Studying DEAD for Alive: the Molecular Pathogenesis of DEAD-box Helicase 41 in Myeloid Malignancies

DDX41 is a DEAD-box helicase. Mutations in DDX41 are associated with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), and R525H is the most frequent mutation. However, the molecular pathogenesis remains unknown. We found that DDX41 utilizes its unwinding and annealing activities to regulate the homeostasis of dsDNA and ssDNA, which in turn modulates the cGAS-STING pathway (Singh et al, Cell Reports, 2022). In addition, we found that DDX41 is an R-loop resolvase upon DNA damage, and the absence/mutations of DDX41 results in R-loop accumulation that induces genome instability. DDX41 is also required for the formation of stress granules and P-bodies under stress conditions (unpublished). Collectively, our results demonstrate that DDX41 is a multi-functional protein; dysregulating any of its functions may lead to MDS/AML.