分子細胞生物学研究所セミナー

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演題 **Developing a Transcriptional Roadmap for Studying Cohesin's Role in Cornelia de Lange Syndrome.**

日時 **４月８日（金）15：00 ～ 16：30**

場所 **東京大学分子細胞生物学研究所**
生命科学総合研究所Ｂ棟 ３階 301 会議室

主催 **東京大学分子細胞生物学研究所**
ゲノム情報解析研究分野（連絡先：20756）

The cohesin complex, and accessory regulatory proteins, plays a critical role in several basic cellular processes including its canonical role in sister chromatid cohesion as well as several more recently described roles including DNA repair, long-range chromosomal architectural integrity, stem cell maintenance and pluripotency and regulation of gene expression. The interest in cohesin's role in transcriptional regulation was heightened after mutations were identified in the human NIPBL gene in Cornelia de Lange syndrome (CdLS), a multisystem developmental disorder. NIPBL (Scc2 in yeast) is a cohesin regulatory protein that plays a critical role in the loading and unloading of the cohesin complex onto chromosomes. Mutations in additional cohesion structural (SMC1, SMC2, Rad21) and regulatory (HDAC8) subunits were also found to cause CdLS. Subsequently mutations in other cohesin related proteins have been identified in other developmental disorders collectively termed "cohesinopathies". Clinical manifestations of CdLS include intellectual disability, growth retardation, craniofacial abnormalities including cleft palate, limb defects, gastrointestinal defects, cardiac and hematopoietic abnormalities. Our work seeks to advance our understanding of cohesin's role in the regulation of gene expression and sister chromatid segregation in

the undifferentiated state, and during normal and pathological in vitro hematopoiesis, cardiogenesis and neural patterning. We have generated three induced pluripotent stem cell (iPSC) lines from CdLS patients carrying endogenous mutations in cohesion associated gene, NIPBL. We are comprehensively investigating 1) The mechanism by which cohesin controls global gene expression in undifferentiated iPSCs and during blood, heart and brain developmental-specific stages and attempting to 2) recapitulate the CdLS-related disease phenotypes in patient-derived iPSCs to model structural and intellectual birth defects associated with CdLS. Analysis of gene expression in the undifferentiated state shows more than 1500 differentially expressed genes in NIPBL cells compare to controls, with post-translational modifications, cell cycle, gene expression and DNA repair, recombination and replication among the most significant processes altered. IPSC-derived cell types, hematopoietic progenitor cells (HPCs; CD41+/CD235+/CD43+), megakaryocytes (MEGs, CD41+/CD42+), cardiomyocytes (VCAM+/SIRPA+), and neural progenitors (PAX6+/NESTIN+) have reduced NIPBL mRNA expression (~18-25% decrease) relative to control cell lines. Whole genome transcriptional analysis coupled with evaluations of epigenetic modifiers on these cells will be focused at identifying distinct networks and/or mechanisms responsible for the multiorgan defects identified in our patients. We have focused on the CdLS mutant gene NIPBL, which has served as the framework to develop an infrastructure where our methodologies can be applied to other cohesin genes and the related cohesinopathies to study changes in the transcriptome and epigenome.