Detailed structure and regulation of ATR kinase

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Cai Gang (蔡刚) at the Hefei National Laboratory for Physical Sciences at Microscale and School of Life Sciences, University of Science and Technology of China, becomes the first to determine the structure of the ATR-ATRIP complex in near-atomic detail, which reveals the regulatory mechanism of ATR activity and may shed lights on future cancer therapy. Related study was published in *Science* (2017, 358: 1206—1209).

The ATR protein is the apical kinase to cope with the prevalent single strand DNA breaks and DNA replication stress. The ATR signaling abnormalities disturb cell viability and cause clinically distinct disorders including several kinds of cancers. *In vivo*, the ATR activity must be tightly regulated to maintain cellular homeostasis. Upon DNA damage, the ATR should be immediately activated; whereas, accidental ATR activation in the absence of DNA damage could induce cell death.

It has long been a central question to determine the activation mechanism of ATR kinase—how it responds to DNA damage and how it is activated. To learn more about the detailed architecture of the ATR-ATRIP complex and possible ways to therapeutically target it, their group used cryo-electron microscopy (cryo-EM) to analyze the yeast ATR-ATRIP complex and produced the crystal clear, three-dimensional structure at near-atomic 3.9 Å resolution. The high-resolution structure shows ATR-ATRIP forms a dimer of heterodimers and illuminates critical regulatory sites of the ATR kinase, which is poised for catalysis due to the immobilized activation loop. Upon DNA damage, specific ATR activators could immediately release the inhibition on the activation loop and culminate in full ATR kinase activity.

Owing to its pivotal roles in the regulation of genomic integrity, ATR has been a potentially viable therapeutic target. Development of more specific and efficient ATR inhibitors holds the promise for significant cancer treatment improvement. The ATR-ATRIP structure illuminates regulatory regions such as the PRD and Bridge domains that could be potentially targeted by more efficient ATR inhibitor design. The specific ATR inhibitors may be developed to lock the ATR kinase into the inactive state. Therefore, the work provides a molecular blueprint for the development of novel ATR inhibitors as potential cancer therapeutic agents.

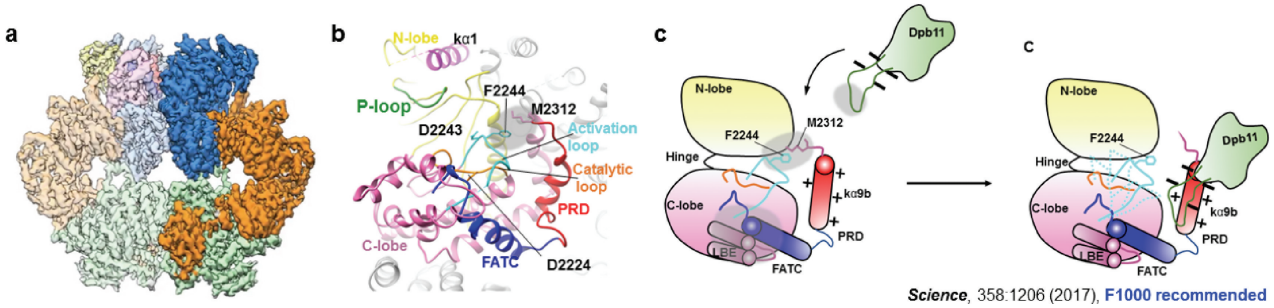

Figure Structure of ATR-ATRIP complex (a,b) and working model for the mechanism of ATR activation (c).