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Invited Mini Review

Whole-genome doubling is a double-edged sword: the heterogeneous role of whole-genome doubling in various cancer types

Eunhyong Chang[1,2] *& Joon-Yong An*[1,2,3,*]

[1]Department of Integrated Biomedical and Life Science, Korea University, Seoul 02841, [2]L-HOPE Program for Community-Based Total Learning Health Systems, Korea University, Seoul 02841, [3]School of Biosystem and Biomedical Science, College of Health Science, Korea University, Seoul 02841, Korea

Whole-genome doubling (WGD), characterized by the duplication of an entire set of chromosomes, is commonly observed in various tumors, occurring in approximately 30-40% of patients with different cancer types. The effect of WGD on tumorigenesis varies depending on the context, either promoting or suppressing tumor progression. Recent advances in genomic technologies and large-scale clinical investigations have led to the identification of the complex patterns of genomic alterations underlying WGD and their functional consequences on tumorigenesis progression and prognosis. Our comprehensive review aims to summarize the causes and effects of WGD on tumorigenesis, highlighting its dualistic influence on cancer cells. We then introduce recent findings on WGD-associated molecular signatures and genetic aberrations and a novel subtype related to WGD. Finally, we discuss the clinical implications of WGD in cancer subtype classification and future therapeutic interventions. Overall, a comprehensive understanding of WGD in cancer biology is crucial to unraveling its complex role in tumorigenesis and identifying novel therapeutic strategies. [BMB Reports 2024; 57(3): 125-134]

INTRODUCTION

Whole-genome doubling (WGD), characterized by the duplication of a complete set of chromosomes, is prevalent in human cancers. It occurs in 30-40% of patients with different cancer types (1-3). Genomic studies have primarily focused on chromosomal alterations, including aneuploidy or somatic copy number alterations (SCNA), in tumor genomes. In contrast, WGD is a more specific phenomenon in which amplification occurs on the entire chromosome, involving molecular signatures and biological pathways in certain patients or cancer subtypes. WGD mitigates the detrimental effects of mutations and facilitates the rapid accrual of genetic aberrations, playing a pivotal role in tumorigenesis (2, 4-7). Conversely, cancer cells harboring WGD exhibit genomic instability that can culminate in apoptosis, senescence, and immune-mediated clearance (8-10). Therefore, WGD exerts a dualistic influence on cancer cells, concurrently conferring advantages and disadvantages. The precise influence of WGD on tumor advancement remains controversial and may profoundly vary with the specific tumor type under consideration. Although WGD has been implicated as a negative prognostic factor in colorectal, pancreatic, and breast cancers, contrasting studies have shown its association with improved survival outcomes in bladder urothelial carcinomas (1, 4, 11). Furthermore, the prevalence of WGD in different cancer types exhibits substantial heterogeneity (1, 2). Therefore, adopting a context-specific perspective when evaluating the role of WGD in cancer is imperative.

In this comprehensive review, we summarize the potential triggers of WGD and the mechanisms by which WGD influences tumor progression. Moreover, we highlight recent discoveries regarding WGD-associated molecular signatures across pan-cancer studies and diverse cancer types. Finally, we discuss the clinical applications of WGD with respect to cancer subtype classification and future therapeutic interventions.

CAUSE AND EFFECT OF WGD

Cause of WGD

Various scenarios that cause WGD can be divided into two categories: one in which the entire genome doubles within a single nucleus, and the other in which there are two or more nuclei within a single cell. Endoreduplication (mitotic bypass) and endomitosis (mitotic slippage) are the primary mechanisms driving genome doubling within a single nucleus (Fig. 1). These processes are triggered by replicative stress from various

*Corresponding author. Tel: +82-2-3290-5646; Fax: +82-2-916-5943; E-mail: joonan30@korea.ac.kr

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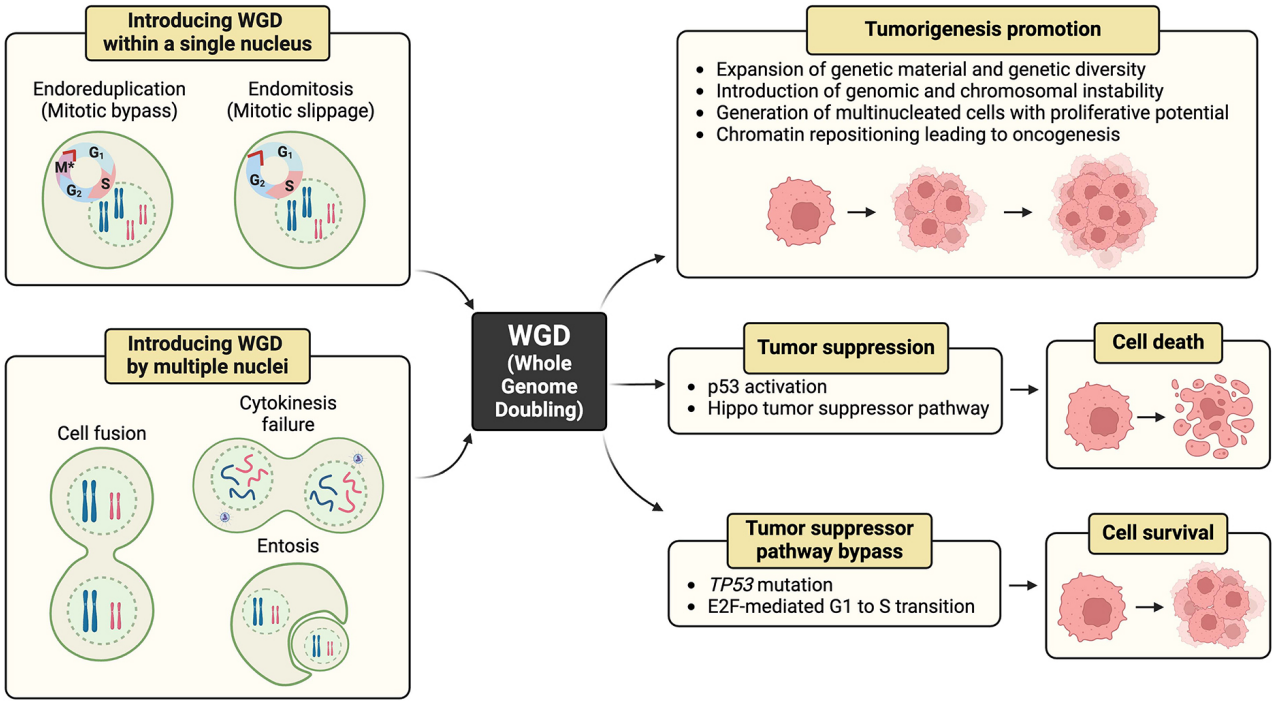

Fig. 1. Possible causes and effects of WGD. WGD can arise from diverse scenarios, categorized into introduction within a single nucleus and introduction by multiple nuclei. WGD exhibits dual effects, either promoting or suppressing tumors. Tumor-suppressing pathways can induce cell death, but these can be bypassed through *TP53* mutations or other genetic alterations associated with E2F-mediated G1 to S transition. The figure is created with BioRender.com.

sources. A study illustrated that extensive telomere shortening in p53-deficient cells leads to replicative stress and prolonged DNA damage signaling, initiating endoreduplication, including bypassing mitosis and cell transitioning from G2 to G1. Subsequently, cells can enter a second S phase even without conventional mitosis, leading to WGD facilitated by the degradation of the replication inhibitors geminin and Wip1 through the action of APC/Cdh1 (12, 13). Moreover, in cells with functional p53, replicative stress resulting from *CCNE1* amplification can activate APC/Cdh1, promoting endoreduplication (14). This indicates that regardless of p53 status, cells under replicative stress may undergo endoreduplication through APC/Cdh1 activation.

Endomitosis is similar to endoreduplication in that the cell division process is omitted, but the cells enter mitosis. If kinetochores are not properly attached to the mitotic spindles, the spindle assembly checkpoint (SAC) induces mitotic arrest before entering anaphase. Following SAC activation, cyclin B is continuously degraded via proteolysis, causing cells to exit mitosis and enter the G1 phase, eventually leading to a WGD event (15).

The presence of multiple nuclei within a single cell causes WGD in various instances, as observed during failure of cytokinesis, cell fusion, and entosis (Fig. 1). Cytokinesis is the last step of the cell cycle, involving the division of a cell into two daughter cells, and failure of this step generates cells with two nuclei, doubling the genome. Cytokinesis failure is one of the mechanisms that induces errors in chromosome segregation, such as chromosome non-disjunction, where one daughter cell contains both chromosome copies, promoting cleavage furrow defects and eventually leading to the formation of binucleated cells (16).

Cell fusion has also been implicated in WGD. The activation of oncogenes or inactivation of p53, combined with viral-induced cell fusion, can produce tetraploid primary human cells (17). This suggests that seemingly harmless viral infections can initiate cancer development by inducing WGD.

Entosis (cell cannibalism) is defined as a large cell engulfing a smaller cell, creating a cell-in-cell structure. The term “entosis” was coined after the Greek word entos, which means inside, into, or within. During entosis, two epithelial cells establish adherent junctions, facilitated by E-cadherin, followed by engulfment through a mechanism dependent on Rho-GTPase and Rho-kinase (18). Notably, entosis induces WGD by interfering with cell division, leading to the formation of binucleate engulfing cells, potentially contributing to tumor progression (19). Therefore, WGD may occur due to various circumstances, including errors in the cell cycle and the unification of two

cells, ultimately contributing to tumorigenesis.

WGD promotes tumorigenesis

WGD plays a crucial role in promoting tumorigenesis, and several mechanisms and consequences contribute to its impact on cancer development. Initially considered an event predominantly relevant to evolution and certain physiological processes in specialized cell types, WGD is increasingly recognized as a crucial driver of tumorigenesis in humans. Unlike fish and amphibians, where polyploidization is well tolerated, WGD is not well tolerated in humans (20, 21). However, specialized human cell types, including hepatocytes, megakaryocytes, myoblasts, and trophoblasts, undergo physiological polyploidy to support wound healing and tissue regeneration (21). This physiological polyploidy provides the foundation for understanding the potential role of WGD in cancer development.

WGD promotes tumorigenesis due to an increase in the genetic material, conferring redundancy and genetic diversity to cancer cells. WGD may be a crucial evolutionary step that offers redundant genes, creating opportunities for new evolutionary pathways. Normal cells may exploit WGD as a short-term strategy to expand gene function for adapting to environmental stressors (22). Conversely, cancer cells, known for their rapid evolution, often undergo WGD events to mitigate detrimental somatic alterations and foster clonal evolution. This is particularly evident in cancers with a high rate of deleterious alterations, such as lung squamous cell carcinoma and triple-negative breast cancer (5).

The role of WGD in promoting tumorigenesis is associated with chromosomal instability (CIN). Most cancer cells are extensively aneuploid and exhibit dynamic karyotypic alterations involving the gain or loss of entire chromosomes. WGD often occurs early in cancer development, contributing to CIN, which expedites the gain of oncogenes and removal of tumor suppressor genes, driving tumorigenesis. This process involves the generation of tetraploid cells that serve as intermediates in promoting CIN and aneuploidy. Further, the existence of supernumerary centrosomes, a characteristic feature of tetraploid cells, contributes to aggressive tumor behavior and tumorigenesis (2, 17, 23-25).

Moreover, WGD-induced genomic instability can lead to the generation of multinucleated giant cells with proliferative potential and stem-like characteristics. These cells can undergo multipolar mitosis and revert to diploids, contributing to tumor relapse after initial therapy. This multistep process of evading cell death through WGD, followed by depolyploidization, has been implicated in tumor formation and therapy resistance (26-28).

Furthermore, a recent study revealed how WGD-positive cells acquire oncogenic properties by investigating the 3D chromatin architecture of mononucleate WGD cells lacking p53. In normal cells, chromosomes are spatially highly organized because their structure is crucial for normal gene expression. However, when cells undergo WGD, the boundaries between the active transcription site (compartment A) and the suppressed site (compartment B) become less distinct, resulting in the repositioning of chromatin sites linked to oncogenes into compartment A, whereas tumor suppressors are shifted to compartment B, leading to oncogenesis (9, 29).

Overall, tumorigenesis promotion by WGD involves diverse mechanisms, including expansion of genetic material, CIN, aneuploidy, and breakdown of conserved genomic topologies. This genomic complexity provides cancer cells with the raw materials and evolutionary flexibility necessary for rapid evolution and adaptation, making WGD a critical player in cancer development and progression.

WGD induces tumor suppressor pathways

A recent study revealed that cells accumulate significant DNA damage in the initial S phase after WGD, regardless of its origin (endoreduplication, endomitosis, or cytokinesis failure). Using single-cell DNA sequencing, this study revealed that WGD cells in S phase already exhibited aberrant karyotypes with several amplified and deleted genomic regions before their first division. This was attributed to a shortage of DNA replication factors during the S phase in WGD cells, leading to a reduction in replication sites and an increase in replication stress (30). This study demonstrated that DNA damage occurs immediately after WGD. In response to this damage signal, cells employ various mechanisms to suppress the proliferation of WGD cells by halting the cell cycle by activating the p53 and Hippo tumor suppressor pathways.

The tumor suppressor p53 plays a central role in inducing cell cycle arrest in genome-doubled cells resulting from various cellular events, as evidenced by several studies (1, 2, 10, 14). One study focused on $p21^{WAF1}$, a transcriptional product of p53 that causes a G2 delay following DNA damage. Cells adapted to DNA damage after G2 delay, progressed to mitosis, experienced insufficient chromosome segregation, and re-entered the G1 phase in a tetraploid state. However, $p21^{WAF1}$ again induced G1 arrest, blocking further cell proliferation (31). Notably, elevated levels of $p21^{WAF1}$ and repression of Skp2 for CDK2 inactivation, hypophosphorylation of pRb, and elevated concentrations of cyclin E collectively prevent the dissemination of errors in mitosis (10, 32).

In addition to the DNA damage response, p53 is also activated by the Hippo tumor suppressor pathway. WGD activates LATS2 kinase, a key player in the Hippo tumor suppressor pathway, which inactivates the transcriptional regulators YAP and TAZ and stabilizes p53 (8). In addition, LATS2, in coordination with ASPP1, shunts p53 to pro-apoptotic promoters, promoting the death of polyploid cells (33). Collectively, these findings highlight the role of the Hippo tumor suppressor pathway and p53 in orchestrating cell cycle arrest and preventing the proliferation of WGD cells arising from replication stress.

Bypass of tumor suppressor pathway in WGD

WGD employs intricate strategies to circumvent tumor-suppressive effects, primarily through mutations in *TP53* or other genes that disrupt the G1 arrest capabilities. Numerous studies have consistently identified *TP53* mutations as the predominant gene alterations associated with WGD (1, 2, 34). Notably, even in *TP53* wild-type tumors, WGD can emerge with a high SCNA background, including amplifications in *MDM2*, *CCNE1*, and *CCND1* and deletions in *CDKN2A*, all of which are intricately linked to the E2F-mediated G1 to S transition (1, 34). These findings underscore the adaptability of WGD in navigating diverse genetic landscapes, employing alternative mechanisms to bypass tumor suppressor pathways and ensuring its progression in both *TP53*-mutated and wild-type contexts.

WGD IN VARIOUS CANCER TYPES

Pan-cancer

Several large-scale genomic studies have systematically investigated the genomic characteristics of WGD in various cancer types (Table 1). Quinton *et al*. analyzed approximately 10,000 primary tumor samples across 32 different tumor types from The Cancer Genome Atlas (TCGA) and found that approximately 36% of primary tumors experienced at least one WGD event during their evolutionary trajectory (2). Further, they estimated the WGD fraction in the entire genome using the ABSOLUTE algorithm (34, 35) and determined the WGD status of the tumors. WGD-positive tumors were significantly enriched for *TP53* and *PPPR21A* mutations. Although genes involved in inflammatory processes were downregulated, WGD-positive tumors showed increased gene expression in cell proliferation and DNA repair pathways. Notably, *KIF18A*, a mitotic kinesin protein-encoding gene, was crucial for WGD-positive cell viability. Recently, Steele *et al*. scrutinized copy number alterations across 9,873 tumors and 33 cancer types from TCGA and found eight copy number signatures associated with WGD (36). These signatures included high ploidy (CN2, CN3), a focal LOH signature prior to genome doubling events (CN10, CN11), chromosomal instability in conjunction with one genome doubling event (CN12), and chromosomal- or arm-scale losses before WGD events (CN14, CN15, CN16).

Bielski *et al*. prospectively collected data from patients with advanced cancer (9,692 panel-based sequenced samples) and found that approximately 30% of the cases were WGD-positive (1). Similar to the findings of Quinton *et al*., WGD-positive tumors were significantly associated with *TP53* mutations. However, a substantial proportion (46%) of WGD-positive tumors were *TP53*-wild-type and were enriched for *RB1* and *BAP1* mutations and *CCNE1* amplification, indicating a deficiency in E2F-mediated G1 arrest.

In addition to the availability of large-scale genomic datasets, significant advances have been made in bioinformatics tools for predicting WGD in tumors. The FACETS algorithm, applicable to whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted sequencing data (37), was employed for WGD detection. Samples were defined as WGD-positive if the fraction of major allele copy number exceeded 2 across more than half of the autosomal genome. In a parallel study, the PURPLE algorithm was used to successfully detect WGD events in 56% of the cases from 2,520 pairs of metastatic solid tumors and normal tissue (38, 39). This algorithm is a purity ploidy estimator for WGS data and provides a comprehensive assessment of WGD status (39). Overall, these studies collectively are a valuable resource for WGD in tumors and the genetic associations and signatures of WGD across diverse cancer landscapes.

Lung cancer

Among all cancer types, lung cancer is the most common and exhibits one of the highest WGD frequencies. Notably, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) were the second and seventh most frequent bearers of WGD events, respectively, in prospectively sequenced cohorts of patients with advanced cancer (1). Subtypes of NSCLC: lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LSCC) showed 59 and 55% prevalence of WGD, respectively, in TCGA datasets (2). Complementary insights gleaned from the TRACERx initiative, which offers multi-regional data, indicate that 77% of patients with NSCLC experience at least one WGD event during the course of tumor progression, with 19% of tumors harboring subclonal WGD events, suggesting that WGD predominantly constitutes an early event in NSCLC tumorigenesis (40).

The high incidence of WGD in lung cancer may be due to the high rate of LOH within these tumors (5). Analysis of the TRACERx and TCGA datasets revealed that LOH precedes WGD and that haploid LOH and the frequency of WGD events were correlated across various tumor types. Notably, LSCC exhibited an enrichment of widespread LOH and concurrent WGD. Using a simulation model to gain insights into the progression of lung cancer, this study revealed that the positive correlation between LOH and WGD arises from their complementary roles, whereas deleterious mutations within the LOH region have the potential to trigger cell death. The subsequent occurrence of WGD following LOH serves as a buffering mechanism by increasing the number of genome copies, thereby enhancing cell viability (5).

Further evidence suggests that oncogene co-mutations play a pivotal role in the context of WGD in lung cancer, with these driver mutations preceding WGD events. In particular, patients with *EGFR*/*RB1*/*TP53*-mutant lung cancer exhibit a higher propensity for WGD than patients with other lung cancers (41). Evolutionary history reconstructions employing timing models have underscored that mutations in *TP53*, *RBM10*, *KRAS*, and *EGFR* manifest earlier than WGD in lung cancer among never-smokers (42). In addition, multi-region sequencing of Asian patients with LUAD has revealed that several truncal alterations in *TP53*, *CDKN2A*, and *RB1* collectively contribute to

Table 1. Findings and genetic alterations associated with WGD in diverse cancer types

Study	Cancer type	Description	Genomic associations
Quinton *et al*. (2021)	Pan-cancer	Up-regulation of a spindle-assembly checkpoint, DNA-replication factors, and proteasome pathways in WGD tumors	*TP53*/*PPPR21A* mutations
Priestley *et al*. (2019)	Pan-cancer	A high frequency of WGD in metastatic tumors	
Lopez *et al*. (2020)	Pan-cancer	WGD is caused by the high rate of LOH, especially in LSCC and TNBC	*TP53*/*PTEN*/*ZNF750*, *NOTCH1*/*SMAD4* mutations in LOH region
Bielski *et al*. (2018)	Pan-cancer	Association of WGD in wild-type *TP53* with G1 arrest defect me diated by E2F	*CCNE1* amplification, *RB1*/*BAP1* mutations
Carter *et al*. (2012)	Pan-cancer	A high frequency of WGD in epithelial cancers, such as colorectal, breast, lung, ovarian, and esophageal cancers; a high incidence of WGD in recurrent tumors	LOH in chromosome 9 and 10, and gains of chromosome 7 in glioblastoma
Offin *et al*. (2019)	Lung cancer	APOBEC-associated mutations and *EGFR*/*RB1*/*TP53* triple mutants	*EGFR*/*RB1*/*TP53* mutations
Zhang *et al*. (2021)	NSCLC	WGD in never smokers with tumor-suppressor gene mutations	*TP53*/*RBM10*/*KRAS*/*EGFR* mutations
Frankell *et al*. (2023)	NSCLC	Negative prognosis associated with sub-clonal WGD	*TP53* mutation, SBS4 signature
Bruin *et al*. (2014)	NSCLC	APOBEC signature related to WGD after sub-clonal separation in smokers	APOBEC signature
Nahar *et al*. (2018)	LUAD	WGD in *EGFR*-mutant Asian LUADs with truncal alterations including *TP53*, and loss of *CDKN2A* and *RB1*	*TP53*/*CDKN2A*/*RB1* mutations
Berenjeno *et al*. (2017)	Breast cancer	Centrosome amplification and WGD led by *PIK3CA* activation	*PIK3CA* mutation
Choudhary *et al*. (2016)	Breast cancer	A high frequency of TNBC and Her2 positive tumors; a higher risk of recurrence and death in WGD tumors	
Yates *et al*. (2017)	Breast cancer	Oncogene mutations including *TP53*, *GATA3*, *PI3KCA*, *AKT1*, and *ERBB2* occur before WGD in primary breast cancers	*TP53*/*GATA3*/*PI3KCA*, *AKT1*/*ERBB2* mutations
Newcomb *et al*. (2021)	Her2-driven breast cancer	A frequency of WGD in recurrent tumors and decreased tumor growth	
Minussi *et al*. (2021)	TNBC	WGD caused by clonal *TP53* mutation and LOH in primary TNBC and consequent transient genomic instability after WGD	*TP53* mutation and LOH
Kim *et al*. (2021)	CRC	A higher frequency of WGD in early-onset CRC than in late-onset CRC, especially in non-hypermutated early-onset CRC	*TP53*/*APC* mutations; focal amplifications in *MYC*, *IRS2*, and *EGFR*
Kabel *et al*. (2023)	CRC	Increased ctDNA detection likelihood, especially in early-stage disease, significantly augments with WGD presence	
Dewhurst *et al*. (2014)	CRC	WGD's early occurrence in CRC enhances aneuploidy tolerance and chromosome segregation error resilience, correlating with poorprognosis and heightened sensitivity for high-risk CRC detection compared to aneuploidy alone	Chromosome 4q loss
Benhard *et al*. (2021)	CRC	WGD enhances cell proliferation by boosting mitogenic signaling, establishing bipolar spindles, and reducing cell cycle inhibitor and DNA damage signaling	*SPINT2* and *USP28* loss
Vigano *et al*. (2018)	COAD	Up-regulation of stress and interferon signaling pathways in WGD; increased phosphorylation of mitotic proteins (KIF20B, TPX2, AURKA, and PLK1)	
Chan-seng-yue *et al*. (2020)	PDAC	High frequency of WGD in metastatic PDAC and its association with mutant *KRAS* imbalance	*KRAS* mutation
Baslan *et al*. (2022)	PDAC	Genomic progression in the development of PDAC via WGD	LOH in *TP53*
Notta *et al*. (2016)	PDAC	A high frequency of chromothripsis in WGD associated with poor outcome and metastasis	*TP53* mutation
Sakamoto *et al*. (2020)	PDAC	A high frequency of WGD in metastatic tumors	
Favero *et al*. (2015)	Glioblastoma	Subsequent replacement of clonal *IDH1* mutation by WGD in recurrent tumors	Translocation between *PDGFRA*-*CDK4* amplification

WGD: Whole-genome doubling; NSCLC: Non-small cell lung cancer; LUAD: Lung adenocarcinoma; TNBC: Triple-negative breast cancer; CRC: Colorectal cancer; COAD: Colorectal adenocarcinoma; PDAC: Pancreatic ductal adenocarcinoma; ctDNA: Circulating tumor DNA; LOH: Loss-of-heterozygosity; SBS4 signature: Single base substitution signature 4. It is one of the mutation signatures documented by the Catalogue Of Somatic Mutations In Cancer (COSMIC). This signature indicates direct DNA damage by mutagens in tobacco smoke (74).

the dysregulation of the cell cycle and consequently to WGD (43). Moreover, multi-region sequencing of 401 patients with NSCLC showed that WGD in NSCLC is preceded by the *TP53* mutation (40).

Smoking and high cytosine deaminase APOBEC-induced mutation loads are major risk factors for lung cancer. Notably, WGD is more likely to occur in tumors with smoking and APOBEC signatures in their genome. A truncal event of single-base substitution 4, a signature of smoking-induced mutations, increases the likelihood of subsequent WGD events in NSCLC (40). In ex-smokers with NSCLC, WGD tends to arise in the context of the smoking signature before subclonal diversification. However, in current smokers with sustained carcinogen exposure, the prevalence of smoking-related mutations diminished over time, whereas a signature representing the oncogenic mutations generated by some APOBEC family members increased, resulting in WGD after subclonal separation (44). Another study observed a correlation between APOBEC-associated mutations and *EGFR*/*RB1*/*TP53* triple-mutant lung cancers, which were also associated with an increased risk of WGD events (41).

Therefore, although WGD is an early event in tumorigenesis, haploid LOH, co-mutations in oncogenes, smoking signatures, and APOBEC mutation signatures occur earlier than WGD in lung cancer. Despite the prevalence of WGD in lung cancers, the relationship between WGD and overall survival remains unclear, except for the notable observation that subclonal WGD appears to be a negative prognostic factor for NSCLC (40).

Breast cancer

Breast cancer is a malignancy frequently associated with WGD. WGD has been observed in approximately 44 and 58% of patients with primary and metastatic breast cancer, respectively (2, 38). Clinically, breast cancer is classified as hormone receptor-positive (characterized by the presence of the estrogen receptor or progesterone receptor), HER2-positive (regardless of the hormone receptor status), or triple-negative breast cancer (TNBC). The prevalence of WGD varies across these subtypes. TNBC and HER2-positive breast cancers exhibit a higher incidence of WGD than hormone receptor-positive breast cancer (5, 45). Furthermore, analysis of the haploid LOH proportion in these breast cancer subtypes has revealed interesting patterns. TNBC and hormone receptor-positive samples displayed high and low proportions of haploid LOH, respectively, corresponding to their WGD prevalence. However, HER2-positive breast cancer exhibited a high proportion of WGD despite a low proportion of haploid LOH, indicating a unique genomic landscape (5).

WGD is more likely to occur in metastatic or recurrent breast tumors than in primary breast cancers, and its role may differ between primary and recurrent tumors (2, 38, 46). Single-cell DNA sequencing of eight primary TNBC samples revealed that after multiple LOH events and WGD, chromosomal aberrations continued to develop during primary tumor growth in TNBC (47). Although WGD promotes tumor growth in primary tumors, WGD in recurrent tumors is associated with decreased cell proliferation and increased survival under stress conditions, decelerating tumor formation and tumor growth in HER2-driven breast cancer (46). Similar to lung cancer, LOH and oncogene mutations, including those in *TP53*, *GATA3*, *PIK3CA*, *AKT1*, and *ERBB2*, have been reported to occur before WGD in breast cancer (5, 47-49). Notably, sustained activation of the PI3K pathway due to *PIK3CA* mutations induces centrosome amplification and increases tolerance to spontaneous WGD (48).

WGD is associated with poor survival in patients with breast cancer (1, 45). In particular, among patients with ER-positive/HER2-negative breast cancer, those with *TP53*-wild-type tumors significantly associated with a worse prognosis, whereas *TP53*-mutant samples did not show such significance (1). As mutation load is not a predictive factor for prognosis in these patients, WGD is an independent predictor of survival in *TP53*-wild-type ER-positive and HER2-negative breast cancers (1). WGD frequently occurs in breast cancer, particularly in TNBC and HER2-positive breast cancers, and is more common in metastatic and relapsed tumors than in primary tumors. Both lung and breast cancers experience oncogenic mutations before WGD. However, although the prevalence of WGD in breast cancer is lower than that in lung cancer, it contributes to worse survival in breast cancer, which is not necessarily the case in lung cancer. This suggests that although WGD is prevalent in many types of cancer, its impact can vary among different cancer types.

Colorectal cancer

Previous research has consistently emphasized the pivotal role of WGD as a critical prognostic factor in colorectal cancer (CRC). Notably, one study revealed that among *KRAS*-mutant CRCs, patients undergoing WGD exhibited a notably worse prognosis than those without WGD. Notably, WGD itself, rather than the accompanying chromosomal aberrations, can be used to predict prognostic outcomes (1). WGD has a better predictive performance than aneuploidy, making it a valuable prognostic marker for high-risk CRCs (4).

Although patients with CRC have been classified into molecular subtypes (50), a recent study revealed a distinct subtype of a non-hypermutated WGD event. This subtype is characterized by focal amplification in *MYC*, *IRS2*, and *EGFR*, along with early functional loss of *TP53*. Additionally, WGD is more prevalent in early-onset CRC, suggesting unique genomic alterations in specific CRC subgroups (51). Mutation timing analysis revealed that WGD often occurs as an early event preceding copy number losses in the majority of CRC cases, with subsequent selection favoring the loss of chromosome 4q (4). Notably, tolerance to aneuploidy and chromosome segregation errors is increased in WGD tumors (4, 52), due to the deletion of several genes (52). For example, the loss of *SPINT2*

correlates with the bypassing of G1 arrest, and deletion of *USP28* promotes centrosome clustering and facilitates cell proliferation.

Previous studies have demonstrated the clinical implications of WGD in CRC. A recent study analyzed the WES data of circulating tumor DNA (ctDNA) from 833 patients with CRC and found that WGD was associated with a 53% increased likelihood of detecting ctDNA (53). Therefore, WGD significantly enhances ctDNA detection, particularly in the early stages of disease, thereby aiding in the early detection of CRC. Another study revealed increased phosphorylation of the mitotic proteins KIF20B, TPX2, AURKA, and PLK1 in WGD cells through quantitative proteomic analysis of colorectal adenocarcinoma cell lines. Importantly, WGD in CRC cells exhibits heightened sensitivity to compounds targeting PLK1, suggesting that applying PLK1 inhibitors in patients with WGD-positive colon cancer may be a promising therapeutic strategy (54). Therefore, a comprehensive understanding of WGD may further delineate better diagnostic and therapeutic strategies, ultimately improving the outcomes for patients with CRC with WGD.

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC), characterized by its aggressiveness and limited therapeutic options, is a formidable adversary in the field of oncology. Recent studies have found a positive correlation between WGD and the metastatic potential of PDAC (55, 56). One study identified five distinct subtypes of PDAC, each associated with unique molecular signatures (55). Notably, basal-like-A and -B subtypes demonstrated intriguing links between *KRAS* imbalance and ploidy status, with minor and major imbalances in diploid and tetraploid tumors, respectively. Furthermore, a high frequency of *KRAS* imbalance and WGD was observed in metastatic PDAC tumors, indicating the role of WGD in fostering *KRAS* imbalance during metastatic progression.

Additionally, WGD in PDAC is intricately linked to the evolutionary dynamics of the disease. WGD tumors have a high incidence of *TP53* mutations and chromothripsis, a phenomenon of catastrophic genome rearrangement. A study revealed that chromothripsis occurred on chromosomes 8 and 15 before WGD and on chromosomes 13, 16, and 18 after WGD. Further, patients with chromothripsis had worse overall survival, indicating the clinical implications of these genomic aberrations (57). Another study further elucidated genomic evolution during PDAC development. The sequential phases involved LOH in *TP53*, accretion of deletions, WGD, and increased amplification, suggesting stepwise progression of genomic alterations and a complex landscape in advanced PDAC (58). Owing to its association with metastasis and involvement in the evolutionary dynamics of the disease, WGD has emerged as a central player in the intricate interplay of genetic alterations in PDAC.

Glioblastoma

Despite the small fraction of patients with WGD (2, 34, 38), investigations have consistently reported instances of chromosomal amplification in glioblastomas. A comprehensive analysis of 40 glioblastomas using fluorescence *in situ* hybridization (FISH) identified 26 cases with an excess of chromosome 7 copies, of which 17 exhibited high-level *EGFR* gene amplification as extra-chromosomal circular DNA (ecDNA) (59). This was further delineated by a copy number signature (CN8) that was strongly correlated with ecDNA (36). In glioblastomas, this signature is enriched on chromosome 7, where the *EGFR* is located. This signature has also been described as a large-amplicon phenotype, referred to as tyfonas (60). Chromosome 7 amplification occurs before WGD in glioblastoma (34). Chromosomal 12q amplification has also been frequently reported in glioblastomas. WGS and FISH data from glioblastoma showed that *CDK4* and *MDM2* were located in 12q, possibly due to chromothripsis (61), which further showed an association with the large-amplicon phenotype, tyfonas (60). A patient with 12q amplification showed substantial disease remission after personalized treatment with the CDK4/6 inhibitors, nelfinavir, and leflunomide (62).

Therefore, understanding intratumor heterogeneity within glioblastomas and its relationship with WGD is essential. One study revealed a correlation between the co-occurrence of *EGFR* and *CDK4* amplification and increased infiltration of immunosuppressive macrophages in glioblastoma using spatial protein profiling and single-cell spatial mapping of FISH (63). This highlights the importance of high-throughput assessment at the single-cell level for predicting the immune state of glioblastoma, which is a critical factor in devising effective therapeutic strategies. The evolution and clonal dynamics of WGD in glioblastomas have also been investigated. An in-depth analysis of a recurrent glioblastoma case revealed that a clonal *IDH1* mutation was later supplanted by a WGD event and translocation between the *PDGFRA* and *CDK4* regions of amplification. The disease progressed despite rapid sequencing and targeted therapy, underscoring the complexity of WGD-driven glioblastoma and the challenges in managing its evolution (64).

CLINICAL IMPLICATIONS OF WGD IN CANCER

Understanding the mechanisms underlying WGD in cancer has significant implications for developing novel therapeutic interventions. Targeting the vulnerabilities associated with WGD, such as specific genes or pathways, holds promise for more effective and selective cancer treatments. A notable example is the identification of KIF18A as a potential therapeutic target for WGD-positive tumors (2). Furthermore, multi-omics studies integrating genomic and proteomic datasets of cancer patients (65) have revealed some proliferative subtypes characterized by chromosomal instability and upregulated cell cycle or proliferation pathways (3, 66-72). This implicates WGD as the

underlying biological mechanism of these subtypes. Further investigation is required to elucidate the key phospho-signaling pathways and guide the development of targeted therapies for WGD subtypes.

Moreover, the clinical impact of WGD extends to the prediction of patient responses to antitumor treatments. Recent research has indicated that patients with metastatic melanoma with WGD exhibit better responses to immune checkpoint blockade (73). This observation highlights the potential utility of WGD as a predictive marker for treatment response in specific cancers. To further elucidate the role of WGD in cancer, in-depth investigations into tumor microenvironments and intratumor heterogeneity are crucial. Single-cell DNA or RNA-seq data may be useful for providing insight into how WGD influences these aspects of cancer biology. Continued research in this direction will contribute to a more comprehensive understanding of the role of WGD in cancer and its potential applications in personalized medicine.

CONCLUSION

WGD can emerge in various scenarios, and its impact on tumor progression varies greatly. Recent discoveries leveraging large-cohort genomics and transcriptomics have demonstrated how WGD shapes the development of malignancies in each tumor type and how it can be used for personalized therapies. Further studies are warranted to understand how WGD affects the tumor microenvironment and identify novel therapeutic target proteins to cure tumors with WGD. In addition, as WGD occurs early in tumorigenesis, more research is required to employ WGD for the early detection of tumors.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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