Delineation of a new mechanism underlying accurate mitosis and chromosome stability

With the support by the National Natural Science Foundation of China, the Ministry of Science and Technology of China and Chinese Academy of Sciences, the research team led by Prof. Yao Xuebiao (**姚雪彪**) and Prof. Liu Xing at the University of Science and Technology of China and Anhui Key Laboratory of Cellular Dynamics and Chemical Biology, cooperated with Profs. Teng Maikun, Niu Liwen, Zang Jianye, Tian Changlin and Wang Zhiyong from the University of Science and Technology of China, and Prof. Ding Xia from Beijing University of Chinese Medicine, and reported the identification of a novel mechanism involving the CDK1—TIP60—Aurora B axis that orchestrates accurate mitosis and chromosomes stability. This work was published in *Nat Chem Biol* (2016, 12: 226—232).

The kinetochore is a super-molecular complex assembled at each centromere in eukaryotes. It provides a chromosomal attachment point for the mitotic spindle, linking the chromosome to the microtubules and functions in initiating, controlling and monitoring the movements of chromosomes during mitosis. The maintenance of chromosome stability is pivotal for cell health. The team showed that Aurora kinase B, the catalytic subunit of chromosome passenger complex, which governs faithful chromosome segregation by correcting erroneous kinetochore-microtubule interaction, was a cognate substrate of acetyltransferaseTIP60, a haplo-insufficient tumor suppressor. They also found that TIP60 was essential for maintaining chromosome stability as either TIP60 knock-down or inhibition by small chemicals resulted in micronucleus and bi-nucleates, hallmarks of genomic instability. Mechanistic analyses showed that TIP60-dependent acetylation of Aurora B-antagonized PP2A mediated de-phosphorylation of the kinase at threonine 232, thus sustained the activation of Aurora B at aberrantly attached kinetochores, and ensured an accurate error correction. They also established that CDK1/cyclinB1-dependent phosphorylation was required for TIP60 activity, suggesting that the newly characterized CDK1-TIP60-Aurora B signaling cascade governs genomic stability against tumorigenesis during cell division. These findings define a conserved signaling axis in the eukaryotic kingdom that integrates protein phosphorylation and acetylation to cell cycle progression to maintenance of genomic stability, which highlights a key role of tumor suppression TIP60 in the quality control of cell division.

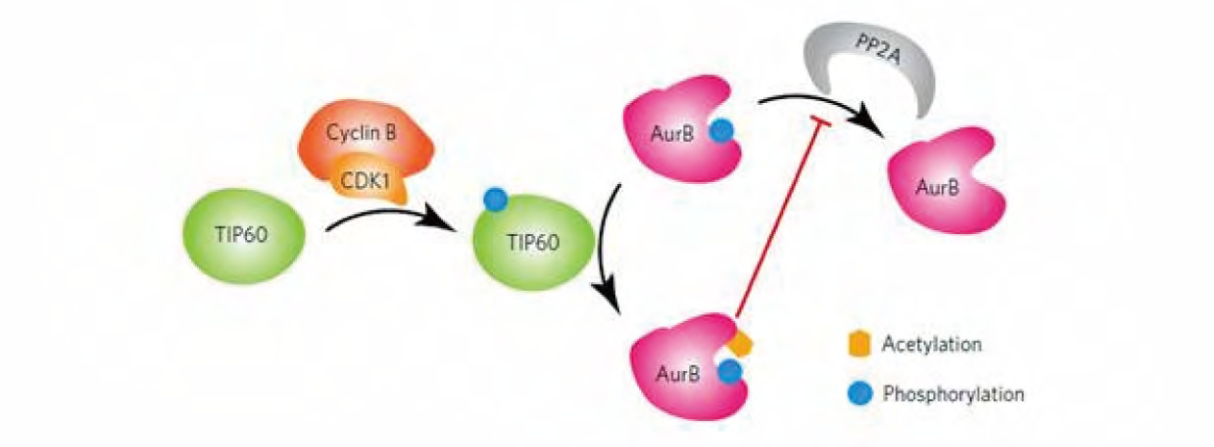

Figure Model for CDK1—TIP60—Aurora B signaling axis.