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REVIEW

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When cyclin-dependent kinases meet viral infections, including SARS-CoV-2

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Abstract

Cyclin-dependent kinases (CDKs) are protein kinases that play a key role in cell division and transcriptional regulation. Recent studies have demonstrated the critical roles of CDKs in various viral infections. However, the molecular processes underpinning CDKs' roles in viral infection and host antiviral defense are unknown. This minireview briefly overviews CDKs' functions and highlights the most recent discoveries of CDKs' emerging roles during viral infections, thereby providing a scientific and theoretical foundation for antiviral regulation and shedding light on developing novel drug targets and therapeutic strategies against viral infection.

KEYWORDS

CDKs, DNA viruses, RNA viruses, viral infection

1 | INTRODUCTION

Cyclin-dependent kinases (CDKs), including 20 members, are a family of serine/threonine kinases, collaborating with cyclins to guarantee proper cell-cycle progression.[1] CDKs are the primary regulators of cell division, capable of forming a heterodimer with cyclins to catalyze the phosphorylation of various substrates, resulting in cell-cycle transformation at various phases.[2]

The transcriptional CDK–cyclin complex controls gene expression through phosphorylation regulation. CDK7–cyclin H has been discovered to be involved in transcription.[3] However, the fundamental mechanism of mammalian CDK7–cyclin H transcription promotion requires additional exploration. A conserved subcomplex, the CDK8-dependent kinase module, interacts with the multisubunit transcriptional coactivator complex to control RNA polymerase II (RNA pol II)-dependent transcription.[4] By phosphorylating the negative elongation factor, CDK9, a component of the heterodimer of positive transcriptional elongation factor b (P-TEFb), controls the extension times of RNA pol II-dependent transcription.[5] CDKs are also crucial in viral infection because they induce type I interferon (IFN-I) via post-transcriptional regulation.[6]

CDKs are well-known for their function in cell-cycle regulation. Interestingly, the CDKs play important roles in antiviral responses, our recently published review has summarized how CDKs play their functions in antiviral innate immunity.[7] Interestingly, CDKs' pharmacological inhibitors affect viral infections,[8,9] suggesting that CDKs are also important in viral infections because DNA and RNA viruses may change CDKs and regulate the host cell cycle to produce a favorable environment for replication by deregulating cell-cycle checkpoints.[9,10] Our minireview will discuss current findings on the functions of CDKs in RNA viruses and DNA viruses to better understand the particular roles of CDKs during viral infection.

2 | THE EMERGING ROLES OF CDKS DURING VIRAL INFECTION

2.1 | The emerging roles of CDKs during RNA virus infection

2.1.1 | Human immunodeficiency virus (HIV)

Seven CDK family members have been found to have functions in the HIV replication cycle. Inhibitory phosphorylation of the antiviral factor sterile alpha motif histidine-aspartic acid domain (SAMHD1) by CDK1, CDK2, and CDK6 promotes HIV-1 reverse transcription in activated $CD4^+$ T cells and transformed cell lines.[11–16] Furthermore, Cyclin L2, a CDK11 regulatory partner, has been found to bind to SAMHD1 and target it for proteasome-mediated degradation, boosting HIV-1 replication in macrophages.[17] CDK2 has been shown to phosphorylate several cellular proteins involved in HIV-1 replication, such as CDK7, CDK9, and the viral transactivator of transcription (TAT) protein to enhance HIV-1 provirus RNA Pol II transcription[18–23] (Figure 1).

CDK7 is a subunit of transcription factors IIH (TFIIH), a universal RNA Pol II transcription factor.[24] In vitro, recombinant transcription factor nuclear factor NF-kappa-B p65 subunit (p65) drives HIV transcription by stimulating RNA Pol II carboxy-terminal dormain (CTD) phosphorylation via the CDK7 kinase module of TFIIH. By phosphorylating the CTD at the end of the RNA Pol II subunit, CDK7 can stimulate transcription initiation. CDK7 phosphorylates the S5 residue in the CTD of the phosphorylated RNA Pol II large subunit, consisting of 52 heptapeptide repeats. Under some circumstances, the recruitment of CDK7 from the TFIIH complex may be the rate-limiting step for HIV-1 reactivation from the latent phase.[25]

CDK9 belongs to a group of CDKs that activate RNA Pol II by stimulating elongation, a process in which RNA Pol II continues to synthesize additional RNA strands as it progresses along with the DNA template. The RNA Pol II elongation factor, also known as P-TEFb, comprises CDK9 and Cyclin T1.[26] The HIV-1 viral protein Tat hijacks CDK9 and Cyclin T1 to enhance transcription elongation and stimulate nascent viral RNA capping.[27–29]

Cyclin T1 can promote CDK11 transcription in activated $CD4^+$ T cells, and CDK11 is involved in HIV-1 provirus gene expression.[30]

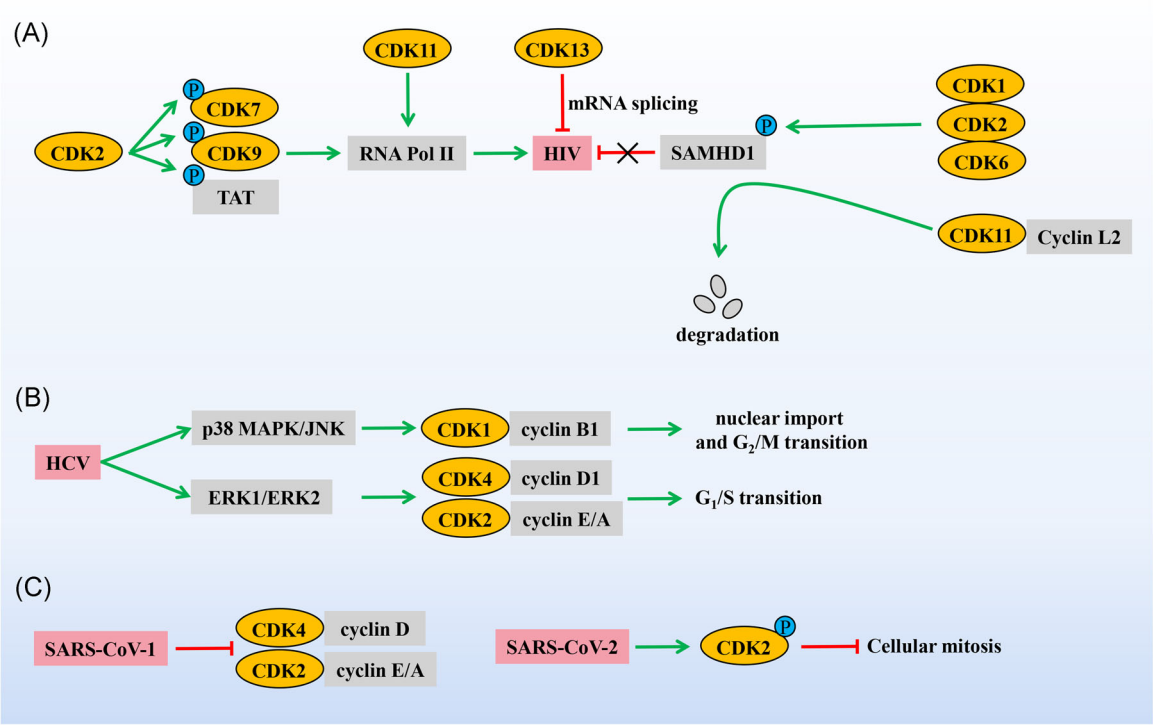

FIGURE 1 The roles of CDKs during RNA virus infection. (A) CDK1, CDK2, and CDK6 inhibit SAMHD1 antiviral function via phosphorylation and inactivation. CDK11 cooperates with Cyclin L2 to induce SAMHD1 degradation. CDK2 promotes CDK7, CDK9, and TAT phosphorylation to enhance RNA Pol II transcription of HIV-1. CDK11 is recruited to RNA Pol II to enhance the HIV transcripts. CDK13 enhances HIV-1 mRNA splicing to reduce viral production. (B) HCV increases the cyclin B1–CDK1 complex activity and nuclear import via p38 MAPK and JNK pathways to regulate the G_2/M transition and increases the cyclin D1–CDK4 and cyclin E/A–CDK2 complexes activity via ERK1/2 pathway to regulate the G_1/S transition. (C) SARS-CoV-1 suppresses the activity of the cyclin D-CDK4 and cyclin A/E–CDK2 complexes, and SARS-CoV-2 enhances the phosphorylation of CDK2 to inhibit cellular mitosis. CDK, cyclin-dependent kinase; cellular signal-regulated kinase; HIV, human immunodeficiency virus; HCV, hepatitis C virus; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; P, phosphate; SARS-CoV-1, Severe acute respiratory syndrome coronavirus-1; SAMHD1, Sterile alpha motif histidine-aspartic acid domain-containing protein 1; TAT, transactivator of transcription

CDK11 is recruited to RNA Pol II via the transcription/export and THO complex once within the viral genome, where it phosphorylates serines at position 2 in the CTD, improving 3′-terminal processing of all viral transcripts and increasing HIV replication. The cleavage of viral transcripts is considerably attenuated in its absence. Higher amounts of CDK11, on the other hand, lengthen HIV polyA tails and improve the stability of mature viral transcripts. CDK11 is essential for all HIV mRNA species' cotranscriptional processing[31] (Figure 1). These findings suggest that CDK11 is a promising HIV therapeutic drug development target.

CDK13 has been implicated in mRNA splicing.[32] HIV-1 Tat was shown to interact with CDK13 in vivo and in vitro. Furthermore, CDK13 can enhance splicing by phosphorylating ASF/SF2. CDK13 silencing results in a considerable increase in viral output, whereas ectopic expression of CDK13 inhibits viral production by reducing viral proteins Gag and Env production[33] (Figure 1). However, whether CDK13 plays a role in viral transcriptional activation needs further investigation.

CDKs are two-lobed proteins with an amino-terminal β-sheets lobe and a carboxyl-terminal α-helices lobe. The catalytic core of CDKs is wedged between these two lobes and is occluded by the T-loop, a CDK segment. The two CDK lobes rotate upon binding a cyclin, and the T-loop becomes accessible to an activating kinase. Phosphorylation of the T-loop is required for CDK catalytic activity because it displaces the T-loop, allowing substrates to reach the enzyme's catalytic core.[1]

In summary, CDK activity is modulated by the cyclin regulatory subunit and T-loop phosphorylation/dephosphorylation, suggesting that CDKs function regulation might be potential therapeutic targets against HIV-1 infection.[34] The availability of deoxy-ribonucleoside triphosphate, essential for viral DNA synthesis, is increased when the transcription of CDK1, CDK2, and similar cyclins are activated. CDK1/2 and related cyclins activate viral DNA synthesis and promote HIV-1 and herpes simplex virus 1 (HSV-1) replication.[35] Herrmann et al. showed that increasing CDK9 and Cyclin T1 mRNA and protein enhances TAK (the pan-RAF inhibitor) activity in peripheral blood cells.[36] Furthermore, Tat has been shown to target P-TEFb, comprising CDK9 and cyclin T1.[28,29,37] P-TEFb, which permits the virus to infect multiple cells while remaining latent until the host cell is activated, is directly linked to Tat transactivation and HIV replication[38] (Figure 1A). The underlying mechanisms by which CDKs regulate the HIV replication cycle appear complicated. More studies are needed to determine whether HIV uses one or more CDKs and coordinates the network to promote HIV infection.

2.1.2 | Hepatitis C virus (HCV)

HCV is highly heterogenetic and mutable. HCV replication in liver cells can induce structure and function alterations in the liver cells and interfere with protein synthesis, leading to liver cells apoptosis.[39,40] Inhibition of p38 and ribonucleic acid-dependent protein kinase (PKR) activity, HCV increases cyclin B1–CDK1 complex activity through p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) pathways and induces nuclear import of cyclin B1–CDK1 complex (Figure 1B). However, further studies are needed to investigate the special relationship between CDKs and MAPK, the JNK pathway, and PKR.

All cyclin–CDK complexes, particularly cyclin-B1–CDK1 complexes, are activated by HCV. The extracellular signal-regulated kinase 1/2 (ERK1/2) pathway is essential for regulating the G_1/S phase and its related cyclin–CDK complex. In addition, HCV infection increases the cyclin D1–CDK4 and cyclin E–CDK2 complexes activity involving the early S and G_1/S transition[41] (Figure 1B). However, more investigations into the involvement of CDKs in the ERK1/2 pathway are needed to understand HCV pathogenesis better.

2.1.3 | Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

SARS-CoV-2 infection strongly regulates CDK signaling pathways to provide favorable circumstances for viral replication, particularly by lowering CDK1/2 activity, resulting in an S/G2-like phase arrest, similar to that generated by other RNA viruses.[42,43] Although the mechanism is unknown, earlier research with other coronaviruses has shown that the nucleocapsid protein (N protein), which is highly conserved among these viruses, plays an important part in this process.[44] The N protein suppresses the activity of the cyclin D-CDK4 and cyclin A/E–CDK2 complexes in SARS-CoV-1. Direct binding of the N protein to cyclin D inhibits the cyclin D–CDK4 complex. The activity of the cyclin A/E–CDK2 complexes is suppressed by either indirect downregulation of CDK2, cyclin E, or direct binding to the cyclin A–CDK2 complex.[44] SARS-CoV-2 has also been demonstrated to enhance the phosphorylation of CDK2 at locations T14 and Y15, inhibiting premature cellular entrance into mitosis (Figure 1C). In addition, pharmacologic inhibition of the p38, CK2, CDK, AXL, and PIKFYVE kinases has antiviral activity, indicating their potential for coronavirus disease 2019 (COVID-19) treatment.[42] A study of global changes in kinase activity during SARS-CoV-2 infection reveals that CDK signaling pathways are severely downregulated.[42] Because a pharmacological CDK4/6 inhibitor is listed as a potential antiviral drug against SARS-CoV-2,[45] CDKs may be considered targets against SARS-CoV-2.

2.2 | The emerging roles of CDKs in DNA virus infection

2.2.1 | HSV-1

CDK1 and CDK2 are not expressed in dormant neurons, and they can be induced in stressed ones. According to antigen expression analysis, latent HSV-1 reactivation is linked to CDK2 expression in neurons and CDK4 translocation to the neuronal nucleus. Explant-induced HSV-1 reactivation ex vivo may need CDK2. It remains to be

determined whether CDK2 is also essential for HSV-1 reactivation in vivo (Figure 2A). HSV-1 reactivation may not involve CDK3 in neurons.[46] During acute neuronal infection, CDK5 was activated by DNA damage response (DDR), and HSV-1 infection induced p35 altered CDK5 subcellular localization and enhanced CDK5 kinase activity.[47] However, the underlying mechanism by which CDKs trigger HSV-1 gene expression is unknown.

In cells infected with wild-type HSV-1, CDK9 is necessary for the optimum accumulation of mRNAs and proteins regulated by ICP22, and both CDK9 and ICP22 colocalize with RNA Pol II[48,49] (Figure 2B). ICP22, as an immediate-early (IE) protein of HSV-1, interacts with P-TEFb and prevents its recruitment from suppressing HSV-1 α, β, and γ genes promoters, whereas VP16 might counteract ICP22's transcriptional suppression by recruiting P-TEFb to the viral α-gene promoter[50] (Figure 2C). HSV-1 may have a complicated regulatory mechanism to ensure that transcription of early and late viral genes may occur during high-activity periods following infection when both DNA replication and transcription are active. However, the underlying mechanism by which ICP22 affects and regulates CDK9 activity during HSV-1 infection has to be investigated further.

2.2.2 | Human cytomegalovirus (HCMV)

Depending on the HCMV infection phase and CDK types, several CDKs perform diverse roles in the HCMV replication cycle. CDK1 and CDK2 block immediate-early (IE) gene transcription initiation during early infection.[51] HCMV is then favorably regulated by CDKs. CDK7 and CDK9 are recruited to viral transcription sites and catalyze RNA Pol II hyperphosphorylation to enhance viral transcripts,[52–58] whereas CDK2 is essential for HCMV DNA synthesis, infectious progeny production, and late gene expression.[39–46] PROTAC THAL-SNS032, a CDK9 inhibitor discovered in a recent study, has potent anti-HCMV efficacy.[59] As a result, CDKs sequentially regulate the HCMV replication cycle and might be prospective targets for developing anti-HCMV treatment[60] (Figure 2D).

2.2.3 | Kaposi's sarcoma-associated herpesvirus (KSHV)

KSHV may encode K-cyclin, a homolog of D-type cyclins that works with CDK6 to trigger apoptosis.[61] In addition, K-cyclin interacts with

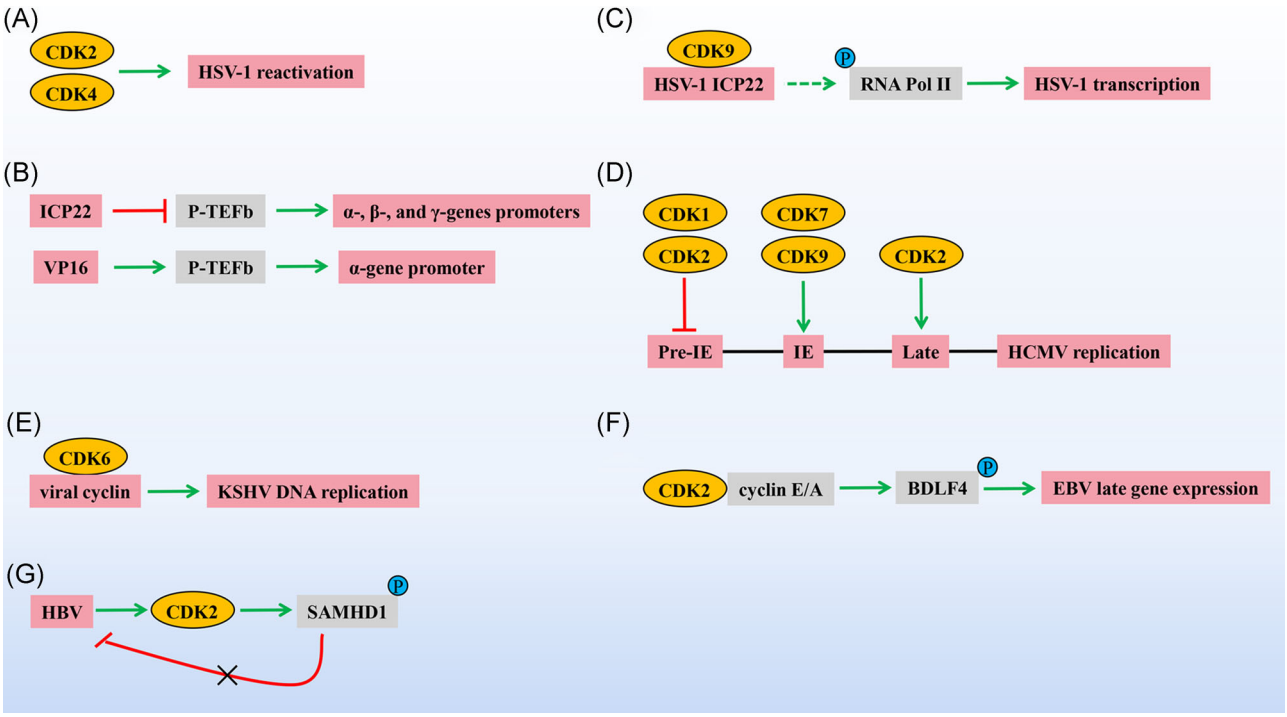

FIGURE 2 The roles of CDKs during DNA virus infection. (A) CDK2 and CDK4 are associated with latent HSV-1 reactivation. (B) CDK9 and ICP22 might regulate RNA Pol II phosphorylation to affect HSV-1 transcription. (C) ICP22 interacts with P-TEFb and prevents its recruitment from suppressing HSV-1 α-, β-, and γ-genes promoters, while VP16 recruits P-TEFb to the viral α gene promoter. (D) CDK1 and CDK2 suppress HCMV IE gene transcription initiation, CDK7 and CDK9 catalyze RNA Pol II hyperphosphorylation to enhance HCMV transcripts, and CDK2 is required for HCMV DNA synthesis, infectious progeny production, and late antigen expression. (E) KSHV cyclin interacts with CDK6 to initiate nuclear viral DNA replication. (F) Cyclin A- and E-associated CDK2 complexes phosphorylate BDLF4 and prevent its proteasomal degradation, contributing to EBV late gene expression. (G) HBV recruits cyclin E2 to bind CDK2 and further phosphorylated SAMHD1 to abrogate its restriction of HBV replication. EBV, Epstein-Barr virus; HSV-1, herpes simplex virus 1; HCMV, human cytomegalovirus; HBV, hepatitis B virus; IE, immediate-early; KSHV, Kaposi's sarcoma-associated herpesvirus; P, phosphate. The green arrows mean enhancement, the red T-shape mean T-shape, and the dashed arrow means the effect is uncertain

CDK9 to induce p53 phosphorylation and cell growth arrest.[62] However, it is unclear whether these regulations will affect KSHV infection or replication. Another investigation found that viral cyclin interacts with CDK6 to initiate viral DNA replication in the nucleus[63] (Figure 2E). MicroRNAs (miRNAs) are also involved in regulating CDKs and KS carcinogenesis. Host miR-127-3p-mediated SKP2 repression increases the CD inhibitor $p21^{Cip1}$. However, knockdown of cyclin E, cyclin A, or CDK2 activates the RB protein tumor suppressor pathway and inhibits the transcriptional activities of E2F and Myc, two key oncoprotein transcription factors involved in KSHV tumorigenesis.[64] Thus, it is necessary to investigate whether CDKs influence KSHV tumorigenesis by regulating KSHV infection and replication.

2.2.4 | Epstein-Barr virus (EBV)

BcRF1 formed the vPIC complex with five viral proteins (BDLF4, BGLF3, BFRF2, BVLF1, and BDLF3.5) during EBV infection to regulate late viral gene expression and cyclin A and E-associated CDK2 complexes phosphorylated BDLF4, preventing BDLF4 proteasomal degradation and contributing to late gene expression[65] (Figure 2F). However, the functions of other CDKs in EBV infection are still unknown.

2.2.5 | Hepatitis B virus (HBV)

Phosphorylation and dephosphorylation of the HBV core protein (HBc) in its C-terminal domain (CTD) are required for capsid assembly and viral replication, and cellular CDK2 phosphorylates and incorporates the functionally critical S/T-P sites of the HBc CTD into viral capsids, which is required for viral infection.[66,67] Another study discovered that HBV recruited cyclin E2 to bind CDK2, phosphorylating SAMHD1 and removing its restriction on HBV replication[41] (Figure 2G).

3 | CONCLUSION

CDKs are involved in cell division control and transcription modulation. Furthermore, CDKs are important participants in viral infections as it is becoming increasingly clear that DNA and RNA viruses require CDKs to assist viral replication. CDK1, CDK2, and CDK6 inactivate antiviral protein SAMHD1 phosphorylation, and CDK11 collaborates with Cyclin L2 to induce SAMHD1 degradation to facilitate HIV-1 replication. CDK2 regulates the phosphorylation of CDK7, CDK9, and TAT to enhance HIV-1 provirus RNA Pol II transcription; CDK11 increases the length of HIV polyA tails and the stability of mature viral transcripts; CDK2 and CDK4, on the other hand, have antiviral properties. CDK13 inhibits HIV-1 replication by enhancing mRNA splicing. Furthermore, knocking out tripartite motif-containing 29 (TRIM29) reduces cyclin B1, cyclin D1, and CDK2 and causes cell-cycle arrest at the G0/G1 phase.[68] TRIM29, on the other hand, promotes DNA and RNA virus infections by negatively regulating innate immune responses.[69–71] As a result, whether CDKs play their roles during RNA and DNA virus infection by collaborating with TRIM29 or other proteins needs tfio be investigated further.

As a result, CDKs' biological activities are complex and underestimated, suggesting that they might be novel targets for fighting and treating viral infections, specifically those caused by newly emerging viral diseases, such as the SARS-CoV-2 virus responsible for the recent coronavirus outbreak.

AUTHOR CONTRIBUTIONS

Yan Yan, Yan-dong Tang, and Chunfu Zheng drafted and wrote the manuscript and designed the artwork.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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