World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i35.12522

World J Gastroenterol 2014 September 21; 20(35): 12522-12525
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Mitotic crossover - an evolutionary rudiment which promotes carcinogenesis of colorectal carcinoma

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Author contributions: Each author indicated gave substantial contributions to the conception and design of the article, acquisition of data, drafting of the article, critical revision for important intellectual content, and final approval of the version to be published.
Supported by The Ministry of Science and Education (partially), Republic of Serbia, No. 175091
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Received: February 23, 2014 Revised: April 22, 2014
Accepted: May 19, 2014
Published online: September 21, 2014

Abstract

Mitotic crossover is a natural mechanism that is a main source of the genetic variability of primitive organisms. In complex organisms such as mammals, it represents an evolutionary rudiment which persisted as one of the numerous DNA repair mechanisms, and results in the production of homozygous allele combinations in all heterozygous genes located on the chromosome arm distal to the crossover. This event is familiar as loss of heterozygosity, which is one of the key mechanisms responsible for the development and progression of almost all cancers. We propose the hypothesis in which mitotic crossover is a principal source of the increased loss of heterozygosity that leads to the initiation and progression of colorectal carcinoma. The hypothesis could be tested by *in vitro* inhibition of Rad51 protein, orthotopic grafting of human colon cancer tissue into the gut of mice, and treatment with potential inhibitors. After these procedures, the frequency of mitotic crossover would be estimated. The development of selective inhibitors of mitotic crossover could stop further carcinogenesis of colorectal carcinoma, as well as many other neoplastic events. Loss of heterozygosity is an event responsible for carcinogenesis, its reduction by selective inhibitors of mitotic crossover could have a positive effect on cancer chemoprevention, as well as on growth reduction and a cessation in the progression of earlier developed tumors.

Key words: Mitotic crossing over; Loss of heterozygosity; Carcinogenesis; Inhibitors; Colorectal carcinoma; Cancer chemoprevention

Core tip: We propose the hypothesis in which mitotic crossover is a principal source of the increased loss of heterozygosity that leads to the initiation and progression of colorectal carcinoma. The development of selective inhibitors of mitotic crossover could stop further carcinogenesis of colorectal carcinoma, as well as many other neoplastic events. Loss of heterozygosity is an event responsible for carcinogenesis, and its reduction by selective inhibitors of mitotic crossover could have a positive effect on cancer chemoprevention, as well as on growth reduction and a cessation in the progression of earlier developed tumors.

Rovcanin B, Ivanovski I, Djuric O, Nikolic D, Petrovic J, Ivanovski P. Mitotic crossover - an evolutionary rudiment which promotes carcinogenesis of colorectal carcinoma. *World J Gastroenterol* 2014; 20(35): 12522-12525 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i35/12522.htm DOI:

http://dx.doi.org/10.3748/wjg.v20.i35.12522

INTRODUCTION

Approximately 3.5 billion years have passed since biotic evolution began. Life forms started to change dramatically from the time of the last common ancestor. After the development of multicellular organisms, a need appeared for cellular specialization for different functions. This need initiated a time dependent sequence where cells pass through proliferation, differentiation, and maturation. Specificity of different function comes from a biodiversity that exists in the hierarchical level of the whole biosphere, as well as in each individual organism. This biodiversity is a result of the long-term struggle with various mechanisms that initiate the creation of differentiation among cells. This difference comes as a result of mutational events and numerous recombination events. When we say numerous, we refer to recombination mechanisms among bacteria (transformation, conjugation, and transduction), as well as meiotic and mitotic crossover among eukaryotes[1,2]. Meiotic crossover is the most important mechanism of genetic recombination which affects homologous chromosomes during prophase I of meiosis, and creates the great variety of genetic information that leads to increased biodiversity[3]. However, meiotic crossover is the privilege of a very low number of species compared to the total number of species living on Earth. Although asexual organisms do not have a great quantum of genetic alterations during reproduction, they have developed mitotic crossover, a mechanism that is responsible for most of their genetic variations. Presumably it must take place when homologous chromosomal segments are accidentally paired in asexual cells such as body cells[4]. It could potentially have a great influence on the evolution of diploid asexual organisms, as well as having an important role as a mechanism for repairing double stranded breaks and other DNA replication errors via homologous recombination. Since there are other DNA repair mechanisms that can correct the same errors, mitotic crossover is not the exclusive mechanism responsible for reparation of these errors. Instead, it is one of the numerous factors that develop slight genetic differences between monozygotic twins[5], and results in the production of homozygous allele combinations in all heterozygous genes located on the chromosome arm distal to the crossover. This event is denoted as a loss of heterozygosity (LOH). LOH can also occur after the deletion of a normal allele, chromosome arm, or the entire chromosome containing the normal allele. In females, inactivation of the X chromosome carrying the normal allele can result in LOH as well as the non-balanced chromosomal aberration known as isochromosome. Thus, when a mitotic crossover occurs, genes that were previously recessive are expressed in the form of homozygotes, thereby creating a new phenotype. By increasing homozygosity, mitotic crossover acts to improve the efficiency of selection in asexual populations which are subjected to directional selection[6]. Many genes need to be maintained in the heterozygous genotype state in order to obtain the proper function of their products[7,8]. If some genes become homozygous, then many important mechanisms such as cell proliferation and its control can become compromised and spiral out of control[9]. A LOH event is especially important in the promotion of cancer genesis. Tumor suppressor genes, which code for proteins that inhibit uncontrolled cell proliferation, are recessive genes which are required in the dominant homozygous or heterozygous states[10]. The exception is the X-linked tumor suppressor gene WTX (Wilms' tumor gene on the X chromosome). Since males only have one X chromosome, a damaging point-mutation in WTX or its deletion is all that is needed to eliminate tumor-suppression. Females are also at risk if the mutation or deletion occurs on the X chromosome that is not inactivated[11]. However, excluding the WTX gene, heterozygous cells will not undergo aberrant cell proliferation leading to tumor formation. If the normal copy of the gene is lost, the cell becomes predisposed to abnormal growth, and if enough mutations accumulate, a tumor may form[12]. However, LOH at a heterozygous locus also can lead to a homozygous dominant genotype if the recessive allele is lost, although this outcome is usually undetectable because it produces no obvious change in phenotype. Thus, in terms of species survival, the benefits of homozygosity at some points in ontogeny and phylogeny may outweigh the risks of LOH in adults.

GENETIC EVOLUTION OF THE MALIGNANT TRANSFORMATION OF COLORECTAL CARCINOMA

Colorectal carcinogenesis is a multistep process in which a series of genetic and epigenetic events lead to the transition from normal mucosa polyps to carcinoma. Colorectal carcinoma (CRC) develops through a multistep process of tumor suppressor inactivation and proto-oncogene activation by mutations and/or allelic loss. The sequence includes the mutation of several genes: loss of adenomatous polyposis coli gene located on the long arm of chromosome 5 (5q), activation of K-Ras-2 proto-oncogene located on the short arm of chromosome 12 (12p), loss of colorectal cancer (DCC) gene on the long arm of chromosome 18 (18q), and loss of p53 gene located on the short arm of chromosome 17 (17p)[13]. Since the spontaneous somatic mutation frequency is not sufficient to account for such a number of mutations, it has been presumed that other mechanisms are responsible for colorectal carcinogenesis, among which are the loss of genes that maintain genome stability and mediate damage repair[14].

HYPOTHESIS

What is the principal mechanism that drives precancerous lesions and benign tumors through the sequence of events that result in malignancy and dissemination? We propose the hypothesis that mitotic crossover is an evolutionary rudiment which was important for the reproduction of asexual organisms, but has a negative impact on genome integrity that could lead to disease. Accordingly, we propose that mitotic crossover is a principal source of increased LOH that leads to the initiation and progression of CRC.

HYPOTHESIS EVALUATION

It has been proven that mitotic crossover occurs more frequently in tumor cells. Several studies have confirmed an increased mitotic crossover index in colorectal carcinoma cells[15-17]. LOH of tumor suppressor genes is believed to be one of the key steps to the carcinogenesis of colorectal cancer. LOH, the loss of one allele at a specific locus, is caused by a deletion mutation or the loss of one chromosome of a pair. When this occurs in a tumor suppressor gene locus where one of the alleles is already abnormal, it can result in neoplastic transformation[18-20]. Loss of heterozygosity can be identified in cancers by noting the presence of heterozygosity at a genetic locus in an organism's germline DNA and the absence of heterozygosity at that locus in the cancer cells[21]. Loss of heterozygosity in colorectal cancer was first reported by Vogelstein *et al*[22], with it also being demonstrated that small and large allelic deletions are associated with a worse disease prognosis. Ozaslan and Aytekin showed the interrelationship between LOH, loss of tumor suppressor gene initiation, and progression of CRC. They observed LOH at various loci on different chromosomes, namely 1p, 1q, 4q, 5q, 8p, 9q, 11q, 12p, 14q, 15q, 17p, 17q, 18p, 18q, and 22q in CRCs[23]. Mao *et al*[24] reported that LOH frequencies among CRC patients were: 5q (25%), 18q (25%), and 17p (28%). Wan *et al*[20] reported an increased frequency of allelic losses in chromosome region 12p, where the K-Ras-2 gene is located. These studies showed that frequent LOH events include those chromosome regions which include tumor suppressor genes whose loss is necessary for colorectal carcinogenesis. Some studies have reported that increased mitotic crossover frequency in tumor cells is a result of a mismatch repair mechanism defect[25-27]. There are no literature data about neoplasms which originate from terminally differentiated cells such as Purkinje neurons, Betz neurons, and alpha motoneurons. This indicates that carcinogenesis cannot occur in tissues which do not have mitotic potential, including the presence of mitotic crossover.

HYPOTHESIS TESTING

A possible application of the aforementioned findings could be the development of mitotic crossover inhibitors which could stop further carcinogenesis of CRC. The arrangement of the mitotic crossover processing machinery is followed by the assembly of several protein components. This signaling cascade includes the association and mutual cooperative binding of RAD 50, RAD 51, RAD 52, RPA, PALB 2, BRCA 1, BRCA 2, and many other related proteins[28]. The cascade of events which enable the association and activation of the aforementioned proteins is supposed to be compromised in order to inhibit the course of mitotic crossover. The most adequate hotspots for mitotic crossover inhibition would be members of the RAD protein family, especially RAD 51, which is the most important and highly conserved effector protein for mitotic crossover[29].

If these inhibitors could be designed, there would be several ways to test this hypothesis. The first includes the usage of commercial human colon cancer cell lines (HT-29) that could serve for the evaluation of mitotic crossover frequency[30]. Since mitotic chiasmata can be visualized under a microscope, it could be possible to investigate how the application of specific mitotic crossover inhibitors in cell cultures has an effect on the mitotic crossover frequency.

A second option for the testing of this hypothesis could be an *in vivo* orthotopic graft of human colon cancer into the gut of mice using 020588 human colon cancer cell lines[31]. One group of mice would be administered with mitotic crossover inhibitors, while the other would not. This model would have to show how the application of mitotic crossover inhibitors affects tumor growth and leads to its withdrawal.

CONCLUSION

In this study, we propose a hypothesis in which mitotic crossover is an evolutionary rudiment in vertebrates whose effects on the genome lead to LOH and cancer genesis. Therefore, it is a principal mechanism for the promotion colon cancer genesis and tumor progression. Mitotic crossover is supposed to be the main source of increased LOH in the tumor cells of patients with CRC. If this hypothesis appears correct and if mitotic crossover inhibitors could be developed, their application could significantly slow down the progression of CRC among affected patients. Mitotic crossover inhibitors could be a protective therapy for patients with familiar colon polyposis. Since LOH is a common event that is intertwined in the carcinogenesis of all tumors, its reduction by selective inhibitors of mitotic crossover could have a positive effect on cancer chemoprevention, as well as on growth reduction and a cessation in the progression of earlier developed tumors.

REFERENCES

1 **Narra HP**, Ochman H. Of what use is sex to bacteria? *Curr Biol* 2006; **16**: R705-R710 [PMID: 16950097 DOI: 10.1016/j.cub.2006.08.024]

2 **Xu T**, Rubin GM. Analysis of genetic mosaics in developing and adult Drosophila tissues. *Development* 1993; **117**: 1223-1237 [PMID: 8404527]

3 **Alberts B**. Molecular biology of the cell. 4th ed. New York: Garland Science, 2002: 1136-1138
4 **Côté GB**, Gyftodimou J. Twinning and mitotic crossing-over: some possibilities and their implications. *Am J Hum Genet* 1991; **49**: 120-130 [PMID: 2063864]
5 **Aguilera A**, Chávez S, Malagón F. Mitotic recombination in yeast: elements controlling its incidence. *Yeast* 2000; **16**: 731-754 [PMID: 10861900]
6 **Mandegar MA**, Otto SP. Mitotic recombination counteracts the benefits of genetic segregation. *Proc Biol Sci* 2007; **274**: 1301-1307 [PMID: 17360283 DOI: 10.1098/rspb.2007.0056]
7 **Therman E**, Kuhn EM. Mitotic crossing-over and segregation in man. *Hum Genet* 1981; **59**: 93-100 [PMID: 7035337]
8 **Griffiths AJF**, Gelbart WM, Miller JH, Lewontin R. Modern genetic analysis. 2nd ed. New York: W. H. Freeman, 2002: 234-236
9 **Beroukhim R**, Lin M, Park Y, Hao K, Zhao X, Garraway LA, Fox EA, Hochberg EP, Mellinghoff IK, Hofer MD, Descazeaud A, Rubin MA, Meyerson M, Wong WH, Sellers WR, Li C. Inferring loss-of-heterozygosity from unpaired tumors using high-density oligonucleotide SNP arrays. *PLoS Comput Biol* 2006; **2**: e41 [PMID: 16699594 DOI: 10.1371/journal.pcbi.0020041]
10 **Sherr CJ**. Principles of tumor suppression. *Cell* 2004; **116**: 235-246 [PMID: 14744434 DOI: 10.1016/S0092-8674(03)01075-4]
11 **Yoo NJ**, Kim S, Lee SH. Mutational analysis of WTX gene in Wnt/ beta-catenin pathway in gastric, colorectal, and hepatocellular carcinomas. *Dig Dis Sci* 2009; **54**: 1011-1014 [PMID: 18720004 DOI: 10.1007/s10620-008-0458-9]
12 **Callahan R**, Cropp C, Sheng ZM, Merlo G, Steeg P, Liscia D, Lidereau R. Definition of regions of the human genome affected by loss of heterozygosity in primary human breast tumors. *J Cell Biochem Suppl* 1993; **17G**: 167-172 [PMID: 8007695]
13 **Bedeir A**, Krasinskas AM. Molecular diagnostics of colorectal cancer. *Arch Pathol Lab Med* 2011; **135**: 578-587 [PMID: 21526956 DOI: 10.1043/2010-0613-RAIR.1]
14 **Brenner BM**, Stoler DL, Rodriguez L, Karpenko MJ, Swede H, Petrelli NJ, Anderson GR. Allelic losses at genomic instability-associated loci in villous adenomas and adjacent colorectal cancers. *Cancer Genet Cytogenet* 2007; **174**: 9-15 [PMID: 17350461 DOI: 10.1016/j.cancergencyto.2006.11.001]
15 **Hoffmann GR**. Induction of genetic recombination: consequences and model systems. *Environ Mol Mutagen* 1994; **23** Suppl 24: 59-66 [PMID: 8162910]
16 **Bertagnolli MM**, Redston M, Compton CC, Niedzwiecki D, Mayer RJ, Goldberg RM, Colacchio TA, Saltz LB, Warren RS. Microsatellite instability and loss of heterozygosity at chromosomal location 18q: prospective evaluation of biomarkers for stages II and III colon cancer--a study of CALGB 9581 and 89803. *J Clin Oncol* 2011; **29**: 3153-3162 [PMID: 21747089 DOI: 10.1200/JCO.2010.33.0092]
17 **Wang W**, Li YF, Sun XW, Chen G, Zhan YQ, Huang CY, Wan DS, Pan ZZ, Zhou ZW. Correlation analysis between loss of heterozygosity at chromosome 18q and prognosis in the stage-II colon cancer patients. *Chin J Cancer* 2010; **29**: 761-767 [PMID: 20663324]
18 **Zheng HT**, Peng ZH, Zhou CZ, Li DP, Wang ZW, Qiu GQ, He L. Detailed deletion mapping of loss of heterozygosity on 22q13 in sporadic colorectal cancer. *World J Gastroenterol* 2005; **11**: 1668-1672 [PMID: 15786547]
19 **Zhou CZ**, Qiu GQ, Fan JW, Wang XL, Tang HM, Huang L, Sun YH, Peng ZH. Refined mapping of loss of heterozygosity on 1q31.1-32.1 in sporadic colorectal carcinoma. *World J Gastroenterol* 2008; **14**: 1582-1587 [PMID: 18330952 DOI: 10.3748/wjg.14.1582]
20 **Wan J**, Li H, Li Y, Zhu ML, Zhao P. Loss of heterozygosity of Kras2 gene on 12p12-13 in Chinese colon carcinoma patients. *World J Gastroenterol* 2006; **12**: 1033-1037 [PMID: 16534842 DOI: 10.3748/wjg.v12.i7.1037]
21 **Cacev T**, Jokić M, Spaventi R, Pavelić K, Kapitanović S. Loss of heterozygosity testing using real-time PCR analysis of single nucleotide polymorphisms. *J Cancer Res Clin Oncol* 2006; **132**: 200-204 [PMID: 16283382 DOI: 10.1007/s00432-005-0051-y]
22 **Vogelstein B**, Fearon ER, Kern SE, Hamilton SR, Preisinger AC, Nakamura Y, White R. Allelotype of colorectal carcinomas. *Science* 1989; **244**: 207-211 [PMID: 2565047 DOI: 10.1126/science.2565047]
23 **Ozaslan M**, Aytekin T. Loss of heterozygosity in colorectal cancer. *Afr J Biotechnol* 2009; **8**: 7308-7312
24 **Mao X**, Hamoudi RA, Talbot IC, Baudis M. Allele-specific loss of heterozygosity in multiple colorectal adenomas: toward an integrated molecular cytogenetic map II. *Cancer Genet Cytogenet* 2006; **167**: 1-14 [PMID: 16682279 DOI: 10.1016/j.cancergencyto.2005.08.030]
25 **Harfe BD**, Jinks-Robertson S. Mismatch repair proteins and mitotic genome stability. *Mutat Res* 2000; **451**: 151-167 [PMID: 10915870 DOI: 10.1016/S0027-5107(00)00047-6]
26 **Kerr DJ**, Midgley R. Defective mismatch repair in colon cancer: a prognostic or predictive biomarker? *J Clin Oncol* 2010; **28**: 3210-3212 [PMID: 20498404 DOI: 10.1200/JCO.2010.28.9322]
27 **Fransén K**, Klintenäs M, Osterström A, Dimberg J, Monstein HJ, Söderkvist P. Mutation analysis of the BRAF, ARAF and RAF-1 genes in human colorectal adenocarcinomas. *Carcinogenesis* 2004; **25**: 527-533 [PMID: 14688025 DOI: 10.1093/carcin/bgh049]
28 **Helleday T**. Pathways for mitotic homologous recombination in mammalian cells. *Mutat Res* 2003; **532**: 103-115 [PMID: 14643432 DOI: 10.1016/j.mrfmmm.2003.08.013]
29 **Aylon Y**, Kupiec M. New insights into the mechanism of homologous recombination in yeast. *Mutat Res* 2004; **566**: 231-248 [PMID: 15082239 DOI: 10.1016/j.mrrev.2003.10.001]
30 **von Kleist S**, Chany E, Burtin P, King M, Fogh J. Immunohistology of the antigenic pattern of a continuous cell line from a human colon tumor. *J Natl Cancer Inst* 1975; **55**: 555-560 [PMID: 1159834]
31 **Agrez MV**, Chua FK, Fagan K, Heath JW, Ferguson NW. A human colon cancer cell line established from collagen matrix cultures transplanted into nude mice. *Immunol Cell Biol* 1991; **69** (Pt 3): 205-213 [PMID: 1959934 DOI: 10.1038/icb.1991.30]

P- Reviewer: Sahu RP **S- Editor**: Ma N **L- Editor**: Rutherford A **E- Editor**: Zhang DN

Published by **Baishideng Publishing Group Inc**
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ISSN 1007-9327
35>