O20. Interaction between Trastuzumab and ErbB2 analyzed by molecular dynamics simulation

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ABSTRACT Human epidermal growth factor receptor 2 (ErbB2) is a transmembrane oncoprotein that is over expressed in breast cancer. A successful therapeutic treatment is a monoclonal antibody called Trastuzumab which interacts with the ErbB2 extracellular domain (ErbB2-ECD). A better understanding of the detailed structure of the receptor-antibody interaction is indeed of prime interest for the design of more effective anticancer therapies. For this purpose, we have used molecular dynamics simulation (MD) at the atomistic and coarse grained scales. These methodologies can provide fine details about the molecular interactions between these proteins and give useful information to understand its biological action. The atomistic scale simulations were performed on the ECD / Trastuzumab Fab complex. In addition to the well established interaction between the Trastuzumab Fab and the ErbB2 domain IV epitope, a nascent interaction between domain II and the constant fragments of the Fab antibody is observed. This additional interaction is facilitated by a genuine hinge movement at the domain III/domain IV interface. (see the schematic representation on the left).

On the other hand, the coarse grained simulations were performed on the full ErbB2 receptor including the lipid bilayer. Starting from the Bagossi’s model, built using experimental information and homology modeling, a structural analysis of the influence exerted by the monoclonal antibody on the full receptor was carried out. Several multimicrosecond simulations arrived to structures of the protein complexes compatible with experimental observations. The ErbB2 ectodomain as well as the intracellular domain approached the bilayer surface, as can be observed on the two molecular representations (antibody-free system on the center and Fab including system on the right). However, the Trastuzumab Fab hindered the approximation of the ECD to the membrane, whereas the antibody effect is less notorious on the cytoplasmic domain, where the signaling cascade starts (the Fab molecule is represented in green). These findings support the idea that the main bioactive action of Trastuzumab is on the extracellular fragment, at least on the ErbB2 monomer.

References:
