

**REVIEW ARTICLE**

# The role of NRG1 and its receptor HER3 in gastrointestinal tumors

**Yue Zhao<sup>1</sup>, Yuting Yong<sup>1</sup>, Yuanshuai Li<sup>1</sup>, Wenling Zhan<sup>1</sup>, Yuyang Song<sup>2,3,4</sup>, Chong Li<sup>2\*</sup>, Wenting Pan<sup>1\*</sup>, and Xinlong Yan<sup>1\*</sup>**

<sup>1</sup>Beijing Key Laboratory of Environmental and Viral Oncology, College of Chemistry and Life Science, Beijing University of Technology, Beijing, China

<sup>2</sup>Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

<sup>3</sup>Zhongke Bio-Manufacturing Innovation Center, Beijing, China

<sup>4</sup>Zhongke Jianlan (Beijing) Medical Research Institute, Beijing, China

## Abstract

Neuregulin 1 (NRG1), as a key ligand of the epidermal growth factor receptor family, plays a crucial role in the initiation, progression, and metastasis of various solid tumors by binding to human epidermal growth factor receptor 3 (HER3) and activating downstream signaling pathways. In recent years, *NRG1* gene fusions have been identified as rare oncogenic drivers in gastrointestinal tumors, with their abnormal expression in gastric and colorectal cancers closely associated with poor patient prognosis. This paper systematically reviews the biological functions and mechanisms of the NRG1/HER3 signaling axis in gastrointestinal tumors, while outlining research progress on its potential as a therapeutic target. Given the rapid development and exploratory nature of this field, this narrative review synthesizes key biological discoveries and clinical advances from current literature. It further explores the clinical prospects and challenges of therapeutic strategies targeting the NRG1/HER3 pathway, including treatment efficacy heterogeneity, complex mechanisms of drug resistance, and clinical limitations of different targeted agents. This review aims to provide a theoretical reference for subsequent research and clinical practice.

**Keywords:** Drug resistance; Gastrointestinal tumors; Gene fusion; HER3; NRG1; Targeted therapy; Tumor microenvironment

### \*Corresponding authors:

Chong Li  
(lichong@zjktianlan.com);  
Wenting Pan  
(wentingpan@bjut.edu.cn);  
Xinlong Yan  
(yxlong2000@bjut.edu.cn);

**Citation:** Zhao Y, Yong Y, Li Y, *et al.*  
The role of NRG1 and its receptor  
HER3 in gastrointestinal tumors.  
*Cancer Plus.* 2026;8(3):025520093.  
doi: 10.36922/CP025520093

**Received:** December 28, 2025

**Revised:** February 24, 2026

**Accepted:** March 6, 2026

**Published online:** August 21, 2026

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## 1. Introduction

Gastrointestinal malignancies rank among the most prevalent and lethal cancer types globally. The gastrointestinal tract, or digestive system, is a complex network of organs that includes the entire digestive tract, as well as the salivary glands, liver, gallbladder, and pancreas.<sup>1</sup> Gastric cancer stands as the fifth leading cause of cancer-related deaths worldwide, with patients typically exhibiting low five-year survival rates.<sup>2</sup> Colorectal cancer has surged to become the third most common malignancy globally, with annual new cases continuing to climb.<sup>3-5</sup> Despite continuous advancements in traditional treatments such as surgery, chemotherapy, and radiotherapy, along with significant breakthroughs in targeted therapy and immunotherapy in recent years, the overall prognosis for gastrointestinal cancer patients remains poor.<sup>6,7</sup> This is particularly true for advanced-stage patients, who frequently experience treatment resistance and distant

metastasis. Consequently, deepening the understanding of its pathogenesis and identifying novel effective therapeutic targets have become urgent challenges for both clinical and basic research.<sup>8,9</sup>

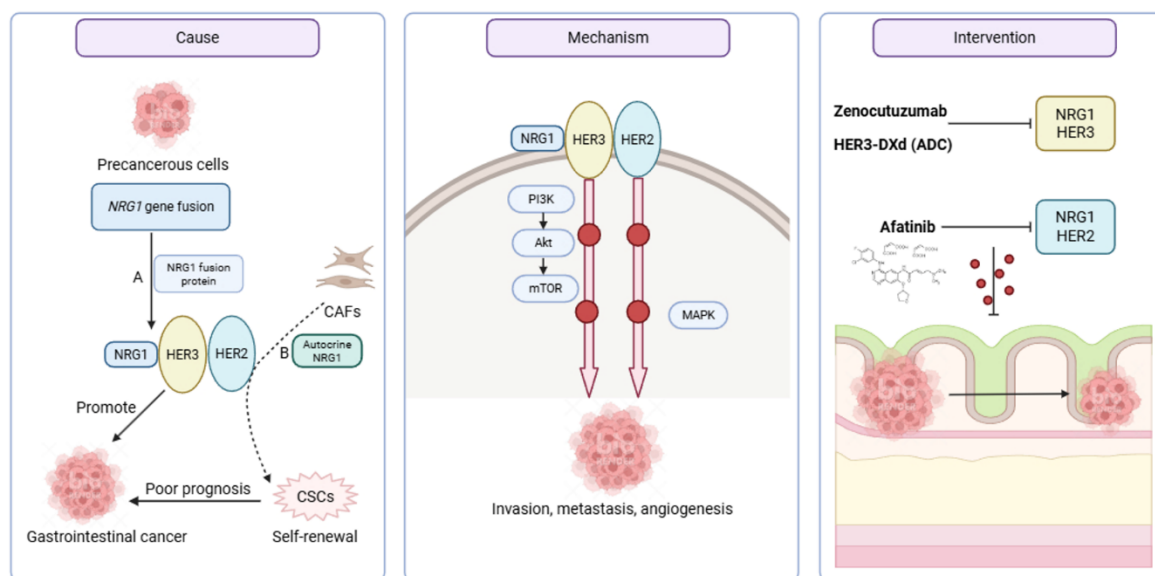
Neuregulin 1 (NRG1), a ligand of human epidermal growth factor receptors 3 and 4 (HER3 and HER4), was initially studied extensively for its crucial roles in the development of the nervous and cardiovascular systems.<sup>10,11</sup> In recent years, with the widespread adoption of high-throughput sequencing technologies, *NRG1* gene fusions have been progressively identified across multiple solid tumors, including gastrointestinal malignancies such as cholangiocarcinoma, pancreatic cancer, and colorectal cancer.<sup>12,13</sup> These findings established *NRG1* fusions as rare oncogenic drivers with significant roles in tumorigenesis and progression, while also opening new avenues for developing targeted therapeutic strategies.

This review systematically examines the biological functions, pathogenic mechanisms, and clinical research advances of the NRG1/HER3 signaling pathway in gastrointestinal tumors. It also provides an outlook on the current status and challenges of targeted drugs targeting this pathway (such as afatinib, zenocutuzumab, and patritumab deruxtecan [HER3-DXd]), aiming to offer a theoretical reference for subsequent research in this field (Figure 1).

## 2. Current status of gastrointestinal tumors and the prevalence of *NRG1* fusions

Gastrointestinal malignancies encompass multiple organs of the digestive system, including colorectal cancer, gastric adenocarcinoma, pancreatic adenocarcinoma, esophageal cancer, anal canal cancer, and other malignant intestinal lesions,<sup>1,14</sup> causing immense suffering for patients. Currently, treatment options for this disease are limited.<sup>15</sup> Traditional surgery and chemoradiotherapy often fail to achieve complete cure, resulting in persistently high mortality rates and generally poor prognosis.<sup>16</sup> In colorectal cancer treatment, targeted drugs such as dovitinib and nintedanib are now clinically applied.<sup>4,5</sup> Notably, certain molecular pathways are particularly significant in colorectal cancer, including the Wnt signaling pathway and pathways associated with the epidermal growth factor receptor (EGFR), such as the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), KRAS, and transforming growth factor beta signaling pathways.<sup>17-19</sup> These pathways are major research focuses because alterations affecting them occur frequently and contribute to colorectal carcinogenesis.

Gene fusions arise from genomic rearrangements, including chromosomal inversions, interstitial deletions, duplications, or translocations, leading to the formation of hybrid genes.<sup>20</sup> These disrupt normal transcription or



**Figure 1.** The core role of *NRG1* gene fusion in cancer: NRG1 activates the HER2/HER3 signaling pathway, driving tumor progression and stem cell characteristics. It also demonstrates targeted therapeutic strategies targeting this pathway and indicates its close association with poor prognosis in gastrointestinal cancers. Created in BioRender.com. Yue Zhao (2026). <https://BioRender.com/qvu0jtr>

Abbreviations: Akt: Protein kinase B; CAFs: Cancer-associated fibroblasts; CSCs: Cancer stem cells; HER: Human epidermal growth factor receptor; MAPK: Mitogen-activated protein kinase; mTOR: Mechanistic target of rapamycin; NRG1: Neuregulin 1; PI3K: Phosphoinositide 3-kinase.

splicing processes, thereby promoting the initiation and progression of various solid tumors. The mammalian neuregulin family comprises four genes—*NRG1*, *NRG2*, *NRG3*, and *NRG4*—of which *NRG1* has been studied most extensively.<sup>21</sup> Initially identified in lung cancer, multiple *NRG1* fusion subtypes have now been characterized across diverse gastrointestinal tumors.<sup>22,23</sup> Numerous studies have elucidated its core pathogenic mechanism: the *NRG1* fusion protein binds to HER3, forming the strongly signaling HER2–HER3 heterodimer that persistently activates downstream PI3K/Akt and mitogen-activated protein kinase (MAPK) signaling pathways, thereby driving tumorigenesis.<sup>24</sup> Its potential oncogenic role and therapeutic value have garnered significant attention.

### 3. NRG1/HER3 signaling and tumor biology

*NRG1* fusions are rare but therapeutically actionable oncogenic drivers across several solid-tumor types. The *NRG1* protein primarily binds to the HER3 receptor on the cell membrane, triggering phosphorylation of intracellular domains to activate downstream signaling pathways that regulate key cellular behaviors such as survival and proliferation.<sup>25</sup> Among these, the HER2–HER3 heterodimer is considered the most potent form of signal activation, typically driving tumorigenesis through robust phosphorylation and downstream signaling.<sup>26</sup> Furthermore, *NRG1* signaling enhances tumor cell invasion and metastasis capabilities, alters cell morphology and the microenvironment, and promotes intravascular angiogenesis.<sup>17</sup> Consequently, *NRG1* fusions are increasingly recognized as pivotal factors in the biology of solid tumors.

The HER family comprises four members: HER1, HER2, HER3, and HER4.<sup>27</sup> *NRG1*, acting as a ligand for HER3 and HER4, activates multiple cellular signaling pathways that promote carcinogenesis and metastasis.<sup>28</sup> In gastric cancer, HER1 and HER2 expression levels serve as a prognostic factor and potential target for novel biologics, particularly in HER2-positive cancers.<sup>29</sup> Multiple studies have also demonstrated that heterodimerization of HER family members plays a critical role in the progression of colorectal cancer.<sup>3,30</sup>

### 4. Mechanism of action of NRG1/HER3 signaling pathway in malignant tumors

Based on the next-generation sequencing (NGS) analysis of 25,203 patients with solid tumors by Xiang *et al.*<sup>31</sup> and the RNA sequencing study of 4,397 samples by Severson *et al.*<sup>32</sup>, *NRG1* fusions exhibit low overall frequency but widespread distribution across gastrointestinal tumors, showing relative enrichment in esophageal cancer followed

by colorectal cancer. This fusion event exhibits high heterogeneity, with over 40 partner genes identified, most commonly *CD74*, alongside novel fusion partners such as *DDHD2*, *BIN3*, and *CCAR2*. Breakpoints predominantly cluster within the intronic region of the *NRG1* gene's 5' end, though the vast majority retain functional epidermal growth factor (EGF)-like domains.<sup>32</sup> Notably, different fusion partners may influence downstream signaling intensity by either preserving or disrupting the EGF-like domain, thereby affecting tumor biology and sensitivity to targeted therapies. Clinical genomic features indicate that *NRG1* fusions in gastrointestinal tumors predominantly exhibit microsatellite stability. Except in colorectal cancer, they typically show mutual exclusivity with other driver gene mutations, suggesting their nature as an independent oncogenic driver event.

*NRG1* primarily induces heterodimerization between HER3 and other HER family members such as HER2 by binding to its specific receptor HER3.<sup>33</sup> This sustained activation of key downstream signaling pathways ultimately promotes tumor cell proliferation, survival, invasion, and metastasis.<sup>34,35</sup> Notably, elevated expression levels of HER2 and HER3 have been demonstrated to correlate significantly with poor prognosis in various gastrointestinal tumors, including colorectal and gastric cancers.<sup>36</sup> This makes the *NRG1*/HER3 axis a highly promising therapeutic target. Furthermore, recent studies reveal that *NRG1*/HER3 signaling plays complex roles in maintaining tumor stem cell properties, inducing treatment resistance, and regulating the tumor immune microenvironment.<sup>17</sup> The underlying mechanisms require further elucidation.

Importantly, the aberrant activation of this signaling axis is not confined to advanced malignancies but is also pivotal during the initiation of precancerous lesions. For instance, fusion genes such as *SLC3A2::NRG1* have been directly identified in pancreatic intraductal papillary mucinous neoplasms,<sup>37,38</sup> indicating that dysregulated *NRG1* signaling may serve as an early molecular event in the malignant transformation of certain precancerous lesions.<sup>37,39</sup>

### 5. The role of NRG1/HER3 in the tumor microenvironment and tumor stem cells

Cancer stem cells (CSCs) constitute a critical cellular subset driving gastrointestinal tumorigenesis, chemotherapy resistance, and postoperative recurrence.<sup>40</sup> Recent studies reveal that the *NRG1*/HER3 signaling pathway serves as a core regulatory axis maintaining the malignant phenotype of this cellular subset.<sup>41</sup> Furthermore, cancer-associated fibroblasts (CAFs) in the tumor microenvironment

continuously secrete NRG1, nourishing CSCs via paracrine signaling to confer survival advantages and mediate immune evasion.<sup>40,42</sup>

Within the tumor microenvironment, stromal-derived NRG1 confers stem-like survival advantages to tumor cells by activating HER3 signaling. This signaling axis continuously transmits anti-apoptotic signals through the PI3K/Akt pathway, enabling tumor cells to survive under stress conditions and maintain proliferative potential—a critical foundation for chemotherapy resistance and the persistence of minimal residual disease.<sup>43</sup> Concurrently, NRG1/HER3-mediated stromal–epithelial crosstalk reshapes the tumor niche, creating a microenvironment conducive to stemness maintenance and immune evasion. This adaptive alteration facilitates distant tumor implantation and recurrence. Clinical evidence indicates that high expression of transmembrane NRG1 in stromal cells correlates significantly with advanced disease stage and reduced survival in colorectal cancer patients. This suggests that targeting this paracrine circuit may represent an effective strategy for depleting the tumor stem cell pool and overcoming therapeutic resistance.<sup>42,43</sup>

Given the pivotal role of the NRG1/HER3 pathway in CSCs, targeting this pathway has emerged as a highly promising strategy for eradicating CSCs, reversing drug resistance, and inhibiting metastasis. Preclinical studies confirm that HER3-targeting antibody-drug conjugates (ADCs), such as HER3-DXd,<sup>44</sup> effectively eliminate heterogeneous tumor cells and demonstrate potent killing potential against CSCs. The bispecific antibody zenocutuzumab efficiently blocks the binding of NRG1 to HER2/HER3, thereby suppressing CSCs' stemness signaling at its source.<sup>45</sup> In the future, combining such targeted therapies with standard chemotherapy, radiotherapy, or other pathway inhibitors may achieve deep depletion of the CSC reservoir in gastrointestinal tumors through multi-pathway synergy, ultimately improving patient prognosis.

## 6. Therapeutic strategies targeting NRG1/HER3

Research progress on *NRG1* fusion genes in gastrointestinal malignancies follows a clear chronological trajectory. In 2014, Fernandez-Cuesta *et al.*<sup>46</sup> first reported the *CD74::NRG1* fusion gene in lung cancer. Its presence was subsequently confirmed in gastrointestinal tumors such as colorectal cancer, preliminarily revealing its oncogenic potential.<sup>4</sup> However, targeted therapeutic approaches were lacking at that time. Beginning in 2019, research has increasingly focused on targeted therapies. The irreversible pan-HER inhibitor afatinib demonstrated clinical activity in some gastrointestinal tumor patients harboring *NRG1*

fusions, becoming an early representative of repurposing existing drugs. Concurrently, the bispecific antibody zenocutuzumab emerged, designed to efficiently block NRG1-induced HER2/HER3 heterodimerization.<sup>45</sup> It demonstrated significant and durable efficacy in early clinical trials for advanced refractory solid tumors, including pancreatic and colorectal cancers, marking the entry into a precision-driven treatment era.<sup>47</sup> In recent years, research focus has further shifted toward overcoming tumor heterogeneity and drug resistance.<sup>48</sup> Preclinical studies of novel ADCs<sup>26,49</sup> such as HER3-DXd are expanding therapeutic options for future treatments.<sup>44</sup>

Afatinib, an irreversible pan-HER inhibitor, has demonstrated antitumor activity in preclinical models and in some patients with *NRG1*-fusion-positive tumors.<sup>50,51</sup> Although afatinib has been approved for first-line treatment of advanced non-small cell lung cancer patients with sensitizing *EGFR* mutations, data regarding the characteristics of patients with *NRG1* fusion-driven tumors and their response to afatinib or other systemic therapies remain limited.<sup>52</sup>

Zenocutuzumab overcomes tumor cell resistance to HER3-targeted therapy through two mechanisms: inhibiting tumor proliferation by blocking growth and survival pathways, and recruiting and enhancing immune effector cells to eliminate tumors.<sup>53</sup> On the other hand, NRG1 can induce carcinogenesis and promote metastasis. Recent studies indicate that activation of the PI3K/Akt pathway via the NRG1/HER3 signaling pathway may contribute to resistance against HER3-targeted therapies.<sup>54</sup> Consequently, inhibiting this signaling pathway is considered a potential strategy to overcome resistance to anti-HER3 treatments.

In clinical colorectal cancer samples, high levels of HER3 protein expression are frequently observed on the cancer cell plasma membrane, and this biomarker correlates with reduced patient survival rates.<sup>55</sup> Therapeutic strategies targeting the HER3 signaling pathway, when combined with DNA-damaging agents, cytotoxic drugs, antimetabolites, or multi-targeted kinase inhibitors, are anticipated to hold significant value in enhancing chemotherapy sensitivity in colorectal cancer patients.

## 7. NRG1 fusion tumors: Heterogeneity and mechanisms of drug resistance

The heterogeneity and drug resistance mechanisms of *NRG1* fusion tumors represent key challenges affecting the long-term efficacy of targeted therapies.<sup>56</sup> First, this heterogeneity manifests as diversity in fusion partner genes (e.g., *CD74*, *SLC3A2*, *VAMP2*).<sup>38,57</sup> Different fusion partners may influence the extracellular domains of

fusion proteins, their expression levels, and the activation intensity of downstream signaling pathways, leading to varying sensitivities to the same targeted drug.

Regarding mechanisms of drug resistance, patients who initially respond to treatment may develop acquired resistance through multiple pathways.<sup>58</sup> First, activation of bypass signaling is a common mechanism; for example, amplification or overexpression of the *MET* gene can circumvent inhibited HER family signaling and reinitiate tumor proliferation.<sup>59</sup>

Recent studies have further identified fibroblast growth factor receptor 1 (FGFR1) signaling as a critical compensatory pathway that becomes engaged upon NRG1/HER3 axis inhibition.<sup>60</sup> Notably, FGFR1 activation can fully substitute for NRG1 loss in sustaining tumor cell survival, while conversely, NRG1/HER3 signaling confers resistance to FGFR1 inhibition, revealing a bidirectional plasticity between these pathways.<sup>61</sup> This functional interdependence enables tumor cells to dynamically switch signaling dependencies in response to therapeutic pressure. Clinical evidence supports this mechanism, as increased FGFR1 expression has been observed in post-treatment tumor specimens from patients progressing on HER2/HER3 or PI3K inhibitors.

Second, following treatment with pan-HER inhibitors such as afatinib, tumor cells may acquire secondary mutations in HER family receptors (e.g., EGFR, HER2), preventing effective drug binding to the target and leading to treatment failure.<sup>62</sup> Additionally, continuous secretion of the NRG1 ligand by stromal cells in the tumor microenvironment may maintain HER3 activation via paracrine signaling, thereby diminishing the efficacy of targeted therapies.<sup>63</sup>

In addition to bypass signaling pathways, emerging evidence suggests that targeting protein homeostasis through chaperone proteins may offer alternative therapeutic strategies. For instance, andrographolide has been shown to induce ferroptosis in pancreatic cancer by disrupting the heat shock protein 90–glutathione peroxidase 4 (GPX4) interaction and promoting GPX4 ubiquitination, representing a novel mechanism distinct from conventional HER family inhibition.<sup>64</sup>

To overcome these challenges, future therapeutic strategies should focus on combination therapies, such as administering HER3-targeted agents together with MET inhibitors or downstream PI3K/mTOR pathway inhibitors. Concurrently, dynamic genomic monitoring via serial biopsies or liquid biopsies is crucial for timely detection of drug-resistant clones and guiding subsequent precision treatments.

## 8. Other investigational drugs and combination strategies targeting the NRG1/HER3 pathway

Beyond afatinib and zenocutuzumab, other investigational drugs targeting the NRG1/HER3 pathway show promising prospects, further expanding therapeutic strategies. Among these, novel ADCs are particularly noteworthy.<sup>44</sup> For instance, the HER3-targeting ADC HER3-DXd effectively eliminates tumor cells with heterogeneous expression through its unique “bystander effect.”<sup>65,66</sup> Its potent antitumor activity has been demonstrated in preclinical models harboring *NRG1* fusions, offering a novel approach to overcoming tumor heterogeneity.

The therapeutic value of HER2-targeted drugs in *NRG1* fusion tumors warrants attention. Although the primary receptor for NRG1 is HER3, its oncogenic effects are highly dependent on forming heterodimers with HER2. Therefore, monoclonal antibodies targeting HER2 (such as trastuzumab<sup>67</sup>) and ADC trastuzumab deruxtecan (T-DXd<sup>68,69</sup>) may theoretically be effective against some *NRG1* fusion tumors, particularly those that also exhibit HER2 expression or amplification. Preclinical studies suggest that in *NRG1* fusion-driven models, combined inhibition of HER2 and HER3 may produce a synergistic effect, providing a rationale for a “dual-target” combination strategy.

Emerging evidence from preclinical studies reinforces the rationale for combined targeting of HER2 and HER3. A novel anti-HER3 monoclonal antibody, SIBP-03, has been shown to specifically block both ligand-dependent and ligand-independent HER3 activation, and importantly, it synergizes with trastuzumab to enhance antitumor activity both in vitro and in vivo, an effect attributed to more profound inhibition of HER3-mediated PI3K/Akt signaling.<sup>70</sup> This synergistic potential is further exemplified by the development of bispecific ADCs targeting HER2 and HER3, which demonstrate superior internalization and antitumor efficacy compared to their monospecific counterparts, effectively recapitulating the benefits of combination therapy within a single agent.<sup>71</sup> The biological basis for this synergy is also supported by mechanistic studies showing that HER3 upregulation serves as an adaptive resistance mechanism to various targeted therapies, and that pan-HER inhibition—simultaneously blocking HER2, HER3, and other family members—can effectively overcome this escape pathway.<sup>72</sup> Collectively, these findings suggest that in *NRG1* fusion-driven tumors, the therapeutic efficacy of HER2 or HER3 inhibition alone may be limited by compensatory signaling, whereas dual or pan-HER targeting strategies could yield more durable responses by comprehensively disrupting the heterodimeric signaling network.

Combination therapy strategies represent a core direction for future development. Given that NRG1/HER3 signaling can activate multiple downstream pathways including PI3K/Akt and MAPK, combining it with downstream pathway inhibitors theoretically yields stronger and more durable therapeutic effects.<sup>73</sup> For instance, in colorectal cancer models, combination regimens of HER3-targeted agents with antimetabolites (e.g., 5-fluorouracil)<sup>74</sup> or mitogen-activated protein kinase kinase (MEK) inhibitors (e.g., trametinib) have demonstrated superior tumor suppression compared to monotherapy.<sup>75</sup> Furthermore, considering the potential regulatory role of HER3 signaling in the immune microenvironment, exploring combinations of HER3 inhibitors with immune checkpoint inhibitors has emerged as a key area of research to overcome immune resistance and expand the patient population benefiting from these therapies.

## 9. Detection of NRG1 fusions and candidate biomarkers

Currently, immunohistochemistry, fluorescence in situ hybridization, reverse transcription polymerase chain reaction, and next-generation sequencing have become common methods for detecting *NRG1* fusions in tumor samples.<sup>76</sup> *NRG1* gene fusions and their downstream signaling pathways are considered viable targets for therapeutic intervention. Accurate detection of *NRG1* gene fusions is a prerequisite for implementing targeted therapy; however, its clinical diagnosis remains challenging.<sup>77</sup> Currently, immunohistochemistry, though simple and rapid, can only provide indirect evidence such as HER3 phosphorylation and exhibits a high false-positive rate.<sup>78</sup> Fluorescence in situ hybridization is the gold standard for detecting gene rearrangements, but it lacks sensitivity for fusions with unknown partner genes and has low throughput.<sup>79</sup> Reverse transcription polymerase chain reaction offers high sensitivity but requires prior knowledge of fusion breakpoints, limiting its coverage of novel fusions. NGS, particularly RNA sequencing, enables precise identification of novel fusion partners<sup>24</sup> and is emerging as the preferred method for detecting *NRG1* fusions.<sup>80</sup>

Furthermore, liquid biopsy technology based on circulating tumor DNA demonstrates unique potential in dynamically monitoring gene mutations, evaluating treatment response, and exploring resistance mechanisms, particularly for patients with advanced disease for whom tumor-tissue acquisition is challenging.<sup>81</sup> Moving forward, standardizing detection technologies, establishing multi-platform validation strategies, and expanding NGS-based

screening coverage will be crucial for precisely identifying patient populations who benefit from NRG1-targeted therapy.

Research on NRG1/HER3 as a biomarker is transitioning from basic science to clinical application. Large-scale genomic analyses reveal that *NRG1* fusions occur in 0.11% to 0.25% of pancreatic, gastric, and colorectal cancers.<sup>31,32</sup> These fusion-positive tumors are consistently microsatellite stable and exhibit exclusivity toward other driver gene mutations, defining a distinct molecular subtype. Regarding prognostic value, multiple studies have confirmed that HER3 membrane expression levels correlate negatively with prognosis in gastrointestinal cancer patients.<sup>82</sup> However, its utility as a treatment response predictor remains controversial. Notably, research has demonstrated that *NRG1* fusion status serves as an actionable biomarker independent of histological type to guide treatment with zenocutuzumab, gaining regulatory approval. Its predictive value surpasses that of HER3 expression levels.<sup>83,84</sup>

## 10. Future outlook and challenges

Current clinical evidence indicates that therapeutic agents targeting the NRG1/HER3 axis present a complex picture in terms of efficacy and safety, with their clinical limitations becoming increasingly apparent. A case series of afatinib revealed marked heterogeneity in treatment response and complex resistance patterns: while some patients achieved sustained remission exceeding 27 months, others experienced rapid progression.<sup>85</sup> Post-resistance testing demonstrated dynamic changes in *SMAD4* mutation clones, suggesting clonal selection may contribute to acquired resistance.<sup>85</sup> Dose escalation strategies successfully reversed progression in certain patients. Zenocutuzumab established the most definitive efficacy data to date in its registration studies, achieving a 42% objective response rate in the pancreatic cancer cohort.<sup>83</sup> Overall, the clinical application of these drugs requires balancing efficacy heterogeneity, complex resistance mechanisms, and safety risks. The widespread adoption of RNA-based next-generation sequencing and the exploration of combination therapy strategies will be key directions for optimizing treatment in the future.

Beyond novel therapeutic agents, advanced drug delivery systems hold promise for improving the clinical utility of existing compounds. For example, sericin-coated nanostructured lipid carriers have been successfully employed to enhance the oral bioavailability and therapeutic efficacy of hesperidin in gastric ulcer models. Similar strategies could potentially be adapted to improve the delivery of NRG1/HER3-targeted agents, particularly

those with poor solubility or limited gastrointestinal absorption.<sup>86</sup>

## 11. Conclusion

The NRG1/HER3 signaling axis plays a central driving role in gastrointestinal tumors. This signaling axis plays a crucial role in tumorigenesis, progression, metastasis, and treatment resistance. Mesenchymal-derived NRG1 in the tumor microenvironment confers stem-like properties to tumor cells via paracrine signaling, reshaping the microenvironment to favor immune evasion and further exacerbating tumor invasiveness and therapeutic resistance. Clinical evidence indicates that high expression of transmembrane NRG1 in stromal cells correlates significantly with advanced disease staging and reduced survival in colorectal cancer patients. This suggests that NRG1/HER3 signaling serves not only as an intrinsic driver within tumor cells but also as a pivotal node in tumor–microenvironment interactions.

While targeted therapies against NRG1/HER3 have shown clinical promise, their application is tempered by significant therapeutic heterogeneity, emerging resistance mechanisms, and unresolved safety concerns that vary across different drug classes.

Future research should focus on the following key directions: First, promote the clinical adoption of RNA-based next-generation sequencing technology to enhance the sensitivity and accuracy of *NRG1* fusion detection, enabling precise identification of patients who may benefit. Second, conduct in-depth analysis of resistance mechanisms such as bypass activation (e.g., MET amplification, FGFR1 signaling compensation) and clonal evolution to provide theoretical foundations for combination therapy strategies. Third, explore multi-target combination approaches, including dual HER2/HER3 targeting, combination with downstream pathway inhibitors (PI3K/mTOR, MEK), and combination with immune checkpoint inhibitors to overcome feedback signaling compensation and immune evasion. Finally, to address the challenge of the rarity of *NRG1* fusions, innovative clinical trial designs such as basket trials and platform trials should be adopted, establishing international multicenter registration studies to accelerate data accumulation. Through multidimensional synergistic advancement, NRG1/HER3-targeted therapy holds promise to transition from proof-of-concept to true precision medicine, delivering sustained clinical benefits for gastrointestinal cancer patients.

## Acknowledgments

None.

## Funding

None.

## Conflict of interest

The authors declare they have no competing interests.

## Author contributions

*Conceptualization:* Xinlong Yan

*Writing–original draft:* Yue Zhao, Yuting Yong, Yuanshuai Li, Wenling Zhan, Yuyang Song

*Writing–review & editing:* Chong Li, Wenting Pan, Xinlong Yan

All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

Not applicable.

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