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How Do EBV, HPV and HIV Converge on the USP7–MDM2–p53 Axis to Promote Oncogenesis?

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Abstract

The USP7-MDM2-p53 pathway is a crucial tumour-suppressive mechanism that multiple oncogenic viruses exploit to evade the host immune system. Emerging evidence shows that multiple oncogenic viruses, including Epstein–Barr virus (EBV), human papillomavirus (HPV), and human immunodeficiency virus (HIV), exploit this pathway to subvert host tumour defences and promote oncogenesis. This review synthesises current understanding of how each virus interacts with the USP7–MDM2–p53 network, including EBV's use of EBNA1 to sequester USP7, HPV E6/E7-driven p53 degradation and stabilisation of viral oncoproteins, and HIV Tat/Nef-mediated suppression of p53 via MDM2 stabilisation. Although differing taxonomically and mechanistically, these viruses that inactivate p53 converge on USP7 as one of the regulatory fulcrums. By locating this convergence, we have identified USP7 as a common target with translational potential. Targeting USP7 with small-molecule inhibitors or CRISPR-based approaches holds promise but poses challenges due to concerns over specificity and toxicity, making it a promising yet complex approach for antiviral and anticancer strategies. This review is the first to synthesise evidence that EBV, HPV, and HIV converge on USP7 as a shared regulatory hub, despite their taxonomic and mechanistic differences. Targeting USP7 presents a promising but challenging therapeutic strategy, warranting further research into virus-specific inhibitors and combinatorial approaches.

Keywords

MDM2, oncogenesis pathways, p53, USP7, Viral hijacking, Viral oncogenesis.

INTRODUCTION

The p53 tumour suppressor protein is crucial for preserving genomic integrity because it is activated in response to cell stress and prevents malignant transformation [1]. p53 stabilises and accumulates in response to DNA damage or oncogene activation, triggering transcriptional programs that lead to cell cycle arrest, senescence, or apoptosis [2] (Figure 1). By inducing cyclin-dependent kinase inhibitors, such as p21CIP1/WAF1, p53 causes G1/S checkpoint arrest, allowing time for DNA repair. If the damage is irreparable, p53 orchestrates apoptotic pathways by upregulating pro-apoptotic proteins, such as BAX, PUMA, and NOXA [3]. Given its central role in tumour suppression, p53 is a frequent target of viral subversion. Oncogenic viruses have evolved diverse strategies to disrupt p53 function, often converging on the USP7-MDM2 regulatory node.

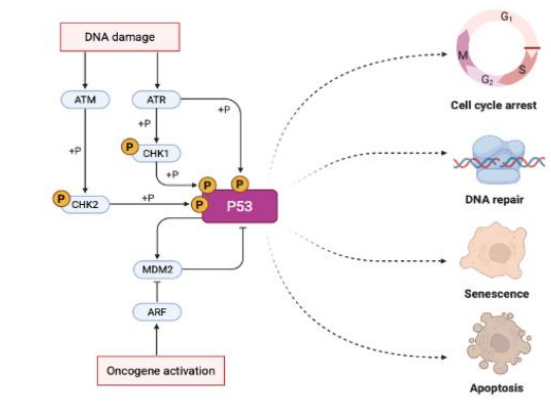

Figure 1.
P53 regulation and signalling. ATM primarily responds to double-strand breaks in DNA, while ATR is activated by a broader spectrum of DNA lesions. ATM phosphorylates p53 indirectly via CHK2, whereas ATR phosphorylates p53 both directly and indirectly through CHK1. Phosphorylated p53 triggers downstream processes, including cell cycle arrest, DNA repair, senescence, and apoptosis. MDM2 negatively regulates p53 through a feedback loop, maintaining its levels at low levels under normal conditions. However, upon oncogene activation, ARF inhibits MDM2, leading to the stabilisation of p53 and the initiation of tumour-suppressive activities. ARF= Alternate Reading Frame; ATM= Ataxia-Telangiectasia Mutated; ATR= Ataxia-Telangiectasia and Rad3-Related; CHK= Checkpoint Kinase; MDM2 - Mouse Double Minute 2 (Homolog). This figure was created using Biorender.

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Mutations of the TP53 gene are found in more than 50% of human cancers, including those of the lung, colorectal, and ovarian types [4]. In virus-related cancers, however, p53 is usually functionally inactivated by different mechanisms, including direct degradation, destabilisation, or subversion of its regulatory pathways [5]. Unlike genetic mutations, these viral pathways cause a quick and reversible silencing of p53 in infected cells, an unusual advantage to viral persistence and oncogenesis.

This review explores a fundamental question in viral oncology: How do EBV, HPV, and HIV target the USP7–MDM2–p53 pathway to drive oncogenesis? These viruses, which vary in structure, tropism, and life cycle, appear to hijack a shared molecular axis, USP7-mediated control of the MDM2–p53 interaction to inactivate one of the body's strongest tumour-suppressive mechanisms. This overlap is not accidental but rather a chronic infection that suppresses p53-dependent cell cycle arrest, apoptosis, and innate immune responses, thereby permitting oncogenesis and cell transformation.

Each of EBV, HPV, and HIV has evolved methods to capture the USP7–MDM2–p53 regulatory circuit, resulting in the degradation or sequestration of p53 and thereby creating a pro-oncogenic environment [6]. Answering this question can provide a deep understanding of viral oncogenesis and offer new therapeutic avenues against virus-associated cancers.

Whilst previous research has examined the individual impacts of EBV, HPV, and HIV on p53, the mechanistic overlaps directly implicate USP7 as a regulatory hub that bridges these unrelated viral pathogens together in the context of their cancer-causing characteristics have remained understudied. The USP7–MDM2–p53 pathway is well-established in the field of tumour biology, but its role as a shared antiviral target in multiple oncogenic viruses has not been previously synthesised.

This review therefore aims to:

1) Map how EBV, HPV, and HIV interact with the USP7–MDM2–p53 pathway.
2) Assess the functional consequences of these interactions for host cell transformation and viral persistence.
3) Evaluate emerging therapeutic approaches targeting this axis, including USP7 inhibitors and CRISPR-based strategies.

MATERIALS AND METHODS

A literature search was conducted using PubMed, Web of Science, and Google Scholar to identify relevant studies published between 2000 and 2025. The search terms included combinations of the following keywords: "USP7," "MDM2," "p53," "USP7-MDM2-p53 axis," "deubiquitination," "ubiquitin-proteasome system", "Epstein-Barr virus," "EBV," "human papillomavirus," "HPV," "HIV," "viral oncogenesis," "viral hijacking", "tumour suppression," "apoptosis," "cell cycle arrest," "viral latency," "oncoproteins".

The inclusion criterion was as follows: 1) Original research articles, reviews, meta-analyses; 2) Studies explaining the mechanistic interaction between EBV, HPV, or HIV and the USP7-MDM2-p53 pathway; 3) Preclinical and clinical studies of USP7 inhibitors or CRISPR-based interventions; 4) Publication in English using full-text articles Only articles with available full-text either in print or online were considered. The excluded studies were as follows: 1) Non-peer-reviewed articles, conference abstracts or editorials without experimental validation; 2) Studies devoted to only p53 mutations without viral implication; 3) Redundant studies with duplicate datasets.

Relevant data were retrieved and classified as: Mechanistic insights: How EBV (EBNA1), HPV (E6/E7), and HIV (Tat/Nef) control USP7-MDM2-p53. Therapeutic approaches: USP7 inhibitors (e.g., P5091, FT827), CRISPR strategies, and their efficacy/limitations. Gaps and contradictions: Discrepancies in substrate-switching models or tissue-specific USP7 effects.

RESULTS AND DISCUSSION

Normal Function of the USP7–MDM2–p53 Pathway

To understand how viruses hijack this tumour-suppressive network, it is essential to first examine the normal physiological configuration of the USP7–MDM2–p53 axis, a molecular circuit that safeguards genomic stability by regulating p53 turnover in accordance with the cell's stress status [7]. Under normal conditions, p53 is maintained at low levels to prevent unnecessary apoptosis, but under stress, it is rapidly stabilised to initiate cell cycle arrest or apoptosis [8].

MDM2, an E3 ubiquitin ligase, is the negative regulator of p53. In a classical autoregulatory feedback loop, activated p53 induces the transcription of the MDM2 gene and the resulting MDM2 protein will then bind to p53's N-terminal transactivation domain and ubiquitinate its C-terminal lysine residues, marking it for proteasomal degradation [9]. This tightly regulated feedback loop enables the rapid suppression of p53 activity once cellular stress is resolved to restore homeostasis.

USP7 (also known as HAUSP) is a key regulator of this axis, counteracting MDM2-mediated ubiquitination [10]. It can affect the ubiquitination, hence the stability of MDM2 and p53. In the non-stressed state, USP7 interacts with and stabilises MDM2, which in turn indirectly facilitates p53 destruction [11]. Conversely, when it comes to genotoxic stress, the complex formed between USP7 and MDM2 is broken down due to the phosphorylation of USP7 proteins, causing it to prioritise p53 as a substrate [8]. Therefore, USP7 either suppresses tumour growth or inhibits p53, depending on the cellular context.

During the resting condition, the expression of p53 is repressed utilising a two-step pathway of transcriptional regulation of MDM2 and MDM2-mediated polyubiquitination. The proteasome recognises the ubiquitinated p53 proteins and destroys them, thereby

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keeping basal p53 levels down [12]. This forms a dynamic balance, allowing for the rapid accumulation of p53 in cells responding to cellular stress.

During stress adaptations, such as after DNA damage or oncogene induction, the interface between p53 and MDM2 is disrupted by post-translational mechanisms (e.g. by phosphorylation of p53 or USP7. Meanwhile, USP7 alters the substrate specificity to deubiquitinate p53, stabilising it to allow its accumulation and downstream transcriptional activity [11]. This is a stress-induced modulation that renders the actions of p53 reversible and adaptable, thereby maintaining the cell fate decision between survival and apoptosis.

USP7 is a deubiquitinating enzyme that is multi-domaining in its composition, consisting of:

- N-terminal TRAF-like domain (residues 53–205): binds to target proteins such as p53 and MDM2 through specific peptide motifs (P/A/E-x-x-S) [13]
- Catalytic domain (residues ~208–560): cleaves ubiquitin chains from substrates, terminating their ubiquitin tagging.
- C-terminal UBL (ubiquitin-like) domains: stabilise the catalytic core and assist in substrate recognition [14].

The TRAF-like domain is particularly important in substrate selection and is a shared binding interface for both p53 and MDM2 [13]. In basal conditions, structural evidence reveals that USP7 has an increased affinity to MDM2 [15], which further enhances the degradation of p53. However, when this balance is destabilised under stress, any alterations to USP7 or its substrates can upset this balance.

Two models can explain the selective substrate preference of the USP7:

- Default Preference Model: When unstressed, USP7 has a default preference to engage with MDM2, stabilising it and indirectly leading to p53 degradation [16].
- Context-Dependent Switching Model: Phosphorylation or acetylation of USP7, MDM2, or p53, or stress-induced localisation of USP7 to the nucleus exchanges binding preferences toward p53 stabilisation [13].

Collectively, these processes enable USP7 to function as a stress-responsive p53 regulator, capable of switching between tumour suppressor and p53 suppressor activities, depending on the cellular environment.

Viral Hijacking of Host Cellular Pathways

Viruses have developed intricate strategies to subvert the cellular machinery of their hosts, thereby enhancing viral replication, evading host immune responses, and enabling them to survive in a permissive intracellular environment [17]. The USP7 suppressor axis is one of the most promising prospects in viral interventions, as USP7 is involved in apoptosis, DNA repair/telomere regulation, and cell cycle arrest. This axis enables viruses to evade the host immune response and may contribute to the oncogenic switch [18].

Viral Hijacking of the USP7-MDM2-p53 Pathway

Pirating of the pathway by the USP7-MDM2-p53 virus plays a critical role in preventing the occurrence of tumours in normal cells. Although they share quite different structures, tropisms, and life cycles, three examples of viruses that utilise this pathway to suppress p53-mediated tumour suppression are EBV, HPV, and HIV [6]. These viruses target distinct cell types, yet all target USP7 as a regulatory hub, suggesting its role is conserved across tissues [19]. Thereby, they can induce a block against apoptosis or activate cell survival, thereby establishing a viral replication effect that may lead to oncogenesis.

Justification for Virus Selection: EBV, HPV, HIV

These viruses have not only been selected based on their high oncogenic potential but also for their ability to suppress p53 through different viral mechanisms. These viruses exemplify three major groups of human pathogens: herpesviruses, papillomaviruses, and retroviruses that exploit USP7 control of MDM2-p53 to promote oncogenesis [6]. This decision can also be explained by the fact that they lead to an immense global disease burden, and each virus is related to high rates in the case of cancer worldwide [20].[20].

Table 1: Comparative Summary of Cancer Burden and Rationale for Viral Inclusion

Virus	Cancer Burden	Rationale for Inclusion
EBV	Implicated in approximately 200,000 cancer cases annually [21]	A latent tumour virus that has an indirect effect on p53 through viral proteins and evasion of the immune system
HPV	Responsible for over 600,000 cancer cases annually; cervical cancer alone caused over 342,000 deaths worldwide in 2020 [22]	A high-burden oncogenic virus that directly inactivates p53 with well-characterised viral oncoproteins
HIV	Elevates cancer risk under chronic immunosuppression; cancer is a leading cause of death in people living with HIV, particularly in low-resource settings [23]	Illustrates the means by which immune dysregulation and indirect inactivation of p53 may have a role in virus-associated tumourigenesis

Abbreviation: EBV: Epstein–Barr virus; HIV: Human immunodeficiency virus; HPV: Human papillomavirus.

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The selection of these viruses was based not only on their high prevalence rate and oncogenicity, but also on the fact that each virus belongs to a different class of viruses that all utilise the USP7-MDM2-p53 pathway. This convergence presents a comparative framework for understanding how distinct oncoproteins of several viruses, as well as diverse oncogenic molecular pathways, have evolved to subvert a common cellular tumour suppressor pathway, leading to oncogenesis.

Viral Hijacking Mechanism

Although these distinct viruses vary in their life cycles and host cell tropisms, EBV, HPV, and HIV use common mechanisms to manipulate the USP7-MDM2-p53 network. These viral proteins interfere with the anti-proliferative activities of p53 by inducing its proteolysis, suppressing transcriptional activity, or destabilising it [6]. This manipulation not only facilitates viral replication but also helps cells survive and, under certain circumstances, undergo transformation.

Impact of Viral Oncoproteins on p53

Epstein-Barr Virus (EBV)

EBV, a gamma-herpesvirus, infects more than 90% of the adult population globally [22]. It is associated with several malignancies, including Burkitt lymphoma, nasopharyngeal carcinoma, and Hodgkin lymphoma. One of EBV's key viral proteins, Epstein-Barr nuclear antigen 1 (EBNA1), directly binds to the USP7 TRAF-like domain, exhibiting a higher binding affinity for USP7 than for p53 [24]. This preferential binding leads to the destabilisation of p53, thereby inhibiting p53-induced growth arrest and apoptosis in EBV-infected B cells [11]. In addition to this, EBNA1 recruits USP7 to the viral origin of replication (oriP), where it co-opts USP7's chromatin-remodelling functions that would otherwise act on tumour suppressor genes [25].

Human Papillomavirus (HPV)

HPV, particularly HPV types 16 and 18, is a leading cause of cervical and head-and-neck cancers. HPV's E6 and E7 oncoproteins play central roles in the virus's oncogenic potential. The E6 protein forms a complex with the cellular E3 ligase E6AP, resulting in the ubiquitination and subsequent proteasomal degradation of p53 [19]. By inactivating p53, HPV bypasses critical cell cycle checkpoints, thus facilitating viral replication. Additionally, HPV E7 binds to USP7, stabilising the E7 protein and enhancing its ability to inactivate the retinoblastoma protein (pRb), which pushes infected cells into S phase and promotes uncontrolled proliferation [26]. Inhibiting USP7 destabilises E7 and suppresses tumourigenic phenotypes in HPV-positive cell lines [26].

Human Immunodeficiency Virus (HIV)

HIV is not traditionally considered an oncogenic virus, but its chronic infection and immunosuppressive effects significantly elevate the risk of cancer in infected individuals. HIV's accessory protein Tat plays a central role in viral transcription and replication. Tat binding to MDM2 causes deubiquitination by stabilising proteins and upregulates viral gene expression [27]. This indirectly inhibits the p53 pathway, leading to increased immune malfunction and cell survival. Moreover, HIV-1 Nef associates directly with p53, targeting it to ubiquitination and degradation through increased activity of the E6AP proteasomal complex, dampening p53's tumour suppressive roles [5]. HIV-1 Tat also promotes phosphorylation of MDM2 at Ser166 by activating AKT, which results in higher levels of p53 ubiquitination and destruction, further stabilising the viral replication context [28]. Unlike EBV and HPV, which bind directly to p53 or its modulators, HIV works on the USP7-MDM2-p53 pathway by causing USP7-mediated stabilisation of MDM2, thereby allowing the degradation of p53 and facilitating viral persistence [6].

The USP7-MD2-p53 axis is manipulated in EBV, HPV, and HIV to repress p53-induced apoptosis, cell cycle arrest, and cell survival, all of which contribute to viral persistence and malignancy.

Key Mechanisms in Viral Hijacking of the USP7–MDM2–p53 Axis

1. EBV: USP7 is bound preferentially to EBNA1 to cause destabilisation of p53 and inhibition of apoptosis in EBV-infected cells. This interplay is essential for the virus to achieve long-term latency and evade host immune surveillance [24].
2. HPV: E6 and E7 oncoproteins of HPV show clear differences in the interruption of the USP7-MDM2-p53 pathway. E6 triggers the depletion of p53 via E6AP, whereas E7 interacts with USP7, stabilising the viral oncoprotein in a way that advances cell cycle progression by deactivating pRb [26]. Both interventions prevent p53 functionality, thereby stimulating the replication of the virus and tumour formation.
3. HIV: HIV mediates the p53 regulatory pathway by influencing p53 indirectly via USP7-MDM2. HIV-1 Tat stabilises MDM2, which increases p53 degradation, and Nef recruits p53 degradation via stimulation of the E6AP. They reduce the tumour suppressive activities of p53 and lead to HIV-related malignancies in immunocompromised individuals [5].

In spite of the fact that the mechanisms of action employed by EBV, HPV, and HIV are different, there are a number of similarities when considering how these viruses subvert the USP7-MDM2-p53 pathway:

1. Targeting USP7: The three viruses use USP7 to exploit p53. EBV sequesters USP7 to prevent the stabilisation of p53, whereas HPV utilises it to stabilise the E7 oncoprotein. HIV, on the other hand, stabilises MDM2 using USP7, which then leads to the destabilisation of p53 [24].

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2. Disruption of p53 Function: The viruses target p53 activity by direct degradation of the protein (HPV), sequestration (EBV), and indirectly via MDM2 stabilisation (HIV). In either scenario, it denies p53 the ability to execute tumour-suppressor duties, including cell cycle arrest and killing [5].
3. Facilitating Oncogenesis: The manipulation of the USP7-MDM2-p53 axis by these viruses also leads to cellular changes that facilitate viral replication and the progression of oncogenesis. This avoidance of growth regulation by p53 enables the maintenance of chronic infections by these viruses as well as the development of cancer [25].

Variable Strategies: Viral Protein Involvement

1. EBV: Binds USP7 through EBNA1 to directly inhibit p53 stabilisation, aiding immune escape and latent infection – gamma-herpesvirus's exclusive strategy [24]
2. HPV: The E6 and E7 proteins of HPV directly target p53 degradation and stabilise viral oncoproteins, making HPV a highly effective oncogenic virus, particularly in cervical and other HPV-associated cancers [19].
3. HIV: Uses a more indirect approach, stabilising MDM2 through Tat and promoting p53 degradation via Nef. This indirect manipulation of p53 by HIV is unique among the three viruses discussed [27].

Table 2: Viral Hijacking Mechanisms

Virus	Viral Protein(s)	Interaction Mechanism	Effect on p53	Model System
EBV	EBNA1	Binds USP7 TRAF-like domain	Sequesters USP7; destabilises p53	EBV-infected B cells
HPV	E6, E7	E6 → E6AP → p53 degradation; E7 binds USP7	p53 degradation; E7 stabilisation, promoting cell cycle progression	HPV-transformed cervical cancer cells
HIV	Tat, Nef	Stabilises MDM2, enhancing p53 degradation; Nef recruit E6AP → p53 degradation	Indirect suppression of p53 activity, promoting cell survival	HIV-infected T cells

Abbreviations: EBNA1: Epstein-Barr Virus Nuclear Antigen 1; **E6**: HPV Oncoprotein 6; **E7**: HPV Oncoprotein 7; **E6AP**: E6-Associated Protein; **HIV**: Human Immunodeficiency Virus; **MDM2**: Mouse Double Minute 2; **p53**: Tumor Protein p5; **USP7**: Ubiquitin-Specific Protease 7; **TRAF**: Tumour Necrosis Factor Receptor-Associated Factor

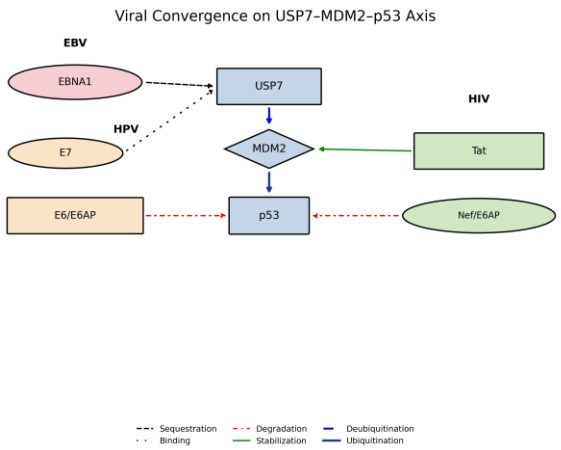

Figure 2. Viral Convergence on the USP7-MDM2-p53 Axis. HBV, HPV and HIV exploit the host USP7-MDM2-p53 pathway to undermine the p53-mediated tumour-suppressive responses.

EBV's EBNA1 sequesters USP7, reducing its ability to deubiquitinate MDM2 and stabilise p53. HPV's E7 binds USP7, while the E6/E6AP complex targets p53 for ubiquitin-dependent degradation. HIV's Tat stabilises MDM2 to enhance p53 ubiquitation, and Nef, in association with E6AP, further promotes p53 degradation.

This figure was created using Biorender.

Despite the diverse entry processes, tropism, and latency options, the three viruses similarly exploit USP7 by competing with p53, stabilising viral oncoproteins, or opposing p53-mediated transcriptional programs. One of the points of convergence is the targeting of USP7's TRAF domain [13], indicating it is a shared vulnerability of several viruses.

Despite tremendous progress made towards understanding the pathway in USP7, MDM2, and p53, the majority of ongoing research activities rely heavily on overexpression systems in immortalised cancer cell lines [7]. Such models can overestimate protein-protein interactions and do not accurately reflect physiological levels of expression, which means the findings from these designs may not be applicable to in vivo conditions. Therefore, the interactions should be confirmed in more in vivo models, including genetically engineered mice and organoids [29].

Moreover, there is limited knowledge of the tissue specificity of USP7's activity. Although numerous studies have implicated the epithelial and hematopoietic systems, there is a lack of information on the activity of USP7 in the nervous system, endocrine tissues, or during developmental conditions. The non-cancerous roles of USP7 are just starting to be unravelled using tissue-specific deletion of USP7 in a mouse model. Comparative studies of knock-in mouse models or knock-out mouse models have shown that ablation

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of USP7 during early development is lethal in vivo [30]. Applying conditional deletions or chemical blocks (such as P22077) has been identified as a potential solution to overcome this shortcoming; however, it is also limited in its performance.

An example is P22077, which is not bioavailable and has off-target effects; therefore, it is inappropriate to study it in animals [31]. Physiologically relevant models, including inducible knock-out, lineage tracing, and editing in primary tissues, would be beneficial to the field in this respect. These models may provide additional insights into how the specificity of USP7 substrates is controlled under different cellular conditions, as well as whether this regulation could be exploited as a therapeutic strategy.

Finally, the role of the virome and its implications on the p53-USP7-MDM2 pathway are understudied [32]. Recently discovered pathogens, such as Merkel cell polyomavirus and Kaposi sarcoma-associated herpesvirus (KSHV), may also interfere with the pathway but are not well-characterised currently. Such interactions will not only help in understanding how the evolutionary arms race between viruses and host tumour suppression mechanisms has evolved, but also in determining new frontiers of therapeutics.

Future Therapeutic Approaches

Tumours originating from the USP7-MDM2-p53 lose their potential as a target that expresses sensitivity to hijacking by a virus; thus, there has been considerable potential appeal in targeting the axis to achieve a therapeutic advantage [7].

USP7 Inhibitors

The oncoprotein-MDM2 relationship of USP7 makes it an attractive target for cancer therapeutics [7], as it affects the stability of both proteins in a similar manner. While USP7 inhibitors show promise in preclinical studies, their potential systemic toxicity (e.g., gut epithelium apoptosis) may limit their clinical use. The small-molecule inhibitors of USP7 are designed to bind to the active site of this deubiquitinase, thereby preventing the deubiquitination of MDM2 and stabilising p53 [11]. P5091 is one of the earliest and best-investigated inhibitors, increasing the apoptosis of multiple myeloma and neuroblastoma cells to render them sensitive to p53-dependent transcription again. Similarly, P22077, a more specific USP7 inhibitor, has been demonstrated preclinically to be efficacious in the acute myeloid leukaemia and Ewing sarcoma models by blocking MDM2 stabilisation [31].

The realisation of allosteric inhibitors, including GNE-6640 and FT827, has established a new frontier of therapeutics [33]. The compounds achieve activity through a conformational change, which reduces the substrate affinity of USP7 without competing with ubiquitin binding [31]. Notably, GNE-6640 has shown strong activity and favourable pharmacokinetics in preclinical models, demonstrating clinical potential. Despite the encouraging results, the study has several limitations. Firstly, most available inhibitors exhibit weak specificity because USP7 shares structural similarity with other deubiquitinases [34]. Off-targets would also be capable of stealing the essential cellular functionality, hence, causing toxicity. Secondly, poor bioavailability and hindrance to crossing the blood-brain barrier, especially with virus-induced tumours of the central nervous system [35]. Finally, a USP7 inhibitor would inadvertently stabilise p53 in (normal) tissues, inducing unwanted apoptosis/senescence [7], particularly in those (like the gut epithelium or bone marrow) having high cellular turnover. Unlike MDM2 inhibitors, USP7 targeting may disrupt viral latency but risks broader substrate effects.

Genome Editing Approaches

The potential function of CRISPR-Cas9 and other genome-editing platforms has revolutionised molecular biology, enabling investigators to dissect gene function with unparalleled clarity [36]. For the USP7–MDM2–p53 axis, CRISPR has already been utilised to knock out USP7, MDM2, or p53 in different cell lines in order to clarify their respective roles in cellular homeostasis and viral infection outcomes. CRISPR has also enabled the modelling of viral hijacking mechanisms [36]. For instance, EBNA1-binding domains in USP7 have been selectively ablated in EBV-transformed lymphoblastoid cell lines, demonstrating that disruption of EBNA1–USP7 interaction hinders viral replication and B-cell immortalisation [37]. Similarly, disruption of the E6 gene by CRISPR in HPV-positive cervical cancer cells reactivates the function of p53 and induces apoptosis, validating the concept of complex-dependent targeting through viral oncogenes [38]. Beyond gene knock-out, gene expression can be precisely and reversibly regulated by the interference and activation of gene expression through CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) [4]. CRISPR has also been introduced with point mutations and small insertions, without the generation of double-strand breaks, which maximises the safety profile and minimises the off-target effects [39].

Although CRISPR-Cas9 technologies offer promising opportunities to interfere with virus-altered host pathways, several translational hurdles remain. Delivery platform concerns are also major issues of CRISPR-based methods, specifically challenges in delivering these techniques in a tissue-specific manner with high transduction and stable expression. Working viral vectors, including adeno-associated viruses (AAVs), show packing limitations and unpredictable tropisms, which can hamper effective editing in specific infected or transformed cell types [40]. Furthermore, off-target effects are a cause of concern, especially when editing cell cycle or DNA repair control genes, as these effects are associated with genotoxicity, especially with the editing of the components of the p53 pathway. The low immunogenicity of Cas9 proteins and the inaccessibility of editing reversal also complicate clinical

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use. Hence, despite CRISR being a highly investigative and even therapeutic technology, improvements in the engineering of delivery vectors, algorithms for calculating off-targets, and profiling safety are needed before it can be used in vivo as a reliable method of CRISPR to target virus-related oncogenesis.

CONCLUSION

This review provided data on the mechanism by which EBV, HPV and HIV converge mechanistically to disrupt host tumour suppression by hijacking the USP7–MDM2–p53 axis, destabilising p53 and weakening the cell's apoptotic response to stress. By targeting p53 regulation via various viral proteins, each of the viruses will interfere with p53 regulation at some point, either by promoting its degradation, disrupting its transcription activity, or by inhibiting its stabilisers, resulting in immune escape, extended cell survival, and the onset of malignancy. USP7 is revealed as a molecular hub in this mechanism, being a substrate chooser that can stabilise p53 or promote the activity of MDM2 as an oncogenic protein.

Therapeutic combinatorial approaches should be investigated. Preclinical trials suggest that USP7 inhibitors, including P5091 and FT671, can restore p53 function and enhance apoptosis in virus-transformed cells. Nevertheless, their efficacy may be enhanced by rational combination with antiviral treatments, particularly in environments where viral persistence is a cause of chronic immune dysregulation and oncogenesis. For example, USP7 inhibition, when combined with established antiretrovirals in HIV-related malignancies, or HPV vaccines and immune-based therapies, could have synergistic effects and restrain tumour growth more significantly than single treatments.

Lastly, genome-editing technology, such as CRISPR, has remarkable promise when applied to experimental models of viral oncogenesis. However, the existing problems with CRISPR delivery, such as vector tropism, off-target effects, and immunological reactions to Cas9, need to be resolved before these advancements can be effectively translated into clinical practice.

To conclude, a more thorough mechanistic elucidation of the USP7–MDM2–p53 axis, as manipulated by oncogenic viruses, will be necessary to develop effective interventions. These revelations have the potential to initiate new therapeutic paradigms that restore host tumour suppressor activity while simultaneously counteracting viral persistence and oncogenic transformation.

REFERENCE

[1] Zhang H, Xu J, Long Y, Maimaitijiang A, Su Z, Li W, Li J. *Unraveling the guardian: p53's multifaceted role in DNA-damage response and tumor treatment strategies.* **Int J Mol Sci.** 2024; 25(23):12928. https://doi.org/10.3390/ijms252312928

[2] Chen J. *The cell-cycle arrest and apoptotic functions of p53 in tumor initiation and progression.* **Cold Spring Harb Perspect Med.** 2016; 6(3):a026104. https://doi.org/10.1101/cshperspect.a026104

[3] Karimian A, Ahmadi Y, Yousefi B. *Multiple functions of p21 in cell cycle, apoptosis and transcriptional regulation after DNA damage.* **DNA Repair.** 2016; 42:63–71. https://doi.org/10.1016/j.dnarep.2016.04.008

[4] Wang Z, Strasser A, Kelly GL. *Should mutant TP53 be targeted for cancer therapy?* **Cell Death Differ.** 2022; 29(5):911–920. https://doi.org/10.1038/s41418-022-00962-9

[5] Ali A, Farooqui SR, Rai J, Singh J, Kumar V, Mishra R, Banerjea AC. *HIV-1 Nef promotes ubiquitination and proteasomal degradation of p53 tumor suppressor protein by using E6AP.* **Biochem Biophys Res Commun.** 2020; 529 (4):1038–1044. https://doi.org/10.1016/j.bbrc.2020.05.188

[6] Tornesello ML, Annunziata C, Tornesello AL, Buonaguro L, Buonaguro FM. *Human oncoviruses and p53 pathway deregulation at the origin of human cancers.* **Cancers (Basel).** 2018; 10(7):213. https://doi.org/10.3390/cancers10070213

[7] Harakandi C, Nininahazwe L, Xu H, Liu B, He C, Zheng YC, et al. *Recent advances on the intervention sites targeting USP7–MDM2–p53 in cancer therapy.* **Bioorg Chem.** 2021; 116:105273. https://doi.org/10.1016/j.bioorg.2021.105273

[8] Liu J, Cao L, Wang Y, Zou Y, Guo Q, Chen S, et al. *The CHK2–USP7 axis stabilizes p53 under oxidative stress.* **Cell Rep.** 2024; 43(6):114366. https://doi.org/10.1016/j.celrep.2024.114366

[9] Chao CCK. *Mechanisms of p53 degradation.* **Clin Chim Acta.** 2015; 438:139–147. https://doi.org/10.1016/j.cca.2014.08.015

[10] Al-Eidan A, Wang Y, Skipp P, Ewing RM. *The USP7 protein interaction network and its roles in tumorigenesis.* **Genes Dis.** 2020; 7(6):748–758. https://doi.org/10.1016/j.gendis.2020.10.004

[11] Qi S, Cheng G, Xiao C, Xu ZY, Xu B, Zhang W, et al. *Targeting USP7-mediated deubiquitination of MDM2/MDMX –p53 for cancer therapy.* **Front Cell Dev Biol.** 2020; 8:233. https://doi.org/10.3389/fcell.2020.00233

[12] Levine AJ. *p53: 800 million years of evolution and 40 years of discovery.* **Nat Rev Cancer.** 2020; 20(8):471–480. https://doi.org/10.1038/s41568-020-0262-1

[13] Cheng J, Li Z, Gong R, Fang J, Yang Y, Sun C, et al. *Molecular mechanism for the substrate recognition of USP7.***Protein Cell.** 2015; 6(11):849–852. https://doi.org/10.1007/s13238-015-0192-y

[14] Kim RQ, van Dijk WJ, Sixma TK. *Structure of USP7 catalytic domain and three Ubl-domains reveals a connector α-helix with regulatory role.* **J Struct Biol.** 2016; 195(1):11–18. https://doi.org/10.1016/j.jsb.2016.05.005

[15] Tavana O, Gu W. *Modulation of the p53/MDM2 interplay by HAUSP inhibitors.* **J Mol Cell Biol.** 2017; 9(1):45–52. https://doi.org/10.1093/jmcb/mjw049

[16] Pozhidaeva A, Bezsonova I. *USP7: Structure, substrate specificity, and inhibition.* **DNA Repair.** 2019; 76:30–39. https://doi.org/10.1016/j.dnarep.2019.02.005

[17] Ahmed K, Jha S. *Oncoviruses: How do they hijack their host and current treatment regimes.* **Biochim Biophys Acta Rev Cancer.** 2023; 1878(5):188960. https://doi.org/10.1016/j.bbcan.2023.188960

[18] Ameya G, Birri DJ. *The molecular mechanisms of virus-induced human cancers.* **Microb Pathog.** 2023; 183:106292. https://doi.org/10.1016/j.micpath.2023.106292

e-ISSN: 2583-0023

[19] Martinez-Zapien D, Ruiz FX, Poirson J, Mitschler A, Ramirez J, Forster A, et al. *Structure of the E6/E6AP/p53 complex required for HPV-mediated degradation of p53.* **Nature.** 2016;529(7587):541–545. https://doi.org/10.1038/nature16481

[20] Mui U, Haley C, Tyring S. *Viral oncology: Molecular biology and pathogenesis.* **J Clin Med.** 2017; 6(12):111. https://doi.org/10.3390/jcm6120111

[21] Shannon-Lowe C, Rickinson A. *The global landscape of EBV-associated tumors.* **Front Oncol.** 2019; 9:713. https://doi.org/10.3389/fonc.2019.00713

[22] Wong Y, Meehan MT, Burrows SR, Doolan DL, Miles JJ. *Estimating the global burden of EBV-related cancers.* **J Cancer Res Clin Oncol.** 2021; 148(1):25–39. https://doi.org/10.1007/s00432-021-03824-y

[23] Engels EA, Shiels MS, Barnabas RV, Bohlius J, Brennan P, Castilho J, et al. *State of the science and future directions for research on HIV and cancer.* **Int J Cancer.** 2023;154(4):596–606. https://doi.org/10.1002/ijc.34727

[24] Bojagora A, Saridakis V. *USP7 manipulation by viral proteins.* **Virus Res.** 2020; 286:198076. https://doi.org/10.1016/j.virusres.2020.198076

[25] Mei Y, Messick TE, Dheekollu J, Kim HJ, Molugu S, Josue L, et al. *Cryo-EM structure and functional studies of EBNA1 binding to the Epstein–Barr virus oriP*. **J Virol.** 2022; 96(17):e00949-22. https://doi.org/10.1128/jvi.00949-22

[26] Miller AK, Munger K, Adler FR. *A mathematical model of cell-cycle dysregulation due to HPV infection.* **Bull Math Biol.** 2017; 79(7):1564–1585. https://doi.org/10.1007/s11538-017-0299-9

[27] Zhang Q, Jia Q, Gao W, Zhang W. *The role of deubiquitinases in virus replication and host innate immune response.* **Front Microbiol.** 2022; 13: https://doi.org/10.3389/fmicb.2022.839624

[28] Lata S, Sood V, Banerjea AC. *HIV-1 Vif up-regulates Tat expression via AKT signaling: Role of deubiquitinase USP17 and NQO1*. **Front Microbiol.** 2021; 12:679228. https://doi.org/10.3389/fmicb.2022.828430

[29] Tackmann NR, Zhang Y. *Mouse modelling of the MDM2/MDMX–p53 signalling axis.* **J Mol Cell Biol.** 2017; 9(1):34–44. https://doi.org/10.1093/jmcb/mjx006

[30] Nininahazwe L, Liu B, He C, Zhang H, Chen ZS. *The emerging nature of USP7: A new target in cancer therapy*. **Drug Discov Today.** 2021; 26(2):490–502. https://doi.org/10.1016/j.drudis.2020.10.028

[31] Turnbull AP, Ioannidis S, Krajewski WW, Pinto-Fernandez A, Heride C, Martin ACL, et al. *Molecular basis of USP7 inhibition by selective small-molecule inhibitors.* **Nature.** 2017; 550(7677):481–486. https://doi.org/10.1038/nature24451

[32] Tamayo-Trujillo R, Guevara-Ramírez P, Cadena-Ullauri S, Paz-Cruz E, Ruiz-Pozo VA, Zambrano AK. *Human virome: Implications in cancer*. **Heliyon.** 2023; 9(3):e14500. https://doi.org/10.1016/j.heliyon.2023.e14086

[33] Kategaya L, Di Lello P, Rougé L, Pastor R, Clark KR, Drummond J, et al. *USP7 small-molecule inhibitors interfere with ubiquitin binding.* **Nature.** 2017; 550(7677):534–538. https://doi.org/10.1038/nature24006

[34] Li P, Liu HM. *Recent advances in the development of USP7 inhibitors.* **Eur J Med Chem.** 2020; 191:112107. https://doi.org/10.1016/j.ejmech.2020.112107

[35] Lin A, Giuliano CJ, Palladino A, John KM, Abramowicz C, Yuan ML, et al. *Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials.* **Sci Transl Med.** 2019; 11(509):eaaw8412. https://doi.org/10.1126/scitranslmed.aaw8412

[36] Gebre M, Nomburg JL, Gewurz BE. *CRISPR–Cas9 genetic analysis of virus–host interactions.* **Viruses.** 2018; 10(2):55. https://doi.org/10.3390/v10020055

[37] Chen C, Addepalli K, Soldan SS, Josue L, Preston-Alp S, Patel RJ, et al. *USP7 inhibitors destabilize EBNA1 and suppress Epstein–Barr virus tumorigenesis.* **J Med Virol.** 2025; 97(1):e70168. https://doi.org/10.1002/jmv.70168

[38] Wang LW, Trudeau SJ, Wang C, Gerdt C, Jiang S, Zhao B, Gewurz BE. *Modulating gene expression in EBV-positive B cell lines with CRISPRa and CRISPRi.* **Curr Protoc Mol Biol.** 2018; 121:31.13.1–31.13.18. https://doi.org/10.1002/cpmb.50

[39] Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. *Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage.* **Nature.** 2016; 533(7603):420–424. https://doi.org/10.1038/nature17946

[40] Yin H, Song CQ, Suresh S, Wu Q, Walsh S, Rhym LH, et al. *Structure-guided chemical modification of guide RNA enables potent non-viral in vivo genome editing.* **Nat Biotechnol.** 2017; 35(12):1179–1187. https://doi.org/10.1038/nbt.4005