The HER3/ErbB3 receptor: A promising target in cancer drug therapy

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This last decade, the development of drugs targeting specifically RTKs has revolutionized the therapeutic guidance of many cancers including breast, lung, colon and liver cancers. Drugs targeting EGFR and HER2, two members of the HER family, have gained Food and Drug Administration and European Medicines Agency approvals in oncology. Clinical and translational studies have provided extensive information regarding the molecular mechanisms involved in cancer cell response to anti-HER therapies. A significant contribution of HER3, another member of the HER family, has recently emerged from these studies. Thus, HER3 presence may correlate with responses to treatments that target EGFR and HER2. Surprisingly, HER3 may also provide a route for resistance to anti-HER drugs and to drugs targeting other RTKs.

Abbreviations: HER, human epidermal growth factor receptor; RTKs, receptor tyrosine kinases; EGFR, epidermal growth factor receptor; IGF-1R, insulin-like growth factor type 1 receptor; IGF, insulin-like growth factor; EGF, epidermal growth factor; TGF-α, transforming growth factor-α; HB-EGF, heparin-binding EGF-like growth factor; TK, tyrosine kinase.

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EGFR and HER2 are the most studied HER receptors in cancer. They are hyperactivated in many human epithelial cancers. Aberrant receptor activation results from increased amounts at the plasma membrane, structural alterations (point mutations or truncations) and/or ligand overproduction. These dysregulations influence cancer cell proliferation, survival, angiogenesis, invasion and metastasis. As a result, EGFR and HER2 have been visioned as potential prognostic factors and therapeutic targets [4,5]. The role of HER4 in cancer is less clear as it may cause inhibition of cell proliferation [6].

**HER3 status in cancer**

Increased expression of HER3 often accompanies overexpression of EGFR and of HER2 and is detected in breast [6,7], lung [8], liver [9], colon [10], stomach [11] and prostate cancers [12]. The contribution of heterodimerized HER3 to tumour physiology may depend upon the relative expression of HER receptors. For example, HER2/HER3 complex rather than HER2/EGFR is the major oncogenic unit in HER2-amplified breast cancer [13,14]. HER3 overexpression alone or in association with other HER partners is often associated with a poor prognosis in immunohistochemical studies [6,7,9,11,15–17].

HER3 overexpression may result from amplification of the ERBB3 gene (located on chromosome 12q13). There is also some experimental evidence showing that the activation of AP-2 transcription factor- and αvβ4 integrin-dependent pathways may increase HER3 expression in cancer cells [18,19]. By down-regulating HER3 expression or by neutralizing ligand-binding, it has been shown that the heregulin/HER3 signalling pathway exerts a crucial role on proliferation, tumorigenicity and/or metastatic potential in colorectal, gastric and mammary cancer cells [20–22]. A supportive role for HER3 in colon carcinogenesis has been recently obtained in vivo by showing that the intestine-specific genetic ablation of ERBB3 results in a dramatic reduction of intestinal tumours in the ApcMin mouse model of colon cancer [23].

Membrane, cytoplasmic and nuclear expressions of HER3 have been reported both in normal and cancer cells [24]. However, nuclear expression of HER3 seems to be more frequent in hyperplasia prostate tissues, and becomes much more pronounced in prostate cancer cells [25].

**HER3 as a predictive marker of tumour cell response to EGFR/HER2 therapies**

Targeting the HER family has been intensively pursued in the last decade as a cancer treatment strategy. Efforts have been made to inhibit the activity of EGFR and HER2 by designing antibodies against the ligand-binding domain (cetuximab, panitumumab and trastuzumab) and small molecules against the TK domains (erlotinib, gefitinib and lapatinib) [4,5]. If EGFR and HER2 are engaged in heterodimers with HER3, therefore EGFR and HER2 inhibitors will prevent HER3 transphosphorylation and downstream activation of the PI3K/AKT pathway.

Molecular analyses aimed to identify predictive markers of response to EGFR tyrosine kinase inhibitors (TKIs)
have revealed that a high expression of HER3 is associated with a high sensitivity to gefitinib and erlotinib in lung adenocarcinoma and colorectal tumour cells [8,20,26,27]. The efficacy of anti-HER2 therapy is associated with HER3 inhibition in mammary cancer cells [28]. These experimental data are supported by clinical studies. Thus, a recent phase II study shows that high phosphorylated levels of HER3 together with high phosphorylated levels of HER2 are predictive of favourable response to lapatinib (a bispecific EGFR/HER2 reversible TKI) in patients with advanced inflammatory breast cancer [29]. In addition, a correlation between the expression of herereglin and clinical response to trastuzumab-based therapies has been reported in patients with breast cancer [30].

**HER3 reactivation as a molecular mechanism of resistance to therapies targeting RTKs**

It is frequently observed that patients who initially respond to EGFR and HER2 inhibitors ultimately become refractory to treatment. The understanding of molecular mechanisms of acquired resistance to EGFR and HER2 inhibitors has provided valuable leads to enhance the efficacy of these drugs [31,32]. In this regard, there is increasing evidence showing that the reactivation of the HER3 signalling pathway makes a significant contribution to acquired resistance.

Thus, the induction of HER3 phosphorylation has been identified as a major resistance mechanism to EGFR TKIs in breast cancer cells chronically exposed to gefitinib [33]. Moreover, in lung cancer cells, acquired resistance to gefitinib has been linked to the amplification of the RTK c-MET and to the subsequent activation of the HER3/PI3K signalling pathway [34]. The HER3 pathway may also confer resistance to immunotherapies targeting the HER system. Thus prolonged exposure of lung cancer cells with the anti-EGFR antibody cetuximab induces perturbations in EGFR internalization/degradation and a subsequent paradoxical EGFR-dependent activation of HER3 [35]. High expression of herereglin/HER3 can predict escape from the anti-HER2 antibody trastuzumab in breast cancer cells [36,37]. There are also lines of evidence showing that EGFR/HER2 therapies have limited activity in tumours where they fail to markedly inhibit the herereglin/HER3 pathway [38–40].

Interestingly, HER3 may confer cancer cell resistance to therapies targeting unrelated RTKs. In tumours where c-MET receptor is overexpressed due to genomic amplification (specially in 10–15% of gastric cancer), c-MET is constitutively active, rendering the malignant cells highly dependent on c-MET signalling for proliferation and survival (‘c-MET-addicted cells’). Several small molecule c-MET inhibitors have been developed and have shown powerful antitumour efficacy in vitro as well as in mouse models, which has led to clinical trials in humans [41]. However, it seems that c-MET inhibition leaves c-MET-addicted cancer cells vulnerable to HER3-mediated reactivation of the PI3K/AKT pathway [42].

The IGF axis is frequently dysregulated in tumours mainly due to the overexpression of the ligands IGF-1 and IGF-2 and of their main receptor IGF-1R. Drugs targeting IGF-1R (neutralizing antibodies as well as TKIs) are currently evaluated in clinical trials [43]. A recent work from our laboratory shows that hepatocellular carcinoma cells overcome the specific inhibition of IGF-1R with the monoclonal antibody AVE1642 through increased expression and phosphorylation of HER3 [44]. These results reinforce the notion that IGF-1R and EGFR pathways cooperate in hepatoma cells [45]. HER3-dependent signalling also confers resistance to TKIs against IGF-1R (BMS-536924, PQIP) in breast, ovarian and colon cancer cells [46,47].

**Therapeutic strategies to inhibit HER3-dependent signalling in cancer**

In a recent computational model of the HER signalling network [48], HER3 has been identified as a key node. This model predicts that HER3 antagonist would inhibit combinatorial, ligand-induced activation of the HER3-PI3K network more potently than do current marketed therapeutics. Moreover, combinatorial therapies including HER3 targeting may ameliorate tumour responses to diverse therapies by limiting escape mechanisms and resistance.

Up to now, the potential of HER3 as a target for cancer treatment has been less appreciated than other HER members due to its defective kinase activity. Nonetheless, blockade of HER3-dependent pathways could be accomplished by different mechanisms:

- blockade of the ligand-binding site in HER3 [37];
- ligand trapping (as recently shown with hermodulins [49]);
- prevention of HER3 heterodimerization.

Two antibodies interfering with HER3 heterodimerization have been described. Thus, pertuzumab (2C4) is an anti-HER2 antibody, which binds to the subdomain II dimerization arm and inhibits ligand-induced HER2/HER3 heterodimerization. Due to its action mechanism, pertuzumab is more efficient in naive cells that trastuzumab which targets only HER2. Pertuzumab may also rescue cells with acquired resistance to trastuzumab [13,50,51]. MM-121 is a monoclonal antibody that efficiently blocks HER3 activation and heterodimerization with EGFR [48]. MM-121 effectively treats non-HER2-amplified tumours in multiple xenografts. The above-mentioned strategies will interfere with the membrane HER3 pool. However, one might keep in mind that HER3 may be also present in cell nucleus [24]. In this regard, the development of strategies able to diminish ERBB3 gene expression could be very helpful. Recently, the histone deacetylase inhibitor SNDX-275 [52] as well as elisidepsin (PM02734) [53], a marine-derived cyclic peptide, have been reported to exhibit such properties.

**Conclusions**

HER3 plays a key role in driving oncogenic cellular proliferation and survival in several human tumours through EGFR/HER3 and/or HER2/HER3 dimers. As a result, EGFR and HER2 inhibitors block HER3-dependent signalling though the PI3K/AKT pathway by preventing HER3 transphosphorylation, which is considered to be a molecular marker of the efficacy of HER TKIs. However, it seems that in some cases such inhibition is transitory and compensatory mechanisms allow cancer cells to restore the HER3 signalling pathway.
Moreover, HER3 reactivation is thought to be involved in the resistance to IGF-1R and c-MET inhibitors. Therefore, novel therapies or combinations blocking HER3 may provide strategies to overcome acquired resistance and to increase the effectiveness of targeted therapies.

Conflict of interest statement

Nothing declared.

References

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