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HER2 EXPANDS TUMOR-INITIATING BREAST CANCER CELLS IN THE SIDE POPULATION - IMPLICATIONS FOR TARGETED INTERVENTION
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[Purpose] HER2 overexpression in breast cancer (BC) is a predictive factor for poor response to chemotherapeutics. Since T-ICs in the side population (SP), a distinct cell fraction owing ATP-binding cassette (ABC) transporters that function as drug efflux pump, are drug-resistant, we examined the role of HER2 on T-ICs in the SP of BC. [Methods] The SP was determined amongst various human BC cell lines including primary cell cultures obtained from patients. We characterized the SP for T-IC markers and BCRP expression, and examined impact of HER2 on the engraftment of SP cells in in vivo tumorigenicity assay. [Results and Discussion] The SP was shown to be predominant T-ICs in luminal subtype of BC. Besides, HER2 expression was significantly correlated with occurrence of the SP, where the ABC transporter breast cancer resistance protein (BCRP) increased. Further analysis shows that modulating HER2-mediated signaling by AG825 and trastuzumab was able to reduce the SP cells and prevent their engraftment in NOD/SCID mice. Our findings indicate an essential role of HER2 in T-ICs in the SP, which may account for the poor responsiveness of HER2+ BCs to chemotherapy, as well as their aggressiveness. [Conclusions] HER2 provides a therapeutic target particularly for T-ICs in luminal type breast carcinomas.

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QUANTITATIVE INVESTIGATION OF THE SYNERGISTIC ROLE OF P-GLYCOPROTEIN (P-GP/ABCB1) AND BREAST CANCER RESISTANCE PROTEIN (BCRP/ABCG2) IN LIMITING THE BRAIN AND TESTIS PENETRATION OF ERLOTINIB AND MITOXANTRONE
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[Purpose] P-gp and Bcrp, which are colocalized on the luminal side of the endothelial cells in the brain and testis, play a significant role in limiting the tissue penetration of xenobiotic compounds. The present study was carried out to quantitatively examine the synergetic effect of P-gp and Bcrp in limiting the brain and testis penetration of their common substrates. [Methods] The transcellular transport across the monolayers of polarized cell lines expressing mouse Bcrp or Mdr1a and their corresponding control cells was investigated. The tissue-to-plasma concentration ratios (Kp) were obtained in the plasma, brain, and testis at the end of a 2-h systemic infusion. [Results and Discussion] Erlotinib, and mitoxantrone were identified as common substrates of P-gp and Bcrp in vitro. The brain-to-plasma ratio (Kpbrain) and testis-to-plasma ratio (Kptestis) of those compounds were markedly increased in Mdr1a/-/Bcrp+/- mice compared with Mdr1a/-/Bcrp-/- mice. Based on the ratio of the Kp in the three knockout strains relative to the wild-type strain, in vivo PSBcrp and PSBcrp, the intrinsic efflux transport by P-gp and Bcrp, respectively, was determined for their common substrates at the barriers. Those PS values explained the impact of P-gp and/or Bcrp dysfunction on the accumulation of their common substrates in brain and testis. [Conclusions] The present study shows that P-gp and Bcrp synergistically limit the brain and testicular distribution of their common substrates and a synergetic effect is due to the additive effect of the efflux transport activities of each transporter.