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Developmental Cell

Gene Dosage Imbalance Contributes to Chromosomal Instability-Induced Tumorigenesis

Highlights

- Chromosome-wide gene dosage imbalances contribute to aneuploidy-induced cell death
- Chromosome-wide gene dosage imbalances induce a tumorigenic behavior
- The DDR pathway reduces the levels of CIN-induced aneuploidy and tumorigenesis
- Gene dosage imbalances induce ROS, which contribute to CIN-induced tumorigenesis

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In Brief

Many solid tumors exhibit chromosomal instability (CIN) and contain an abnormal number of chromosomes or chromosomal parts. Clemente-Ruiz et al. identify multiple mechanisms that buffer the deleterious effects of CIN in proliferating epithelial tissues and demonstrate that chromosome-wide gene dosage imbalances contribute to the induction of cell death and tumorigenesis.

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Gene Dosage Imbalance Contributes to Chromosomal Instability-Induced Tumorigenesis

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SUMMARY

Chromosomal instability (CIN) is thought to be a source of mutability in cancer. However, CIN often results in aneuploidy, which compromises cell fitness. Here, we used the dosage compensation mechanism (DCM) of *Drosophila* to demonstrate that chromosome-wide gene dosage imbalance contributes to the deleterious effects of CIN-induced aneuploidy and its pro-tumorigenic action. We present evidence that resetting of the DCM counterbalances the damaging effects caused by CIN-induced changes in X chromosome number. Importantly, interfering with the DCM suffices to mimic the cellular effects of aneuploidy in terms of reactive oxygen species (ROS) production, JNK-dependent cell death, and tumorigenesis upon apoptosis inhibition. We unveil a role of ROS in JNK activation and a variety of cellular and tissue-wide mechanisms that buffer the deleterious effects of CIN, including DNA-damage repair, activation of the p38 pathway, and cytokine induction to promote compensatory proliferation. Our data reveal the existence of robust compensatory mechanisms that counteract CIN-induced cell death and tumorigenesis.

INTRODUCTION

Aneuploidy, defined as an abnormal number of chromosomes or parts thereof, is a common feature in human cancer, and more than 68% of human solid tumors are aneuploid (Duijf et al., 2013). Chromosomal instability (CIN), which refers to the high rate at which chromosome structure and number change over time, has been proposed to be a source of mutability, as the gain of oncogene-carrying chromosomes or the loss of tumor suppressor gene-carrying chromosomes help the tumor cell population to pass through critical steps of tumorigenesis (Hanahan and Weinberg, 2011). However, CIN is highly deleterious for the cell, and elevating chromosome mis-segregation rates alone is not sufficient to generate stable aneuploidy in cultured cells (Thompson and Compton, 2008). Aneuploidy results in an unbalanced genome with different copy numbers for genes on different chromosomes, and the resulting metabolic imbalance is proposed to play a fundamental role in the compromised fitness of aneuploid cells (Tang and Amon, 2013). Analysis of gene expression data from aneuploid cells in several organisms has revealed a consistent up-regulation of genes involved in the stress response (Sheltzer et al., 2012; Stingele et al., 2012). This response is independent of the identity of the genes with altered copy numbers, and appears to be a consequence of the stoichiometric imbalances (Tang and Amon, 2013). In addition to the erroneous kinetochore/microtubule attachments that lead to full-chromosome mis-segregation, merotelic attachments are frequently observed in cells with high levels of CIN. Consequently, lagging chromosomes are common and can be trapped during cytokinesis. These chromosomes, which are being pulled simultaneously to the two poles of the cell, can be broken, and activate the DNA damage response (DDR) pathway (Janssen et al., 2011).

Drosophila larval epidermal primordia have proved useful model systems to elucidate the molecular mechanisms underlying oncogene-driven tumorigenesis (Pastor-Pareja and Xu, 2013) and to demonstrate the contribution of CIN and DNA damage-induced genomic instability to tumor growth (Dekanty et al., 2012, 2015). CIN generated upon depletion of genes involved in the spindle assembly checkpoint (SAC) or spindle assembly leads to the production of highly aneuploid cells, which are removed from the tissue by c-Jun N-terminal kinase (JNK)-dependent apoptosis. When highly aneuploid cells are prevented from entering this process, JNK activation drives the expression of mitogenic molecules and matrix-metalloproteases, which induce tumor-like tissues that grow extensively and metastasize when transplanted into the abdomen of adult hosts. The observation that CIN induces a general and rapid response of the tissue and that this response relies on the activity of the JNK stress response pathway in highly aneuploid cells opens the possibility that aneuploidy-induced stoichiometric imbalances and CIN-induced DNA damage play a key role in JNK activation and CIN-induced tumorigenesis.

Here, we found that multiple mechanisms buffer the deleterious effects of CIN in proliferating epithelial tissues. These include X chromosome dosage compensation, activation of the DDR and p38 signaling pathways, and induction of cytokines to promote compensatory proliferation. Similar to mammalian cells (Foijer et al., 2014; Thompson and Compton, 2010; Williams

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