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Structure-function insight into the two-component DNA repair system of *Mycobacterium tuberculosis*

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Double-stranded break (DSB) is considered the most detrimental form of DNA damage encountered by living systems across species. In nature, covalent breaks in the DNA duplex are induced by environmental factors and endogenous by-products. If not readily repaired, one such break in the genomic DNA is sufficient to arrest all cellular processes and may further result in cell death. Thus, the reparation of DSBs is critical for genomic stability and sustenance of all living systems. Across species, DSBs are repaired by two repair pathways: Homologous Recombination (HR) and Non-Homologous End Joining (NHEJ). Being a template-dependent repair system, HR is ineffective during the dormant/non-replicating phases of the cell cycle due to the absence of a duplicate copy of the genome. Like many intracellular pathogens, *Mycobacterium tuberculosis* spends a considerable part of its life cycle in dormancy within the host immune cells (macrophages) and proliferates only when the host becomes immunocompromised. The ability of *M.tuberculosis* to maintain a prolonged inactive state confers to its unparalleled resistance to the host immune system and antibiotics. During this period of latency, the bacterium resides in a genotoxic environment, imposed by the host defensive reactive species (H2O2, O2- etc.). The NHEJ repair complex is an indispensable arsenal of the pathogen to cope with this vulnerability and promote sustenance in dormancy. The Mycobacterial NHEJ pathway is a two-component repair system, composed of a rate limiting DNA binding protein Ku and a multifunctional DNA ligase. In this study, we have employed *in silico* and *in vitro* tools to get a structural-function insight and decipher the DNA binding properties of Ku. We have implemented molecular dynamics simulation to understand the DNA protein interface and predict critical amino acid residues responsible for the remarkable affinity of the complex. The computational findings were further validated *in vitro* with complementary biochemical and biophysical techniques to delineate the DNA protein interaction on quantitative parameters. resently, we have ventured to elucidate the three dimensional structure of Ku and Ku-DNA complex using X-ray crystallography and cryo-EM,respectively.