LPS Award was presented to Patrice Y. Ohouo (Smolka lab) in May 2013 for the best BMCB paper.

DNA-repair scaffolds dampen checkpoint signalling by counteracting the adaptor Rad9

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Abstract

In response to genotoxic stress, a transient arrest in cell-cycle progression enforced by the DNA-damage checkpoint (DDC) signalling pathway positively contributes to genome maintenance. Because hyperactivated DDC signalling can lead to a persistent and detrimental cell-cycle arrest, cells must tightly regulate the activity of the kinases involved in this pathway. Despite their importance, the mechanisms for monitoring and modulating DDC signalling are not fully understood. Here we show that the DNA-repair scaffolding proteins Slx4 and Rtt107 prevent the aberrant hyperactivation of DDC signalling by lesions that are generated during DNA replication in Saccharomyces cerevisiae. On replication stress, cells lacking Slx4 or Rtt107 show hyperactivation of the downstream DDC kinase Rad53, whereas activation of the upstream DDC kinase Mec1 remains normal. An Slx4-Rtt107 complex counteracts the checkpoint adaptor Rad9 by physically interacting with Dpb11 and phosphorylated histone H2A, two positive regulators of Rad9-dependent Rad53 activation. A decrease in DDC signalling results from hypomorphic mutations in RAD53 and H2A and rescues the hypersensitivity to replication stress of cells lacking Slx4 or Rtt107. We propose that the Slx4-Rtt107 complex modulates Rad53 activation by a competition-based mechanism that balances the engagement of Rad9 at replication-induced lesions. Our findings show that DDC signalling is monitored and modulated through the direct action of DNA-repair factors.