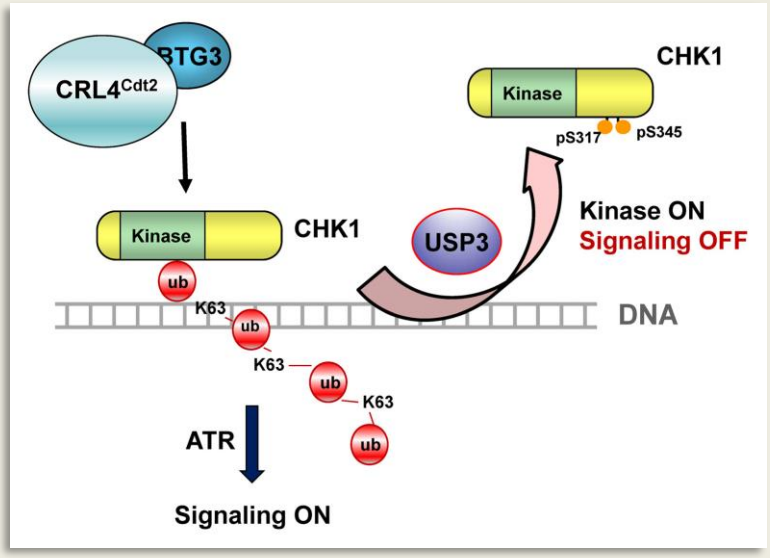
Locking and unlocking of the cell cycle checkpoint kinase CHK1

Protein modification plays a pivotal role in cell cycle control, in particular, phosphorylation and ubiquitination. These modifications often work hand in hand in transducing signals that regulate cell cycle progression.



CHK1 is a Ser/Thr kinase that is phosphorylated and activated in response to DNA damage. It has been known for some time that the response is critical for cell cycle control and maintenance of genome stability; however, it remained elusive how CHK1 is targeted to chromatin and how it is released following its activation for the ensuing action. A team led by Dr. Sheau-Yann Shieh in the Institute of Biomedical Sciences first discovered in 2013 that K63-linked polyubiquitination of CHK1 targets the kinase to chromatin for activation but paradoxically also blocks the access of its substrates (1). The key to unlocking CHK1 was recently uncovered. A post-doctoral fellow Dr. Yu-Che Cheng in her group found that the deubiquitinating enzyme USP3, by removing the ubiquitin chain, releases CHK1 from the chromatin and at the same time making the kinase fully accessible to its substrates (2). Thus, the work highlights a molecular switch (ubiquitination) that spatiotemporally controls the activity of CHK1.

As several CHK1 inhibitors are being tested in clinical trials for treating cancer, understanding how CHK1 is regulated has become ever more important. The discovery of USP3 has no doubt offered a new avenue for targeting the activity of CHK1.

1. Cheng, Y.-C., Lin, T.-Y., and Shieh, S.-Y. (2013). Candidate tumor suppressor BTG3 maintains genomic stability by promoting Lys63-linked ubiquitination and activation of the checkpoint kinase CHK1. Proc. Natl. Acad. Sci. USA 110: 5993-5998.
2. Cheng, Y.-C. and Shieh, S.-Y. (2018). Deubiquitinating enzyme USP3 controls CHK1 chromatin association and activation. Proc. Natl. Acad. Sci. USA, doi: 10.1073/pnas.1719856115, in press.