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Epidermal growth factor-receptor activation modulates Src-dependent resistance to lapatinib in breast cancer models

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Introduction: Src tyrosine kinase overactivation has been correlated with a poor response to human epidermal growth factor receptor 2 (HER2) inhibitors in breast cancer. To identify the mechanism by which Src overexpression sustains this resistance, we tested a panel of breast cancer cell lines either sensitive or resistant to lapatinib.

Methods: To determine the role of Src in lapatinib resistance, we evaluated the effects of Src inhibition/silencing in vitro on survival, migration, and invasion of lapatinib-resistant cells. In vivo experiments were performed in JIMT-1 lapatinib-resistant cells orthotopically implanted in nude mice. We used artificial metastasis assays to evaluate the effect of Src inhibition on the invasiveness of lapatinib-resistant cells. Src-dependent signal transduction was investigated with Western blot and ELISA analyses.

Results: Src activation was higher in lapatinib-resistant than in lapatinib-sensitive cells. The selective small-molecule Src inhibitor saracatinib combined with lapatinib synergistically inhibited the proliferation, migration, and invasion of lapatinib-resistant cells. Saracatinib combined with lapatinib significantly prolonged survival of JIMT-1-xenografted mice compared with saracatinib alone, and impaired the formation of lung metastases. Unexpectedly, in lapatinib-resistant cells, Src preferentially interacted with epidermal growth factor receptor (EGFR) rather than with HER2. Moreover, EGFR targeting and lapatinib synergistically inhibited survival, migration, and invasion of resistant cells, thereby counteracting Src-mediated resistance. These findings demonstrate that Src activation in lapatinib-resistant cells depends on EGFR dependent rather than on HER2-dependent signaling.

Conclusions: Complete pharmacologic EGFR/HER2 inhibition is required to reverse Src-dependent resistance to lapatinib in breast cancer.

Biography

Lucia Nappi graduated as MD in 2008 and achieved her residency in Medical Oncologist in 2014 at the University of Naples "Federico II". During the last 5 years she focused on the study of mechanisms of resistance to anti-HER drugs in differeent tumors (lung, colorectal, breast). Since September 2013, she is working as Postdoctoral Fellow at the Vancouver Prostate Centre, Vancouver, BC, Canada. She is studying the role of chaperone molecules in the resistance to hormone and chemotherapy drugs in prostate cancer.

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