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Seminar Series

Thursday
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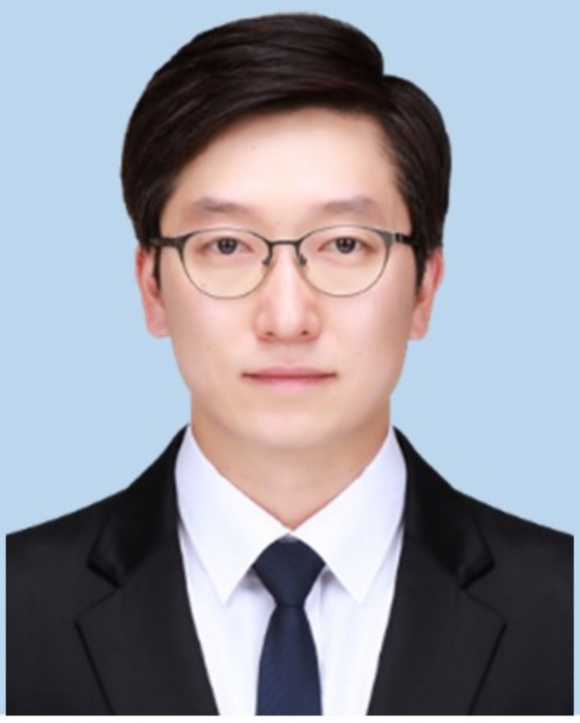
This seminar will be held in the manner of online and offline both.

Offline: Jukhyun Bio Auditorium (RM.121)
Online: Zoom ID 315 451 8934 (Password: 101320)



Switching DCAFs: Regulation of DNA replication and mitosis by recruiting CRL4 to chromatin

연사 장상민 교수

소속 충북대학교

Host 박철승 교수

언어: 한국어

학력

2012 Ph.D. in Molecular and Cellular Biology
Chung-Ang University

2008 M.S. in Molecular and Cellular Biology
Chung-Ang University

2006 B.S., in Dept. of Life Science, Chung-Ang University

경력

2020 - Now Assistant Professor, Dept. of Biochemistry, Chungbuk National University

2015 - 2020 Postdoctoral Research, Developmental Therapeutics Branch, Center for Cancer Research, NCI, NIH

2012-2015 Postdoctoral Research, Dept. of Life Science, Chung-Ang University

Abstract

Cell proliferation involves continuous oscillation between synthesis of DNA during interphase and subsequent chromosome separation during mitosis. Transitions between these major events are orchestrated by posttranslational modifications to insure the preservation of genomic information. Cullin-RING E3 ubiquitin ligases (CRLs) regulate cell cycle control and DNA replication by mediating ubiquitination of effector proteins. We found that RepID (DCAF14/PHIP), WD40-containing protein that selectively binds and activates a group of replication origins, plays a crucial architectural role via recruitment of CRL4 complex to chromatin during interphase. CRL4 recruitment on chromatin was initiated prior to DNA synthesis mediated by RepID-dependent manner. RepID-depleted cells exhibited diminished CRL4 chromatin loading that leads to accumulation of CRL4 substrates including CDT1, p21 or SET8. Lack of function of chromatin-bound CRL4 in RepID-deficient cells was compensated by alternative ubiquitin ligase complex, SKP2- containing CRL1, to progress through the cell cycle. RepID depletion markedly increased cellular sensitivity to SKP2 inhibitors, which triggered massive genome re-replication. Both RepID and SKP2 interacted with distinct, non-overlapping groups of replication origins, suggesting that selective interactions of replication origins with specific CRL components execute the DNA replication program and maintain genomic stability by preventing re-initiation of DNA replication.

We also found that RepID plays a crucial role during mitosis by recruiting CRL4 to condensed chromosomes. RepID interacts with BUB3 which is known as spindle assembly checkpoint protein (SAC) localized on kinetochore during mitosis. BUB3 expression was decreased along with mitotic progression by CRL4-dependent ubiquitination. RepID was temporally dissociated from CRL4 prior to BUB3 degradation while retinoblastoma binding protein (RBBP7) which is one of the DCAFs localized on mitotic spindle acts as a functional DCAF by incorporating into CRL4 for BUB3 ubiquitination. Failure of BUB3 ubiquitination mediated by RepID or CRL4RBBP7 depletion exhibited delayed mitotic exit and remarkably high sensitivity to paclitaxel. During interphase, BUB3 is protected from ubiquitination by associating with PML bodies and is targeted by CRL4CDT2 in promyelocytic leukemia (PML)-deficient cells. These observations provide new insights of the CRL4 roles in cell cycle, switching machinery from architectural to functional DCAF in CRL4, and new strategies for cancer therapy together with manipulating expression/function of RepID.