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Elucidating genomic instability and its outcomes as cancer origin

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ABSTRACT

Increased propensity of alterations in the genome during the life cycle of cells is called as genomic instability. It is a major cause of oncogenesis. There are four major mechanisms that control the genome instability while the normal cells divide. These mechanisms are DNA replication of high precision and accuracy in S-phase, mitosis involving precise chromosome separation, correct repair of infrequently occurring DNA damage, and cell cycle development in synchronized manner. This briefly throws light on processes at molecular level that play significant role in preventing oncogenesis through genomic instability.

Keywords: DNA, RNA, Genes, Instability, Cancer, Implications.

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INTRODUCTION

Genomic instability as a major driving force of tumorigenesis. In normal circumstances, healthy somatic cells undergo cell division to form exactly same duplicate genome that equally divides to form daughter cells containing same genetic material as parent cells. Abnormally high number of errors in cell division results in various nature of genome alterations and aberrations in the daughter cells [1-4]. Some of these important alterations include specific genes mutations, gene amplifications, rearrangements or deletions of chromosome segments, entire chromosome gain or loss etc. Increased frequency of alterations in genome sequence may impair cell division cycles, uneven cell growth and death, and ultimately cancer. As stated earlier, genomic instability is defined as higher chances and tendency of genomic alterations in cell division process. Here, genomic instability results due to failure of parental cells to duplicate the genome accurately and formation of daughter cells with inaccurate distribution of the genomic material. The process of cell division in normal tissues proceeds with high-fidelity, regulated tightly to avoid neoplasm and cancer initiation. at the molecular level process of oncogenesis can be viewed as a series of cell divisions that involves accumulation of genomic alterations. A pre-cancerous cell formation from a normal cell can be seen as result of alteration(s) of vital genes in a progenitor cell. Not all pre-cancerous cells may lead to cancer, however add on genomic alterations can allow their further growth to initiate cancer. Consequently, increased number of neoplastic cells can consolidate to a clinical stage that can be diagnosed as cancer. Further genetic alterations among the cancer cells can result in subpopulations of cells with even more aggressive properties [5-10]. Thus, the accumulation of genome with altered sequences is a triggering factor and an impetus for tumorigenesis. During neoplastic transformation and progression, genetic changes occur and accumulate in distinct subsets of cell populations, establishing a critical point in this model of tumorigenesis. Thus, heterogeneity observed in cancer can be attributed to the diverse genetic background among the cancer cells.

Mechanisms of genomic stability

Major mechanisms used to maintain genomic integrity. Since uncontrolled cell growth results in cancer, and tumorigenesis is triggered by the accumulation of genomic alterations during cell, it becomes imperative to understand how genomic stability is preserved during cell divisions and tumorigenesis is averted during normal tissue growth. Genomic stability during normal cell division process follows four mechanisms: (i) DNA replication of high precision and accuracy in S-phase, (ii) mitosis involving precise chromosome separation and distribution

among daughter cells (iii) correct repair of infrequently occurring DNA damage in all phases of cell cycle, and (iv) checkpoint control with progress of cell cycle. Other mechanism(s) can be considered as outcome of genomic instability and may aid in development of cancerous cells. Such mechanisms include apoptosis (programmed cell death) and senescence (loss of cells ability to grow and divide). In all four mechanisms numerous molecular processes are involved. For example, in the S-phase, the entire genomic DNA duplication is an accurate process with high fidelity occurring only once for a cell and only once per cell cycle. Genomic instability is evident with any tendency for errors in this process [11-14].

The major mechanisms to minimize genomic alterations in association with DNA replication are as following. (i) proofreading activities by DNA polymerases and High-fidelity of base-pairing. (ii) Mismatch repair machinery mainly in repeat DNA sequences, mismatched bases, and replication slippage resulting in secondary DNA structures (iii) Timely resolution of slowed down replication forks. Various forms of replication blockages often pause or even collapse DNA replication forks. Timely re-start of replication process ensures duplication of the genome in entirety and minimizes the likelihood of further genome alterations. Proteins of homologous recombination and other DNA repair processes are required for this process. (iv) Maturation of Okazaki fragments. While DNA synthesis proceeds, multiple Okazaki fragments represent duplicated lagging strand. RNA primer and a short DNA segment (i.e. a segment) at the 5′ - end of each Okazaki fragment is a synthesized by a low-fidelity DNA polymerase. The DNA segments and the RNA primers are removed before the ligation of Okazaki fragments. Here, genomic alterations may results with dysfunction in Okazaki fragment maturation. (v) Replication licensing mechanisms to ensure that the entire genome is duplicated completely once and only once per cell cycle [15-19]. The assembly of pre-replication complex at the site of replication origin before S-phase probably controls this regulation. (vi) Newly synthesized DNA is reassembled into chromosomes in co-ordinated manner. (vii) Other critical mechanisms for accurate replication include exact duplication of epigenetic signatures on the newly synthesis DNA and chromatin telomere maintenance.

Interrelating genomic stability with cancer

It is significant to note that the outcome of the DNA repair varies in fixing genomic instability. Rearrangements of genome segments or alterations on the DNA sequence may take place while execution of some of the repair processes to fix DNA double helix chemical damages. This type of repair is commonly called as 'error-prone' repair. Noticeably, it may lead to genomic instability, although it can prevent further genomic alterations otherwise arising from the initial DNA damage [20-24]. In contrast, 'error-free' repair processes may not only preserve the original genome structure, but also fix the chemical damage to the DNA, an example is the repair of DNA DSBs. The 'error-free' homologous recombination repair of DSB is less likely to cause genomic alterations. Conversely, the non-homologous end-joining pathway carry high risk of mutations and/or genome rearrangements, hence 'error-prone'. Nonetheless, the basis of this classification is relative risk to produce errors. Accordingly, it is to be remembered that the 'error-free' repair sometimes undeniably causes errors and the 'error-prone' repair does not always produce errors [26-30].

Cell cycle progression is co-ordinated by Checkpoints. The progression of the cell cycle is highly coordinated since the cell division is conducted in an orderly, systematic and logical manner. Significant propensity for genomic alterations is evident with premature entry of a cell into the next cell cycle phase [31-35]. Checkpoints at every phase of the cell cycle are built to ensure smooth progression from one phase to the next with minimum risk of genomic alteration. Removal of risk factors (such as spindle abnormality prior to anaphase, DNA damage in G1/S/G2 phase, etc.) by delaying the entry into the next phase reduces the risk of genomic alterations. In addition, severely damaged or high risk cells from the dividing pool are eliminated by cell cycle checkpoints that effectively trigger some processes (e.g. mitotic catastrophe, apoptosis, and senescence) [36-41].

CONCLUSION

The relationship between genomic instability and cancer is complex and almost every major aspect of cell and molecular biology is involved. In this review, we collect nine review articles to cover 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 cell cycle checkpoints and regulation of mitosis are integral parts of the genome stability maintenance system, reviews in these aspects are not included due to space limitation.

REFERENCES

1. Zahreddine, Hiba, and Katherine Borden. (2013) "Mechanisms and insights into drug resistance in cancer." Frontiers in pharmacology 4: 28.
2. Goodwin, Jonathan F., Matthew J. Schiewer, Jeffry L. Dean, Randy S. Schrecengost, Renée de Leeuw, Sumin Han, Teng Ma et al. (2013) "A hormone-

DNA repair circuit governs the response to genotoxic insult." Cancer discovery 3, no. 11: 1254-1271.

3. Poche, D.M., Garlapati, R.B., Mukherjee, S., Torres-Poché, Z., Hasker, E., Rahman, T., Bharti, A., Tripathi, V.P., Prakash, S., Chaubey, R. and Poché, R.M., (2018). Bionomics of Phlebotomus argentipes in villages in Bihar, India with insights into efficacy of IRS-based control measures. PLoS neglected tropical diseases, 12(1), p.e0006168.
4. Filipi?, Metka. (2012)"Mechanisms of cadmium induced genomic instability." mutation research/fundamental and molecular mechanisms of mutagenesis 733, no. 1-2: 69-77.
5. Li, Ling, Shuo Hu, and Xiaoyuan Chen. (2018) "Non-viral delivery systems for CRISPR/Cas9-based genome editing: Challenges and opportunities." Biomaterials 171: 207-218.
6. Langie, Sabine AS, Gudrun Koppen, Daniel Desaulniers, Fahd Al-Mulla, Rabeah Al-Temaimi, Amedeo Amedei, Amaya Azqueta et al. (2015) "Causes of genome instability: the effect of low dose chemical exposures in modern society." Carcinogenesis 36, no. Suppl_1: S61-S88.
7. Mishra, A., Nizammuddin, S., Mallick, C.B., Singh, S., Prakash, S., Siddiqui, N.A., Rai, N., Carlus, S.J., Sudhakar, D.V., Tripathi, V.P. and Möls, M., (2017). Genotype-phenotype study of the middle Gangetic plain in India shows association of rs2470102 with skin pigmentation. Journal of Investigative Dermatology, 137(3), pp.670-677.
8. Bhattacharjee, Pritha, Mayukh Banerjee, and Ashok K. Giri. (2013) "Role of genomic instability in arsenic-induced carcinogenicity. A review." Environment international 53: 29-40.
9. Tu, Thomas, Magdalena A. Budzinska, Annette E. Maczurek, Robert Cheng, Anna Di Bartolomeo, Fiona J. Warner, Geoffrey W. McCaughan, Susan V. McLennan, and Nicholas A. Shackel. (2014) "Novel aspects of the liver microenvironment in hepatocellular carcinoma pathogenesis and development." International journal of molecular sciences 15, no. 6: 9422-9458.
10. Friboulet, Luc, Daniel Barrios-Gonzales, Frédéric Commo, Ken André Olaussen, Stephan Vagner, Julien Adam, Aïcha Goubar et al. (2011) "Molecular characteristics of ERCC1-negative versus ERCC1-positive tumors in resected NSCLC." Clinical Cancer Research 17, no. 17: 5562-5572.
11. Thakur, Jitendra, and Kaustuv Sanyal. (2013) "Efficient neocentromere formation is suppressed by gene conversion to maintain centromere function at native physical chromosomal loci in Candida albicans." Genome Research 23, no. 4: 638-652.
12. Yadav, M.P., Padmanabhan, S., Tripathi, V.P., Mishra, R.K. and Dubey, D.D., (2012). Analysis of stress-induced duplex destabilization (SIDD) properties of replication origins, genes and intergenes in the fission yeast, Schizosaccharomyces pombe. BMC research notes, 5(1), pp.1-10.
13. Lim, Hui Kheng, P. V. Asharani, and M. Prakash Hande. (2012) "Enhanced genotoxicity of silver nanoparticles in DNA repair deficient mammalian cells." Frontiers in genetics 3: 104.
14. Yue, Jingyin, Steven Huhn, and Zhiyuan Shen. (2013) "Complex roles of filamin-A mediated cytoskeleton network in cancer progression." Cell & bioscience 3, no. 1: 1-12.
15. Bosch-Presegue, L., and A. Vaquero. (2014) "Sirtuins in stress response: guardians of the genome." Oncogene 33, no. 29: 3764-3775.
16. YináZhang, Kenneth. (2015) "A multifunctional phosphorescent iridium (III) complex for specific nucleus staining and hypoxia monitoring." Chemical Communications 51, no. 37: 7943-7946.
17. Pratihar, A.S., Tripathi, V.P., Yadav, M.P. and Dubey, D.D., (2015). Chromosomal context and replication properties of ARS plasmids in Schizosaccharomyces pombe. Journal of biosciences, 40(5), pp.845-853.
18. Santibáñez-Andrade, Miguel, Ericka Marel Quezada-Maldonado, Álvaro Osornio-Vargas, Yesennia Sánchez-Pérez, and Claudia M. García-Cuellar. (2017) "Air pollution and genomic instability: The role of particulate matter in lung carcinogenesis." Environmental pollution 229: 412-422.
19. Rauti, Rossana, Mattia Musto, Susanna Bosi, Maurizio Prato, and Laura Ballerini. (2019) "Properties and behavior of carbon nanomaterials when interfacing neuronal cells: How far have we come?." Carbon 143: 430-446.
20. MacKinnon, Ruth N., and Lynda J. Campbell. (2011) "The role of dicentric chromosome formation and secondary centromere deletion in the evolution of myeloid malignancy." Genetics research international.
21. Tripathi, V.P. and Dubey, D.D., (2017). A replication-time-controlling sequence element in Schizosaccharomyces pombe. Chromosoma, 126(4), pp.465-471.
22. Wang, Jianwei, Lina Zhou, Zhi Li, Ting Zhang, Wenpeng Liu, Zheng Liu, Yate-Ching Yuan et al. (2015) "YY1 suppresses FEN1 over-expression and drug resistance in breast cancer." BMC cancer 15, no. 1: 1-15.
23. Kurelac, Ivana, Alan MacKay, Maryou BK Lambros, Erica Di Cesare, Giovanna Cenacchi, Claudio Ceccarelli, Isabella Morra et al. (2013) "Somatic complex I disruptive mitochondrial DNA mutations are modifiers of tumorigenesis that correlate with low genomic instability in pituitary adenomas." Human molecular genetics 22, no. 2: 226-238.
24. Leung, Wendy, Ryan M. Baxley, George-Lucian Moldovan, and Anja-Katrin Bielinsky. (2019)

"Mechanisms of DNA damage tolerance: Post-translational regulation of PCNA." Genes 10, no. 1: 10.

25. Tripathi, Vishnu P., M. K. Aneebuddin, C. Alex, and Keshav S. Moharir. (2021) "Evaluating Clinical Applications of Liquid Biopsy by Combining Circulating Tumor DNA and Tumor cells." Current Research in Pharmaceutical Sciences: 107-111.
26. Vodenkova, Sona, Zdenka Polivkova, Ludovit Musak, Zdenek Smerhovsky, Hana Zoubkova, Sylvie Sytarova, Elena Kavcova et al. (2015) "Structural chromosomal aberrations as potential risk markers in incident cancer patients." Mutagenesis 30, no. 4: 557-563.
27. Yang, Hsin-Ling, Ssu-Ching Chen, Kai-Yuan Lin, Mei-Tsun Wang, Yu-Chang Chen, Hui-Chi Huang, Hsin-Ju Cho, Lai Wang, KJ Senthil Kumar, and You-Cheng Hseu. (2011) "Antioxidant activities of aqueous leaf extracts of Toona sinensis on free radical-induced endothelial cell damage." Journal of ethnopharmacology 137, no. 1: 669-680.
28. Andriani, Grasiella A., Jan Vijg, and Cristina Montagna. (2017) "Mechanisms and consequences of aneuploidy and chromosome instability in the aging brain." Mechanisms of ageing and development 161: 19-36.
29. Tripathi VP, Goo D, Maidya BN, Aneebuddin MK. (2022)New Trends in Interrelation of Infectious Colorectal Cancer with Intestinal Microbiota. Arch Gastroenterol Res.;3(1):18-22.
30. Müllner, Elisabeth, Helmut Brath, Armen Nersesyan, Marlies Nitz, Alice Petschnig, Marlies Wallner, Siegfried Knasmüller, and Karl-Heinz Wagner. (2014) "Nuclear anomalies in exfoliated buccal cells in healthy and diabetic individuals and the impact of a dietary intervention." Mutagenesis 29, no. 1: 1-6.
31. Zhang, Xin, Deyong Jia, Huijuan Liu, Na Zhu, Wei Zhang, Jun Feng, Jun Yin et al. (2013) "Identification of 5-iodotubercidin as a genotoxic drug with anti-cancer potential." PLoS One 8, no. 5: e62527.
32. Huang, Yi-Yuan, Li Dai, Dakim Gaines, Roberto Droz-Rosario, Huimei Lu, Jingmei Liu, and Zhiyuan Shen. (2013) "BCCIP suppresses tumor initiation but is required for tumor progression." Cancer research 73, no. 23: 7122-7133.
33. Tripathi VP, Roberto Jetsu, (2022) Traditional Herbs Role in Enhancement of Antitumor Responses of Agonistic CD40-Antibody by Reducing Myeloid-derived Suppressor Cells. Chem. Res. J 7, no. 1: 1-5.
34. Hughesman, Curtis B., XJ David Lu, Kelly YP Liu, Yuqi Zhu, Catherine F. Poh, and Charles Haynes. (2016) "A robust protocol for using multiplexed droplet digital PCR to quantify somatic copy number alterations in clinical tissue specimens." PloS one 11, no. 8: e0161274.
35. Pawlowska, Elzbieta, and Janusz Blasiak. (2015) "DNA repair-a double-edged sword in the genomic stability of cancer cells-the case of chronic myeloid leukemia." International journal of molecular sciences 16, no. 11: 27535-27549.
36. Thanasopoulou, Angeliki, Dimitrios J. Stravopodis, Konstantinos S. Dimas, Juerg Schwaller, and Ema Anastasiadou. (2012) "Loss of CCDC6 affects cell cycle through impaired intra-S-phase checkpoint control." PloS one 7, no. 2: e31007.
37. Lu, Huimei, Yi-Yuan Huang, Sonam Mehrotra, Roberto Droz-Rosario, Jingmei Liu, Mantu Bhaumik, Eileen White, and Zhiyuan Shen. (2011) "Essential roles of BCCIP in mouse embryonic development and structural stability of chromosomes." PLoS genetics 7, no. 9: e1002291.
38. Tripathi VP, Ahmed H, Renulos N, Aneebuddin MK. (2022) Elucidating the Role of Chemokines in Infectious Diseases and Gastric Cancer. Arch Gastroenterol Res.;3(1):23-26.
39. Browning, Cynthia L., and John Pierce Wise Sr. (2017) "Prolonged exposure to particulate chromate inhibits RAD51 nuclear import mediator proteins." Toxicology and applied pharmacology 331: 101-107.
40. Jönsson, K. Ingemar. (2019) "Radiation tolerance in tardigrades: current knowledge and potential applications in medicine." Cancers 11, no. 9: 1333.
41. Smith, Martyn T., Kathryn Z. Guyton, Nicole Kleinstreuer, Alexandre Borrel, Andres Cardenas, Weihsueh A. Chiu, Dean W. Felsher et al. (2020) "The key characteristics of carcinogens: relationship to the hallmarks of cancer, relevant biomarkers, and assays to measure them." Cancer Epidemiology and Prevention Biomarkers 29, no. 10: 1887-1903.