NBS1 is directly involved in ATR activation

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Many recent studies have provided evidence for a role for Nbs1 as a damage sensor and activator acting upstream of ATM in cellular response to DSB. There is also evidence for a direct physical interaction between ATM and Nbs1. In addition, both of Nbs1 and ATM are involved in DSB repair by the homologous recombinational DNA repair system. We found that Chk1 phosphorylation (Ser-345) and FancD2 ubiquitination induced by various DNA replication-stalling agents, such as cisplatin, pierisin, UV and hydroxy urea, were severely diminished in Nbs1-/-/- DT40 cells. However, Chk1 phosphorylation and FancD2 ubiquitination induced by these agents were not significantly compromised in conditional Mre11-knockout cells. Furthermore we found that Nbs1 interacts with TopBP1 and ATR in 293T cells. These results indicate that Nbs1 but not the Mre11/Rad50/Nbs1 complex plays unique role in ATR-mediated Chk1 phosphorylation and FancD2 ubiquitination. This functional relationship between Nbs1 and ATR may explain the embryonic lethality of *NBS1* knockout in mice, which is distinct from the non-essential feature of ATM in mice and human. Furthermore, other clinical features of NBS (Nijmegen breakage syndrome caused by a hypomorphism in *NBS1*), such as microcephaly, developmental delay, and characteristic facial features, which are also seen in ATR-Seckel patients, are not seen in A-T patients, who display progressive cerebellar ataxia. These shared clinical features in ATR-Seckel and NBS patients further support the functional relationship between Nbs1 and ATR.