Arg tyrosine kinase is involved in homologous recombinational DNA repair

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Ataxia telangiectasia (A-T) is an autosomal recessive disease characterised by radiosensitivity and chromosomal instability. The 350 kDa product of *ATM*, the gene responsible for A-T, is related to a family of large phosphatidylinositol 3 (PI3)-kinase domain-containing proteins involved in cell cycle control and/ or DNA repair. The other members of this family include ATR and DNA-dependent protein kinase. Recent work has shown ATM to act on a number of important effector proteins involved in the cellular reaction to DNA damage, including c-Abl. c-Abl is an ubiquitously expressed nonreceptor-type tyrosine kinase and is activated by DNA damage in an ATM-dependent manner. It plays important roles in growth arrest and apoptosis, and may also function in DNA repair through the phosphorylation of Rad51, a key molecule in homologous recombinational (HR) DNA repair. Arg (Abl-related gene), the only other known member of the c-Abl family, shares considerable structural and sequence homology with c-Abl in the N-terminal SH3, SH2, and tyrosine kinase domains, and abnormal variants of Arg are implicated in some human lymphoid malignancies. However, the roles played by Arg in the cellular response to DNA damage are unknown. To study possible roles for Arg in cellular response to ionizing radiation (IR), we generated *Arg-/-* cells from a chicken B cell line (DT40) by targeted disruption. We found that, unlike *c-Abl -/-* DT40 cells but similar to *ATM-/-* DT40 cells, ionizing radiation (IR)-induced Rad51 focus formation is reduced in *Arg-/-* DT40 cells. This is consistent with the findings that *Arg-/-* DT40 cells display hypersensitivity to IR, elevated frequencies of IR-induced chromosomal aberrations, and reduced targeted integration frequencies. All of these abnormalities in DNA damage repair are also observed in *ATM-/-* but not in *c-Abl-/-* DT40 cells. Finally, we found that Arg interacts with and phosphorylates Rad51 in 293T cells. These results suggest that Arg plays a role in homologous recombinational DNA repair by phosphorylating Rad51