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PARP1 roles in chromosomal translocations and DNA integration

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Abstract

Chromosomal translocations occur frequently in cancer, yet mechanisms by which translocations are generated are poorly understood. Translocation junctions in acute leukemias suggest that they arise when broken chromosomes are joined by non-homologous end joining (NHEJ). NHEJ comprises at least two pathways: classical NHEJ (cNHEJ) involves Ku, DNA-PKcs, XRCC4, and LigIV, and alternative NHEJ (aNHEJ) involves PARP1 and LigIII. cNHEJ factors repress translocations, and conversely aNHEJ factors DNA Ligase III and CtIP promote translocations. Because PARP1 displacement of Ku is a rate-limiting step in aNHEJ, we tested whether small molecule PARP1 inhibitors could prevent chromosomal translocations. We found that clinically achievable concentrations of PARP1 inhibitors olaparib and rucaparib, as well as siRNA knockdown of PARP1, strongly repressed chromosomal translocations, implying that PARP1 is critical for this process. Olaparib also reduced ionizing radiation-induced translocations in normal human fibroblasts and VP16-generated translocations in a murine hematopoietic progenitor line. These results define PARP1 as a critical mediator of chromosomal translocations, and raise the possibility that oncogenic translocations occurring after high dose chemotherapy or radiation could be prevented by treatment with clinically available PARP1 inhibitors. DNA integration is widely used in the laboratory to create transgenic cell lines and animals. Random integration is a major barrier to efficient gene targeting in the laboratory, and it poses significant risks during gene therapy. Because DNA integration likely involves DNA end-joining, we are also investigating whether PARP1 inhibition suppresses DNA integration and may therefore be used to enhance gene targeting.

Biography

Professor Nickoloff has studied DNA damage and repair mechanisms for 30 years and published more than 100 peer-reviewed reports. He served on Radiation Therapy and Biology and Molecular Genetics B study sections. He was designated “Distinguished Foreign Scientist” by the Japan National Institute of Radiological Sciences in 2011. He served for 8 years as Chair of the Department of Molecular Genetics and Microbiology at the University of New Mexico School of Medicine, and since 2008 as Head of the Department of Environmental and Radiological Health Sciences at Colorado State University. He is currently an Associate Editor for *Genetics*.