Binding of ATR-ATRIP to the RPA-ssDNA complex

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

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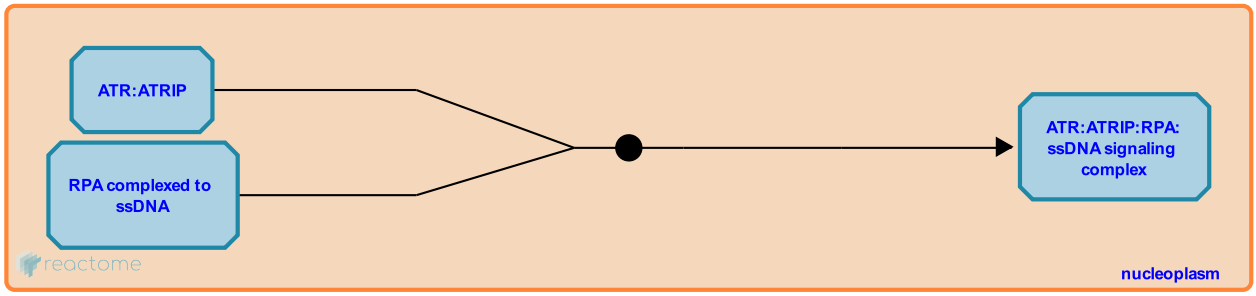
Stable identifier: R-HSA-176250

Type: binding

Compartments: nucleoplasm



ATR kinase activity is stimulated upon binding of the ATR-ATRIP complex to an RPA-ssDNA complex. ATR can subsequently phosphorylate and activate the checkpoint kinase Chk1, allowing further amplification of the checkpoint signal. The ATR and Chk1 kinases then modify a variety of factors that can lead to stabilization of stalled DNA replication forks, inhibition of origin firing, inhibition of cell cycle progression, mobilization of DNA repair factors, and induction of apoptosis. This checkpoint signaling mechanism is highly conserved in eukaryotes, and homologues of ATR and ATRIP are found in such organisms as S. cerevisiae (Mec1 and Ddc2, respectively), S. pombe (rad3 and rad26, respectively), and X. laevis (Xatr and Xatrip, respectively).

The ATR (ATM- and rad3-related) kinase is an essential checkpoint factor in human cells. In response to replication stress (i.e., stresses that cause replication fork stalling) or ultraviolet radiation, ATR becomes active and phosphorylates numerous factors involved in the checkpoint response including the checkpoint kinase Chk1. ATR is invariably associated with ATRIP (ATR-interacting protein) in human cells. Depletion of ATRIP by siRNA causes a loss of ATR protein without affecting ATR mRNA levels indicating that complex formation stabilizes the ATR protein. ATRIP is also a substrate for the ATR kinase, but modification of ATRIP does not significantly regulate the recruitment of ATR-ATRIP to sites of damage, the activation of Chk1, or the modification of p53.

While the ATR-ATRIP complex binds only poorly to RPA complexed with ssDNA lengths of 30 or 50 nt, binding is significantly enhanced in the presence of a 75 nt ssDNA molecule. Complex formation is primarily mediated by physical interaction between ATRIP and RPA. Multiple elements within the ATRIP molecule can bind to the RPA-ssDNA complex, including residues 1-107 (highest affinity), 218-390, and 390-791 (lowest affinity). Although the full-length ATRIP is unable to bind ssDNA, an internal region (108-390) can weakly bind ssDNA when present in rabbit reticulocyte lysates. ATR can bind to the ssDNA directly independent of RPA, but this binding is inhibited by ATRIP. Upon binding, the ATR kinase becomes activated and can directly phosphorylate substrates such as Rad17.

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Editions

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