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The role of HER3, the unpretentious member of the HER family, in cancer biology and cancer therapeutics

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Abstract

Many types of human cancer are characterized by deregulation of the human epidermal growth factor receptor (HER) family of tyrosine kinase receptors. In some cancers, genomic events causing overactivity of individual HER family members are etiologically linked with the pathogenesis of these cancers, and constitute the driving signaling function underlying their tumorigenic behavior. HER3 stands out among this family as the only member lacking catalytic kinase function. Cancers with driving HER3 amplifications or mutations have not been found, and studies of its expression in tumors have been only weakly provocative. However, substantial evidence, predominantly from experimental models, now suggest that its non-catalytic functions are critically important in many cancers driven by its' HER family partners. Furthermore, new insights into the mechanism of activation in the HER family has provided clear evidence of functionality in the HER3 kinase domain. The convergence of structural, mechanistic, and experimental evidence highlighting HER3 functions that may be critical in tumorigenesis have now led to renewed efforts towards identification of cancers or subtypes of cancers wherein HER3 function may be important in tumor progression or drug resistance. It appears now that its failure to earn the traditional definition of an oncogene has allowed the tumor promoting functions of HER3 to elude the effects of cancer therapeutics. But experimental science has now unmasked the unpretentious role of HER3 in cancer biology, and the next generation of cancer therapies will undoubtedly perform much better because of it.

Keywords

HER3; ErbB3; resistance; tyrosine kinase inhibitor

Background

The human epidermal growth factor receptor (HER) family are a family of four homologous receptor tyrosine kinases (RTKs) consisting of EGFR (HER1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). These receptors have a general structure consisting of an extracellular domain (ECD), an intracellular kinase domain (KD), and an intracellular c-terminal tail. Their signaling activity is greatly enhanced by extracellular ligands that bind

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and stabilize an ECD conformation that is highly favorable for dimerization with another receptor. A consequence of dimerization is the activation of the intracellular KD and phosphorylation of the c-terminal tail tyrosine residues, leading to the recruitment of signaling molecules and activation of intracellular signaling pathways. The HER family appears to be unique in the mechanism by which dimerization induces their activation. In most other RTKs, dimerization leads to the transphosphorylation of the active site of the KD producing a covalently activated kinase that then phosphorylates substrates until inactivated by phosphatases. In the HER family, dimerization leads to the allosteric activation of one KD by another without a requirement for phosphorylation of the active site loop [1](Figure 1). The allosterically activated kinase in turn phosphorylates the c-terminal tail of its dimerization partners. This mechanism for RTK activation provides tighter control of signaling activity, and largely restricts potential phosphorylation substrates to the c-terminal tails of dimerizing family members rather than unrelated intracellular substrates. This also provides for a diversity of homodimer and heterodimer complexes forming within the HER family with potential functional differences among them. In experimental models, there are clearly differences in signaling activity induced by the various homodimer and heterodimer combinations. In general, heterodimers are more active signaling complexes and the HER2-HER3 heterodimer is the most active signaling dimer in this family [2,3]. This inherent diversity in possible dimerization pairs, coupled with diversity in ligand-binding specificity of their ECDs and diversity in docking activities of their c-terminal tails generates a plethora of possible signaling activities inherent in this family. We are just beginning to identify unique attributes among individual HER family members that may serve to resolve some of this complexity. The most unique member in this family appears to be HER3.

The allosteric mode of activation imparts unique attributes to the activating KD. In particular, catalytic function is not required in a KD when it functions as the activating partner in a KD dimer. In fact HER3, lacks catalytic function altogether [4–6] and most likely HER3 evolved as a dedicated and specialized activating KD in this family. Consistent with this, HER3 is the only HER family member that is unable to generate a signal through homodimerization and is an obligate partner for heterodimerization with the other family members [2,3]. In addition, the c-terminal tail of HER3 is unique in that it contains six consensus phosphotyrosine sites which bind the SH2 domain of the three regulatory subunits of PI3K [7–9]. This ability is not present in EGFR or HER2, although HER4 also contains a single PI3K-binding site, present in only one of its isoforms [10]. HER3 is also unique in the functions of its ECD. While the HER3 ECD has the ability to bind numerous ligands, the ligand-associated ECD is an obligate heterodimer and the HER3 ECD appears unable to homodimerize [11]. Whether these unique aspects of HER3 are an evolutionary coincidence or functionally related to each other are not known. But PI3K signaling is a critical regulator of many cellular processes and its premature activation must be avoided. And since HER3 is an access point for activation of the PI3K pathway, it is plausible that nature placed a higher threshold for phosphorylation of the HER3 signaling tail, and the evolution of the HER3 ECD and KD into structures that are unable to activate through simple homodimerization functions to protect the PI3K signaling pathway from premature activation. As such, the signaling activities of the HER3 c-terminal tail depend entirely on the available repertoire and expression levels of other HER family members and ligands.

In addition to its inability to autophosphorylate and signal without partners, additional restraints appear to protect HER3 from premature signaling activity. In the absence of ligand activation, the HER3 c-terminal tail binds and covers its activation surface *in trans*, restraining its allosteric activation functions [6](Figure 1). In addition, the clustering of HER3, based on both ECD interactions and ICD interactions, appears to provide yet additional restraint through its sequestration away from EGFR and HER2 [6,12]. HER4 may

also participate in HER3 sequestration [6]. This may underlie the favorable prognostic role of HER4 expression observed in patients with early stage breast cancer [13–15].

When engaged in heterodimer complexes with other HER proteins, HER3 functions not only as a specialized allosteric activator of all other HER proteins, but also as their signaling substrate. The HER3 c-terminal tail contains 14 tyrosines, which when phosphorylated, can potentially dock numerous SH2 or PTB binding proteins involved in a number of different intracellular signaling pathways. The binding activities of many of these phosphotyrosines have been demonstrated in peptide binding assays [16,17]. The true physiologic function of these signaling activities have not all been confirmed and remains to be defined. The one signaling activity of the HER3 c-terminal tail that is critically important and well established is its ability to activate PI3K through six phosphotyrosine residues that can bind and activate the PI3K heterodimer [7–9]. When recruited to the membrane by tyrosine phosphorylated HER3 residues, the complex containing the regulatory and catalytic subunits of PI3K, phosphorylates membrane phosphoinositides. In particular, generation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) recruits and activates the PH-domain containing kinases, PDK1 and Akt. This link to Akt identifies HER3 as a critical signaling node in the HER family, through which HER proteins can access and regulate the activities of Akt. Akt phosphorylates and controls the activities of many downstream signaling molecules involved in diverse cellular functions including growth, proliferation, survival, and metabolism [18]. In particular, Akt influences the activities of two mTor-containing complexes that function to coordinate cellular growth and metabolic activities in response to the availability of nutrients and energy [19,20].

The functional role of HER3 in malignancy

Each of the HER family proteins have been etiologically linked with the development of some type of human cancers through overexpression or mutational activation, including cancers of the breast, lung, head and neck, brain, and skin. But since the functions of HER proteins are highly interdependent, mechanistic studies have frequently revealed the involvement of more than one HER protein in the pathogenesis of these cancers. In particular, HER3 has not thus far been implicated as a driving oncogene, but has only been identified as an obligate partner in HER family oncogenesis. HER3 is not transforming when overexpressed [21] and currently there are no known activating mutations and/or genomic alterations that are known to confer oncogenic activity to HER3 [22–24]. But its role as an obligate partner is now well established in some breast cancers and increasingly suspected in several other cancers.

In particular, HER3 plays a critical role in HER2-mediated transformation and is indispensable for continued tumor cell growth and proliferation in tumors driven by HER2 overexpression. In two different knockdown models, a loss of functional HER3 in HER2 amplified breast cancer cell lines results in a reversion of transformed growth equal to that which is seen with a loss of HER2 [25,26]. In contrast, the loss of EGFR expression by shRNA knockdown does not affect HER2-driven tumors, confirming that HER3 is specifically essential for HER2-driven tumorigenesis [26]. Consistent with this, the majority of HER2 amplified breast tumors coexpress HER3 but the coexpression of EGFR is inconsistent [26,27]. A critical function of HER3 in HER2-mediated transformation is the activation of PI3K/Akt signaling. Consistent with this, HER2-amplified breast cancers show widespread activation of Akt [28,29]. While functionally important in the HER2-amplified subset of breast cancers, the role of HER3 in other types of breast cancers is much less clear. Its level of expression across all breast cancers does not appear to have a correlation with tumor biology. Numerous descriptive series have looked at the impact of HER3 expression

on tumor characteristics and disease outcome in breast cancers and the results have been conflicting and inconclusive [14,24,30–33].

HER3 has been shown to be highly expressed in melanomas and its expression correlates with proliferation, advanced disease stage and poor prognosis [34,35]. Its catalytic partner is unlikely to be HER2 since HER2 expression is low or absent in most melanomas [36]. High expression of HER3 in melanoma, in the absence of HER2 expression, suggests that HER3 may be functioning as an allosteric activator of EGFR or HER4 in these lesions [37]. In particular, recent evidence showing frequent mutational activation of HER4 in a subset of melanomas has highlighted HER4 as potentially important in this subset of melanomas [38]. Melanoma metastases frequently show even higher expression of HER3 compared with primary tumors and in experimental models knockdown of HER3 reduces melanoma cell migration and invasion [34]. This suggests that HER3 may play a role in cell migration and invasion. How HER3 might affect cellular motility mechanistically is yet to be determined.

Although HER family proteins have not been implicated in the pathogenesis of prostate cancer, HER3 is overexpressed in some prostate cancers. Experimental evidence suggests that HER3 is required for many of the transformed characteristics of prostate cancer cells including motility *in vitro* and tumorigenicity *in vivo* [39]. The existing data does not identify a HER family partner for HER3 in this disease. Clearly much more work is necessary to better define the function of HER3 and other HER family members in the biology of prostate cancers.

Although normal colonic tissue has little to no HER3 expression, HER3 is expressed in a significant proportion of colorectal cancers [40–44]. An intestinal specific HER3 knockout mouse model shows that a loss of HER3 results in loss of HER4 expression suggesting that in the colon, HER4 may be dependent on HER3 and that the HER3-HER4 heterodimer may have a specific function in this tissue type. When crossed to the *Apc^{Min}* mice who rapidly develop intestinal and colorectal tumors, loss of HER3 almost completely prevents colonic tumorigenesis and the small intestinal tumors that do develop in the absence of HER3 show reduced Akt signaling and increased apoptosis [45]. This study gives insight into how HER3 might function in a heterodimer with HER4 to prevent apoptosis in a subset of colorectal cancers. In light of the fact that EGFR directed therapies do show some clinical activity in colon cancers, further investigation into HER3's role in apoptosis in these tumors is warranted.

The role of HER3 is well established in specific subsets of lung cancers but less well defined in the broader scope of lung cancers. Reports of expression or overexpression of HER3 in lung cancers vary considerably from 18–100% and at least some groups find that overexpression correlates with shorter survival times [46–50]. Brain metastases that develop in patients with non-small lung cell lung carcinomas (NSCLC) demonstrate higher levels of phosphorylated HER3 than the primary tumors further linking HER3 signaling with the biology of this disease and possibly with its ability for invasive or metastatic growth [49]. A subset of NSCLCs are driven by mutationally activated EGFR, and these cancer are sensitive to EGFR tyrosine kinase inhibitors (TKIs) [51,52]. A substantial body of experimental evidence functionally implicates HER3 in the pathogenesis of these EGFR-driven lung cancers. In a comparison of lung cancer cell lines that are sensitive or resistant to the EGFR TKI gefitinib, the best marker of sensitivity to gefitinib is the sensitivity of HER3 signaling and HER3-dependent activation of PI3K [53]. The EGFR-HER3 interdependency is seen in tumor cell types harboring mutationally activated EGFR, but is also seen in some cancers with wild-type EGFR, revealing a role for HER3 that extends beyond the context of mutationally activated EGFR. Treatment of patients with gefitinib is highly effective in tumors with mutationally activated EGFR, although the development of

acquired resistance is universal. While resistance typically develops as a result of secondary mutational events within the EGFR kinase domain rendering EGFR drug-resistant [54], rarely resistance can also develop through overactivity of the cooperating proto-oncogene c-MET and the c-MET-dependent phosphorylation of HER3, further highlighting the central role of HER3 in the pathogenesis of this disease [55].

Mounting evidence suggests a functional role for HER3 in ovarian cancers, but mechanistic insight into its precise role in this cancer subtype is currently lacking. Reports of the expression of HER3 in ovarian tumors vary widely from 3–90% [56–61]. In a recent study, the expression of HER3 does appear to correlate with decreased survival [62]. Sheng *et al* have identified an autocrine signaling loop involving phosphorylated HER3 in a subset of primary ovarian cancers and ovarian cancer cell lines [63]. The knockdown of HER3 inhibits proliferative growth *in vitro* and tumorigenic growth *in vivo* in some ovarian cancer cell lines. The functional importance of HER3 appears to be restricted to ovarian cancer cells with basal HER3 phosphorylation as the loss of HER3 in cells that lack HER3 phosphorylation does not have a similar affect. These data support the idea that the expression of HER3 may not be an indicator of its functional involvement in tumors, rather that it is the signaling activity of HER3, revealed by its phosphorylation, that identifies its functional role. The HER family partner that underlies the functions of HER3 in ovarian tumor remains to be defined.

HER3 is notably overexpressed in the childhood glioma, pilocytic astrocytoma while other pediatric brain tumors do not show the same levels of HER overexpression [64]. In astrocytic glioma cell lines, constitutive HER3 phosphorylation was associated with an inhibition of apoptosis as opposed to increased cell proliferation that has been reported in other tumor types [65]. Radiation induced pediatric glioblastomas display a different gene expression profile compared with *de novo* pediatric glioblastomas and frequently have even higher expression of HER3 [66]. Recent insight into the molecular classification of adult glioblastomas was undertaken by the Cancer Genome Atlas Research Network to classify glioblastomas through gene expression profiling. This analysis revealed several distinct molecular subtypes of this disease and the expression of HER3 shows significant differences among the subtypes, and its overexpression is one of the signature genes of the proneural subtype [67].

The role of HER3 in treatment failure

In specific cancer subtypes, the driving role of specific HER family proteins is well established. This has led to the development of targeted therapies which seek to inactivate the driving oncoprotein and induce a complete remission of the cancer. This hypothesis, that oncogene addicted tumors can be cured by inhibiting their oncogenic driver, remains one of the most promising paradigms and most eagerly pursued avenues in cancer therapeutics. However, targeted therapies to HER family proteins have not yet lived up to this potential, despite conclusive evidence implicating HER protein involvement in the pathogenesis of some cancers. The analysis of drug resistance in several HER family driven cancers appears to highlight a central role for HER3 in mediating treatment failure. The interdependent nature of HER family signaling has been appreciated for more than a decade now, but due to its lack of intrinsic kinase activity and lack of autophosphorylation ability, HER3 had been considered a slave member of the family, whose functions are entirely dependent on the other members. The implication of this for cancer therapeutics had been that any relevant functions of HER3 would consequentially be inhibited by treatments that target the driving oncogenic HER family member in a given cancer type. As such, none of the targeted therapies until recently have directly targeted HER3 and even the agents considered pan-HER inhibitors spare the functions of HER3. This paradigm appears to have greatly

underestimated the functional role of HER3 in human cancers, and mounting evidence from a number of different cancer subtypes now appears to implicate the functions of HER3 as a major cause of treatment failure. As this evidence continues to mature, it is becoming more apparent that effective therapy of some types of cancers will require the concomitant targeting of HER3 functions.

The disease wherein the oncogenic role of HER proteins is best understood and most convincingly established is the HER2-amplified subtype of breast cancers. This has led to the development of several types of targeted therapies intended to inactivate HER2. These therapies have measurable clinical benefits and at least two such drugs are already in clinical practice. But their clinical activities are below what we would expect from inhibiting such a critical tumor driver. The anti-HER2 monoclonal antibody trastuzumab when administered as a single agent to patients with HER2-overexpressing metastatic breast cancer results in response rates between 11–26%, falling below expectations [68–70]. Furthermore, the majority of the responses to trastuzumab as either monotherapy or in combination with chemotherapy are transient and resistance inevitably develops. However, trastuzumab may not be a direct test of the oncogene inactivation hypothesis of cancer therapy since the mechanism of action remains unknown, and it is not a very effective inhibitor of HER2 signaling. In fact, trastuzumab does not affect HER2-HER3 signaling in HER2-amplified cancer cells very well [71–74]. On the other hand, HER family TKIs provide a much more compelling mechanistic basis for inactivation of HER2. Kinase function is essential for HER2-driven tumorigenesis [75] and inhibition of its catalytic kinase activity is a highly rational mechanistic basis for anti-tumor agents. However TKIs also show only modest and short-lived efficacy in clinical studies [76–81]. Recent work from our lab has identified the central role of HER3 in this paradox. Although this disease is driven by the overexpression of HER2, treatment of these cancer cells with HER family selective TKIs inactivates HER2-HER3 transphosphorylation for only several hours and drug therapy ultimately fails to durably suppress HER3 phosphorylation and downstream PI3K/Akt signaling [82]. This is observed with all classes of HER family TKIs including different structural classes and both reversible and irreversible inhibitors. The failure to durably inactivate HER3 signaling averts the apoptotic consequence of TKI therapy and significantly undermines their anti-tumor efficacy against this type of cancer. Mechanistic studies show that this is due to a substantial upregulation of HER2-HER3 transactivation, driven by residual HER2 activity that functions to restore PI3K/Akt signaling despite continued drug therapy. In this tumor subtype, the role of cross-talk with other RTKs such as c-MET or IGF1R or autocrine feedback loops induced by the induction of ligands has been interrogated but there is no compelling evidence to support it [83] (and unpublished data). These revelations have redefined the functionally relevant driver of this disease as the HER2-HER3 heterodimer. The redefinition is an important one, particularly in the realm of drug development, since the durable inactivation of the HER2-HER3 driver now defines the bar for the development of effective therapies for this disease. A quantitative analysis of the HER2-HER3 tumor driver reveals that it is endowed with a signal buffering capacity that protects it against a nearly two-log inhibition of HER2 catalytic activity by TKIs, revealing a substantial barrier in the treatment of this disease [83]. The HER2-HER3 driver can be effectively and durably suppressed by treatments that fully inactivate HER2 catalytic function. While the complete inactivation of HER2 kinase requires concentrations of TKI that are not tolerable *in vivo*, such doses are tolerable and much more effective in intermittent dosing, and non-continuous treatment schedules afford one approach that is currently being explored in clinical studies [83].

The mechanisms that function to protect HER2-HER3 signaling from TKI therapy in HER2-amplified cancers are largely related to the dynamic nature of HER3 as the expression and signaling functions of HER3 are highly regulated through a multitude of mechanisms, and in

fact, HER3 is likely the most highly regulated member of the HER family. In the case of HER2-amplified tumors, treatment of HER2-amplified tumor cells with TKIs leads to a compensatory increase in HER3 expression, HER3 membrane localization, and decreased HER3 dephosphorylation, resulting in significantly enhanced HER3 signaling [82]. The compensatory upregulation of HER3 signaling is specifically induced in response to the loss of downstream Akt signaling revealing the reciprocal regulation of HER3 by Akt in this tumor cell type (Figure 2). This is best shown by the observed upregulation of HER3 signaling in response to the experimental inactivation of Akt, and the observed downregulation of HER3 signaling in response to the experimental induction of Akt activity [83].

The specific mechanisms through which Akt can regulate HER3 appear to be multiplex as well as redundant, suggesting that multiple signaling events downstream of Akt, working through different efferent pathways, can regulate HER3 signaling function. Akt can manipulate the signaling functions of HER3 through mechanisms including transcriptional, translational, and post-translational regulation and control of its localization and trafficking. Using a chemical biological approach, we have interfered with each of the components of the HER3/PI3K/Akt signaling pathway including HER2, PI3K, Akt, or mTor. We find that while each manipulation induces an upregulation of HER3 signaling, the pathways involved are different, revealing a plurality of mechanisms in place that link HER3 signaling function with downstream networks (unpublished data). Data from our group and from many others shows that HER3 signaling can be induced through mechanisms that include its transcriptional upregulation, its translational upregulation, through prolongation of its protein half-life, through the inhibition of its dephosphorylation, through the promotion of its membrane localization and increased complex formation with its HER family partners, or through an induction of its ligands in an autocrine fashion. Its transcriptional upregulation is seen when HER2-amplified breast cancer cells are exposed to TKI therapy [83]. Its translational upregulation may be mediated through increased activity of the raptor complex of mTor and its substrate 4EBP1 [84]. Its protein half life may be affected through modulation of negative regulators of HER family proteins, including NRDP1 or LRIG1 [85–88]. Its membrane localization can be further promoted through increased vesicular trafficking to the membrane, mediated through the Akt regulation of nitric oxide pathway or increased membrane retention through MUC4 [89](and unpublished data). Its dephosphorylation can be inhibited through the inhibition of tyrosine phosphatases by increased oxidative stress [82] or through more specific, but yet undefined mechanisms. Its activation state can be increased through the autocrine production of its ligands [63]. HER3 levels can be also be negatively regulated via miRNAs as has been observed with miR205 whose expression decreases HER3 levels and restores sensitivity of HER2 amplified cells to HER TKIs [90].

The importance of HER3 as a cause of drug resistance has also emerged in the treatment of NSCLCs. The best marker of sensitivity to gefitinib in NSCLC cells is its ability to inactivate HER3 signaling [53]. TKI-induced HER3 inactivation even identifies TKI-sensitive NSCLCs that lack the mutational activation of EGFR, identifying its central role in the pathogenesis of this type of lung cancer. Treatment of NSCLCs driven by mutationally activated EGFR ultimately leads to the development of secondary mutations within the EGFR kinase domain, in particular the T790M mutation, which renders the kinase resistant to erlotinib or gefitinib and the emergence of TKI resistant disease [54]. A consequence of the development of EGFR resistance is that HER3 and downstream PI3K signaling become similarly resistant to TKI therapy [91]. EGFR resistance can be overcome with certain classes of irreversible TKIs, and the re-inhibition of EGFR in these resistant cells similarly leads to the re-inhibition of HER3 and PI3K signaling, further highlighting the central role of HER3 in mediating sensitivity or resistance [91]. Some NSCLCs develop resistance to

TKIs without any evidence of secondary mutations in EGFR. In some of these cancers, this appears to be due to EGFR-independent HER3 signaling through cross-talk with the heterologous RTK, c-MET. In these NSCLCs, the development of TKI resistance is associated with the MET-dependent phosphorylation of HER3 [55]. This occurs due to amplification of the *c-MET* gene and overexpression of the MET protein [55]. Amplification of *c-MET* may be a pre-existing genotype that is selected for during drug therapy [92]. The direct mechanism by which MET may induce HER3 phosphorylation is not yet clear. In addition, resistance to gefitinib or erlotinib also develops in some cases of NSCLC without the development of secondary mutation in EGFR and without amplification of c-MET. While these tumors have EGFR proteins that remain sensitive to TKI therapy, HER3 and PI3K signaling appear to be resistant [55,92]. This finding uncouples the role of EGFR and HER3, further highlighting the central role of HER3 in the pathogenesis of these lung cancers, and suggests that while EGFR can be ultimately dispensable for tumor progression, HER3 is apparently indispensable.

Our understanding of HER family function in cancer has matured in several stages over the past 3 decades. From the earliest points in the 1980s came clear evidence of oncogenic activation of individual members in some cancers. In the mid-1990s came an appreciation of the cooperative nature of signaling among members of this family. In the early to late 2000s came deep mechanistic and structural insights into how these receptors generate signals. These developments in the basic sciences were paralleled in the pharmaceutical sector by the development of successive generations of HER-targeting therapies for the treatment of cancer. Because HER3 did not emerge in screens for oncogenes early on, its relevance to human cancer and cancer therapeutics eluded us for many years. But the experience with drug resistance in several classes of HER-targeting therapies, and mechanistic insights into the nature of HER family signaling now highlight the previously unrecognized, but critical role of HER3 as the unpretentious member of this family of protooncogenes.

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Figure 1.

Schematic representation of the activating functions of HER3. When bound by ligand, the HER3 extracellular domain (ECD) adopts a conformation that is highly favorable for dimerization with other HER family members. Dimerization is shown here with HER2, but is similar with all other HER family members. When dimerized with HER2, the HER3 kinase domain interacts in an asymmetrical mode with the HER2 kinase domain. This allosteric interaction activates the HER2 kinase domain. The activated HER2 kinase domain phosphorylates the c-terminal tail of HER3, which leads to the generation of intracellular signaling. In the inactivate state, the HER3 kinase domain is engaged in homotypic interactions including intra-dimer N-lobe interactions and cross-dimer C-lobe-c-tail interactions that potentially create daisy chain clusters of inactive HER3 molecules. The conformation of the HER3 ECD in these clusters is not well understood and speculated in this schematic.

Figure 2.

Schematic representation of the feedback regulation of HER3 by Akt. When phosphorylated, the HER3 c-terminal tail binds the PI3K heterodimer, recruiting it to the membrane and resulting in the phosphorylation of membrane phosphoinositides and ultimate generation of membrane phosphatidylinositol triphosphate (PIP3). Akt and PDK1 dock to the membrane PIP3 via their PH domains. The phosphorylation of the activation loop of Akt by PDK1, and the phosphorylation of the hydrophobic motif of Akt by mTor leads to the full activation of Akt. Akt phosphorylates numerous cytoplasmic substrates. At least in some cancers, activated Akt reciprocally regulates HER3 signaling functions, completing a negative feedback loop that functions to preserve HER3 and consequent Akt signaling, vital for tumorigenic survival.