betacellulin (BTC), epiregulin (EREG), and epigen (EPGN). Amino acid residues that constitute the domains in the individual EGFR ligands are listed. EGF consists of nine EGF-like repeats. (**B**) The yellow region includes aligned amino acid sequences of EGF-like domains in seven EGFR ligands and neuregulin 1-4 (NRG1-4). Asterisks (*) indicate strictly conserved residues. The domains I and III EGFR interacted with the N57 residue of EREG. (**C**) Arrowheads indicate proximal and distal sites of cleavage in the EGF-like domains, which release to soluble ligands. (**D**) The ligand binds to the ERBB receptor to form receptor homodimers and heterodimers, and activates the intrinsic kinase domain that recruits proteins to activate intracellular signaling pathways. (**E**) Soluble ERBB ligands can bind to and activate their receptors (such as EGFR) through endocrine (distant cells), paracrine (adjacent cells), or autocrine (same cell) ways.

2. The Expression Levels of EREG during Cancer Progression

2.1. The Outcomes of EREG Expression and KRAS Mutation

The survival outcomes of patients with lung cancer are substantially related to EGFR mutations (such as L858R and exon 19 deletion or insertion) or overexpressed ERBB family members that promote EGFR activity by increasing dimerization or ATP affinities [18][19]. The specific inhibition of EGFR through treatment with tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib, initially showed satisfactory clinical outcomes [20]. Although patients with metastatic colorectal cancer (mCRC) exhibited a high efficacy to anti-EGFR antibodies such as cetuximab or panitumumab, drug resistance was also observed in cancer cells [21][22]. Most patients with CRC who undergo anti-EGFR therapy exhibit an increased EGFR copy number; however, the degree of EGFR expression does not seem to correlate with the blockade of EGFR signaling. The increased EGFR gene copy number is mostly associated with a better outcome of anti-EGFR monoclonal antibodies treatment, particularly among those patients with wild-type KRAS [23]. However, in KRAS-mutated patients, the difference often did not exist. The compensation of alternative signaling pathways in various oncogenic mutations and different cell contexts, including aberrant EREG expression, may lead to the unfavorable outcomes of anti-EGFR therapies in various cancer cells [22][24].

In NSCLC cells, EREG acts as an ERBB ligand and a potential transcription target of oncogenic KRAS signaling [25]. The oncogenic activation of the MEK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) signaling pathway by mutant EGFR, KRAS, or BRAF genes may induce EREG overexpression [26]. When the number of EGFR ligands is increased, these ligands can bind to EGFR/ERBB and activate downstream signaling pathways, including MEK/ERK and PI3K/AKT, through an autocrine loop mechanism (**Figure 2**). Patients with NSCLC exhibiting high EREG expression and KRAS mutations had shorter OS and disease-free survival than did patients with low EREG expression and wild-type KRAS [26]. In addition, *EREG* mRNA levels are higher in pancreatic ductal adenocarcinoma (PDA) tissues than in normal and chronic pancreatitis tissues [27]. The findings of whole-exome sequencing analysis also indicated that *EREG* expression is induced in oncogenic KRAS-driven PDAs [28]. Notably, the oncogenic driver mutations, such as EGFR and KRAS, are commonly observed in lung adenocarcinoma [29]. Moreover, tumor-promoting functions were blocked by anti-EREG antibodies or an EGFR-tyrosine kinase inhibitor (EGFR-TKI, gefitinib or erlotinib) in NSCLC [30]. Thus, it is regarded as likely that a subset of NSCLC patients with high EREG expression and driver mutation are beneficial for anti-EGFR or targeting EREG treatments.

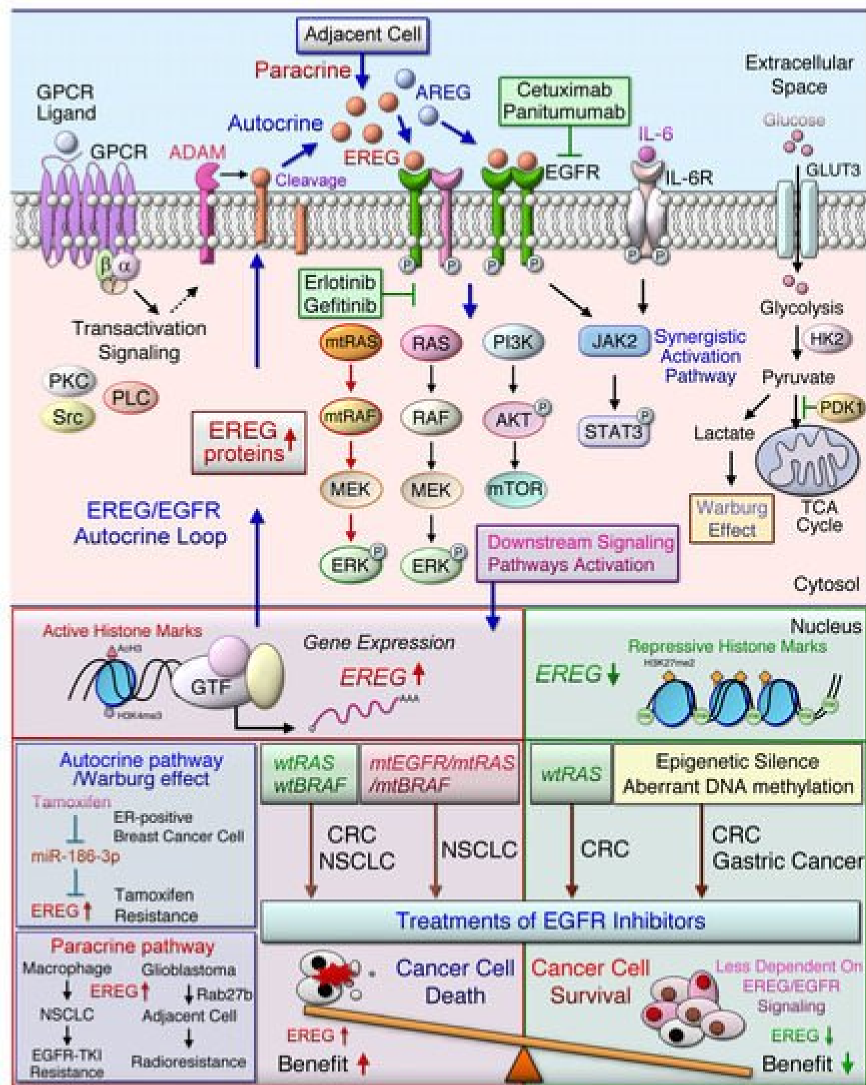

Figure 2. The EGFR/ERBB signaling pathway mediated by EREG leads to the cancer development and distinct drug response. G-protein-coupled receptor (GPCR) activation induces the cleavage of transmembrane epiregulin (EREG) protein and then secretes mature EREG. Soluble EREG binds to ERBB, such as epidermal growth factor receptor (EGFR) and ERBB4, which initiate the downstream signaling cascade, whereas the ligand protein is cleaved by a disintegrin and metalloproteinase enzyme (ADAM). The homodimerized or heterodimerized ERBB activate RAS (rat sarcoma)/RAF (rapidly accelerated fibrosarcoma) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT (a serine/threonine protein kinase) signaling cascades and synergistically activate, signal transducer and activator of transcription (STAT) 3 signaling pathways, which then induced the upregulation of *EREG* downstream signaling pathways. Oncogenic mutations in EGFR, KRAS, or BRAF genes in non-small cell lung cancer (NSCLC) cells lead to the constitutive activation of the downstream signaling, which in turn upregulates *EREG* expression. Treatment with anti-EGFR antibodies, such as cetuximab or panitumumab, in patients with metastatic colorectal cancer (mCRC) with wild-type RAS improved patient outcomes. EREG overexpression was found in wild-type, mutant EGFR (mtEGFR), or mutant BRAF (mtBRAF) NSCLC cells that are sensitive to anti-EREG antibodies or an EGFR-tyrosine kinase inhibitor (EGFR-TKI, gefitinib or erlotinib). EREG might diminish TKI-induced NSCLC cell apoptosis through EGFR/ERBB2 and AKT signaling pathways. However, the low-level expression of AREG and EREG in CRC cells indicates that tumors are less dependent on EGFR,

which is particularly prone to cause EGFR inhibitors resistance. Aberrant genetic alterations, including mutant RAS (mtRAS) and mtBRAF in CRC, induce resistance to anti-EGFR therapy. Low EREG expression was caused by aberrant histone modification and DNA methylation in a subset of cancer patients, such as those with gastric cancer, which cause resistance to anti-EGFR therapy. The miR-186-3p/EREG axis as a key regulatory pathway can induce the Warburg effect through EGFR signal activation, thereby increasing the expression of glycolytic genes, including glucose transporter 3 (GLUT3), hexokinase 2 (HK2), and pyruvate dehydrogenase kinase 1 (PDK1) in breast cancer cells resistant to tamoxifen. In addition, Rab27b mediates radioresistance in highly malignant glioblastoma (GBM) cells through the EREG-mediated paracrine pathway.

2.2. Alternative Signaling Pathways

Low *AREG* and *EREG* mRNA levels in mCRC tumor tissues are associated with BRAF mutations and correlated with shorter OS in patients with cancer-receiving oxaliplatin/fluoropyrimidine and bevacizumab as combinational treatment [31]. The expression levels of AREG and EREG ligands are coordinately regulated, and EGFR downstream signaling pathways can be activated by the autocrine/paracrine ligand loop to promote cancer progression (**Figure 3**A). The low-level expression of *AREG* and *EREG* indicate that tumors are less dependent on EGFR; thus, it is particularly prone to drug resistance to EGFR inhibitors (**Figure 3**B). However, in certain tumors (such as CRC) with aberrant genetic alterations, including RAS [32], BRAF [31], PIK3CA [33], EGFR S492R mutations [34], PTEN loss [35], and STAT3 phosphorylation [36] confer insensitivity to anti-EGFR therapy through constitutive activation of EGFR downstream signaling cascades regardless of EGFR blockade (**Figure 3**C). Additionally, EGFR downstream pathways can be activated by compensatory activation of growth factor receptors, including insulin-like growth factor 1 receptor (IGF-1R) [37], MET (MET proto-oncogene, receptor tyrosine kinase) [38], ERBB2 [39], and VEGFR [40] (**Figure 3**D). These alternative pathways may trigger intracellular signaling pathways to bypass EGFR and induce tumor cell growth and proliferation, leading to resistance to anti-EGFR therapies. High AREG and EREG expression levels in patients with mCRC with wild-type RAS could indicate the better efficacy of anti-EGFR therapies [41]. Furthermore, BRAF mutation, accompanied by low *AREG* and *EREG* mRNA expression levels, was correlated with poor survival outcomes in patients with mCRC treated with oxaliplatin/fluoropyrimidine and bevacizumab [31].

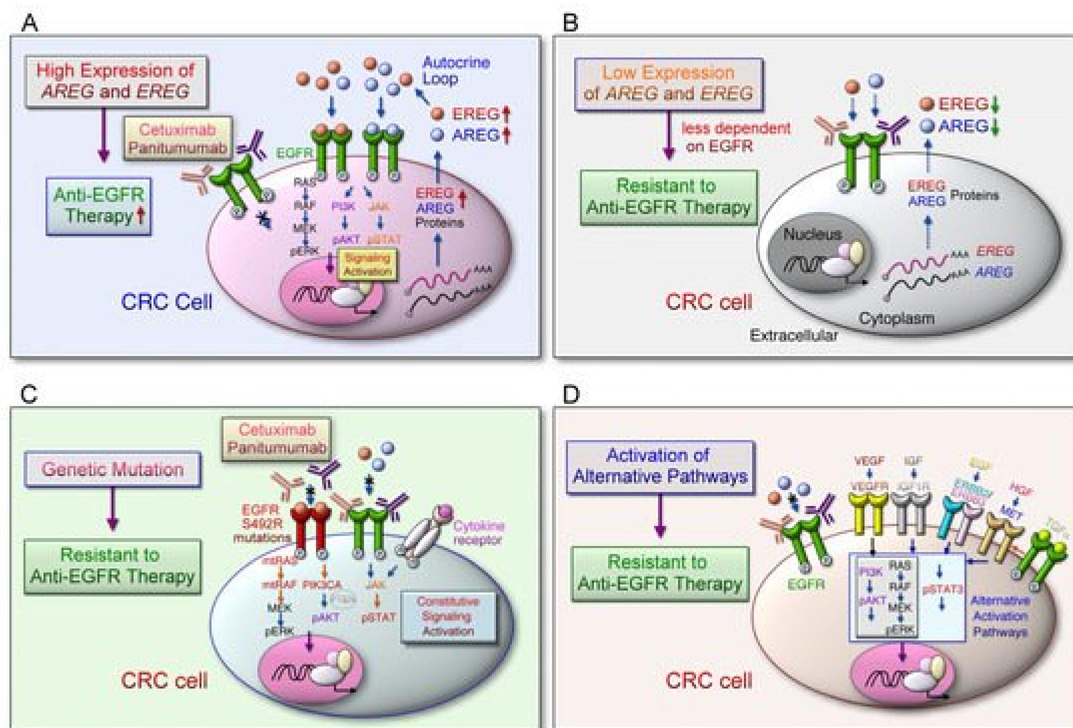

Figure 3. The alternative pathways and mechanisms bypass targeting EREG-mediated EGFR signal activation in colorectal cancer cells. (**A**) The expression of AREG and EREG are coordinately regulated by an autocrine loop through EGFR downstream signaling activation, which plays an important role in tumor growth and survival. The EGFR ligand binds to the EGFR and causes downstream signaling pathways that are essential for cell growth and proliferation. Cetuximab or panitumumab prevents the ligand from binding to EGFR, thereby blocking EGFR signaling. (**B**) Low *AREG* and *EREG* gene expression levels are associated with resistance to anti-EGFR therapy. The low expression levels of AREG and EREG indicate that tumor progression is less dependent on EGFR activation; therefore, the cancer cells are particularly prone to less response to EGFR inhibitor treatment. (**C**) Aberrant genetic alterations, including RAS, BRAF, PIK3CA, EGFR S492R mutations, PTEN loss, and STAT3 phosphorylation in the EGFR signaling pathways induce resistance to anti-EGFR therapy. These constitutively activate the downstream signal cascade of EGFR leading to resistance to anti-EGFR therapy, regardless of EGFR blockade. (**D**) Aberrant activation of the alternative pathways can induce resistance to anti-EGFR therapy. EGFR downstream effectors can be activated by activating compensatory membrane growth factor receptors, including IGF-1R, MET, HER2 and VEGFR. The stimulation of the corresponding growth factors causes the intracellular signaling pathway to bypass EGFR and induce tumor cell growth and proliferation, leading to resistance to anti-EGFR therapy.

3. Actions of EREG in the TME

3.1. EREG Promotes Tumorigenicity

In a COX2-overexpression mouse model, EREG was the most highly expressed growth factor in bladder carcinoma and promoted cancer cell proliferation [42]. Dual knockdown of EREG and N-RAS induces cell cycle

arrest and suppresses liver cancer cell growth through AKT, ERK, and retinoblastoma protein (Rb) pathways [43]. Salivary adenoid cystic carcinoma (SACC) cells showed high EREG expression that promoted migration and invasion through activated AKT and ERK signaling pathways [44]. EGFRs were constitutively activated by autocrine EREG expression in SACC cells that conferred metastatic ability through downstream AKT/ERK and STAT3 signaling pathways and snail/slug protein stabilization [45]. AREG and EREG mediate the activation of the EREG downstream signaling pathway, and the overexpression of both ligands promoted basal cell clonogenic survival, which was blocked by cetuximab in basal-like HNSCC (**Figure 4**A) [46]. EREG activated EGFR–ERK signaling pathway and induced C-Myc expression, thus promoting oncogenic transformation in patients with HNSCC and increasing sensitivity to erlotinib [11]. Cytoplasmic EREG accumulating in ovarian cancer tissues may act through autocrine and paracrine release and bind to EGFR in the TME [47]. EREG derived from fibroblasts promotes the proliferation of intestinal epithelial cells through the ERK pathway in colitis-associated tumor development [48]. Depletion of MUC1 deficiency in fibroblasts and epithelial cells led to increased EREG expression that promoted lung cancer development through the EGFR/AKT pathway [49]. This finding suggested that the tumor-promoting role of MUC1 is compensated by increased EREG production in the TME. Depletion of tumor suppressor gene-Indian hedgehog increased EREG/*Adenoma Polyposis Coli* (Apc) pathway-driven intestinal epithelial transformation in colonic stromal cells [50]. Collectively, the results indicate that autocrine and paracrine EREG may mainly activate EGFR downstream pathways in various cancer TMEs that contribute to tumorigenesis (**Figure 4**).

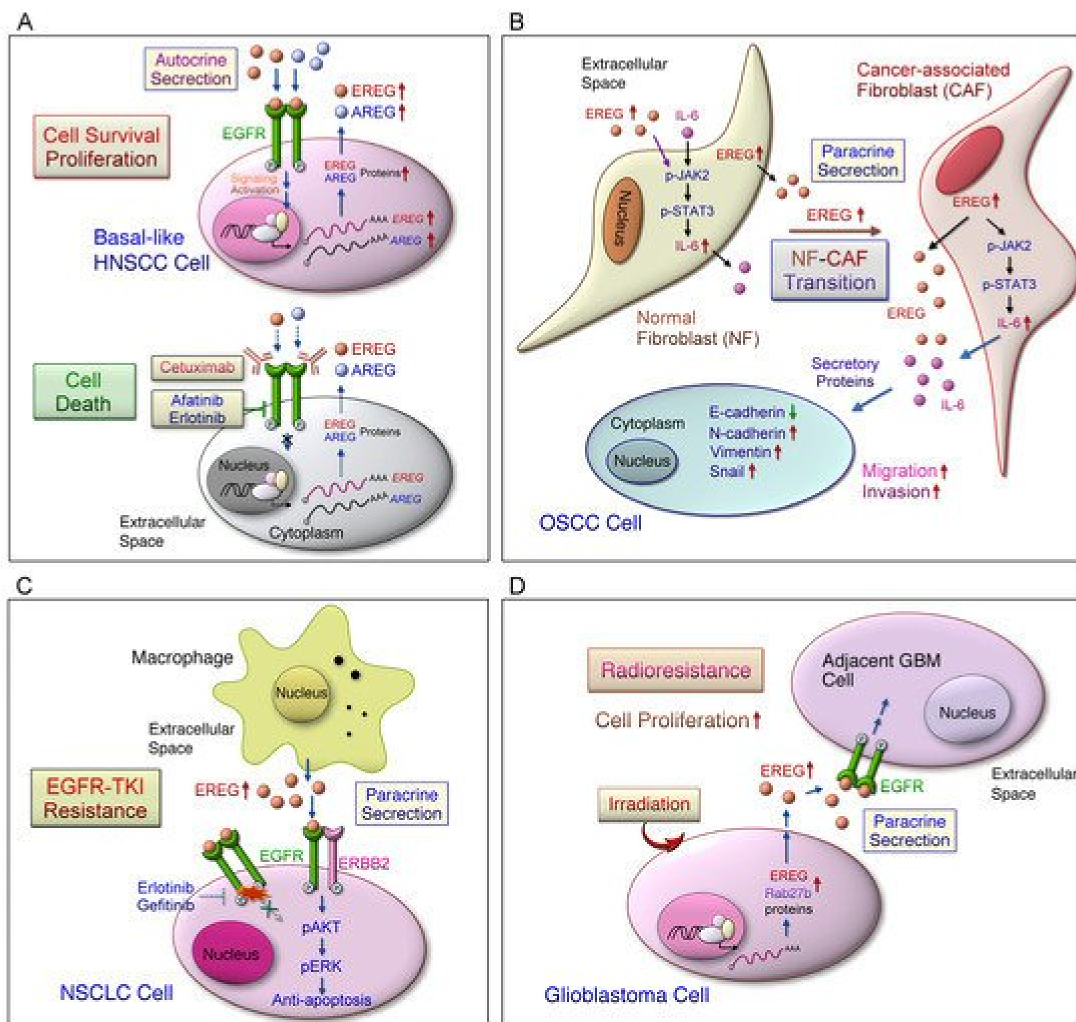

Figure 4. Elevated EREG expression in certain cell types may alter tumorigenesis and therapeutic response in the tumor microenvironment. (**A**) Inter-tumor heterogeneity may hinder the therapeutic efficiency of anti-EGFR treatments in head and neck squamous cell carcinomas (HNSCC). This may be caused by the dysregulated expression of factors, such as EREG, involved in the EGFR signaling pathway. Notably, basal-like cell lines are more sensitive to EGFR blockade alone or in combination with treatments targeting MEK, mTOR, or ERBB2. Additionally, EREG expression may be a predictive functional marker of anti-EGFR therapy in basal-like HNSCC. (**B**) The local resident normal fibroblasts (NFs) are converted to cancer-associated fibroblasts (CAFs) in oral squamous cell carcinoma (OSCC), which exhibit tumor-supportive properties. EREG is the most remarkably upregulated gene in CAFs. Overexpression of EREG in NFs activated the CAF phenotype. Mechanistically, the JAK2/STAT3 pathway was enhanced by EREG in parallel with increased IL-6 expression. IL-6 induced the JAK2/STAT3/EREG pathway in a feedback loop. Moreover, EREG-induced CAF activation promotes the epithelial-mesenchymal transition (EMT) necessary for migration and invasion, which depends on JAK2/STAT3 signaling and IL-6. (**C**) Among EGFR ligands, EREG significantly reduces the sensitivity of cells to EGFR TKI, which may be correlated with the resistance to erlotinib in NSCLC patients. EREG induces AKT phosphorylation in an ERBB2-dependent manner and attenuates TKI-induced apoptosis. Regardless of treatment, EREG induces the formation of EGFR/ERBB2 heterodimers. However, overexpression or knockdown of EREG in cancer cells has little effect on TKI sensitivity. EREG-rich macrophage conditioned medium induces EGFR-TKI resistance. (**D**) Rab27b mediates radioresistance in highly malignant glioblastoma (GBM) cells. In addition, Rab27b promotes the proliferation of neighboring cells through EREG-mediated paracrine signals after irradiation.

3.2. EREG Mediates Tumor Metastasis

EREG promotes tumor progression and metastasis in various cancers. EREG is overexpressed in bladder cancer, which leads to a high risk of lung metastasis [51]. A set of lung metastasis signature (LMS) genes, including EREG, COX2, and MMP1/2, was identified in breast cancer cells with lung metastasis potential [52]. LMS genes mediate primary tumor growth, angiogenesis, and metastatic extravasation in breast cancer [53]. Moreover, the blockade of these mediators by combination drugs (cetuximab/celecoxib/GM6001) significantly reduced metastatic progression. KAP1 overexpression activates EREG, COX2, and MMPs, that stimulated tumor cell proliferation [54]. K14 is highly expressed in breast epithelial tumor cell clusters that are a key regulator of distant organ metastasis through the activation of EREG signaling [55]. In colon cancers with liver metastasis, EREG was identified as a metastasis-associated gene through gene expression analysis [56]. In addition, up-regulation of EREG/ERK/AKT signaling in SACC cells increased the potential of lung metastasis [44]. EREG overexpression in normal fibroblasts mediated the cancer-associated phenotype, which promoted EMT through JAK2/STAT3 and IL-6 signaling pathways [57] (**Figure 4**B). The findings suggest that EREG is required for fibroblast transformation in OSCC progression and that EREG-mediated OSCC migration and invasion can be therapeutically targeted in the TME. Anti-EREG antibody significantly repressed cell adhesion and spread in EREG-expressing colon cells, but exerted a slight effect on their growth [58]. Moreover, the anti-EREG antibody efficiently inhibited downstream EGFR signaling activated by EREG, but not by EGF. These findings indicated that EREG–EGFR signaling is associated with cell adhesion and migration.

3.3. EREG Expression Correlates with Cancer Stem Cell Characteristics

EREG expression was increased in CRC cells and was associated with cancer stem cell (CSC) characteristics [59]. In lung adenocarcinoma, LGR5 expression was examined through IHC staining, and its expression was significantly correlated with large tumor size, TNM stage, and poor prognosis [60]. LGR5-positive cells with CSC properties with increased cell proliferation ability and were converted to LGR5-negative cells with drug resistance state when exposure to chemotherapy drugs treatment. EREG protein expression levels were both detected in LGR5-positive and drug-resistant LGR5-negative colon cancer cells. Besides, the anti-EREG antibody exhibited antitumor activity against tumors derived from the LGR5-positive and LGR5-negative cells in a metastatic model. This is the first demonstration of the establishment of stable cell lines having CSC properties and the ability to transition between the two distinct states, a proliferating and a drug-resistant state. In addition, treatment with anti-EREG antibodies could effectively combat tumor metastasis when CSCs are abundant in the early stages of cancer development, indicating that targeting EREG may be an option for CSC and drug resistance therapy. Analysis of the epigenetically regulated mRNA expression-based stemness index (mRNAsi) in The Cancer Genome Atlas data set revealed that a higher EREG-mRNAsi score was correlated with shorter OS in patients with glioma [61]. Collectively, EREG overexpression results in CSC properties and plays a critical role in metastasis during tumor progression. EREG expression is potentially induced in colon CSCs and associated with drug resistance. EREG is usually overexpressed in various cancers, including glioma and lung cancer; however, whether the expression of EREG plays a critical role in distinct types of cancers with CSC properties that confer tumor metastasis and drug resistance remains unclear.

3.4. EREG Mediates Drug Resistance

EGFR-TKI, gefitinib, and targeted therapy in Asian patients with NSCLC with EGFR mutations yielded more favorable outcomes in terms of the objective response rate and median PFS relative to carboplatin/paclitaxel chemotherapy [62]. However, acquired resistance within 9–14 months still occurred, although EGFR-TKI treatment demonstrated an initial improvement in clinical outcomes [62][63]. Thus, studies should examine how to overcome EGFR-TKI resistance in cancer therapies. A recent study revealed that the EREG ligand causes TKI (such as erlotinib) resistance in patients with NSCLC [64] (**Figure 4**C). EREG reduced TKI-induced cellular apoptosis through EGFR/ERBB2 and AKT signaling pathways. However, no significant difference was noted in TKI resistance after EREG overexpression or knockdowns. EREG was mainly expressed in macrophages in the NSCLC TME, as observed through single-cell RNA sequencing [64]. Notably, EGFR-TKI resistance increased after treatment with conditional medium obtained from EREG-enriched macrophages. EREG produced by tumor-associated macrophages (TAMs) causes NSCLC cell drug resistance in the TME; however, the interplay of critical factors such as EREG expression in various TMEs in terms of different space, time, boundaries, cell types, and contexts remains unclear.

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