Tsinghua-*Science* Workshops

Epigenetics Structure and Function

Session 12: Histone and DNA modifications at the nucleosomal level

Thursday, December 2nd, 2021 8-10 pm (GMT +08:00, Beijing)
20:00-20:45
Cynthia Wolberger, Johns Hopkins University School of Medicine, USA
Molecular basis of histone code cross-talk
20:45-21:00 Q&A

21:00-21:45
Peter Jones, Van Andel Institute, USA
Methylation of DNA in a Nucleosomal Context
21:45-22:00 Q&A

Host

Prof. Haitao Li

Dr. Haitao Li received his doctorate degree in molecular biophysics at the Institute of Biophysics, Chinese Academy of Sciences in 2003. He then performed his postdoctoral research at Memorial Sloan-Kettering Cancer Center and was promoted to Senior Research Scientist there in 2006. Li joined the School of Medicine at Tsinghua University as a tenure-track associate professor in 2010 and became full professor with tenure in 2016. Li currently serves as associate director of the Beijing Advanced Innovation Center for Structural Biology and associate dean of the School of Medicine, Tsinghua University.

Li's research is focused on gaining molecular and mechanistic insights into epigenetic regulation impacting on health and disease. His group mainly applies structural and biochemical approaches, blended with other cellular and omic techniques to study key recognition and catalysis events involved in epigenetic regulation, and to investigate the complexity of the molecular ecosystem coupling epigenetics, metabolism and signaling. Other endeavors of the lab include structure-guided drug discovery and biointeraction-profiling tool development. Li's major contribution to science has been the elucidation of the molecular basis underlying modification-dependent histone/DNA readout and catalysis by epigenetic readers, writers and erasers, such as PHD finger, YEATS, SETD2 and ALKBH1. Dr. Li has authored more than 100 scientific publications that have received over 11,000 citations. Li is the recipient of multiple awards, including the CC Tan Life Science Innovation Award, Promega Innovation Award for Cell Biology, the Young Scholar of China Award in Cancer Research, the Wuxi PharmaTech Life Science and Chemistry Awards, Mao Yi-sheng Science and Technology Award for Beijing Youth, the HFSP Young Investigators Grant Award, and the National Science Fund for Distinguished Young Scholars of China.

Speakers

Prof. Cynthia Wolberger

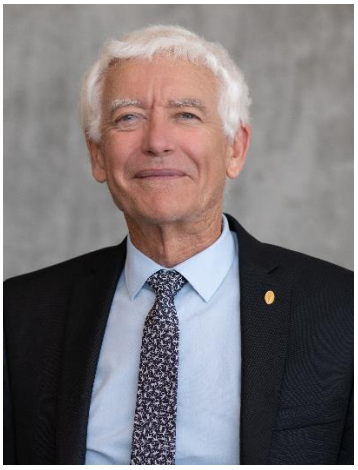
Cynthia Wolberger is a Professor and Director of the Department of Biophysics and Biophysical Chemistry at the Johns Hopkins University School of Medicine, where her group studies the structural basis of transcription regulation and ubiquitin signaling using cryo-EM and x-ray crystallography. She received an A.B. in Physics from Cornell University and a Ph.D. in Biophysics from Harvard University, and did postdoctoral research at UCSF and at the Johns Hopkins School of Medicine. In both her graduate and postdoctoral studies, she studied the structural basis of transcription factor binding to DNA. Since establishing her own research group at Johns Hopkins, she has made major contributions to the understanding of the molecular mechanisms underlying combinatorial regulation of transcription, post-translational modification of histone proteins, and ubiquitin signaling. A current focus or her research is on the interplay between histone ubiquitination and regulation of

transcription. Dr. Wolberger is a recipient of the Protein Society's Dorothy Crowfoot Hodgkin Award, the AACR Award for Outstanding Achievement in Chemistry in Cancer Research, and is a Fellow of the Biophysical Society and the American Association for the Advancement of Science. She is a member of the National Academy of Sciences, the National Academy of Medicine and the American Academy of Arts and Sciences.

Molecular basis of histone code cross-talk

Reversible post-translational modifications of histone residues plays a central role in gene regulation. Monoubiquitination of histone H2B is a hallmark of actively transcribed chromatin and plays a non-degradative role in regulating transcription. H2B monoubiquitination stimulates deposition of two other activating marks, methylation of histone H3 K4 and K79, by two different methyltransferases. The talk will cover structural and biochemical studies that have provided insights into the mechanism by H2B monoubiquitination stimulates the methyltransferases, Dot1L and COMPASS. The talk will also cover recent studies aimed at identifying novel inhibitors of H2B-specific deubiquitinating enzymes that are misregulated in cancer.

Prof. Peter Jones



Peter Jones was born in Cape Town, raised and attended college in Rhodesia (now Zimbabwe), and received his Ph.D. from the University of London. He joined the University of Southern California in 1977 and served as Director of the USC Norris Comprehensive Cancer Center between 1993 and 2011. Dr. Jones became Chief Scientific Officer of Van Andel Institute in 2014. He helped pioneer the field of epigenetics, particularly its role in cancer, and helped develop novel therapies for cancer. He has published more than 300 scientific papers and received several honors, including an Outstanding Investigator Award from the National Cancer Institute. He and his colleague Stephen Baylin shared the Kirk Landon Award for Basic Cancer Research from the AACR in 2009 and the Medal of Honor from the American Cancer Society in 2011. Dr. Jones is a past President of the American Association

for Cancer Research and was elected a Fellow of the American Association for the Advancement of Science in 2009 and a Fellow of the AACR Academy in 2013. He was elected a member of the National Academy of Sciences of the United States in 2016, the American Academy of Arts and Sciences in 2017 and received an honorary Doctor of Science from Stellenbosch University in 2018.

Methylation of DNA in a Nucleosomal Context

The methylation of DNA in chromatin is much more complex than in solution. DNA wrapped around the nucleosome is refractory to *de novo* methylation by either eukaryotic or prokaryotic methyltransferases at the same time as the methylation machinery in a cell is firmly anchored to the nucleosomes. The two *de novo* methyltransferases, DNMT3A and DNMT3B, are differentially expressed as multiple isoforms and there are at least ten splice variants of DNMT3B some of which are catalytically inactive. *De novo* methylation of DNA by DNMT3A requires the participation of accessory proteins, such as DNMT3L and DNMT3B3 and is achieved by a ternary complex of two molecules of DNMT3A and two molecules of DNMT3L or alternatively DNMT3B3. We investigated the structure of a ternary complex of DNMT3A2 with DNMT3B3 on nucleosomal substrates containing short pieces of linker DNA on each side of the nucleosome. I will present the cryo-EM structure of this complex which is very unusual in that it binds both to the protein part of the nucleosome and to the linker DNA. The structure predicts that nucleosomes must be moved or remodeled in order for *de novo* methylation to occur which is consistent with in vivo data. Most studies investigating the role of Dnmt3a in embryonic development have focused on knockouts of both Dnmt3a1 and Dnmt3a2 at the same time. We therefore engineered a mouse knocked out for Dnmt3a2 to determine the role of this isoform in embryonic development. Mice heterozygous or homozygous for Dnmt3a2 were viable. Interestingly, analysis of the genomic distribution of CpG methylation showed that Dnmt3a2 is required for full methylation of both enhancers and CTCF motifs. Further studies to investigate the roles of Dnmt3a2 in development and cancer are underway.