

Editorial

Genomic instability and cancer: an introduction

Genomic instability refers to an increased tendency of alterations in the genome during the life cycle of cells. It is a major driving force for tumorigenesis. During a cell division, genomic instability is minimized by four major mechanisms: high-fidelity DNA replication in S-phase, precise chromosome segregation in mitosis, error free repair of sporadic DNA damage, and a coordinated cell cycle progression. This introduction summarizes the major molecular processes that contribute to these mechanisms in the context of prevention of genomic instability and tumorigenesis.

Genomic instability as a major driving force of tumorigenesis.

The ultimate goal of cell division for most non-cancerous somatic cells is to accurately duplicate the genome and then evenly divide the duplicated genome into the two daughter cells. This ensures that the daughter cells will have exactly the same genetic material as their parent cell. Failure to achieve this purpose, or abnormally high-frequency of errors during this process will result in various forms of genome alterations in the daughter cells. Those alterations include, but are not limited to, various forms of mutations on specific genes, amplifications, deletions or rearrangements of chromosome segments, gain or loss of an entire chromosome(s), etc. Accumulation of these genomic alterations may cause dys-regulation of cell division, imbalance between cell growth and death, and cancer. Genomic instability is defined as a process prone to genomic changes or an increased propensity for genomic alterations. During cell division, genomic instability is

associated with the failure of parental cells to accurately duplicate the genome and precisely distribute the genomic material among the daughter cells.

In normal tissues, cell divisions are tightly regulated to avoid neoplastic transformation or tumorigenesis. As simplified in Figure 1, the molecular process of tumorigenesis can be viewed as the accumulation of genomic alterations during a series of cell divisions. The alteration(s) of critical genes in a progenitor cell can transform a normal cell into a pre-cancerous cell. Although the pre-cancerous cells may not be clinically considered as cancer, additional genomic changes would allow some of them to gain further growth advantages. Hence, this new population of neoplastic cells can progress to a clinical status that can be diagnosed as cancer. Additional genetic alterations among the cancer cells can result in sub-populations of cells with even more aggressive properties. Thus, the accumulation of genomic alterations is not only a hallmark but also a driving force for tumorigenesis. A critical point in this model is that various forms of genetic changes may occur and accumulate in distinct subsets of cell populations during neoplastic transformation and progression. This accounts for the diverse genetic background among the cancer cells, contributing to the heterogeneity observed in cancer.

Guest Editor

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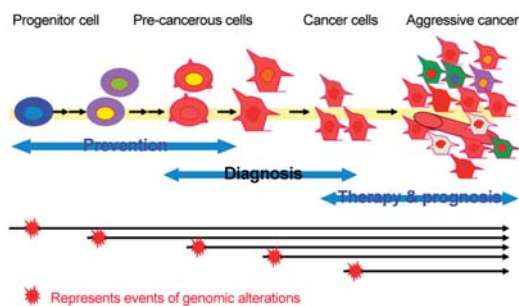


Figure 1 Cancer as a disease of genomic instability and its implication for cancer interventions.

Major mechanisms used to maintain genomic integrity. Because cancer is the result of uncontrolled cell growth, and the accumulation of genomic alterations during cell division is a driving force for tumorigenesis, understanding how genomic stability is maintained during cell

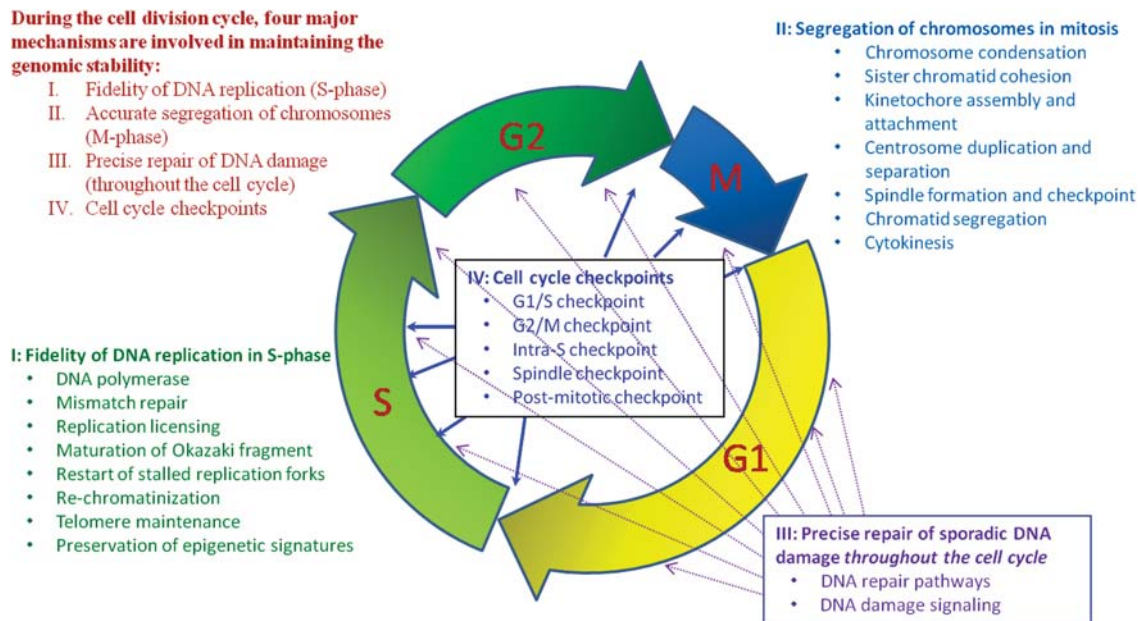


Figure 2 Overview of the major mechanisms to maintain genomic stability during the cell cycle.

divisions is critical to reveal the mechanisms by which tumorigenesis is prevented during normal tissue growth. In principle, the normal mammalian cells mainly resort to four mechanisms to maintain their genomic stability during cell division (as outlined in Figure 2): (i) high-fidelity of DNA replication in S-phase, (ii) accurate distribution of chromosomes among daughter cells during mitosis, (iii) error-free repair of sporadic DNA damage throughout the cell cycle, and (iv) cell cycle progression and checkpoint control. Other mechanism(s), such as dys-regulation of cell fate control, including apoptosis and senescence, can be viewed as consequences of genomic instability and may further contribute to the growth advantage of cancerous cells. Among each of the four major mechanisms, multiple molecular processes are involved.

DNA replication fidelity. In the S-phase, the entire genomic DNA is accurately duplicated once and only once per cell cycle. Any tendency for errors in this process would constitute genomic instability. The major mechanisms to minimize genomic alterations in association with DNA replication are as following. (i) High-fidelity of base-pairing and proofreading activities by DNA polymerases. (ii) Mismatch repair machinery to correct not only mismatched bases, but also secondary DNA structures

resulted from replication slippage, especially in repeat DNA sequences. (iii) Timely resolution of stalled replication forks. DNA replication forks often pause or even collapse after encountering various forms of replication blockages. These stalled replication forks have to be re-started in time to ensure the complete duplication of the genome and to minimize the possibility of further collapse that may cause genome alterations. This process requires the proteins involved in homologous recombination and other DNA repair processes. (iv) Maturation of Okazaki fragments. During DNA synthesis, the lagging strand is duplicated in the form of multiple Okazaki fragments. At the 5'-end of each Okazaki fragment, there is a RNA primer and a short DNA segment (i.e. α segment) synthesized by a low-fidelity DNA polymerase. The RNA primers and the α segments will be removed before the Okazaki fragments are ligated. Dysfunction in Okazaki fragment maturation may contribute to genomic alterations. (v) Replication licensing mechanisms to ensure that the entire genome is duplicated completely once and only once per cell cycle. This regulation is likely controlled by the assembly of pre-replication complex at replication origin sites prior to S-phase. (vi) Coordinated re-assembly of chromosomes from newly synthesized DNA. (vii) Other mechanisms such as telomere

maintenance and duplication of epigenetic signatures on the newly synthesis DNA and chromatin are also considered critical for replication fidelity.

Precise chromosome segregation in mitosis. Once the DNA and chromosomes are duplicated in S-phase, the next critical phase in cell division susceptible to genomic instability is mitosis. During mitosis, the sister chromatids are equally distributed in the daughter cells. This is coordinated by many processes including: (i) chromosome condensation, (ii) sister chromatid cohesion, (iii) centrosome duplication and separation, (iv) kinetochore assembly and attachment, (v) spindle formation and checkpoint, (vi) chromosome segregation, (vii) cytokinesis, etc. Dys-regulation of any of these processes would cause mis-segregation of chromatids and chromosomal instability in the forms of aneuploidy and polyploidy, which are commonly observed in cancer. Of a special note is that some of the chromosomal aberrations associated with genomic instability displayed during mitosis can be a consequence of S-phase defects. For examples, the duplication of centrosomes is believed to be coordinated with DNA replication, and an impaired resolution of replication intermediates prior to entry to mitosis would increase the risk for mitotic errors.

Error-free repair of sporadic DNA damage. Throughout the cell cycle, the

genome encounters various forms of spontaneous and induced DNA damages. When these damages are left un-repaired, it will not only affect cell functions but also renders a higher risk for errors during DNA replication and chromosome segregation. The DNA damages are repaired by several well-defined repair pathways, including base excision repair, nucleotide excision repair, DNA double-strand break (DSB) repair, etc. Mismatch repair, a special type of nucleotide excision repair to fix mismatches that may not be considered chemical damage to DNA, is mainly associated with replication.

Of significance to genomic instability is that, the outcome of the DNA repair varies. Completion of some of the repair processes to fix chemical damages to the DNA double helix may cause alterations on the DNA sequence or rearrangements of genome segments. This type of repair is referred to as 'error-prone' repair. Clearly, its outcome can contribute to genomic instability, although it may prevent further genomic alterations that would otherwise arise from the initial DNA damage. In contrast, other repair processes may not only fix the chemical damage to the DNA but also preserve the original genome structure, which is regarded as 'error-free' repair. One example is the repair of DNA DSBs. The homologous recombination repair of DSB is considered less likely to cause genomic alterations, thus 'error-free'. On the other hand, the non-homologous end-joining pathway has a high risk of producing mutations and/or genome rearrangements, thus 'error-prone'. However, this classification is based on the relative risk to produce errors. One should keep in mind that, the 'error-prone' repair does not always produce errors and the 'error-free' repair sometimes undeniably causes errors.

The activities of repair pathways and their coordination with other cell functions

(such as cell cycle progression and cell death) are regulated by a DNA damage signaling network. Dys-regulation of this network would significantly impair the coordinated effort to repair DNA damage thus can contribute to genomic instability.

In addition to its implications in genomic instability and tumorigenesis, DNA damage repair pathways are highly relevant to cancer therapy. Radiation and many chemotherapeutic agents are used for cancer therapy due their abilities to cause DNA damage in cancer cells. Hence, repair capability is a critical determinant in therapeutic outcome. Targeted inhibition of an appropriate DNA repair pathway in cancer cells is considered an effective way to enhance therapeutic efficacy.

Checkpoints to coordinate cell cycle progression. Because the cell division is conducted in an orderly manner, the progression of the cell cycle is highly coordinated. Premature entry of a cell into the next cell cycle phase would result in significant propensity for genomic alterations. Cell cycle checkpoints are built to ensure that progression from one phase to the next is under a condition of minimum risk of genomic alteration. This is accomplished by delaying the entry into the next phase until the risk factors (such as DNA damage in G1/S/G2 phase, spindle abnormality prior to anaphase, etc.) are removed. Another important function of cell cycle checkpoint is to effectively trigger some processes (e.g. apoptosis, mitotic catastrophe, and senescence) to eliminate the severely damaged or high risk cells from the dividing pool.

The mechanisms of several cell cycle checkpoints have been well established. The G1/S checkpoint is to restrict damaged cells from entering S-phase, as cells with DNA damage would have much high risk of DNA replication errors. It holds the cells at G1/S boundary until

DNA damage and high-risk factors are removed, or it triggers apoptosis and senescence to eliminate the severely damaged cells from the cycling pool. The G2/M checkpoint prevents cells from premature entry into mitosis, and in this way it minimizes chromosome segregation errors. The intra-S checkpoint helps to delay the firing of replication origins or slows down DNA duplication during S-phase in order to minimize replication errors. The mitotic spindle checkpoint ensures normal spindle function in order to minimize chromosome segregation errors. The post-mitotic checkpoint can prevent daughter cells of abnormal mitosis from entering the next interphase. All these checkpoints are essential to reduce genomic instability during cell cycle progression.

The current issue of JMCB. As outlined above, the relationship between genomic instability and cancer is complex. It involves almost every major aspect of cell and molecular biology. In this special issue, we collect nine review articles to cover a few aspects related to DNA replication, DNA damage response and repair, and to exemplify their implications in cancer therapy. The specific topics are: restart of stalled replication forks, replication licensing, maturation of Okazaki fragments, RecQ and Blm helicases in resolving stalled replication forks, RAD9 checkpoint protein in tumorigenesis, microRNA regulation of p53, epigenetic regulation of DNA damage repair, DNA repair polymorphism and cancer risk, and synthetic lethality and viability in the context of tumorigenesis and therapy. Although the regulation of mitosis and cell cycle checkpoints are integral parts of the genome stability maintenance system, reviews in these aspects are not included due to space limitation.