Identified in a genetic screen for mutants that are sensitive to ionizing radiation, XRS2 is a member of the RAD52 epistasis group. Other members of this group include RAD50, RAD51, RAD52, RAD54, RDH54, RAD55, RAD57, RAD59, and MRE11. All members of the RAD52 epistasis group are involved in the repair of double-stranded breaksin DNA. Mutants are defective in the repair of DNA damage caused by ionizing radiation and the alkylating agent methyl methanesulfonate, in the maintenance of telomere length, in mitotic and meiotic recombination, and in mating-type switching because DSB intermediates are involved in these processes.Mre11p, Rad50p, and Xrs2p comprise the Mre11 complex. Mre11p/Rad50p/Xrs2passociation is stable with a predicted stoichiometry of 2:2:1, however, Rad50p and Xrs2p do not interact in the absence of Mre11p. Complex functions include DNA binding, exonuclease and endonuclease activities, DNA unwinding, and DNA end recognition. In addition to the repair processes listed above, which are mostly dependent upon homologous recombination, the MRX complex also facilitates DSB repair via nonhomologous end-joining as well as introduction of DSBs in meiosis, detection of damaged DNA, DNA damage checkpoint activation, telomerase recruitment, and suppression of gross chromosomal rearrangements. The Mre11 complex is conserved structurally and functionally from archaea to humans, but only the individual proteins Mre11p and Rad50p are widely and highly conserved; Xrs2p conservation is weak and its homologs are only present in eukaryotes. In contrast to yeast mre11, rad50, and xrs2 null mutants, which are viable, loss of activity in any of the vertebrate homologs results in embryonic lethality or cell death.Mutations in the functional homolog of XRS2, human NBS1, have been linked to the autosomal recessive disorder Nijmegen Breakage Syndrome. This disease is characterized by the molecular features of chromosomal instability and increased sensitivity to radiation, and the clinical phenotypes of microcephaly, growth retardation, immunodeficiency, and predisposition to cancer. Xrs2p binds DNA in a structure-specific manner and has been shown to be important for targeting the MRX complex to DNA ends. The N-terminal domain contains a conserved forkhead-associated domain that is not required for any of the major MRX complex functions in yeast. The C-terminal domain contains both Mre11p and Tel1p binding sites that mediate translocation of Mre11p to the nucleus and Tel1p phosphorylation of Xrs2p (