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Roles of PARP-1 and PALB2 in controlling DNA resection and strand invasion during DSB repair

Endogenous DNA double-strand breaks (DSBs) are extremely hazardous for a cell. If left unrepaired, DSBs can drive cells to genomic instability and tumor development. Our laboratory focuses on the intricate network of homologous recombination (HR) enzymes responsible for repairing DSBs. This seminar will focus on two key aspects of HR, DNA resection and strand invasion. Following the formation of DSBs, PARP-1 is rapidly recruited and activated through its binding to free DNA ends. PARP-1 synthesizes a structurally complex polymer composed of ADP-ribose units that facilitates local chromatin relaxation and the recruitment of DNA repair factors. Here, we identify a novel function for PARP-1 in DNA double-strand break resection. Remarkably, inhibition of PARP-1 leads to hyperresected DNA double-strand breaks. We show that loss of PARP-1 and hyper resection are associated with loss of Ku, 53BP1 and RIF1 resection inhibitors from the break site. Furthermore, PARP-1 abrogation leads to an increase of homologous recombination in vivo. Our work has direct implications for the clinical use of PARP inhibitors. Inherited mutations in PALB2 are associated with a predisposition for ovarian, breast and pancreatic cancers. PALB2 was identified BRCA2 interacting protein, essential for BRCA2 anchorage to nuclear structures and strand invasion. We will present our work in deciphering the functions of PALB2 in HR. Predicting the functional consequences of PALB2 mutations or variants has been challenging as they can lead to different biological effects. Using a novel CRISPR/Cas based homologous recombination assay, biochemical and cellular assays, we performed a structure-function analysis of PALB2 using PALB2 truncated mutants (R170fs, L531fs, Q775X and W1038X). These studies allowed us to uncover a PALB2 regulation mechanism by which cancer cells could drive genomic instability. The assays presented here will be valuable tools for the functional assessment of PALB2 variants, or other homologous recombination genes, in cancer etiology.

Biography

Jean-Yves Masson is an internationally recognized expert in DNA repair mechanisms. Throughout his career, Dr Masson focused on radiation and chemicals that impede DNA replication to induce DNA double-strand breaks (DSBs). Failure to remove these breaks leads to cell death, genetic mutations, gross chromosome rearrangements, and to cell transformation and cancer. He is one of the few world experts on PALB2, a protein which is getting scientific and public attention as PALB2 mutations increase breast cancer by 6-8 fold. He established that PALB2 deficient cells are very sensitive to PARP inhibitors, a very promising therapeutic avenue for breast/ovarian cancer. Dr Masson was recently inducted as a Canadian Academy of Health Sciences fellow.

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