

EFFECTS OF ANEUPLOIDY ON CHROMOSOME SEGREGATION AND CELLULAR PHENOTYPE

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Cancer cells display distinct aneuploid karyotypes (i.e., abnormal chromosome numbers) and typically mis-segregate chromosomes at high rates, a phenotype referred to as chromosomal instability (CIN). Recent studies have shown that anaphase lagging chromosomes arising due to merotelic kinetochore attachment (attachment of a single kinetochore to two spindle poles instead of just one) are the major chromosome segregation defect responsible for whole-chromosome instability in cancer cells. Indeed, we find that whereas lagging chromosomes occur at significantly higher frequencies in CIN vs. non-CIN cells, other mitotic chromosome segregation defects (e.g., chromosome bridges or acentric fragments) occur at similar frequencies in CIN and non-CIN cancer cells. While it is readily apparent how chromosome mis-segregation in the form of anaphase lagging chromosomes can cause aneuploidy, the effect aneuploidy has on chromosome segregation is unclear. To test the effects of aneuploidy on chromosome segregation we utilized the colorectal cancer cell line DLD1 (2n=46) and variants of this line containing defined artificial trisomies for chromosomes 7 and 13 (DLD1+7 and DLD1+13, respectively). We found that DLD1+7 and DLD1+13 cells displayed higher rates of chromosome mis-segregation compared to the parental cell line. Furthermore, we found that cells with trisomy 13 display a distinctive cytokinesis failure phenotype. Interestingly, chromosome 13 encodes for *SPG20* (Spastic Paraplegia 20, or Spartin), a gene involved in cytokinesis completion. We showed that up-regulation of *SPG20*, brought about by trisomy 13, is both required and sufficient for the cytokinesis failure phenotype. Indeed, overexpression of Spartin in DLD1 cells reproduced the cytokinesis failure phenotype observed in DLD1+13 cells. We further determined that Spartin overexpression prevented localization of Spastin, another cytokinesis protein, at the midbody. Finally, we showed that siRNA-mediated Spartin knock down rescued both the cytokinesis failure defect and Spastin midbody localization in the DLD1+13 cell line. Overall, our study shows that aneuploidy *per se* induces chromosome mis-segregation in cancer cells. Moreover, our data indicate that different aneuploidies can yield distinct cellular phenotypes/behaviors that are driven by up-regulation of specific genes encoded on the aneuploid chromosome.