Zinc finger protein ZNF384 is an adaptor of Ku to DNA during classical non-homologous end-joining

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Abstract

DNA double-strand breaks (DSBs) are among the most deleterious types of DNA damage as they can lead to mutations and chromosomal rearrangements, which underlie cancer development. Classical non-homologous end-joining (cNHEJ) is the dominant pathway for DSB repair in human cells, involving the DNA-binding proteins XRCC6 (Ku70) and XRCC5 (Ku80). Other DNA-binding proteins such as Zinc Finger (ZnF) domain-containing proteins have also been implicated in DNA repair, but their role in cNHEJ remained elusive. Here we show that ZNF384, a member of the C2H2 family of ZnF proteins, binds DNA ends in vitro and is recruited to DSBs in vivo. ZNF384 recruitment requires the poly(ADP-ribosyl) polymerase 1 (PARP1)-dependent expansion of damaged chromatin, followed by binding of its C2H2 motifs to the exposed DNA. Moreover, ZNF384 interacts with Ku70/Ku80 via its N-terminus, thereby promoting Ku70/Ku80 assembly and the accrual of downstream cNHEJ factors, including APLF and XRCC4/LIG4, for efficient repair at DSBs. Altogether, our data suggest that ZNF384 acts as a 'Ku-adaptor' that binds damaged DNA and Ku70/Ku80 to facilitate the build-up of a cNHEJ repairosome, highlighting a role for ZNF384 in DSB repair and genome maintenance.