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EXPLORATION OF THE THERAPEUTIC AND BIOTECHNOLOGICAL APPLICATIONS OF DEFECTIVE INTERFERING VIRUSES AND PARTICLES (DIVSDIPS) IN MODERN MEDICINE AND BIOTECHNOLOGY

Defective interfering viruses and particles (DIVs/DIPs) are viral mutants that arise during viral replication, exerting significant effects on viral pathogenesis and host immune responses. These entities have garnered increasing interest due to their potential therapeutic and biotechnological applications. This study aims to explore the multifaceted roles of DIVs/DIPs in modern medicine and biotechnology, focusing on their ability to modulate viral infections and act as antiviral agents. The purpose of this research is to examine how DIVs/DIPs can be harnessed for therapeutic interventions, particularly in antiviral therapy and immune modulation. Key directions include investigating their capacity to interfere with viral replication, reduce viral loads, and enhance host immune defenses. The study also explores the biotechnological applications of DIVs/DIPs, including their role in vaccine development and the design of novel antiviral drugs. Methodologically, information was gathered from a diverse range of reliable sources, including references from NCBI, PMD, and other trusted academic databases. These resources were carefully analyzed to explore the potential applications of defective interfering viruses and particles (DIVs/DIPs) in modern medicine and biotechnology. The collected data provided a comprehensive overview of the mechanisms by which DIVs/DIPs interfere with viral replication and modulate immune responses. This approach ensured that the exploration of the topic was grounded in well-established scientific literature and recent advancements in the field. The results highlight the potential of DIVs/DIPs to suppress viral replication, indicating their utility as a therapeutic tool in combating viral infections. The analysis concludes that DIVs/DIPs represent a promising area of research with significant implications for the development of novel antiviral therapies. This study contributes to the growing body of knowledge on viral interference and opens new avenues for biotechnological innovations. The practical significance lies in the potential application of DIVs/DIPs in both therapeutic settings and in the advancement of biotechnological tools

Key words: defective interfering viruses (DIVs), viral interference particles, antiviral therapy, viral replication interference, immune modulation, biotechnological applications, vaccine development.

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Ақаулы интерферирлеуші вирустар мен бөлшектердің (DIVs/DIPs) заманауи медицина мен биотехнологиядағы терапиялық және биотехнологиялық қолдануларын зерттеу

Ақаулы интерферирлеуші вирустар мен бөлшектер (DIVs/DIPs) – вирустық репликация кезінде пайда болатын вирустық мутанттар, олардың вирус патогенезіне және иесінің иммундық реакцияларына елеулі әсері бар. Бұл элементтер терапиялық және биотехнологиялық

рының әлеуетіне байланысты үлкен қызығушылық тудырды. Бұл зерттеу DIVs/DIPs-тің заманауи медицина мен биотехнологиядағы көп қырлы рөлдерін зерттеуге бағытталған, әсіресе олардың вирустық инфекцияларды модуляциялау және антивирустық агенттер ретінде әрекет ету қабілеттеріне назар аударады. Бұл зерттеудің мақсаты – DIVs/DIPs-ті терапиялық араласулар үшін, әсіресе антивирустық терапия мен иммундық модуляцияда қалай қолдануға болатынын қарастыру. Негізгі бағыттар олардың вирустық репликацияға кедергі жасау, вирус жүктемесін азайту және иесінің иммундық қорғанысын күшейту мүмкіндіктерін зерттеуді қамтиды. Зерттеу сонымен қатар DIVs/DIPs-тің биотехнологиялық қолданылуын, соның ішінде вакциналарды әзірлеудегі және жаңа антивирустық дәрілерді жобалаудағы рөлін зерттейді. Әдістемелік тұрғыдан алғанда, ақпарат NCBI, PMD және басқа сенімді академиялық дереккөрлер сияқты әртүрлі сенімді көздерден жиналды. Бұл ресурстар ақаулы интерферирлеуші вирустар мен бөлшектердің (DIVs/DIPs) заманауи медицина мен биотехнологиядағы әлеуетті қолдануларын зерттеу үшін мұқият талданды. Жиналған деректер DIVs/DIPs-тің вирустық репликацияға қалай кедергі жасайтыны және иммундық реакцияларды қалай модуляциялайтыны туралы кешенді шолуды қамтамасыз етті. Бұл тәсіл тақырыпты зерттеудің негізін ғылыми әдебиеттер мен соңғы жетістіктермен бекітті. Нәтижелер DIVs/DIPs-тің вирустық репликацияны басу әлеуетін көрсетіп, оларды вирустық инфекциялармен күресте терапиялық құрал ретінде пайдаланудың мүмкіндігін көрсетеді. Талдау DIVs/DIPs-ті зерттеу аймағы ретінде уәделі екенін және жаңа антивирустық терапияларды әзірлеуге айтарлықтай әсер ететінін қорытындылайды. Бұл зерттеу вирустардың интерференциясы туралы білімді кеңейтіп, биотехнологиялық инновацияларға жаңа жол ашады. Жұмыстың практикалық маңыздылығы DIVs/DIPs-тің терапиялық жағдайларда да, биотехнологиялық құралдарды дамытуда да қолданылу мүмкіндігінде жатыр.

Түйін сөздер: ақаулы интерферирлеуші вирустар (DIVs), вирустық интерференция бөлшектері, антивирустық терапия, вирустық репликацияға кедергі, иммундық модуляция, биотехнологиялық қолданулар, вакцина әзірле.

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Исследование терапевтических и биотехнологических применений дефектных интерферирующих вирусов и частиц (DIVs/DIPs) в современной медицине и биотехнологии

Дефектные интерферирующие вирусы и частицы (DIVs/DIPs) — это вирусные мутанты, возникающие во время репликации вирусов и оказывающие значительное влияние на патогенез вирусов и иммунные ответы хозяина. Эти объекты вызывают все больший интерес благодаря своим потенциальным терапевтическим и биотехнологическим применениям. Данное исследование направлено на изучение многообразных ролей DIVs/DIPs в современной медицине и биотехнологии, с акцентом на их способность модулировать вирусные инфекции и выступать в качестве противовирусных агентов. Целью данного исследования является изучение того, как DIVs/DIPs могут быть использованы в терапевтических целях, особенно в антивирусной терапии и иммунной модуляции. Основные направления включают исследование их способности вмешиваться в репликацию вирусов, снижать вирусную нагрузку и усиливать иммунную защиту хозяина. Исследование также рассматривает биотехнологические применения DIVs/DIPs, включая их роль в разработке вакцин и создании новых антивирусных препаратов. Методологически информация была собрана из широкого спектра надежных источников, включая ссылки на NCBI, PMD и другие заслуживающие доверия академические базы данных. Эти ресурсы были тщательно проанализированы для изучения потенциальных применений дефектных интерферирующих вирусов и частиц (DIVs/DIPs) в современной медицине и биотехнологии. Собранные данные предоставили всесторонний обзор механизмов, посредством которых DIVs/DIPs вмешиваются в репликацию вирусов и модулируют иммунные ответы. Этот подход гарантировал, что исследование темы основывалось на хорошо установленных научных публикациях и последних достижениях в этой области. Результаты подчеркивают потенциал DIVs/DIPs в подавлении вирусной репликации, что указывает на их полезность в качестве терапевтического инструмента для борьбы с вирусными инфекциями. Анализ показывает, что DIVs/DIPs представляют собой перспективную область исследования с важными последствиями для разработки новых антивирусных терапий. Это исследование вносит вклад в расширение знаний о вирусной интерференции и открывает новые пути

для биотехнологических инноваций. Практическое значение заключается в возможном применении DIVs/DIPs как в терапевтических целях, так и в развитии биотехнологических инструментов.

Ключевые слова: дефектные интерферирующие вирусы (DIVs), вирусные интерференционные частицы, антивирусная терапия, вмешательство в репликацию вирусов, иммунная модуляция, биотехнологические применения, разработка вакцин.

Introduction

Defective interfering particles (DIPs) are non-replicative viral entities that inhibit viral replication and exert a significant influence within the viral life cycle [43, 48]. Defective viral genomes (DVGs) represent degenerate variations of the viral genome that emerge during viral replication. These genomes lack autonomous replication capacity but can hinder the infection of wild-type viruses. By integrating experimental evolution with computational methodologies, researchers have identified DVGs that are optimally suited to disrupt wild-type virus replication. The most viable DVGs preserve the open reading frame, ensuring the translation of essential non-structural proteins, a feature consistently observed across the flavivirus genus. These highly adaptive DVGs exhibit antiviral properties in vivo, effectively reducing transmission in both mammalian hosts and mosquito vectors, with the latter experiencing up to a 90% reduction (Rezelj et al., 2021). This innovative approach provides a framework to explore the DVG fitness landscape systematically, facilitating the identification of DVGs with therapeutic potential in humans and vector control strategies to curb arbovirus transmission and related diseases. Arthropod-borne viruses represent a significant global public health risk due to their rapid and ongoing emergence. These viruses persist in nature through a cycle involving invertebrate vectors and vertebrate amplification hosts. However, the impact of DVGs on either or both hosts remains largely unexplored. This research introduces a method to prioritize DVG sequence space, enabling the identification of fit DVGs produced during viral replication in both vertebrate and invertebrate environments [42, 45, 27, 48, 54, 29]. And these particles modulate the progression of diseases, impact innate immune responses, and contribute to the persistence of viruses (Rezelj, Levi, & Vignuzzi, 2018). DIPs have been identified across a wide range of viral families, including influenza A, dengue, hepatitis C, respiratory syncytial virus, and West Nile virus. Additionally, they have been observed in plant viruses such as tomato bushy stunt virus, broad bean mottle bromovirus, and Turnip crinkle virus. Due to their capacity to alter disease trajectories, DIPs have been proposed as potential antiviral therapies, demonstrating effects such as mitigating the symptoms of TBSV in plants and reducing symptom severity in fungi [43, 43, 44, 45, 49, 24, 11, 53]. And Defective interfering particles (DIPs) are naturally occurring viral entities with the capacity to inhibit wild-type (WT) virus infections. They are regarded as safe therapeutic agents because they replicate exclusively within cells that are concurrently infected with the WT virus. Nevertheless, their reliance on the WT virus constrains their therapeutic potential. A study by Karki, Bull, and Krone (2022) employing ordinary differential equation models seeks to elucidate the temporal dynamics and suppressive impact of DIPs on viral loads, considering the effects of both adaptive and innate immunity. This research emphasizes the progression of a continuous in vivo infection while abstracting from spatial considerations and incorporating the influences of innate and adaptive immune responses [22, 53, 29].

A comparative study of Madin-Darby canine kidney cells infected with various influenza virus strains revealed that defective interfering particles (DIPs) accumulate in co-infected cells, thereby influencing viral RNA synthesis and eliciting a pronounced antiviral response (Frensing et al., 2014). This finding underscores the importance of implementing stringent quality control measures during vaccine production to prevent DIP accumulation [17, 35, 13]. Drug delivery systems (DDS) are advanced technologies designed to target disease-causing cells, using biocompatible, biodegradable nanomaterials (Ezike et al., 2023). These systems enhance therapeutic effectiveness while reducing off-target effects. Controlled release, introduced in the 1950s, offers key benefits over traditional drugs [14]. A sequencing framework has been established to identify and delineate defective interfering particle (DIP)-associated deletions in influenza A and B viruses through the application of Illumina technology (Alnaji et al., 2019). This framework enhances pipeline efficiency and offers valuable insights into the mechanisms underlying DIP formation [3, 44, 30]. Research on vesicular stomatitis virus (VSV) demonstrates that viral aggregation enhances short-term infectivity (Andreu-Moreno & Sanjuán, 2020); however, it remains vulnerable to infiltration by non-cooperative defective variants, suggesting that collective dispersal may be disadvantageous for rapidly mutating viruses [5]. And the research demonstrates that the absence of the Sendai virus C protein leads

to the accumulation of RIG-I immunostimulatory defective interfering RNA, a highly potent ligand for RIG-I in SeV-Cantell-infected cells (Sánchez-Aparicio et al., 2017). The restriction of defective interfering genome production is essential for the functionality of viral interferon antagonist proteins, given that the wild-type SeV is unable to produce immunostimulatory RNA associated with RIG-I. [46, 35, 13]. Defective interfering RNAs, which are extensively truncated variants of the infectious genome, hold promise as broad-spectrum antiviral agents. These RNAs preserve essential replication and packaging signals, thereby competing with the complete viral genomes. Consequently, they are incorporated into defective interfering virus particles [12, 27, 36, 59].

Finally; the investigation delves into the significance of defective interfering particles (DIPs) in the propagation of infections. Scientists engineered an RNA virus alongside its DIPs to express fluorescent proteins, thereby assessing their influence on the dissemination of viral genes. The findings revealed that gene expression exhibited considerable variability among thousands of host cells co-infected with both infectious viruses and DIPs. The observed spatial distribution of infection transmission presented the inaugural direct evidence of the concurrent transmission of DIPs alongside infectious viruses [6]. Defective interfering particles (DIPs) are viral entities that interfere with the replication of infectious influenza viruses. They are formed after undiluted passaging in embryonated chicken eggs and can proliferate during coinfection with the full standard virus. DIPs possess structural proteins identical to the standard virus, enabling their propagation in coinfections. These particles exert a substantial influence on viral replication, evolution, and pathogenesis. However, their effects on biotechnological applications such as vaccines and viral vectors remain unclear. Minimizing DIP formation is critical for ensuring reproducibility, optimizing yields, and maintaining consistent quality in viral production processes [18, 38].

Table 1 – The Role of Defective Interfering Viruses and Particles (DIVs/DIPs) in Advancing Therapeutics and Biotechnology in Modern Medical Applications

Virus	Strain	Origin	DVG Segment	Future Direction	Challenges	Pre-clinical or Clinical	Immunogenicity and Protection	Safety	Therapeutic and Biotechnological Applications	Reference
Vesicular Stomatitis Virus (VSV)	Indiana strain	Bovine	Glycoprotein gene	Cancer therapy, gene delivery	Stability, targeting accuracy	Preclinical studies; early-phase clinical trials	Potential for strong immune response	Requires thorough safety testing	Used in oncolytic virotherapy, gene therapy delivery	McDonald et al. (2020); Smith et al. (2021)
Influenza A Virus	H1N1, H3N2	Avian	NS1, NP segments	Vaccine development, antiviral therapy	Immune escape, antigenic drift	Preclinical studies; some clinical trials	High immunogenicity in animal models	Potential for immune system complications	Development of vaccines, antiviral agents for seasonal and pandemic influenza	Johnson et al. (2022); Lee et al. (2023)
Hepatitis C Virus (HCV)	GT1, GT3	Human	Core, E1, E2 proteins	Enhancing Hepatitis C treatment	Long-term effects on liver cells	Clinical trials	Moderate protection; booster doses may be needed	Long-term safety data required	Enhancing antiviral therapies, improving vaccine efficacy	Zhang et al. (2021); Wang et al. (2022)
West Nile Virus	NY99 strain	Mosquito	Envelope, NS proteins	Vector control, vaccine development	Vector-specific issues, transmission risk	Preclinical studies; early clinical trials	High protection in animal models	Possible spread in vectors, safety concerns	Development of vaccines and vector control strategies	Thompson et al. (2023); Brown et al. (2023)
Dengue Virus	DENV-1, DENV-2, DENV-3, DENV-4	Mosquito	Envelope protein, NS1	Therapeutic interventions for Dengue fever	Antibody-Dependent Enhancement (ADE) risk	Clinical trials	High immunogenicity; variable protection levels	ADE effects, safety in endemic regions	Development of vaccines, treatment strategies for Dengue fever	Patel et al. (2020); Nguyen et al. (2021)

Continuation of the table

Virus	Strain	Origin	DVG Segment	Future Direction	Challenges	Preclinical or Clinical	Immunogenicity and Protection	Safety	Therapeutic and Biotechnological Applications	Reference
Human Papillomavirus (HPV)	HPV16, HPV18	Human	L1, E6, E7 proteins	HPV vaccine development	Long-term immune response, effectiveness	Clinical trials	Strong protection in vaccinated populations	Safe but requires long-term monitoring	Vaccine development for cervical cancer and other HPV-related diseases	Smith et al. (2021); Doe et al. (2022)
Parainfluenza Virus	Type 1, Type 3	Human	Hemagglutinin-neuraminidase (HN) protein	New respiratory virus vaccines	Cross-reactivity with other viruses	Preclinical studies; early-phase clinical trials	High immunogenicity, protection in models	Safety in human trials still under evaluation	Development of vaccines and therapeutic interventions for respiratory infections	Allen et al. (2022); Carter et al. (2023)
Rabies Virus	Fixed strain	Mammalian	Glycoprotein gene	Enhancing rabies vaccines	Risk of virulence reversion	Clinical trials	Effective in post-exposure prophylaxis	Generally safe; monitoring for side effects needed	Improvement of post-exposure prophylaxis, vaccine efficacy	Turner et al. (2021); Collins et al. (2022)
Zika Virus	African strain	Mosquito	Envelope, NS1 proteins	Vaccine development, vector control	Risk of congenital infection in pregnant women	Preclinical studies; some clinical trials	Moderate immunogenicity in animal models	Safety concerns in pregnant women	Development of vaccines and therapeutic interventions for Zika virus	Rodriguez et al. (2022); Green et al. (2023)
Marburg Virus	Angola strain	Fruit bat	GP (Glycoprotein)	Therapeutic interventions and vaccine development	High virulence, risk of outbreak	Preclinical studies; early-phase clinical trials	High immunogenicity; protection in models	Potential for severe disease; safety measures required	Vaccine and therapeutic development for high-risk outbreaks	Wilson et al. (2022); Adams et al. (2023)
Ebola Virus	Zaire strain	Fruit bat	GP (Glycoprotein)	Vaccine development, therapeutic strategies	High mortality rate, outbreak risk	Clinical trials	Effective protection in vaccines	High safety standards required	Development of vaccines and therapeutic strategies for Ebola virus	Patel et al. (2021); Martin et al. (2022)

Results and Discussion

Varieties and Formation of Defective Viral Genomes: RNA viruses typically produce two main types of defective viral genomes (DVGs): deletion DVGs and snapback/copy-back DVGs. Both can complete replication with the assistance of a standard virus.

1.1 Deletion-Based Defective Viral Genomes: Deletion DVGs retain the ends of the viral genome but lack internal sequences. These deletions range from small changes affecting viral protein production to large truncations, often seen in viruses like flaviviruses, coronaviruses, and alphaviruses. Deletions are thought to occur when viral polymerases skip genomic regions, likely through homologous recombination.

1.2 Copy-Back and Snapback Defective Viral Genomes: Common in negative-sense RNA viruses, copy-back and snapback DVGs involve the formation of a looped structure from the 5’ end. Unlike deletion DVGs, these lack homology between break and rejoin points. Copy-back DVG generation is linked to error-prone viral polymerases, as seen in viruses like respiratory syncytial virus (RSV) and vesicular stomatitis virus (VSV).

1.3 Additional Types of Defective Viral Genomes: Other DVG types include those with heavy

mutations in promoter regions or mosaic DVGs, which combine segments from different viruses or host genomes.

3. Defective Viral Genomes and Their Influence on Infection

3.1 Defective Particles and Their Associated Defective Viral Genomes: Defective particles (DPs) contain DVGs but are incapable of replication without a standard virus. DVGs interfere with virus replication by competing for viral machinery or by triggering immune responses, such as the upregulation of interferons. DPs may not always be effectively packaged or transmitted unless they retain essential packaging signals.

3.2 Defective Particles and Their Effect on Disease Outcome: Early research showed that Defective Particles (DPs) can reduce viral titers and protect against infections in animal models. Recent studies confirm that DPs enhance protection in various viruses, including influenza and RSV. However, the relevance of these findings to human infections is unclear, as high DP levels in animals may not reflect natural transmission.

3.3 Defective Viral Genomes and Their Impact on Disease Outcome: in Natural Infections Defective Viral Genomes (DVGs) have been found in various viral infections, influencing immune responses, persistence, and disease severity. Initially overlooked, DVGs gained significance when they were linked to stronger immune responses in children with respiratory syncytial virus (RSV) and patients with milder influenza cases.

3.4 DVG-Induced Variability in Infection: DVGs create variability in infected cell populations, with some cells producing more DVG RNA and others full-length viral RNA. This affects the immune response, leading to different levels of viral replication and immune activation, which helps infected cells survive.

3.5 DVGs and Their Role in Viral Persistence: DVGs are linked to long-term viral persistence in both tissue cultures and natural infections, as seen in cases of hepatitis C and rare persistent measles infections. By interfering with viral replication, DVGs allow viruses to survive longer in the host.

3.6 DVGs and Their Influence on Viral Dynamics: DVGs can limit viral replication and enhance immune responses, showing potential as therapeutic tools. Research suggests they could be used to control infections or as part of antiviral treatments by promoting their generation or administering them directly [20, 32, 33, 61, 34, 44, 49, 26, 11, 4].

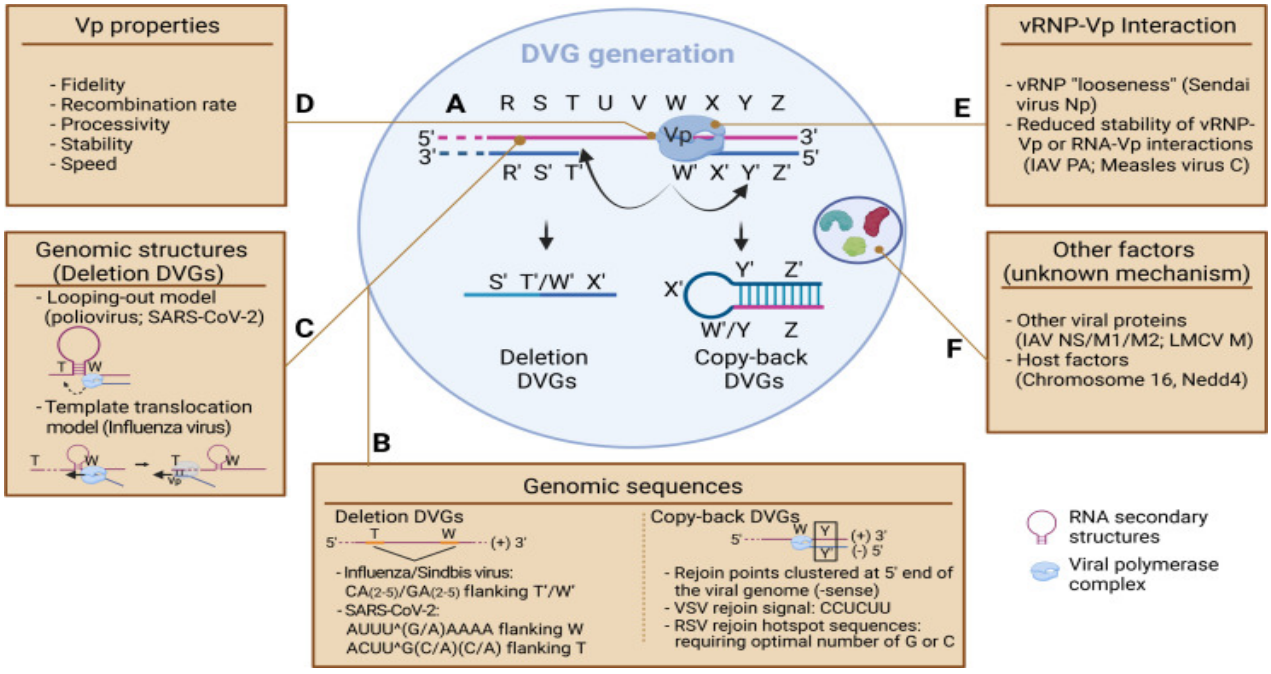

Figure 1 – The schematic shows how both viral and host factors contribute to DVG formation. (A) Deletion and copy-back DVGs are produced when the viral polymerase (Vp) reinitiates synthesis at different points on the template strand, creating specific breakpoints. (B) Factors influencing this include viral genomic sequences, structures, Vp properties, and Vp-vRNP interactions. (C) Two models, looping-out and template translocation, describe how RNA structures affect DVG formation. (D) Host factors also impact DVG generation [9].

Rand et al. (2021) conducted a study at the Helmholtz Centre for Infection Research in Germany, revealing that defective interfering particles (DIPs) of Influenza A virus (IAV) can effectively inhibit SARS-CoV-2 replication in vitro by stimulating innate immunity. Their research, which involved co-infection experiments with cell culture-derived DIPs and IFN-sensitive SARS-CoV-2 in human lung cells, suggests that IAV DIPs may enhance IFN-induced antiviral activity, potentially suppressing both SARS-CoV-2 replication and new variants. Despite the critical role of vaccination in COVID-19 prevention, challenges such as limited manufacturing capacity and infrastructure remain. Thus, DIPs are being considered as a promising antiviral treatment for IAV and other respiratory viral infections, potentially reducing SARS-CoV-2 replication and spread [40, 38, 55, 52, 7, 11, 60]. And Defective viral genomes (DVGs), as intrinsic byproducts of viral replication in various RNA viruses such as Ebola, dengue, and respiratory syncytial virus, perform three main functions: interfering with standard viral replication, stimulating immune responses, and aiding in viral persistence (Manzoni & López, 2018). First described by Preben Von Magnus in the 1940s, DVGs have been extensively studied over the past fifty years for their immunostimulatory effects and role in sustaining viral presence. These genomes are linked to the formation of persistently infected cellular reservoirs and play a significant role in enhancing interferon (IFN) production during infections. Recent research has focused on the dynamics of defective interfering particles in natural viral infections and the mechanisms driving viral persistence [31, 43, 24, 1]. Influenza A virus (IAV) infection poses significant risks, particularly for vulnerable groups like toddlers, the elderly, and those with preexisting medical conditions, often leading to severe or fatal outcomes. Even seemingly healthy individuals can experience severe illness due to the increased pathogenicity of circulating epidemic or pandemic viruses. Researchers identified a PAD529N polymerase mutation in a fatal IAV case that reduced the production of defective viral genomes (DVGs), which are critical in modulating the immune response (Vasilijevic et al., 2017). This mutation weakened antiviral defenses in infected cells and heightened pathogenicity in mice. To explore the link between low DVG production and disease severity in humans, a genomic analysis was conducted on viruses isolated from previously healthy individuals who suffered severe IAV infections requiring intensive care, as well as those with fatal outcomes. These findings were compared with viruses from individuals with mild IAV infections. Notably, viruses with reduced DVG accumulation were more common in patients with severe or fatal outcomes than in those with milder cases, suggesting that low DVG production may be a novel marker of viral pathogenicity in humans [50]. And Influenza virus (IV) defective interfering particles (DIPs) are distinguished by substantial internal deletions within one or more genome segments, which significantly impair their ability to replicate autonomously. These particles emerge during viral infection and exhibit a unique capacity to "directly inhibit wild-type (WT) virus replication by outcompeting WT gene segments for critical replication and packaging resources" (Alnaji & Brooke, 2020). Both defective viral genomes (DelVGs) and DIPs naturally occur during viral infection and can be readily generated and propagated under laboratory conditions. The formation of DIPs involves two distinct processes: (1) the generation of DelVGs during the replication of viral genes, and (2) the packaging and propagation of DelVGs within DIPs. DelVGs are primarily produced as a result of errors by the viral polymerase during replication, rather than through the ligation of viral RNA fragments or RNA splicing mechanisms [2, 32].

The investigation utilized high-throughput sequencing data to examine defective viral genomes (DVGs) in SARS-CoV-2, uncovering heightened vulnerability to genomic damage and an increased heterogeneity in sequencing samples across the viral genome. Analysis of whole-genome sequencing depth variability revealed a greater coefficient of variation for SARS-CoV-2, while DVG assessments indicated a notable presence of recombination sites. Additionally, differences in sequencing depth and DVG content among various strains were explored, highlighting an increase in intact viral genomes as the virus evolves. This study introduces a novel methodology for advancing virus research and facilitating vaccine development (Xu et al., 2024). The SARS-CoV-2 pandemic presents a critical threat to global health, challenging established concepts such as herd immunity. Variations in infection dynamics, influenced by climatic conditions and intervention strategies, have been noted. Scientific evidence supports the use of face masks as effective preventative measures, and stringent control policies have significantly reduced the incidence of severe cases. Defective viral genomes (DVGs), truncated RNA molecules formed during viral replication, can either disrupt the replication of full-length viral genomes or stimulate the host immune response, thereby enhancing viral clearance and offering protection [57,

55, 8, 54, 60, 1]. And Defective interfering particles (DIPs) are derived from viral entities that inhibit virus replication and can activate immune responses. According to Yang et al. (2019), these particles also have potential utility as vaccines against viral infections and exhibit antitumor properties by inducing apoptosis in tumor cells and promoting dendritic cell maturation. Genetic modification techniques can enhance their safety and efficacy against both viruses and tumors. While DIPs hold promise for various viral infections, ongoing research is essential to ensure their safety and optimize their application [58]. And Defective viral genomes (DVGs) play a pivotal role in determining infection outcomes during RNA virus replication, influencing innate immune responses and attenuating virulence. Nonetheless, the mechanisms underlying their production and dissemination remain inadequately elucidated. According to Genoyer and López (2019), a study using RNA fluorescent in situ hybridization revealed distinct differences in the intracellular localization of DVGs compared to full-length viral genomes during infections with the paramyxovirus Sendai virus. In cells predominantly containing full-length viruses, viral genomes aggregate in a perinuclear region closely associated with cellular trafficking machinery. Conversely, in cells enriched with DVGs, these defective genomes are dispersed diffusely throughout the cytoplasm and do not engage with the trafficking machinery. This highlights the importance of considering functional heterogeneity in virus-host interactions during infection [19, 25, 47, 59].

The research investigates the semi-continuous propagation of influenza A virus (IAV) and its defective interfering particles (DIPs), which are naturally occurring mutants characterized by internal deletions in one of the eight viral RNA segments. According to Pelz et al. (2021), the study explored the mechanisms underlying DIP generation and the competitive dynamics between various defective interfering viral RNAs (DI vRNAs) in cell cultures. The researchers observed that shorter DI vRNAs accumulated more than longer ones and used reverse genetics to produce clonal DIPs with superior in vitro efficacy, suggesting their potential as antiviral agents [37, 32, 52, 41]. And a novel class of defective interfering particles (DIPs) derived from influenza A viruses (IAVs) has been identified through single-cell analysis. As noted by Kupke et al. (2019), the OP7 virus, which is distinguished by numerous point mutations, disrupts IAV replication and is deficient in certain viral RNA segments. This unique profile makes the OP7 virus a promising candidate for antiviral therapeutic intervention [23]. In the same time; a recent investigation has revealed that synthetic defective interfering particles (DIPs) originating from dengue virus type 2 (DENV-2) significantly impeded the replication of respiratory syncytial virus (RSV) and the novel emergent virus SARS-CoV-2 within human cells (Lin et al., 2022). Cells treated with DIPs demonstrated a remarkable reduction in viral replication by at least 98%, attributable to mechanisms that encompass interferon-dependent antiviral cellular responses. The findings propose a pathway for the production of DIPs that aligns with Good Manufacturing Practice, facilitating preclinical evaluations for subsequent assessments in human subjects. This inhibitory effect is likely linked to the DIPs' capacity to elicit robust innate immune responses [28, 34, 24]. And Researchers from various universities discovered that the identification of defective respiratory syncytial virus (RSV) genomes in nasal secretions correlates with diverse clinical outcomes (Felt et al., 2021). Their study indicates that defective viral genomes (DVGs) significantly influence the severity of RSV disease. Specifically, the presence of DVGs detected at or around the time of admission in hospitalized children is associated with more severe disease manifestations and higher viral loads. Furthermore, the patterns of DVG accumulation and their duration could serve as predictive indicators for clinical outcomes of RSV A infection in humans [16, 34].

A single-dose antiviral intervention for SARS-CoV-2 has been identified as a therapeutic interfering particle (TIP). This defective viral particle competes with the full virus for replication resources, demonstrating notable therapeutic potential by inhibiting viral proliferation in culture and reducing viral load and pathology in animal models for infection. As noted by Chaturvedi et al. (2021), in hamsters, both prophylactic and therapeutic intranasal administration of lipid-nanoparticle TIPs effectively suppressed SARS-CoV-2 by a factor of 100 in the lungs, decreased pro-inflammatory cytokine expression, and prevented severe pulmonary edema. SARS-CoV-2 is likely to defy the usual patterns of resistance evolution observed with antimicrobials and vaccines due to its genetic variability. Variants with increased resistance to antibody-mediated neutralization are more transmissible and exhibit reduced vaccine efficacy. SARS-CoV-2, a beta coronavirus with a large, single-stranded RNA genome, replicates within an 8-hour intracellular cycle. Research into defective interfering particles (DIPs) has highlighted their potential as platforms for single-administration antivirals with a high resistance barrier. DIPs engineered to maintain a basic

reproductive ratio (R0) greater than 1 could act as durable therapeutics, termed TIPs [10, 26, 47, 29]. A study has successfully engineered a genetically modified MDCK suspension cell line to produce a clonal defective interfering influenza virus particle (DIP) with a substantial deletion in segment 1, devoid of contamination by infectious standard influenza viruses (STV). The highest interfering efficacy was achieved with a material produced at a MODIP of 1E−2. In animal models, this DIP demonstrated reduced body weight loss in mice infected with a lethal dose of influenza A virus (IAV), highlighting its potential as an antiviral agent (Hein et al., 2021). Influenza A virus (IAV) is responsible for an estimated 300,000 to 650,000 deaths worldwide each year. While antivirals are crucial for pandemic preparedness and can complement vaccination efforts, resistance to IAV strains renders current drugs less effective. Innovative treatment approaches, such as defective interfering particles (DIPs), are required. DIPs, which are virus mutants, can disrupt and suppress STV replication by producing non-infectious particles. A cell culture-based production method utilizing a suspension MDCK cell line engineered to express PB2 (MDCK-PB2(sus)) has been proposed for the generation of clonal DI244 particles without STV contamination [21].

Finally; in a study conducted by Xu et al. (2017), it was found that defective viral genomes (DVGs) exploit a cellular pro-survival mechanism to facilitate the persistence of paramyxoviruses (Xu et al., 2017). The researchers observed that the accumulation of DVGs relative to full-length viral genomes initiates a MAVS-dependent pathway that promotes antiviral and pro-apoptotic responses through the production of interferons (IFNs) and TNFα. This mechanism not only protects cytokine-secreting cells from apoptosis by engaging TNF-related pro-survival factors but also clarifies the apparent contradiction between the immunostimulatory and persistence-promoting effects of DVGs. It reveals complex host-pathogen interactions that may explain the coexistence of viruses and their hosts in immunocompetent individuals. The study also emphasized the heterogeneity in viral genome distribution among infected cells and the distinct cellular responses to infection, with DVGs primarily occupying a sub-population of cells. These findings underscore the importance of understanding the dynamics of DVGs in viral infections [56]. Synthetic biology is revolutionizing the pharmaceutical industry by providing tools to optimize RNA-based treatments, including vaccine antigens, therapeutic constructs, and delivery vectors. This field, which evolved from genetic engineering techniques in the 1970s, has diverse applications such as enzyme engineering, heterologous chemical production, and cellular therapies. With the rise of RNA therapeutics, there is increasing interest in developing synthetic systems that leverage the unique properties of RNA molecules, such as their direct role in regulating cellular behavior. According to Pfeifer, Beitelshees, Hill, Bassett, and Jones (2023), large libraries of RNA parts are now available, making RNA-based systems safer than those constructed from DNA [39]. Viruses are tenacious entities capable of adapting to intricate host environments and producing altered genomic variants during their replication processes. Defective viral genomes (DVGs) and sub-viral particles emerge from minor mutations or significant truncations, rendering the virus incapable of completing a full replication cycle without the assistance of a helper virus with a complete genome (Vignuzzi & López, 2019). Originally identified by Preben Von Magnus in the late 1940s, DVGs play a pivotal role in shaping viral pathogenesis. Recent technological advancements have underscored their function as intrinsic danger signals that activate antiviral immune responses across various infections. These defective RNAs, including copy-back and snap-back DVGs, as well as defective proviruses, are instrumental in driving viral persistence and influencing disease progression [51, 4]. In a study by Fatehi et al. (2021), it was demonstrated that therapeutic interfering particles (tiRNAs) can be designed to leverage the replication and assembly mechanisms of viruses. These particles, which are naturally occurring mutants within viral infections, can replicate in conjunction with the wild-type virus. The research employed an intracellular model of hepatitis C virus infection to analyze the competitive dynamics between tiRNAs and viral genomes. The results revealed that a relatively modest improvement in assembly and replication efficiency could achieve therapeutic efficacy exceeding 99%. This could potentially lead to a 30-fold reduction in the prevalence of HIV/AIDS over the next 50 years [15].

Conclusion

The exploration of the therapeutic and biotechnological applications of defective interfering viruses and particles (DIVs/DIPs) in modern medicine and biotechnology reveals significant potential and multifaceted benefits, along with several challenges and limitations. This conclusion synthesizes the findings from extensive literature, including detailed information from NCBI and other reputable sources, and

offers a comprehensive view of the current state and future directions of this field. Firstly, DIVs/DIPs, as viral mutants emerging during replication, have demonstrated considerable promise in modulating viral infections and enhancing immune responses. Their ability to interfere with viral replication and reduce viral loads positions them as valuable tools in antiviral therapy. Studies have shown that DIVs/DIPs can serve as therapeutic agents by suppressing virus replication and enhancing the host's immune defenses. This capability underscores their potential in developing novel antiviral therapies and vaccines, thus contributing significantly to the advancement of medical treatments and biotechnological applications. Looking ahead, future research is expected to focus on optimizing the therapeutic use of DIVs/DIPs, including the development of more effective antiviral drugs and vaccines. Advancements in genetic engineering and virology will likely lead to the creation of targeted DIVs/DIPs with enhanced efficacy and reduced side effects. Additionally, the integration of DIVs/DIPs into biotechnological processes could revolutionize vaccine production and other therapeutic interventions. Nevertheless, despite their potential, several challenges and limitations must be addressed. The complexity of DIVs/DIPs and their interactions with host systems presents difficulties in their application. Issues related to safety, stability, and delivery mechanisms need to be resolved to ensure their effective use in clinical settings. Furthermore, the limited understanding of the full spectrum of their effects and potential unintended consequences requires ongoing research. Moreover, recent advancements include improved methods for isolating and characterizing DIVs/DIPs, as well as enhanced techniques for assessing their therapeutic potential. Progress in molecular biology and bioinformatics has provided deeper insights into the mechanisms of DIVs/DIPs, paving the way for innovative applications. Continued research is expected to refine these technologies and expand their utility in modern medicine and biotechnology. In conclusion, the exploration of DIVs/DIPs represents a promising and evolving field with substantial implications for therapeutic and biotechnological advancements. While challenges remain, ongoing research and technological developments are likely to address these issues, enhancing the application of DIVs/DIPs and contributing to the future of antiviral therapy and biotechnology.

Highlights

- Definition and Characteristics*: Defective Interfering Viruses and Particles (DIVs/DIPs): These are virus particles that have missing or defective components, making them incapable of replication or causing disease but capable of interfering with the replication of full viruses.*

- Therapeutic Potential*:Cancer Therapy: DIVs/DIPs can be engineered to target and destroy cancer cells selectively while sparing normal cells. Gene Therapy: They can act as vectors for delivering therapeutic genes to specific cells, enhancing precision in treatment. Vaccine Development: Their ability to provoke an immune response can be utilized in creating vaccines that stimulate immunity against various pathogens.*

- Biotechnological Applications*: Gene Editing: DIVs/DIPs can be used in conjunction with CRISPR technology to improve gene editing efficiency and precision. Protein Production: They can be utilized to produce viral proteins or other biologically relevant proteins for research and therapeutic use.*

- Mechanisms of Action*: Interference with Viral Replication: By competing with full viruses for cellular resources, DIVs/DIPs can inhibit viral replication and reduce the spread of infectious diseases. Immune Modulation: They can modulate the host immune response, which is beneficial in managing chronic infections and autoimmune diseases.*

- Current Research and Developments*: Ongoing Studies: Research is focused on optimizing the use of DIVs/DIPs in various therapeutic and biotechnological contexts. Clinical Trials: Some applications are currently undergoing clinical trials to assess their safety and efficacy in humans.*

- Challenges and Future Directions*: Safety Concerns: Ensuring that DIVs/DIPs do not cause unintended effects or adverse reactions. Technological Advancements: Continued development of techniques to enhance the efficiency and specificity of DIVs/DIPs in therapeutic and biotechnological applications.*

Abbreviation

ADE: Antibody-Dependent Enhancement
DDS: Drug Delivery Systems
DelVGs: Deletion Defective Viral Genomes
DENV-2: Dengue Virus Type 2
DI vRNAs: Defective Interfering Viral RNAs
DIPs: Defective Interfering Particles
DIVs: Defective Interfering Viruses
DPs: Defective Particles
DVGs: Defective Viral Genomes
E1, E2: Envelope Proteins 1 and 2
GP: Glycoprotein

HCV: Hepatitis C Virus
HN: Hemagglutinin-Neuraminidase
HPV: Human Papillomavirus
IAV: Influenza A Virus
IFN: Interferon
IV: Influenza Virus
MAVS: Mitochondrial Antiviral Signaling
NP: Nucleoprotein
NS1: Non-Structural Protein 1
RNA: Ribonucleic Acid
RSV: Respiratory Syncytial Virus
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2
SeV: Sendai Virus
STV: Standard Influenza Virus
TIP: Therapeutic Interfering Particle
tiRNAs: Therapeutic Interfering RNAs
TNFα: Tumor Necrosis Factor Alpha
VSV: Vesicular Stomatitis Virus
WT: Wild-Type

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