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Drug resistance modeling for personalized management of breast cancer

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Drug resistance (DR) is a main driver of post-chemotherapy recurrence and metastasis and therefore a challenging hindrance to tumor therapy. Several mechanisms including increased drug efflux and drug detoxification, enhanced DNA repair and apoptosis inactivation are behind DR. Aberrant intracellular signaling pathways and factors of the tumor microenvironment promote these mechanisms by contributing to clonal selection and subclonal mutations as the main manifestations of tumor inhomogeneity. This inter- and intra-tumor heterogeneity is a determinant factor in shaping tumor DR. Such tumor diversity requires modeling the disease to recapitulate the original tumor features at subcellular and molecular levels as an individualized platform for dissection of DR, drug screening and drug discovery for targeted therapy. Here, I will present details of our study on trastuzumab resistance modeling and how it provides windows of opportunities to dissect molecular events behind resistance. Then I will discuss application of new technologies, including ranging from NGS and gene network analyses to genome editing and optogenetics, in tumor models with the aim of personalization of DR reversal, drug discovery and tumor re-sensitization by co-treatment strategies and drug-drug interaction.

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