Chemical Probes of Receptor Assembly in Signaling

Laura L. Kiessling*
Departments of Chemistry and Biochemistry, University of Wisconsin-Madison

Multiprotein complexes are the critical mediators of signal transduction. Aberrant assembly of signaling proteins can be deleterious; dysregulation of signaling protein complexes occurs in cancer cells and in the presence of some viral pathogens. Despite their importance, the molecular mechanisms by which such higher order protein assemblies transduce signals are difficult to study and therefore obscure. By developing strategies that exploit the modularity of signaling proteins, we are creating new classes of compounds to investigate and control signal transduction.

Our approach is to generate multifunctional ligands that perturb the organization of multiprotein complexes. To assemble such multifunctional ligands, we employ modern polymer chemistry. Living polymerizations are reactions in which chain elongation occurs more readily than termination processes, and they afford polymers with defined lengths, valencies, and arrangements of functional groups. We have used synthetic materials of defined lengths to investigate signal transduction mechanisms.

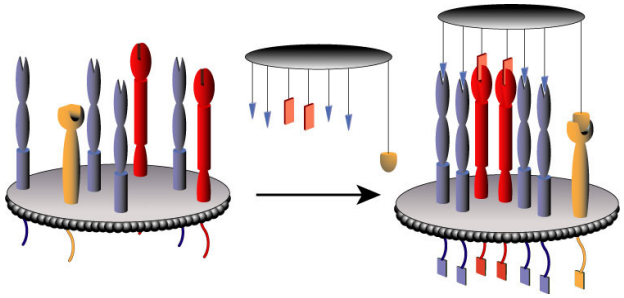

Figure 1. Multifunctional ligands can alter the intrinsic organization of cell-surface proteins.

We have used our multifunctional ligands to investigate several different signaling pathways. One example is the chemotactic signaling system in bacteria, which offers a powerful and compelling opportunity to achieve a complete molecular-level understanding of a signaling pathway: A wealth of functional and structural data has been accumulated on the system, and the chemoreceptor array can be analyzed both in vitro and in whole cells. Using multifunctional ligands, we found a role for inter-receptor interactions in chemotactic signal amplification. Intriguingly, our mechanistic studies indicate that pre-existing multiprotein complexes are loosened upon the addition of attractant. These results offer an alternative to the paradigm that signaling molecules act by clustering their target receptors. Indeed, our studies indicate that signals can be transmitted with high sensitivity via the *disruption* of intrinsic protein–protein interactions.

An overview of our strategy for investigating signaling and examples of its use will be presented.