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Letter to the Editor

Low rates of aneuploidy promote tumorigenesis while high rates of aneuploidy cause cell death and tumor suppression *

Sir,

An abnormal chromosome number, a condition known as aneuploidy, is a common characteristic of tumor cells. Because of this correlation, Boveri proposed aneuploidy to be a cause of tumorigenesis 100 years ago [1,2]. However, this hypothesis remained untested due to the difficulty of selectively generating aneuploidy in the absence of other defects, particularly DNA damage. We determined that cells and mice with reduced levels of the mitosis-specific, centromere-linked motor protein CENP-E develop aneuploidy and chromosomal instability *in vitro* and *in vivo* in the absence of other defects, including DNA damage. CENP-E reduction causes aneuploidy and chromosomal instability due to the missegregation of one (or a few) whole chromosomes per division [3]. As Boveri had proposed, the low rate of whole chromosome aneuploidy caused by CENP-E heterozygosity in the absence of other defects drives an elevated level of spontaneous spleen and lung tumors. However, aneuploidy due to CENP-E heterozygosity suppressed tumors in three different contexts: spontaneous tumors of the liver, tumors caused by treatment with the carcinogen DMBA, and tumors caused by homozygous loss of the p19/ARF tumor suppressor [4]. All three contexts in which CENP-E heterozygosity suppressed tumors had a pre-existing level of aneuploidy that could be increased by depletion of CENP-E, supporting the hypothesis that high rates of chromosome missegregation promote cell death and tumor suppression. Consistently, additional weakening of the mitotic checkpoint by reduction in Mad2 as well as CENP-E resulted in elevated levels of cell death and decreased rates of tumor development as compared to reduction of CENP-E or Mad2 individually. These findings indicate that while low rates of chromosome missegregation promote tumorigenesis, as Boveri had predicted, higher rates of chromosome missegregation produce cell death and tumor suppression.

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