Allosterism in MutS Proteins and How DNA Mismatch Recognition Signals Repair: Molecular Dynamics Simulations

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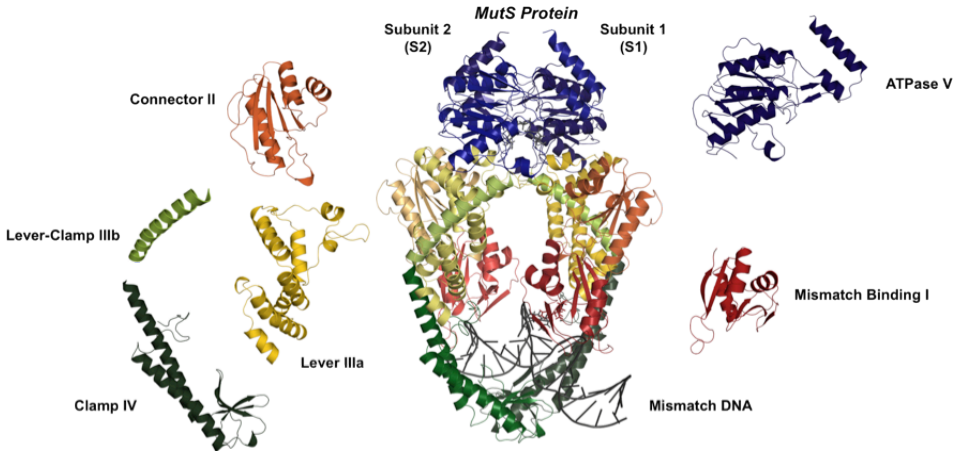
Abstract: Allosteric communication in multi-domain protein architectures is crucial in complex biological processes such as DNA mismatch repair (MMR) [Hingorani et al.]. MutS proteins (below) initiate MMR through recognition of mismatch DNA and signaling downstream repair. Mismatch recognition by MutS is followed by a marked decrease in the rate of ATP hydrolysis and DNA binding affinity. However, the nature of the coupling between the ATPase sites and DNA-binding site ~70 Å away remains a mystery, mainly because MutS is a relatively large dimeric protein. We have performed all-atom molecular dynamics simulations (150 ns) on ATP-bound and ATP-free MutS complexes with mismatch DNA to understand the effect of ATP binding on structural networks connecting the ATPase sites and DNA-binding site. In particular, the eigenvectors of the correlation matrix reveal networks of mutually correlated residues, which are related to the paths of allosteric communication in MutS. Overall, several specific MutS structural components thought to be involved in allosteric coupling between DNA-binding and ATPase domains are present in the four largest eigenvalues: A) the involvement of domain II, which resides at the connection between domains V and III, appears in most of the correlations, especially in eigenvector 1; B) From eigenvector 1, MutS rigid domains III and V move together as a unit supporting their key role in the transmission of the signal from the, more flexible, DNA binding region to the ATPase site; C) the salient networks of correlated residues from eigenvector 4 (MutS-ATP-DNA) and eigenvector 3 (MutS-DNA) predominantly involve highly conserved long α-helical levers (IIIb and IV); D) networks derived from eigenvectors 1 and 4 in the MutS-ATP-DNA complex directly involve mismatch binding and ATPase sites. The corresponding networks from the MutS-DNA complex (eigenvectors 1 and 3) are similar, but do not directly link the two sites.



References: Antony, E.; Hingorani, M. M. *Biochemistry*, **2003**, *42*, 7682-7693. Jacobs-Palmer, E.; Hingorani, M. M. *J. Mol. Biol.* **2007**, *366*, 1087-1098. Tessmer, I.; Yang, Y.; Zhai, J.; Du, C.; Hsieh, P.; Hingorani, M. M.; Erie, D. A. *J. Biol. Chem.* **2008**, *283*, 36646-36654. Acknowledgement: This project is a collaboration with Dr. Susan Pieniazek and Prof. Manju Hingorani.