Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks

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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


Reactome database release: 72

This document contains 1 pathway and 35 reactions (see Table of Contents)
Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks

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Compartments: nucleoplasm

Activated ATM phosphorylates a number of proteins involved in the DNA damage checkpoint and DNA repair (Thompson and Schild 2002, Ciccia and Elledge 2010), thereby triggering and coordinating accumulation of DNA DSB repair proteins in nuclear foci known as ionizing radiation-induced foci (IRIF). While IRIFs include chromatin regions kilobases away from the actual DSB site, this Reactome pathway represents simplified foci and events that happen proximal to the DNA DSB ends. In general, proteins localizing to the nuclear foci in response to ATM signaling are cooperatively retained at the DNA DSB site, forming a positive feedback loop and amplifying DNA damage response (Soutoglou and Misteli 2008).

Activated ATM phosphorylates the NBN (NBS1) subunit of the MRN complex (MRE11A:RAD50:NBN) (Gatei et al. 2000), as well as the nucleosome histone H2AFX (H2AX) on serine residue S139, producing gamma-H2AFX (gamma-H2AX) containing nucleosomes (Rogakou et al. 1998, Burma et al. 2001). H2AFX is phosphorylated on tyrosine 142 (Y142) under basal conditions (Xiao et al. 2009). After ATM-mediated phosphorylation of H2AFX on S139, tyrosine Y142 has to be dephosphorylated by EYA family phosphatases in order for the DNA repair to proceed and to avoid apoptosis induced by DNA DSBs (Cook et al. 2009). Gamma-H2AFX recruits MDC1 to DNA DSBs (Stucki et al. 2005). After ATM phosphorylates MDC1 (Liu et al. 2012), the MRN complex, gamma-H2AFX nucleosomes, and MDC1 serve as a core of the nuclear focus and a platform for the recruitment of other proteins involved in DNA damage signaling and repair (Lukas et al. 2004, Soutoglou and Misteli 2008).

RNF8 ubiquitin ligase binds phosphorylated MDC1 (Kolas et al. 2007) and, in cooperation with HERC2 and RNF168 (Bekker-Jensen et al. 2010, Campbell et al. 2012), ubiquitinates H2AFX (Mailand et al. 2007,..
Huen et al. 2007, Stewart et al. 2009, Doil et al. 2009) and histone demethylases KDM4A and KDM4B (Ma-
llette et al. 2012).

Ubiquitinated gamma-H2AFX recruits UIMC1 (RAP80), promoting the assembly of the BRCA1-A complex at DNA DSBs. The BRCA1-A complex consists of RAP80, FAM175A (Abraxas), BRCA1:BARD1 heterodimer, BRCC3 (BRCC36), BRE (BRCC45) and BABAM1 (MERIT40, NBA1) (Wang et al. 2007, Wang and Elledge 2007)

Ubiquitin mediated degradation of KDM4A and KDM4B allows TP53BP1 (53BP1) to associate with histone H4 dimethylated on lysine K21 (H4K20Me2 mark) by WHSC1 at DNA DSB sites (Pei et al. 2011).

Once recruited to DNA DSBs, both BRCA1:BARD1 heterodimers and TP53BP1 are phosphorylated by ATM (Cortez et al. 1999, Gatei et al. 2000, Kim et al. 2006, Jowsey et al. 2007), which triggers recruitment and activation of CHEK2 (Chk2, Cds1) (Wang et al. 2002, Wilson and Stern 2008, Melchionna et al. 2000).

Depending on the cell cycle stage, BRCA1 and TP53BP1 competitively promote either homology directed repair (HDR) or nonhomologous end joining (NHEJ) of DNA DSBs. HDR through homologous recombination repair (HRR) or single strand annealing (SSA) is promoted by BRCA1 in association with RBBP8 (CtIP), while NHEJ is promoted by TP53BP1 in association with RIF1 (Escribano-Díaz et al. 2013).

**Literature references**


**Editions**

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ATM phosphorylates NBN

Location: Recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks

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