Wednesday, April 13, 2022
4:00 P.M.

Ackert Hall, Room 120

Biochemistry & Molecular Biophysics **Seminar**

Beta-Genus Human Paillomaviruses and Non-Melanoma Skin Cancers

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Some members of the beta genus of human papillomaviruses (beta-HPV), including HPV8, may promote non-melanoma skin cancers by destabilizing the host genome during transient infections. Mutations are most likely during mitosis and when DNA is damaged. We have previously shown that the E6 protein from HPV8 (HPV8 E6) impairs cellular responses that protect the host genome from these risks. For example, HPV8 E6 makes it more likely that UV causes replication forks to collapse into double stranded breaks in DNA (DSBs) and then hinders the homologous recombination and non-homologous end joining (NHEJ) pathways from repairing these lesions. HPV8 E6 also reduces cellular responses (e.g., hippo pathway activation, p53 accumulation, growth inhibition) to failed cytokinesis. As a result, HPV8 E6 promotes polyploidy and aneuploidy. Despite these discoveries, important outstanding questions remain. For instance, HPV8 E6 delays rather than abrogates DSB repair. Yet, the repair pathway responsible for fixing these lesions has not been reported. Regarding the risk of mutations during mitosis, the increase in aneuploidy suggests that HPV8 E6 causes aberrant chromosome segregations. However, this has not been demonstrated. Here, we report that HPV8 E6 promotes the repair of DSBs by microhomology-mediated end joining (MMEJ), a tertiary and mutagenic repair mechanism. Interestingly, inhibition of NHEJ initiation prevents HPV8 E6 from delaying DSB repair by causing cells to be more reliant of MMEJ. We also present data showing that HPV8 E6 decreases the abundance of BLM helicase and by doing so promotes anaphase bridge and micronuclei formation. HPV8 E6 prevents the cell cycle arrest that should accompany the presence of micronuclei leading to chromothripsis, a mutagenic process where hundreds to thousands of mutations occur in a single chromosome during 1-2 progressions through the cell cycle. Together, our data provide novel evidence of the genome destabilizing potential of HPV8 E6.