Published in final edited form as:
J Carcinog Mutagen. 2014 ; 5: . doi:10.4172/2157-2518.1000165.

Genomic Instability and Cancer

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Abstract

Genomic instability is a characteristic of most cancer cells. It is an increased tendency of genome alteration during cell division. Cancer frequently results from damage to multiple genes controlling cell division and tumor suppressors. It is known that genomic integrity is closely monitored by several surveillance mechanisms, DNA damage checkpoint, DNA repair machinery and mitotic checkpoint. A defect in the regulation of any of these mechanisms often results in genomic instability, which predisposes the cell to malignant transformation. Posttranslational modifications of the histone tails are closely associated with regulation of the cell cycle as well as chromatin structure. Nevertheless, DNA methylation status is also related to genomic integrity. We attempt to summarize recent developments in this field and discuss the debate of driving force of tumor initiation and progression.

I. INTRODUCTION

The maintenance of genomic stability is essential for cellular integrity to prevent errors from DNA replication, endogenous genotoxic stress such as reactive oxygen species (ROS) from cellular metabolism, and exogenous carcinogen insults; for example, ultraviolet light, ionizing radiation or DNA damaging chemicals. It is believed that tumor initiation and progression result from acquired genomic alteration within the original normal cells, and selection of more aggressive sub clones as an aftermath(Nowell 1976). Tumor cell population appears to be more genetically unstable than normal cells. The genomic instability provides individuals a shorter cell cycle and/or an advantage of bypassing intracellular and immunological control systems, thereby give cancerous cells a growth advantage and being selected as malignantly transformed cells. Much research has been directed toward genomic instability to understand and control the initiation and progress of tumors in hope of conquering cancer, a worldwide leading cause of death.

Genomic instability includes small structure variations such as increased frequencies of base pair mutation, microsatellite instability (MSI), as well as significant structure variation such

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as chromosome number or structure changes, which is also called chromosome instability (CIN)(Al-Sohaily et al. 2012, Roschke and Kirsch 2010). The mechanisms underlying the origin of these instabilities still remain elusive, but there are several hypotheses trying to explain the driving force of tumor initiation and progression through genomic instability. The major ones include (1) mutator phenotype results from loss of gene function and (2) oncogene induced DNA replication stress model (Loeb 1991, 2001, Negrini et al. 2010). Here in this chapter, we are going to discuss the evidence supporting or disputing these hypotheses and new research findings in this area.

II. GENOMIC INSTABILITY

A. Increased Frequencies of Base Pair Mutation

Evidence has been found in hereditary cancers that loss of function of DNA repair genes will cause increased frequencies of base pair mutation. For example, hereditary MYH-associated polyposis, in which biallelic germline mutations in *MYH*, a DNA base excision repair (BER) gene, results in increased G•C to T•A transversion frequencies and cancer (Al-Tassan et al. 2002).

This evidence along with MSI found in other hereditary DNA damage repair gene mutation cases have indicated that loss of genomic integrity maintenance genes might be a cause of genomic instability as well as the initiation of cancer. It has been proposed that an early step in tumor progression is the expression of a mutator phenotype resulting from mutations in genes that normally function in the maintenance of genetic stability (Loeb 2001).

B. MSI

Microsatellites are simple tandem nucleotide repeats, repetitive motifs of 1 to 6 nucleotides, scattering widespread the human genome (Ellegren 2004). MSI has been detected in many solid malignancies. It is most commonly found in hereditary malignancies such as the hereditary nonpolyposis colorectal cancer syndrome (HNPCC) (Aaltonen et al. 1993). MSI has also been found in sporadic colorectal, stomach, endometrial and ovarian cancer samples. A literature analysis shows MSI may indicate a favorable prognosis in colorectal, gastric, pancreatic and probably oesophageal cancers but a poor prognosis in non small cell lung cancer. In clinical studies colorectal cancers demonstrating MSI respond better to chemotherapy while *in vitro* studies using MSI positive cell lines show resistance to radiotherapy and chemotherapy (Lawes et al. 2003).

Microsatellite integrity in the genome is believed to be maintained by the mismatch repair (MMR) system, which corrects single base mismatches and insertion-deletion loops on the nascent DNA strand (Kunkel 1995). It is generally accepted that MSI is largely attributable to the failure of repairing insertion-deletion loops arising from replication slippage (Genschel et al. 1998).

C. CIN

Chromosome instability describes an increased rate of chromosome missegregation in mitosis resulting in an incorrect chromosome number and/or abnormal chromosome

structure (Rao et al. 2009). Although CIN has been long recognized as a hallmark of a majority of tumors, it remains inconclusive if CIN is an early step or a final demonstration of cancer progression.

Equal segregation of chromosomes during mitosis is pivotal for the maintenance of genomic stability. Failure of accurate chromosome segregation inevitably leads to cell death or malignant transformation. Accurate chromosome segregation during cell division is monitored and safeguarded by several closely linked yet distinctly different molecular machineries.

III. CARE TAKER GENES AND PATHWAYS INVOLVED IN GENOMIC STABILITY MAINTENANCE

A. DNA Damage Check Point

The p53 tumor suppressor serves as a central node in a complex signal transduction network known as the p53 pathway, which has evolved as a major defense barrier against cancer. This pathway recognizes diverse forms of oncogenic stress within the cellular environment and translates them into appropriate cellular responses to minimize tumorigenic consequences. In response to stress, p53 halts cell proliferation to prevent the propagation of DNA damage and/or directly helps in its repair. Activated p53 induces programmed cell death (apoptosis) or senescence as a last attempt to avoid possible malignant transformation when the damage is too severe and beyond repair. (Efeyan et al. 2006, Zhang et al. 2011).

The ataxia telangiectasia-mutated (ATM) protein is a cellular serine/threonine kinase that plays a key role in mediating the cellular response to DNA damage (Bhatti et al. 2011). In response to DNA damage, ATM gets phosphorylated at Ser-1981 and activated. The activated ATM phosphorylates multiple substrates including p53, γH2AX and Chk2 (Smith et al. 2010). ATM-mediated phosphorylation of p53 on serine 15 plays a critical role in activating p53 function in response to DNA damage (Zhang et al. 2011).

p53 not only responds to DNA damage but also oncogenic stress. This reaction is through its upstream p19Arf and MDM2 pathway. Arf is not usually expressed in normal tissues but is induced by sustained and elevated proliferation signals that may stem from oncogenic stress (Lowe and Sherr 2003). For example, physiologic thresholds of Myc and Ras signaling do not activate Arf gene expression, but overexpression of Myc and oncogenic Ras induces Arf (Palmero et al. 1998, Zindy et al. 1998). Induced Arf then antagonizes Mdm2 activity to stabilize p53 which leads to cell cycle arrest or apoptosis. This process counteracts oncogenic proliferation signaling by inducing growth arrest or apoptosis in cells that might otherwise give rise to tumors.

B. DNA Repair Pathway

DNA damage may predispose individuals to increased tumorigenesis when left unchecked. Therefore, there are multiple evolutionarily conserved pathways within cells that respond to such errors by recruiting DNA repair processes or initiating apoptosis. The process of DNA repair is closely coupled with the DNA damage response (DDR), which involves the

recruitment and localization within distinct nuclear foci of DNA damage sensors, mediators, transducers and effecter proteins (Polo and Jackson 2011). Currently, several DNA repair pathways are known to be recruited following DNA damage. In general, can be listed as nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), DNA double strand break repair (DSBR).

The nucleotide excision repair (NER) involves more than 25 proteins that function to replace modified nucleotides with the correct ones(Mitchell et al. 2003). DNA lesions formed by UV light, exogenous chemicals such as benzo (a) pyrene, aflotoxin B1, and chemotherapeutic agents like cisplatin are usually repaired by the nucleotide excision repair system. NER operates through several steps involving recognition of the lesion site, incision of the damaged DNA strand, DNA synthesis, and finally ligation of the uncoupled flanks by specific ligase enzymes (Mitchell et al. 2003). Three distinct NER pathways, namely, global genomic repair (GGR), transcription-coupled repair (TCR), and differentiation-associated repair (DAR) have been identified (Nouspikel et al. 2006). Of these, GGR pathway functions by repairing nearly all damaged sites in the whole genome, whereas TCR is solely involved in removal of the lesions that block the transcription of the constitutively expressed genes (Tornaletti and Hanawalt, 1999). Each component of the NER pathway is important in achieving successful repair of the injured sites. Functional genetic defects in the genes of NER-associated proteins are found to be related to certain diseases such as xeroderma pigmentosum, Cockayne's syndrome, Trichothiodystrophy, and various types of cancers (Lindahl, 1974; de Boer and Hoeijmakers, 2000).

The base excision repair (BER) mechanism is based on replacement of the modified bases via deamination, methylation, and oxidation with the correct ones (Lindahl 1974). Modified bases are removed by specific DNA glycosylase enzymes that function in specific recognition and excision of the structurally changed bases from the genome. Apurinic/ apyrimidinic sites are formed following excision of the bases, and the correct bases are rapidly synthesized by polymerase delta/epsilon. Finally, remaining free ends are faithfully ligated by ligase enzymes (Jaroudi and SenGupta 2007).

The mismatch repair (MMR) system especially functions in removing base mismatches formed by exogenous and endogenous agents that cause base deamination, oxidation, and methylation. Moreover, the MMR system plays a role in repairing the base-base mismatches derived from insertions/deletions and replication errors. Replication errors are made by DNA replication machinery that incorporates approximately one wrong nucleotide per 107 additions. Unfortunately, about 0.1% of mistakes generated by DNA replication machinery cannot be repaired by MMR and may lead to genetic mutations (Li G. M. 2008). MMR system comprises basic steps including recognition of the DNA lesion, strand discrimination, excision and repair. MutS and MutL proteins participate in detecting the mismatched bases in prokaryotic cells. Similar to prokaryotic cells, MutS (MSH1–6, MLH1 and MLH3) and MutL (PMS1 and PMS2) homologues are reported to be responsible for recognizing the mismatched sites. The heterotetrameric complex created by the interaction of two different MutS and MutL homologues proteins detects the mismatched bases and certain loop structures (Sengupta et al. 2007). Following that, the mismatched base pairs are

excised by exonucleases I enzyme, and then missing nucleotides are correctly synthesized by polymerase δ enzyme (Modrich 2006).

DNA double strand breaks are repaired by the DNA double strand break repair (DSBR) system. There are two major DSB repair pathways, one is called nonhomologous end joining (NHEJ), in which broken DNA strand ends are ligated by specific ligase enzymes; the other is called homologous repair (HR). Since the NHEJ pathway lacks a homologous sequence control system, it is recognized as error-prone. Deletion, inversion, and other types of abnormalities in the genome could occur as a consequence of the NHEJ repair process (You et al. 2009). On the other hand, HR operates in an error-free manner as it repairs the broken ends dependent on the homologous DNA sequence (Jackson 2002). Which of the two pathways is chosen is basically determined by whether KU (KU70 and KU80) or RAD52 binds to the damaged region. The HR pathway initiates when the KU protein interacts with the damaged site. If the RAD52 binds to the broken ends prior to KU, the NHEJ mechanism is commenced to repair the damage (Bassing and Alt 2004).

Breivik and Gaudernack have proposed that in some tissues during some conditions, the cost of DNA repair might exceed the cost of errors (Breivik and Gaudernack 1999, 2004). This model predicts that genetic stability is configured for an optimal cost-benefit relationship; meaning natural selection is not expected to have produced the best genetic stability available in the human body, but only the best compromise of DNA repair and the cost of these systems. In tissues where proliferation rates are critical, such as the colon epithelium, any repair mechanism that delays cell division might be disadvantageous for the function of that organ.

C. Mitotic Checkpoint

In order to maintain chromosomal stability during cell division, eukaryotic cells have evolved a number of surveillance mechanisms termed checkpoints that monitor completion of essential molecular and cellular processes of one stage before entering another. The mitotic checkpoint monitors the completion of bi-orientation attachment of spindle microtubules to all condensed chromosomes before initiation of nuclear division during mitosis. A number of conserved proteins have been identified and characterized that are required for the checkpoint function. These proteins include Bub1, Bub3; Mad1, Mad2 and Mad3 (Cahill et al. 1998, Hoyt et al. 1991, Li R. and Murray 1991, Olesen et al. 2001, Weiss and Winey 1996). In addition to the orthologs of Bub and Mad families that consist of core components of the spindle checkpoint in mammalian cells, several additional gene products including Shugoshin, Aurora B, Plk1 and PP2A also play a role in spindle checkpoint control (Dai J. et al. 2006, Mistry et al. 2010, Resnick et al. 2006, Riedel et al. 2006, Takaki et al. 2008, Yao et al. 1997).

Bub1 is a serine/threonine protein kinase functioning as a master organizer of the inner centromeric region (ICR), required for recruitment of chromosomal passenger complex and Shugoshin to ICR (Roberts et al. 1994, Taylor and McKeon 1997). Bub1 promotes the assembly of outer kinetochore components including CENP-F and BubR1 (a yeast Mad3 homolog) during the cell cycle (Boyarchuk et al. 2007). An analysis of 6 cultured CIN cell lines (SW480, HT29, V400, V429, Caco2, and SW837) shows that some of the tested CIN

cell lines carried certain mitotic checkpoint genes mutation and all of them had a phenotype similar to that seen in yeast cells with genetic alterations of mitotic checkpoint genes(Cahill et al. 1998). Such results are consistent with the possibility that aneuploidy can be due to defects in mitotic checkpoint. This possibility is also supported by the fact that the expression of naturally occurring *hBUB1* mutants converted the normal checkpoint status of MSI cells to the defective type characteristic of CIN cells (Cahill et al. 1998). However, a screen for mutations of the mitotic checkpoint genes *hBUB1*, *hBUB1B*, *hBUB3* and *TTK* in six aneuploid bladder cancer cell lines and 15 human bladder tumors didn't detect mutations; loss of heterozygosity (LOH) for these genes was 6.7% of the cases; indicating that neither mutational inactivation or LOH of these mitotic checkpoint genes are common(Olesen et al. 2001).

Shugoshin, meaning “Spirit Guardian” in Japanese, serves as a protector of the centromeric cohesion in the yeast and high eukaryotes (Kitajima et al. 2004, Rabitsch et al. 2004). Suppression of Shugoshin function results in premature separation of sister chromatids in mitosis (Lee J. et al. 2008, McGuinness et al. 2005). Depletion of Sgo1 through RNA interference (RNAi), a family member of Shugoshin, results in the formation of extra centrosomal foci and premature separation of paired mother and daughter centriols (Wang et al. 2008); indicates Shugoshin gene functions in centrosome dynamics during the cell cycle (Wang et al. 2008). In consistent with Shugoshin's role in the suppression of CIN, its deregulated expression and/or activity have been found in malignant transformation and tumor development. An analysis of genes deregulated in breast cancers shows that BR-85 mRNA, which codes for human Sgo1, is over-expressed in a majority of breast cancer tissues tested and that serum antibodies against NY-BR-85 are also detected in breast cancer patients (Scanlan et al. 2001). A separate study reveals that human colorectal cancers with Sgo1 down-regulation exhibit a clinicopathological character of chromosomal instability (Iwaizumi et al. 2009). Moreover, a novel SGOL1 variant has been detected in human colon cancer (Kahyo et al. 2011). This transcript skips exon 3, leading to an early termination of the open reading frame within exon 4 (Kahyo et al. 2011). Haploinsufficiency of SGO1 results in CIN manifested as mis-segregation of chromosomes and formation of extra centrosomal foci in both murine embryonic fibroblasts and adult bone marrow cells (Yamada et al. 2012). Enhanced CIN observed in SGO1-deficient mice is accompanied by an increase in formation of aberrant crypt foci and tumor development after exposure to azoxymethane (AOM), a colon carcinogen (Yamada et al. 2012).

Aurora B is a member of the conserved protein kinases of the Aurora family (Carmena and Earnshaw 2003). It is also characterized as a chromosome passenger protein which mediates mitotic checkpoint functions during mitosis (Adams et al. 2001, Nigg 2001). The kinase activity of Aurora B is required for stable activation of the spindle checkpoint; more importantly, Aurora B is primarily responsible for phosphorylation of histone H3 serine 10 (H3S10) during mitosis (Carmena and Earnshaw 2003). In fact, H3S10 phosphorylation is the major mitosis-specific phosphorylation of histone molecules and is thought to play a role in super-condensation and supercompaction of chromosomes during mitosis in higher eukaryotic cells (Johansen and Johansen 2006).

Polo like kinases are named after POLO, a gene encoding a protein serine/threonine kinase in Drosophila (Dai W. et al. 2002). Plk1 is the best characterized member of the Polo kinase family. Depletion of Plk1 results in mitotic arrest that is partly due to alterations of important cell cycle molecules including anaphase promoting complex/cyclosome (APC/C) (Dai W. et al. 2002). During prophase, Plk1 is also involved in controlling so-called the "prophase pathway" that regulates arm cohesion of sister chromatids through direct phosphorylation of Scc1, an integral component of the cohesin complex (Wang and Dai 2005). Cohesin not only plays a major role in the regulation of sister chromatid cohesion during the cell cycle but also functions as a transcriptional insulator for the genome (Wendt and Peters 2009).

Protein phosphatase 2A (PP2A) exists primarily as a heterotrimeric complex which is composed of the scaffolding A subunit (PP2A-A), the variable regulatory subunit B (PP2A-B), and the catalytic subunit (PP2A-C) (Ingebritsen and Cohen 1983). As a serine/threonine phosphatase, PP2A regulates numerous molecular processes through dephosphorylating various substrates (Shi 2009). Recent studies indicate that PP2A also localizes centromeres during mitosis and that its activity is essential for the maintenance of centromeric cohesion of sister chromatids before anaphase entry (Clarke et al. 2005, Kitajima et al. 2006, Riedel et al. 2006, Tang et al. 2006).

D. Telomere Maintenance

Human telomeres are composed of TTAGGG tandem DNA repeats with associated proteins. Telomeres form caps that keep the ends of chromosomes from being recognized as double strand breaks, thereby prevent chromosome fusion (Holliday 2012, Londono-Vallejo and Wellinger 2012). In human, telomeres are maintained in germ cells, and shortened when somatic cells divide which limits cell proliferation. This is achieved by down regulation of telomerase. It's not a surprise to find that cancer cells at high proliferation rate can successfully maintain the length of their telomeres, most often through the expression of telomerase, only 10% of human tumors maintain telomeres through an alternative mechanism (Reddel and Bryan 2003). However, cancer cells exhibit a high rate of telomere loss at the same time, even with high levels of telomerase. A critical feature of the spontaneous telomere loss in cancer cell lines is that it occurs at a low enough frequency so that the cells do not die. Telomere loss contributes to chromosome instability and tumor cell progression (Fouladi et al. 2000, Lo et al. 2002, Sabatier et al. 2005). Excessive telomere shortening prior to the expression of telomerase can lead to chromosome fusion, which has been proposed as a mechanism for chromosome instability (Maser and DePinho 2002).

Mouse model with a depletion of the RNA component of telomerase (mTERC) exhibit progressive telomere shortening and ultimately chromosomal instability (end-to-end fusions) as a result of ageing and successive generational mating (Lee H. W. et al. 1998, Rampazzo et al. 2010). Telomere shortening in ageing $mTERC^{-/-}$ mice is associated with increased rates of cancer, suggesting that the genetic instability associated with telomere dysfunction can facilitate transformation *in vivo*(Rudolph et al. 1999). On the other hand, in cultured human cells, high level expression of telomerase facilitates malignant transformation (Hahn et al. 1999).

IV. HYPOTHESES OF EARLY STEPS IN TUMOR PROGRESSION AND THEIR SUPPORTS

With the research techniques dramatically improved, more gene mutations, gains and losses in human tumors are found. They are usually large and chromosome rearrangements often encompass many genes that do not contribute to tumorigenesis. Therefore, differentiating "driver" from "passenger" requires validation.

A. Loss of Gene Function Leads to Mutator Phenotype

The mutator phenotype hypothesis states that genomic instability is present in precancerous lesions and drives tumor development by increasing the spontaneous mutation rate (Fig. 1) (Loeb 1991, 2001). The identification of mutations in DNA repair genes in hereditary cancers provides strong support for the mutator hypothesis (Nikitin and Luftig 2012, Singh et al. 2012). Proponents of the mutator hypothesis attribute the genomic instability in precancerous lesions to mutations in caretaker genes; that is, genes that primarily function to maintain genomic stability (Loeb 1991, 2001). Indeed, in inherited cancers, germ line mutations targeting DNA repair genes are present in every cell of the patient's body. Thus, a single event, loss of the remaining wild type allele, would lead to genomic instability and drive tumor development, as predicted by the mutator hypothesis.

Another example illustrating this point of view is Bloom syndrome, which results in an increased predisposition to spontaneous tumor formation in all tissues, even those that are not directly exposed to tumorigenesis insults. Bloom syndrome is caused by inactivation of a RecQ helicase family, which plays an important role in resolving HR intermediates and controlling blocked replication forks, as well as telomere maintenance (Singh et al. 2012).

A series of mutation screening of familial breast cancer patients and Fancony anemia patients who are charactized by chromosome instability has found mutations in *CHEK2*, *ATM*, *NBS1*, *RAD50*, *BRIP1*, and *PALB* are associated with doubling of breast cancer risks. Among these genes, most are involved in the DDR pathway (Walsh and King 2007).

The study of viral infectious cancer etiology show some support to the mutator phenotype hypothesis from chromosome instability point of view. In this case, virus infection attenuates mitotic checkpoint and DDR pathway, causing chromosome instability in precancerous lesions. Accumulated aneuploid cells have the potential to promote tumorigenesis (Nikitin and Luftig 2012). Several viral proteins precisely target mitotic checkpoint with potentially catastrophic consequences on the chromosome stability of surviving cells. HTLV-1 Tax abolishes host cell mitotic checkpoint by directly targeting and prematurely activating the APC/C (Liu et al. 2005), as well as Mad 1 resulting in highly aneuploid cells (Jin et al. 1998). Similarly, the Epstein-barr virus protein EBNA3C is capable of decreasing the levels of the mitotic checkpoint protein BubR1 (Gruhne et al. 2009, Leao et al. 2007). However, virus infection usually affects multiple machineries in host cells. These altered machineries act in concert to help virus proliferate, just like what has been found in cancer cells.

B. Oncogene Induced DNA Replication Stress Model

Oncogene induced DNA replication stress model argue against the mutator phenotype model by putting oncogene rather than mutation of genome care taker genes as the driving force of tumor initiation (Fig. 2). The barriers against tumor initiation can be categorized into (1) activation of the DNA damage checkpoint and thereby induce apoptosis or cell cycle arrest (Bartkova et al. 2005, Gorgoulis et al. 2005) (2) Arf- mediated oncogene-induced senescence (Braig et al. 2005, Zindy et al. 1998). From oncogene induced DNA replication stress model, the genomic instability is first generated by DNA replication stress due to elevated proliferation rate. The cells lack of any of these two barriers will be selected due to their growth advantage thereby develop an even larger scale of genomic instability.

This idea is supported by evidence that uncontrolled E2F activity activates an ATM-dependant growth-suppressive DDR, which means elevated DNA replication indeed induces stress which is responded by DDR(Powers et al. 2004, Rogoff et al. 2004). An *in vitro* model based on the critical roles of AR in prostate development and tumor progression shows that abnormally activated growth signal is able to induce DNA breaks and genomic instability rapidly(Lin et al. 2009). Nevertheless, Halazonetis group has shown that expression of oncogenes leads to DNA replication stress and genomic instability, explaining the high frequency of p53 mutations in human cancers (Gorgoulis et al. 2005, Negrini et al. 2010).

V. DNA PROMOTER METHYLATION AND HISTONE MODIFICATION

The hypotheses and evidence considering genomic instability discussed above might be overrated and yet underrated. The mutations found in these genes and pathways may not be potent enough to impair protein function thereby induce genomic instability, yet epigenetic change alone is enough to dramatically change functional protein level for genome integrity maintenance. Hypermethylation and/or hypomethylation of promoter or first exon of cancer related genes (tumor suppressor genes or oncogenes) may mimic the effect of mutations.

Long interspersed nuclear element (LINE) is a kind of retrotransposon. During retrotransposition, LINE DNA is transcribed to RNA and processed. The processed RNA is reverse-transcribed by the LINE-1 encoded reverse transcriptase and the cDNA copy is inserted into a new chromosomal location(Luning Prak and Haoudi 2006). LINE is heavily methylated in all cell types in mammals. Hypomethylation of LINE induces transcriptional activation of these sequences, which contributes to genomic instability and facilitates tumor progression. The methylation of CpG dinucleotides in LINE and other retrotransposon sequences hosts defense against retrotransposon activation (Bestor 2000).

Accumulating evidence indicates that remodeling of chromatin structures are crucial for establishing stable epigenetic states that restrict or permit chromosome rearrangements in a number of diseases such as cancer and other syndromes involving chromosomal instability(Bartova et al. 2008, Slotkin and Martienssen 2007). In eukaryotic cells, chromatin structures are dynamic and need to be constantly altered to accommodate DNA replication, gene transcription and stress responses. Alterations in the interaction between DNA and histones, together with the recruitment of nuclear proteins, cause changes in the chromatin

structure, a process which is commonly referred to as chromatin remodeling (Hogan and Varga-Weisz 2007). Histone tails are subject to multiple post-translational modifications such as phosphorylation, methylation, acetylation, and ubiquitination. It has been suggested that the combination of these distinct covalent modifications of histones constitutes the “the histone code” that regulates a variety of cellular processes, including mitosis and meiosis (Xu et al. 2009). Covalent histone modifications are essential for chromatin remodeling and they also impact mitosis through modulation of the activity and subcellular localization of proteins important to spindle checkpoint regulation (Koch et al. 2008, Perera and Taylor 2010, Yamagishi et al. 2008). For example, tri- methylation of histone H3 lysine 9 (H3K9) is tightly related to heterochromatinization (Elgin 1996) and recruitment of checkpoint proteins to centromeres (Koch et al. 2008, Perera and Taylor 2010, Yamagishi et al. 2008). Recent studies have shown that many of the components that are critical for spindle checkpoint control such as Bub1, are also involved in regulating chromatin remodeling (Kawashima et al. 2010). In fact, these proteins seem to coordinate histone modifications and chromatin remodeling with cell cycle progression during mitosis.

VI. CONCLUSION REMARKS

In spite of tremendous knowledge we've accumulated about genomic integrity, the ubiquitous mechanism of tumor initiation still remain elusive. It's still possible that all the hypotheses are valid in different settings. Despite of the unsettled debate of “driver” and “passenger” in tumor initiation and genomic instability, the research effort has lead to chemotherapeutic drugs used in clinical settings to target genomic instability related molecules. Great progress has been made to explore the possibility to activate checkpoints that monitor genomic integrity.

Acknowledgement

We would like to thank Nedda Tichi for her administrative assistance. This work was supported by NIEHS ES000260

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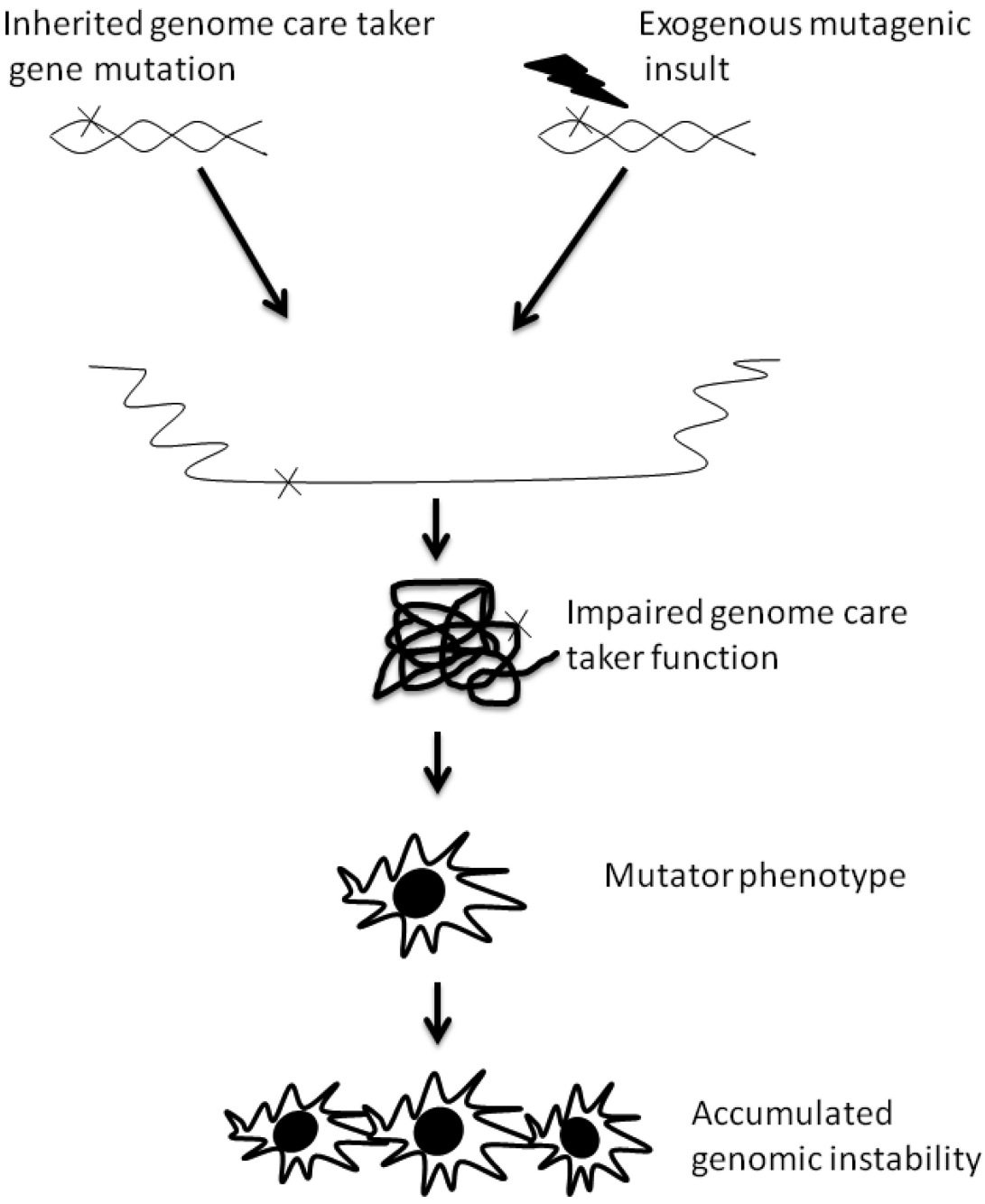

Figure. 1. Mutator phenotype hypothesis

Mutator phenotype hypothesis states that genomic instability drives tumor development by increasing the spontaneous mutation rate.

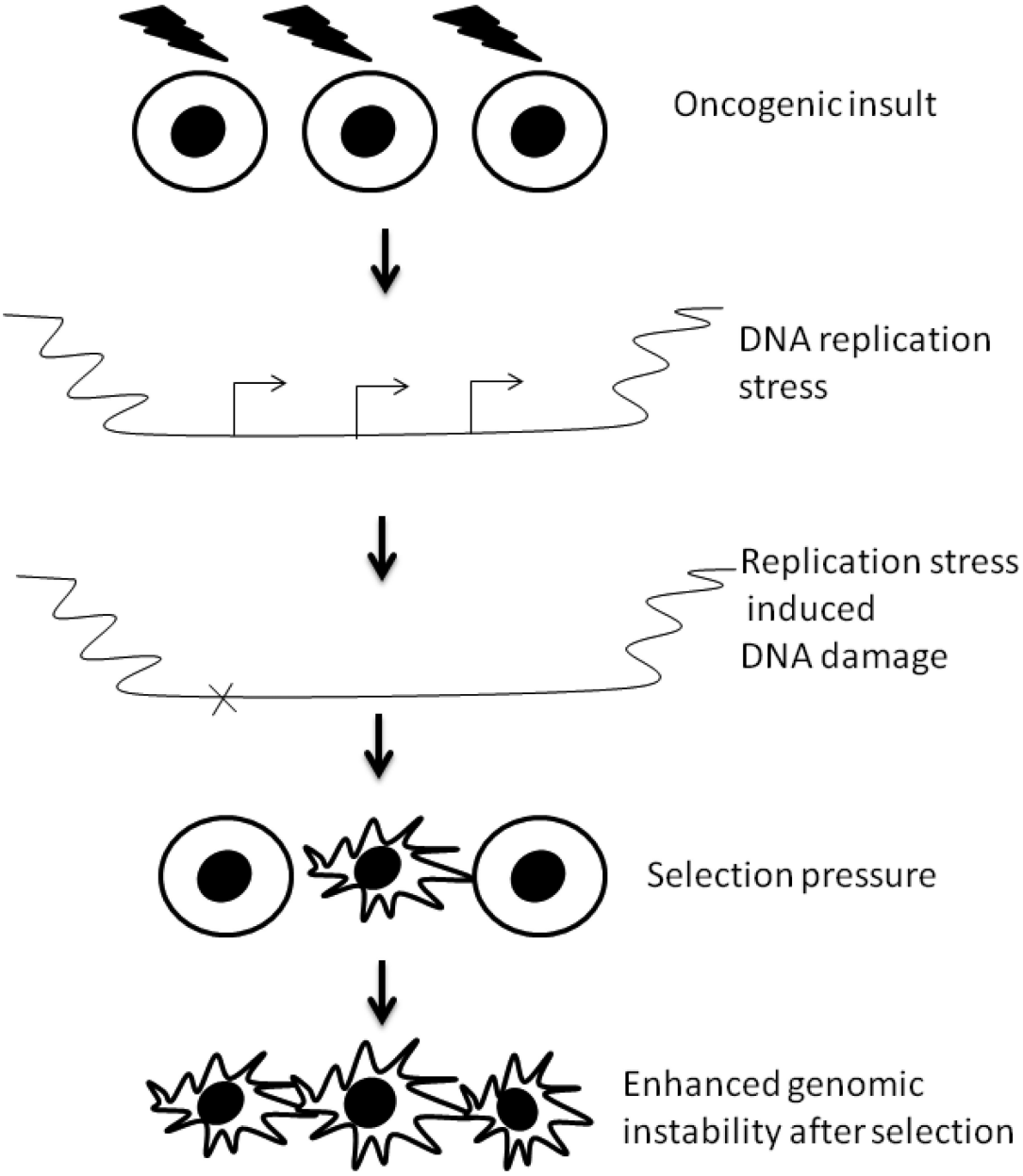

Figure. 2. Oncogene induced DNA replication stress model

Oncogene induced DNA replication stress model argue against the mutator phenotype model by putting oncogene rather than mutation of genome care taker genes as the driving force of tumor initiation.