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Summary of Outstanding Research of Prof. Ganesh Nagaraju

The genetic material DNA in all our cells is susceptible to various types of damage both from endogenous and external sources. Among many forms of DNA damage, DNA double-strand breaks (DSBs) are the most dangerous types of lesions that arise spontaneously as well as by radiations or chemicals. There are two major pathways of DSB repair; non-homologous end joining (NHEJ) and homologous recombination (HR). In contrast to NHEJ, HR has been considered an error-free pathway in repairing DSBs, thereby maintaining genome integrity and suppressingtumorigenesis. Indeed, mutations in the genes that regulate HR are known to cause chromosome instability and cancer susceptibility genetic diseases. RAD51 and RAD51 paralogs play an important role in HR-mediated DSB repair. Germline mutations in these genes are known to cause Fanconi anemia, and breast and ovarian cancers. Although HR is critical for DSB repair, unregulated HR can impair genome duplication and compromise genome stability. The factors and the mechanism underlying HR regulation are poorly understood.

Ganesh's group recently demonstrated a novel role of RTEL1 helicase in suppressing hyper-recombination during DNA replication to promote error-free genome duplication. By employing several novel tools and techniques, including DNA fiber, iPOND assays and chromatin IP studies his work revealed mechanistic insights into HR regulation by RTEL1 helicase. In the absence of RTEL1, RAD51-mediated hyper-recombination impairs genome duplication, and this replication defect can be rescued by co-depletion of RAD51 and RAD51 paralogs. Stalled replication forks undergo excessive remodeling by RAD51 and impair DNA replication. Expression of HR defective RAD51 mutants rescues replication defect in RTEL1 deficient cells. Finally, they showed that RTEL1 anti-recombinase function is dependent on its interaction with PCNA and helicase activity.This elegant work is published in a reputed ***Cell Reports*** journal (2024). RTEL1 helicase mutations lead toHoyeraal-Hreidarsson syndrome and Dyskeratosis congenita, characterized by developmental abnormalities, bone marrow failure and telomere dysfunction. In addition,individuals with mutations in *RTEL1* are also predisposed to high-grade glioma, astrocytomas, and glioblastomas. His work provides insights into RTEL1 mutations leading to genetic diseases and cancer. His elegant work deserves great appreciation and encouragement.

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