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ERBB2 oncogenicity: ERBIN helps to perform the job

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Abbreviations: ERBB2, v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; ERBIN, ERBB2 interacting protein; HER2, human epidermal growth factor receptor 2; HSP90, heat shock protein 90; MMTV-Neu, mouse mammary tumor virus-Neu; PDZ, PSD95/Discs Large/ZO-1; PML-RARa, promyelocytic leukemia-retinoic acid receptor a; PyVT, polyomavirus middle T antigen

ERBB2 (v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2) is an oncogenic tyrosine kinase receptor that is overexpressed in breast cancer. Antibodies and inhibitors targeting ERBB2 are currently available, although therapeutic failures remain frequent. We discuss here recent data showing that the scaffold protein ERBB2IP (ERBB2 interacting protein, best known as ERBIN) regulates ERBB2 stability and may represent a future therapeutic target.

The mode of action of approved targeted therapies for cancer treatment mostly consists of inhibiting the function of the oncogenic target. Although effective, these drugs are not totally efficient, in part due to remaining active oncoprotein in the cancer cell. The perfect drug would ideally degrade the bad guy, definitively eliminating the roots of the disease. Such a drug, arsenic trixoxyde, has been very successfully developed to treat acute promyelocytic leukemia by eradicating the promyelocytic leukemia–retinoic acid receptor a (PML-RARa) fusion product through SUMO-dependent proteasomal degradation.[1] It is thus anticipated that a better knowledge of the mechanisms of oncoprotein degradation would benefit the development of innovative and efficient drugs.

v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2; also named human epidermal growth factor receptor 2 or HER2) is a tyrosine kinase receptor whose gene amplification and protein overexpression leads to a poor prognosis in breast cancer. This genetic lesion is retrieved in 15–20% of cases of breast cancer and is associated with metastatic development. For almost 10 years, so-called ERBB2-positive patients have been treated with potent monoclonal antibodies (trastuzumab, pertuzumab), and more recently with tyrosine kinase inhibitors (lapatinib).[2] Although there is no doubt that these drugs have improved patient care, relapse is frequent. ERBB2 induces a strong mitogenic pathway in cancer cells by activating classic tyrosine kinase downstream molecules such as RAS, MAPK, and PI3K. ERBB2 protein levels are controlled by heat shock protein 90 (HSP90), a chaperon protein that binds the ERBB2 intracellular domain and protects the protein from proteosomal degradation. HSP90 inhibitors such as geldanamycin that induce ERBB2 degradation have been developed and have entered into clinical trials.[3] More than a decade ago, our laboratories identified ERBB2 interacting protein (ERBB2IP, best known as ERBIN), which has a PSD95/discs large/ZO-1 (PDZ) domain that interacts with ERBB2.[4,5] The ERBIN–ERBB2 interaction is highly specific as ERBIN has no affinity for other members of the ERBB2/HER family (EGFR, ERBB3/HER3, and ERBB4/HER4). ERBIN stabilizes ERBB2 at the plasma membrane through its PDZ interaction, and is necessary for the function of the receptor in the myelination of axons in the peripheral nervous system.[6] *Erbin* knock-out mice (*erbin*$^{-/-}$) are viable and fertile, despite their neurological defects. *Erbin* mutation leads to decreased amounts of ErbB2 at the plasma membrane of mammary epithelial cells.[7] These data obtained in a physiological context enabled investigation into the role of ERBIN in tumor growth promoted by ERBB2. Transgenic mouse mammary tumor virus (MMTV)-Neu (*Neu*$^{+/+}$) mice express oncogenic Neu, the rat homolog of ERBB2, in the mammary gland and form tumors similar to ERBB2-positive breast cancer. Remarkably, *Erbin*$^{-/-}$*Neu*$^{+/+}$ mice exhibit a very significant delayed appearance of mammary tumor development compared to animals bearing oncogenic Neu in a wild-type Erbin background.[7] Tumor

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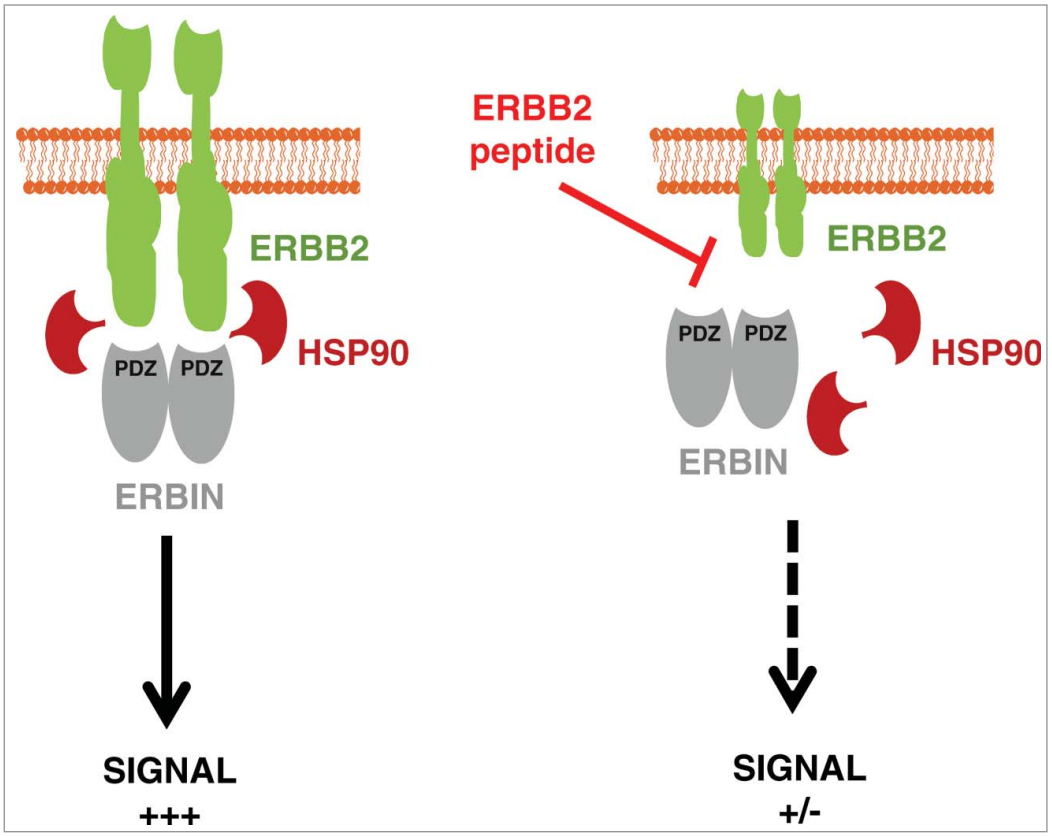

Figure 1. Disruption of the ERBB2–ERBIN complex decreases ERBB2 levels and limits oncogenicity. On the left, ERBB2 forms a complex with ERBIN and HSP90 at the plasma membrane. This interaction stabilizes ERBB2 and allows a potent mitogenic signal. On the right, disruption of the ERBB2–ERBIN complex with a peptide mimicking the C-terminal sequence of ERBB2 induces degradation of ERBB2 leading to lower amounts of ERBB2 and decreased mitogenicity. ERBB2, v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; ERBIN, ERBB2 interacting protein; HSP90, heat shock protein 90: PDZ, PSD95/Discs Large/ZO-1.

growth was diminished in the absence of Erbin and correlated with lower amounts of total and active ErbB2. No effect was observed on protein levels of other Erbin interactors such as integrin-β4, Smad2, and Smad3. Moreover, a lower rate of cell proliferation was detected in Neu-driven tumors and in 2D and 3D cultures of human cancer cells deficient for ERBIN expression. This led to the conclusion that ERBIN stabilizes ERBB2 and is a component of the oncogenic program of this tyrosine kinase receptor. Complementary results were obtained with 2 other mouse models developed to answer the following important questions. First, does Erbin inhibit mammary gland tumorigenesis in general? The answer is clearly no, as Erbin deficiency had no effect on the development of mammary tumors induced by MMTV-PyVT (polyomavirus middle T antigen is another strong oncoprotein). Second, is the Erbin–ErbB2 interaction implicated in this process? The answer to this is yes, as deletion of the Erbin PDZ domain in the mouse genome led to a similar decrease in Neu-driven tumoral development as complete Erbin deficiency.

So how does Erbin function to stabilize ErbB2? Obviously not by transcriptional regulation, as Erbin deficiency did not affect *ErbB2* mRNA levels. In fact, the answer to this question came from the discovery that ERBIN promotes the formation of a complex containing itself, ERBB2, and HSP90, another stabilizing molecule for the receptor. Disruption of this complex by a competitor peptide for the ERBIN PDZ-ErbB2 interaction or by geldanamycin condemned ERBB2 to proteasomal degradation. This mechanism highlighted the importance of the very C-terminal sequence of ERBB2 in protein stability, as previously shown,[8] and the role of ERBIN in maintaining receptor levels in collaboration with a chaperon (**Fig. 1**). It remains to be determined how ERBIN participates in this stabilizing process at the molecular level, and whether other parts of the protein outside of the PDZ domain can perform the job, either alone or with associated partners. Of interest, ERBIN was found to be overexpressed in ERBB2-positive breast cancer, suggesting that it may represent a suitable target for drug development. Even though development of protein–protein interaction inhibitors mimicking the ERBB2 PDZ binding site is no easy task, these data form the basis for strategies aiming to target the ERBIN PDZ–ERBB2 interface with the objective of promoting degradation of the oncoprotein.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Ablain J, Nasr R, Bazarbachi A, de Thé H. The drug-induced degradation of oncoproteins: an unexpected Achilles' heel of cancer cells? Cancer Discov 2011; 1:117–27; PMID:22586354l; http://dx.doi.org/10.1158/2159-8290.CD-11-0087
2. Higgins MJ, Baselga J. Targeted therapies for breast cancer. J Clin Invest 2011; 121:3797–3803; PMID:21965336
3. Scaltriti M, Dawood S, Cortes J. Molecular pathways: targeting hsp90–who benefits and who does not. Clin Cancer Res 2012; 18:4508–13; PMID:22718860; http://dx.doi.org/10.1158/1078-0432.CCR-11-2138
4. Borg JP, Marchetto S, Le Bivic A, Ollendorff V, Jaulin-Bastard F, Saito H, Fournier E, Adélaïde J, Margolis B, Birnbaum D. ERBIN: a basolateral PDZ protein that interacts with the mammalian ERBB2/HER2 receptor. Nat Cell Biol 2000; 2:407–14; PMID:10878805; http://dx.doi.org/10.1038/35017038
5. Huang YZ, Wang Q, Xiong WC, Mei L. Erbin is a protein concentrated at postsynaptic membranes that interacts with PSD-95. J Biol Chem 2001; 276:19318–26; PMID:11279080; http://dx.doi.org/; http://dx.doi.org/10.1074/jbc.M100494200
6. Liang C, Tao Y, Shen C, Tan Z, Xiong WC, Mei L. Erbin is required for myelination in regenerated axons after injury. J Neurosci 2012; 32:15169–80; PMID:23100438; http://dx.doi.org/10.1523/JNEUROSCI.2466-12.2012
7. Tao Y, Shen C, Luo S, Traoré W, Marchetto S, Santoni MJ, Xu L, Wu B, Shi C, Mei J, et al. Role of Erbin in ErbB2-dependent breast tumor growth. Proc Natl Acad Sci U S A. 2014; 111:E4429–4438; PMID:25288731; http://dx.doi.org/10.1073/pnas.1407139111
8. Lerdrup M, Bruun S, Grandal MV, Roepstorff K, Kristensen MM, Hommelgaard AM, van Deurs B. Endocytic down-regulation of ErbB2 is stimulated by cleavage of its C-terminus. Mol Biol Cell 2007; 18:3656–3666; PMID:17626164; http://dx.doi.org/10.1091/mbc.E07-01-0025