THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Hem Sapkota

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
Department of Cell Biology

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Biomedical Research Center, Room 109

Determinants and Consequences of Cohesion Fatigue in Mammalian Cells

COMMITTEE IN CHARGE: Gary J. Gorbsky, PhD (Chair); Susannah Rankin, PhD; Scott M. Plafker, PhD; Leonidas Tsiokas, PhD; Karla K. Rodgers, PhD

ABSTRACT: In mitosis, replicated chromosomes are accurately segregated into two daughter cells. Error-free sister chromatid separation is essential to maintain genomic stability. In normal mitosis, sister chromatids separate only in anaphase when cells exit mitosis. However, cells delayed at metaphase separate their chromatids in an asynchronous and untimely manner while remaining arrested in mitosis, a phenomenon termed cohesion fatigue. The complete list of predisposing factors, mechanisms, and consequences of cohesion fatigue are unknown.

In this study, we report multiple factors affect the timing of cohesion fatigue. Our results show that stronger spindle pulling forces or reduced levels of chromosome-bound cohesin accelerate the timing of cohesion fatigue onset. The well-known cohesin removal pathway, the Wapl-mediated prophase pathway, does not play an active role during fatigue after cells have reached metaphase. However, inhibition of prophase pathway prior to mitotic entry enriches chromosome-bound cohesin and that in turn can delay the timing of cohesion fatigue. Furthermore, transient opening of any specific cohesin gate is not the cause of cohesion fatigue. Our data suggest that cohesion fatigue is a unique and novel phenomenon that does not utilize canonical cohesin removal pathways.

Transient delays at metaphase lead to significant increases in interkinetochore distances. Cells delayed transiently at metaphase are more likely to undergo erroneous anaphase where incidents of chromosome segregation defects such as lagging chromosomes, anaphase bridges, and micronuclei formation are elevated. These findings establish cohesion fatigue as a novel source of aneuploidy.