Overview of the “1SBA: integrative approaches towards understanding of gene expression” session at the 57th BSJ meeting

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Dynamic interactions between proteins and nucleic acids are involved in many essential biological processes such as DNA replication, repair, and transcription. Recent advances in experimental and theoretical techniques have greatly increased our understanding of gene transcription at the molecular and cellular levels, and there is a need for integrative approaches to combine the data and knowledge obtained from multiple techniques. In this session, we discussed how hybrid approaches using single-molecule imaging, X-ray crystallography, cryo-electron microscopy (cryo-EM), and computer simulations could contribute to the comprehensive understanding of gene expression.

Kazuhiro Maeshima (National Institute of Genetics) reported that RNA polymerase II (RNAP II) globally constrains the dynamics of chromatin (Babokhov et al. 2019; Nagashima et al. 2019). Their single-nucleosome imaging in human cells and Brownian dynamics simulations with a spring-beads model showed slow movement of chromatin in the presence of active RNAP II. He suggested that chromatin domains are weakly connected through “Hub,” which includes clusters of active RNAP II and transcription factors, and RNAP II is released from the Hub at the elongation stage.

Kayo Nozawa (The University of Tokyo) determined the three-dimensional (3D) structure of Mediator by using X-ray crystallography (Plaschka et al. 2016; Nozawa et al. 2017). She proposed an atomic structural model of the RNAP II-Mediator complex based on the cryo-EM data of the complex and homology models of the component proteins constructed using X-ray crystal structures. She suggested that the

conformational change in the Mediator stimulates phosphorylation of the C-terminal domain of RNAP II, allowing for transition from the pre-initiation to elongation stages.

Shun-ichi Sekine (RIKEN BDR) reported the cryo-EM structures of the RNAP II-nucleosome complex at the elongation stage (Kujirai et al. 2018; Ehara et al. 2019). He and his colleagues revealed multiple snapshot structures representing the RNAP II passage through a nucleosome in the absence and presence of the transcription elongation factors. He proposed molecular mechanisms underlying nucleosomal DNA transcription, where the transcription elongation factor Elf1 has an essential role in facilitating the passage of nucleosomal barriers by modulating interactions between RNAP II, histone, and DNA.

Takaharu Mori (RIKEN CPR) developed a new computational technique for the flexible fitting of cryo-EM data to accelerate structure refinement of large biomolecular systems (Mori et al. 2019), and also proposed a new scheme that refines the structure of flexible proteins effectively. He carried out all-atom molecular dynamics (MD) simulations of the RNAP II complex after the refinement of the cryo-EM structure and revealed that the binding of transcription factors to RNAP II could affect the fluctuation of DNA.

Cheng Tan (Kyoto University) developed a new method for efficient coarse-grained (CG) MD simulations of protein-DNA complex (Tan and Takada 2018). To introduce sequence-specific interactions between protein and DNA in the simulation, he integrated two different experimental data: high-throughput protein binding assays and 3D structures of the complexes. He applied the method to a nucleosome complexed with transcription factors and observed allosteric effects induced by the binding of multiple transcription factors.

Hiroaki Yokota (The Graduate School for the Creation of New Photonics Industries) proposed a kinetic mechanism of DNA unwinding mediated by the UvrD helicase (Yokota et al. 2013). The protein repairs DNA damaged by ultraviolet (UV) light and base-pair mismatches. Therefore, it plays a crucial role in maintaining the genome integrity. By using single-

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molecule fluorescence imaging approach (Yokota 2020), he revealed that UvrD adopts an oligomeric form when it unwinds DNA and discussed the role of the C-terminal residues in the oligomerization.

As demonstrated by all speakers in this session and previous studies (Cardoso et al. 2012), protein-DNA interactions take place across various temporal and spatial scales. Although recent cryo-EM experiments have enabled us to solve the 3D structures of protein-DNA complexes at near-atomic resolution, there are still big gaps between the insights obtained from the structural analysis and single-molecule imaging. Multi-scale approaches that connect those insights using computational techniques will further expand our knowledge for the sequence-structure-dynamics-function relations of proteins and DNA at the sub-micrometer scale.

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