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Caretakers and gatekeepers

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Cellular gatekeepers include the proteins that regulate cell-cycle progression in response to DNA damage, whereas DNA repair pathways function as genomic caretakers. The p53 and ATM (ataxia-telangiectasia-mutated) proteins behave as cellular gatekeepers, while the non-homologous end-joining (NHEJ) DNA repair machinery acts as a genomic caretaker. NHEJ factors include Ku70, Ku80 and the DNA-PK enzyme, plus XXRC4 and DNA Ligase IV (Lig4), which function in ligation. In the March 13 Proceedings of the National Academy of Science, Sekiguchi *et al*. report that mutation of the *ATM* gene rescues the embryonic lethality and neuronal apoptosis associated with *Lig4* deficiency in mice (*Proc Natl Acad Sci USA* 2001, **98:**591-596). *ATM* deficiency failed to relieve defects in lymphocyte development due to the absence of *Lig4*. These results are similar to observations in *Lig4-/-p53-/-*mice. *ATM* deficiency also increased the genome instability, senescence and growth defects of *Lig4*-deficient fibroblasts. Surprisingly, Sekiguchi *et al*. report that deletion of *ATM* caused early embryonic lethality when combined with mutations in *Ku* or *DNA-PK* genes. They conclude that the DNA-PK holoenzyme must have an additional NHEJ-independent function.

References

1. Cancer-susceptibility genes. Gatekeepers and caretakers.

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4. DNA ligase IV deficiency in mice leads to defective neurogenesis and embryonic lethality via the p53 pathway.