The function of the histone variant H2A. Z on DNA replication origin selection

With the support by the National Natural Science Foundation of China and the Chinese Academy of Sciences, the research led by Dr. Li GuoHong (李国红) and Dr. Zhu MingZhao (朱明昭) from the Institute of Biophysics of the Chinese Academy of Sciences, has demonstrated that the histone variant H2A. Z facilitates the licensing and activation of early DNA replication origins, which was published in *Nature* (2020, 577: 576—581).

DNA replication is a tightly regulated process that ensures the precise duplication of the genome during cell proliferation. In eukaryotes, DNA wraps around histone octamers to form chromatin in the nucleus. The licensing and activation of DNA replication origins are regulated by both the DNA sequence and chromatin features. However, the chromatin-based regulatory mechanisms remain largely uncharacterized.

In this study, through biochemical and cell biological approaches, they found that H2A. Z-containing nucleosomes bind directly to the histone lysine methyltransferase enzyme SUV420H1, promoting the demethylation of histone H4 on its lysine 20 residue. The H2A. Z with H4K20me2 modification nucleosomes then recruited ORC1 (origin recognition complex subunit 1) to help accomplish the licensing of DNA replication origins (Figure).

In addition, through genome-wide studies in HeLa cells, their results showed that the signals of H4K20me2, ORC1 and nascent DNA strands (indicating active DNA replication origins) co-localize with H2A. Z, and the depletion of H2A. Z results in decreased H4K20me2, ORC1 and nascent-strand signals. H2A. Z-regulated replication origins have a higher firing efficiency and earlier replication timing compared with other origins.

Furthermore, they conditionally knocked out (CKO) H2az1/H2az2 in T cells and found that in H2A. Z CKO mice the activated T cells have defects in cell proliferation and DNA replication.

In summary, this study describes a novel epigenetic regulation mechanism for DNA replication origin selection and offers a new way of understanding DNA replication regulation in eukaryotes. Importantly, this regulatory pathway can potentially serve as a target for cancer treatment and regulation of T cell function during immunotherapy.

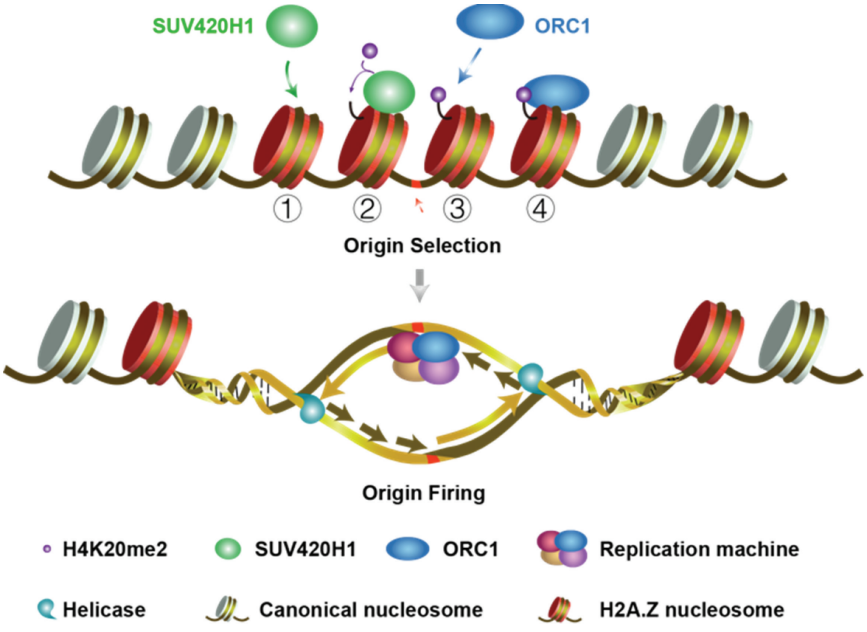

Figure Origin selection: H2A. Z nucleosomes bind Suv420H1 directly (①) to establish H4K20me2 on chromatin (②), which then recruits ORC1 (③) to bind to replication origins (④). Origin firing: H2A. Z-Suv420H1-H4K20me2-ORC1 axis selectively license and activate early replication origins. (The image by Dr. Li's lab)