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MINI REVIEW

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

Le récepteur HER3/ErbB3 : une cible prometteuse dans le traitement du cancer

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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. This review presents an update on HER3 status in cancer and on its potential impact on therapies targeting RTKs.

HER3, a member of the HER family

The HER family of RTKs consists of four closely related receptors with distinct binding specificities: EGFR (ErbB1/HER1), HER2 (ErbB2) for which no ligand as been described so far, HER3 (ErbB3) and HER4 (ErbB4). The prototype HER receptor contains an extracellular ligand-binding domain, a transmembrane region, and an intracellular region (Fig. 1A). Except for HER3, the intracellular region contains a TK activity. Upon ligand-binding, the conformation of HER receptors is modified which facilitates receptor dimerization into homodimers or heterodimers. The combinatorial formation of HER receptor dimers is dictated by the nature of the ligand. Only HER2 homodimerizes in the absence of ligand. Dimerization results in receptor autophosphorylation and in the subsequent recruitment of proteins involved in a variety of signalling cascades including the Ras/ERK and PI3K/AKT cascades. The sets of recruited cytoplasmic proteins depend largely on the nature of the dimerized receptor [1—3].

In the HER family, HER3 is unique since it lacks intrinsic TK activity and cannot autophosphorylate. Therefore,

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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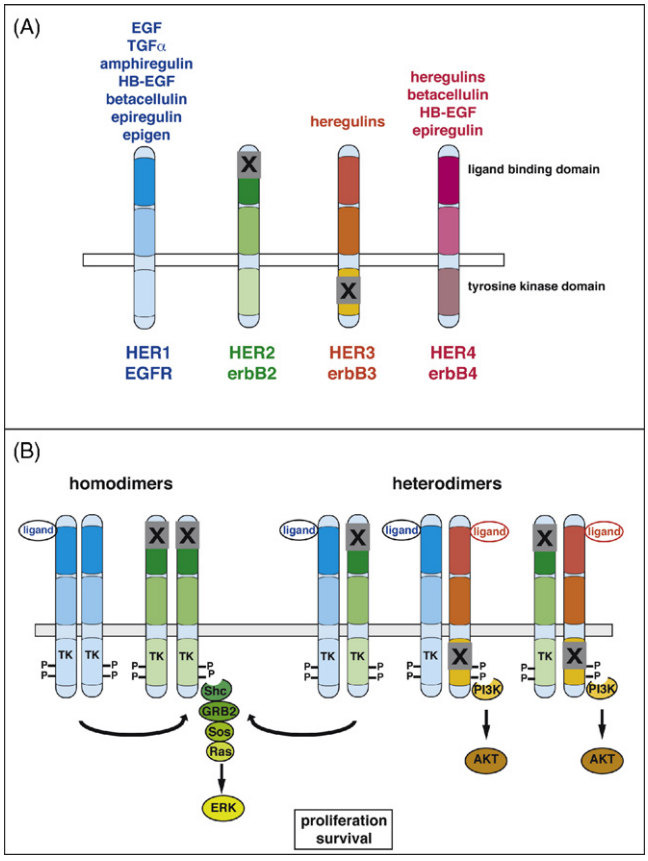

Figure 1 Structure and activation of the HER receptor family. A. The HER family consists of four closely related members: EGFR (ErbB1/HER1), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). These receptors contain an extracellular ligand-binding domain (except for HER2 for which no ligand as been described so far), a transmembrane region, and an intracellular region with a TK activity (except for HER3). Seven different EGFR ligands have been identified: epidermal growth factor (EGF), transforming growth factor-α (TGF-α), heparin-binding EGF-like growth factor (HB-EGF), betacellulin, amphiregulin, epiregulin and epigen. Some of these ligands may also bind to HER4. Heregulins (also called neuregulins) bind exclusively to HER3 and HER4 and exist as multiple isoforms. B. Upon ligand-binding, the conformation of HER receptors is modified which facilitates receptor dimerization into homodimers or heterodimers. HER2 can homodimerize in the absence of ligand. The well-characterized dimers in cancer cells are presented. Dimerization results in receptor autophosphorylation and in the subsequent recruitment of proteins involved in a variety of signalling cascades including the Ras/ERK and PI3K/AKT cascades. Phosphorylated tyrosine residues of HER3 have the highest affinity for PI3K among HER receptors. Consequently, the activation of HER3 results in a strong activation of the PI3K/AKT signalling pathway.

upon engagement of heregulin/neuregulin to HER3, it undergoes transphosphorylation on cytoplasmic tyrosine residues in complex with EGFR, HER2 or HER4. Once phosphorylated, HER3 has the highest affinity for PI3K among HER receptors. Consequently, the activation of HER3 results in a strong activation of the PI3K/AKT signalling pathway (Fig. 1B).

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 accompagnies 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 $\alpha_6\beta_4$ 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 Apc^{Min} 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)