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Structural and functional analyses of ATP-dependent regulation of MutL

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DNA mismatch repair (MMR) is a kind of excision repair system that removes the mismatched bases. It is known that the functional deficiency of MMR is one of the main causes of hereditary nonpolyposis colorectal cancers in human. The MutL protein plays a central role in MMR and is composed of two conserved domains. In human MutL and its homologues, it is thought that the binding of ATP to N-terminal domain (NTD) induces structural change of both domains, and then suppresses the non-specific endonuclease activity of C-terminal domain (CTD). However, its biochemical details have not been verified.

In this study, we prepared and characterized each domain (NTD or CTD) of *Aquifex aeolicus* MutL (aqMutL) that shows endonuclease activity like human MutL, and is suitable for various biochemical studies because of its high stability [1]. First, tertiary structures of the two domains of aqMutL were predicted by Rosetta program (http://boinc.bakerlab.org/) (Figure 1). Second, quaternary structure of CTD, that forms a dimer, was suggested by cross-linking experiment and small-angle scattering measurement at the SPring-8 beamline (BL45XU). Third, biochemical properties of NTD were also characterized, and the interaction between NTD and CTD was examined. Finally, the ATP-dependent structural change was investigated by mass spectrometry coupled with H/D exchange for full-length MutL or its deletion mutants. These results demonstrated that the binding of ATP to NTD induces structural change of CTD, and NTD regulates the endonuclease activity of CTD.

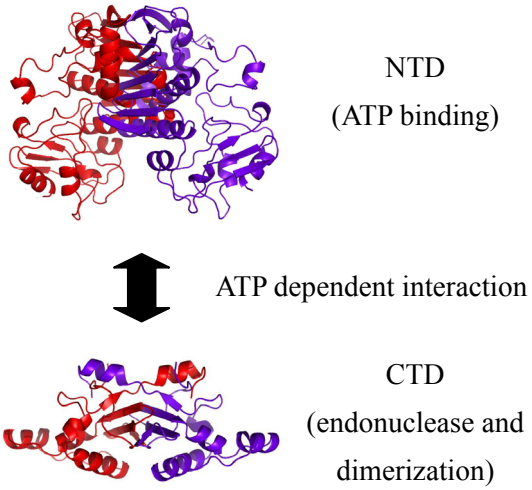

Figure 1: The structural model of aqMutL NTD and CTD

Reference

[1] Fukui, K. (2010) *Journal of Nucleic Acids,* ID 260512