Biparatopic DARPin agents for Anti-ErbB2 Therapy

Intermolecular Trapping of ErbB2/HER2 Receptor Induces pan-ErbB Inhibition and Overcomes the Signaling Robustness in ErbB2-Dependent Cancers

ErbB2 (HER2/Neu) is a receptor tyrosine kinase directly linked to malignancies of different origin and the target of the therapeutic monoclonal antibodies trastuzumab (Herceptin®) and pertuzumab (Perjeta®) as well as tyrosine kinase inhibitors such as lapatinib (Tykerb®). Although targeted agents against ErbB2 show high response rates in first line therapy, tumors develop therapeutic resistance within several months and the management of cancer drug resistance remains one of the major clinical challenges. Compensatory mechanisms, such as relief of AKT-ErbB3-negative feedback, are known to desensitize ErbB2-dependent tumors to targeted therapy. Recently, we have described yet another adaptation route leading to reactivation of the PI3K/AKT pathway, which acts independently of ErbB3 re-phosphorylation (1). This signaling bypass of phospho-ErbB3 operates in HER2-positive cancer cells via RAS-PI3K crosstalk and is attributable to ErbB2 homodimers. Consequently, blocking these compensatory mechanisms is predicted to potentiate the effect of incomplete ErbB2/3 blockade as it occurs during treatment by trastuzumab and pertuzumab. In the present work, we have developed a novel class of biparatopic anti-ErbB2 Designed Ankyrin Repeat Proteins (DARPin), which effectively downregulate oncogenic ErbB2/3 signaling and exert tumoricidal activity as naked molecules without effector function or cytotoxic payload both in 2D- and 3D-cell culture models as well as in orthotopically xenografted animals (1). By creating an intermolecular trap with biparatopic DARPin agents, which simultaneously engages two distinct ectodomain epitopes of ErbB2, the receptors adopt a conformation incapable of forming productive interactions (2). Such a trapping obstructs signaling from all functional ErbB2 homo- and heterodimer complexes, thereby achieving a pan-ErbB inhibition. The ensuing dephosphorylation of both ErbB2 and ErbB3 results in persistent attenuation of downstream signaling and overcomes adaptive responses incorporated into the ErbB oncogenic network. These novel insights into the mechanisms underlying oncogenic network robustness provide a guide to overcome adaptive resistance to current ErbB2/ErbB3-targeted therapy and we demonstrate a novel approach to engineer cell-specific apoptosis based on a structurally and mechanistically understood principle.


Date & time: Thursday, February 16, 2017 at 05:30 pm
Location: Lecture Hall Y03-G-85, UZH Irchel

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