Structural characterization of epigenetic enzyme complexes

Epigenetic regulation of gene expression play important role in the biological processes of embryogenesis, differentiation, stem cell renewal and cell proliferation. It permits the generation of many different cell types from the same DNA. Factors that control epigenetic regulation include histone acetylation and methylation processes as well as DNA methylation. In this project, we will do structural characterization of two epigenetic enzyme complexes including Protein arginine methyltransferases-5 (PRMT5) and DNA methyltrasferase-1 (DNMT1) using cryo-electron microscopy.

Protein arginine methyltransferases-5 (PRMT5)

Protein methylation is a significant regulator of biological function; protein arginine methyltransferases (PRMTs, a family of nine enzymes in humans) methylate arginine amino acids in many proteins, including histones. As PRMTs are critical components of a range of biological processes and frequently deregulated in certain cancers, these enzymes are emerging targets for cancer chemotherapy. In particular, PRMT5 is overexpressed in tumors and elevated activity is correlated with poor clinical prognosis. The writing and erasing of Histone post-translational modifications (PTMs; *e.g.* arginine methylation) is a dynamic 'libretto' decoded by a specific sub-type of proteins: the readers. These well-orchestrated events provide an attractive way to explaining cancer progression and the drift from healthy cell lines. To further illustrate the Histone Code Hypothesis, our preliminary data provide a framework to deciphering a novel and universal alphabet with the discovery of PTM crosstalk. Learning such an alphabet and using it towards cellular re-programming will provide an unprecedented approach to curing numerous metabolic disorders. One of our methyltransferase candidates ─PRMT5 and its substrate presenter MEP50─ does form a macromolecular assembly of 432 kDa. The Cryo-EM technology will provide novel insights of this important drug target; indeed, making an inventory of specific substrate/methyltransferase site of recognition will move our work forward.

DNA methyltrasferase-1 (DNMT1)

Human DNA methyltransferase-1 (DNMT1) enzyme is involved in maintaining the epigenetic state of DNA by replicating CpG methylation properties from parent to daughter strand of the DNA. It has been proposed that DNMT1 produces heritable DNA methylation pattern via cell division. In contrast to genetic mutations, epigenetic changes are reversible and recovery of normal gene function and cell type is achievable. For these reasons, there has been interest in the potential of DNMT1 inhibitors as therapeutic against cancer. DNMT1 is a multi-domain enzyme with 160 kDa molecular mass. The aim of this project to characterize DNMT1 (full length and truncated variant) with the transition state inhibitors. The co-crystallization of DNMT1 with DNA and inhibitors have been difficult. In this respect, high resolution Cryo-EM will play crucial role in the structural characterization of DNMT1 complexes.