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Molecular and hydrodynamic properties of human epidermal growth factor receptor HER2 extracellular domain and its homodimer: Experiments and multi-scale simulations

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Abstract

Background: In a broad range of human carcinomas gene amplification leads to HER2 overexpression, which has been proposed to cause spontaneous dimerization and activation in the absence of ligand. This makes HER2 attractive as a therapeutic target. However, the HER2 homodimerization mechanism remains unexplored. It has been suggested that the "back-to-back" homodimer does not form in solution. Notwithstanding, very recently the crystal structure of the HER2 extracellular domain homodimer formed with a "back-to-head" interaction has been resolved. We intend to explore the existence of such interactions.
Methods: A combination of experiments, molecular dynamics and hydrodynamic modeling were used to monitor the transport properties of HER2 in solution.
Results & conclusions: We have detected the HER2 extracellular domain homodimer in solution. The results show a high degree of molecular flexibility, which ultimately leads to quite higher values of the intrinsic viscosity and lower values of diffusion coefficient than those corresponding to globular proteins. This flexibility obeys to the open conformation of the receptor and to the large fluctuations of the different domains. We also report that for obtaining the correct hydrodynamic constants from the modeling one must consider the glycosylation of the systems.
General significance: Conformational features of epidermal growth factor receptors regulate their hydrodynamic properties and control their activity. It is essential to understand the dynamics of these systems and the role of the specific domains involved. To find biophysical correlations between dynamics and macroscopic transport properties is of general interest for researches working in this area.

Keywords: HER2 homodimer, hydrodynamic properties, molecular dynamics, hydrodynamic modeling, conformational fluctuations.