Genes & Diseases (2025) 12, 101354

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REVIEW ARTICLE

HER3: Unmasking a twist in the tale of a previously unsuccessful therapeutic pursuit targeting a key cancer survival pathway

Omkar Desai [a,b,c,1], Moeez Rathore [a,b,1], Christina S. Boutros [a,b,c], Michel'le Wright [a,b], Elizabeth Bryson [a,b], Kimberly Curry [a,b], Rui Wang [a,b,c,*]

[a] Department of Surgery, Case Western Reserve University, Cleveland, OH 44106, USA
[b] Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH 44106, USA
[c] Department of Surgery, Division of Surgical Oncology, University Hospitals Cleveland Medical Center, Cleveland, OH 44106, USA

Received 18 March 2024; received in revised form 29 April 2024; accepted 30 April 2024
Available online 17 June 2024

KEYWORDS
Cancer;
ErbB3;
HER3;
Neuregulin;
Tumor microenvironment

Abstract HER3, formally referred to as ERB-B2 receptor tyrosine kinase 3, is a member of the ErbB receptor tyrosine kinases (also known as EGFR) family. HER3 plays a significant pro-cancer role in various types of cancer due to its overexpression and abnormal activation, which initiates downstream signaling pathways crucial in cancer cell survival and progression. As a result, numerous monoclonal antibodies have been developed to block HER3 activation and subsequent signaling pathways. While pre-clinical investigations have effectively showcased significant anti-cancer effects of HER3-targeted therapies, these therapies have had little impact on cancer patient outcomes in the clinic, except for patients with rare *NRG1* fusion mutations. This review offers a comprehensive description of the oncogenic functions of HER3, encompassing its structure and mediating signaling pathways. More importantly, it provides an in-depth exploration of past and ongoing clinical trials investigating HER3-targeted therapies for distinct types of cancer and discusses the tumor microenvironment and other critical determinants that may contribute to the observed suboptimal outcomes in most clinical studies using HER3-targeted therapies. Lastly, we suggest alternative approaches and the exploration of novel strategies to potentially improve the efficacy of targeting the pivotal oncogenic HER3 signaling pathway in future translational investigations.

* Corresponding author. Department of Surgery, Case Western Reserve University, 10900 Euclid Ave., Cleveland, OH 44106-7284, USA.
E-mail address: rxw517@case.edu (R. Wang).
Peer review under responsibility of Chongqing Medical University.
[1] These authors contributed equally to this work and shared the first authorship.

https://doi.org/10.1016/j.gendis.2024.101354

Introduction

The ErbB family of receptors (also known as human epidermal growth factor receptor family) is one of the most extensively studied receptor tyrosine kinase (RTK) families. It consists of four distinctive receptors: i) epidermal growth factor receptor (EGFR, also known as HER1/ErbB1), ii) ERB-B2 receptor tyrosine kinase 2 (ErbB2, also known as HER2), iii) ERB-B2 receptor tyrosine kinase 3 (ErbB3, also known as HER3), and iv) ERB-B2 receptor tyrosine kinase 4 (ErbB4, also known as HER4).[1] ErbB family receptors are structurally akin, being single-chain modular glycoproteins featuring an extracellular ligand-binding domain, a singular transmembrane domain, a juxta-membrane domain, and an intracellular tyrosine kinase domain followed by C-terminal regulatory regions (Fig. 1A).[2] ErbB receptors are expressed in both mesenchymal and epithelial cells and are activated by receptor-specific soluble ligands, following which they undergo a conformational change, inducing homodimerization or heterodimerization (mainly at the juxta-membrane domain regions),[3] leading to the activation of downstream signaling intracellularly. Importantly, HER2 lacks a receptor domain while displaying robust tyrosine kinase activity, and in contrast, HER3 encompasses a ligand-binding domain but the kinase domain has weak activity and is often considered as "kinase-dead".[4] Consequently, these two receptors often do not operate independently and demonstrate receptor cooperativity, wherein "kinase-dead" HER3 and HER2 often heterodimerize with each other or other ErbB receptors, and occasionally with other RTKs, to mediate downstream signaling.[5] The binding of ligands to EGFR or HER4 induces dimerization either with itself to form homodimers, or with other ErbB receptors to form heterodimers (Fig. 1B).[6] EGFR exhibits binding affinity towards a minimum of seven ligands, including epidermal growth factor (EGF), transforming growth factor-alpha (TGFα), heparin-binding EGF-like growth factor, amphiregulin, epiregulin, betacellulin, and epigen, whereas HER3 and HER4 are activated by neuregulin 1/2 (NRG1/2) and neuregulin 3/4 (NRG3/4), respectively.[7,8] In contrast, HER2 lacks identified ligands and remains persistently in an open conformation with an exposed dimerization loop, necessitating a ligand-bound heterodimerization partner for signaling to occur.[2]

The ErbB family downstream signaling pathways are strongly associated with cell proliferation, survival, and cancer development.[1,9] Mutation or up-regulation of EGFR and HER2 are associated with the development of many types of malignancies and have been reviewed extensively by others.[10] The crosstalk between the ErbB family of receptors which enhance and diversify downstream signal transduction is becoming a major survival mechanism of cancer cells, and contexts such as the tumor microenvironment are critical for the activation of HER3 and other ErbB family receptors. This review will focus on discussing the pro-cancer role of HER3. HER3 overexpression has been observed in various types of solid tumors, including breast cancer,[11] cervical cancer,[12] colorectal cancer (CRC),[13] gastric cancer,[14] melanoma,[15] non-small cell lung cancer (NSCLC),[16] ovarian cancer,[17] and pancreatic cancer.[18] In this review, we will discuss key aspects of HER3 signaling, including the structure of HER3 and the involved downstream signaling axis, HER3 gene mutations, and more importantly, focus on reviewing pro-cancer roles of HER3 in various cancer types and associated pre-clinical and clinical studies. We will also discuss recent developments in HER3-

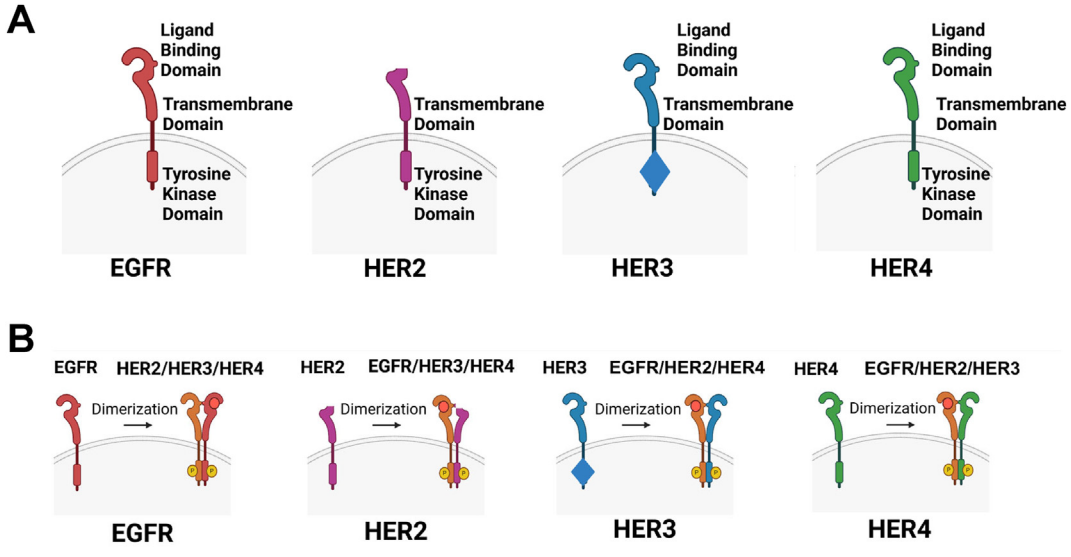

Figure 1 Schematic illustration of ErbB receptor structures and dimerization patterns. ErbB, ERB-B2 receptor tyrosine kinase.

directed therapies and the new roles of HER3 in tumor microenvironment-mediated signaling pathways. Lastly, we will provide our take on the future directions of developing novel HER3-targeted therapies.

Structure of HER3

HER3 was first discovered in 1989 by Kraus et al, with the human encoding gene *ERBB3* being identified on chromosome 12q13.[19] As mentioned earlier, HER3 consists of a large extracellular ligand-binding ectodomain, a transmembrane domain, and a short juxta membrane segment, followed by an intracellular tyrosine kinase domain and a tyrosine-containing carboxy-terminal tail (Fig. 2A).[1,20] The ectodomain is further divided into four sub-domains (I—IV), comprising two cysteine-rich regions (II and IV) and two flanking domains (I and III).[21] In the absence of a ligand, HER3 remains inactive due to the binding between subdomains II and IV.[22] Upon ligand binding at the binding pocket in domains I and IV,[21,22] the inactive conformation is altered to expose these domains for subsequent activation.[21] Distinct from other RTKs, HER3 is considered a "kinase-dead" receptor with 1000-fold weaker kinase activity than fully activated EGFR.[1,23,24] As a result, HER3 predominantly heterodimerizes with EGFR and HER2, and to a lesser extent with HER4,[1] which have significant kinase activity upon activation. However, it is worth noting that Wang and colleagues have reported that K742 in HER3 has weak but detectable pseudokinase activity and leads to auto-phosphorylation activation without other receptors.[23,25,26]

HER3 signaling pathways

Currently, three HER3 ligands have been identified: neuregulin 1/1b (NRG1/1b, also known as heregulins) and neuregulin 2 (NRG2).[27] NRG-activated HER3 leads to activations of two downstream signaling pathways: the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3K) pathways (Fig. 2B).[28] Signaling through the MAPK pathway begins with the activation of RAS by an RTK (in this case HER3), leading to the phosphorylation and activation of RAF, MEK, and MAPK in turn. MAPK regulates the activities of transcription factors including AP-1 (activator protein 1), NF-κB (nuclear factor-kappa B), and p53, all of which play critical roles in regulating cellular functions including proliferation, differentiation, apoptosis, and stress response.[29] Constitutively activating mutations in *RAS* genes are commonly found in cancer. These mutations lead to the activation of the MAPK cascade signaling independently of HER3 and other RTKs, promoting cancer development and progression.[30] However, a recent study reported that HER3 inhibition attenuates cell and tumor growth in both *RAS* wild-type and mutant CRC,[31] suggesting HER3-targeted therapies may be used for treating patients with *RAS*-mutant CRC who could not receive EGFR-targeted therapies.

For activating the PI3K pathway, the C-terminal intracellular domain of HER3 has six consensus phosphor-tyrosine sites that bind to the regulatory p85 subunit of PI3K.[32] This interaction leads to the phosphorylation of membrane phosphoinositides, which leads to the recruitment and activation of Akt (protein kinase B) and PDK1 (pyruvate dehydrogenase kinase 1).[19] Akt regulates a variety of protein functions that are involved in cell survival, apoptosis, cell cycle progression, and cell migration, all of which contribute to cancer development and progression.[33] Together, HER3 is a key upstream effector of MAPK and PI3K signaling cascades that are involved in cancer cell growth and survival. Therefore, many HER3-targeted therapies aim to inhibit receptor activation to attenuate these pro-cancer signaling cascades to block cancer cell growth and survival.[19]

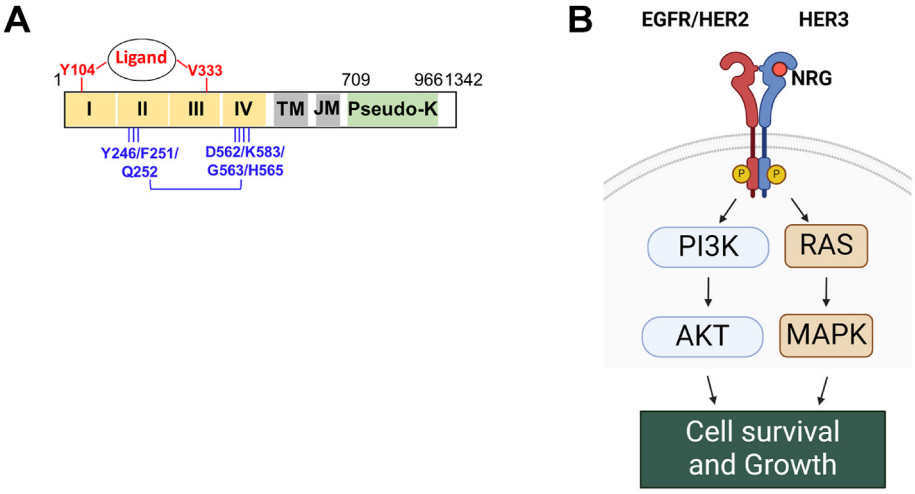

Figure 2 Schematics of HER3 structure and downstream signaling. **(A)** Full-length HER3 (amino acid residues 1—1342) with four receptor domains (I—IV, yellow), a transmembrane and a short juxta membrane domain (TM and JM, respectively, gray), and a pseudo kinase domain (Pseudo-K, green). Y104 and V333 are for ligand binding (red). Numbers indicate amino acid positions. **(B)** Upon ligand binding with NRG, HER3 dimerizes with either EGFR or HER2, activating downstream MAPK and PI3K signaling pathways. HER2/3, human epidermal growth factor receptor 2/3; NRG, neuregulin; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase.

Mutations

Prior studies by Jaiswal et al found that HER3 mutations were found in approximately 12% of gastric, 11% of colon, 4% of breast, 1% of NSCLC, and other types of cancer, primarily occurring in the extracellular domain[34] (summarized in Table 1). For example, HER3 mutations such as V104M, P262H, or G284R, promoted pro-tumor phenotypes including migration and anchorage-independent growth in colonic or breast non-neoplastic epithelial cell lines.[34–36] Additional studies showed that these mutations activated downstream signaling pathways, particularly Akt, which led to cell growth and survival.[37,38] Jaiswal and team also investigated the oncogenic properties of these mutations by screening cohorts with different tumor types for synonymous mutations of HER3.[34] Many of the mutations were in regions that were conserved among HER3 orthologs, suggesting functional relevance. Moreover, HER3 mutations were also found to be ligand-independent and promote tumor growth. The T355 to isoleucine (T355I) mutation was particularly noteworthy, as it was associated with increased levels of HER3 and ERK1/2 phosphorylation and downstream cyclin D1 activation in estrogen receptor-positive and HER2-overexpressing breast cancer.[28,39,40] Other mutations such as tyrosine kinase domain (TKD) mutations were also found to have high oncogenicity.[34] Collier et al found that the E909G TKD mutation increased HER2/HER3 heterodimer kinase activity *in vitro* with purified proteins. On the other hand, no frameshift, nonsense, or intronic HER3 mutations were reported in cancer-related studies.[40]

Role of HER3 in distinct cancer types and related clinical studies

Breast cancer

Breast cancer affects one in eight women across the United States and is associated with high mortality, metastasis, and relapse. It often exhibits overexpression of estrogen, progesterone, or HER2 receptors. Among these, triple-negative breast cancer stands out as the most aggressive phenotype, characterized by the absence of receptor expression.[53] Breast cancer is a heterogeneous disease, with distinct receptor expression profiles in different patients.[54] The overexpression of ErbB family receptors, specifically HER3, is a strong indicator of worse patient overall clinical outcomes, including metastasis, tumor growth, and recurrence.[55–57] HER3 activation promotes cell growth and survival of HER2-positive tumors and usually leads to resistance to HER2-targeted therapy in patients with breast cancer.[55,58–60] High expression of HER3 has been shown to cause resistance to tamoxifen and trastuzumab therapies in HER2 overexpressing breast cancer cells.[61] To tackle this issue, therapeutic approaches targeting HER3 have been created. These approaches involve the use of monoclonal antibodies (mAbs) to inhibit the HER3 receptor, leading to its internalization and subsequent degradation.[28,61] Numerous clinical trials have been undertaken to assess the effectiveness of HER3-targeted therapies in the management of patients with breast cancer, and these investigations are discussed herein.

Table 1 HER3 and NRG1 gene alterations in distinct types of cancer.

Cancer type	*HER3* amplification	*HER3* mutations	*NRG1* fusions	Reference
Breast	Yes	E928G, V104L, G284R, T355I, T389K, M91I, D297Y/A/H/N/V, S846I, E1261A	*ADAM9*, *COX10-AS*, *AKAP13*	34,40,41–43
Non-small cell lung cancer	Yes	E928G, A232V, V714M, E332K/Q, D297Y/A/H/N/V, S846I	*CD74*, *SDC4*, *SLC3A2*, *TNC*, *MDK*, *DIP2B*, *RBPMS*, *MRPL13*, *ROCK1*, *DPYSL2*, *PARP8*	34,40,41,43–46
Colorectal cancer	Yes	V104L/M, P262H/S, G284R, A232V/T, G325R, D297Y, S846I, E928G/K/Q, M60K, V295A, T355A/I, M60R, R103G/H, N126K, R475W	*POMK*	34,40,41,43,45
Pancreatic cancer	Unknown	Unknown	*ATP1B1*, *APP*, *CDH1*, *VTCN1*	43,45
Gynecologic cancer (ovarian)	Yes	L536L, V104M, V438I, D1149E	*SETD4*, *TSHZ2*, *ZYMYM2*, *RAB3IL1*	43,45,47
Head and neck cancer	Unknown	M91I	*THBS1*, *PDE7A*	45,48
Prostate cancer	Unknown	Unknown	*STMN2*	49
Gastric cancer	Yes	A232V, E928G, P262H/S, T389K, V104L, 1218delE, A172P, D297Y, V654G, K926R, L930W, Q809R, H228R, G284R, D297Y/A/H/N/V, T355I/P, R426W, S846I	Unknown	34,40,50–52

Note: HER3, human epidermal growth factor receptor 3; NRG1, neuregulin 1.

Trastuzumab is currently the standard of care for treating patients with HER2-positive breast cancer. However, as discussed earlier, HER3 overexpression and ligand-dependent HER2-HER3 interactions can lead to treatment resistance and evasion of drug-induced apoptosis.[61] To address this, a humanized HER3-specific mAb, patritumab (U3-1287), was developed, which inhibits ligand binding and triggers receptor internalization for degradation.[62] Patritumab blocked cancer cell growth *in vitro* and re-sensitized tumors to trastuzumab therapy in HER2-positive breast cancer in pre-clinical models.[61,63] However, findings from a phase Ib/II clinical trial evaluating the combination of patritumab with trastuzumab and paclitaxel in patients with HER2-positive metastatic breast cancer showed no improvement compared with standard-of-care therapy (NCT01512199). Alternatively, an antibody drug conjugate (ADC) version of patritumab with a cytotoxic payload, U3-1402 (also known as HER3-Dxd), is being assessed in combination with DS-1062 (anti-TROP2 mAb) for treating patients with HER3-positive metastatic breast cancer (NCT04699630). Additional discoveries in the anti-cancer effects of this HER3-targeted ADC will be elaborated upon later in this review.

Meanwhile, multiple other HER3-targeting mAbs were developed and assessed in clinical studies for treating patients with breast cancer. Seribantumab (previously known as MM-121) was developed to block the ligand neuregulin and HER3 binding (NRG-HER3) and was developed as a full-length IgG2 mAb to avoid toxicities in non-cancerous tissues. It exhibited anti-proliferative effects *in vitro* and *in vivo* in cells expressing HER2 and HER3.[64,65] However, a phase II clinical trial (NCT01151046) used the combination of seribantumab with exemestane (endocrine therapy) in patients with HER2-negative metastatic breast cancer showed negligible effect on progression-free survival (PFS). Interestingly, a subset of patients in the trial with high levels of NRGs in tumor tissues had increased PFS, suggesting HER3-targeted therapies can be effective when the targeted pathway is highly active.[65] The effects of seribantumab and other specific antibodies in patients with high levels of NRG-induced HER3 activation will be further discussed in subsequent sections. Elgemtumab (LJM716) is another HER3-specific mAb which blocks phosphorylation of HER3/Akt. Investigated in patients with HER2-positive metastatic breast cancer, its efficacy was limited when co-administered with BYL719, a PI3K inhibitor (NCT02167854). However, favorable outcomes were observed when combined with trastuzumab.[66]

In contrast to the aforementioned mAbs, bispecific antibodies simultaneously targeting HER3 and a different ErbB receptor have also been developed. MM-111 is a novel HER2/HER3 bispecific antibody that has demonstrated a good safety profile in a phase I study but had little additional benefit when combined with standard-of-care chemotherapy in treating patients with advanced HER2-positive breast cancer (NCT01304784).[67,68] Zenocutuzumab (MCLA-128) is another HER2/HER3 bispecific antibody that has been used in combination with trastuzumab in patients with HER2-positive breast cancer and in combination with endocrine treatment in patients with ER-positive/low HER2-expressing breast cancer (NCT03321981). Although these treatments were well tolerated, their effects on outcomes of patients with breast cancer remain limited or unclear. Sapitinib (AZD8931), an EGFR/HER2/HER3 inhibitor, was employed in conjunction with endocrine therapy to address endocrine resistance in patients with hormone-sensitive advanced breast cancer.[69] Nonetheless, it did not augment endocrine responsiveness and was associated with greater toxicity. It is worth mentioning that other than the recent trial using HER3-ADC (NCT04699630), most prior clinical studies in breast and other types of cancer did not evaluate HER3 expression before recruiting participants, potentially leading to unfavorable effects on the study outcomes. This limitation observed in most clinical studies concerning HER3-targeted therapy will be further discussed in this review article.

Non-small cell lung cancer

Lung cancer is the leading cause of cancer-related death worldwide, with NSCLC accounting for 82% of all cases.[70] Although HER3 expression has only been found in 30%—40% of NSCLC tumors,[44,71,72] it is considered a key mediator of the development of resistance to EGFR-targeted therapies with tyrosine kinase inhibitors (TKIs), partially via activation of the PI3K/Akt pathway.[44,72,73] Consequently, HER3-targeted mAbs, such as patritumab, seribantumab, and lumretuzumab have been assessed for treating patients with NSCLC.

Patritumab blocked lung cancer cell growth *in vitro* and *in vivo*, and in a phase II clinical trial, combining the HER3 antibody patritumab with a pan-HER inhibitor erlotinib led to increased PFS in patients with advanced NSCLC with high NRG expression (NCT01211483).[74—76] In a separate phase I study, the use of patritumab and erlotinib combination in patients with NSCLC also led to stable disease as the best response without dose-limiting toxicities.[77] However, as this line of investigation continued in a phase III clinical trial (NCT02134015), the study was prematurely terminated as it failed to reach the pre-defined criteria. Similar to patritumab, seribantumab has exhibited robust anti-cancer efficacy in pre-clinical studies of NSCLC.[78] Furthermore, the recent CRESTONE trial (NCT04383210) showcased an objective response rate (ORR) of 36% in patients with NSCLC. However, a phase II study evaluating seribantumab in combination with docetaxel was terminated due to the lack of significant improvement in PFS (NCT02387216). In contrast, another phase II trial revealed a potential benefit when employing seribantumab in conjunction with erlotinib. This observation was based on a prespecified retrospective subgroup analysis of patients whose tumors exhibited high levels of NRG expression.[78] This underscores that elevated levels of NRG and the consequent activation of HER3 represent a potential predictive biomarker for the responsiveness of patients to HER3-targeted therapy.

In NSCLC, another HER3-targeted mAb, lumretuzumab (RG7116), has also been used and demonstrated significant antibody-dependent cell-mediated cytotoxicity.[79] However, the combination of lumretuzumab with carboplatin and paclitaxel as first-line treatment of patients with NSCLC showed limited effect and most patients discontinued the treatment due to disease progression (NCT02204345).[79] Similarly, combining lumretuzumab with cetuximab (EGFR-specific antibody) had little impact on patients with HER3-

expressing NSCLC (NCT01482377), although the combination blocked NSCLC cell growth in pre-clinical studies.[80] Similar to breast cancer, although HER3-specific antibodies significantly blocked NSCLC cell growth and survival in pre-clinical studies, findings from clinical trials suggest HER3-targeted therapies have limited efficacy in patients, except for patients with NRG-high and HER3-activated phenotypes. While most HER3-targeted clinical trials have been unsuccessful in NSCLC, it is crucial to acknowledge that, like studies for breast cancer, HER3 expression levels in NSCLC tumors were not examined and used for patient recruitment, which is a major pitfall in the study design given that only approximately 30%—40% of patients with NSCLC exhibit HER3 expression.

Colorectal cancer

CRC is the second most common cause of cancer-related death in the United States.[81] HER3 overexpression has been observed in a significant subset of patients with CRC and has been associated with poor prognosis.[82—86] A preclinical study analyzed patient samples and found that 80% of primary CRC tumors and 82% of CRC liver metastases had high levels of HER3 proteins, determined by immunohistochemistry.[85] In another study, immunohistochemistry analysis showed that HER3 expression was detected in 93% of metastatic CRC tumors.[87] These findings suggest that HER3 may be a potential therapeutic target in treating patients with CRC, particularly those with advanced disease. Our laboratory's pre-clinical investigations have shown that the inhibition of HER3 significantly attenuates the survival of CRC cells.[31,88] Several HER3-targeted mAbs, including seribantumab, REGN1400, Av-203, and KTN3379 have been tested either alone or in combination with EGFR-targeted therapies in phase I and phase II trials in patients with CRC, but the outcomes of these trials have shown severe toxicities.[55,89] Meanwhile, in a phase I clinical trial, the use of patritumab resulted in stable disease as the best response with no dose-limiting toxicities.[90] Duligotuzumab, a dual-action antibody targeting HER3/EGFR, was employed in a phase II trial (NCT01652482). However, this trial yielded no PFS or overall survival (OS) advantages.[91] Duligotuzumab has also been tested in combination with cobimetinib (MEK inhibitor) in patients with locally advanced or metastatic CRC-harboring mutant *KRAS* (NCT01986166). Nevertheless, this combination was associated with increased toxicity and limited efficacy in comparison to cobimetinib or duligotuzumab monotherapy. A phase I/II study examined the toxicity and efficacy of the pan-HER inhibitor sapitinib combined with standard-of-care chemotherapy in patients with metastatic CRC (NCT01862003). Although sapitinib showed a low toxicity profile, no improvement was seen in the ORR.[92]

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) presently ranks as the third highest cause of cancer-related death in the United States, and its incidence is projected to increase in the next decade.[93] Most patients with PDAC present with metastasis at the time of diagnosis, and almost all patients eventually develop distant metastasis.[2—4] Unfortunately, treatment options for patients with metastatic PDAC are limited, and the 5-year survival is only 3%.[4] Recent research suggests that NRG secreted by liver endothelial cells can activate the HER3-Akt signaling pathway in metastatic PDAC cells that express HER3. This suggests that HER3-targeted therapies may be effective in treating patients with HER3-positive metastatic PDAC.[5] Pre-clinical studies have demonstrated that HER3-targeted therapies are effective in attenuating tumor growth in PDAC.[6] Based on these findings, numerous clinical trials have been initiated to further evaluate the efficacy of HER3-targeted therapies in PDAC. As mentioned earlier, the CRESTONE phase II clinical trial is currently evaluating the safety and efficacy of seribantumab in patients with advanced solid tumors that have *NRG1* gene fusion mutations (NCT04383210). Preliminary data from the trial suggests that seribantumab has a favorable safety profile and has demonstrated a durable response in patients with *NRG1* gene fusion, including a 33% ORR in patients with PDAC. Another ongoing phase II clinical trial is investigating the efficacy of zenocutuzumab (MCLA-128) in patients with solid tumors harboring an *NRG1* gene fusion (eNRGy) (NCT02912949). Among the patients with pancreatic cancer enrolled in the trial, an objective response was observed in 39% of patients.[94] The data derived from these clinical trials substantiates the efficacy of HER3-targeted therapies in treating patients with PDAC, particularly those exhibiting HER3 expression or *NRG1* gene fusion. More information regarding *NRG1* gene fusion in HER3-targeted therapies will be discussed later in this review.

Gynecologic cancer

Gynecologic cancers are a significant health concern for women worldwide, with ovarian cancer ranking as the fifth leading cause of cancer-related death in women, with a 5-year relative survival rate of only 49%.[95] In pre-clinical investigations, overexpression of HER3 is commonly observed in gynecologic cancers.[96,97] Up to 68% of ovarian tumors have been detected with HER3 overexpression (either at protein or mRNA levels), which is correlated with an unfavorable patient prognosis and an increased prevalence of metastasis.[17,47,96,97] Similar to other types of cancer, elevated HER3 expression is linked to the development of acquired resistance to standard-of-care treatment in ovarian cancer.[28,98,99] Additional investigations examined the correlation between HER3 expression and patient survival in cervical cancer and found that HER3 expression was significantly associated with reduced disease-free survival (DFS) and OS.[100] For HER3-targeted therapies, seribantumab has been tested in gynecologic cancers in combination with EGFR-targeted mAb, as well as other chemotherapeutic agents such as gemcitabine, carboplatin, and pemetrexed (NCT01447225, NCT02538627). These studies have largely shown a lack of success.[55,101] Interestingly, within a phase II clinical trial, the addition of seribantumab alongside paclitaxel demonstrated an elevated median PFS in patients diagnosed with platinum-resistant/refractory ovarian cancer exhibiting high NRG levels (NCT01447706).[102] These results again imply that the

assessment of NRG/HER3 expression could serve as a crucial biomarker for identifying individuals with gynecologic cancers who may derive benefits from HER3-targeted therapies.

Head and neck cancers

Head and neck cancers account for 4% of all cancers in the United States and have caused an estimated 277,597 deaths worldwide in 2020.[103] A few but significant studies in head and neck squamous cell carcinoma (HNSCC) indicate that positive HER3 expression is linked to worse outcomes.[104,105] Meanwhile, pre-clinical studies using multiple HER3-targeted mAbs (LMJ716, RG7116, REGN1400, and seribantumab) have shown potent inhibition of cancer cell and tumor growth, but a clinical trial using LMJ716 failed to provide conclusive information (NCT01598077).[44,106] Similarly, the EGFR/HER3 dual antibody, duligotuzumab, also showed limited efficacy in a phase IB clinical trial when used in combination with cisplatin/5-fluorouracil or carboplatin/paclitaxel for recurrent or metastatic HNSCC.[107] Likewise, in another phase IB clinical trial of patients with HNSCC, the combination of patritumab with cetuximab plus a platinum-containing agent demonstrated a tumor response rate of 47%, but 40% of patients discontinued treatment due to disease progression or adverse events.[108]

Prostate cancer

Prostate cancer is the most diagnosed cancer and the second leading cause of cancer-related death in men.[70] In a study that examined the tumor samples of castration-resistant prostate cancer, it was found that HER2 and HER3 were highly expressed.[49] Additionally, *in vivo* studies have shown that activation of the NRG-HER3 signaling has been linked to anti-androgen therapy resistance in prostate cancer.[109] Although blocking EGFR and HER2, which are essential for HER3 activation, by afatinib did not improve outcomes of patients with prostate cancer in the clinic,[110] a recent pre-clinical study using prostate cell lines showed that direct inhibition of HER3 by patritumab (antibodies) or U3-1402 (patritumab ADC) exhibited anti-tumor effects *in vitro*, suggesting HER3 inhibition could impede tumor growth in patients with prostate cancer.[49] As such, further evaluation of HER3-targeting in patients with prostate cancer is warranted in prospective clinical trials.

NRG1 gene fusion mutations

The identification of oncogenic gene fusions or rearrangements has been observed in various solid tumors. This has led to the successful identification and targeting of oncogenic gene fusions as one of the most significant advancements in oncology.[111,112] *NRG1* fusion mutations were first identified in NSCLC.[113] They are caused by DNA rearrangements, resulting in the creation of a "chimera protein" by the fusion of NRG1 domains with partner proteins (such as ATP1B1 (ATPase Na^+/K^+ transporting subunit beta 1), APP (amyloid beta precursor protein), CD74 (leukocyte differentiation antigen 74), and SDC4 (syndecan 4); summarized in Table 1).[43,114] As a result, *NRG1* fusion proteins are highly expressed on the cell membrane and induce HER3 activation. Although the occurrence of *NRG1* rearrangements is rare, with the incidence of 0.5% in pancreatic cancer, 0.3% in NSCLC, 0.2% in breast cancer, and 0.1% in colorectal cancer,[43] multiple studies in distinct cancer types discussed above have determined that the presence of *NRG1* fusion mutations is associated with enhanced anti-cancer effects caused by HER3-targeted therapies.

In addition, the eNRGy1 global multicenter registry for *NRG1* gene fusions has shown an objective response rate of 25% in lung cancer patients treated by afatinib (clinically available EGFR/HER2 inhibitors),[115] and a pre-clinical study demonstrated that *NRG1* gene fusion and rearranged cancer cell lines exhibited heightened sensitivity to tarloxotinib, a prodrug of a potent irreversible inhibitor of EGFR/HER2.[116] In recent clinical studies, a phase II clinical trial evaluating the efficacy of zenocutuzumab (MCLA-128) in patients with *NRG1* gene fusion cancer showed an ORR of 34% and a median duration of response of 9 months.[94] In a study analyzing patients with advanced PDAC, those with *NRG1* gene fusion-positive tumors that were treated with afatinib demonstrated a significant and rapid response while on therapy.[117]

As a result, a phase II clinical trial was initiated to specifically assess the safety and efficacy of seribantumab in patients with advanced solid tumors harboring *NRG1* gene fusion mutations (NCT04383210, CRESTONE). Preliminary data from this clinical trial indicates that seribantumab has a favorable safety profile with few dose-limiting toxicities and has produced a durable response in patients with *NRG1* gene fusion, with an ORR of 36% in NSCLC and 33% in PDAC.[118] Also, another phase II clinical trial is currently underway to study the efficacy of afatinib in advanced *NRG1*-rearranged malignancies (NCT04410653). These findings emphasize the significance of *NRG1* fusions as a predictive biomarker, suggesting their utility in identifying patients likely to benefit from HER3-targeted therapy. Together, these observations collectively suggest HER3-targeted therapies can be effective when precisely directed toward the specific population such as with *NRG1* gene fusion mutations, or HER3 expression as discussed above for lung cancer.

Antibody—drug conjugates

ADCs provide targeted delivery of cytotoxic drugs (referred to as "payload") to tumor cells via antibody carriers, ensuring precision in drug delivery. Over the last decade, more than ten ADCs have gained approval, with several others in clinical development, reshaping the landscape of cancer therapy.[119] A notable example is U3-1402, a pioneering HER3-targeted ADC utilizing patritumab as the carrier and DXd, a derivative of exatecan (topoisomerase I inhibitor), as the payload. Early reports from a phase I/II clinical trial revealed promising anti-tumor efficacy in patients with HER3-expressing metastatic breast cancer, boasting a 47% ORR and a disease control rate of 94% (NCT02980341).[120] In a separate clinical study, the utilization of HER3-DXd in patients with EGFR TKI-resistant NSCLC exhibiting HER3 expression demonstrated clinical efficacy, showcasing a 39% ORR and a median PFS of 8 months.[121,122]

Recent findings also indicate that HER3-DXd displayed *in vitro* anti-tumor activity against HER3-positive cells, regardless of clinically relevant HER3 mutations.[123] Furthermore, in a pre-clinical study using xenograft tumors, co-administration of U3-1402 with a PD-L1/PD-1 antibody in HER3-positive colorectal and lung cancer cell lines exhibited significantly enhanced anti-tumor immunity by sensitizing tumors to PD-1 blockade.[124] In those studies, the authors speculated that the *de novo* antigens caused by the cytotoxic payload, Dxd, sensitized cancer cells to immunotherapies which had limited clinical impact as a monotherapy in solid tumors.[124] Additionally, clinical analyses revealed a high frequency of tumor-specific HER3 expression among patients with solid tumors resistant to PD-1 blockade.[124] These promising results suggest that exploring the combination of HER3-targeted ADC with immune checkpoint blockade could yield beneficial effects, warranting further investigation in future clinical trials. Moreover, in pre-clinical models of multidrug-resistant triple-mutant lung cancer and double-mutant CRC, a novel self-immolation T moiety and exatecan ADC effectively overcame chemoresistance and showed improved intra-tumoral pharmacodynamic response.[125] These findings highlight the potential of ADCs to broaden the spectrum of responsive patient populations and applicable tumor types.

Tumor microenvironment and HER3 signaling

In recent years, extensive research has been conducted to characterize the effects of the tumor microenvironment on cancer cells. The tumor microenvironment consists of cellular components such as the tumor cells and non-neoplastic stromal cells including immune cells, fibroblasts, endothelial cells, and a non-cellular component of the extracellular matrix.[126] In addition to oncogenic alterations in cancer cells, crosstalk between cancer and stromal cells in the tumor microenvironment has also been identified as a key factor in activating HER3 for the development and progression of cancer (Fig. 3). For example, fibroblasts express and secrete NRGs to activate the HER2-HER3 pathway in breast cancer.[127] Moreover, our recent studies suggest that HER3 is a key mediator of the pro-survival effects of the surrounding microenvironment. With a focus on liver metastases, which occur in over 80% of advanced CRC and PDAC cases, we collectively discovered that the surrounding liver microenvironment activates cancer-associated HER3, promoting cell growth and chemoresistance in CRC and PDAC cells.[88,128–131] Specifically, we determined that the liver-specific endothelial cell-rich microenvironment secretes soluble factors to activate HER3 in a paracrine fashion, and we found that blocking HER3 activity effectively blocked liver endothelial cell-induced CRC tumor growth. Interestingly, we found that although liver endothelial cells secrete NRGs, the canonical HER3 ligands are not the primary mediator of endothelial cell-induced HER3 activation.[88] Based on these findings it is also noteworthy that the efficacy of HER3-targeted therapy relies on the HER3 expression in cancer cells, suggesting future clinical trials should employ HER3 expression as a key predictive marker for HER3-targeted therapy efficacy.

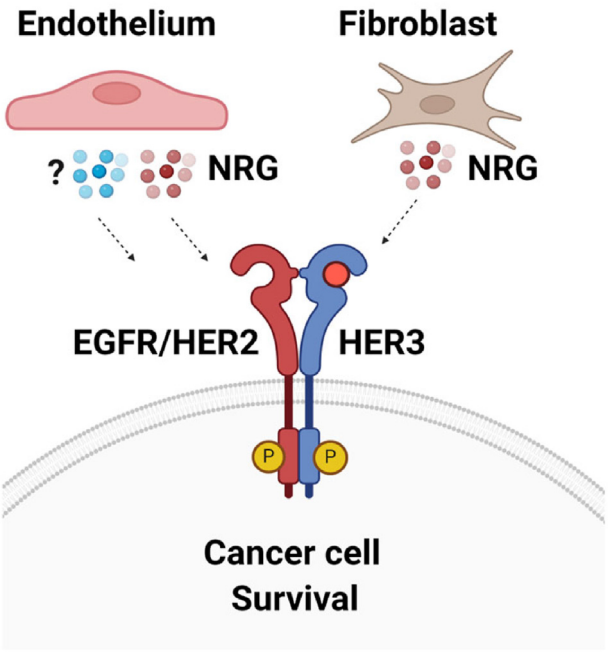

Figure 3 Schematic illustration of cancer-associated HER3 activated by the microenvironment components. HER3, human epidermal growth factor receptor 3.

Aside from endothelial cells and cancer-associated fibroblasts,[128,132] HER3 also plays a role in immune cell biology and functions. Breast cancer cell-secreted NRGs activate macrophage-associated HER3 which in turn promotes the expression of JAG1 (jagged 1) and increases cancer cell invasion.[133] Similarly, HER3 signaling regulates MHC I (major histocompatibility complex class I)-related chains A and B (MICA and MICB) in breast cancer cells and leads to natural killer-mediated toxicity in breast cancer.[134] Moreover, studies in cervical cancer suggest that HER3 methylation in cancer cells is associated with the presence of macrophages, effector memory CD8 T-cells, activated CD8 T-cells, regulatory T cells, immature B cells, T helper 1 cells, and myeloid-derived suppressor cells but the mechanism remains unclear.[135] Meanwhile, as HER3 expression is commonly detected in cancer, it has been assessed as a potential antigen for engineered CD4 T targeting in breast cancer and head and neck cancer,[136,137] and the HER3 vaccine is being assessed as a potential strategy for cancer treatment/prevention either alone or in combination with immunotherapies.[138] Together, these studies suggest HER3 mediates immune cell functions in various types of cancer, although much work is needed to further elucidate the involved mechanisms.

Discussion

The role of HER3 overexpression and oncogenic mutations in various solid tumor types is well documented. Both pre-clinical and clinical studies have shown that overexpression of HER3 is associated with tumor cell proliferation, chemoresistance, and overall worse survival. Most pre-clinical investigations employed either subcutaneous xenografts or

primary orthotopic models and demonstrated the anti-cancer effects of HER3 inhibition principally on primary tumors, as described above for each cancer type. On the other hand, clinical trials investigating HER3-targeted therapies were mostly conducted in patients with advanced metastatic tumors that failed to respond to prior standard-of-care therapies. For instance, in breast cancer, the HER3-specific antibody patritumab demonstrated significant anti-cancer effects on xenografts and primary tumors in pre-clinical studies and in patients with metastatic breast cancer in clinical trials.[61,139] However, there is no information on the effects of the antibodies on primary tumors in those patients or in patients only with primary tumors. Meanwhile, based on the preclinical studies from our laboratory that demonstrated that the liver microenvironment secretes soluble factors to activate cancer-associated HER3, we hypothesize that HER3 is highly active in liver metastases compared with primary tumors, suggesting that therapeutic interventions may yield greater efficacy in patients with liver metastases.[88,128]

In contrast, most clinical studies assessing HER3 inhibitors and antibodies, mostly in patients with metastatic tumors, showed limited impact in improving patient survival. One potential key reason for the failed outcomes is that, in most trials, HER3 expression in patients was not assessed and used as a selection criterion for patient recruitment. Our laboratory has shown that HER3-targeted therapies are only effective in cells and tumors that express HER3,[128] implying that previous clinical trials failed potentially because a substantial number of enrolled patients had HER3-negative tumors, especially the patients with lung cancer wherein only 30%—40% tumors are HER3-positive.[44,71,72] Thus, the results of those "negative clinical trial results" are debatable and call for further investigation. The significance of incorporating relevant biomarkers into HER3-targeted therapies is further supported by the consistent finding across various studies that individuals with *NRG1* gene fusion mutations exhibit notable positive responses to HER3-targeted treatments.[94,115—117] While significant studies used cancer cell lines and retrospectively analyzed archived patient tumor tissues and detected HER3 overexpression at mRNA levels (either by quantitative PCR or RNA sequencing), most clinical trials overlooked the assessment of HER3 expression. Among those few clinical studies in metastatic breast cancer, NSCLC, and HNSCC, HER3 expression was assessed by immunohistochemistry staining using biopsy tissues, followed by established histological scoring of staining intensity and distribution across tumor samples (*e.g.*, 0 for no staining or membrane staining in $\leq$10%, 1+ for faint or barely perceptible incomplete membrane staining in >10%, 2+ for weak-to-moderate complete membrane staining in >10%, and 3+ for circumferential membrane staining that is complete, intense, and in >10%).[140—143] Despite that, determining HER3 expression in clinical studies remains a challenge partially due to variations in antibody specificity for immunohistochemistry staining and potential spatial heterogeneity in HER3 cell surface localization. Hence, establishing HER3 expression as a predictive biomarker for patient response to HER3-targeted therapies and developing reliable and rapid methods for assessing HER3 expression in cancer will have significant implications in future clinical trials for treating patients with solid tumors.

Within the scientific community, a prevailing belief is emerging that resistance to established HER3-targeted therapies could stem from alternative mechanisms of HER3 activation. In our laboratory, we identified that soluble factors released by the tumor microenvironment could activate HER3 independently of NRG1, and the subsequent HER3 activation does not rely on the conventional heterodimerization of HER3 with other ErbB receptors such as EGFR and HER2.[88,128] Recent preliminary unpublished data from our laboratory indicates that leucine-rich α-2-glycoprotein 1 (LRG1), secreted by the EC microenvironment, can directly bind to and activate HER3 as a novel ligand, distinct from NRGs.[144] While the precise mechanism of LRG1-HER3 binding remains unknown, our findings suggest alternative activation mechanisms of HER3, which may contribute to the development of resistance to HER3 antibodies, and warrant further investigations for developing strategies to block HER3 activation.

Lastly, significant findings from pre-clinical and clinical investigations indicate that cancer cells may counteract ErbB receptor inhibitions by up-regulating other RTKs (non-targeted ErbB receptors or others) as adaptive resistance mechanisms. For example, lung cancer develops resistance to EGFR inhibitors by over-activation of HER3.[145] As a result, combining EGFR and HER3 inhibitions had superior anti-cancer effects compared with EGFR inhibitors alone. Similarly, in breast cancer, developed resistance to trastuzumab is associated with increased HER3 expression.[146] According to this paradigm, when exposed to HER3-targeted antibodies and inhibitors, cancer cells may activate alternative survival pathways to sustain proliferation in a HER3-independent manner. Concurrent inhibition of multiple ErbB family receptors has been attempted through the administration of sapitinib, a pan-HER inhibitor, in clinical trials for patients with breast cancer and CRC, but the interventions did not yield improvements in patient outcomes.[69,92] This implies that sapitinib may not be effective, necessitating the development of a novel drug with comparable action, or unidentified resistance mechanisms may contribute to this outcome. Notably, in contrast to previous unsuccessful clinical trials, the assessment of HER3 expression/activation emerges as a pivotal predictive biomarker for identifying patients who could derive benefits from combination therapies in future clinical trials.

Conclusion

As outlined in this review, HER3 plays a critical role in the oncogenesis of various cancer types. The tumor microenvironment significantly influences the activation of HER3 and the promotion of cancer cell survival. While HER3 as a therapeutic target holds promise, the way it has been addressed in prior clinical trials was suboptimal. The lack of a predictive biomarker for patient selection in these trials could be a contributing factor. Additionally, alternative mechanisms of HER3 activation, such as by a new ligand, LRG1, and the potential involvement of other acquired resistance mechanisms, could also contribute to this phenomenon. Therefore, identifying HER3 expression as a predictive biomarker, developing reliable and feasible assays to evaluate HER3 expression, and elucidating

alternative HER3 activation mechanisms will improve the effectiveness of current HER3-targeted therapies. Furthermore, improving existing therapies by developing novel ADCs and combining HER3-targeted therapies with other standard-of-care regimens may enhance patient outcomes in future clinical trials. In summary, HER3 stands out as a pivotal target in cutting-edge cancer therapies, offering the potential for enhanced outcomes through a deeper comprehension of the tumor microenvironment and the molecular mechanisms underlying cancer progression.

CRediT authorship contribution statement

Conceptualization, O.D., M.R., C.B., and R.W.; data curation, O.D., M.R., C.B., E. B., and R.W.; writing — original draft and revising, O.D., M.R., C.B., M. W.M., C. K., and E. B.; R.W.; visualization, E. B. and R. W.; supervision, R.W.; funding acquisition, R.W.; review of the manuscript, all authors.

Conflict of interests

R.W. is a member of the editorial board for *Genes & Diseases* but was not involved in the editorial review or the decision to publish this article. All other authors declare that there are no competing interests.

Funding

This work was supported by the National Institutes of Health (No. R00CA225756, R37CA278982 to R.W.) and the U.S. Department of Defense (No. HT9425-23-1-0657 to R.W.).

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