

Review Article

Cancer Prevention, the Need to Preserve the Integrity of the Genome at All Cost

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INTRODUCTION

Current studies on the human genome show that it consists of about 22,000 genes. They are transferred from one organism to another and code different proteins and enzymes that carry out biochemical reactions of life. However, cell growth and proliferation may become abnormal when genes responsible for their normal proliferation are lost.^[1-3]

In 1944, Deoxyribonucleic acid (DNA) was proven to be the chemical entity, in which genetic information of cells is carried in. Years on, Watson and Crick showed with clarity the structure of the DNA. To avoid mutations, DNA replication is done with high fidelity.^[1] Replication errors may arise during DNA synthesis from mutagenic agents such as chemicals, viruses, ionizing, and ultraviolet radiations which constantly attack the DNA.^[4] Are we all going to succumb to malignant diseases that may develop

ABSTRACT

Introduction: The entire genetic information carried by an organism makes up its genome. Genes have a diverse number of functions. They code different proteins for normal proliferation of cells. However, changes in the base sequence of genes affect their protein by-products which act as messengers for normal cellular functions such as proliferation and repairs. Salient processes for maintaining the integrity of the genome are hinged on intricate mechanisms put in place for the evolution to tackle genomic stresses. **Aim:** To discuss how cells sense and repair damage to their deoxyribonucleic acid (DNA) as well as to highlight how defects in the genes involved in DNA repair contribute to cancer development. **Methodology:** Online searches on the following databases such as Google Scholar, PubMed, Biomed Central, and SciELO were done. Attempt was made to review articles with keywords such as cancer, cell cycle, tumor suppressor genes, and DNA repair. **Results:** The cell cycle, tumor suppression genes, DNA repair mechanism, as well as their contribution to cancer development, were discussed and reviewed. **Conclusion:** Knowledge on how cells detect and repair DNA damage through an array of mechanisms should allay our anxiety as regards cancer development. More studies on DNA damage detection and repair processes are important toward a holistic approach to cancer treatment.

KEYWORDS: Cancer, deoxyribonucleic acid, genes, genome

from these events knowing that mutations tip the balance of the perturbed genome in favor of malignancy?

Vast literature on how cells maintain the integrity of its genome exists. It can be justifiably argued that available literature on different mechanisms in humans to avert malignancies has outpaced the speed of proliferation of even the most aggressive tumors. Thus, an overview of these mechanisms with emphasis on how cells sense, repair DNA damage, and how defects in genes involved in DNA repair contribute to cancer development will pave way for easier understanding of how the integrity of the genome is maintained.

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METHODOLOGY

Online searches on the following databases such as Google Scholar, PubMed, Biomed Central, and SciELO, were done. Attempt was made to review articles with keywords such as cancer, cell cycle, tumor suppressor genes (TSGs), and DNA repair. Articles that published from 2000 till date were reviewed.

RESULTS

The Cell Cycle

Phases of the cell cycle have been well known for about 40 years. Key molecular steps on how cells grow and divide have been shown.^[5] The cell cycle is made up of phases comprised of DNA replication and cell division. These processes are carefully regulated in normal cells. Phases of the cell cycle is divided into G1, S (where DNA replication occur), second gap phase G2, and mitosis phase. During mitosis, two daughter cells which can begin a new cell cycle are produced. G0 phase accounts for cells in quiescent forms.^[6,7]

In late G1 phase, cells acquire the ability to go through the cell cycle with relative independence from extracellular signals. This point in the late G1 is called restriction point. Loss of restriction point possibly is a universal step toward cancer development. Simply put, dysfunction of G1 cell cycle progression promotes tumor formation.^[8-10]

Cell cycle checkpoints

Each phase of the cell cycle has monitoring mechanisms known as checkpoints This is to say that cell cycle checkpoints are genetically determined signaling pathways that delay execution of certain cell cycle events until earlier events are deemed satisfactory.^[11-13] The CDC2 gene discovery in the 1960s turned out to be a gold mine of information on cell cycle regulation. It codes a kinase, an enzyme that participates in many aspects of the cell function. The engine of the cell cycle is fueled by different proteins and enzymes: cyclins, cyclin-dependent kinases (CDKs), and cyclin-dependent kinase inhibitors (CDKIs), which are responsible for the progression of the cell cycle from one phase to another and also inhibiting the cell cycle.^[1,3] See Figure 1. When coupled with an associate cyclin, CDKs phosphorylate and activate protein products of different TSGs, CDKI genes, and DNA repair genes.

During interphase, DNA damage initiates cell cycle arrest and allows time for repair. The primary goal of different checkpoints to genomic stress is to inactivate CDKs or maintain them in an inactivate state until the cell is deemed fit to progress further into the cell cycle.^[14] Evidence has also shown that perturbation of these is another step closer to cancer development.^[15]

Apart from cell cycle progression and inhibition, a labyrinth of cyclins, CDKs, and CDKIs also participates in DNA repair. For clarity and brevity, we concentrate on some TSGs active at each checkpoint of the cell cycle. It is important to note that there may be some overlap of these TSGs at different checkpoints of the cell cycle.

These genes work in a concerted fashion by assisting one another and acting as a backup in halting the progression of the cell cycle at different check points at the event of DNA damage. They may also initiate DNA repair by signaling recruitment of protein complexes for repairs at the site of DNA damage. TSGs may also be viewed as housekeepers or gatekeepers in relation to their functions. The housekeepers orchestrate DNA repair by recruiting DNA repair proteins at the site of DNA damage along with other functions. The gatekeepers initiate apoptosis or senescence to eliminate cells whose DNA damage is beyond repair. However, some TSGs such as p53 have both housekeeper and gatekeeper functions.

G1 phase and related tumor suppressor genes

A lot is known about the retinoblastoma gene (Rb) as it was the first TSG to be discovered. When activated in response to DNA damage, pRb the protein product of Rb gene put brakes on how the cell advances into the cell cycle by binding to the transcription factor E2F in the hypophosphorylated form. pRb is accountable for majority of G1 checkpoint activities.^[16,17] A study from assay protocols in wild-type Rb in Rb-mutant cells demonstrates that Rb can stop the cell cycle and even induce senescence in cells with badly damaged DNA.^[18]

The ataxia telangiectasia mutated (ATM) gene has its central role in the repair of double-strand DNA breaks. Its response to DNA damage includes numerous processes with recognition of damaged DNA, recruitment of repair proteins, as well as signaling to different cell cycle checkpoints.^[19,20]

When activated, ChK2 gene encoded protein is known to inhibit Cdc25C phosphatase preventing entry into mitosis and cell cycle arrest in G1. A mutation in this gene is a predisposition to familial breast cancers as well as other types of malignancies.^[19,20] When activated, ChK2 gene encoded protein is known to inhibit CDC25C phosphatase preventing entry into mitosis and cell cycle arrest in G1. A mutation in this gene is a predisposition to familial breast cancers as well as other types of malignancies.^[21,22]

Numerous academic write ups refer to p53 as the master guardian of the genome, molecular policeperson, or executioner. It brings about its tumor suppressor activity in part by upregulating CDKI p21, thereby stopping the

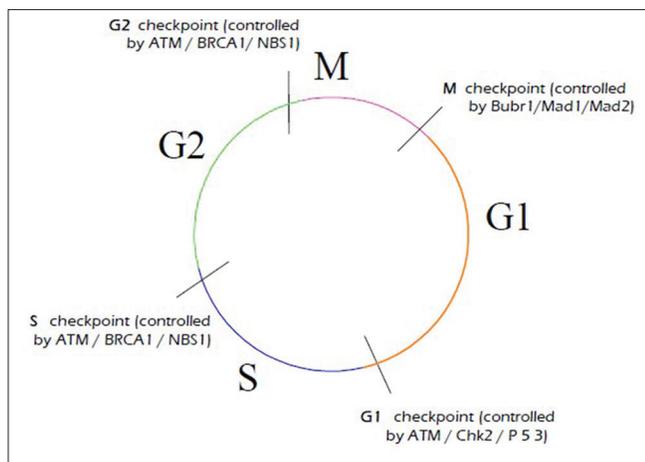


Figure 1: Tumor suppressor gene active at different cell cycle checkpoints

cell cycle in the event of DNA damage and giving the cell an opportunity to repair the damage. If the damage is beyond repair, the cells undergo a form of programmed cell death known as apoptosis which is vital in the elimination of damaged cells. Both p53 and p21 appear to be essential for maintaining G1 and G2 checkpoints.^[16,23,24] Different cytotoxic agents used in treating cancers can induce the expression of p53 and ultimately give rise to apoptosis in these cells. Furthermore, p53 involvement in regulating the expression of proteins, especially the Bcl-2 family, which are also involved in the process of apoptosis, is worthy of note.^[25]

S/G2 phase and related tumor suppressor genes

Similar TSGs play different roles at S and G2 checkpoints. It is still critical that cells in need of repair at G2 and S checkpoints get repaired because the probability that the cells with damaged DNA get to the end of the cell cycle increases as cells advance into the cell cycle.

The discovery of BRCA1 and BRCA2 genes raised questions as of whether they should be classified as TSGs. They are actually involved in DNA repair and maintenance of genomic integrity and are therefore considered as “caretakers” rather than “gatekeepers” in respect to other TSGs.^[1] They are widely expressed in different tissues during the S and G2 phases.^[26] Nullizygous BRCA1 or BRCA2 embryos die around the time of gastrulation. Surprisingly, these embryos reveal a proliferative defect and induction of the p53-dependent cell cycle inhibitor p21.^[27]

Identification of nibrin or Nijmegen breakage syndrome 1 (NBS1) gene highlighted the molecular mechanisms of double-strand break (DSB) repair in response to DNA damage and senescence if the need arises.^[28,29] The first evidence of possible association NBS1 carriers and cancer

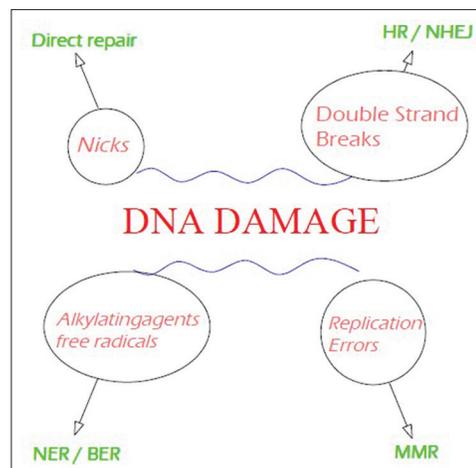


Figure 2: Different types of deoxyribonucleic acid damage and associated repair mechanisms

risk came from family data studies, highlighting that blood relatives of NBS patients with the 657del5 founder mutation had a high probability to develop malignancy.^[30] On DNA damage, NBS1 protein products recruit and forms multimeric repair complexes and channel them toward the site of DNA damage. These processes correspond to S and G2 cell cycle checkpoints.^[31]

M phase checkpoint and related tumor suppressor genes

Mitosis checkpoint is the last checkpoint of the cell cycle. A biological system with carefully designed backups to avert malignancies as the cell cycle is most likely to fail on exhaustion of these backups, irrespective of how tightly regulated they are.

Prior the mitosis phase in the cycle, the M checkpoint also validates the integrity of the cell before it goes through mitosis or meiosis to avoid propagating genetic defects to daughter cells. The centrosome as the primary microtubule-organizing center plays an essential role in maintaining chromosome stability. Aurora kinases: BubR1, Mad1, and Mad2 among other kinases control the M checkpoint.^[32] BubR1 protein kinase (PK) is central to the mitotic checkpoint. Microtubules of cells in need of repair recruit BubR1 and Mad1 and get attached to kinetochores giving rise to an inhibitory effect mitotic arrest as a consequence.^[33]

DEOXYRIBONUCLEIC ACID REPAIR

Detection of DNA damage is a crucial step in maintaining the integrity of the genome. Repair of the damage is another important factor. Eukaryotic cells use multiple pathways to maintain genomic integrity in response to DNA damage.^[34] The different mechanisms employed in DNA repair are direct repair, base excision repair (BER), nucleotide excision repair (NER), and repair of

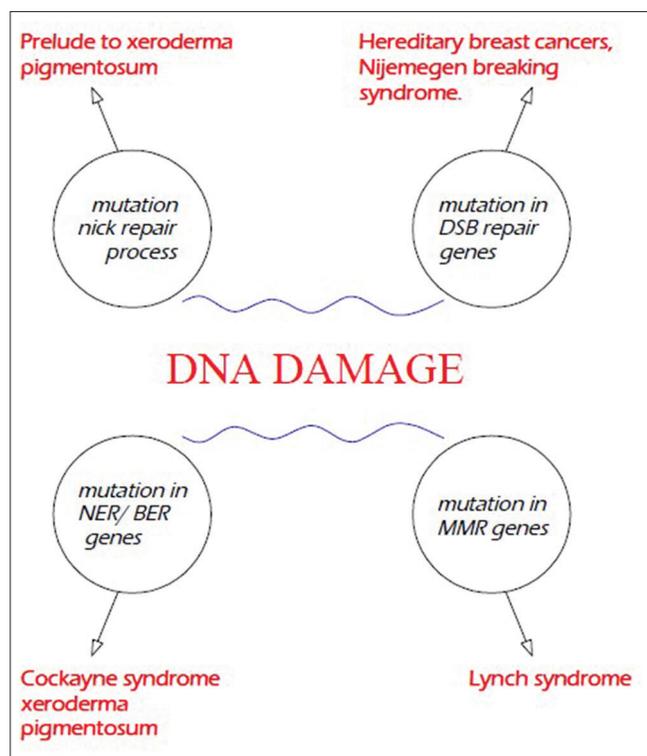


Figure 3: Defects in deoxyribonucleic acid repair gene and associated cancers to these defects

DSBs (which can be homologous or nonhomologous).^[35] These repair mechanisms act in a similar manner in the sense that the damaged DNA is excised, re-synthesized, and ligated.^[36,37] see Figure 2.

Direct repair

Direct repair acts directly on damaged nucleotides and converting them to their original structure. Only few forms of damaged nucleotides can be repaired this way. It repairs nicks and some forms of alkylation. Nicks are repaired by direct repair only if the damage involves a broken phosphodiester bond without damage to the 5-phosphate and three hydroxyl groups of the nucleotides. Removal of miscoding alkylating lesion, e.g., O-methyl guanine is removed by O-methylguanine-DNA methyl transferase in humans.^[38]

Nucleoside excision repair

The foremost contribution of excision repair processes to recovery of cells from DNA damage was manifested from the greatly increased sensitivity of mutant cells that were defective in this repair process.^[39] NER is the major DNA repair mechanism and plays a backup to other DNA repair mechanisms. It is also a pathway for the recognition and repair of a wide range of DNA lesions.^[40,41] Transcription factor IIIH (basal transcription factor) is a ten-subunit protein complex required for unwinding of DNA for repair. Photosensitive form of trichotiodystrophy is caused by inherited mutations

of three of the subunits of basal transcription factor, an important complex in NER.^[42] NER is essential in repairing thymine–thymine dimers caused by ultraviolet light. Thymine–thymine dimers disrupt both replication and transcription of DNA. Genes such as XPA-XPG, CSA, and CSB are worthy of note in NER because they play important roles in this repair system. Furthermore, components of NER pathway were in part discovered by mutation in these genes.^[36,43]

Base excision repair

BER is the main system employed in removing nucleotides damaged by intracellular processes such as free radical oxidations and deamination of cytosine.^[37] Lesions from oxidation and deamination cause little distortion to the DNA and are tackled by BER.^[44] The altered base is hydrolyzed by a family of N-glycosidases leaving an abasic site (AP site) that is cleaved by an AP endonuclease. New DNA is synthesized at the site by a ligase, thus completing the repair.^[37,45,46]

Repair of double-strand breaks

DNA DSBs are usually secondary to harmful agents such as ionizing radiation and chemical agents.^[11] DSBs must be repaired as they bring about the disruption of genomic integrity. Two different pathways involved in DSB to the DNA are homologous recombination or nonhomologous end joining (HR and NHEJ).^[47-49] Response to DSBs is a complex signaling network which activates several metabolic processes with the key activator protein ATM. This targets and activates the DNA repair enzyme polynucleotide kinase/phosphate which is crucial for cellular survival after a DSB.^[50] ATM also phosphorylates a range of substrates that include p53, H2AX, BRCA1, BLM, FANCD2, and NBS1 and many others involved in repair of double-strand DNA breaks. NBS1 forms a complex with MRE11-RAD50 nuclease (mre11-rad50-nbs1 [MRN] complex) and recruits these proteins to the site of DSBs in both HR and NHEJ. Furthermore, MRN complex defects in cells make them very sensitive to DNA-damaging agents.^[11,51,52] Underlying mechanism in aforementioned types of DSBs in the DNA is similar in respect to their associated DNA repair genes and protein complexes. A major difference is use of available broken end of a DNA segment to serve as a repair template for homologous repair and not for nonhomologous repair.

Nonhomologous end joining

It is a major pathway for repair of DNA DSBs of somatic cells.^[53] Three mechanisms have been defined by studies for NHEJ: single strand, template directed, and postrepair ligations. Key biochemical enzymes and proteins involved in NHEJ include DNA ligase

IV, Pol X family DNA polymerases, and Ku proteins.^[54,55,56] A key role in NHEJ is played by DNA-dependent PK (DNA-PK) which has a DSB recognition role and activation of other components involved in the repair. DNA-PK is made up of a Ku protein and a catalytic sub-unit. Ku protein has a strong affinity for DNA broken ends. It holds them together while the catalytic subunit of DNA-PK is activated as DNA ends are processed, aligned, and ligated by the enzyme DNA ligase IV and its binding partner XRCC4.^[57] Joining of broken DNA ends in NHEJ has little or no base pairing. This makes this repair pathway error prone.^[58-60]

Homologous recombination

A ubiquitous process and less error prone pathway for DNA DSB repair with a highly accurate template for the process in the S or G2 phase of the cell cycle.^[61-63] Undamaged sister chromatid is used as a template for synthesizing DNA at the damaged point.^[64] When DSB occurs, ATM kinase is activated leading to MRN complex activation at the site of the damage. Rad51 and Rad54 proteins are key components of the HR machinery. MRN complex prepares a 3' tail for Rad51 nucleoprotein filament which invades the homologous duplex. Rad54 does a homologous sequence search, and the invading strand (a copy) is displaced by the 3' end of the invading sequences. Strand invasion may be one ended or two ended and converted to Rad51 nucleofilaments with both invading the homologous sequence. DNA synthesis follows one-ended filament invasion.^[11,65,66] Newly synthesized DNA dissociates from the repair template and gets attached to the broken duplex. Resulting microfilament may give rise to holiday junctions and branch migrations and must be resolved by a group of highly specialized endonucleases which catalyze cleavage of these junctions. These gaps are resolved by Rad51 and its paralogs XRCC2, XRCC3, and Rad51B.^[11,67] BRCA1 and two genes respond to DSBs. However, BRCA1 have been shown orchestrate homology directed repairs.^[68] Controlled HR is crucial for the preservation of repetitive sequences of ribosomal gene cluster because uncontrolled HR may lead to chromosome translocations, loss of heterozygosity, and deletion of repetitive sequences.^[69]

Mismatch repair

Mismatch repair (MMR) mechanism repairs copy errors made during DNA replication. Two mismatch recognition complexes found in humans are hMuts and hMutL. They both either bind to a loop or a mismatch. After recognition, other complexes post meiotic segregation increased 2 (PMS2) with their components assemble a repair complex and the DNA mismatch is removed, re-synthesized, and ligated to complete the repair.^[70]

DEFECTS IN DEOXYRIBONUCLEIC ACID REPAIR GENES AND HOW THEY CONTRIBUTE TO CANCER DEVELOPMENT

Defects in DNA repair genes are forerunners to different cancers. Mutation in MMR genes MSH1, MSH2, and MSH6 may give rise to Lynch syndrome. Lifetime risk of developing colon cancers in people with mutation in these MMR genes is about 75% by 70 years. Microsatellite instability (short-repeated segments of DNA all through the genome) is corrected by MMR process.^[71,72]

About 5%–10% of breast and ovarian cancers are believed to be hereditary with many of these secondary to germline mutations in BRCA1 and BRCA2 genes. They are vital for DSB repair by HR. Tumors deficient in these genes are very susceptible to DSB by chemotherapy.^[73,74]

NBS is rare autosomal recessive disorder increase predisposition to different cancers. Affected people have a mutation in their NBS1 gene. Therefore, they cannot evoke the MRN complex activated by protein products of the NBS1 gene when there is DNA damage. Over 90% of patients homozygous for a founder mutation in 65del5 in NBS gene appear to be more at risk with cancer development.^[75] People who suffer from xeroderma pigmentosum and Cockayne syndrome have increased susceptibility to ultra violet light induced cancers because of mutations in their XPA-XPG genes involved in NER See Figure 3.^[76,77]

CONCLUSION

Knowledge on how cells detect and repair DNA damage through an array of mechanisms should allay our anxiety as regards cancer development. However, some people may lack this ability due to some defects in their DNA repair, cell cycle regulation, and TSGs. Studies on DNA damage detection and repair processes as well as creation of inhibitors and activators these systems should be encouraged because, when cells become malignant, their compassion may be far from our reach.

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Conflicts of interest

There are no conflicts of interest.

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