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Mechanisms of Trastuzumab Resistance and Opportunities to Overcome Therapeutic Resistance

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Trastuzumab is a humanized monoclonal antibody directed against extracellular domain IV of Human Epidermal Growth Factor Receptor 2 (HER2) and is approved for the treatment of HER2-positive breast cancers either alone or in combination with chemotherapeutic agents [1,2]. HER2 is a member of HER/ErbB family of receptor tyrosine kinases, which play important role in breast cancer development and progression [1]. HER2 is overexpressed in approximately 20-30% of invasive breast cancer and is associated with poor disease-free survival and poor response to chemotherapy [3-5]. Over the past two decades, the development of monoclonal antibodies targeting HER2 has been intensely pursued as important cancer therapeutic strategy. While treatment with trastuzumab very successfully improves outcomes for women with HER2-positive breast cancer, therapeutic resistance to trastuzumab, including primary and acquired resistance, pose a significant hurdle in the treatment of HER2-positive breast cancers [2,6,7]. Better understanding of molecular mechanisms underlying primary or acquired resistance to trastuzumab is critical to improving the survival of patients with HER2-positive breast cancer.

Based on cell culture, xenograft models and clinical studies, mechanisms of trastuzumab resistance can be generally grouped as either related to the aberrant HER2 receptor signaling at the cell surface or to the deregulated signaling of the intracellular molecular players downstream of HER2 receptor [2]. The examples of the aberrant HER2 signaling at the cell surface include expression of p95HER2 truncated form which lacks the extracellular trastuzumab-binding domain [8], overexpression of MUC4 glycoprotein on the cell surface, which blocks trastuzumab binding site on HER2 [9], increased heterodimerization of HER2 with other HER family members such as HER1/EGFR [10] or with other receptor tyrosine kinases such as IGF-IR [11]. Among downstream molecular players whose deregulation may contribute to trastuzumab resistance are upregulation of small GTPase, Rac1 and IQGAP1 [12,13] leading to the inhibition of trastuzumab-induced degradation of HER2 [13], loss of PTEN [14] and expression of activating mutations in the PI3K (*PIK3CA*) [15], both of which result in hyperactivation of the PI3K/Akt signaling pathway, and upregulation of Src activity [16], which can further activate HER1 and HER3 and promote trastuzumab resistance in a PI3K/Akt-dependent or PI3K/Akt-independent manner [16]. However, to date, there is no clinically useful biomarker that can be used to inform patient selection for trastuzumab therapy [17]. Analysis of mechanisms contributing to trastuzumab resistance in the context of well designed and prospective clinical trials with tumor samples taken before and after acquisition of resistance to trastuzumab is needed in this area of clinical research.

Several therapeutic avenues are undertaken to overcome trastuzumab resistance in breast cancer patients. Tyrosine kinase inhibitors (TKIs), such as neratinib and lapatinib, are tested either alone or in combination with trastuzumab for trastuzumab-resistant disease [18,19]. Small molecular inhibitors targeting PI3K (XL147 and BKM120), mTOR (everolimus and temsirolimus) and Hsp90 (tanespymicin) are also tested in Phase I and II clinical studies in trastuzumab-resistant breast cancer [2,20,21]. Combination of trastuzumab with another monoclonal antibody, which targets different epitope on HER2- pertuzumab is currently under clinical evaluation for the treatment of trastuzumab-resistant disease [22,23]. Antibody-drug conjugates (ADC) are therapeutic agents where a monoclonal antibody is linked to highly cytotoxic compounds via a linker and used to deliver cytotoxic agent to the antigen positive tumor cell [24]. Ado-trastuzumab emtansine is an ADC which was tested and recently approved for the treatment of trastuzumab resistant breast cancers [25]. In addition to clinically tested therapies there are also several novel therapeutic approaches in different pre-clinical models which may hold promise in future. In cell culture experiments, successful targeting of trastuzumab resistant cells was achieved by using anti-HER2 conjugated silica gold nanoshells and near infrared laser [26]. In another preclinical study, anti-HER2 immunoconjugates were generated by linking human anti-HER2 scFv named Erbicin to either human RNase or to the Fc region of IgG1 [27]. Both immunoconjugates have significant activity against trastuzumab resistant breast cancer cells [27]. As development of these agents continues, more information will be acquired about their potential to overcome trastuzumab resistance in clinical studies. Identification of predictive biomarkers for trastuzumab resistance accompanied by development and clinical testing of novel agents in patients who progress on trastuzumab has potential to bring more effective and safer therapies.

Although there were multiple mechanisms of trastuzumab-resistance proposed based on the clinical and preclinical studies, the question remains how the knowledge gained from these studies can be translated into the next generation of monoclonal antibodies to overcome therapeutic resistance to trastuzumab [2]. Based on literature and data from our laboratory [13], we propose a new approach by designing an antibody-drug conjugate (ADC) based on the mechanisms of trastuzumab resistance [2]. In this ADC, trastuzumab is conjugated to a small molecule that has ability to inhibit the cellular target(s) that has been demonstrated to contribute to trastuzumab-resistance. This proposed strategy may increase the magnitude and duration of the response to trastuzumab treatment [2].

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