Amplification of LAPTM4B and YWHAZ contributes to chemotherapy resistance and recurrence of breast cancer - DTU Orbit (26/02/2019)

Amplification of LAPTM4B and YWHAZ contributes to chemotherapy resistance and recurrence of breast cancer

Adjuvant chemotherapy for breast cancer after surgery has effectively lowered metastatic recurrence rates. However, a considerable proportion of women suffer recurrent cancer at distant metastatic sites despite adjuvant treatment. Identification of the genes crucial for tumor response to specific chemotherapy drugs is a challenge but is necessary to improve outcomes. By using integrated genomics, we identified a small number of overexpressed and amplified genes from chromosome 8q22 that were associated with early disease recurrence despite anthracycline-based adjuvant chemotherapy. We confirmed the association in an analysis of multiple independent cohorts. SiRNA-mediated knockdown of either of two of these genes, the antiapoptotic gene YWHAZ and a lysosomal gene LAPTM4B, sensitized tumor cells to anthracyclines, and overexpression of either of the genes induced anthracycline resistance. Overexpression of LAPTM4B resulted in sequestration of the anthracycline doxorubicin, delaying its appearance in the nucleus. Overexpression of these two genes was associated with poor tumor response to anthracycline treatment in a neoadjuvant chemotherapy trial in women with primary breast cancer. Our results suggest that 8q22 amplification and overexpression of LAPTM4B and YWHAZ contribute to de novo chemoresistance to anthracyclines and are permissive for metastatic recurrence. Overexpression of these two genes may predict anthracycline resistance and influence selection of chemotherapy.

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