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Conformation and hydrodynamics of HER2/Trastuzumab complexes: experiments and multiscale simulations

J.F. Vega[1], J. Ramos[1], V. Cruz[1], P. Hu[2], J. Cortés[3, 4] and J. Martínez-Salazar[1]

[1] *BIOPHYM, Department of Macromolecular Physics, Instituto de Estructura de la Materia, IEM-CSIC, C/ Serrano 113 bis, 28006 Madrid, Spain*

[2] *Sino Biological, Inc., 14 Zhonghe Street, Beijing Development Area, Beijing, China*

[3] *Ramon y Cajal University Hospital, Ctra. de Colmenar Viejo, km 9,100, 28034 Madrid, Spain*

[4] *Vall D'Hebron Institute of Oncology (VHIO), Paseo Vall Hebron 119-129, 08035 Barcelona, Spain*

jf.vega@csic.es

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family having tyrosine kinase activity. Most of the studies on HER2 have been focused on breast cancer, but it was also found to be related to other types of cancer [1]. HER2 has been intensely evaluated as a therapeutic target. HER2 receptors can exist on the cell surface as monomers, homodimers and heterodimers. It has been shown that trastuzumab antibody (TZM), an approved therapeutics for treatment of HER2-overexpresing breast cancer, blocks HER2 homodimer activity [2]. In our study, we use a recombinant HER2 extracellular domain (ecHER2) to study the formation of complexes with TZM by means of light scattering and size exclusion chromatography, along with multiscale simulations based on atomistic molecular dynamics and continuum hydrodynamic models [3]. The measured ecHER2 molecular mass (M_w) indicates that the receptor ectopic domain *mainly* exists as monomer in solution under the experimental conditions used. However a measurable amount of dimer has been detected. Primary structure information reveals a calculated monomer M_w of 71 kDa, but the measured M_w is 88.7 ± 1.8 kDa as a result of glycosylation [4]. We have found that the inclusion of the carbohydrate chains in the computational models is critical in order to achieve good correlation between experimental and simulated properties. Two types of complexes, ecHER2/TZM and ecHER2/TZM/ecHER2, have been detected and their properties measured and calculated using the multiscale simulations. The calculated diffusion coefficients and molecular densities are in excellent agreement with the experimental values. Both experiments and simulations prove that the complexes show high degree of structural flexibility, and reveal the true dynamics of the complexes in solution, an insight beyond what is known from the crystal of partial structures.

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