ESCRT-III maintains nuclear envelope integrity of micronuclei

Flores-Rodriguez, N.[1], Willan, J.[2], Cleasby, A.[2], Woodman, P.[3], Bryant, H.[4] and Ciani, B.[2,5]

[1] The University of Sydney, Australia, [2] CMID, University of Sheffield, United Kingdom, [3] School of Medicine, University of Manchester, United Kingdom, [4] Institute of Cancer Studies, University of Sheffield, United Kingdom, [5] Chemistry, University of Sheffield, United Kingdom

Micronuclei are extranuclear chromatin structures surrounded by a nuclear envelope membrane. Micronuclei originate during mitosis from lagging chromosomes or chromosome fragments which rebuild their own nuclear envelope (NE) away from the main chromatin mass. However, micronuclei are prone to nuclear envelope collapse and loss of nuclear envelope integrity allows cytosolic enzymes to enter the micronucleus causing DNA fragmentation. Chromosome fragments can be stitched back together randomly by the DNA double strand breaks repair pathway, thus micronuclei can be re-incorporated into the main genome during the next cell cycle. This phenomenon, called chromothripsis, generates oncogenic mutations linked to several cancers. NE integrity is maintained by the ESCRT-III membrane remodeling complex, which seals nuclear envelope membranes in telophase for completion of mitosis and also repairs the NE after a mechanical injury. Here we address whether the ESCRT-III complex is functional at the nuclear envelope of micronuclei. In unsynchronized cancer cell lines, we observe a persistent presence of the ESCRT-III complex on micronuclei in interphase. These structures have a broken lamina network, endoplasmic reticulum membrane infiltration and have lost nuclear envelope organization. We show that impairment of ESCRT-III function affects the proportion of micronuclei that lose NE organisation and lamina integrity, implicating ESCRT-III nuclear envelope repair activity in the maintenance of genome stability.