Poster Presentation

MS109.P01

Structure study of UHRF1, recoginition of epigenetic marks.

K. Arita[1,2], M. Ariyoshi[2], K. Sugita[2], H. Tochio[2], M. Shirakawa[2]

[1]*Yokohama City University, Graduate school of Medical Bioscience, Yokohama, Japan,* [2]*Kyoto University, Graduate school of Engineering, Kyoto, Japan*

Two major epigenetic traits, histone modifications and DNA methylation, regulate various chromatin-template processes in mammals. The pattern of these epigenetic traits is cooperatively established in early embryogenesis and cell development, and inherited during the cell cycle. UHRF1 (also known as Np95 or ICBP90) is believed to play an important role in linking the two major epigenetic traits. UHRF1 has five functional domains, UBL, Tandem Tudor (TTD), pland homeo domain (PHD), SET and RING-associated doain (SRA) and RING finger. To maintain DNA methylation pattern, UHRF1 recognizes hemi-methylated DNA generated during DNA replication through interactions with its SRA domain, and recruit maintenance of DNA methyltransferase Dnmt1 to the site [1], [2]. UHRF1 also recognizes histone H3 containing tri-methylated Lys9 (H3K9me3) via its TTD-PHD moiety. [3]. To obtain the structural basis for recognition of epigenetic marks by UHRF1, we determined the crystal structure of the SRA domain in complex with hemi-methylated DNA. The structure showed that the DNA binding caused a loop and an N-terminal tail of the SRA domain. Interestingly, the methyl-cytosine base at the hemi-methylation site was flipped out from the DNA helix, which has not observed in other DNA binding proteins. These results suggest that the Base flip out mechanism is important event for maintenance of DNA methylation. We also determined the crystal structure of TTD-PHD region of UHRF1 in complex with H3K9me3 peptide. To our surprise, the linker region between the reader modules, which is predicted as an intrinsically disorder, was formed a stable structure with binding to the groove of TTD and plays an essential role in the formation of histone H3 binding hole between the reader modules. The structure revealed how multiple histone modifications were simultaneously decoded by the linked histone reader modules of UHRF1.

[1] *Sharif J, Muto M, Takebayashi S, et al., Nature 2007, 450, 908-912.,* ***[2]*** *Ostick M, Kim JK, Esteve PO, et al., Science 2007, 317, 1760-1764.,* ***[3]*** *Karagianni P, Amazit L, Qin J, Wong J. Mol Cell Biol 2008, 28, 705-717*

Keywords: maintenance of DNA methylation, histone modification