Researchers illuminate mechanisms that regulate DNA damage control and replication

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Scientists at Burnham Institute for Medical Research (Burnham) have demonstrated important new roles for the protein kinase complex Cdc7/Dbf4 or Cdc7/Drf1 (Ddk) in monitoring damage control during DNA replication and reinitiating replication following DNA repair. Since Ddk is often deregulated in human cancers, this new understanding of its role in DNA damage control could help shape new cancer therapies. The research was published in the December 24 issue of *Molecular Cell*.

Accurate DNA replication is essential for maintaining the stability of the genome. When errors occur, replication halts through a quality control process called the S-phase checkpoint. Replication is only restarted after the errors have been repaired. One of several proteins required for DNA replication, Ddk has long been thought to play an important role in the S-phase checkpoint, despite the lack of definitive evidence. In this study, Burnham researchers show that Ddk actively controls S-phase checkpoint signaling and plays a crucial role in triggering the re-initiation of DNA replication once damage has been repaired.

"This protein kinase complex is not only monitoring DNA replication, it's also monitoring the S-phase checkpoint," says Wei Jiang, Ph.D., the study's principal investigator. "If replication is accurate, then Ddk allows DNA synthesis to continue normally. If there is DNA damage, replication is halted at this checkpoint. The most important thing is to stop replication in order to allow for DNA repair and to avoid catastrophe for the cell. Our study demonstrates that Ddk not only

activates the initiation of DNA replication, but it also monitors the checkpoint during DNA damage control and eventually overrides the checkpoint to re-initiates DNA replication."

These findings suggest a highly complex role for Ddk in DNA replication, S-phase checkpoint monitoring and DNA replication re-initiation after repair. The roles of Ddk in controlling the DNA replication machinery for genome stability and fidelity may make it an excellent target for the development of new cancer treatments.

Source: Burnham Institute