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CHROMOSOMAL INSTABILITY AND DNA REPAIR MECHANISMS IN GENOME INTEGRITY MAINTENANCE

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ABSTRACT
The cellular functioning and the accurate transmission of genetic information require genome integrity. Nonetheless, chronic exposures to endogenous and exogenous stimuli cause DNA damage and chromosomal instability (CIN), which is one of the signs of most human diseases. CIN involves numerical and structural changes in the chromosomes and is intimately linked with cancer, genetic and aging. This review provides a summary of the molecular pathways involved in chromosomal instability and the molecular pathways of DNA damage response (DDR) homeostatic mechanisms. The major DNA repair processes, such as base excision repair, nucleotide excision repair, mismatch repair, homologous recombination, and non-homologous end joining are mentioned in the context of their interactions. Its role in the progression of a disease is mentioned, and the interaction between the defective DNA repair and CIN propagation is brought to light. Recent discoveries in the field of genomic technologies and experimental techniques have enhanced our cognitions of genome maintenance processes. Also, DNA repair pathways treatment, including synthetic lethality and activity of PARP, are considered. With all this, the issue with understanding the complexity of the genome stability networks still exists. On the whole, this review synthesizes existing knowledge, reveals the gaps in the research, and provides future directions related to enhancing the integrity of genomes and managing diseases.

KEYWORDS: Chromosomal instability, DNA repair mechanisms, genome integrity, DNA damage response, genomic instability, cancer genetics

1. INTRODUCTION
The role of genome integrity to the survival, development, and normal operation of all living organisms is observed because it implies adequate storage and transfer of genetic information during each division of cells (Aguilera & García-Muse, 2013; Negrini et al., 2010). Genome stability is highly needed to ensure homeostasis in cells, gene expression, and prevent mutation accumulation which can cause a disease (Hanahan and Weinberg, 2011; Tubbs and Nussenzweig, 2017). Nonetheless, the genome is constantly tested by diverse endogenous and exogenous variables that cause the damage to DNA (Ciccia and Elledge, 2010, p. 217; Zeman and Cimprich, 2014). The sources that are endogenous are reactive oxygen species that are formed in the course of the cellular metabolism, replication errors, and non-targeted base changes, whereas the exogenous factors involve ultraviolet (UV) radiation, ionizing radiation, environmental toxins, and chemical mutagens (Aguilera & García-Muse, 2013; Tubbs & Nussenzweig, These insults may lead to various forms of DNA damage, which include single-strand, double-strand, base, and bulky adducts (Ciccia, 2010; Marteijn et al., 2014). Unless DNA damage is repaired properly, it may interfere with genomic stability leading to the emergence of chromosomal instability (CIN) which is a condition that is characterized by a higher rate of chromosomal alteration (Negrini et al., 2010; Burrell et al., 2013). CIN occurs in two major manifestations: numerical chromosomal instability, where these gains or losses of entire chromosomes cause aneuploidy, and structural chromosomal instability, whereby chromosomes undergo rearrangements in the form of deletions, duplications, inversions, and translocations (Negrini et al., 2010; Jeggo & Löbrich, 2 These mutations can cause great changes in the dose of genes, interfere with the regulatory elements, and form fusion genes eventually leading to the phenomenon of genomic heterogeneity (Burrell et al., 2013; Hanahan and Weinberg, 2011). Instability on chromosome has been identified as a general characteristic of cancer

and it has also been identified as the cause of several genetic disease and ageing (Hanahan and Weinberg, 2011; Lord and Ashworth, 2012). In order to mitigate the adverse outcomes of DNA damage and maintain genome integrity, cells have developed an elegant set of surveillance and repair programs altogether referred to as the DNA damage response (DDR) (Ciccia & Elledge, 2010; Blackford and Jackson, 2017). The DDR includes the institution of damage perception, signal transduction and stimulation of suitable repair pathways, regulation of cell cycle control points and, in extreme instances, induction of apoptosis (Ciccia & Elledge, 2010; Polo & Jackson, 2011). Some of these sensor and transducer proteins, such as ataxia telangiectasia mutated (ATM), ATM- and Rad3-related (ATR), and DNA-dependent protein kinase (DNA-PK) proteins, are important in sensing initiations of DNA lesions and coordinating subsequent repair mechanisms (Blackford and Jackson, 2017; Scully et al., 2019). A variety of DNA repair mechanisms act in a concerted fashion to respond to a certain type of DNA damage. Base excision repair (BER) is mainly utilized to repair small lesions of bases and oxidative damage (Krokan and Bjoro as, 2013), whereas nucleotide excision repair (NER) is used to heal large lesions of DNA (bulky adducts) and helix-deforming lesions (Marteijn et al., 2014). Mismatch repair (MMR) is the process that maintains replication fidelity with the help of correcting the mismatches of base pairs and deletions-insertions loops (Jiricny, 2013). To fix the damages of the two strands, a homologous recombination (HR) method with a sister chromatid as a template is a repair method that is error-free and provides a faster mechanism compared to non-homologous end joining (NHEJ) (Chang et al., 2017; Ceccaldi et al., 2016). These pathways are very important in regulating and balancing genomic stability (Scully et al., 2019; Helleday, 2012). Although considerable achievements have been made in the comprehension of the mechanisms of the repair and instability of chromosomes, much information is yet to be established regarding the complexity of their interactions (Ceccaldi et al., 2016; Jeggo and Löbrich, 2015). Specifically, no one knows entirely how the defects of the DNA repair pathway interplay with the development of chromosomal instability (Burrell et al., 2013; Tubbs and Nussenzweig, 2017). Moreover, these processes are regulated context-dependently in both disease and normal cell types and are further complicated by the fact that they seem to differ across disease and cell type (Aguilera et al., 2013; Scully et al., 2019). The purpose of the review is to give a concise and encompassing review of chromosomal instability and DNA repair processes during genome structure maintenance. It summarizes existing data, outlines the essential molecular interactions, presents the existing research gaps, and elaborates on the new trends and treatment options that can be utilized to enhance the current knowledge and clinical care of the diseases related to genome instability (Lord and Ashworth, 2016; Bronder, 2021).

2. LITERATURE REVIEW: CURRENT ADVANCES IN CHROMOSOMAL INSTABILITY AND DNA REPAIR

Over the last several decades, the study of chromosomal instability (CIN) and the DNA repair process has been developed under the influence of the development of such technologies as molecular biology, genomics, and high-throughput sequencing (Aguilera & García-Muse, 2013; Tubbs & Nussenzweig, 2017). Initial pioneering research laid the groundwork of the fundamental principles of the structure, replication faithfulness, and repair of the DNA, and the importance of genome maintenance was a crucial process in cell survival (Ciccia & Elledge, 2010; Polo and Jackson, 2011). Early identification of the DNA repair pathways such as the base excision repair (BER) and the nucleotide excise repair (NER) offered an idea on how cells repair damage due to environmental and metabolic stress factors (Krokan and Bjoroas, 2013; Marteijn et al., 2014). At the same time, cytogenetic studies showed that cancer cells had chromosomal abnormalities, which then resulted in the discovery that chromosomal instability is a major characteristic of tumorigenesis (Negrini et al., 2010; Hanahan and Weinberg, 2011). Following studies added to the knowledge of CIN by separating a distinction between numerical and structural chromosomal instability and determining their etiology (Negrini et al., 2010; Burrell et al., 2013). It has been shown that mitotic checkpoint malfunction, centrosome duplication, and spindle formation are the causes of chromosome mis-segregation and aneuploidy (Burrell et al., 2013; Jeggo and Löbrich, 2015). Simultaneously, replication stress and telomere dysfunction have been considered to represent significant factors in precipitating structural chromosomal changes, both translocation and deletions (Zeman and Cimprich, 2014; Tubbs and Nussenzweig, 2017). These results have made CIN become a dynamic and multifactorial process that helps to contribute to the genomic heterogeneity and disease development (Burrell et al., 2013; Hanahan and Weinberg, 2011). The research on DNA repair has also extended the complexity of the systems of the genome maintenance (Ciccia and Elledge, 2010; Scully et al., 2019). The discovery of the mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ) pathways has offered a detailed system of comprehending the way the cells react to the various types of DNA damage (Jiricny, 2013; Chang et al., 2017; Ceccaldi et al., 2016). More current research studies have proposed complex regulatory processes in the interactions between the major proteins of ATM, ATR, BRCA1/2, and p53 that regulate the processes of DNA damage sensing, signaling, and repair (Blackford and Jackson, 2017; Lord and Ashworth, 2016). New evidence also points out the fact that alternative and backup repair mechanisms, including alternative end joining (Alt-EJ) that cause genomic instability in case of canonical pathway disruption (Chang et al., 2017; Ceccaldi et al., 2016). Notably, the recent literature focuses on close interplay between impaired mechanisms of repairing DNA damage and the formation of chromosomal instability (Jeggo, 2015, and Lobrich, 2017). The interference with HF repair pathways, especially the homologous recombination, has been revealed to trigger error-prone repair events, which would persist in the development of chromosomal aberrations (Scully et al., 2019; Ceccaldi et al., 2016). Genomic and single-cell sequencing works involving high throughput have given a more in-depth look into this relationship

and found that genomic instability changes with time and plays a role in disease heterogeneity, particularly cancer (Burrell et al., 2013; Bronder, 2021). Irrespective of these developments, there are a number of limitations and gaps in the research. A lot of the research concentrates on single pathways in a vacuum without having a systems-wide view of DNA repair networks and their interactions with each other to achieve genome stability (Aguilera et al., 2013; Scully et al., 2019). Also, it is not well studied that these mechanisms are regulated by the context of various cell types and diseases (Tubbs and Nussenzweig, 2017; Jeggo and Lobrich, 2015). It is also not only that more integrative methods that employ both experimental and computational technologies are needed to establish the dynamic nature of the relationship between CIN and DNA repair (Burrell et al., 2013; Bronder, 2021). The summary of important literature on chromosomal instability and DNA repair processes has been presented in Table 1, which shows the major discoveries, methods, and limitations of the research to present a summarized perspective on the current trends in research.

Table 1. Summary of Key Literature on Chromosomal Instability and DNA Repair

Author/Year	Study Type	Focus Area	Key Findings	Limitations
Allis & Jenuwein (2016)	Review	Epigenetic regulation	Epigenetic modifications influence genome stability and repair pathways	Limited focus on CIN-specific mechanisms
Bannister & Kouzarides (2011)	Review	Histone modifications	Chromatin structure regulates DNA repair accessibility	Lacks integration with chromosomal instability
Buenrostro et al. (2015)	Experimental	Chromatin accessibility (ATAC-seq)	Genome-wide chromatin profiling aids understanding of repair dynamics	Limited direct link to CIN mechanisms
Bonev & Cavalli (2016)	Review	3D genome organization	Genome architecture influences DNA repair and stability	Mechanistic insights into CIN are limited
Argelaguet et al. (2019)	Experimental	Multi-omics analysis	Integration of epigenomics and transcriptomics reveals dynamic genome regulation	Complex data interpretation
Atlasi & Stunnenberg (2017)	Review	Epigenetic control	Epigenetic interplay regulates DNA repair pathways	Insufficient disease-specific analysis

3. Chromosomal Instability and Its Molecular Basis

3.1 Types of Chromosomal Instability

Chromosomal instability (CIN) is the accelerated rate of changes in chromosomes during cell division which results in genomic heterogeneity and impaired integrity of the genome. It is widely divided into two large types, which include numerical chromosomal instability and structural chromosomal instability and have vital roles in disease pathogenesis especially in cancer. Numerical chromosomal instability entails the loss or gain of complete chromosomes leading to the abnormal number of chromosomes which is normally referred to as aneuploidy. The disease is mainly caused by abnormalities in the process of segregation of the chromosomes during mitosis. The malfunction of the spindle assembly checkpoint, centrosomes amplification and the inappropriate attachments of the kinetochore-microtubules may cause the asymmetric distribution of the chromosomes between the daughter cells. This leads to a change of gene dosage and that distorts the balance between oncogenes and tumor suppressor genes. These disequilibria are known to cause dysfunction in the cells and tumorigenesis. Constant numerical instability also enhances the rate of genomic change, with more heterogeneity in cell populations and enhanced disease pathogenesis. Structural chromosomal instability on the other hand is the change in chromosome structure and not its number. The changes involve deletions, duplications, inversion, insertions, and translocations, which are usually caused by repairing the DNA double strain abuse. Structural instability is primarily caused by replication stress, defective abatement pathways, and telomere dysfunction. Specifically, incorrect repair via homology-dependent mechanisms that are inaccurate like non-homologous end joining may produce chromosomal rearrangements. A decrease or malfunction of telomeres may result in the fusion of the ends of chromosomes, causing breakage-fusion- Bridge cycles which cause intricate genomic restructuring. Such structural changes have the ability to interfere with the functioning of genes, form oncogenic fusions genes, or even alter regulatory elements, which have significant impact on the gene expression and cellular behaviour. Combined, numerical and structural chromosomal instability are important processes that cause genomic instability and are involved in the development of diseases, progression, and resistance to treatment.

3.2 Molecular Causes of Chromosomal Instability

Chromosomal instability (CIN) is a consequence of a combination of various interrelated molecular processes that affect proper replication, segregation and preservation of chromosomes. The most notable ones include replication stress, telomere dysfunction and mitotic errors, all of which are essential in the impairment of genome integrity. Chromosomal instability is largely conditioned by replication stress, which transpires when the replication of the DNA is hindered by factors like DNA lesions, a deficiency of nucleotides, or antagonism between replication and

transcription apparatus. These breaks may cause stopped or broken replication forks leaving behind the piling up of DNA double-strand breaks (DSBs). Unless such breaks are successfully mended, they may also result in the occurrence of chromosomal rearrangements, deletions, and duplications, and thus, facilitating genomic instability. The other important mechanism of CIN is telomere dysfunction. The protective ends of the chromosomes called telomeres ensure the ends are not taken to be considered as DNA damage. Telomere uncapping can be induced by progressive shortening of telomeres or changes in structure resulting in end to end fusions of chromosomes. During cell division these fused chromosomes continue to undergo breakage-fusion-bridge (BFD) cycles and produce complex chromosomal rearrangements and amplifications that play a major role in creating genomic instability. Mitotic errors also contribute to the acceleration of the chromosomal instability by derailing the correct segregation of the chromosomes during the cell division. Lagging chromosomes and chromosome mis-segregation may be caused by defects in the spindle assembly checkpoint, defective kinetochore-microtubule attachments, and centrosome defects. Such errors have a tendency to cause micronuclei and aneuploidy, which are characteristic of chromosomal instability and are common in cancer cells. The association of these molecular processes leads to cascade of genomic changes which eventually culminate in chromosomal instability. Figure 1 shows that replication stress, telomere dysfunction, and mitotic errors are all contributive to the accumulation of DNA damage and mal-adaptive DNA repair, giving rise to an aneuploidy and rearrangements of chromosomes.

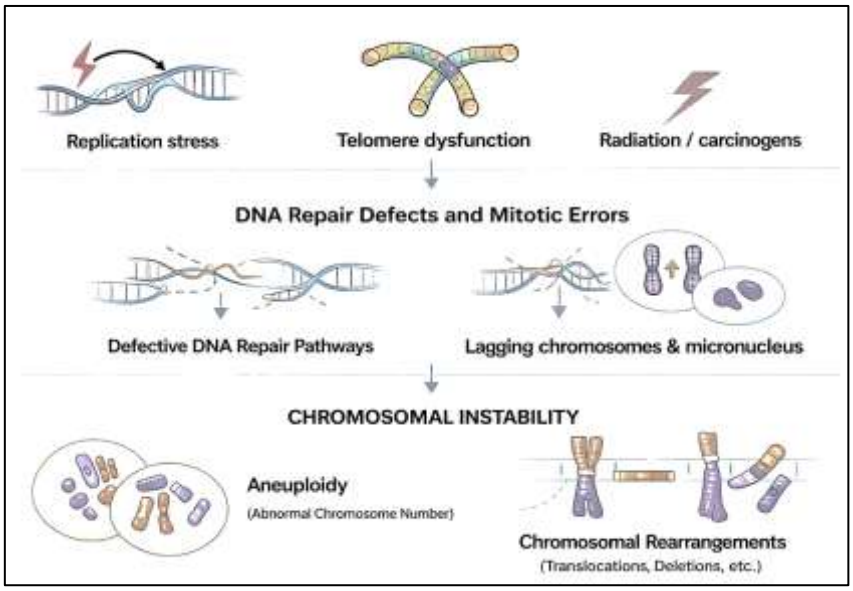

Figure 1. Mechanisms Leading to Chromosomal Instability

Diagrammatic illustration on the molecular processes involved in chromosomal instability. The DNA damage caused by replication stress, telomere dysfunction and external causes like radiation, together with the failure to repair the damage through the DNA repair pathways as well as mitotic error, contribute to chromosomal instability. The resultant consequences are aneuploidy and rearrangements of the chromosomes, which adds to the heterogeneity of genomes and the progression of diseases.

4. DNA Damage Response and Repair Mechanisms

4.1 Types of DNA Damage

DNA damage is obtained in many forms due to endogenous processes at metabolic level and exogenous factors which are related to the environment, and this is a constant threat to genome integrity. These damages may either impact the structure, order or stability of DNA and unless repaired properly, they might cause mutation, chromosomal instability and disease. Single-strand breaks (SSBs) are considered to be one of the most frequent types of DNA damage, an event, which concerns the breakage of a single strand of the DNA helix. Oxidative stress, spontaneous hydrolysis or enzymatic activity are the common causes of SSBs. Unrepaired SSBs can interfere with DNA replication and transcription, although the latter is less severe than the previously-described cases in general, and both may transform into more dangerous lesions. Conversely, the double strand breaks (DSBs) are considered to be among the most severe forms of DNA damage, since both of the strands of the DNA helix are cut. DSBs may occur due to ionizing radiation, collapse of replication fork or mechanical stress of the chromosomes. These lesions are very harmful since they might result in rearrangement, deletions or translocation of the chromosomes was there to be repaired inaccurately. The other prominent category is the base modifications and oxidative damage, which are caused by the reactive oxygen species (ROS) produced in the normal cellular metabolism. These modifications have the ability to change the nature of base pairing resulting to mutations in the process of replication of the DNA. Examples of these are the formation of 8-oxoguanine and deamination of cytosine. The ultraviolet (UV) radiation and chemical carcinogens tend to induce bulky DNA adducts and thymine dimers. These lesions damage the DNA helix hindering the process of replication and transcription. Otherwise, they may lead to mutagenesis and genomic instability. Moreover, there are also mismatches and loop deletion-

insertion that are mostly found in the DNA replication process as a result of polymerase errors. These mistakes may not be corrected, and they may result in changes in protein structure and cause frameshift mutations. The combination of these different types of DNA damage suggests that the response to DNA damage, DNA damage repair, and DNA damage detection is critical to ensure genome stability and avoid progression of disease through effective and tightly controlled DNA damage repair (DDR) processes.

4.3 DNA Repair Pathways

To maintain the integrity of the genome that is subjected to various types of DNA damage, cells are supported by various DNA repair pathways. These pathways vary in terms of substrate selectivity, repair fidelity and molecular pathway but are all involved in the maintenance of chromosomal stability. These huge repair systems are base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), non-homologous end joining (NHEJ) and the alternative end joining (Alt-EJ). Base excision repair (BER) mainly fills up small base lesions due to oxidation, alkylation, deamination and unrepaired spontaneous losses of the base. The activation of this pathway is done by the DNA glycosylases which identify and excise the damaged bases, which is followed by end processing, gap filling and ligation. BER is critical in repairing the endogenous damage produced during the normal cell metabolism and its pivotal role is to inhibit the accumulation of mutations. Nucleotide excision repair (NER) is a DNA repair mechanism that removes large DNA damage that invert the DNA helix (e.g. ultraviolet-induced photo-products and chemical adducts). NER incorporates damage recognition, local unwinding of the strand of DNA, excising the damaged oligonucleotide, and synthesizing its repair as a template using the awake strand. This is a critical pathway of environmental mutagen resistance in cells as well as transcriptional and replicative fidelity. Mismatch repair (MMR) compensates the base base mismatches and deletion-insertion loops formed during replication of the DNA. Verifying genome fidelity and preventing microsatellite instability MMR does not allow errors related to replication and thereby suppresses the effects of the latter. Malformations of MMR are highly linked with mutation overload and cancer prone. Homologous recombination (HR) is a very precise repair mechanism of the DNA double-strand break especially when there is a sister chromatid, which can be used as a template, in the S and G2 phases of the cell cycle. HR also provides proper repairing information with the help of homologous sequence, which limits the possibility of deletions or rearrangements. The important proteins in this pathway are BRCA1, BRCA2 and RAD51 that mediate end resection, strand invasion and repair synthesis. Non-homologous end joining (NHEJ) is a fast albeit inaccurate process of repairing broken strands of DNA that have been broken by two strands. In comparison to HR, NHEJ does not need a long sequence homology and is able to take place in the entire cell cycle. This route entails recognition by end of DNA, processing, and direct ligation although incorrect joining could cause small inserts, deletions, or rearrangements of chromosomes. Alternative end joining (Alt-EJ) or microhomology-mediated end joining is a repair mechanism that works as an alternative to canonical NHEJ or HR in the event that these repair systems are impaired. The short homologous sequences used to stabilize Alt-EJ are flanking the site of breakage and are more prone to errors, which usually lead to deletions and translocations. Despite it being a compensatory repair process, the constant usage of Alt-EJ may cause genomic instability. The key DNA repair pathways, their respective types of DNA damage and proteins that are involved in each of these mechanisms are summarized in Table 2. These pathways work in very strict coordination with signals of DNA damage response to provide proper recognition of lesions, regulation of checkpoints and choice of repair pathways. With Figure 2, it is reflected that the integrated DNA damage response network connects different types of DNA damage to particular sensor proteins, transducer kinases, checkpoint mediators, and downstream repair pathways thereby ensuring the stability of the genome in physiological and stressful conditions.

Table 2. DNA Repair Pathways and Key Proteins

Repair Pathway	Major Type of DNA Damage	Key Proteins	Functional Role
BER	Oxidized bases, alkylated bases, abasic sites, single-strand lesions	OGG1, MUTYH, APE1, POLβ, XRCC1, LIG3, PARP1	Repairs small base lesions and endogenous oxidative damage
NER	Bulky adducts, UV-induced pyrimidine dimers, helix-distorting lesions	XPC, XPA, XPB, XPD, XPF-ERCC1, XPG	Removes bulky lesions and restores helix integrity
MMR	Base mismatches, insertion–deletion loops	MSH2, MSH6, MLH1, PMS2	Corrects replication errors and suppresses microsatellite instability
HR	Double-strand breaks, stalled or collapsed replication forks	BRCA1, BRCA2, RAD51, MRN complex, ATM	High-fidelity repair using homologous template
NHEJ	Double-strand breaks	KU70, KU80, DNA-PKcs, XRCC4, LIG4	Rapid end joining of DSBs, often error-prone
Alt-EJ	Double-strand breaks when HR or NHEJ is impaired	PARP1, POLθ, LIG3, XRCC1	Backup end joining pathway associated with deletions and rearrangements

Schematic representation of the DNA damage response (DDR) between the various forms of DNA damage (DSBs, SSBs, replication stress, and base lesions) and sensor proteins (MRN, RPA) and molecular kinases (ATM, ATR, DNA-PK). These signify checkpoint regulators (CHK1, CHK2, p53) to deploy cell-cycle arrest and repair coordination through significant pathways, such as BER, NER, MMR, HR, NHEJ and Alt-EJ, to ensure genome stability.

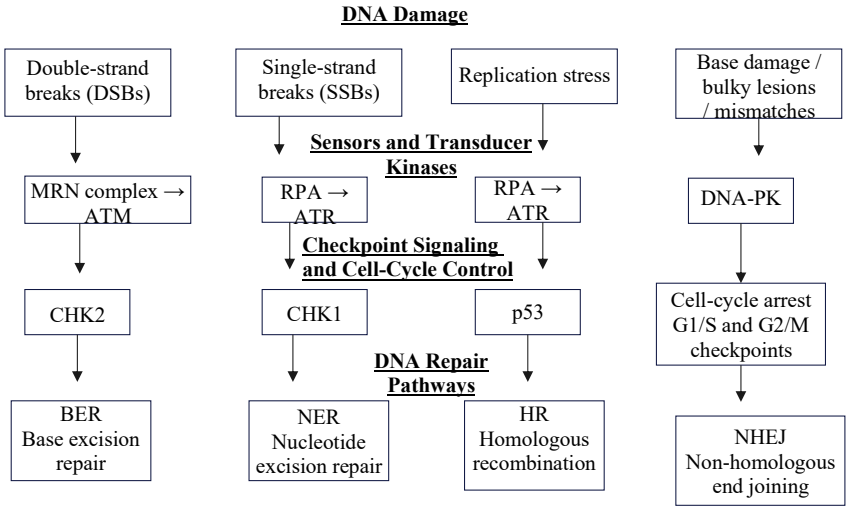

Figure 2. Integrated DNA Damage Response and Repair Network

5. Interplay Between Chromosomal Instability and DNA Repair

CIN and DNA repair are in a very dynamic and reciprocal relationship that is complex and is interaction prone to affect genome integrity. Instead of being separate, DNA repair pathways and chromosomal stability are closely connected with each other by mechanistic crosstalk and regulatory negative and positive feedback loops as well as by progressive amplification of genomic modifications. It is necessary to have mechanistic crosstalk of DNA repair pathways and chromosome stability to ensure genomic faithfulness. The homologous recombination (HR), non-homologous end joining (NHEJ) and mismatch repair (MMR) are DNA repair systems that have a direct impact on the structural and numerical stability of chromosomes. As an example, correct repair of the chromosomal architecture can be maintained efficiently through the homologous template based repair of HR, but defective pathways such as NHEJ or the end joining (Alt-EJ) process can induce insertion, deletion and rearrangements of the chromosomes. Also, malfunctioning of DNA repair factors, such as BRCA1/2 and the MRN complex, may cause a defective repair of the damage, resulting in replication stress, mis-segregation of the chromosomes, and the accumulation of structural distortions. Therefore, the two opposites of the mechanisms of high-fidelity repair and error-prone repair are important determinants of the degree of chromosomal instability. Feedback loops also make this relationship more complicated as they produce self-fueling loops of dysfunction of damage and repair. Continuous damage to DNA triggers DNA damage response (DDR) signaling pathways that regulate the selection of repair pathways and the cell-cycle. But in the instance of repair failure accumulation of unresolved lesions in the DNA may occur, resulting in further replication stress and augmentation in DDR signaling. This vicious circle is capable of increasing genomic instability with time. In addition chromosomal instability in itself may interfere with the expression and activity of important DNA repair genes, by deleting, amplifying, or altering the epigenetics of genes, thus impairing the ability to repair damage, which complicates the build-up of damage. Genome instability propagation is the final result of this interaction. When chromosomal instability is triggered, it may propagate during further cell division process by processes like breakage-fusion-bridge cycles, micronuclei formation and aneuploidy. Such processes produce new lesions in DNA as well as structural abnormalities, which further causes stress to the repair machinery. This propagation is seen as the cause of intratumoral heterogeneity, resistance to therapy and progression of the disease in cancer cells. Notably, moderate instability levels can cause adaptability, but extreme cases of genomic instability can cause cell death thus exhibiting a fine balance between the maintenance and instability of a genome. On the whole, chromosomal instability and DNA repair have well managed interactions that may either maintain the integrity of the genome or lead to gradual increase in deterioration of the genome. The knowledge of this balance is essential to the design of specific therapeutic approaches that can be used to take advantage of DNA repair defects in disease like cancer.

6. ROLE IN HUMAN DISEASES

DNA repair defects and chromosomal instability (CIN) are considered to be a key to the pathogenesis of a broad spectrum of human diseases, including cancer, inherited genetic disorders, as well as age-related degenerative disorders. Genome instability causes the build-up of mutations, chromosomal deviations and the change in gene expression which eventually impacts the functioning of the cell and the health of the organism in question. Chromosomal instability is considered to be a hallmark in cancer that promotes tumor formation, development

and heterogeneity. Mutations in significant DNA repair mechanisms, especially homologous recombination and mismatch repair, play a role in the excessive build-up of genetic mutations leading to oncogenesis. Gene mutations in BRCA1, BRCA2, and TP53 cause inability to repair the DNA damage correctly, which increases the level of genomic instability and predisposition to tumors. Also, CIN allows tumor evolution through the production of diverse populations of cells, which allows cancer cells to accommodate stress in their environment and become resistant to treatments. These mechanisms have clinical importance since they can be targeted by treatment like PARP inhibitors that take advantage of the deficiencies in the repair of DNA in cancer cells. Hereditary defects of DNA repair also lead to genetic disorders. To illustrate, the Fanconi anemia is an example of diseases caused by the failure to repair the interstrand crosslinking of DNA, which leads to the breaking of the chromosomal and failure of bone marrow. Likewise, mutations in the ATM gene result in ataxia-telangiectasia which causes defects in the process of DNA damage signaling, neurodegeneration and cancer predisposition. Other disorders like Lynch syndrome, which have been associated with the mismatch repair deficiency, lead to the microsatellite instability and predisposition to colorectal malignancy, among others. These circumstances indicate that DNA repair systems are important in ensuring that genome stability is achieved in various tissues. The gradual accumulation of DNA damage and loss of efficiency of repair mechanisms also have a close connection with aging and degenerative diseases. The sustained damage to genomes over time helps in cellular senescence, tissue dysfunction and predisposes the cells to age related diseases like neurodegeneration and cardiovascular disease. The processes are further enhanced by chromosomal instability which encourages genomic changes that disrupt the homeostasis of the cells. The interaction between increased accumulation rates of DNA damage and decreased repairing capacity is viewed as one of the factors of biological aging.Table 3 contains the synthesis of the significant DNA repair defects and the human diseases associated with them with emphasis on the impacted pathways and clinical outcomes. Collectively, these data underline the fact that the impairments in the DNA repair and chromosomal stability are not only the primary causes of disease development but also one of the most significant targets of therapeutic intervention.

Table 3. DNA Repair Defects and Associated Diseases

Disease	Defective Gene/Pathway	Type of Instability	Clinical Impact
Cancer (general)	BRCA1/BRCA2 (HR), TP53	Chromosomal instability, mutations	Tumor progression, therapy resistance
Breast/Ovarian Cancer	BRCA1, BRCA2	Defective homologous recombination	Increased cancer susceptibility
Lynch Syndrome	MSH2, MLH1, MSH6 (MMR)	Microsatellite instability	Colorectal and other cancers
Fanconi Anemia	FANCA, FANCD2 (FA pathway)	Chromosomal breakage	Bone marrow failure, cancer risk
Ataxia-Telangiectasia	ATM	Impaired DDR signaling	Neurodegeneration, cancer predisposition
Xeroderma Pigmentosum	XPA–XPG (NER)	UV-induced DNA damage accumulation	Skin cancer, photosensitivity
Aging-related Disorders	Multiple pathways (BER, NER, HR decline)	Accumulated DNA damage	Tissue degeneration, functional decline

7. EXPERIMENTAL AND COMPUTATIONAL APPROACHES.

To comprehend chromosomal instability (CIN) and DNA repair process, a set of experimental measurements and computational model is necessary that allows one to identify, measure and analyze genomic changes. These approaches would give important information concerning the molecular aspects of genome instability and its clinical consequences. Experimental assays are very crucial in defining the nature of DNA damage and chromosomes abnormalities. Karyotyping and fluorescence in situ hybridization (FISH) are the most common classical cytogenetic methods used to identify the large-scale chromosomal changes, such as aneuploidy, translocations, and deletions. The comet assay and γ-H2AX foci formation assay are usually used to measure the amount of breaks in DNA strands, as well as to measure the amount of DNA damage on a single cell level. Moreover, the imaging studies with the use of advanced methods and live-cell microscopy allow observing the instances of mitotic errors, i.e., mis-segregation of chromosomes and formation of micronuclei. The effectiveness and precision of individual DNA repair mechanisms such as homologous recombination and non-homologous end joining are also determined by functional assays, such as reporter-based systems. The recent developments in genomics have greatly contributed to the capabilities of examining genome instability in high resolution. Whole-genome sequencing and targeted sequencing are next-generation sequencing (NGS) technologies that enable the identification of all the mutations, structural variation, and copy number variations related to chromosomal instability. Single-cell sequencing methods also can give information on the heterogeneity of cells and how the genomic changes can dynamically evolve in specific cells. These methods are especially useful in the study of cancer, where intratumoral heterogeneity is the central factor that has an influence on disease progression and resistance to various therapies. High-throughput data on genomic analysis and interpretation requires computational and bioinformatics tools, which are necessary to analyze and interpret large and complex data. The patterns of genomic instability can be identified with the help of algorithms of variant calling, copy number

analysis, and structural variation detection. The approach of integrating multi-omics, which involves the combination of genomic, transcriptomic, and epigenomic data, offers the systems view of the DNA repair network and its regulation. The methods of machine learning and artificial intelligence are currently being used to make predictions about the deficiency of DNA repair, recognize the signatures of genomic instability, and view potential therapeutic targets. Combined, experimental and computational methods can be used to gain complementary information about the process of chromosomal instability and DNA repair. They are vital in terms of helping to understand more about the genome maintenance, and even better, to test and treat diseases associated with genome instability.

8. THERAPEUTIC IMPLICATIONS

The improved comprehension of the chromosomal instability (CIN) and DNA repair processes has resulted in the establishment of specific therapeutic approaches targeting the utilization of the flaws in the process of maintaining genome. These methods aim at the selective destruction of cancer cells that have a defective mechanism of repairing damaged DNA and minimizing the destruction of normal cells, which enhances the effectiveness of treatment besides the low level of side effects. Inhibition of DNA repair pathways has become one of the opportunities in cancer treatment. Tumor cells tend to have impairments on certain repair systems, and they are more inclined to rely on alternative ways of survival. This can be used to prevent the release of compensatory mechanisms to cause the build up of DNA damage beyond an acceptable limit causing cell death. The technique is especially useful in cancers with the defect in homologous recombination medical repair. Primarily, the application of poly(ADP-ribose) polymerase (PARP) inhibitors can be listed among the most successful cases of the DNA repair-targeted therapy. The single-strand break repair involves the use of PARP enzymes in repairing the base excision repair pathway. PARP inhibition results in the replication fork collapsing to create two strand breaks. In cells that lack homologous recombination, like those that have BRCA1 or BRCA2 mutations, the repair of such lesions cannot be precisely done leading to the death of the cell. PARP inhibitors have shown to be of clinical use in the treatment of breast, ovary as well as prostate cancer. Synthetic lethality forms the basis of the numerous DNA repair-targeted therapies. Synthetic lethality is where cell death is caused by the overlapping mutation of two genes or two pathways, but the mutation of each individual is adaptable. When it comes to DNA repair with in-built defects to one pathway, the cancer cells would be very reliant on the other repair mechanisms. The selectivity of killing cancer cells over normal cells with these secondary pathways is achieved by their differing capacities of overcoming the cancer repair mechanisms in cancer cells. This approach has expanded the targeted therapies beyond the PARP inhibition and is still continuing to develop new therapeutic agents. The outcome of treatment is further improved by the application of the knowledge of DNA repair to precision medicine methods. Treatments can be designed to address the specifics of the molecular profile of an individual patient by detecting certain genetic mutations and repair defects in a particular tumor. The BRCA mutations, the microsatellite instability and the genomic instability are becoming biomarkers to direct the treatment choices and elucidate therapeutic response. This personalized data is efficient as well as minimizing of redundant therapy and drug-related toxicity. In summary, therapeutic methods aimed at the repairing of the DNA repair pathways can be considered the potent method of treating the diseases related to the genome instability. Further studies of molecular aspects of DNA repair and chromosomal instability will help to develop more efficient and targeted treatment, which will eventually have a positive impact on the patient.

9. CONCLUSION AND FUTURE PERSPECTIVES.

Chromosomal instability (CIN) and DNA repair are inherent regulators of genome integrity, which are determinant in cell homeostasis, disease progression, and treatment response. This summary points out that CIN is caused by various molecular events such as replication stress, dysfunctional telomeres and mitotic errors whereas the DNA repair mechanisms serve as important protective mechanisms which identify and repair genomic damage. The complexity in the interaction of these systems defines the stability of cells and their movement towards genomic instability and illness. An important lesson that can be learned as a result of the research conducted today is the need to have chromosomal instability and the DNA repair mechanisms integrated into a coherent framework. The processes are closely linked with each other by intricate signaling pathways, owing to feedback loops and crosstalk between pathways. This integration is necessary to interpret disease mechanisms that are important in cancer where heterogeneity, evolution, and disruption of therapy is driven by genomic instability. In spite of massive progress, there are still a number of drawbacks. Most of the studies are done on individual pathways independently of each other without understanding the interactions between the different repair mechanisms as a system. Also, the interpretation of the cell type, disease, and environmental variation makes the interpretation of the mechanisms of genome instability difficult. There is also the challenge of how to be able to translate molecular understanding into clinical interventions and this underscores the necessity of more integrative and translational studies. It can be addressed by emerging technologies which have potential opportunities. Complex genomic data and prediction of DNA repair deficiencies is increasingly being analyzed by artificial intelligence and machine learning. Genome editing using CRISPR offers potent solutions to validate functional repair pathways with high power and single-cell and spatial genomics provide the analysis of genomic instability and heterogeneity of the cells in high-resolution. Such advances should play an important role in unraveling the mystery of genome maintenance. Further studies are needed on the creation of integrative models that will integrate molecular, genomic and computational data to help in a better understanding the dynamics of

chromosomal instability and DNA repair. Increasing the number of identified predictive biomarkers and therapeutic targets will also contribute to the development of precision medicine. Clinically, it is a very important priority to be able to translate these findings into specific therapies and customized treatment approaches. To conclude, the interrelations of chromosomal instability and DNA repair can only be properly understood regarding further development of basic research as well as the clinical application. It will be important in the future to continue interdisciplinary approaches towards increased stability of genome-based diagnostics, therapeutic interventions, and, ultimately, patient outcomes in diseases related to genome instability.

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