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Modulations of protein-protein interactions of EGFRs: Structure, inhibition, dynamics and its implications in breast cancer

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Abstract

Proteins interact with each other in a highly specific manner, and these specific interactions play key roles in many cellular processes. In normal life processes, these protein-protein interactions are well coordinated to perform the functions of the cells. Any deregulation of this process can lead to the development of many diseases. HER2, a member of EGFR proteins, is overexpressed in approximately 30% of breast cancers. HER2 is known to form heterodimers with other EGFR proteins such as EGFR and HER3, and is a major therapeutic target in breast cancer treatment. We have designed a number of peptidomimetics to target domain IV of HER2 protein to inhibit HER2-mediated signaling. One of such peptidomimetics, compound **5**, exhibited antiproliferative activity with IC_{50} values in the nanomolar range against HER2 overexpressing breast cancer cell lines SKBR-3 and BT-474. To further investigate the structure-activity relationship of peptidomimetics several analogs were designed. Some of these analogs exhibited antiproliferative activity against breast cancer cell lines in nanomolar concentration. PathHunter and proximity ligation assay results indicated the inhibition of HER2 heterodimerization by these compounds. Furthermore, *in vivo* studies in xenograft model of breast cancer suggested that these compounds delayed the breast tumor growth. Compound 5 was conjugated with BODIPY fluorescent probe to evaluate the binding and internalization of **5**. These results suggest that small peptidomimetic molecules can inhibit protein-protein interactions of EGFRs, which can be therapeutically useful for controlling breast cancer. The project is supported by National Institute of General Medical Sciences from the grant 8P20GM103424 (NIH)

Biography

Dr. Seetharama Satyanarayanajois (Jois) is an Associate Professor in the department of basic pharmaceutical sciences, college of pharmacy, University of Louisiana at Monroe. Jois obtained his PhD degree in the molecular biophysics unit at the Indian Institute of Science, Bangalore, India. During the past several years, he has worked extensively on the design of peptide/peptidomimetic molecules to target proteins that are important in human diseases using computational and experimental techniques. He is the author and co-author of more than sixty publications. He has edited a special series in Methods in Molecular Biology, Drug Design and Discovery –Methods and Protocols (Humana Press 2011).