Synopsis of Original Research Paper

Celluar aging and abnormal regulation of telomeres in skin fibroblasts from a patient with an accelerated aging disorder.

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Nijmegen Breakage Syndrome (NBS) is an autosomal recessive disorder characterized by chromosome instability, defect in repair of double strand break and high incidence of lymphoid cancers . Here, we show that NBS1 is recruited to telomere ends by alternative mechanism, in which NBS1 interacts with TRF2, possibly through telomeric DNA, and forms discrete foci in ATM-independent manner. This is demonstrated by the evidences that NBS1 foci are formed in ATM-defective cells, and that both NBS cells lacking FHA/BRCT domains and S278/343A clone, mutated in ATM-phosphorylated sites, can interact with TRF2. Moreover, C-terminus of NBS1, MRE11 nuclease-binding region, was essential for the interaction with TRF2. It is consistent that NBS1 lacking the C-terminus was failed to elongate the short telomere length in NBS cells, although transfection both with full length of the NBS1 cDNA and of the S278/343A cDNA restored the telomere length. Furthermore, the short G-tail length of NBS cell line has not changed significantly following transfection with NBS1 cDNA lacking of the C-terminus region, while the full length of cDNA complements the G-tail length. These findings suggest that NBS1 is recruited to telomere by MRE11/RAD50/NBS1 complex formation in ATR- and ATM-independent manner and is implicated in telomere length maintenance, possibly through G-tail regulation.