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Investigating the formation and rupture of micronucleir and the consequence of cytosolic DNA release in early mammalian embryogenesis

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Abstract

The loss and/or gain of whole chromosomes, or aneuploidy, that arises during mammalian preimplantation development can lead to embryo arrest, implantation failure, or spontaneous miscarriage in natural conception and assisted reproduction. Segregation errors can occur meiotically during gametogenesis, or post-zygotically from mitotic cleavage divisions, resulting in the formation of abnormal nuclear structures known as micronuclei that are spatially isolated from the main nucleus. Micronuclei have been detected in embryos from various mammals and are likely a precursor to a dynamic process called cellular fragmentation (CF), or cytoplasmic blebbing. Once formed, a micronucleus may either fuse back with the primary nucleus or persist and undergo unilateral inheritance in subsequent mitotic divisions. Recent studies have shown that the nuclear envelope of micronuclei in somatic cells is quite fragile, and disruptions may cause genetic material to be released into the cytoplasm, triggering the activation of the cyclic GMP-AMP (cGAS)-cyclic GMP-AMP receptor stimulator of interferon genes (STING) DNA-sensing pathway. Using a non-human primate model and a combination of time-lapse imaging, embryo immunostaining, and single-cell DNA sequencing (scDNA-seq), we sought to determine whether the cGAS-STING pathway is functional during preimplantation development and if there are differences in micronuclei fate between young and aged rhesus macaque females. Time-lapse imaging demonstrated an increased propensity for micronucleation at the zygote stage, CF prior to the first mitosis, and/or multipolar divisions with blastomere asymmetry in the embryos from aged females. Immunolabeling of the embryos with antibodies to cGAS and LAMIN-B1 revealed positive cGAS immunosignals in micronuclei with no or defective nuclear envelope at both the cleavage and blastocyst stage. Current work is focused on comparing copy number variation in embryos from young versus aged females by scDNA-seq and whether nuclear rupture and the release of cytosolic DNA is an attempt to resolve chromosome mis-segregation or if it exacerbates aneuploidy.