Role of erbB3 receptors in cancer therapeutic resistance

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ErbB3 receptors are unique members of the erbB receptor tyrosine kinases (RTKs), which are often aberrantly expressed and/or activated in human cancers. Unlike other members in the family, erbB3 lacks or has impaired kinase activity. To transduce cell signaling, erbB3 has to interact with other RTKs and to be phosphorylated by its interactive partners, of those, erbB2 is the most important one. ErbB3 is frequently co-expressed with other RTKs in cancer cells to activate oncogenic signaling, such as phosphoinositide-3-kinase/protein kinase B (Akt) pathway, mitogen-activated protein kinase kinase (MEK)/mitogen-activated protein kinase (MAPK) pathway, Janus kinase (Jak)/signal transducer and activator of transcription (Stat) pathway, etc. and thereby promote tumorigenesis. Numerous studies have demonstrated that activation of erbB3 signaling plays an important role in the progression of a variety of tumor types, such as erbB2-overexpressing breast cancer, castration-resistant prostate cancer, platinum refractory/resistant ovarian cancer, epidermal growth factor receptor TKI-resistant non-small-cell lung cancer, and others. Basic research on the underlying mechanisms implicated the functions of erbB3 as a major cause of treatment failure in cancer therapy. Thus, concomitant inhibition of erbB3 is thought to be required to overcome the resistance and to effectively treat human cancers. This review focuses on the latest advances in our understanding of erbB3-initiated signaling in the development of resistance to cancer treatments.

Keywords erbB3; receptor tyrosine kinase; cell signaling; resistance; cancer

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Introduction

The erbB receptor tyrosine kinase (RTK) family, including the epidermal growth factor receptor (EGFR), erbB2 (HER2/neu), erbB3 (HER3), and erbB4 (HER4), is arguably the most important receptor family in the context of development and tumorigenesis [1,2]. These receptors are widely expressed in epithelial, mesenchymal, and neuronal cells [3]. Abnormal expression of erbB receptors is involved in carcinogenesis of diverse types of human cancers [4,5]. The shared molecular structure of erbB receptors consists of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain containing a region with tyrosine kinase activity and a non-catalytic region of C-terminal tail. Unlike other family members, erbB2 has no known ligands. When a ligand binds to EGFR, erbB3, or erbB4, a dimerization arm in their extracellular domains is exposed and receptor–receptor interactions are promoted [6]. Dimerization of erbB receptors is an essential step for the activation of the cytoplasmic signaling pathways [5,7]. ErbB receptors normally exist as inactive monomers with molecular folding to prevent dimerization, with the exception of erbB2 [8,9]. ErbB2 is in a constitutively active conformation with an exposed dimerization arm even in the absence of a ligand [8], thus making it the most preferred dimerization partner for other erbB receptors [10]. As a consequence of erbB receptor dimerization, the intracellular tyrosine kinases are activated and the tyrosine residues on C-terminal tails are phosphorylated, leading to the recruitment of adaptor proteins, and activation of the downstream signaling, such as phosphoinositide-3-kinase (PI-3K)/protein kinase B (Akt) pathway, mitogen-activated protein kinase kinase (MEK)/mitogen-activated protein kinase (MAPK) pathway, and Janus kinase (Jak)/signal transducer and activator of transcription (Stat) pathways, Src kinase, etc., imparting various biological responses, including cellular proliferation, maturation, survival, apoptosis, and angiogenesis [5,11].

ErbB3 receptor has long been considered an inactive 'pseudokinase' [12,13], although a recent study suggested that it possesses weak kinase activity that can trans-autophosphorylate its intracellular region [14]. To fully transduce cell signaling, however, erbB3 has to be phosphorylated by its interactive partners, of those, erbB2 is the most important one [15]. Like
other family members, erbB3 is often aberrantly activated in a variety of human tumors [1,2]. It is frequently co-expressed with other RTKs in cancer cells to activate oncogenic signaling, with the PI-3K/Akt pathway as the most important one, and thereby promote tumor initiation and progression. Numerous studies on the underlying mechanisms implicate the functions of erbB3 as a major cause of treatment failure in cancer therapy [16]. As the erbB3/PI-3K/Akt signaling also plays a pivotal role in the development of erbB2-overexpressing (erbB2+) breast cancer [17,18], castration-resistant prostate cancer (CRPC) [19], ovarian cancer [20,21], and EGFR tyrosine kinase inhibitor (TKI)-resistant lung cancer [22,23], concomitant inhibition of erbB3 is thought to be required to overcome resistance and effectively treat the cancer patients who have become resistant to the treatments. Several anti-erbB3 monoclonal antibodies (Abs) that prevent activation of erbB3 signaling are actively under preclinical investigations [24–26] and clinical studies (http://www.clinicaltrials.gov). Here, we discuss the latest progress in our understanding of the biology of erbB3 receptors in tumorigenesis and drug resistance of cancer.

The Unique Biology of erbB3 Receptors in Human Cancer Development

ErbB3 has a unique characteristic among the erbB family members. It cannot form homodimers and lacks or possesses much lower intracellular tyrosine kinase activity [14,27]. A sequence comparison of the protein kinases reveals that certain residues, such as Cys-721, His-740, and Asn-815, have non-conservative substitutions in erbB3. These changes diminish the catalytic activity of erbB3 in its tyrosine kinase domain [28]. However, once the ligand, heregulin (HRG) or neuregulin (NRG), binds to erbB3, it recruits another receptor containing tyrosine kinase activity to form a heterodimer, leading to the activation of erbB3. Thus, to fully transduce cell signaling, erbB3 has to be phosphorylated by its interactive partners, of those, erbB2 is the most important one [15]. ErbB3 is a more potent partner than other family members for the oncogenic activity of erbB2 [18,29–31]. It is thought that erbB3 functions primarily to drive erbB2-mediated cell signaling [18,32]. We have shown that erbB3 expression is required to maintain the tyrosine kinase activity of erbB2 in both mouse and human breast cancer cells [33,34], further emphasizing the pivotal role of an erbB3 receptor in erbB2 activation.

Elevated expression of erbB3 is frequently seen in various malignancies, such as cancers of breast, gastric, ovarian, prostate, and bladder, colorectal carcinoma, squamous cell carcinoma of the head and neck, melanoma [18,35,36]. It is worth noting that whereas both amplification and overexpression of erbB3 were observed in some cancers, erbB3 mutations were rarely found in human tumors until recently. Jaiswal et al. [37] were the first to report the identification of erbB3 somatic mutations in ~11% of colon and gastric cancers. Detailed studies demonstrated that the oncogenic activity of mutant erbB3 depends upon the kinase-active erbB2 and the erbB3 mutants transform colonic and breast epithelial cells in a ligand-independent manner [37]. In breast cancer, both mRNA expression and protein levels of erbB3 are up-regulated. Most metastatic breast cancers show expression for either EGFR or erbB2, and less often for both [38]. In contrast, co-expression of erbB2 and erbB3 is common in breast cancer [39] and breast cancer cell lines [40]. Overexpression of endogenous erbB3 and its association with the transgene encoded erbB2, promote mammary tumorigenesis in erbB2/neu-transgenic mice [41,42]. Studies indicated that erbB3 serves as a critical co-receptor of erbB2, and its expression is a rate-limiting factor for erbB2-induced breast cancer cell survival and proliferation [17,18]. In erbB2+ breast cancer tissues, preferential phosphorylation of erbB3, but not EGFR, has been observed [18]. It appears that erbB3 is a preferred dimerization partner for EGFR in melanoma and pancreatic cancer [43,44].

Elevated expression of erbB3 has been reported in 50%–70% of human breast cancers [45–47], and it seems to be associated with tumor size, metastasis, risk of local recurrence, etc. [48,49]. However, the prognostic value of erbB3 expression in breast cancer has rather been poorly documented, and the available data are not conclusive [47–51]. Some studies showed that erbB3 expression, measured by immunohistochemistry (IHCs) [52], fluorescence in situ hybridization and IHC [53], or quantitative real-time PCR (qRT-PCR) [54], significantly reduced the overall and disease-free survival of the breast cancer patients. In contrast, other studies have reported a positive prognostic significance for erbB3 status. In a study that examined the expression of erbB family members with qRT-PCR, a positive main effect of erbB3 mRNA on survival was reported [51]. The expression of erbB3 was also correlated with positive estrogen receptor (ER) and progesterone receptor (PR) status and inversely associated with histological grade [55]. Recently, a study analyzed the transcriptional profiling of erbB genes and showed a correlation of erbB3 mRNA levels with ER positivity and a favorable prognostic value of overall survival [56]. While a definitive explanation for the differences among the studies with respect to the prognostic significance of erbB3 expression in breast cancer cannot be given at present, a number of hypotheses have been proposed. A naturally occurring secreted isoform of erbB3 (p85-soluble erbB3) is unique in that it can bind to the ligand HRG with high affinity, thereby blocks HRG binding to the full-length erbB3 and inhibits HRG-induced activation of erbB3 [57]. This observation could be associated with the positive prognostic value of erbB3 in some studies. Moreover, recent evidence suggests that the subcellular distribution of erbB family members affects substantially their biological activities. ErbB3 pool is mainly within intracellular compartments. It seems that the
levels of phosphorylated erbB3 (P-erbB3) and its activity are associated with erbB3 re-localization to the plasma membrane. Furthermore, it has been demonstrated that ligands such as HRGs may affect the distribution of erbB3 and increase the membrane levels of the receptor [58]. In consequence, the impact of erbB3 on clinical outcomes of breast cancer patients may be better assessed when one considers not only its expression and interactions with other receptors like erbB2, but also its subcellular distribution as well as the expression levels of erbB3 ligands. Nonetheless, overexpression of erbB3 has been generally considered as a poor prognostic factor in breast cancer patients [59]. This was strongly supported by a recent study [60] showing that expression of erbB3 is associated with worse survival in solid tumors, including breast cancer, and the influence of erbB3 may be greater in the tumors where erbB2 is commonly overexpressed.

**ErbB3 Signaling in the Development of Cancer Therapeutic Resistance**

Homo- or heterodimerization of erbB receptors activates multiple downstream signaling pathways, such as PI-3K/Akt, RAS/RAF/MEK/MAPK, Phospholipase Cγ (PLCγ)/Protein kinase C (PKC), Jak/Stat, etc. [13]. The signaling pathways not only contribute to normal development, they also critically involve in multiple biological consequences and thereby promote tumor initiation and progression (Fig. 1). Therapeutic resistance associated with erbB signaling is frequently observed in cancer treatment. Because the expression and functions of erbB3 are regulated through a multitude of mechanisms in a number of cancer types, this highly dynamic nature facilitates erbB3 elicit refractory to many cancer therapeutics [16]. It has been shown that the activation of erbB family, mainly through MAPK, and Stat3 signaling, induces resistance to ALK inhibitors in the treatment of non-small-cell lung cancer (NSCLC) [61]. The erbB3 receptor and a non-RTK Src may form a compensatory signaling to enhance cancer cell survival under ionizing radiation [62]. Activation of both the PI-3K/Akt and the RAS/RAF/MEK/MAPK pathways via amplification of erbB2 or increased levels of the erbB3 ligand HRG results in resistance to EGFR-targeted therapy in colorectal cancers [63]. Thus, a recent study suggests that blockade of both erbB2 and erbB3 exhibits superior antitumor activity when compared with the combination of MEK and Akt inhibitors [64]. Of the four erbB receptors, erbB3 is the best suited to activate PI-3K/Akt signaling, because it has most tyrosine residues on its C-terminal tail, once being phosphorylated, capable of binding to the p85 subunit of PI-3K [15,65]. In fact, among all of erbB dimerization complexes, the erbB2/erbB3 heterodimer is the most biologically active and potent for the activation of the PI-3K/AKT signaling pathway [66,67]. While erbB3 and erbB4 are capable of binding to the p85 regulatory subunit of PI-3K directly, EGFR and erbB2 bind indirectly to p85 through adaptors or through heterodimerization with erbB3 or erbB4 [68,69]. Since the PI-3K/Akt signaling is the most important survival pathway in cell proliferation and its activation often leads to multidrug resistance in cancer treatment [70], it is not surprising that studies on the underlying mechanisms implicated the function of erbB3 as a major cause of treatment failure in cancer therapy [16].

**Resistance to hormonal therapy**

Treatment of ER positive (ER+) breast cancer patients with an anti-estrogen, such as tamoxifen, is commonly used and has significantly improved survival of the patients. However, both primary (de novo) and acquired resistances to tamoxifen frequently occur [71]. The mechanisms contributing to tamoxifen resistance include loss or mutation of ER, alterations in the intracellular signaling of breast cancer cells, ligand-independent ER-mediated transcription, and perturbation of the interactions of ER with some co-repressors [72]. Recently, activation of erbB family members has been linked to resistance to tamoxifen, since the increased erbB receptors facilitate
breast cancer cells to bypass normal endocrine responsiveness [73,74]. It has been shown that the cross-talk between ER and erbB2/EGFR signaling promotes hormone-independent growth of breast cancer cells [75–77]. The importance of erbB3 in the development of tamoxifen-resistant phenotype is emerging. Clinical studies examining a large retrospective group of tamoxifen treated, ER+ breast cancer patients revealed that the patients with co-expression of erbB2 and erbB3 were significantly more likely to relapse on tamoxifen [78]. The tamoxifen-sensitive MCF-7 cells transfected with a HRGβ-2 cDNA become estrogen-independent and resistant to tamoxifen both in vitro and in vivo [77]. Direct demonstration of the involvement of erbB3 in tamoxifen resistance comes from studies of Liu et al. who showed that down-regulation of erbB3 by a siRNA abrogated erbB2-mediated tamoxifen resistance in breast cancer cells [33]. Specific knockdown of erbB3 had no effect on ERα expression or its phosphorylation status, but significantly enhanced tamoxifen-associated growth inhibition in both MCF-7 and the erbB2-transfected MCF-7 (MCF-7/erbB2) cells via increased apoptosis [33]. The molecular mechanism responsible for the increased sensitivity to tamoxifen upon erbB3 down-regulation may be due to decreased levels of P-Akt, as it is well known that activation of PI-3K/Akt signaling is associated with tamoxifen resistance and MCF-7 cells expressing a constitutively active Akt proliferate under reduced estrogen conditions and are resistant to tamoxifen-mediated growth inhibition [79–81]. In addition, the erbB3/PI-3K/Akt signaling has also been shown to play a critical role in the development of CRPC. Although androgen withdrawal therapy (AWT) is currently the primary, first-line, an effective therapeutic intervention for recurrent prostate cancer, most patients ultimately develop resistance and progress to metastatic CRPC (mCRPC) [82]. Elevated expression of erbB3 in CRPC leads to androgen receptor stabilization and activation of PI-3K/Akt signaling [19]. Thus, erbB3 receptors may serve as useful biomarkers for modulating tamoxifen treatment and AWT in luminal B (ER+, erbB2+) breast cancers and CRPC, respectively.

Resistance to targeted therapy

Because of their extensive overexpression in tumor tissues and important function in cancer progression, attempts to target erbB receptors in cancer therapy have been the focus of research and have reached clinical applications. Currently used erbB-targeted therapy in clinic can be divided into two strategies: blocking Ab, such as cetuximab (Erbitux) against EGFR and trastuzumab (Herceptin) against erbB2; small-molecule TKI, such as both gefitinib (Iressa) and erlotinib (Tarceva) targeting EGFR and lapatinib (Tykerb/Tyverb) dual-targeting EGFR and erbB2. These EGFR- and/or erbB2-targeted therapies have been successfully used in the treatment of various human cancers, including (cetuximab for) metastatic colorectal cancers and head and neck tumors, (gefitinib and erlotinib for) EGFR mutant NSCLC, and (trastuzumab and lapatinib for) erbB2+ breast cancers and gastric cancers. However, almost all the tumors inevitably developed resistance to the therapeutic Abs and/or the inhibitors within 1 year. Numerous studies indicated that activation of erbB3 signaling is one of the major mechanisms contributing to the resistance to EGFR- and/or erbB2-targeted therapy [63,83]. It has been reported that a subset of colorectal cancer patients who exhibit either de novo or acquired resistance to cetuximab-based therapy has erbB2 amplification or high levels of circulating HRG, which induces activation of erbB3 signaling [84]. While multiple mechanisms exist in EGFR-TKI (gefitinib and erlotinib) resistance [63], another RTK MET amplification has been shown to lead to gefitinib resistance in lung cancer treatment by activating erbB3 signaling [22]. A recent study showing that dual targeting of EGFR and erbB3 is able to overcome acquired resistance to cetuximab and erlotinib further emphasized the importance of erbB3 signaling in resistance to EGFR-targeted therapy [23].

Trastuzumab (also known as Herceptin, a humanized monoclonal Ab against erbB2) is the first erbB2-targeted therapy approved by Food and Drug Administration (FDA) and has significantly improved the outcomes of early and metastatic erbB2+ breast cancer patients [85,86]. Unfortunately, resistance to trastuzumab is common and currently represents a huge clinical problem [87,88]. Tremendous efforts have been made to better understand the molecular mechanisms of trastuzumab resistance and to develop novel strategies/agents that can overcome the resistant phenotypes [89]. At the level of receptor complex, dimerization between erbB2 and another RTK, such as erbB3, EGFR, or the insulin-like growth factor I receptor (IGF-1R), may impair trastuzumab binding to erbB2. At the level of intracellular signaling, activation of the PI-3K/Akt pathway and Src kinase have been identified as the major determinants of trastuzumab resistance [90,91]. It is well documented that both erbB3 and IGF-1R-initiated signaling pathways contribute to trastuzumab resistance [92–94]. Nonetheless, the relationship between erbB3 and IGF-1R in trastuzumab resistance remains unclear. We recently discovered that the erbB2 receptor simultaneously interacted with erbB3 and IGF-1R to form a trimeric complex in trastuzumab-resistant breast cancer cells, and that it was the heterotrimORIZATION of erbB3/erbB2/IGF-1R, not the heterodimer of erbB2/erbB3, or IGF-1R/erbB2, that played a critical role in the breast cancer cells resistant to trastuzumab [95]. Further studies showed that specific knockdown of either erbB3 or IGF-1R was able to reverse trastuzumab resistance, and significantly enhances trastuzumab-mediated growth inhibitory effects on the otherwise resistant cells. For the downstream signaling, specific knockdown of erbB3 decreased the levels of both P-Akt and P-Src, whereas IGF-1R knockdown only gave rise to reduction of P-Src [95]. Our data suggested that erbB3 and IGF-1R initiate different signaling pathways contributing to
trastuzumab resistance—erbB3 activates both PI-3K/Akt signaling and Src kinase, whereas IGF-1R mainly elicits Src activation.

Lapatinib is another erbB2-targeted therapy approved by FDA and has been used to treat erbB2+ breast cancer that has progressed after trastuzumab-based therapy [96]. Unfortunately, the efficacy of lapatinib is also compromised by resistance [97]. Some evidence showed that lapatinib and trastuzumab do not share common mechanisms of resistance, since lapatinib has activity in trastuzumab-resistant breast cancer [98]. However, a recent report indicated that loss of PTEN and the resulting activation of PI-3K/Akt signaling lead to lapatinib resistance [99]. Increased Src family kinase activity is also thought to be a mechanism of lapatinib resistance [100], and a recent study showed that a small-molecule Src inhibitor, saracatinib, significantly enhances lapatinib-mediated antitumor activity against breast cancer brain metastasis [101]. As we have shown that erbB3 activates both PI-3K/Akt signaling and Src kinase in the trastuzumab-resistant breast cancer cells [95], it is conceivable to hypothesize that activation of erbB3 signaling will induce lapatinib resistance as well. Nonetheless, whether erbB3 may function as a predictive biomarker for lapatinib sensitivity in breast cancer treatment remains to be further elucidated.

In addition to causing resistance to erbB-targeted therapy, transcriptional up-regulation of erbB3 has been recently shown to involve in the resistance to RAF/MEK inhibitors in the treatment of melanoma and BRAF mutant thyroid carcinomas [102,103]. It appears that different tumor types utilize distinct mechanisms to up-regulate erbB3. The RAF inhibitor PLX4720 in melanoma enhanced erbB3 expression through a transcription factor, FOXD3 [102], whereas inhibition of RAF in thyroid cancers with vemurafenib (PLX4032) induced erbB3 transcription via decreased promoter occupancy by the transcriptional repressors C-terminal-binding proteins 1 and 2 (CtBP1/2) [103]. Once again, the increased erbB3 depended upon erbB2 to activate the downstream signaling Akt [102] or MAPK [103], and thereby resulted in resistance to the RAF inhibitors. Thus, in both the studies, therapeutic targeting of erbB2 with lapatinib was able to overcome the resistant phenotypes [102,103]. In light of the importance of enhanced erbB3 expression, we hypothesize that novel strategy inactivating the erbB3 signaling or reducing erbB3 protein levels may exhibit an even better efficacy in combination with the RAF inhibitors.

Resistance to chemotherapy
Chemotherapy, as an important conventional approach to treat human cancers, usually exerts antitumor activity via induction of apoptosis. The tumor cells with enhanced survival signaling and/or defects in apoptotic pathways may escape from chemotherapy. Since erbB3 (via interactions with other RTKs, particularly erbB2) is a potent activator of the survival signaling, PI-3K/Akt pathway, it is understandable that activation of erbB3 signaling also results in chemoresistance in cancer treatment. Docetaxel-based chemotherapy has been established as the standard of care for mCRPC. However, only half of the patients benefit from docetaxel, and those who respond initially once again become resistance and eventually die of mCRPC [82,104]. Mechanistic studies suggested that activation of erbB3 mainly through PI-3K/Akt signaling plays a vital role in the progression of mCRPC into docetaxel resistance [19]. Increased secretion of HRG has been found in a subset of ovarian cancers, and thereby stimulates ovarian cancer cell proliferation via activated erbB3/HRG autocrine loop [21]. Recent studies suggested that erbB3 signaling may also contribute to chemoresistance in ovarian cancer, since the chemotherapeutic drug doxorubicin up-regulates HRG to activate the erbB3/PI-3K/Akt signaling in ovarian cancer cells [105]. It was postulated that targeting of erbB3 may significantly sensitize ovarian tumors to the toxic effects of platinum-based or other chemotherapy regimens [20]. Our early studies showed that co-expression of erbB2 and erbB3 in human breast cancer cell lines induced activation of PI-3K/Akt signaling and was associated with an increased resistance to multiple chemotherapeutic agents, such as paclitaxel, doxorubicin, 5-fluorouracil, etoposide, and camptothecin [70]. In identifying the key downstream mediator that contributes to chemoresistance, we discovered that elevated expression of erbB3 confers paclitaxel resistance in erbB2+ breast cancer cells via PI-3K/Akt-dependent up-regulation of Survivin [106]. A large body of evidence indicated that Survivin functions as a critical inhibitor of apoptosis to promote cell survival and proliferation, and regulates mitosis during cell cycle progression [107]. Survivin is selectively expressed in a variety of human malignancies and its overexpression positively correlates with poor prognosis, tumor recurrence, and therapeutic resistance [107]. Thus, novel strategies targeting Survivin, such as antisense oligonucleotide and pharmacological inhibitors may significantly enhance chemotherapeutic efficacy and are currently under clinical testing for cancer treatment [107–109]. Nonetheless, the precise mechanism by which the erbB3 signaling specifically up-regulates Survivin, but not the functionally related molecules, like Mcl-1 and Bcl-xL in erbB2+ breast cancer cells [106] remains unknown.

Perspectives
Studies on erbB RTKs have primarily focused on EGFR and erbB2 in cancer research. Recent advances dramatically improve our understanding of erbB3 as an obligate partner for other RTKs and draw our attention to the important role of erbB3 in both primary and acquired resistances to cancer therapeutics. The erbB3 signaling in cancer progression,
particularly tumor recurrence following drug resistance has several implications for future investigations. ErbB3 may be considered as a valuable biomarker to predict the efficacy of EGFR- and/or erbB2-targeted therapy in the treatment of NSCLC and erbB2+ breast cancer, respectively. Therapeutic targeting of erbB3 may be an efficient way to conquer treatment failure and significantly enhance antitumor activity of hormonal therapy, EGFR/erbB2-targeted therapy, chemotherapy, and radiotherapy. Although the unique biological features of erbB3 receptor in cancer biology have been thoroughly investigated, several critical questions remain unanswered. First, activation of the erbB3 signaling, mainly through PI-3K/Akt and MEK/MAPK pathways, not only confers drug resistance in cancer treatment, but also promotes tumor metastasis [110–114]. The key downstream mediators that are responsible for erbB3 signaling-mediated cancer progression remain unclear. We discovered that the PI-3K/Akt-dependent up-regulation of Survivin played a pivotal role in erbB3-mediated paclitaxel resistance in erbB2+ breast cancer cells, and specific knockdown of Survivin abrogated the resistance [106]. However, it is not known whether the increased Survivin leads to resistance to all therapeutic agents; and the precise mechanism of erbB3/PI-3K/Akt-mediated up-regulation of Survivin needs to be elucidated. Identification of additional mediators of erbB3 signaling may provide more opportunities to develop novel strategies revoking drug resistance and tumor metastasis. Secondly, both erbB2 and erbB3 have defects when they are considered individually. The two receptors rely on each other to elicit the most biologically active and potent activation of PI-3K/Akt signaling via heterodimerization [66,67]. Nonetheless, the molecular basis of erbB2/erbB3 co-expression in tumor cells remains elusive. It is unclear whether the same mechanisms are utilized by the tumor cells to simultaneously regulate erbB2 and erbB3, or tumor cells overexpress one receptor first and subsequently enhance the expression of the other. Finally, it is well-known that the ligand, HRG is critical to induce activation of erbB3 signaling. Aberrant production and/or maturation of HRG will alter tumor cell survival and proliferation. We believe that studies on the dysregulation of HRG in various human cancers may further our understanding of the ligand’s biological function in erbB3 signaling-mediated tumor initiation and progression and facilitate the development of novel approaches for cancer treatment. In conclusion, erbB3 is a focal point in erbB receptors-mediated tumorigenesis, and as such, constitutes a new potential biomarker and important target for cancer therapy.

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**References**

10. Graus-Porta D, Beerli RR, Daly JM and Hynes NE. ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signaling. EMBO J 1997, 16: 1647–1655.
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