Atomic Simulation of Complex DNA DSBs and the Interactions with the Ku70/80 Heterodimer

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DNA double strand breaks (DSBs) induced by ionizing radiation (IR) usually contain modified bases such as 8-oxo-7,8-dihydroguanine (8-oxoG) and thymine glycol, apurinic/apyrimidinic (AP) sites, 2-deoxyribonolactone, or single-strand breaks (SSBs). The presence of such lesions in close proximity to the DSB terminus makes the DNA nicks more difficult to repair and rejoin than endogenously induced simple DSBs, and as such a major determinant of the biological effects of high linear energy transfer (LET) radiation as encountered in space travel. In this study we conducted molecular dynamics simulations on a series of DNA duplexes with various complex lesions of 8-oxoG and AP sites, in an effort to investigate the effects of such lesions to the structural integrity and stability of DNA after insulted by IR. We also simulated the interaction of such complex DSBs with the Ku70/80 heterodimer, the first protein in mammalian cells to embark the non-homologous end joining (NHEJ) DNA repair pathway. The results indicate, compared to DNA with simple DSBs, the complex lesions can enhance the hydrogen bonds opening rate at the DNA terminus, and increase the mobility of the whole duplex, thus they present more deleterious effects to the genome integrity if not captured and repaired promptly in cells. Simulations also demonstrate the binding of Ku drastically reduces structural disruption and flexibility caused by the complex lesions, and the interactions of Ku with complex DSBs have a different potential energy landscape from the bound structure with simple DSB. In all complex DSBs systems, the binding of DSB terminus with Ku70 is softened while the binding of the middle duplex with Ku80 is tightened. This energy shift may help the Ku protein to secure at the DSB terminus for a longer time, so that other end processing factors or repair pathways can proceed at the lesions before NHEJ repair process starts. These atomic simulations may provide valuable new insight into the selective action of repair proteins on damaged DNA.