IJAE
Vol. 123, n. 1 (Supplement): 100, 2018
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

ERBB2 activation leads to an anti-oncogenic signalling

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Approximately 20% of breast cancers display ERBB2 (HER2) gene amplification and/or protein overexpression. In cancer cells, ERBB2 can function both in the homodimeric and heterodimeric form. Moreover, it represents the preferred partner of other members of the ERBB receptor family. Strikingly, ERBB2-containing heterodimers are more oncogenic than other ERBB combinations, mostly by promoting cell proliferation via ERK activation and cell survival via the AKT pathway. AKT signalling plays a fundamental role in driving breast carcinogenesis and is downmodulated in response to the binding of the humanized therapeutic antibody Trastuzumab (TZ) to ERBB2. How ERBB2 differentially modulates AKT in ERBB2-overexpressing BrCa cells upon TZ treatment, remain unclear. Our findings show that TZ treatment of ERBB2-positive breast cancer cell lines triggers the homodimerization and the activation of ERBB2, leading to an previously unidentified signalling cascade causing an ERK-dependent AKT dephosphorylation, via PP2A Ser/Thr phosphatases. The immunophilin Cyclophilin A (CyPA) plays a key role in this pathway, as a negative modulator of AKT de-phosphorylation, by competing with PP2A phosphatases for binding to AKT. Upon TZ treatment ERK promotes CyPA redistribution to ERBB2, allowing the binding of PP2A to phospho-AKT. Finally, we report that CyPA silencing reverts TZ-resistant human ERBB2-positive breast cancer cell lines to a TZ-responsive state. In conclusion, we show that in breast cancer cells TZ promotes ERBB2 activation, working as a "putative" ligand of the receptor, and that the outcome of the ERBB2 activity depends on the dimerization status: pro-oncogenic in the hetero- and anti-proliferative in the homodimeric form.

This work was supported by grants from MIUR PRIN-2012, Compagnia San Paolo (grant number 2011.1172 and 2015.0323) to CT, and from AIRC (IG number 12035 and 17109) to CT and GT.

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Key words

Breast cancer, ERBB2, HER2, AKT, ERK, signalling, dimerization, trastuzumab, resistance, Cyclophilin A, Ser/Thr phosphatase, PP2A.