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Review

Conformational selection and induced fit as a useful framework for molecular motor mechanisms

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HIGHLIGHTS

- The mechanisms of ligand binding can be mapped onto the mechanisms of molecular translocation and helicase unwinding.
- Conformational selection can be used to describe Brownian ratchet mechanisms and passive helicase mechanisms.
- Induced fit can be used to describe power stroke mechanisms and active helicase mechanisms.

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ABSTRACT

The linkage between macromolecular binding and conformational change that is ubiquitous in biological molecules can be understood in the context of the mechanisms of conformational selection and induced fit. Here, we explore mappings between these mechanisms of ligand binding and those underlying the translocation of molecular motors and the nucleic acid unwinding of helicases. The mechanism of biased motion exhibited by molecular motors is typically described as either a thermal ratchet or a power-stroke and nucleic acid helicases are characterized by either active or passive unwinding mechanisms. We posit that both Brownian ratchet translocation and passive unwinding are examples of conformational selection and that both power-stroke translocation and active unwinding are examples of induced fit. Furthermore, in ligand-binding reactions, both conformational selection and induced fit may exist in parallel leading to a ligand-dependent flux through the different mechanistic pathways. Given the mappings we describe, we propose that motors may be able to function via parallel ratchet and stroke mechanisms and that helicases may be able to function via parallel active and passive mechanisms.

Contents

1. Introduction

Biology is built upon the ability of macromolecules to transduce information by changing their shape or conformation. However, this

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alone is not sufficient. These conformations must be linked to environmental conditions (i.e. temperature, salt concentration, pH, or the concentration of other molecules) and different conformations must lead to different molecular activities. With these three conditions satisfied, an environmental variable may now produce a change in activity via the modulation of the conformation of a macromolecule. This molecular signaling is ubiquitous in biology and allows for cells to adapt to a changing environment or to enact developmental programs. Evidence for the importance of each of these requirements can be found in the fact that much of the research of biochemistry and biophysics can be described as the investigation of how molecular conformations are linked to environmental conditions and function.

Switches in macromolecular conformation often reveal a dependency on ligand binding in that the distribution of conformers changes in the presence of bound ligand. In this case, one may further inquire as to the *mechanism* that underlies this linkage: How does ligand binding produce a shift in conformation? For example, does the association of the ligand to a ground state conformation create new conformations that were not previously populated or does the ligand select from pre-existing conformations excited by the thermal bath. That is, whether the preferred conformation in a ligand-bound complex is *induced by* ligand association or is *selected from* a pre-existing ensemble. These two extreme possibilities are known as induced fit and conformational selection respectively. The concept of induced fit was introduced by Daniel Koshland and was first used to describe the formation of the catalytically competent conformation of an enzyme active site upon ligand binding [1]. The concept of conformational selection was introduced by Monod, Wyman, and Changeux in their studies of allosteric interactions between subunits of hemoglobin [2]. These limiting cases can be restated as a kinetic problem of which event happens first. In conformational selection, conformational change is followed by ligand binding. In induced fit, ligand binding occurs concomitantly with or is followed by conformational change (Fig. 1).

While distinguishing between conformational selection and induced fit is facile conceptually, the experimental determination of mechanism can be challenging. Historically, the question has been addressed experimentally through the quantification of relaxation kinetics under different molecular concentration regimes [3], via flux-based studies most commonly performed with NMR methodologies [4], or by structurally characterizing intermediate states along either of the two pathways (e.g. the observation of an apo-protein conformation similar to that of the bound complex or a ligand bound complex that has a structure not present in the unbound ensemble) [5]. Recently, a renaissance in this field is rediscovering and redefining how observables acquired from different experimental techniques may be used to eliminate or support either conformational selection or induced fit mechanisms [4, 6–9]. While these concepts are regularly discussed for binding reactions that lead to enzymatic catalysis or signaling, they are not often used to describe the mechanisms of a unique class of proteins for which ligand-coupled cycles of conformational change produce directed motion.

Motor molecules are defined by their ability to convert chemical energy (i.e. the hydrolysis of ATP) into mechanical work (i.e. the movement of RNA polymerase along the DNA during transcription). In the field of molecular motors, the concepts of *Brownian ratchet* and *power stroke* mechanisms are routinely used to divide motors into two classes [10–13]. In the more specific sub-field of nucleic acid helicase motors, the additional concepts of *active* and *passive* helicases are used to distinguish between different modes of nucleic acid unwinding [14,15]. In each case, dual classifications present limiting mechanistic frameworks. While molecular motor conformations do not transduce information in the sense of a signaling pathway, their function is dependent on links between conformational states and ligand states (i.e. binding, hydrolysis, and dissociation). Therefore, these motor classifications should have mappings onto the concepts of conformational selection and induced fit. Here, we directly map the classes of molecular motor function onto the fundamental mechanisms of ligand binding to highlight the capacity of conformational selection and induced fit to broadly describe molecular mechanisms.

2. Thermally activated molecular transitions in covalent and non-covalent reactions

On the length and energy scales relevant for biological molecules, the energy contained in the thermal bath is sufficient to activate transitions between states. The probability of these transitions is inversely related to the highest free energy state (i.e. the transition state) on the lowest free-energy path connecting two states [16,17]. In general, the diffusion of a macromolecule on a multi-dimensional energy landscape determines which conformational states are populated under given

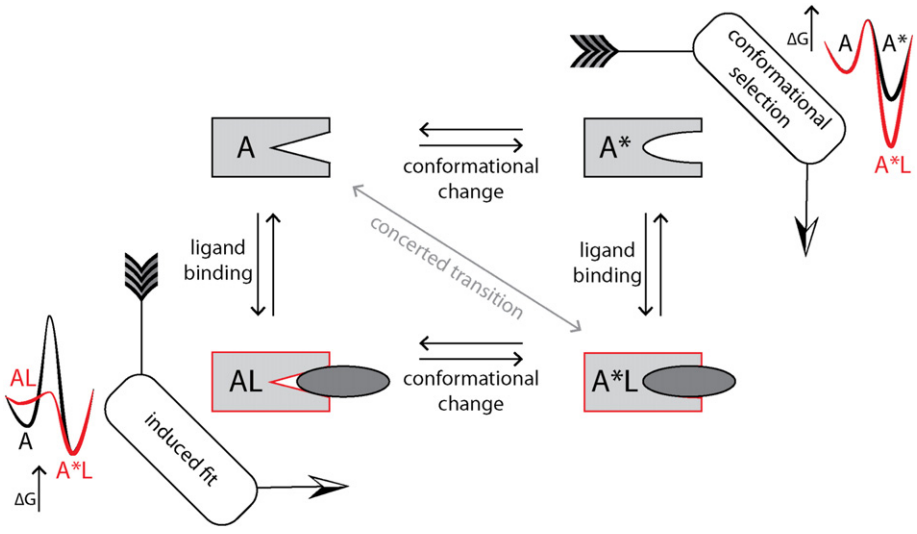

Fig. 1. Parallel pathways of ligand binding: conformational selection and induced fit. The conformational change of a macromolecule (A ↔ A*) is linked to ligand binding (A ↔ AL and A* ↔ A*L). An additional transition is shown as a gray diagonal and is meant to represent a single reaction coordinate in which ligand binding must occur concomitantly with a change in conformation. Conformational selection is represented by the A → A* → A*L pathway. In the pure conformational selection model, there is no AL state and ligand simply reduces the free energy of the A* conformation. Induced fit is represented by the A → AL → A*L pathway. In the pure induced fit model, there is no A* state and ligand binding to A results in the destabilization of A and/or the stabilization of the transition state on the path to A*L. The free energy diagrams in the absence (black) and presence (red) of ligand are shown to illustrate each individual mechanism.