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Physiological Roles of DNA Strand Breaks Pathways in Mammalian

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In mammalian cells, DNA strand breaks(DSBs) can be repaired by at least two pathways, homologous recombination(HR) with homologous sequences and non-homologous end-joining(illegitimate recombinational repair, NHEJ) without significant sequence homology or with microhomology. The Rad52 epistasis group gene products(Rad 51, 52, 54, 55, 57) in yeast and functional homologs are involved in HR repair pathway. NHEJ depends on DNA-Dependent protein kinase(DNA-PKcs, Ku80, and Ku70), XRCC4 and Ligase IV(Jeggo(Review Jacson). While DSBs are predominantly repaired by a homologous recombination pathway in yeast cells, NHEJ appears to be predominant in mammalian cells. In order to determine the physiological roles of DNA strand breaks pathways in mammalian, we generated the mice lacking either HR pathway or NHEJ pathway by mutating Rad51 and Ku80.

Rad51 mutant mice arrested in development shortly after implantation due to a decrease in cell proliferation, followed by program cell death and chromosome loss. The mutant embryos live longer in a p53 mutant background, however double mutant cells failed to proliferate in tissue culture, suggesting the cells lacking HR have a limited life span.

Unlike Rad51 mutant mice, mice lacking Ku80 showed a severe combined immune deficient syndrome due to a defects in formation of coding joints during V9D)J recombination. In addition, mutant mice prematurely exhibited age specific changes of senescence that include osteoponia, atropic skin and age specific mortality. Cells lacking Ku80 undergo premature replicative senescence. However, the mutant mice showed a increased the cancer incidence in a p53 mutant background. Loss of p53 rescued the populations of Ku80 mutant cells from replicative senescence by enabling spontaneous immortalization. These data suggested that p53-dependent cell cycle responses to DNA damages in Ku80 null cells is responsible for developing replicative senescence.

Taken together, chromosomal metabolism including both HR and NHEJ appear to be associated with replicative senescence, which is a likely mechanism that reduces cancer incidence.