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REVIEW

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When 3D genome technology meets viral infection, including SARS-CoV-2

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Abstract

Mammalian chromosomes undergo varying degrees of compression to form three-dimensional genome structures. These three-dimensional structures undergo dynamic and precise chromatin interactions to achieve precise spatial and temporal regulation of gene expression. Most eukaryotic DNA viruses can invade their genomes into the nucleus. However, it is still poorly understood how the viral genome is precisely positioned after entering the host cell nucleus to find the most suitable location and whether it can specifically interact with the host genome to hijack the host transcriptional factories or even integrate into the host genome to complete its transcription and replication rapidly. Chromosome conformation capture technology can reveal long-range chromatin interactions between different chromosomal sites in the nucleus, potentially providing a reference for viral DNA-host chromatin interactions. This review summarized the research progress on the three-dimensional interaction between virus and host genome and the impact of virus integration into the host genome on gene transcription regulation, aiming to provide new insights into chromatin interaction and viral gene transcription regulation, laying the foundation for the treatment of infectious diseases.

KEYWORDS
3D genome, chromatin interaction, HBV, Hi-C, SARS-CoV-2, viral infection

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[Correction added on 25 August 2022, after first online publication: The affiliation 9 has been added for Chunfu Zheng.]

1 | INTRODUCTION

The living organism is a highly complex and precisely regulated system, and the most important carrier to regulate biological activities is the genetic material-DNA. DNA is not linearly arranged in eukaryotes but is delicately folded step by step into a highly compressed chromosomal structure and stored in the nucleus. For the human genome, the expanded length of genomic DNA of a normal somatic cell is about 2 m, while most cells' nuclei diameter is less than 10 μm. Biologists have always been curious to understand the process of DNA folding in detail. In this highly compressed and dynamically changing microspace, how the genetic information is effectively transmitted to RNA and guides protein translation in the genome should be explored. Does DNA have a unique spatiotemporal structure in various nuclei? What is the relationship between this compressed structure and the precise regulation of cell fate determination, growth and development, and other life activities? For decades, biologists have been trying to unravel these mysteries. Due to the limitation of technology development, early research mainly focused on one-dimensional (linear genome sequence, annotation of genes and their regulatory unit) and two-dimensional (different genome sequence interactions) at the genomic level.[1] With the completion of the Human Genome Project (HGP) and the Encyclopedia of DNA Elements (ENCODE), scientists realized that the regulation of subcellular life activities, such as gene transcription, could not be adequately explained at the one-dimensional and two-dimensional levels of the genome.[2,3] Based on the one-dimensional genome sequence and its gene structure, the three-dimensional (3D) spatial structure of the genome must be considered.[4] The 3D genome structure plays a key regulatory role in important biological processes such as gene transcription, DNA replication and repair, cell division, and differentiation.[5–8] Aberrant alterations in long-range interactions can cause the expression changes of developmental and tumor genes, which are closely related to developmental disorders and cancer.[9]

There are many approaches to investigate the interaction between virus and host, of which various omics methods have been employed to investigate the interaction characteristics of both at different levels. Scientists observed chromosome morphology changes in early studies by an electronic microscope.[10] The fast development of epigenetic research techniques enables scientists to understand the interaction between viruses and the nucleus. For example, viral proteins can mimic the host's regulatory proteins to hijack the regulatory system of the host. Based on this, to reshape the chromatin conformation of host cells to regulate gene transcription and expression.[11] During the mitotic stage of the host cell, the viral genome hinges on the host's chromatin to ensure virus genome replication as host mitosis.[12] In addition, viruses also participate in the remodeling process of the cellular microenvironment, affecting the differentiation of cells. Most of these associated genes are related to the maintenance of chromatin conformation.[13,14] At the same time, the chromatin conformation also affects the latent infection of the virus, resulting in different types of latent infection.[15] It has been known that after the virus enters the host cell, the viral genome in the nucleus has a major impact on the host genome spatial structure leading to the viral genome being integrated into the host genome. However, the precise positional relationship between the viral and host genome in 3D space is not well studied. The analysis of this positional relationship is of great significance for elucidating the functioning of the virus.

This review first summarizes the current research progress of the 3D genome and its related technology, followed by the retrospection of the interaction between the virus genome and the host genome. Finally, we highlighted its potential prospects in treating infectious diseases, including SARS-CoV-2, as therapeutic targets.

2 | OVERVIEW OF THE 3D GENOME

Eukaryotic genetic information is stored in linear DNA sequences. However, gene expression requires folding chromatin into a complex 3D structure, forming DNA regulatory elements to achieve precise regulation of gene expression. DNA is encapsulated in histone octamers in chromatin, forming 10 nm nucleosomes that are efficiently and sequentially packaged into a complex multilayered structure (Figure 1). Bickmore et al. analyzed the nuclei in the interphase of chromosome division and found long fragments of nuclear chromatin space and chromatin territory in the nucleus, and there are short fragments of enhancer-promoter junction regions.[16] These 3D structures of chromatin have essential effects on gene expression and regulation. With the assistance of high-throughput chromatin conformation capture (Hi-C) and other technologies, researchers have discovered the existence of topologically associated domains (TADs). TADs, as the basic unit of genome folding, exist stably in various species and affect gene expression.[17] Several TADs in the nucleus comprise a relatively large structural unit called the chromatin compartment. The chromatin compartment is closely related to chromatin activity. Additionally, there is a more refined folded structure inside TADs, called a chromatin loop, which is usually formed by the interaction of promoter and enhancer, and it is the basic functional unit that directly regulates gene expression.[18]

2.1 | Chromosome territory (CT)

In the early 20th century, when cytologists studied animal and plant cells, they found that chromatin is not randomly distributed in the nucleus, and different chromatin occupies different spaces.[19] Then scientists found that in the interphase of living cells, the chromatin organization in the nucleus occupies a specific nonoverlapping region called CT (Figure 1).[20] The localization of CT in the nucleus correlates with gene density. Chromatin with low gene density tends to localize toward the periphery of the nucleus, while chromatin with high gene density occupies a more central position in the nucleus.[21] Other studies have found that CT occupies different cell cycle stages.[22] Each chromatin is confined to a specific nuclear space, and different chromatin overlaps only at CT boundaries.[23] CT overlapping regions may result from the passive mixing of chromatin fibers or may be influenced by the cell's translocation frequency of transcriptional state.[24]

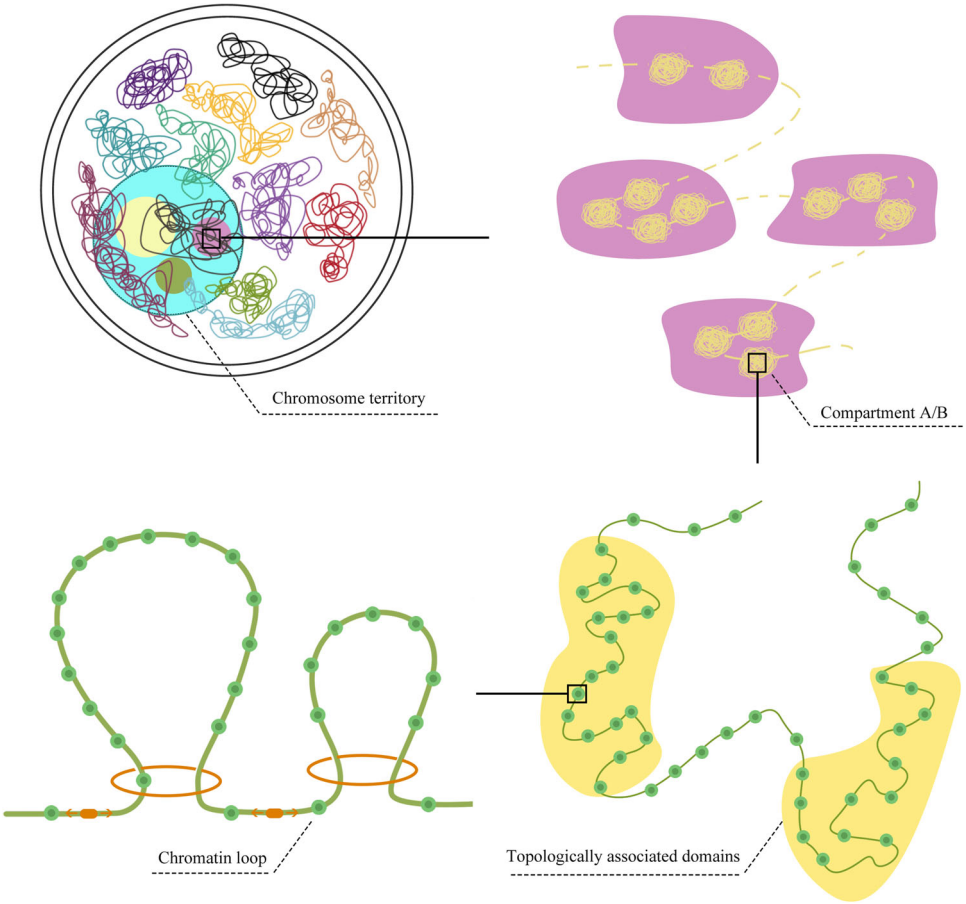

FIGURE 1 Three-dimensional (3D) genome architecture. At the 3D level, the structure of chromatin can be divided into four levels. The chromatin nucleus occupies a specific nonoverlapping region. This region is defined as chromosome territory. Within chromatin, multiple blocks can be observed. Those blocks are separated. This block is defined as Compartment. The finer unit of chromatin is called topologically associated domains (TADs). Each TAD can be an independent unit. The average length is 200 kb to 1 Mb. The finest unit of chromatin is the chromatin loop. It is a ring structure formed by folding simple chromatin fibers that can directly regulate gene expression.

2.2 | Compartments

When examined in detail, chromatin shows separate blocks within the chromatin and different patterns of interactions between adjacent blocks. In addition, the interactions among blocks with a long linear distance can also occur. In 2009, for the first time, the Hi-C technique was used to reveal the true situation of these blocks and proposed another important feature of 3D chromatin structure, namely chromatin compartments (Figure 1). These blocks can be divided into A Compartment and B Compartment.[25] A Compartment is an open chromatin compartment associated with euchromatin, gene-rich regions, and transcriptionally active regions, while B Compartment is a closed chromatin compartment, often found in heterochromatin, gene deserts, and low-transcription regions. Gene expression in B Compartment is lower than that of A Compartment, and this feature is highly correlated with epigenetic features. The A Compartment region is enriched with more transcriptional activation-related histone tags such as H3K36me3, while the B Compartment is enriched with more repressive histone tags such as H3K27me3. A Compartment and B Compartment is not randomly distributed. A Compartment is closer to the interior of the nucleus, and a B Compartment is mainly located near the nuclear lamina. The division of this pattern also corresponds to the distribution of euchromatin and heterochromatin.[26] In addition, there are many mutual transformations between A Compartment and B Compartment in the growth, development, and disease occurrence, indicating that the chromatin compartment has high plasticity.

2.3 | TADs

In 2012, Dekker's group discovered a series of discrete TADs with sizes between 200 kb and 1 Mb in the center of the mouse inactive X chromosome,[27] which is also confirmed by another group.[28] TADs are highly self-associated continuous regions with distinct boundaries between adjacent regions as a secondary structural unit of intracellular chromatin folding (Figure 1). Each TADs can form an independent regulatory unit. The position of TADs in different cells is relatively stable, and the localization is also conserved to a certain extent. Even in the differentiation process, TADs show a relatively stable state, but the frequency of interaction may vary.[28] Because

TADs are involved in regulating DNA replication, transcription, and epigenetic modification, disruption of TAD boundaries can have large-scale effects on gene expression and even lead to disease.

2.4 | Chromatin loop

As the refinement of chromatin interaction exploration at the 3D-genome level, biologists have observed finer structural units than TADs. At a resolution of 1 kb, the most refined structural and functional unit that directly regulates gene expression has been discovered: a ring structure formed by folding simple chromatin fibers —chromatin loops (CL, Figure 1).[29] The CLs do not overlap, and more than 86% of CLs have CCCTC-binding factor (CTCF) and cohesin subunits RAD21 and SMC3, indicating that CTCF and cohesin are also involved in forming Ls, similar to the formation of TAD boundaries. CL formation is closely related to promoters, enhancers, CTCF binding sites, and long-distance interactions. Since enhancers always control nonadjacent genes over long distances through CL, the definition of enhancer target genes is also the focus of research to explore how CL affects gene expression.

3 | 3D GENOME TECHNOLOGY AND ITS DERIVATIVES

Microscopic examinations were used to conduct the original 3D genome study, such as fluorescence in situ hybridization (FISH) and microscopy methods that enable single-cell analysis of gene localization.[30] However, at genome and cell population scales, they have limited throughput and resolution and thus may not be able to discover general principles of nuclear organization or characterize individual genes efficiently and clearly. Chromatin conformation capture technology, originally designed to measure the frequency of two genomic loci interactions in 3D nuclear space, has opened the door to chromosomal interactions. With the progress of science and technological innovation, this approach has evolved in qualitative and quantitative aspects. It can detect pairwise interactions at two specific loci and genome-wide chromatin interactomes. Moreover, combined with epigenetic analysis, the principles of universal genome folding are revealed.

3.1 | 3C (chromatin conformation capture technology)

The 3C technology was developed by Job Dekker in 2002 and was first applied to the study of chromatin interaction in yeast.[31] 3C is mainly used to detect interactions between specific and adjacent DNA loci (Figure 2). This technology first covalently links spatially adjacent chromatin fragments through cell cross-linking and then digests the cross-links with restriction endonucleases. Spatially close DNA fragments are preferentially ligated by T4 DNA ligase at very low DNA concentrations, which greatly reduces random fragment ligation. Finally, quantitative polymerase chain reaction (PCR) is used in 3C technology to detect the relative abundance of newly joined fragments, thereby inferring whether there are physical interactions of target chromatin fragments. 3C technology requires rigorous operation, intermediate quality control, and control settings.

3.2 | 4C (circular chromatin conformation capture technology)

4C technology was developed to screen candidate fragments interacting with the target fragment on a genome-wide scale.[32] The pivotal technique of 4C is to connect the two cross-linked DNA molecules into a circle and perform reverse PCR with specific primers of the target DNA fragment (Figure 2). In this way, only one pair of primers is enough to explore the interaction frequency of a specific site with all possible interaction sites. Comparatively, 3C technology can be summarized as the study of one-to-one technology. 4C technology can be summarized as the study of one-to-many technology.

3.3 | 5C (chromatin conformation capture carbon copy technology)

To capture multilocus-to-multilocus interactions in parallel, a high-throughput 3C sequencing technology called carbon copy chromatin-conformation capture technology was developed, namely 5C technology.[33] After the 3C library is generated, it is amplified by ligation-mediated amplification (LMA), connected with single-stranded oligonucleotide probes in a multiplex PCR reaction, and created to form a 5C library (Figure 2). Finally, the interactions between multiple DNA sequence sites can be measured simultaneously using multiplexed primers and next-generation sequencing techniques.

3.4 | Hi-C

To achieve high-throughput chromatin interaction analysis, Dekker's group developed a high-throughput chromatin conformation capture technology, namely Hi-C technology.[25] This technique is a high-throughput version of the 3C technique, capable of detecting all interactions at all genomic loci of interest (Figure 2). Hi-C technology is established based on 3C technology. After enzymatic cleavage, biotin labeling is added at the end of the fragment. Then streptavidin-coupled magnetic beads are used to enrich the biotin-labeled fragments. Finally, high-throughput sequencing was performed to obtain genome-wide interaction information. Since it can provide high-precision interaction information between all chromatin loci on a genome-wide scale, Hi-C technology is widely used to mine gene regulatory elements, revealing cell spatiotemporal-specific chromatin conformation changes.

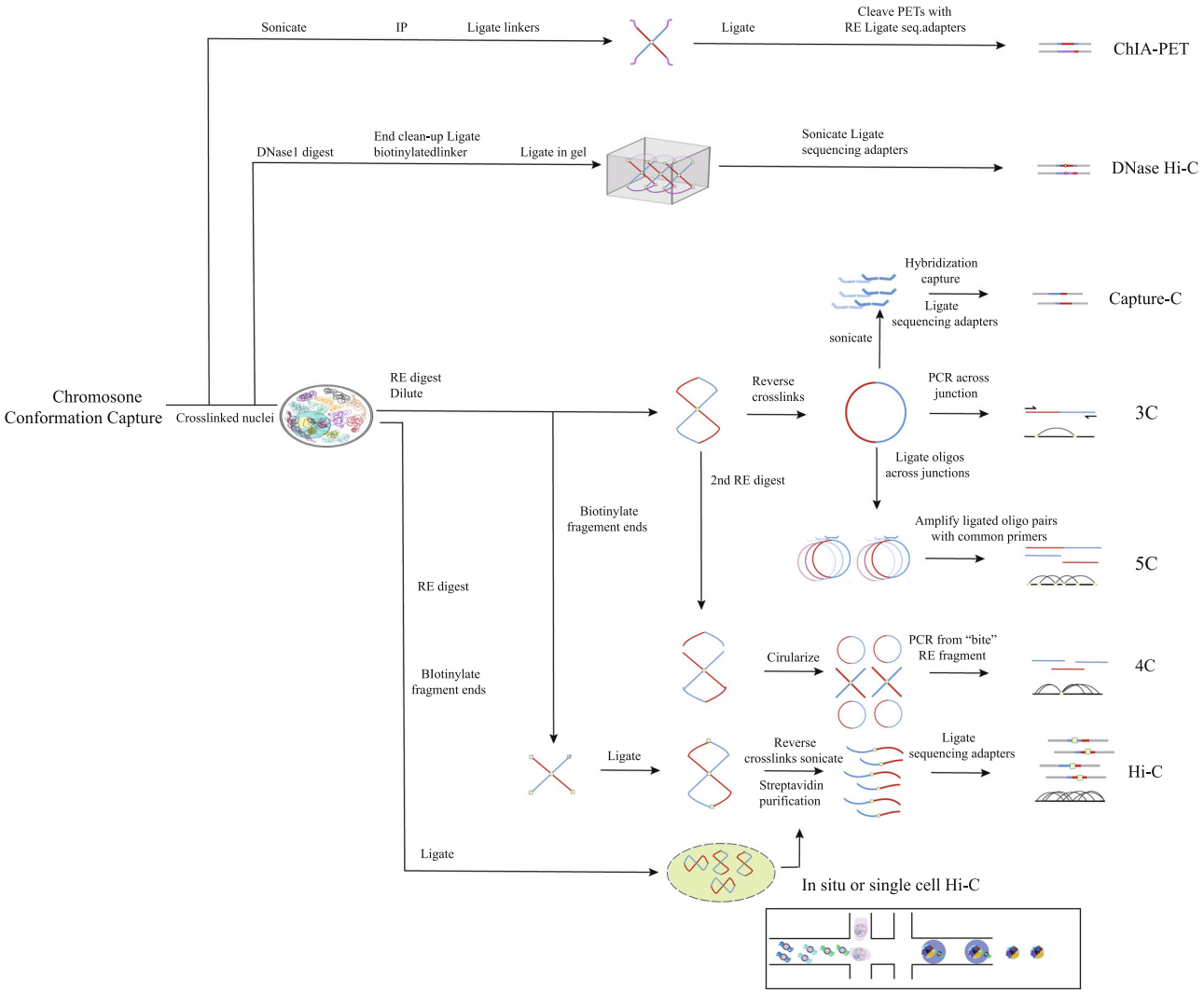

FIGURE 2 Schematic overview of three-dimensional (3D) technology. Several techniques have been employed to investigate chromatin structure from a 3D perspective.

3.5 | ChIA-PET (chromatin interaction analysis using paired-end tag sequencing)

ChIA-PET can be thought of as the combination of Hi-C and ChIP.[34] The technical principle of ChIA-PET is similar to that of ChIP-loop. After co-immunoprecipitating the DNA-protein complex with the specific antibody of the target protein, the library is constructed and sequenced to capture target protein-specific DNA interaction fragments on a genome-wide scale (Figure 2). ChIA-PET enables unbiasedly detect chromatin interactions on a genome-wide scale. This technique is considered an extension of ChIP-loop technology.

3.6 | Other derived technologies

Various Hi-C-derived technologies have been developed based on Hi-C technology, such as digestion-ligation-only Hi-C, tagHi-C, and other methods, including single-cell-based and imaging methods. Table 1 summarizes these methods, and the details of those techniques are not further discussed in this review. In summary, these methods expand the application field of Hi-C technology, reduce experimental noise and cost, and promote the study of chromatin structure.

4 | 3D GENOME AND COMMON VIRUS INFECTION

4.1 | 3D genome and hepatitis B virus (HBV) infection

The HBV was identified about 50 years ago by Dr. Baunch Blumberg and granted the 1976 Nobel Prize in Physiology and Medicine. Since then, the fight between humans and HBV has never stopped. HBV infection is one of the major global public health problems. Globally, around 260 million people suffer from chronic HBV infection, and

TABLE 1 Summary of 3D genome technology

3D technology	Year	Feature	References
3C	2002	One to one	[31]
4C	2006	One to many	[32]
5C	2006	Many to many	[33]
Hi-C	2009	All to all	[25]
ChIA-PET	2009	Protein specific + all to all	[34]
TCC	2011	All to all	[35]
Single-cell Hi-C	2013	All to all	[36]
Capture-C	2014	Many to all	[37]
In situ Hi-C	2014	All to all	[29]
Capture-Hi-C	2015	All to all	[38]
3CPET	2015	ChIP + many to many	[39]
Micro-C	2015	Micrococcal nuclease	[40]
DNase Hi-C	2015	DNase I	[41]
HiChIP	2016	ChIP + Hi-C	[42]
PLAC-seq	2016	Many to many	[43]
BL-Hi-C	2017	All to all	[44]
Single-nucleus Hi-C	2017	Single nucleus	[45]
sciHi-C	2017	Single-cell combinatorial indexing	[46]
GAM	2017	All to all	[47]
OCEAN-C	2018	All to all	[48]
DLO Hi-C	2018	All to all	[49]
Dip-C	2018	Single-cell + all to all	[50]
ChIA-Drop	2019	Single molecule	[51]
tagHi-C	2020	Low input fragmentation	[52]
SPRITE	2021	RNA and DNA	[53]
2D-FISH	1999	Imaging	[54]
3D-FISH	2008	Imaging	[55]
Cryo-FISH	2010	Imaging	[56]
CRISPRainbow	2016	Live cell imaging	[57]
seqFISH	2017	Live cell imaging	[58]
ChromEMT	2017	Imaging	[59]
CRISPR-Sirius	2018	Live cell imaging	[60]
MERFISH	2018	Imaging	[61]
SABER amplifies FISH	2019	Single-cell imaging	[62]

Abbreviations: BL-Hi-C, bridge linker-Hi-C; ChIA-PET, chromatin interaction analysis using paired-end tag sequencing; 3CPET, Chromosome conformation capture (3C) paired end tag sequencing; CRISPR-Sirius: clustered regularly interspaced short palindromic repeats-sirius; DLO, digestion-ligation-only; EMT, electron microscopy tomography; FISH, fluorescence in situ hybridization; GAM: genome architecture mapping; Hi-C, high-throughput chromatin conformation capture; OCEAN-C, open chromatin enrichment and network Hi-C; PLAC proximity ligation-assisted chIP; SABER, signal amplification by exchange reaction-seq; SPRITE, split-pool recognition of Iinteractions by tag extension TCC, tethered conformation capture; 3D, three-dimensional.

nearly 1 million die of liver failure, liver cirrhosis, and hepatocellular carcinoma caused by chronic HBV infection every year. Although there are many available therapeutic weapons against HBV, such as interferon and nucleoside drugs, the HBV genome can form covalently closed circular DNA molecules (cccDNA) in the nucleus of human hepatocytes integrated into the human genome. Its viral DNA can exist stable, so HBV infection can cause long-term chronic infection in the human body and is difficult to clear. Compared with hepatitis C virus (HCV), HBV is more difficult to treat as HBV belongs to the family of Hepadnaviridae, and the cccDNA can utilize host cells' transcription and translation mechanism to synthesize all RNAs and proteins required by HBV. The existing hepatitis B treatment drugs (nucleoside analogs such as lamivudine) can inhibit HBV replication by inhibiting the function of p protein (HBV polymerase), but they cannot remove cccDNA and integrated viral DNA in infected cells. Therefore, if the patients infected with HBV stop regularly taking the antiviral medicine, the viral DNA can use the transcription and translation mechanism of the host cell to resynthesize the RNA and protein required by HBV, thereby completing the virus replication.

On the contrary, HCV is much milder. HCV is a positive-strand RNA virus. There is no cccDNA-like intermediate during its replication. HCV-infected patients can effectively reduce the level of HCV RNA after taking antiviral drugs, thereby eliminating HCV and eventually being cured. Therefore, discovering an efficient approach to clear the long-term stable viral DNA in the human cell nucleus is critical to treating HBV.

Therefore, this leads to a scientific question: how HBV cccDNA is integrated into the human genome and exists stably in host cells, and how can these viral DNA be effectively eliminated? First, clarifying the interaction mode and characteristics between viral DNA and host cells is necessary. To this end, two research teams used 3C-HTGTS technology in HBV-infected HepG2-NTCP cells and found that the interaction of HBV cccDNA with the host genome tends to be rich in active enhancers and promoters of histone modifications such as H3K4me3, H3K9ac, H3K4me1, and H3K27ac.[63] 3C-HTGTS is also a novel one-to-all chromatin interaction test method adopted by this group. This method only needs one step of restriction enzyme digestion and ligation of cross-linked chromatin, and in principle, any endonuclease that recognizes 4 bp sequences can be selected so that the degree of chromatin fragmentation and the detection of chromatin interaction can be detected with higher resolution. It is worth mentioning that the researchers also detected a new interaction pattern with this method: in HepAD38 cells infected by HBV, the integrated form of HBV-DNA can form a chromatin ring structure with the host genomic DNA and tend to interact with the promoter region of the host gene. The study also found that HBV cccDNA interacts with H3K4me1-rich regions in the host genome, and then it was found by chromatin co-immunoprecipitation (ChIP-qPCR) that HBV cccDNA indeed has abundant histone H3K4me1 modification. When the intracellular lysine-specific methyltransferase 2C/D (KMT2C/D), which mediates histone H3K4me1, was knocked down, HBV RNA transcription was significantly downregulated, and HBV surface antigen HBsAg and HBeAg secreted in the supernatant were significantly decreased, and the results suggested that HBV cccDNA could mediate viral transcriptional regulation through host methyltransferase. The greatest difficulty they encountered was too few available and easy-to-use HBV infection models, especially in vivo models.

Another study used Hi-C technology to explore the changes in the 3D structure of the host genome after infecting human hepatoma cells with HBV and Ad5 DNA viruses.[64] They found that HBV infection cannot change the 3D structure of host chromosomes, while Ad5 infection can change the 3D structure of host chromosomes. In addition, they also found that the HBV genome tends to bind to the CpG island region where cytokine cfp1 is rich, and CpG islands are often enriched in highly expressed and deregulated genes during infection; Ad5 is more likely to interact with TSSs and enhancers regions. Meanwhile, the study suggested that the ability of viruses to target specific regions facilitates their replication and transcription.

Tang et al. reported the distribution characteristics of viral DNA molecules in the nucleus of the host 3D genome after HBV infection of hepatocytes.[65] Through HBV sequence-based 4C sequencing analysis (chromosome conformation capture-based sequencing) and high-sensitivity HBV-specific FISH technology, researchers found a specific distribution pattern in the nuclei for invading HBV DNA. In particular, inactively transcribed HBV DNA is preferentially distributed in the nuclear region near host chromosome 19 (chr.19). Moreover, these nuclear HBV DNA molecules are not evenly distributed around chr.19 but mainly cluster around five regions of 12, 37, 44, 52, and 58 Mb on the chromosome. Human chr.19 is relatively smaller but has the highest gene density. These five regions are spatially close with heterochromatin characteristics through Hi-C sequencing, FISH analysis, and multi-omics data integration. Accompanied by the activation of HBV DNA transcription, its enrichment in those five regions on chromosome 19 was significantly reduced, while the enrichment in the transcriptionally active region of the host chromosome was significantly increased.

Further studies have found that this restricted localization mode of HBV is mainly regulated by the interaction of the SMC5/6 (structural maintenance of chromosomes) complex and its viral antagonist HBV × protein (HBx) which is of great significance for the HBV nuclear localization.[66] This study elucidated an important previously unknown feature of HBV, deepened the understanding of HBV infection, and provided new perspectives for developing new treatment options. In addition, the related methods developed in this study also provided a powerful technical means to explore the relationship between virus and host using cccDNA as a model.

Recently, studies found that cccDNA could interact with the human genome 19p13.11 locus in hepatoma cells, including active enhancer elements.[67] This process is mediated by the crosstalk between host cell protein YY1 (Yin-Yang 1) and viral protein HBx, which increases the transcription of the viral cccDNA. This study provided insight into HBV utilizing the host cell to regulate its transcription activity, suggesting that YY1 can be developed as a potential target for the future treatment of HBV infection. In addition, D'arienzo et al. suggested that CTCF could affect HBV transcription activity by repressing the enhancer I.[68]

All in all, HBV can affect the host gene expression by various mechanisms. It cannot only directly influence the gene expression by integrated into the proximal locus of the target gene[69–72] but also perform a function by distal interaction or disrupting the 3D genome structure.[73–76]

4.2 | 3D genome and herpesviruses infection

Herpesviruses are a family of large genomic DNA viruses capable of infecting various vertebrate hosts, including humans. Most eukaryotic DNA viruses, such as herpesviruses, can transport their genomes into the nucleus. Recently, one team utilized pseudorabies virus (PRV) as a model virus and performed chromosome conformation capture analysis to demonstrate specific cross-species genome-wide chromatin interactions between virus and host.[77] The results show that the PRV genome interacts with host chromatin open regions and transcriptionally active regions, mediated by the host DNA-binding protein RUNX1, which helps the virus hijack the host type II RNA polymerase (RNAPII) for efficient transcription of viral genes. RUNX1 inhibitors or RNA interference significantly inhibits the transcription of such viral genes. This discovery provided new insights into the interaction between viral and host genomes and elucidated the molecular mechanism of preferential transcription of viral genes, which also supports opening novel research areas to promote our understanding of herpesvirus gene expression.

KSHV (Kaposi's sarcoma-associated herpesvirus), another type of Herpesviruses, is an important human tumor virus closely related to the occurrence of malignant tumors such as KS (Kaposi's sarcoma), PEL (primary effusion lymphoma) and MCD (multicentric Castleman disease).[78–80] In a recent study, the researchers utilized Capture Hi-C to investigate the genomic structure of KSHV and revealed that the dynamic chromatin structure plays an important role in the gene expression regulation of the virus, which brings a new idea for the treatment of KSHV-mediated tumors in the future.

4.3 | 3D genome and influenza A virus (IAV) infection

Influenza A is a common influenza virus that is highly contagious due to its easy mutation. People infected with the IAV have typical flu symptoms. In a recent study, scientists used the IAV to infect monocyte-induced macrophages and explored the changes at the transcriptomic, epigenetic, and 3D genomics levels.[81] Using different control conditions and control models (Mock infection, NS1 deletion), they found that the NS1 protein can inhibit transcription termination and sustains transcription even after the 3′ end of the gene (up to 850 kb). The continuous transcription downstream of the 3′ end of such genes is the cause of changes in the compactness of the 3D structure of the genome, which can also lead to the transition from B Compartments to A Compartments.

Furthermore, they investigated how continuous transcription downstream of the 3′ end gene affects the 3D structure of the genome. They found that continued transcription downstream of the 3′ end gene was accompanied by enhanced RNAPII signaling at the associated CTCF-binding site and a corresponding decrease in cohesin signaling. Attenuating cohesin signaling in transcribed regions is a direct factor behind the reduction of long-range chromatin interactions and the tighter degree of genome compaction. Through this study, for the first time, it can be found that, at the genome level, gene transcription can affect the 3D structure of the genome and the tightness of genome compression, providing a new perspective on the dynamic changes of the genome. In future work, we can expect researchers to select and generate different models of DNA replication and damage repair to study the impact of these biological functions on the 3D structure of the genome.

4.4 | 3D genome and Epstein–Barr virus (EBV) infection

EBV was discovered in African Burkitt's lymphoma more than 50 years ago, the first human tumor virus.[82] EBV has the characteristics of infecting human and primate B cells exclusively in vitro and in vivo. Recently, scientists reanalyzed previous EBV Hi-C data with 10 kb resolution. Over 15 000 contacts were identified between EBV and the human genome.[29,83] In active chromatin locations, these contacts are highly enriched in H3K27ac and H3K4me1.

Furthermore, these sites are bound not only by TFs regulating B cell growth, such as RUNX3 and IKZF1, but also by factors promoting virus replication and cell proliferation, such as NBS1, NFIC, and HDGF. This study indicated that EBV mainly interacts with the active regions in the human genome of lymphoblastoid cells. In addition, Lieberman and colleagues systematically investigated the global interactions between the host genome and EBV episomes.[84] They showed that the interaction sites are bound by the host cell and viral factors, such as EBF1, RBP-jK, and EBNA1. Meanwhile, epigenetic repressive marks, H3K9me3, are enriched at these loci. In another study, researchers explored the interaction changes from latency to reactivation, and they found that the interaction sites changed from the heterochromatin region to the euchromatin loci.[85] Moreover, researchers presented an “enhancer infestation” model in a recent study to describe a novel mechanism regulating gastric cancer progression.[86] The results indicated that the EBV genome could affect the host epigenome directly, promoting tumorigenesis.

4.5 | 3D genome and parvoviruses infection

Parvovirus is an envelope-less, single-stranded DNA virus with the ability to infect humans.[87] Minute virus of mice (MVM), one type of Parvovirus with a 5 kb genome, can encode two proteins, NS1 and NS2. NS1 is responsible for viral replication, and NS2's function is

unknown.[88] In a recent study, researchers used V3C-seq technology to investigate the global interactions between the virus and the host genome.[89] The results showed that the MVM genome localized to the host genome's DNA damage response (DDR) region, facilitating their replication and infection, which is mainly mediated by NS1 protein. This conclusion is also verified by another study.[90]

4.6 | 3D genome and human leukemia virus infection

Human leukemia virus type 1 (HTLV-1) is also called the human T-cell leukemia virus.[91] This virus can infect and integrate into the host genome. Most infected people are asymptomatic, and only a small part suffer chronic inflammation. In a recent study, Melamed et al. investigated chromatin structure changes after HTLV-1 infection, and they found that HTLV-1 can integrate into the host genome and affect the host gene expression by disrupting the chromatin structure.[92] It can function in two ways: proximal, by which the loop is formed between the virus and host genome; distal, by which the long-range interaction is produced and mediated by the host CTCF protein. In addition, similar mechanisms were conservative in mice.[93]

4.7 | 3D genome and HPV infection

Human papillomavirus, HPV, plays an important role in the occurrence and progression of cervical cancer.[94] HPV can infect and integrate into the host genome whereby executing function. In a previous study, the researchers utilized 3C technology to explore the HPV pathogenesis mechanism in HeLa cells in which the HPV genome is inserted into one allele of the host chromosome 8.[95] They proved that HPV could affect the MYC gene expression by forming long-distance interaction among HPV, 8q24.22, and MYC, thereby promoting cancer progression. In another study, Cao et al. performed multi-omics experiments, including Hi-C assay, to investigate the HPV interactome in patient samples. They found a new regulatory mechanism. HPV can disrupt the host genome by dividing one TAD into two TADs and altering the enhancer's subcellular location from PEG3 to CCDC10, increasing the expression of CCDC10,[96] as demonstrated in a recent study that host genome structure is disrupted by proximal and distal contact between the HPV and host genome.[97] In another study, people found that HPV insertion can alter the chromatin structure by adding a new CTCF binding site, leading to changes in multilayers, including chromatin accessibility, transcription, and post transcription, thus advancing the tumor progression.[98]

5 | 3D GENOME AND SARS-COV-2 INFECTION

SARS-CoV-2, one type of coronavirus, has seriously threatened human health and life since its outbreak in 2020. SARS-Cov-2 can cause different symptoms in patients, including fever, shortness of breath, dry cough, and hyposmia. Even worse, it has been reported that this virus affects the nervous system, including the central and peripheral nervous systems.[99]

As mentioned above, various viruses can integrate into the host genome and affect the 3D chromatin structure. Little is known about whether SARS-CoV-2 has similar behavior. Thus, it is worth to be investigated. Recently, a few studies began to investigate this. Researchers utilized the Hi-C technique to describe the global 3D genome changes after the infection of SARS-CoV-2 in A549 cells expressing ACE2.[100] The results showed that the host chromatin structure was largely remodeled after infection. In addition, the active region A Compartment began to attenuate, accompanied by the occurrence of A/B Compartment mix.

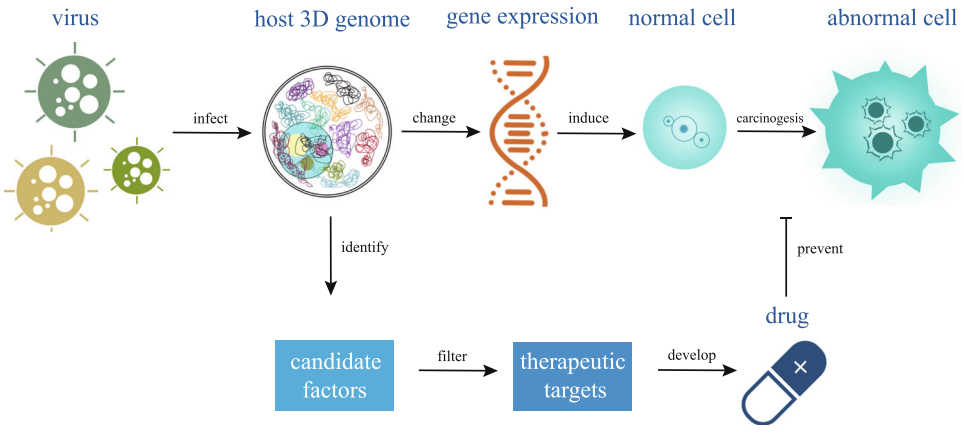

FIGURE 3 Three-dimensional (3D) genome and viral infection. During the process of viral infection, the viral genome can be integrated into the host genome and physiologically change the host's intracellular environment, which may lead to tumorigenesis. The studies of the 3D genome can unravel the mechanism of tumorigenesis from another perspective. It may bring direction to explore strategies for cancer treatments related to viral infection.

Moreover, the contacts within TADs also decreased. Meanwhile, the linker protein cohesion almost disappeared among the TAD boundaries, thus destroying loop extrusion. These together resulted in the upregulation of inflammatory gene expression and the downregulation of the IFN gene expression, which contribute to the causing of the disease. Furthermore, they revealed a novel mechanism by which the virus could directly affect the transcription activity of inflammatory genes, which needs further exploration, which was also confirmed by another research group, observing that the genome-wide disruption of the host chromatin structure and the transition between A and B Compartment.[101] In another study, scientists systematically analyzed the blood samples of patients infected with SARS-CoV-2 using 3D technology.[102] They also developed an algorithm to confer the 3D genome as a biomarker for diagnosing COVID-19 patients.

6 | CONCLUDING REMARKS AND PERSPECTIVES

The discovery of the chromosomal spatial structure has led to new insights into the fundamental mechanisms of chromatin folding that influence gene expression and regulation. In this review, we systematically retrospect current advances in the 3D genome and highlight its applications and achievements in viral infections. The use of 3D genome technology to research new drugs has been increasingly recognized by scientists (Figure 3). However, there are still several issues to be addressed with this technique.

The first is to explore the role of RNA in the 3D genome. Current 3D genomics mainly focuses on the interaction between DNA and protein, while few studies are related to RNA. Several new technologies have been recently developed to interrogate the interaction between RNA and chromatin, such as GRID-seq and split-pool recognition of interactions by tag extension.[53,103] New approaches are needed in the future to elucidate the interactions between DNA, RNA, and proteins.

The second is the consideration of the time dimension. Temporal factors also play an important role in the 3D genome alteration, such as organism development and different periods of viral infection. The four-dimesional nucleosome project was launched to explore this issue.[104] As technology advances, the future direction should focus on clarifying the dynamics of the 3D genome in viral infection, thus further clarifying the mechanism of viral infection.

The third is the involvement of cutting-edge technologies, such as single-cell technology, gene-editing technology, and computational structural prediction. Single-cell technologies can be used to address the problem of heterogeneity. A single-cell-based 3D method can explain why different cells react differently to viral infection. 3D genome combined with gene-editing techniques can be used to study functional aspects of viruses. There have been breakthroughs in reconstructing the 3D structural domains of the RNA genome based on computer algorithms, which may change some of the conclusions of RNA structural biology and further elucidate the interactions between RNA, DNA, and proteins.[105,106] Imaging technology can be developed to visualize the 3D genome directly.

Various diseases seriously threaten human health. Although the research in the biomedical field has developed rapidly, many emerging infectious diseases such as Zika virus disease, dengue fever, and SARS-CoV-2.[107–109] Growing evidence suggests that changes in the 3D genome often accompany the occurrence of diseases. Using 3D genomics to explore alterations in the 3D chromatin structure such as CT, A/B Compartment, TADs, and CL before and after the occurrence of diseases, as well as changes in the interaction between different regulatory elements and target genes, can offer new insights in the pathogenic mechanisms of viral infection. In addition, it can also provide us the possibility of searching for potential biomarkers and screening therapeutic targets, which will finally bring us solutions for treating diseases.

AUTHOR CONTRIBUTIONS

Chunfu Zheng and Weizheng Liang contributed directly to this review. Weizheng Liang wrote the preliminary version of the manuscript. All authors were involved in the manuscript preparation, including figure modification, paper discussion, manuscript writing, and editing. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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