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Editorial

Special issue on conformational selection

The special issue on "Conformational Selection" features five review articles from leaders in the field that summarizes the state-of-the-art of current experimental, theoretical and computational approaches. The reviews will definitely capture the attention of readers interested in basic mechanisms of ligand recognition.

Ligand binding is at the basis of all biological interactions, whether functional or regulatory, and conformational selection addresses the very foundations of how macromolecules behave when free and bound to specific ligands. Fischer's early lock-and-key model of ligand binding envisioned an a priori optimal fit between the ligand and its biological target [1]. Although useful as a conceptual framework, the lock-and-key model fails to capture the inherent conformational plasticity of biological macromolecules so prominently documented by structural biology and single molecule detection. Two important theoretical developments have addressed the role of conformational transitions in ligand binding. First, the induced fit hypothesis promoted by Koshland [2] extended the lock-and-key model to include a conformational transition after the initial binding interaction meant to achieve an optimal fit of the ligand and its biological target. Subsequently, the allosteric model proposed by Monod, Wyman and Changeux [3] introduced the concept of pre-existing conformations accessible to the macromolecule. Conformational selection is conceptually identical to the original MWC model and simply envisions a large ensemble of pre-existing conformations from which the ligand selects the optimal fit [4]. Structural biology has cemented the existence of multiple conformations as a fundamental property of all biological macromolecules [5], which begs the questions of how dominant is conformational selection as a mechanism of ligand binding and what role induced fit plays in molecular recognition. Do existing data on relaxation kinetics support conformational selection as a dominant mechanism of ligand binding? Do conformational selection and induced fit co-exist along pathways of allosteric transduction? Do structural and single molecule data support the bound forms of the macromolecule as genuine new conformations produced by induced fit rather than members of a pre-existing ensemble? Should pre-existing conformations of a macromolecule be considered in computational analysis of ligand binding? The reader will find possible answers to these exciting questions in the five reviews featured in this special issue.

In the first review article, Clore addresses the experimental challenge of identifying sparsely-populated states of proteins in the free and bound states as a requirement for distinguishing between conformational selection and induced fit. He points out that, unless trapped, sparsely-populated states are generally invisible to conventional structural and biophysical techniques, including X-ray crystallography and most NMR measurements. Paramagnetic relaxation enhancement is ideally suited to directly study sparsely-populated states of proteins as illustrated by the application of this technique to maltose binding protein and calmodulin that undergo large rigid body conformational rearrangements upon ligand binding from an open apo state to a closed ligand-bound holo state. Clore shows that the apo state ensemble comprises a small population of partially-closed configurations that are similar but not identical to that of the holo state, thereby highlighting the complementarity and interplay of induced fit and conformational selection and suggesting that the existence of partially-closed states in the absence of ligand facilitate the transition to the closed ligand-bound state.

In the second review article, Vogt, Pozzi, Chen and Di Cera scrutinize the widely held notion that relaxation kinetics can be used to easily distinguish between conformational selection and induced fit based on the dependence of the rate of relaxation to equilibrium, k_{obs}, on the ligand concentration, [L]. The litmus test used for decades by kineticists is that a value of k_{obs} decreasing hyperbolically with [L] is diagnostic of conformational selection, while a value of k_{obs} increasing hyperbolically with [L] is diagnostic of induced fit. Vogt et al. show that this simple conclusion is only valid under the rather unrealistic assumption of conformational transitions being rate-limiting. In the general case, induced fit only produces values of k_{obs} that increase with [L] but conformational selection is more versatile and is associated with values of k_{obs} that increase with, decrease with or are independent of [L]. The richer repertoire of kinetic properties of conformational selection applies to kinetic mechanisms with single or multiple saturable relaxations and explains the behavior of nearly all experimental systems reported in the literature thus far. They conclude that, unlike induced fit, conformational selection is always sufficient and often necessary to account for the relaxation kinetics of ligand binding to a biological macromolecule and is therefore an essential component of any binding mechanism.

In the third review article, Nussinov, Ma and Tsai discuss the interesting hypothesis that conformational selection takes place not once in a given binding or allosteric event, but at every step along an allosteric pathway. This view generalizes conformational selection and makes it applicable to biological processes as diverse as posttranslational modifications and photon absorption. At each step along a propagation pathway of transduction, conformational selection is coupled with induced fit to optimize the interactions, as observed for binding phenomena. The result is a closer interplay between conformational selection and the shift in populations available to the macromolecule.

In the fourth review article, Feixas, Lindert, Sinko and McCammon focus on the mechanisms of recognition that take place in a drug target and focus on the importance of the intrinsic dynamic character of proteins in any binding process. They stress the importance of identifying receptor conformations that play a major role in biomolecular recognition before starting rational drug design efforts and present recent advances in computer-aided drug discovery techniques that have been proposed to incorporate receptor flexibility into structure-based

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drug design. The allowance for receptor flexibility provided by computational techniques such as molecular dynamics simulations or enhanced sampling techniques helps to improve the accuracy of methods used to estimate binding affinities and, thus, such methods can make an important contribution to the discovery of novel drug leads.

In the fifth and last review article, Hatzakis points out that the dominant approaches to the analysis of conformational selection and induced fit rely on NMR spectroscopy and rapid kinetics. In both cases, the techniques report the average behavior of a large ensemble of unsynchronized molecules, often masking intrinsic dynamic behavior of proteins and biologically significant transient intermediates. He makes a strong case for the need to use the power of single molecule measurements to characterize the conformational properties underlying protein function and offers a number of relevant examples.

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