The Role of RAD51 Mutation in Cancer Development

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Genome instability is a major driving force of tumorigenesis. To counteract destructive effects of DNA damage, cells evolved a complex system of DNA repair. RAD51 protein takes the center stage in the repair of highly toxic DNA damage via homologous recombination by forming a helical filament capable of homology search and strand exchange. RAD51 also maintains genome integrity through a recombination-independent role in protecting replication forks from nucleolytic degradation. Recently, RAD51 mutations were identified in several tumor types. However, despite its importance, the mechanism of how these mutations contribute to tumorigenesis remains elusive. This work reports a biochemical characterization of RAD51 S121Y mutation found in a highly aggressive form of uterine carcinosarcoma. While S121Y mutation does not impair DNA binding of RAD51, mutated protein forms a highly unstable filament due to an alteration in the ATPase catalytic cycle. Intriguingly, while RAD51 S121Y retains its recombinase activity, reconstitution of fork protection using synthetic DNA substrates revealed that RAD51 S121Y is unable to efficiently prevent MRE11 exonuclease-mediated DNA degradation. As defect in replication fork protection leads to accumulation of mutations and chromosomal aberrations, these results elucidate a mechanism by which can RAD51 mutations promote tumorigenesis. Moreover, the implication that RAD51 mutations may contribute to genome instability in tumor cells through the defect in fork protection and not the DNA repair defect, raises a serious concern regarding previously considered therapeutic approaches.

Awards Won:

Intel ISEF Best of Category Award of $5,000