Superagonistic Activation of Epidermal Growth Factor Receptor (EGFR) by EGF-related Growth Factors: An *In-silico* Study

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The mechanisms resulting in complex cellular signaling behavior involve many interacting components and cannot be studied by experiments alone. The development of computational models and the integration of these models with experiments could provide valuable insight into the underlying processes. Epidermal growth factor receptor (EGFR) has been identified as a rational target for anticancer strategies and there is need to understand the details of the pathway involved in the activation of EGFR by growth factors like EGF and TGF-α culminating in the activation of mitogen activated protein (MAP) kinase which carries the proliferation message to the nucleus.

Recently, Schoeberl *et al*. [1] developed a deterministic representation of the signaling pathway leading to the activation of MAP kinase cascade by ErbB1. However, the pathway of most signaling pathways involves proteins, which are very small in number, and therefore, stochastic fluctuations may become important. In particular, we have observed that more than 50% of the species in this EGFR signaling pathway developed by Schoeberl et al. exist in less than 1000 copies. Here, we have developed a stochastic model of this signaling pathway and analyzed the superagonistic (increased

mitogenic activity) behavior of EGF/ TGF-α chimeras. Based on our simulations, we show that the entity of ligands is not only characterized by its ligand affinity; enhanced association and dissociation kinetics, trafficking parameters, and dimerization kinetics have also been identified as important properties of the ligands, that significantly impact the mitogenic activity. We found that ligands having same receptor affinity can lead to increased mitogenic activity when (1) association and dissociation kinetics is faster and (2) more receptor is present on the plasma membrane due to increased recycle rate. Reduced dimerization rates may also lead to reduced mitogenic activity. We have used computational analysis to evaluate the impact of these aspects in isolation. The kinetic parameters of extracellular dynamics of receptor-ligand and receptor-receptor interactions play an important role leading to diverse intracellular activities. Finally, our findings are consistent with experimental results.

[1] Schoeberl, B., Eichler-Jonsson, C., Gilles, E.D. and Müller, G. (2002) Nature Biotechnology 20, 370-375.