IN THE SPOTLIGHT

Collateral Genome Instability by DNA Damage in Mitosis

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Summary: Chromosome segregation errors and DNA damage are in a vicious cycle in cancer cells. Bakhoum and colleagues show that the molecular response to damaged DNA during mitosis impairs the chromosome segregation machinery, adding a new level to the already dangerous relations between different kinds of genomic instability. Cancer Discov; 4(11):1256–8. ©2014 AACR.

See related article by Bakhoum et al., p. 1281 (7).

A high rate of changes to a cell’s genome enables the acquisition and evolution of the well-known hallmarks of cancer. As such, virtually all cancer cells exhibit genomic instability in one form or another. For example, at least two thirds of human cancers are mosaic aneuploid as a result of frequent gains and losses of whole chromosomes during cell divisions. Such whole-chromosomal instability (wCIN) can promote gains of extra copies of oncogenes or losses of tumor-suppressor genes, and it allows selection of karyotypes that thrive in certain environments. Tumor relapse following the initial success of anticancer therapies, as well as anticancer drug resistance, has therefore been attributed to wCIN (1). Although the wCIN phenotype is of benefit to the survival of a tumor cell, it can also be detrimental to the therapy. This is because wCIN is replication stress, a term that signifies the response to DNA damage caused by stalled replication forks. The mechanism for this is unknown, but alleviation of replication stress is lethal for some tumor populations. A number of studies have shown that the mitotic cell-cycle checkpoint is activated in this context (Fig. 1). It is not difficult to see that such a cycle may contribute in important ways to tumor heterogeneity and rapid evolution of the tumor cell population.

Another form of genomic instability frequently observed in cancer cells is instability at the level of chromosome structure. Structural CIN (sCIN) encompasses a variety of changes to the genome, including translocations, deletions, inversions, and fragmentations. sCIN is caused by poor repair of damaged DNA, due to, for example, mutations in DNA repair pathway components or inefficient cellular responses to DNA damage. The first response after detection of damage is the DNA damage response (DDR) pathway, of which the kinases ATM and CHK2 are crucial components. The DDR signaling network simultaneously initiates repair and halts the cell-cycle machinery to allow more time for repair to take place. This first response also initiates a second, slower, p53-dependent response (2).

Although they were initially viewed as independent processes, evidence is mounting that wCIN and sCIN are linked in important ways. Micronuclei suffer from replication stress and damaged DNA (4). These laggards can acquire damage during cytokinesis, resulting in deletions and chromosomal translocations in daughter cells (5). These and other types of missegregated chromosomes also form micronuclei, structures often used as a marker in cancer diagnosis. Micronuclei suffer from replication stress and damaged DNA (6). The obvious result of the causal connections between errors in chromosome segregation and DNA damage is a vicious cycle: wCIN can cause DNA damage, which in turn can cause wCIN, and so on and so forth (Fig. 1). It is not difficult to see that such a cycle may contribute in important ways to tumor heterogeneity and rapid evolution of the tumor cell population. In this issue of Cancer Discovery, Bakhoum and colleagues (7) report a surprising novel connection between DNA damage and wCIN. They investigated the consequences of damaging DNA during mitosis and observed an elevated frequency of chromosome missegregations in cancer cells as well as in immortalized normal human cells. The type of missegregation most frequently observed was that of lagging chromosomes. These laggards are the result of hyperstabilization of chromosome–spindle connections and escape detection by the main mitotic cell-cycle checkpoint. Bakhoum and colleagues show that activation of the ATM–CHK2 pathway was responsible for this hyperstabilization, at least in part via the well-known spindle regulators Aurora A and PLK1. Chemical inhibition of ATM, CHK2, Aurora A, or PLK1 prevented not only hyperstabilization of chromosome–spindle connections but also the frequency of lagging chromosomes following mitotic DNA damage. Finally, the authors observed that cell lines most responsive to CHK2 inhibitors (with regard to reducing the frequency of lagging chromosomes) were generally those known to harbor the highest level of mitotic DDR pathway activation.

This new study raises a number of questions related to cancer cell biology and cancer therapy. From a molecular mechanistic view, it will be of interest to examine how the mitotic...
DNA damage activates the DDR, causing lagging chromosomes to form micronuclei that undergo replication stress and are susceptible to pulverization or structural rearrangements of chromosomes damaged during cytokinesis. Moreover, the initial DNA damage is not repaired in mitosis and persists until G1, when double-strand breaks are corrected by the error-prone process of nonhomologous end-joining. If checkpoints fail and damage persists until the next mitosis, the DDR will be active and cause more wCIN, establishing positive feedback between wCIN and sCIN.
vein, DNA-damaging agents may display synergy with anti-mitotic drugs like paclitaxel that kill cells by forcing extensive chromosome missegregations. It will be important to know whether specific cancer types are sensitive to this, and if so whether sensitivity is related to traits such as level of wCIN, and/or endogenous genotoxic stress before drug treatment. Bakhoun and colleagues provide an exciting new lead to further explore these questions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Published online November 3, 2014.

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Cancer Discovery 2014;4:1256-1258.

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