Review Article

Mechanisms and therapeutic targets of ErbB family receptors in hepatocellular carcinoma: a narrative review

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Background and Objective: Hepatocellular carcinoma (HCC) is a highly heterogeneous and aggressive tumor. In recent years, the incidence of HCC has been increasing worldwide. Despite notable advancements in treatment methodologies, the prognosis of HCC patients remains unsatisfactory. ErbB family proteins play important roles in the occurrence, progression, and metastasis of HCC, and their abnormal expression is often closely associated with poor patient prognosis. This article sought to investigate the current status and research progress of ErbB family protein targeted therapy in HCC in recent years to provide a reference for basic research and clinical treatment.

Methods: We performed a comprehensive, narrative review of the latest literature to define the current progress of ErbB family receptors in HCC in both the pre-clinical and clinical arenas.

Key Content and Findings: The ErbB family belongs to the tyrosine kinase (TK) receptor family that comprises four members. These members are closely associated with proliferation, cell cycle regulation, and migration during HCC development through multiple signaling pathways. ErbB-targeted therapy has shown tremendous potential and prospects in the treatment of HCC.

Conclusions: Through in-depth research and the application of ErbB-targeted therapy, broader avenues will be opened for the treatment of HCC and other tumors, leading to more personalized and precise treatment approaches.

Keywords: Hepatocellular carcinoma (HCC); ErbB; targeted therapy; drug resistance

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Introduction

Liver cancer is one of the most common malignant tumors. In 2020, the incidence and mortality rates of liver cancer ranked seventh and third, respectively, among all malignant tumors worldwide (1). Hepatocellular carcinoma (HCC) is the most common histological subtype of primary liver cancer, accounting for approximately 85% to 90% of malignant tumors originating in the liver (2). HCC is highly malignant and invasive, and surgery is a potentially effective means to cure this disease. However, because early clinical symptoms are not obvious, most patients are already in the advanced stage of the disease at the time of diagnosis, and the opportunity for radical surgical resection is lost. Even

Table 1 The search strategy summary

Items	Specification
Date of search	April 20th, 2024
Databases and other sources searched	PubMed/MEDLINE
Search terms used	Liver cancer/hepatocellular carcinoma/HCC/ErbB/EGFR/HER1/HER2/HER3/HER4
Timeframe	All periods
Inclusion criteria	Original Article; Clinical Trial; Meta-analysis; Review; Systematic Review; written in the English language
Selection process	All the authors selected the studies together

HCC, hepatocellular carcinoma; EGFR, epidermal growth factor receptor.

after surgical resection, approximately 70% of patients experience recurrence within 5 years, and approximately two-thirds of these patients will experience relapse within 2 years due to intrahepatic spread (3).

With the advancement of next-generation sequencing (NGS) technology in recent years, a more in-depth understanding of the molecular mechanisms of tumors have been gained (4). This has facilitated the identification of an increasing array of genetic targets implicated in the initiation and progression of tumors. Consequently, the development of targeted therapeutics informed by these discoveries has significantly influenced the enhancement of prognostic outcomes for patients with cancer. In the realm of potential targets for cancer therapy, ErbB receptor family proteins have emerged as significant players. The aberrant expression of members of the transmembrane tyrosine kinase (TK) receptor family plays a role in the initiation and progression of tumors, especially lung cancer, breast cancer, and gastric cancer (5-7). On activation by their respective ligands, these receptors undergo dimerization and autophosphorylation, triggering a cascade of downstream signaling pathways that regulate cellular processes, such as proliferation, differentiation, migration, and survival. In cancer, the overexpression, mutation, or continuous activation of these receptors leads to the dysregulation of these signaling pathways, contributing to oncogenesis and progression (8). Drugs such as trastuzumab and gefitinib have been shown to target these receptors, demonstrating remarkable efficacy in cancer treatment (9,10). Currently, targeted therapeutic strategies against the ErbB family in HCC have been proposed and have undergone preliminary clinical exploration. This article reviews the research progress on ErbB family proteins in HCC to provide a reference for clinical decision making and to guide future research directions. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-837/rc).

Methods

A comprehensive, narrative review of the literature was conducted to examine the current progress of ErbB family receptors in HCC in both the pre-clinical and clinical arenas. Studies from all periods were reviewed from PubMed/MEDLINE using the keywords “liver cancer”, “hepatocellular carcinoma”, “HCC”, “ErbB”, “EGFR”, “HER1”, “HER2”, “HER3”, and “HER4”.

Articles relevant to the topic of this study were fully reviewed. The search strategy is summarized in *Table 1*.

ErbB family members in HCC: expression and mechanism pathways

The ErbB family belongs to the TK receptor family that comprises four members: epidermal growth factor receptor (EGFR; ErbB1 or HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). These members have similar structures, mainly consisting of the extracellular domain, transmembrane domain, and intracellular TK domain (*Figure 1*) (11,12). With the exception of ErbB2, which has no known endogenous ligand, the other receptors promote autophosphorylation and downstream signaling cascades by binding to their respective ligands to form homodimers or heterodimers. However, ErbB2 forms heterodimers with the other three receptors (8). These distinct activated signaling pathways, such as the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, the

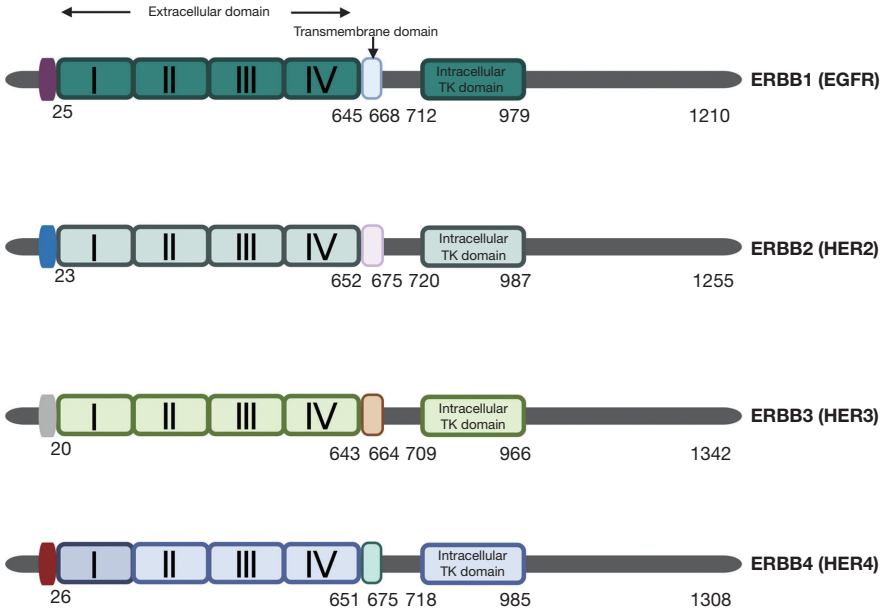

Figure 1 Schematic of the ErbB protein structure. ErbBs contain four N-terminal extracellular domains, transmembrane domains and an intracellular TK domain with catalytic activity. The extracellular domain of ErbB2 is in an active conformation and cannot bind a ligand. The kinase domain of ErbB3 is not fully functional. EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; TK, tyrosine kinase.

Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signaling pathway, and the mitogen-activated protein kinase (MAPK) signaling pathway, govern various cellular functions, including proliferation, cell cycle regulation, and migration (13,14). In living organisms, intercellular communication generates spatially heterogeneous gene expression patterns that are crucial for the development of tissues and organs. Cells can engage in autocrine signaling, where ligands produced by the cell directly activate receptors on the same cell, allowing for a rapid response to its own signals. Another mechanism is paracrine signaling, in which ligands are released into the extracellular environment, diffuse to neighboring cells, and interact with their receptors, facilitating communication between different cell types. In the endocrine mechanism, ERBB ligands secreted by cells are transported through the bloodstream or other body fluids to distant cells, activating ERBB receptors on those cells. This process is similar to hormone action, transmitting signals over long distances within the body to regulate the functions of various tissues and organs (15). Elevated levels of ErbB ligands have been reported in several cancers, including ovarian, gastric, and breast cancer, and are suspected to promote tumor invasiveness (16,17). For instance, amphiregulin (AREG) is overexpressed in various cancers, including HCC, and its role in tumor development and prognosis is well established (18-20). The trafficking, processing, and release of ERBB family ligands determine the scope, intensity, and duration of downstream signal transduction. Endocrine, paracrine, and autocrine mechanisms are recognized modes of ERBB ligand action (21). A critical step in these mechanisms is the ectodomain shedding of membrane-bound EGFR ligands. Protease-mediated cleavage releases soluble EGFR ligands into the extracellular environment, enabling them to participate in autocrine, paracrine, and endocrine signaling. This shedding process not only generates soluble ligands but also leaves a free cytoplasmic tail that can interact with other cytoplasmic proteins to regulate gene expression (22). For example, a gene replacement study on HBEGF has shown that mice expressing non-cleavable HBEGF develop severe heart failure and enlarged heart valves, resembling the phenotype of full HBEGF knockout (23). In contrast, mice expressing constitutively soluble HBEGF exhibit severe hyperplasia in the skin and heart (23). G-protein-coupled receptors (GPCRs) can utilize a metalloprotease-dependent process to transactivate EGFR, generating potent mitogenic signals. This signaling mechanism, known as the "triple membrane-passing signal", is widely observed

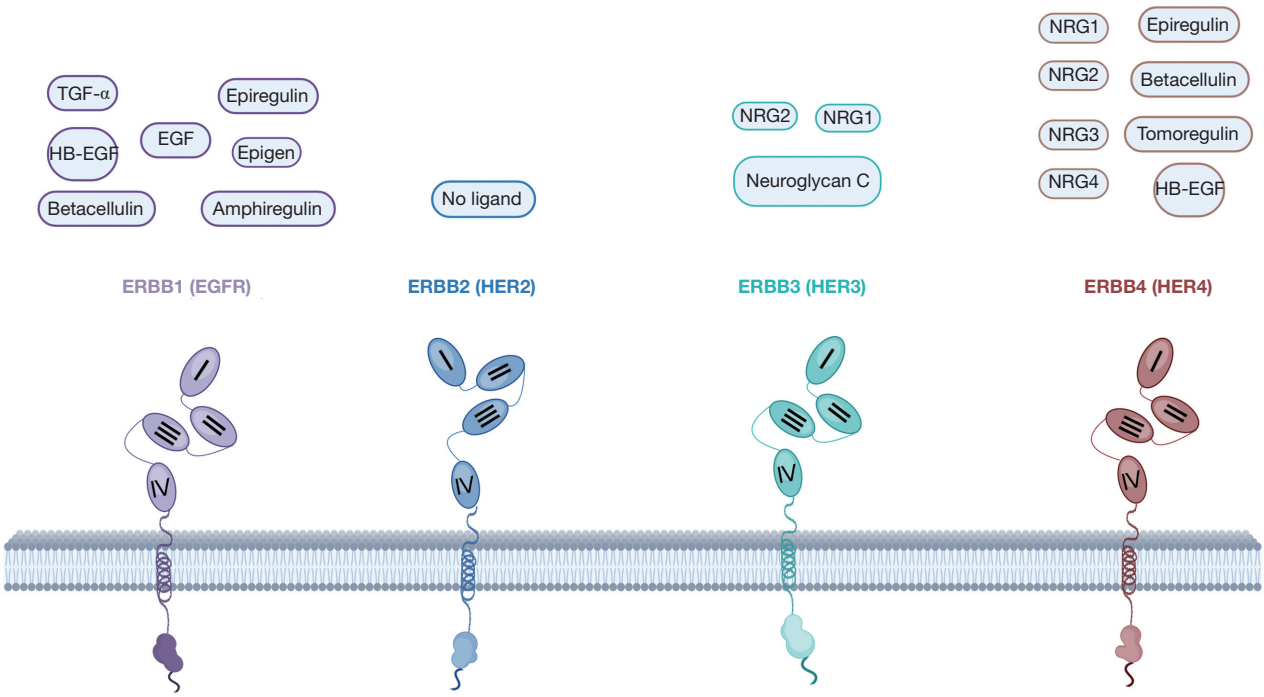

Figure 2 ErbB receptor family and ligands. Representative images show the ligands that can reportedly bind to ErbB receptors. TGF-α, transforming growth factor-α; HB-EGF, heparin-binding EGF-like growth factor; EGF, epidermal growth factor; NRG, neuregulin; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor.

in various cancers and other diseases, modulating cell proliferation, apoptosis, and migration (24). ERBB family ligands can activate EGFR and its downstream signaling pathways through autocrine, paracrine, and endocrine mechanisms, thereby regulating cell proliferation, migration, and survival in different ways.

The development of liver cancer is a complex, multistep process characterized by alterations in several signaling cascades, culminating in the emergence of heterogeneous neoplasms. Research indicates that the ErbB signaling pathway is one of the most commonly mutated pathways in HCC (25). Therefore, exploring the ErbB signaling pathway in HCC could provide greater insights into the biology and progression of this disease, and potential therapeutic strategies.

EGFR in HCC

EGFR, also known as HER1 or ErbB1, belongs to the receptor TK ErbB family and plays a carcinogenic role in various tumors (26). It is known that seven ligands [i.e., epidermal growth factor (EGF), AREG, epigen, epiregulin, betacellulin, heparin-binding EGF-like growth factor, and transforming growth factor (TGF)-alpha] can bind to the extracellular domain of EGFR, inducing receptor dimerization and TK activation, thus triggering downstream signaling pathways (*Figure 2*). This pathway is referred to as the canonical ligand-dependent EGFR signaling pathway, which transduces various signaling pathways, including the renin-angiotensin system (RAS)/rapidly accelerated fibrosarcoma (RAF)/MAP kinase-ERK kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway, PI3K/Akt/mammalian target of rapamycin (mTOR) pathway, and phospholipase C (PLC)/protein kinase C (PKC) pathway (27). As a crucial hub for external growth and survival signals, the EGFR system primarily regulates biological processes, such as cell proliferation, apoptosis, differentiation, and migration (28).

As a member of the ErbB family, EGFR frequently undergoes mutation and/or overexpression in various types of human cancers. EGFR can be phosphorylated at multiple sites, and in the majority of HCCs, the tyrosine residue at position 845 of EGFR is phosphorylated, and its phosphorylation sites are related to the subsequently

activated signaling pathways (29). Mutations in EGFR have been shown to promote tumor development both *in vitro* and in animal models (30,31). In 2003, Fitch *et al.* (32) identified EGFR (Leu863Gln and Dsk5) as a new class of pigmentation mutation (Dsk) phenotype that results in elevated basal EGFR kinase activity and signaling levels, leading to spontaneous primary HCC in mice older than 8 months (33).

EGFR is overexpressed in 68–96% of HCC cases, while mutations occur in only 1% of cases (34-36). A study has shown that EGFR expression is closely related to the degree of differentiation, proliferative activity, incidence of intrahepatic metastasis, and prognosis of HCC patients, with high EGFR expression possibly indicating poor prognosis in HCC patients (37). Song *et al.* (35) discovered that the EGFR/mesenchymal-epithelial transition factor (MET)-induced RAS/MAPK pathway stabilized HCC cells and participated in distant metastasis through circulating tumor cells, while also partially inhibiting the killing ability of immune cells. High phosphorylation levels of EGFR/MET, such as platelet-derived growth factor receptor βand fibroblast growth factor receptor 1, also preserve the elevated phosphorylation status of clinical targets in HCC treatment, which may result in the ineffectiveness of targeted therapies and facilitate extrahepatic metastasis. Ji *et al.* (38) discovered that EGF-EGFR upregulates the expression of T-box (TBX) 19 via the ERK/ nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, and TBX19 further upregulates the expression of EGFR and Rac family small GTPase 1 (RAC1), forming an EGF-TBX19-EGFR-positive feedback loop that promotes liver cancer metastasis.

Abnormal DNA methylation is closely linked to the occurrence, development, and malignant transformation of tumors, and EGFR also plays a role in this process. For example, the hypermethylation of empty spiracle homeobox 1 (EMX1), which binds to the EGFR promoter, promotes EGFR transcription and activates the EGFR-ERK signaling pathway, triggering the onset and metastasis of HCC (39). Su *et al.* (40) reported that sublethal heat treatment boosts EGFR N6-methyladenosine (m6A) modification and its binding with YTH N6-methyladenosine RNA binding protein 1, enhancing EGFR messenger RNA translation and elevating EGFR levels, which in turn fosters malignancy in HCC cells. Concurrently, Quiescin sulfhydryl oxidase 1 (QSOX1) inhibits nuclear factor erythroid 2-related factor 2 (NRF2) activation by promoting EGFR ubiquitination and endosomal trafficking, increasing oxidative stress sensitivity in HCC cells and decreasing their viability (41). The overexpression of 5'-nucleotidase domain containing 2 has been shown to fuel liver cancer cell proliferation and tumor growth by directly engaging with EGFR and augmenting its expression through the modulation of EGFR ubiquitination, thereby stimulating downstream signal transduction (42). These findings highlight the pivotal role of EGFR in the survival and progression of HCC.

EGFR-mediated activation of the PI3K/AKT/mTOR pathway regulates HCC cell survival, proliferation, and the cell cycle, illustrating its central function in cancer cell biology (43). VersicanV1 serves as an upstream activator of EGFR, activating this signaling pathway to enhance the Warburg effect in liver cancer cells, thereby promoting the malignant phenotype of liver cancer cells (44). The PI3K/AKT signaling pathway not only conveys external proliferation signals from receptors on the cell membrane to the nucleus, enhancing cell growth and division, but also elevates the expression of glucose transport proteins on the cell surface, affecting glucose uptake and metabolism, thereby providing the energy and material foundation for rapid cancer cell proliferation (45). In addition, EGFR has been demonstrated to facilitate aerobic glycolysis through a variety of kinase-dependent and kinase-independent mechanisms, profoundly affecting cancer metabolism and progression. Moreover, a study revealed that in cirrhotic mouse models, an interaction between the RAS and the EGFR signaling pathway activates the MAPK pathway, facilitating the transition from liver cirrhosis to HCC.

The angiotensin-converting enzyme inhibitor captopril has been found to effectively mitigate liver fibrosis and decrease the incidence of HCC (46). Additionally, polymorphisms in the EGF gene lead to increased human EGF expression, which exacerbates liver cirrhosis and hastens progression to HCC by activating additional EGFR signaling pathways (47,48). The internalization of EGFR is a critical step in the cellular signaling process, and a study has shown that the ubiquitination of the ultraviolet (UV) radiation resistance-associated gene enhances the lysosomal degradation of EGFR, thereby inhibiting the initiation and development of HCC (49). Sorting nexin 5 facilitates the growth and spread of liver cancer cells through the suppression of EGFR endocytosis and degradation, which in turn triggers the activation of the ERK1/2 signaling pathway (50). The EGFR-related signaling pathway effectively substantiates the concept of "oncogene addiction", whereby cancer cells rely on the sustained specific activation or overexpression of oncogenes to maintain their

proliferation, invasion, and other phenotypes, thereby accelerating cancer progression (51). In addition, cholestatic bile acids activate Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidase, triggering YES-mediated EGFR phosphorylation through a ligand-independent pathway, which in turn activates hepatic stellate cells, thereby promoting the development of liver fibrosis and cirrhosis and increasing the incidence of HCC (52,53). EGFR and ephrin receptor A2 act as cofactors to facilitate hepatitis C virus (HCV) infection in the host, indirectly inducing liver cirrhosis and HCC (54). In summary, EGFR plays a crucial role in the development of HCC, and its underlying mechanisms are worthy of further investigation.

ErbB2 in HCC

ErbB2 (HER2) is a membrane receptor protein that belongs to the EGFR family and regulates cell growth, differentiation, and survival. In a variety of malignancies, including breast cancer, gastric cancer, colorectal cancer, and other cancers, the HER2 gene is overexpressed, and has been identified as an oncogenic driver that is closely associated with poor patient prognosis (55-57). ErbB2 differs structurally from other family members and lacks known natural ligands. Its extracellular domain maintains constitutive activity, allowing spontaneous homodimerization (ErbB2 binding to ErbB2) in cells overexpressing ErbB2 (*Figure 2*). Additionally, ErbB2 tends to form heterodimers with other members of the EGFR family, exhibiting stronger signaling capacity than homodimerization, thus playing a significant role in cellular signaling (58). HER2 typically primarily activates downstream MAPK and PI3K/AKT pathways, regulating tumor cell proliferation and suppressing apoptosis (59).

The overexpression of HER2 typically manifests in tumors through gene amplification. HER2 overexpression has been observed in approximately 20–40% of patients with HCC (34,60). In early studies, it was generally believed that HER2 played a limited role in the occurrence and progression of HCC (61,62). However, with increasing research, new evidence has revealed the complex and diverse role of HER2 in the pathogenesis of HCC. These studies suggest that the overexpression of HER2 is closely associated with poor clinical prognosis in HCC patients, and HER2 may influence the development of HCC through multiple pathways, including promoting the proliferation, invasion, and migration of tumor cells. A bioinformatics analysis of differentially expressed genes in HCC demonstrated that HER2 is a key gene closely associated with the occurrence and progression of HCC (63). Therefore, the role and clinical significance of HER2 in the pathophysiology of HCC are being re-evaluated and further studied.

Additionally, HER2 is considered a factor that promotes tumor metastasis. It is involved in multiple biological processes related to tumor invasiveness and metastatic capability, including matrix degradation, increased proteolytic activity, enhanced vascular permeability, and the growth, proliferation, migration, and differentiation of endothelial cells. These processes not only contribute to the growth of tumors at the primary site but also facilitate the spread of cancer cells through the vascular and lymphatic systems, leading to the formation of metastatic lesions in other parts of the body. A recent study indicated that the overexpression or activation of HER2 leads to the upregulation of β-catenin levels, resulting in increased accumulation of β-catenin in the nucleus (60). This process concurrently disrupts the TGF-β signaling pathway by inhibiting the activation of the small mothers against decapentaplegic 2/3 (SMAD2/3) complex. Such modulation of cellular responses diminishes the growth-inhibitory effects of the TGF-β pathway, thereby facilitating tumor proliferation, invasion, and metastasis (60).

Epithelial-mesenchymal transition (EMT) refers to the primary cellular process by which epithelial cells lose their cell polarity and cell-to-cell adhesion and acquire mesenchymal cell traits, thereby increasing their motility and invasiveness. EMT plays a significant role in tumor metastasis and progression, and HER2 participates in HCC cell EMT through the MAPK/ERK pathway, thereby promoting tumor invasion and migration (64). Moreover, it has been reported that the HER2 protein is upregulated in patients with HCC with a background of hepatitis B virus (HBV) infection, and such patients typically exhibit a poorer prognosis. The HBV-encoded X protein (HBx) is associated with the upregulation of the HER2 protein, leading to increased HER2 expression. Subsequently, this elevated expression may activate Akt activity, thus facilitating IκB kinase-α (IKK-α) nuclear translocation and ultimately enhancing the migratory capability of liver cancer cells (65).

With the in-depth exploration of the multifaceted roles of HER2 in HCC, significant strides can be made toward its clinical application, offering new hope to patients through targeted treatment options. Concurrently, the ongoing debate surrounding whether HER2 can serve as a prognostic factor in HCC needs further exploration to

optimize treatment strategies for HCC patients.

ErbB3 and ErbB4 in HCC

The *ErbB3* (or *HER3*) gene is located on the long arm of human chromosome 12 (12q13), and it encodes a protein with a molecular weight of either 160 or 180 kDa (66). Previously, ErbB3 was thought to lack intrinsic kinase activity, but a recent study has revealed that it possesses weak kinase activity (33). It interacts with other members of the ErbB family to form heterodimers, thereby exerting its function (67). Neuregulin 1 (NRG1) and NRG2 act as ligands that bind to ErbB3, causing a conformational change in ErbB3, thereby facilitating the dimerization, phosphorylation, and activation of signaling pathways (68). There are nine classical ligands capable of activating ErbB4, among which NRG3 and NRG4 are unique (69,70).

ErbB3 and ErbB4 do not play as prominent roles in the TK family as EGFR and HER2; however, due to the overexpression of ErbB3 in certain cancers, it still garners significant interest as a potential therapeutic target. A study on a biocomputational model of the ErbB signaling network revealed that ErbB3 is a critical node in the activation of the ligand-induced ErbB receptor-PI3K axis, and plays a crucial role in the onset and development of cancer (71). Recent studies have also confirmed the critical role of ErbB3 in cellular transformation and cancer. Genetic mutations and methylations of ErbB3 exert a broad regulatory effect on the tumor microenvironment (TME), promoting the onset of cancer (72-74). ErbB3 has six YXXM motifs that bind to the p85 regulatory subunit of PI3K, activating it. The p85 regulatory subunit of PI3K (PI3KR) is one of the most thoroughly studied targets of ErbB3. PI3KR has been shown to promote cell growth and metastasis in a variety of tumors, including HCC. In addition, ErbB3 is significantly overexpressed in 70.4% of HCC patients and is closely associated with microvascular invasion, early recurrence and poor prognosis in HCC patients, while ErbB4 is not significantly expressed (75). The primary mechanism involves the autocrine activation of ErbB3 in HCC through the NRG1/ErbB3 autocrine loop, which in turn induces the PI3K/AKT and MAPK/ERK signaling pathways, playing a key role in the regulation of invasion and migration in HCC. Additionally, the study revealed a secreted isoform of ErbB3 in the serum of HCC patients, and the expression levels of this isoform significantly affected portal vein invasion and metastasis (75). The results of this study indicate that as a potential therapeutic target or co-target, the ErbB3 signaling pathway may be more effective in preventing and treating HCC recurrence and metastasis than in treating advanced HCC. ErbB3 has been reported to be crucial for the formation of HCC tumors and cellular proliferation (33). Ni *et al*. (76) explored the role of epithelial V-like antigen 1 (EVA1) in HCC and found that EVA1 promoted the growth and migration of HCC cells *in vitro* through the ErbB3-PI3K-AKT signaling pathway and induced metastasis *in vivo*.

ErbB4 (or HER4) is a unique member of the ErbB family with growth-inhibitory properties and plays a dual role in cancer initiation and progression. Its constitutively dimerization mutant, HER4 Q646C, has been shown to inhibit pancreatic tumors, breast cancer, and prostate cancer cell lines (77-79). Meanwhile, research also suggests that HER4 may reduce tumor formation and progression by enhancing differentiation and inhibiting growth through the expression of splice variants (80). HER4 may play a protective role in cancer by attenuating the proliferation and oncogenic effects of heterodimerization between other ErbB receptors (81). Recently, Liu *et al*. (82) used carbon tetrachloride and diethylnitrosamine to induce models of liver inflammation and tumors, respectively, in mice. These findings suggest that the absence of ErbB4 contributes to the development of HCC, and ErbB4 deficiency leads to poor differentiation and a poor prognosis in HCC patients. Reduced levels of TP53INP1, which are possibly linked to diminished ErbB4 expression or its absence, indirectly reduce the stability and apoptotic or cell cycle arrest functions of p53, thereby fostering the proliferation, survival, and advancement of HCC tumor cells. Similarly, additional research has reported that the overexpression of ErbB4 inhibits the proliferation and promotes the apoptosis of HCC cells by reducing cell viability and clonogenicity and inducing cell cycle arrest (83). In the context of immunity, the activation of ErbB2 and ErbB4 receptors mediates the induction of interleukin-10 (IL-10) production by immune cells in response to NRG1, thereby exerting inhibitory effects on tumor cells (84). Therefore, ErbB4 may play a protective role in the occurrence and development of HCC, and its specific mechanisms warrant further exploration.

Membrane receptor trafficking and signaling are frequently altered in cancer. Clathrin is an essential structural protein in eukaryotic cells, predominantly involved in endocytosis and vesicle trafficking processes. It forms clathrin-coated vesicles to facilitate the intracellular and extracellular transport of various substances (85).

Clathrin-mediated endocytosis (CME) is the primary pathway for EGFR internalization (86,87). ERBB endocytosis may also involve clathrin-independent endocytosis (CIE) pathways, depending on the ligand bound to ERBB and its concentration (88). For instance, when EGF binds to EGFR, it induces EGFR dimerization and autophosphorylation. This activated form of EGFR dimer undergoes rapid endocytosis, and the internalized EGF-EGFR complex is transported to early endosomes. CME preferentially sorts EGFR to the recycling pathway, where some internalized EGFR is dephosphorylated and recycled back to the plasma membrane, preparing for another round of signaling. A small portion of EGFR, however, is directed to the lysosomal degradation pathway, where it is degraded, thereby regulating the termination of signaling. The CME mechanism of EGF-EGFR, mediated by clathrin and associated adaptor proteins, helps maintain and regulate EGFR signaling and recycling, which is crucial for cell proliferation and tumor development (89,90). Liu *et al.* (91) studied the effect of Clathrin on ErbB receptor signaling in HCC cell lines and found that clathrin knockdown reduced ErbB receptor phosphorylation and, in response to ligand AR, significantly reduced AKT phosphorylation. Meanwhile, clathrin knockdown increased STAT3 phosphorylation regardless of ligand stimulation. A recent study found that during ligand stimulation, atypical CME of ligand-free EGFR monomers occurs parallel to the typical CME of ligand-bound EGFR dimers. The atypical CME of ligand-free EGFR monomers operates via a p38-dependent pathway under stress conditions, requiring phosphorylation at specific sites (Ser-1015, Thr-1017, and Ser-1018) on EGFR, ultimately leading to EGFR internalization and recycling (92). The regulation of ErbB signaling by clathrin in HCC is cell-specific and ligand-specific, further investigation into the relationship between grid and ErbB signaling proteins will contribute to enhancing targeted treatment strategies for the ErbB receptor family.

The ERBB signaling pathway promotes tumor growth by influencing antitumor immune responses within the TME, a complex ecosystem that provides conditions for tumor cell survival and proliferation. T lymphocytes (such as $CD8^+$ T cells and Tregs), myeloid cells (such as macrophages and myeloid-derived suppressor cells), cytokines (such as IL-6 and TNF-α), and exosomes collectively construct a complex immunoregulatory network within the TME, affecting tumor immune evasion and progression (93). In the early stages of tumor development, T lymphocytes recognize and kill tumor cells through immune surveillance. However, as the tumor progresses, tumor cells employ various mechanisms to evade immune surveillance, resulting in altered T lymphocyte function and even immune suppression (94). Increasing evidence indicates that genomic alterations acquired during tumor development can modulate the TME, aiding tumor cells in evading immune surveillance (95). A study has found that ERBB signaling is one of the most extensively mutated pathways mediating antitumor immunity, with elevated levels of ERBB mutations correlating with poor prognosis in cancer patients (96). Mutations in the ERBB signaling pathway lead to complex interactions among different cell types (such as epithelial cells, macrophages, and T cells), creating a microenvironment conducive to tumor growth. In tumors with ERBB pathway mutations, the secretion of midkine (MDK) is significantly increased. MDK interacts with its receptor LRP1, promoting the differentiation of tumor-infiltrating macrophages into immunosuppressive M2 macrophages. These M2 macrophages inhibit antitumor immune responses and promote tumor growth and progression. Additionally, the interaction between macrophage-secreted CXCL10 and its receptor CXCR3 on regulatory T cells (Tregs) activates Tregs, further suppressing antitumor immune responses and leading to tumor progression (97). Wang *et al.* (98) discovered that AREG regulates Treg suppressive function and induces immune tolerance and evasion through the EGFR/GSK-3/Foxp3 axis. $CD8^+$ T cells play a major antitumor role in the TME by releasing various effector molecules to attack and destroy tumor cells. However, mutations in the ERBB signaling pathway can significantly reduce the number of $CD8^+$ tumor-infiltrating lymphocytes (TILs), leading to immunosuppression (99). Moreover, MHC molecules are crucial for tumor antigen presentation. MHC I activates $CD8^+$ T cells to specifically kill tumor cells, while MHC II enhances cytotoxicity through cytokine secretion and participates in the body's positive feedback regulation against tumors (100). EGFR mutations can decrease MHC levels, contributing to immune evasion (101).

Future studies may further elucidate the roles of these receptors in HCC, thereby providing support for the development of new treatment strategies. In summary, the ErbB pathway is one of the most prominently mutated pathways in HCC and plays a crucial role in the development and progression of HCC (*Figure 3*). These findings serve as a crucial foundation for assessing the effectiveness of ErbB pathway-targeted therapies in the clinic or those currently under development for patients

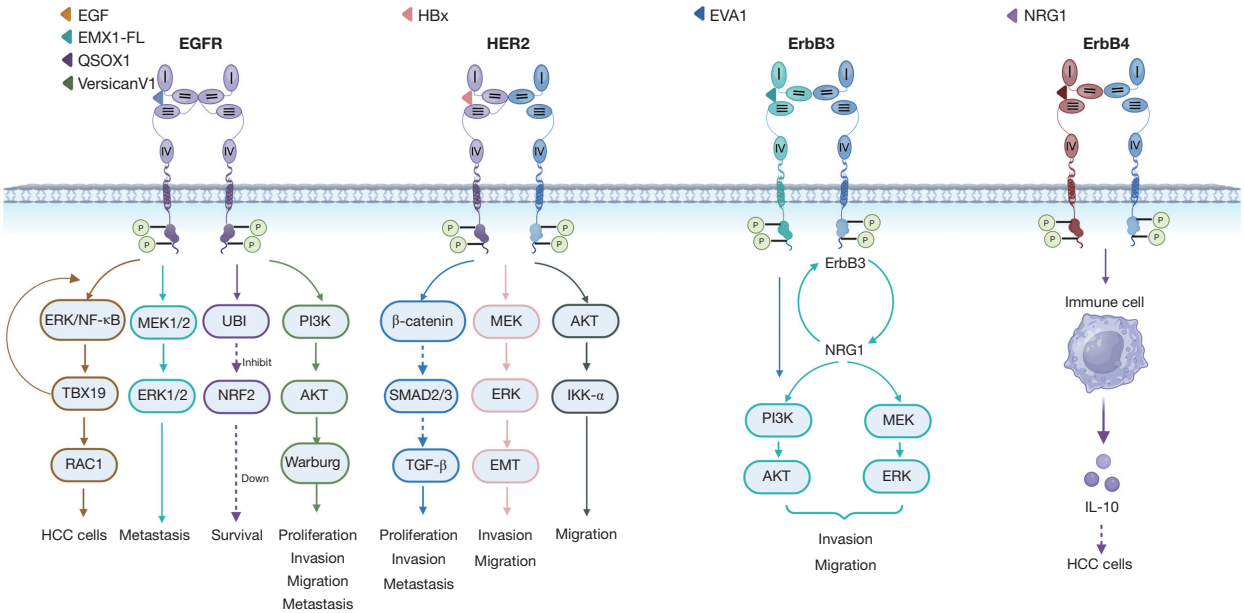

Figure 3 Signaling pathways mediated through ErbB receptors in HCC. Diagram showing functional ErbB dimers and canonical ErbB signaling pathways. (I) The EGF/EGFR signaling pathway promotes HCC metastasis through a positive feedback loop involving TBX19. By regulating the ERK/nuclear factor NF-κB axis, this pathway upregulates TBX19 expression. Overexpressed TBX19 further enhances the expression of EGFR and RAC1, thereby reinforcing the EGF-TBX19-EGFR feedback loop and facilitating the metastatic progression of HCC. EMX1-FL binds to the EGFR promoter, enhancing EGFR transcription and activating the EGFR-MEK1/2-ERK1/2 signaling pathway, which triggers tumor metastasis. QSOX1 inhibits NRF2 activation by promoting the ubiquitination and endosomal transport of EGFR, thereby increasing the oxidative stress sensitivity of HCC cells and reducing their viability. VersicanV1 activates the classical PI3K-AKT pathway of EGFR to promote the Warburg effect in liver cancer cells, thereby enhancing their proliferation, invasion, migration, and metastasis. (II) HER2 leads to increased β-catenin levels by itself, enhancing its accumulation in the nucleus. This process disrupts the TGF-β signaling pathway by inhibiting the activation of the SMAD2/3 complex, thereby promoting tumor proliferation, invasion, and metastasis. HER2 participates in the EMT of HCC cells via the MAPK/ERK pathway, thereby promoting tumor invasion and migration. Additionally, HBx increases HER2 expression and activates Akt activity, leading to the nuclear translocation of IKK-α, which ultimately enhances the migration ability of HCC cells. (III) EVA1 promotes cancer cell growth and migration through the ErbB3-PI3K-AKT signaling pathway and induces metastasis *in vivo*. The NRG1/ErbB3 autocrine loop activates ErbB3, which in turn induces the PI3K/AKT and MAPK/ERK signaling pathways that play a crucial role in regulating the invasion and migration of HCC. (IV) The activation of the ErbB4 receptor mediates the promotion of IL-10 production by immune cells by NRG1, thereby exerting an inhibitory effect on tumor cells. EGF, epidermal growth factor; EMX1-FL, empty spiracles homeobox 1-full length; QSOX1, quiescin sulfhydryl oxidase 1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HBx, hepatitis B virus X protein; EVA1, epithelial V-like antigen 1; NRG1, neuregulin 1; TBX19, T-box transcription factor 19; EMT, epithelial-mesenchymal transition; SMAD2/3, small mothers against decapentaplegic 2/3; IKK-α, IκB kinase-α; MEK, MAP kinase-ERK kinase; ERK, extracellular signal-regulated kinase; RAC1, Rac family small GTPase 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NRF2, nuclear factor erythroid 2-related factor 2; UBI, ubiquitination; PI3K, phosphatidylinositol-3-kinase; AKT, serine/threonine kinase; HCC, hepatocellular carcinoma.

with HCC.

ErbB inhibitors: clinical applications and exploration

With continuous advancements in science and technology, precision medicine has increasingly become a major trend in the field of cancer treatment. This approach largely relies on high-throughput NGS technologies and systematic analyses to achieve highly precise treatments tailored to the individual characteristics of cancers (102). The overexpression and/or functional alteration of oncogenes

Table 2 Clinical trials of ErbB-targeted therapy in hepatocellular carcinoma

Study	Drugs	Phase	Targets	Design	Sample size	Results
Philip 2005, (104)	Erlotinib	II	EGFR	Single-arm	38	Positive
Thomas 2007, (105)	Erlotinib	II	EGFR	Single-arm	40	Positive
Thomas 2009, (106)	Erlotinib + bevacizumab	II	EGFR; VEGFR	Single-arm	40	Positive
Kaseb 2012, (107)	Erlotinib + bevacizumab	II	EGFR; VEGFR	Single-arm	59	Positive
Philip 2012, (108)	Erlotinib + bevacizumab	II	EGFR; VEGFR	Single-arm	27	Negative
Yau 2012, (109)	Erlotinib + bevacizumab	II	EGFR; VEGFR	Single-arm	10	Negative
Chiorean 2012, (110)	Erlotinib + bevacizumab	II	EGFR	Single-arm	14	Negative
Govindarajan 2013, (111)	Erlotinib + bevacizumab	II	EGFR; VEGFR	Single-arm	21	Negative
Hsu 2013, (112)	Erlotinib + bevacizumab	II	EGFR; VEGFR	Single-arm	51	Positive
Zhu 2015, (113)	Erlotinib + sorafenib Placebo + sorafenib	III	EGFR; RAF; VEGFR; PDGFR; KIT	RCT	720	Negative
Kaseb 2016, (114)	Erlotinib + bevacizumab	II	EGFR; VEGFR	Single-arm	44	Positive
Patt 2017, (115)	Erlotinib + GEMOX	II	EGFR	Single-arm	26	Negative
Thomas 2018, (116)	Erlotinib + bevacizumab Sorafenib	II	EGFR; RAF; VEGFR; PDGFR; KIT	Single-arm	90	Negative
Zhu 2007, (117)	Cetuximab	II	EGFR	Single-arm	30	Negative
Asnacios 2008, (118)	Cetuximab + GEMOX	II	EGFR	Single-arm	45	Positive
Weekes 2019, (119)	Cetuximab + regorafenib	Ib	EGFR; RAF; VEGFR; PDGFR; KIT	Single-arm	42	Positive
Ramanathan 2009, (120)	Lapatinib	II	EGFR; HER2	Single-arm	40	Negative
Bekaii-Saab 2009, (121)	Lapatinib	II	EGFR; HER2	Single-arm	26	Negative

EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; RAF, rapidly accelerated fibrosarcoma; PDGFR, platelet-derived growth factor receptor; KIT, receptor tyrosine kinase; HER2, human epidermal growth factor receptor 2; RCT, randomized controlled trial.

are among the primary drivers of cancer cell proliferation and tumor development. Consequently, molecular targeted therapies against these key genes have been extensively researched and applied in recent years, proving to be an effective strategy for cancer treatment (103). In particular, as critical signaling molecules in tumor progression, members of the ErbB family have emerged as focal points in targeted therapy research (*Table 2*). Over the past few decades, small-molecule drugs targeting the ErbB family have been developed and successfully applied to various types of cancer, such as lung, gastric, colorectal, and pancreatic cancers, and have demonstrated significant efficacy (122-125). Currently, with a deeper understanding of the pathogenesis and pathological heterogeneity of cancers, such as HCC, a new era has been initiated for the use of novel targeted treatment strategies, including ErbB small-molecule inhibitors.

Targeting EGFR for HCC treatment

Gefitinib and erlotinib, first-generation EGFR tyrosine kinase inhibitors (TKIs), were approved by the Food and Drug Administration (FDA) for cancer treatment in 2003 and 2004, respectively, and demonstrated significant therapeutic efficacy, particularly in the treatment of advanced non-small cell lung cancer (NSCLC) in the realm of oncology (126,127). However, the therapeutic efficacy of EGFR-TKIs for HCC still requires further exploration.

In a phase II clinical trial involving 38 HCC patients, erlotinib was effective in controlling disease progression in only a minority of patients who were EGFR-positive (104). A subsequent phase II clinical trial also revealed that monotherapy with erlotinib exhibited moderate disease control benefits in approximately half of the 40 patients with advanced HCC (105). In a 16-week phase II single-arm clinical trial of advanced stage HCC patients treated with bevacizumab [a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) α] and erlotinib, the primary endpoint of progression-free survival (PFS) was 62.5%, with an overall clinical response rate of 25%, demonstrating significant clinical efficacy (106). Similar results were also achieved in another 16-week phase II clinical trial (107).

Three phase II studies investigating the efficacy of combining bevacizumab with erlotinib for advanced HCC treatment yielded disappointing results, but this regimen can be used as an alternative for some patients who are intolerant to sorafenib treatment (108,109,111). The potential reasons for the failure of the experiments include the relatively small number of the patients recruited, coupled with the fact that all the participants were recruited from a single institution. Such a scenario significantly limits the extrapolation and accuracy of the findings. Further, the lack of any significant therapeutic response among patients during the administration of sorafenib suggests that the participants might possess intrinsic resistance to antiangiogenic strategies. This intrinsic resistance may have contributed to the unsuccessful outcomes observed in the study.

A subsequent multicenter phase II study conducted in Asian countries revealed that the combination of bevacizumab and erlotinib demonstrated certain efficacy and tolerability in Asian patients (112). Another study evaluating the efficacy and safety of erlotinib combined with docetaxel in patients with refractory hepatobiliary cancer demonstrated preliminary safety and tolerability but no significant difference in efficacy compared to erlotinib monotherapy (110). In a randomized, multicenter, double-blind, placebo-controlled phase III clinical trial (SEARCH III), 720 patients were randomly assigned to receive either a combination treatment of sorafenib and erlotinib or sorafenib with a placebo. The results indicated that the combination of sorafenib and erlotinib did not improve the survival of patients with advanced HCC, and there was a greater incidence of adverse events in the early stages of treatment in the sorafenib and erlotinib groups (113).

Subsequently, Kaseb *et al*. (114) evaluated the efficacy and tolerability of bevacizumab and erlotinib as second-line treatments in 44 patients with sorafenib-resistant HCC. The results showed a median overall survival (OS) of 9.9 months, with a 16-week PFS rate of 43%, demonstrating encouraging efficacy outcomes. Patt *et al*.'s phase II clinical study (115) did not demonstrate a significant survival benefit among HCC patients receiving combination therapy of oxaliplatin, gemcitabine, and erlotinib. Recent results from a multicenter phase II clinical trial indicated that the combination of bevacizumab and erlotinib, compared to sorafenib alone, did not affect the OS of patients with advanced HCC, but the combination therapy resulted in a longer median event-free survival and demonstrated superior safety and tolerability profiles (116).

Rodent models of chronic liver disease and human cirrhosis exhibit similar liver fibrosis/cirrhosis-associated molecular pathway patterns. Consistent with the findings of studies of humans, Fuchs *et al*. (128) evaluated the therapeutic effects of erlotinib in various animal liver injury models and reported that erlotinib effectively inhibits EGFR signaling and prevents the development of HCC. Another animal model study revealed that gefitinib reduces the formation of HCC tumor nodules, effectively inhibiting the progression of HCC (129).

Cetuximab is an EGFR-targeting monoclonal antibody that was first approved by the United States FDA in 2004 for the treatment of advanced colorectal cancer. Common side effects include skin reactions, fatigue, diarrhea, and hypomagnesemia (130). A phase II clinical trial targeting advanced HCC patients demonstrated that while cetuximab exhibited good safety and tolerability, it showed no significant anti-tumor activity against HCC (117). Subsequently, Asnacios *et al*. (118) conducted a phase II clinical trial for advanced HCC using a combination of gemcitabine and oxaliplatin with cetuximab. The results indicated a disease control rate of 20%, with 40% of patients achieving disease stabilization, demonstrating some therapeutic efficacy and good tolerability. A recent phase Ib clinical trial of regorafenib in combination with cetuximab for the treatment of advanced, refractory solid tumors, including HCC, showed that patients treated with regorafenib and a standard dose of cetuximab had good tolerance and a low incidence of adverse toxic reactions, and thus the therapy was efficacious (119).

Targeting ErbB2/3/4 for HCC treatment

Compared to other cancer types, HCC typically exhibits

lower levels of HER2 expression, resulting in less research on HER2 inhibitors in HCC. Trastuzumab, a humanized monoclonal antibody, targets the HER2 receptor by binding to its extracellular subdomain IV. This interaction inhibits signal transduction and promotes antibody-dependent cellular cytotoxicity, among other mechanisms, effectively combating tumor growth (131). Currently, it is primarily used in the treatment of patients with HER2-positive breast cancer and gastric cancer (132,133).

A study conducted *in vitro* revealed that trastuzumab alone has certain anti-tumor effects on liver cancer cell lines (134). Sharafutdinova *et al.* (135) developed an HER2/neu-expressing mouse liver cancer model and showed that trastuzumab treatment significantly curtails tumor growth, underscoring its potential therapeutic efficacy. Shi *et al.* (60) demonstrated that the use of trastuzumab in a rat model for HCC treatment can reduce tumor size and inhibit tumor metastasis. *in vitro* analyses showed that high concentrations of trastuzumab inhibit cell proliferation. In contrast to the aforementioned findings, Hsu *et al.* (136) reported that trastuzumab did not have significant anti-tumor effects on liver cancer cell lines. Currently, there are no clinical trials evaluating the use of trastuzumab for the treatment of HCC, an area that remains to be explored.

Lapatinib, a dual small-molecule TKI targeting EGFR and HER2 developed by GlaxoSmithKline, has been approved by the FDA for the treatment of HER2-positive advanced or metastatic breast cancer following chemotherapy or trastuzumab failure (137). An *in vitro* study has shown that lapatinib induces autophagic cell death in human liver cancer cells, demonstrating its ability to inhibit HCC proliferation and metastasis (138). However, in phase II clinical trials, lapatinib did not show significant efficacy in treating patients with HCC (120,121).

Afatinib, a second-generation irreversible inhibitor targeting the ErbB family, including EGFR, HER2, and HER4, was approved by the FDA and European Medicine Agency in 2013 for treating advanced EGFR mutation-positive NSCLC in adults (139). A pre-clinical study has confirmed that afatinib exerts a significant inhibitory effect on liver cancer cells, leading to the notable suppression of their proliferation, invasion, and migration (140). Specifically, Chen *et al.* (141) showed that afatinib reduces the activity of the ERK signaling pathway in liver cancer cell lines and decreases the expression levels of VEGF and matrix metalloproteinase 9, leading to reduced viability, migration, and invasion of liver cancer cells, thereby inhibiting tumor development. This finding underscores the potential of afatinib as a promising candidate for the treatment of liver cancer.

Canertinib is a panTKI that simultaneously suppresses the activity of HER1 (EGFR), HER2, and HER4. Similar to lapatinib, it achieves favorable therapeutic outcomes in HCC cell lines characterized by mutation signature cluster 1 expression (142). Concurrent research has shown that canertinib inhibits the growth of xenograft tumors in MAN2A1-FER cells and prevents their metastasis in mice (143).

Neratinib is an oral irreversible inhibitor of ErbB1/2/4 that was approved by the FDA in 2017 as an adjuvant treatment for HER2-positive breast cancer (144). Notably, 11% of HCC patients have the HER2 H878Y mutation (145). Hu *et al.* (146) reported that neratinib exhibits compelling sensitivity to this mutation, suggesting that these patients may be a potential beneficiary group.

Based on studies conducted on various HCC cell lines, Lee *et al.* (147) discovered that pelitinib, an EGFR small-molecule TKI, induces Twist1 by inhibiting the MAPK and Akt signaling pathways, thereby suppressing the EMT activity of HCC cells and consequently inhibiting the migration and invasion of Huh7 cells. Additionally, the novel EGFR-TKI EKB-569 significantly blocks the cell cycle of HCC cells, exhibiting greater efficacy than first-generation reversible EGFR-TKIs (148). AST1306 is an orally active, irreversible small-molecule inhibitor that targets the EGFR, HER2, and HER4 signaling pathways. A phase I trial investigating AST1306 demonstrated that the oral administration of AST1306 was safe and well tolerated, and AST1306 exhibited preliminary anti-tumor activity (149).

Overall, HCC is a highly heterogeneous tumor, the occurrence of which can be triggered by a variety of factors, including viral infections (e.g., HBV and HCV), alcohol consumption, metabolism, and other genetic and environmental factors. As a result, the functions of pathways, such as the ErbB pathway, may vary among different tumors or subgroups, leading to variations in the efficacy of these drugs. As we gain a deeper understanding of the role of the ErbB pathway in the pathogenesis of HCC, an increasing number of localized and systemic targeted drugs may emerge, bringing new hope to patients with HCC. Beyond the drugs mentioned, many targeted therapies against the ErbB pathway, such as tucatinib and dacomitinib, have yet to be explored in pre-clinical trials for HCC. The advent of novel targeted therapies holds tremendous therapeutic potential for HCC, necessitating ongoing research and exploration to develop more effective

and safer treatment methods. This is crucial for improving the therapeutic landscape for HCC and enhancing patient outcomes.

ErbB-driven resistance and related targeted therapies

Targeted therapies, which address pathways, such as tumor angiogenesis, tumor cell proliferation, and the TME, are a crucial treatment modality for advanced HCC, and effectively mitigate disease progression and improve patient prognosis. However, over time, some patients develop reduced efficacy and treatment insensitivity, posing a significant challenge of acquired resistance in targeted therapy. Investigating resistance mechanisms and seeking novel therapeutic approaches or strategies to overcome drug resistance are critical issues that targeted therapies need to address. Primary and acquired resistance in HCC is a complex phenomenon involving various factors, such as signaling pathways, hypoxia, cellular autophagy, EMT, and the TME (150).

Hypoxia is a common phenomenon in the TME that significantly affects the biological behavior and metabolism of cancer cells by activating hypoxia-inducible factors (HIFs), particularly HIF-1α, to promote metabolic reprogramming, thus enhancing multidrug resistance in tumors (151). In HCC, hypoxia-mediated pleomorphic adenoma gene-like 2 and HIF-1/2α signaling pathways increase resistance to erlotinib, and 2-methoxyestradiol (2ME2) restores the efficacy of erlotinib by disrupting this signaling pathway (152). An experiment investigating the efficacy of erlotinib and sorafenib in treating HCC organoids and cell lines revealed that erlotinib induces VEGF production in liver cancer cells, leading to drug resistance (153). The overexpression of C-X-C chemokine receptor 4 (CXCR4) has been found to be associated with resistance to gefitinib in HCC. CXCR4 promotes gefitinib resistance in HCC through the caveolin-1 signaling pathway and c-Met signaling pathway (154). The treatment of HCC cells with gefitinib may induce cancer stem cell resistance through the increased nuclear translocation of insulin-like growth factor 1 receptor and the upregulation of Cluster of Differentiation 133 (CD133) expression (155).

Autophagy is an essential intracellular process of self-digestion that degrades and recycles damaged organelles, protein aggregates, and other cellular components through the lysosomal pathway to maintain cellular stability and meet the demands of biosynthesis (156). Autophagy plays dual roles in tumor initiation and progression, acting as a tumor-suppressive mechanism in the early stages but aiding tumor cells in adapting to stress and promoting their survival and growth once a tumor forms (157). Tumor cells enhance autophagy to counteract the cytotoxicity induced by chemotherapy, radiotherapy, or targeted therapy, thereby reducing the effectiveness of drugs. Autophagy is a significant factor in resistance to EGFR-targeted therapy in HCC. Li *et al.* (158) demonstrated that the upregulation of p57 activates the PI3K/AKT/mTOR signaling pathway, thereby attenuating the protective effects of autophagy and promoting the response of HCC cell lines to erlotinib or cetuximab.

EMT not only plays a critical role in the metastatic process of cancer but also contributes to the development of resistance to various anti-tumor treatments, leading to a loss of sensitivity. KIAA1199 is an intracellular protein that is overexpressed in a variety of tumor types. Xu *et al.* (159) reported that KIAA1199 enhances the transmission of EGF signals, accelerates the activation of EMT-related transcription factors, directly affects the loss of cell adhesion and cell polarity, and promotes the transition of epithelial cells to mesenchymal cells. This not only enhances the migration and invasion capabilities of liver cancer cells but also exacerbates cell resistance to targeted therapeutic drugs. EMT has been reported to induce resistance to erlotinib and gefitinib in various types of tumors (160,161). Fuchs *et al.* (162) analyzed the sensitivity of 12 human liver cancer cell lines to erlotinib, gefitinib, and cetuximab by categorizing them into epithelial and mesenchymal types, and found that drug sensitivity was greater in epithelial cell lines. Additionally, reducing integrin-linked kinase activity and AKT activation in mesenchymal cell lines increases the sensitivity to EGFR inhibitors. Another study revealed that the ECM molecule laminin-5 counteracts the continuous dephosphorylation of AKT induced by gefitinib (restoring p-AKT), thereby reducing the sensitivity of HCC to gefitinib (163).

The mutation of EGFR T790M plays a critical role in the rapid onset of resistance to EGFR-TKIs among patients (164). Third-generation EGFR-TKIs, such as osimertinib, initially proved effective in treating these mutated tumors, but resistance emerged shortly thereafter, possibly due to the cis-p.Cys797Ser (C797S) mutation, inactivation of Retinoblastoma 1, and transformation of tumor tissue (165). EGFR C797S mutations, located in the kinase-binding site, also lead to resistance to third-generation irreversible EGFR inhibitors (166). EGFR, HER2, and MET amplification not only affects the initial

response to treatment but also plays a role in tumor evasion by targeted therapies, affecting sensitivity and resistance to EGFR-TKIs while driving tumor growth and survival (167,168).

The heterogeneity of tumors, the plasticity of HCC tumor cells, and escape mechanisms pose additional challenges for HCC-targeted therapy. The ErbB signaling pathway also mediates resistance to other targeted drugs. Currently, drugs such as sorafenib and lenvatinib are approved as first-line treatments for patients with unresectable advanced HCC (169). EGFR plays a pivotal role in mediating sorafenib resistance by activating downstream signaling pathways, such as the RAF/MEK/ERK and PI3K/AKT pathways (170). Kruppel-like factor 4 (KLF4) is a zinc-finger transcription factor involved in cell growth, differentiation, and cell cycle regulation (171). Pang *et al*. (172) reported a positive feedback loop between EGFR and KLF4, where nuclear EGFR induces KLF4 transcription by binding to its promoter, and vice versa. Additionally, EGFR may promote KLF4 expression by activating the RAF/MEK/ERK signaling pathway, thus contributing to sorafenib resistance in HCC. Research has revealed that lenvatinib achieves an overall response rate of approximately 24% in patients with HCC, with inevitable resistance to subsequent treatments affecting patient prognosis (173). A recent study suggests that the activation of EGFR may contribute to lenvatinib resistance (174). Further, clinical trials have demonstrated that combining lenvatinib with gefitinib significantly improves clinical outcomes (175). EGFR is significantly expressed in lenvatinib-resistant HCC cell lines, and Miyazaki *et al*. (176) discovered through whole-genome transcriptome analysis that the EGFR-PI3K-AKT pathway is overly activated. By inhibiting this pathway, resistance to lenvatinib can be overcome (176).

In summary, the abnormal activation of the ErbB family signaling pathway plays a crucial role in the occurrence and development of cancer. Targeting these specific molecules can effectively block their aberrant signal transduction, inhibiting tumor cell proliferation and survival. Moreover, targeting molecules or pathways relevant to cancer can reduce side effects, improving patient tolerance. The abnormal activation of the ErbB signaling pathway also affects the function of immune cells in the tumor microenvironment. Inhibiting ErbB signaling can improve the infiltration and function of immune cells, disrupt tumor cell immune escape mechanisms, restore the immune system's ability to recognize and kill tumors, and enhance anti-tumor immune responses. Therefore, these molecules are promising targets for anti-cancer drugs. The continuous development of novel inhibitors and antibody drugs targeting the ErbB signaling pathway in the future will provide new hope for patients.

To date, the exploration and understanding of resistance mechanisms, particularly those concerning the ErbB pathway, in targeted therapies for liver cancer are still in their early stages. Therefore, more reliable clinical model studies are needed to deepen our understanding of HCC oncology, reduce the occurrence of drug treatment resistance, and benefit more patients with advanced liver cancer.

Advances in and prospects of ErbB combinational therapies

In clinical practice, the combined application of pharmacological treatments or their combination with interventional therapies has demonstrated significant benefits in prolonging patient survival and enhancing quality of life. This not only brings hope to patients but also gradually shifts the traditional treatment paradigms for HCC. With the rise and evolution of precision medicine, the implementation of combined treatment strategies, particularly among patients with advanced HCC, has shown greater therapeutic effects compared to single treatment modalities.

ErbB family inhibitors combined with other therapies have shown significant therapeutic potential in most cancers, including breast cancer, and head and neck cancer (177,178). Based on the results of the CLEOPATRA phase III clinical trial, the combination of pertuzumab and trastuzumab with chemotherapy has been established as the standard first-line treatment for HER2-positive breast cancer, achieving significant success (179). Breast cancer research has shown that the combination of lapatinib and paclitaxel slows the occurrence of brain metastasis compared to the combination of trastuzumab and paclitaxel as a first-line treatment (180). The combination of cetuximab and radiotherapy is an effective treatment regimen for patients with locally advanced head and neck cancer, significantly improving their survival rates (181). Additionally, studies conducted both *in vitro* and *in vivo* have shown that both cetuximab and radiation therapy synergistically reduce cell proliferation and induce apoptosis (182,183).

Multiple studies have shown the potential of applying anti-ErbB-targeted drugs in combination with other

therapeutic strategies for HCC treatment. miR-34a is a microRNA that inhibits tumor growth. Erlotinib and miR-34a exhibit strong synergistic effects on HCC cell models, significantly inhibiting tumor cell growth compared to monotherapy (184). As mentioned earlier, a previous study has shown that the combination of erlotinib with doxorubicin, docetaxel, or SN-38 exhibits significant synergistic anti-tumor effects on HCC cell lines (Huh-7 and HepG2) (185). Current phase II and III clinical trials have investigated the use of erlotinib in combination with bevacizumab or docetaxel. However, due to various factors, such as sample size, the clinical efficacy of these treatments remains controversial. Recent research has revealed that the combined use of erlotinib and 2ME2 has synergistic effects on combating liver cancer, inducing apoptosis in hypoxic liver cancer cells and inhibiting their stem cell characteristics (152). Yu *et al*. (140) reported that the combination of afatinib and an anti-programmed death-1 (PD1) agent inhibits the ErbB2 signaling pathway and indirectly activates the STAT3 pathway, leading to the upregulation of programmed death ligand-1 (PD-L1) expression. This process not only suppresses the direct growth and spread of tumor cells but also modulates the immune microenvironment, enhancing immunotherapy efficacy in liver cancer. The use of natural remedies in adjunctive cancer therapy is also receiving increasing attention. Ethoxy-erianin phosphate (EBTP) is a low-toxicity, antiangiogenic compound derived from the structural modification of the natural product erianin. When combined with afatinib, EBTP effectively targets the VEGF and EGFR signaling pathways, inhibiting the proliferation, motility, and angiogenesis of liver cancer cells and tumor vasculature (186).

Challenges and future directions

In this article, we discussed ErbB signaling, particularly that involving the EGFR family, which plays a significant role in the development and progression of HCC. One of the major challenges in targeting ErbB signaling in HCC is the inherent tumor heterogeneity. HCC tumors exhibit diverse molecular profiles, including variations in ErbB receptor expression levels and downstream signaling pathways. This heterogeneity complicates the development of targeted therapies and necessitates personalized treatment approaches. In addition, resistance to EGFR-targeted therapies is another significant challenge in HCC treatment. Tumor cells can develop various mechanisms to evade EGFR inhibition, such as the upregulation of alternative signaling pathways, mutations in downstream effectors, or activation of compensatory feedback loops. Overcoming these resistance mechanisms requires a deeper understanding of the molecular drivers of HCC progression and the development of combination therapies that target multiple signaling pathways simultaneously.

Conclusions

In conclusion, in the era of precision medicine, exploration into tumor treatment has entered a new age, particularly in the treatment of malignant tumors, where ErbB-targeted therapy has demonstrated tremendous potential and prospects. Despite numerous challenges, including the singularity of treatment strategies, suboptimal clinical efficacy, and controversies in treatment, advancements in technology and in-depth research on targeted therapy and immunotherapy hold promise for the continuous improvement of treatment strategies through the ongoing discovery and validation of new therapeutic approaches and targets. In the future, we believe that through in-depth research and the application of ErbB-targeted therapy, broader avenues will be opened for the treatment of HCC and other tumors, leading to more personalized and precise treatment approaches.

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