ERBB RECEPTORS DIMERIZATION DEFINES BREAST CANCERS SUBTYPES AND CLINICAL OUTCOMES: IMPLICATION FOR CANCER THERAPIES

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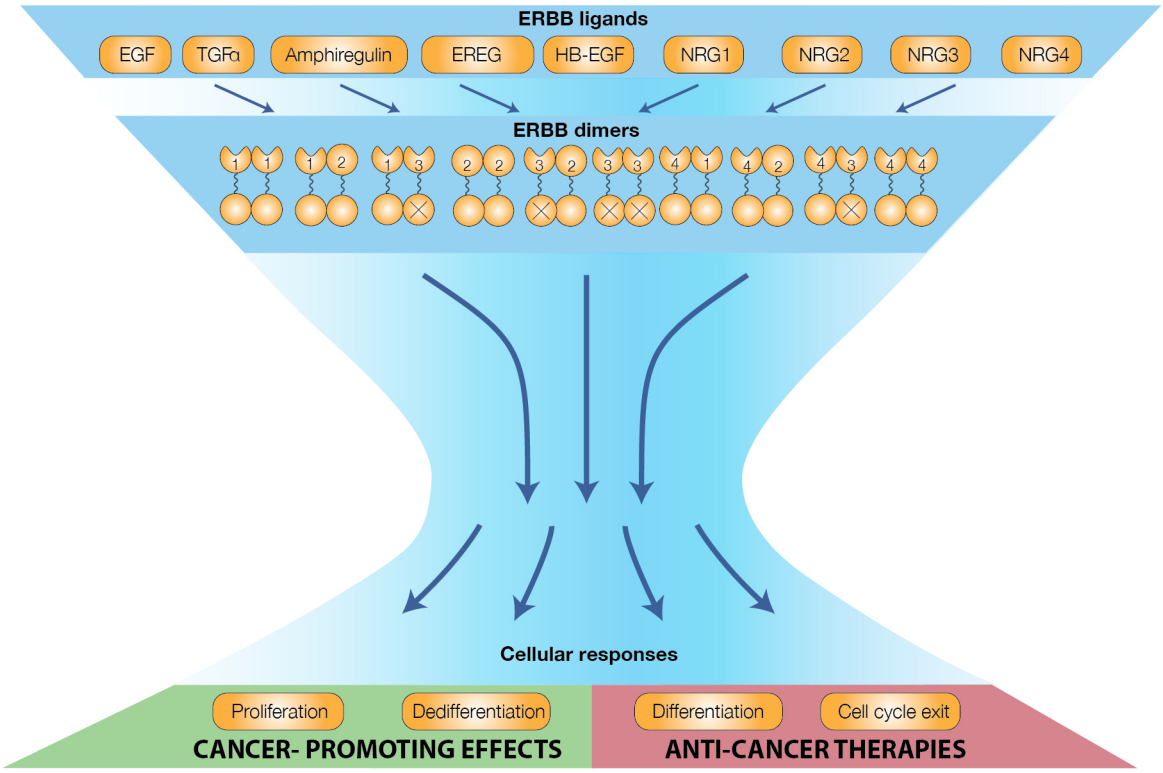
Breast cancers are classified into categories according to specific criteria, such as histopathological type, tumour grade and more recently the gene expression signature. These classifications ensure the best treatment in the context of personalized medicine. ERBB/HER receptors play major roles in the development and progression of various solid cancers, including those arising from the breast tissue. Upon binding of specific ligands, ERBB receptors form homo- and/or hetero-dimers with other members of the family, and these complexes activate a specific signalling cascade. ERBB2/HER2 is unable to bind ligands, yet, it is the preferred heterodimerization partner for other ERBB receptors, amplifying and diversifying the signalling cascade.

In this study we associated the expression level of *ERBB* receptors with molecular subtypes and clinical features. We found that the amount of different *ERBB* mRNAs is predictive of the breast cancer subtypes, with a preponderant expression of ERBB3 and ERBB4 in the luminal subtype. Interestingly, patients' stratification showed that the amount of *ERBB4* receptor positively correlate with patients' survival in luminal cancers, suggesting that the signalling of these receptors may restrain tumour progression. To test this hypothesis, we employed MCF10A cells, a *quasi*-normal breast cell line. We measured cancer stem cell markers and mammosphere forming ability upon combinatorial administration of activators of ERBB3 and ERBB4 (Neuregulins) and ERBB2 inhibitors (Trastuzumab). Our preliminary results unveiled that inhibition of ERBB2 coupled with activation of ERBB4 by Neuregulins promote cancer stem cell differentiation and exhaustion. The same combinatorial strategy also promotes differentiation of ERBB2-overexpressing MCF10A cells. We suggest administration of Neuregulins plus ERBB2-inhibiting agents as a novel differentiation strategy to treat luminal and HER2+ breast cancers.


ERBB ligands
EGF
TGFα
Amphiregulin
EREG
HB-EGF
NRG1
NRG2
NRG3
NRG4
ERBB dimers
1 1
1 2
1 3
2 2
3 2
3 3
4 1
4 2
4 3
4 4
Cellular responses
Proliferation
Dedifferentiation
Differentiation
Cell cycle exit
CANCER- PROMOTING EFFECTS
ANTI-CANCER THERAPIES