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Characterization and targeting of BRIT1 deficiency in Liver cancer

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Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide, and effective treatment of HCC is of urgent need. In HCC, genomic instability is one of major hallmarks, especially in the tumors at the late stage and metastatic tumors. Thus, we seek to explore if targeting genomic instability and defective DNA repair can effectively inhibit HCC growth. BRIT1/MCPH1 is a recently identified key DNA damage and repair proteins. Recently, we identified that BRIT1 is aberrantly expressed in ~25% of HCC samples. In these samples, the locus of BRIT2 gene showed notable loss of heterogeneity (nearly 50%). We also found a somatic mutation in BRIT1, which occurred in the splicing donor site of intro 10 in the BRIT1 gene, leading to a truncated protein. Functional analysis showed that this mutation can cause failure of foci formation of BRIT1 under irradiation. Importantly, given that BRIT1-deficient cells exhibited defective DNA repair described above, our *in vitro* studies showed that the BRIT1-deficient HCC cells are more sensitive to olaparib, the inhibitor of poly (ADP-ribose) polymerase (PARPi), compared to the BRIT1-proficient cells. Furthermore, we also test the inhibitory effect of olaparib in the xenograft mouse model, and found that PARPi can significantly suppress tumor growth of HCC xenografts. Collectively, our results clearly demonstrate that BRIT1 is mutated and aberrantly expressed in HCC, and targeting BRIT1 deficiency by PARP inhibitors in combination with other anti-cancer agents may provide novel and effective targeted therapies to treat BRIT1-deficient HCC.

Biography

Kaiyi Li has studied cancer molecular biology and cancer targeted therapeutics for 15+ years, and she has extensive experience in tumor mouse models, knockout mouse models to study DNA repair genes and targeted cancer therapies for breast and liver cancer. She has published more than 30 peer-reviewed papers in these research areas. Li has served on the editorial boards for the *Global Journal of Surgery*, and *World Journal of Biological Chemistry*. She has also served on numerous review committees for different funding agencies nationally and internationally.

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PARP1 roles in chromosomal translocations and DNA integration

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Chromosomal translocations occur frequently in cancer, yet mechanisms by which translocations are generated are poorly understood. Translocation junctions in acute leukemia 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

Jac A. 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*.