Ten Achievements of 2013 that put KAIST in the Spotlight

Demonstration for how Proteins Recognize Their Cognate Ligands

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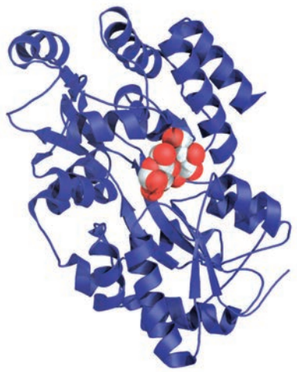


It will be possible to more accurately demonstrate complex biological phenomena in living organisms and eventually in humans. Furthermore, we can understand how various diseases are caused by the errors in specific ligand recognition by proteins in cells. Through this, we can develop therapeutics with greater efficacy in treating diseases.

Interactions between a protein and a ligand are central to all biological processes including signal transduction, cellular regulation, and enzyme catalysis. Understanding the recognition mechanisms of macromolecules therefore provides fundamental insights into how their biological functions are accurately regulated and controlled. Previous studies have simply relied on the structural differences of before and after the ligand binding, and the molecular recognition mechanism of proteins remains unclear. In this regard, the demonstration of the ligand recognition mechanism by tracking the conformational changes in real-time is urgently needed.

Single-molecule FRET (Forster Resonance Energy Transfer) analysis

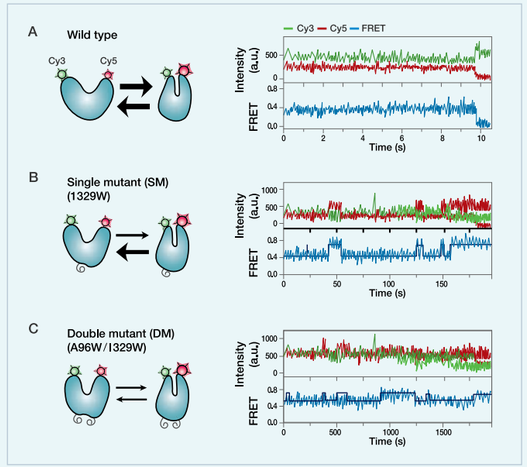
In this study, conformational change of MBP (maltose binding protein) was directly tracked at a single molecular level using single-molecule FRET measurements. MBP is known to undergo conformational change between most stable 'open substate' and 'partially closed state' even without a ligand. Through this approach, we could detect the conformational change of MBP in real- time (Fig. 1).

Results

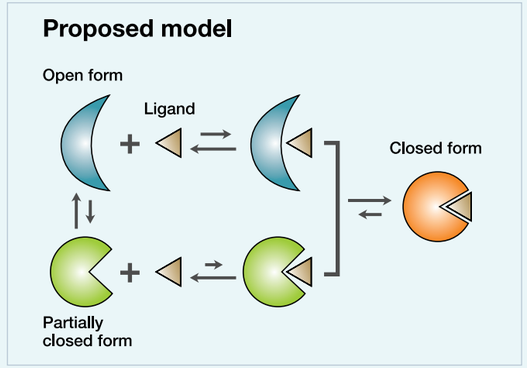
Through a kinetic analysis of conformational change, dwell time of a ligand was determined in closed and open states. Our study provided direct evidence that MBP recognizes a ligand through an "induced-fit" mechanism, not the generally proposed selection mechanism for proteins with conformational dynamics. This is the first experimental result that proves the ligand recognition mechanism of a protein through the analysis of the change in the conformational transition at a single molecular level (Fig. 2).

Conclusion

Our results show that the ligands preferentially bind to the open conformation followed by a structural transition of the proteins into a closed form, directly proving the ligand recognition mechanism, which has been the textbook explanation for the past 50 years. The approach presented in this study provides a new paradigm in elucidating the molecular mechanisms by which proteins exhibiting conformational dynamics recognize and bind their cognate ligands, assisting in the design of more potent drugs and even proteins with novel functions.



(Figure 1) Real-time analysis of proteins at a single molecular level



(Figure 2) Schematic demonstration for how proteins recognizes their cognate ligands

Expectation Effectiveness

First demonstration of a ligand recognition mechanism of a protein by single molecular FRET measurements.

Contributes greatly to the design of more potent drugs and even proteins with novel functions.

Research Funding

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Research Results

- Published in Nature Chemical Biology (2013)
- Nomination of Top 5 among Life Science Research in 2013 in Korea.
- Agawal Award (2013)
- Selected as Faculty of 1000 Prime (2013)