**USP50 suppresses alternative RecQ helicase use and deleterious DNA2 activity during replication**

Nat Commun. 2024 Sep 16;15(1):8102.

**Presenter:** Hung-Chun Pan **Date/Time:** 2025/03/13, 16:20-17:10

**Commentator:** Prof. Hungjiun Liaw **Location:** Room 601, Med College Building

**Background:** The fidelity of DNA replication relies on various helicase and nuclease activities is vital for maintaining genomic stability, especially under replicative stress, which can disrupt replication fork progression and lead to DNA damage. However, the mechanisms that direct these activities during replication remain poorly understood.

**Objective/Hypothesis:** To investigate the role of USP50, a ubiquitin-specific protease, in maintaining replication fork stability and its potential regulation of helicase and nuclease activities under replication stress conditions.

**Results:** Authors identified USP50 as a factor that facilitated the localization of WRN helicase-FEN1 nuclease near replication forks. Overexpressing FEN1 or WRN compensated for the absence of USP50, supporting ongoing replication, enhancing fork restart, and preventing spontaneous DNA breaks. In USP50-deficient cells, the DNA2 nuclease and RECQL4/RECQL5 helicases contributed to fork stalling, reduced recovery, increased single-strand DNA (ssDNA) exposure, and fork collapse. Similarly, in the absence of FEN1, fork restart was inhibited by DNA2 and RECQL4/RECQL5 activity. Notably, inhibiting DNA2 enhanced resistance to hydroxyurea (HU) and improved telomere stability, while suppressing RECQL4 and RECQL5 increased pyridostatin resistance in USP50-depleted cells.

**Conclusion:** This study highlights USP50 as a novel regulator of helicase and nuclease dynamics during DNA replication. By supporting the localization of critical proteins involved in DNA replication and repair, USP50 plays a vital role in maintaining genomic integrity and cellular survival under stress conditions.