REVIEW ARTICLE

Role of Chromosomal Instability in Cancer – An Update

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Abstract

Chromosomal instability (CIN) is a type of genomic instability in which chromosomes are unstable such that either whole or part of chromosomes are deleted or duplicated. CIN is caused by failures in chromosome errors, such as abnormalities in the machinery involved in chromosomal segregation, such as spindle assembly checkpoints, centrosome amplification, incorrect microtubule-kinetochore attachments, or faulty sister chromatid cohesion. CIN is detrimental to healthy cells and is associated with decline, altered metabolism, proteotoxic stress, cell cycle arrest, and DNA damage. CIN is a prevalent characteristic of solid tumors, a prospective therapeutic target for cancer treatment. It plays a significant role in both the development of tumors and the way they respond to treatment. CIN promotes the accumulation of mutations that result in aggressiveness or drug-resistant phenotype. CIN could empower the tumors with increased adaptation capabilities, facilitating adaptive resistance to therapies. Identifying the intricate structure of CIN is essential to comprehending the processes of tumorigenesis as well as producing potent anti-tumor therapies. A description of CIN's effects and causes is given in this review; experts still remain perplexed by the phenomenon's contradictory nature. The prospect of CIN-based anti- cancer treatment is finally examined in this article.

Key words: Chromosome instability, prognosis, therapy, treatment resistance

INTRODUCTION

Chromosomal instability (CIN) has received considerable attention recently due to its implications for cancer detection and treatment. Recent research suggests that clonal heterogeneity and CIN affect the prognosis, assertiveness, treatment responsiveness, and development of cancer.[6] This is due to clonal heterogeneity and CIN both generate differences with the oversight concerning genes (tumor suppressing genomics and proto-oncogenes).[31] This includes differences regarding the amounts of any polypeptide that codes.[60] The evaluation revolves in new research related to that the function. Regarding CIN through malignancy, cells undergo processes that cause CIN, this association together with another developing treatment methods and cancer hallmarks have been assessed as a potential solution for the imbalance.[27]

A BRIEF INTRODUCTION OF CIN AND GENOMIC INSTABILITY

The Characteristics of Malignancy

Genomic instability describes a higher propensity for genome modifications throughout a cell's life cycle. It is one of the leading causes of carcinogenesis and heterogeneity.[52] Genetic changes resulting from genomic instability give tumor cells an advantage over other cells in terms of proliferative

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capacity and survival.[46] Genomic instability is categorized into three kinds based on the genetic degree of alteration: CIN, microsatellite instability (MSI), and also nucleotide instability (NIN).[38] An increased frequency of one or a few nucleotide changes, deletions, and insertions is called NIN. Due to malfunctions with a mechanism for base repair which does not exist, the microsatellite length of the MSI can either increase or decrease.[21]

The ultimate form of instability in the genome is CIN, which is particularly prevalent also less characterized.

The importance of CIN over cancer prognosis and diagnosis has made it more significant in the past few years.[62] The kind of instability in the genome is referred as numerical CIN (increase or reduction of all chromosomes, or aneuploidy), along with structural CIN (increase or reduction in chromosomal regions)[55] [Figure 1]. If the cell has an abnormally large amount of the chromosome, it is regarded to be aneuploid. This disorder can be neither unstable nor stable. In cases where chromosomes indicate variable aneuploidy, the concurrent establishing many distinct genetic tumor divisions is emphasized, enhancing genetic heterogeneity between tumors.[12]

Figure 2 illustrates the many kinds of CIN. The CIN is distinguished among two categories: Both structural CIN and numerical CIN. Whereas structurally CIN is related to the neither acquisition nor demise of chromosomal components, numerical CIN is associated with the gain or loss of entire genomes (polyploidy and aneuploidy).

MECHANISM OF "CIN"

While specific causes of CIN are unknown, abnormal chromosomal segmentation/duplicating through morphogenesis is most likely the cause. Faulty sister chromatid cohesion, atypical centrosome replication, telomere destruction, kinetochore-microtubule attachment oversights, and anomalies at the spindle assembly checkpoint (SAC) are a few of these pathways.[57] Tumor cells exhibiting CIN mis-segregate a piece of DNA around every 4–5 cycles in comparison having steady, androgynous

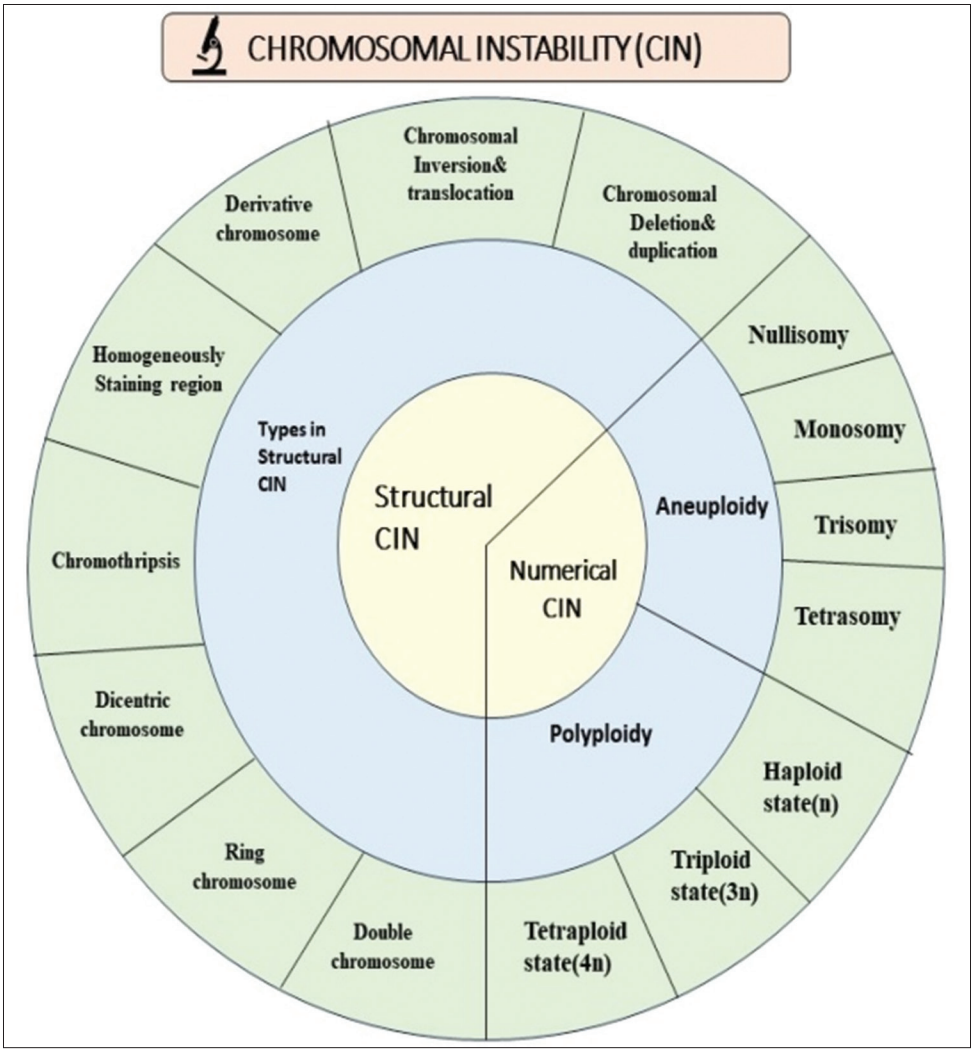

Figure 1: Chromosomal instability

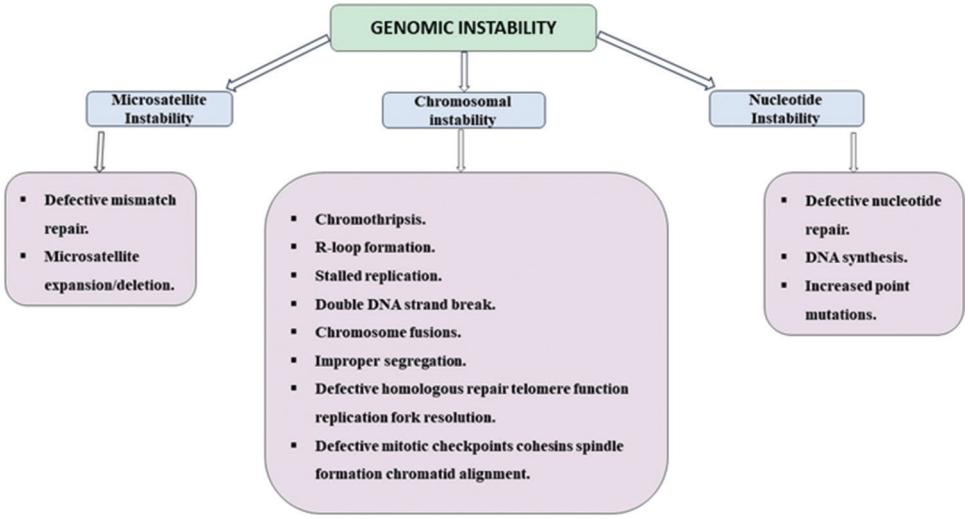

Figure 2: Genomic instability

cells that mis-segregate one chromosome every hundred cell divisions.[59] The SAC works for preserve gene stability by delaying the division of cells through the process of meiosis and mitosis unless precise chromosome. Isolation is assured, ensuring as anaphase begins in order around the attachment of each nucleotide to the spindle micro-tubules.[62] Before anaphase initiating, the kinetochores should seize the spindle's microtubules and attach the sister chromatid of a chromosome to the other side spindle's pole (amphitelic attachment) to chromosome segregation occurred effect with extreme precision. The SAC is inactivated, permitting chromosome separation and division of cells to proceed once every chromosome has properly bidirectional spindle microtubule attachments (amphiboly fixing). Kinetochore activation of the SAC network prevents anaphase from starting and maintains the cohesiveness of the sister chromatid in cases when chromosomes are mis-attached to the spindle (erroneous attachments).[49] A few examples of incorrect attachments are when each ends have a merotely linked sister kinetochore, when each sister kinetochores are syntely linked to the similar pole, or when just a kinetochore is monotely linked to a spindle pole.

Moreover, merotelic attachments are not identified by the SAC and are distinguished by the lack of strain among sister kinetochores. They might cause chromosomal mis-segregation if departed corrected due to the sluggish chromatid migration movement.[36] The key process of CIN in cancer cells is merotely.[24] Undetected merotelic interactions has been proposed as the cause of the CIN phenotype, which is seen in around 85% of all spontaneous carcinomas.[40]

Figure 3 illustrates the development of numerical and structural chromosomal instability (CIN) due to mitotic chromosomal segregation errors. Chromosome addition or deletion (numerical CIN) as/or structural CIN (chromosome structure changes, such as translocations, deletions, and derived chromosomes) can result from dysfunctional chromosomal duplication or segregation during mitosis. Chromosomes are susceptible to further chromosomal changes by both structural and numerical changes, which enhance CIN.

ROLE OF CIN IN CANCER

Control of advanced-stage cancer and the best possible therapy responses are still difficult despite increased research in recent years. Cancer is one of the top causes of mortality. Advancements in technology have expanded our knowledge of human carcinoma as a diverse illness. As an example, quartet novel traits related to cancer were recently identified that may have a role in resistance to treatment as well as in the growth of the disease. Among one of those traits is CIN, which is the cause for inherited variations with or without altered chromosomal count or structure. One common feature of solid tumors, CIN, is a potential target for therapy for the treatment of cancer. It has been established that CIN provides genomic variety which promotes neoplasm sensitivity to toxic chemotherapeutic drugs and high stress levels.[56] While CIN seems to be connected to the management of cancer, there has been mixed reports regarding how it works on the outcome of treatment.[42] Both structural (aneuploidy) and numerical CIN have been shown in cancer studies to affect tumorigenesis and maybe the effectiveness of therapies. Therefore, more research is required to fully comprehend that the part CIN plays in both the development of tumors and the way they respond to treatment.

PART OF CIN ON TUMOR EVOLUTION NOR DEVELOPMENT

The part that CIN plays in the progression of tumors is a topic of considerable debate. A few investigators suggest that CIN is a consequence of expansion of tumors, which frequently

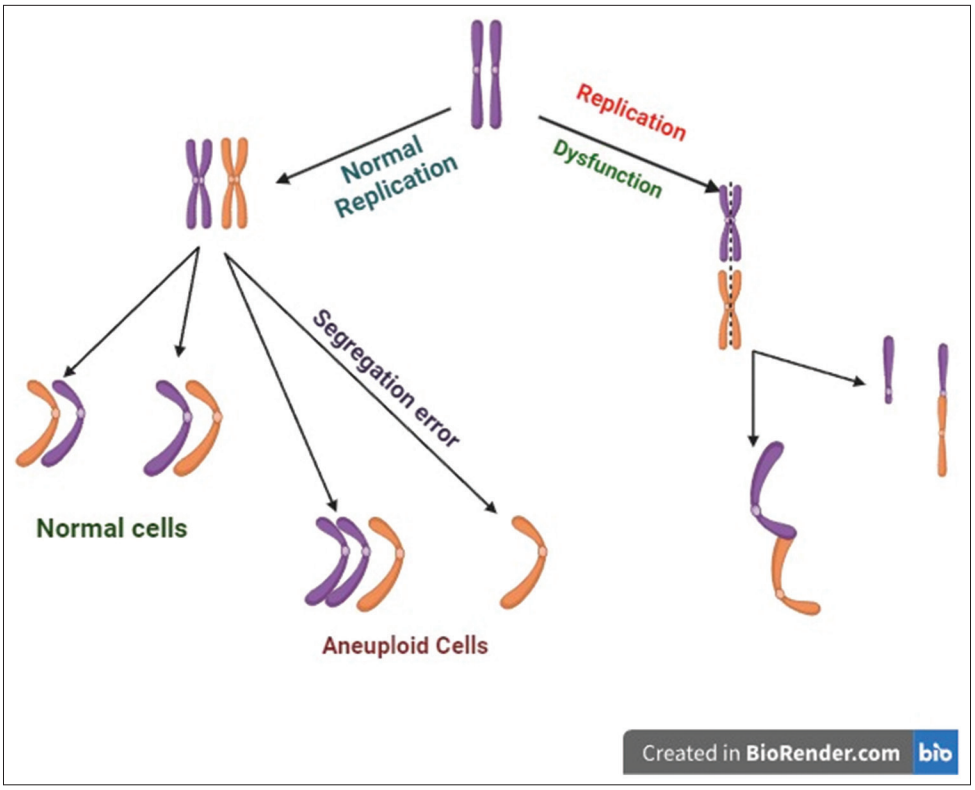

Figure 3: Illustrates the development of numerical and structural chromosomal instability (CIN) due to mitotic chromosomal segregation errors

results in chromosome either increasing or decreasing in cancerous cells,[37] whereas other folks think, it is a beginning phase in carcinogenic which leads to a reduction or deactivation of genes that suppress cancer.[7] In addition, it was recently demonstrated that when cancer advances, CIN encourages the development of alterations leads to destructive or phenotypic drug resistance.[22] According to the impact of aneuploidy on gene activity, chromosomal modifications in copy numbers alter the proportions of protein complexes engaged in functionally or physiological interactions. Proper changes in the protein association networks involved in the splitting of chromosomes or the point where the spindle assemblies can lead to errors in chromosome division, an abnormal number of copies and the ensuing CIN.[6] They have been identified based on the chromosomal changes underlying CIN. Furthermore, therapeutic approaches that specifically target variants in genes and the mechanisms driving cancer have been made clearer by the molecular characterization of chromosomal changes. Furthermore, studies have indicated that CIN and heterogeneity are clinically valuable in human tumors[58] due to their associations. In general, predictive markers for blood-related malignancies and certain solid malignancies have with treatment resistance, poor prognosis, increased the spread of disease, and advancement of cancer.[13] Moreover, the most virulent and invasive cancer types have been observed to have the highest CIN.[44]

"CIN" IN PANCREATIC CANCER

An elevated incidence of harmful alterations to the chromosomal modifications as a result of a compromised DNA repair response is referred to as genomic instability.[43] Several cancers have been linked with suppression or harmful variants in genes that suppress tumor cells, especially in checkpoints as well as the genes involved in DNA repair such as the protein p53, with p16, and "Ataxia Telangiectasia Mutated" (ATM). Genomic instability has also been linked to numerous of these genes. Due to lacking of genome replacement reaction, BRCA1/BRCA2 mutations[20] expose DNA to harmful alterations,[26] which is covered in more detail below. Increased genetic changes, including the insertion or deletion of additional nucleotides and even intrachromosomal translocations, have also been associated to abnormalities in the ATM the genome, thereby which is another crucial genome with responding to DNA damage and replacement.[9]

"BRCAness" and beyond

Multiple abnormalities in genetic restoration mechanisms including the effects they have regarding the metabolic activity of pancreatic ductal adenocarcinoma have been revealed by recent genome-interrogation investigations. ATM, like "ATR (Ataxia-Telangiectasia and Rad3 related)," is a critical mediator in the cellular DNA destruction

reactions and recovery process. Mutations in ATM have been reported in both hereditary and sporadic pancreatic cancers.[50] By triggering a series of events that involve several signal mediators and downstream proteins, ATM starts check point control through p53.[2] Moreover, the ATM and BRCA1/BRCA2 cascades are directly triggered by double-strand DNA breaks to initiate DNA repair[10] [Figure 4]. Two essential peptides, BRCA1/BRCA2, are involved in the activation and functioning of homologous recombination (HR) in the repair of double-strand DNA breaks. BRCAs, in particular BRCA2, recruit DNA repair assembly and interact with homologous repair (HR) starting proteins including RAD51.[47] A higher risk of pancreatic cancer has been linked to mutations in PALB2, which is crucial for recruiting genome repair devices for activation HR.[33] In contrast to alternative DNA with double-strands break healing mechanisms such as single-strand annealing or non-homologous end-joining pathway, homologous DNA is used by HR to repair the breaks, producing results that are high-quality and error-free.[39] Transferring from HR to alternative DNA repair pathways raises the possibility of DNA sequence modifications, which frequently result in harmful genetic material changes due to low-fidelity DNA repair and genetic rearrangement.[61] "BRCAness" refers to certain genotypic and phenotypic characteristics that result from the previously stated non-homologous DNA repair pathway and associated defects in DNA repair and replication.[61] The BRCAness hallmark influences medical characteristics as well as diseased behavior.[28,29] In contrast to the average age of onset of 71 years, people with hereditary BRCA1 mutations, in particular, suffer carcinoma of pancreas at earlier stages (the average age was 60.3), and 30% of these patients had treatable illness during the moment of confirmation.[23,51] In addition, it seems that their average lifespan is higher, especially for those who are receiving platinum-based therapy.[23]

Figure 4 cells lifecycle and checkpoints. When DNA is damaged, numerous mechanisms that control the cell cycle are triggered. Variations in genes that adversely influence the cell cycle have been linked to tumorigenesis in various cancers.

Some examples of Therapy for CIN – Cancer Treatments: Pancreatic Cancer

- Surgery-Complete pancreatectomy, partial pancreatectomy, and biliary enteric bypass
- Radiotherapy-Teletherapy
- Chemotherapy-Capecitabine, fluorouracil, and irinotecan
- Targeted Therapy-Erlotinib.

"CIN" IN BREAST CANCER (BC)

According to information, CIN might encourage the removal or else inactivation of tumor suppressive genes, such as the TP53 gene, which is important in the inhibition of death in BC. The guardian of the genome gene,[30] TP53, is responsible for producing the transcription factor p53, which triggers the transcription of genes related to cellular senescence, apoptosis, metabolism, DNA repair, and other processes that occur after cellular stress. By transactivating a variety of genes that induce apoptosis, such as "BAX,

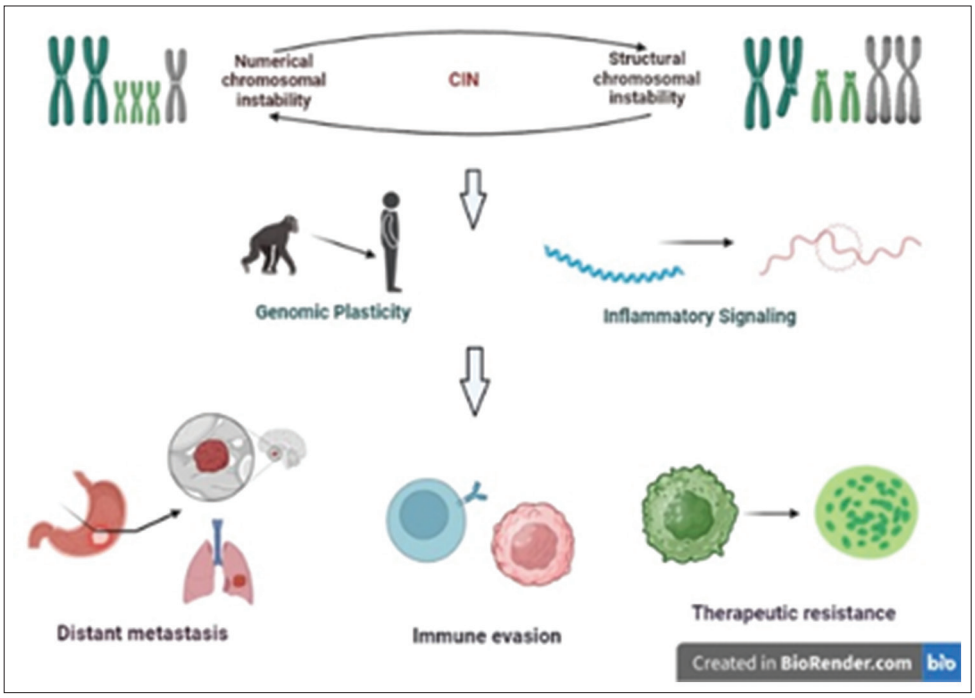

Figure 4: Chromosome instability's complex function in cancer

BID, PUMA, and NOXA," thus inhibiting the protein that hinders apoptosis, BCL2,[35] p53 can activate many pro-apoptotic mechanisms that induce death of cells. Tumor suppressor genes involved in the regulation of apoptosis, such as the TP5 gene, may be favorably affected by CIN in BC, according to evidence. About 20–40% of BC cases had TP53 mutations.[3] Cells may be more susceptible to an increase in CIN in BC if they have TP53 mutations. Indeed, reports have linked TP53 mutations to genomic instability in primary BC.[25]

Research on primary breast cancer (BC) cells showed that cells with abnormal p53 protein production exhibited numerical instabilities in the 17th chromosome, compared to cells without p53 abnormalities in similar BC samples. The study's findings clearly suggest that TP53 mutations are a major factor in the development of breast carcinogenesis[53] and the cause of CIN. Because p53 is involved in the control of centrosome duplication, there is additional evidence linking TP53 mutation to CIN.[19] For example, studies have shown that mice embryonic tissues defective in a protein called p53 make multiple copies of the centrosomes in an individual cell cycle, which is but standards do not exhibit such abnormalities.[5] Human tumors that have TP53 mutations or deletions, which cause widespread CIN, have also been shown to exhibit chromosomal hyper-amplification. Eighteen A complex, bidirectional link between CIN and apoptotic inhibition in cancer is indicated by the above results.

Some examples of therapy for CIN – cancer treatments: BC

- Surgery-Lumpectomy, Breast removal surgery and Maddens mastectomy
- Radiotherapy-Teletherapy and implant radiotherapy
- Chemotherapy-Abraxane
- Hormonal Therapy-Aromatase inhibitors and Ado-Trastuzumab
- Targeted cancer-Monoclonal antibodies.

"CIN" IN RENAL

There are two types of renal cancer: Inherited and sporadic. While there are numerous genetic predispositions for kidney cancer, only 3–4% of cases are hereditary. It briefly summarizes the prevalent subtypes of renal cell tumors, emphasizing their molecular pathological epidemiology.[32] Apart from those mentioned conditions, uncommon cases of hereditary renal carcinoma with a rapid development are predisposed by dislocation of quinone oxidoreductase specific gene alteration (Ricketts *et al*., 2008), tuberous sclerosis, and chromosome 3p translocation (Cohen *et al*., 2008).[48] Based on Gwangwu *et al.* (2012), a significant number of samples of "clear-cell renal cell carcinoma" (ccRCC) had five genes that are known to be associated with renal cancer.[8] The 98 ccRCC included the promoter VHL1, A pair of tumor inhibitors DNA, Ubiquitin carboxy-terminal hydrolase (also known as BAP1) (changed in 8% of the 98 ccRCCs) and TSC1 (changed in 3%), along with the chromatin modification-related genes, including TP53 (altered in 6%), BRG1-associated factor 180 (PBRM1) (changed in 21%), Lys-(K-) particular lysine demethylase 5C (KDM5C3) (changed in 9%), and histone methyltransferase SETD2 (HYPB) (4%).[11] The VHL tumor suppressor genome was often encoded in altered DNA in ccRCC (Creighton *et al*., 2013). Inherited genetic alterations, such as point mutations, 3p25 loss, and insertions or deletions (indels), along with stable epigenetic modifications, are key factors driving initial oncogenic processes, as highlighted by Hakimi *et al*., 2012.[30] According to Masson and Ratcliffe (2014), VHL is a portion of a ubiquitin protein ligase E3 which recognizes substrates and HIF1α and HIF2α are ubiquitylated to be destroyed by proteasomes.[41] Numerous unique, frequently occurring mutations in ccRCC, has been identified by extensive cancer genomic initiatives. These include MTOR (5–6%), BAP1 (6–10%), KDM5C (4–7%), SETD2 (8–12%), and PBRM1 (29–41% of neoplasm specimens) (Xu *et al*., 2016).[64] Ninety percentages of cases with sporadic ccRCC have been reported to have lost chromosome 3p (Junker *et al*., 2003).[34]

Some examples of therapy for CIN – Cancer Treatments: Kidney Cancer

- Surgery-Nephron-sparing surgery, open kidney removal surgery, and complete nephrectomy
- Radiotherapy-External beam radiation therapy used for kidney cancer
- Chemotherapy-Afinitor, Aldesleukin, Avastin, and Bevacizumab.

"CIN" IN PROSTATE CANCER (PC)

The subsequent fastest growing type of cancer in men is PC. In 2012, around 1.1 million men internationally were diagnosed with PC, accounting for 15% of all male cancer illnesses. Nearly, 70% of these cases (759,000) occurred in more industrialized nations.[17]

A significant amount of research has established the presence of the CIN in PC, and several applicant genomes, which include the chromosome 1, 7, 8, 10, 17, and X, have been suggested to be involved play in cancer development.[64] According to Al-Maghrabi *et al*.'s analysis of Graphical CIN (aneuploidy) in PC among individuals, the most common alteration was chromosome 8 gain, followed by the chromosome 7 gain and chromosomal Y anatomy.[1] It found that the most common changes were chromosomal Y anatomy, chromosome 7 gain, and chromosome 8 gain.[1] Furthermore, a strong interrelation was previously established between chromosomal modifications as well as prognosis in PC. Poor outcomes are linked to cancers with 8q rises or more than two.

Furthermore, a recent study looked into the potential for propagation of dispersed cell collections regarding patients with PC who had metastasized. Holcombe *et al*. found in this study that there are regular gains in 8q and xq alteration and prevalent losses in AP223, 10q, 13q, and 16q alteration often identified through PC. The authors state that these findings laid the groundwork for clarifying the connection between genetic variations.

Some examples of Therapy for CIN – Cancer Treatments: PC

- Surgery-Radical prostatectomy, key hole radical prostatectomy, and Da Vinci radical prostatectomy
- Radiotherapy-Radiation brachytherapy, teletherapy, and alpha emitter radiotherapy
- Hormone Therapy-Androgen deprivation therapy, abiraterone acetate, and orchiectomy.

"CIN" IN COLON CANCER

In terms of overall cancer cases, colorectal cancer (CRC) ranks second in women (614,000 cases, 9.2% of the total) and third in men (746,000 cases, 10.0% of the total).[18] About 65% of CRC cases have been found to have CIN, with stage 1 sickness showing the lowest frequency and stage 4 illness showing the highest occurrence.[4] With the lowest frequency in stage 1 and the highest in stage 4 disease, CIN has been determined in 65% of all individuals with CRC.[45] Finding within CRC has revealed frequent deletions at 16p13 as well as 19q13, that have been very much related to negative outcomes in stages two and three of the disease.[45] Significantly, highly hazardous genetic instability populations were identified in both places. Moreover, 70% of the original CRC tumors have ancestral depletion at chromosome 18q21, specifically in cases in which the disease grows worse.[16] Those delete in colonic cancer gene represents one of the suppressor genes for cancer found within this part of the genome.[15] Mutations in this gene are unusual in human colorectal malignancies (6%). SMAD2 as well as SMAD4, that regulate the progression of cells, their proliferation, and cell death, are additionally found in this part of the genome.[14] Although alterations in SMAD2 along with SMAD4 are found in CRCs infrequently.[54]

More importantly, colonic adenomatous polyposis is believed to be correlated with CIN. For example, 60–80% of the polyps illustrated aneuploid transformations, regarding the majority of prevalent irregularities being made the elimination of genomes 17p, 19q, and 22q in addition amplification of chromosomes 13 and 7. Cardoso *et al*.[54]

Some examples of therapy for CIN – Cancer Treatments: Colon Cancer

- Surgery-Polypectomy, local excision, and resection of colon with colostomy
- Chemotherapy-Systemic, chemotherapy, fluorouracil, leucovorin, and oxaliplatin
- Targeted Therapy-Bevacizumab, cetuximab, encorafenib, and regoranfib
- Immunotherapy-Ipilimumab, nivolumab, and pembrolizumab.

CONCLUSION

CIN is a double-edged sword for tumor development, that is, CIN may promote or suppress tumors. There is significant proof of CIN's effects on promoting tumors in a number of carcinomas; although, despite recent advances in our understanding of CIN, its implications must still be understood within the context of cancer as a multifaceted and varied disorder compared for a single where CIN merely plays a simple and autonomous role in tumor progression. So far, the research points to a significant role for CIN in the course of the disease followed by within the symptoms and criticism against treatment. Therefore, as we develop new, high potent anti-cancer treatments, CIN is a crucial objective that must be taken into consideration. In addition, considering that karyotypes associated with cancer are unstable and chaotic and that the primary characteristic of such CIN is the recognition of non-clonal chromosome aberrations (NCCAs) such changes are recognized and reported, and this is clinically significant. Moreover, the discovery of NCCAs may help discover novel treatment options and add to our understanding of cancer since they represent a source of genetic diversity that has not yet been identified.

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