

Nuclear Envelope Instability in Cancer

Joon Kim, PhD

KAIST Graduate School of Medical Science and Engineering

Nuclear envelope rupture, which occurs more frequently in cancer cells than normal cells, is an important mechanism that promotes genome instability. Recent studies have shown that mechanical stress applied to the nuclear envelope during cancer cell migration causes nuclear envelope rupture and DNA damage. Acral melanoma commonly occurs in areas that are not exposed to much sunlight, such as the sole of the foot. Little is known about risk factors and mutational processes of plantar acral melanoma. Here, we show that the nuclear and micronuclear envelope of melanoma cells are frequently ruptured by macroscopic mechanical stress on the plantar surface due to weight-bearing activities. The marginal region of plantar melanoma nodules exhibits increased nuclear morphological abnormalities and collagen accumulations, and is more susceptible to mechanical stress than the tumor center. An increase in DNA damage coincides with nuclear envelope rupture in the tumor margin. Nuclear envelope integrity is compromised by the mechanosensitive transcriptional cofactor YAP activated in the tumor margin. Our results suggest a novel mutagenesis mechanism in melanoma and explain why plantar acral melanoma is frequent at higher mechanical stress points.