

## The good and bad of ERBB receptors in breast - *quanno viniti mi s'allarga lu cori, ma quanno vinni iti puru*

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The mammary gland is a dynamic organ displaying structural changes throughout the female reproductive cycle. The gland differentiation follows defined stages (embryonic, prepubertal and pubertal stages, pregnancy, lactation and involution) connected to sexual development and reproduction. Complex two-way interactions between mammary epithelial cells and the surrounding stroma direct proliferation, duct formation, branching and terminal differentiation during these stages. The members of the ERBB family of receptor tyrosine kinases (RTK) are involved in each of these processes and play distinct and complementary roles.

Altered ERBB signaling, mostly due to over-expression and/or, to a minor extent, mutation of one or more of these receptors, results in aberrant cellular responses leading to breast cancers. Thus, the phenotype induced by altered ERBB modulation in breast cancer may highlight relevant aspects of the molecular mechanisms underlying normal breast development.

In the last 15 years, in collaboration with other groups, we have studied the molecular basis of RTK modulation, and contributed to the definition of relevant molecular events and organelle interactions underlying ERBB1 (EGFR) and ERBB2 internalization and trafficking (1-9). These studies brought us to approach the role of these events (10-18) in cancer pathogenesis and progression, and led to the identification of a key druggable molecular target to revert the resistance to Trastuzumab (Herceptin®), a humanized antibody to ERBB2, representing the front line treatment in ERBB2 over-expressing breast cancer (19).

In this lecture I will review the current knowledge on the role of ERBB receptors in normal breast development, their role in breast cancer onset and progression, and our recent results in the field.

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