c-Abl tyrosine kinase family is involved in the formation of stable chromatin-associated Rad51 complex

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c-Abl tyrosine kinase is activated by DNA damage, such as ionizing radiation (IR), in an ATM-dependent manner, and plays important roles in growth arrest and cell death. Several recent studies also indicate that c-Abl, Arg (the only other known member of the c-Abl family) and Bcr-Abl (the oncogenic form of c-Abl fusion kinase) are involved in DNA repair through the phosphorylation of Rad51, a key molecule in homologous recombination repair (HRR). However, it is unclear how these Abl tyrosine kinase members mechanistically regulate Rad51 functions. We found that Rad51 with the mutation of Arg-167 to Gly (Rad51-R167G) is defective in IR-induced nuclear focus formation, chromatin association and in vivo self-association, though this Rad51 mutant retains the capacity to bind BRCA2 in vivo. Interestingly, we also found that this Rad51 mutant is not effectively phosphorylated by c-Abl and Arg. However, co-transfection of wild-type but not kinase-dead c-Abl or Arg with Rad51-R167G enhanced the chromatin association of Rad51-R167G, suggesting that phosphorylation of tyrosine residues, probably Tyr-315, enhances the chromatin association of Rad51-R167G. We subsequently confirmed the phosphorylation of Tyr-315 by antibodies specific to tyrosine phosphorylated Tyr-315. To study further roles for c-Abl or Arg in the chromatin association of Rad51, we studied effects of Glivec, a relatively specific inhibitor for the c-Abl tyrosine kinase, on the chromatin association of transiently expressed Rad51. We first examined effects of Glivec on Rad51 tyrosine phosphorylation and on phosphorylation-mediated interactions between Rad51 and Arg, and confirmed that Glivec inhibits Rad51 tyrosine phosphorylation mediated by c-Abl or Arg and the interaction between Rad51 and Arg when wild-type Rad51 is transiently co-expressed with Arg or c-Abl. We subsequently found that Glivec effectively inhibits the enhancement of chromatin association of Rad51-R167G mediated by c-Abl or Arg. These results therefore indicate that the c-Abl tyrosine kinase family enhances the formation of stable chromatin-associated Rad51 complexes through phosphorylation of Rad51 mainly on Tyr-54 or Tyr-315 during HRR.