Aberrant centromeric DNA replication induces alphoid centromere instability

The centromere is the center point of cell division, as it recruits the kinetochore, the large proteinaceous complex that orchestrates chromosome segregation in every dividing cell. Not surprisingly, aberrant centromere function leads to mitotic dysfunction and deviant chromosome numbers. These abnormalities may lead to disease, including cancer and birth defects. The centromere-associating kinetochore protein CENP-B has emerged as an important factor in the regulation of the centromeric-chromatin structural landscape. Binding of CENP-B to the CENP-B box is orchestrated epigenetically. Its depletion results in euchromatization of the alphoid centromere array, and is associated with elevated centromeric DNA replication activity. To test the hypothesis that CENP-B mediated aberrant DNA replication may promote genetic insult, we demonstrated that CENP-B depletion induces genomic instability leading to DNA damage, and activates DNA repair signaling. However, CENP-B does not appear to be directly involved in the cellular processes of the DNA damage response. We conclude that CENP-B is required for maintenance of the centromeric chromatin structure as well as centromeric DNA integrity.