Abstract 289: The key role of Mitostatin in the maintenance of genome stability

Angela Lauriola; Andrea Caporali; Sabine Mai; Domenico D'Arca

Author & Article Information

Cancer Res (2017) 77 (13_Supplement): 289.

https://doi.org/10.1158/1538-7445.AM2017-289

Abstract

Genomic instability is a characteristic of most cancers and it refers to an increased tendency of alterations in the genome during the life cycle of cells. The fidelity of DNA replication is highly ensured by different checkpoints; the activation of spindle checkpoints prevents cells from premature entry into mitosis, avoiding incorrect chromosome segregation and aneuploidy, a typical feature of many cancers. Mitostatin, a novel protein, endowed with tumor suppressor activity, has been reported to bind centrosomal proteins Odf2 and ninein, and its depletion causes an alteration of the anchorage of microtubules to the centrosome. Since functional defects of centrosomes are associated to mitotic failure, Mitostatin may have a key role in guarding the fidelity of mitosis in cells.Here we show that the depletion of Mitostatin in cancer cells, synchronized by aphidicolin (G1/S) block and released into nocodazole-containing medium, leads to mitotic slippage and adaptation to the spindle checkpoint in the presence of a spindle inhibitor. Concomitantly, Mitostatin depletion promotes the early degradation of Mad2 and cyclin B1. Since the activated spindle checkpoint delays cell exit from mitosis by preventing cyclin B1 proteolysis, the cyclin B1 early degradation leads to mitotic checkpoint escape and resulting chromosome instability. In particular, we observed a premature sister-chromatid separation, chromosome bridges and mis-segregation in anaphase that are consistent with defective activation of the spindle checkpoint.In this study, we report for the first time that the depletion of Mitostatin induces an increase of numerical and structural chromosomal aberrations compared to control cells. These aberrations include aneuploidy (P=.0005), the formation of triradials (P=.0061) and broken chromosomes (P=.0066). Moreover, 3D nuclear telomere analysis using TeloView shows decreases in telomeric signals (P=.0061), in the total number of aggregates (P=.0027), and in total intensity (P=.018) and single intensity (P=.019) in cells depleted of Mitostatin. These findings suggest that telomere dysfunction is increased in the absence of Mitostatin; the decrease in telomere intensity is associated with ongoing proliferation (mitotic slippage), and the maintenance of telomeric aggregates is indicative of ongoing genomic instability. Taken together, these observations suggest that Mitostatin plays a critical role in guarding the fidelity of mitosis, enabling the optimal activation of

the spindle checkpoint. Thus, low levels of Mitostatin found in certain human tumors may contribute to cellular transformation by promoting genomic instability.

Citation Format: Angela Lauriola, Andrea Caporali, Sabine Mai, Domenico D'Arca. The key role of Mitostatin in the maintenance of genome stability [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017;77(13 Suppl):Abstract nr 289. doi:10.1158/1538-7445.AM2017-289