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ZFP36L1 AS A CENTRAL REGULATOR OF POST-TRANSCRIPTIONAL GENE EXPRESSION: IMPLICATIONS FOR IMMUNE REGULATION AND ANTIVIRAL DEFENCE- A REVIEW

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Abstract
Post-transcriptional regulation of gene expression is a critical determinant of cellular responses to environmental and physiological stimuli. Among the key regulators of mRNA stability are RNA-binding proteins (RBPs), which modulate transcript turnover and translation. The ZFP36 family of RBPs, particularly ZFP36L1, plays a central role in AU-rich element (ARE)-mediated mRNA decay, thereby controlling the expression of genes involved in inflammation, cell proliferation, and stress responses. ZFP36L1 functions as a post-transcriptional repressor by binding to ARE-containing transcripts and recruiting the CCR4–NOT deadenylase complex, leading to mRNA degradation and translational repression. Its activity is dynamically regulated by signalling pathways, including the p38 MAPK–MK2 axis, enabling precise temporal control of gene expression. Emerging evidence indicates that ZFP36L1 regulates diverse RNA regulons, influencing both innate and adaptive immune responses. In addition, recent studies suggest a role for ZFP36L1 in antiviral defence through modulation of interferon-stimulated genes and direct interactions with viral RNA. This review provides a comprehensive overview of the molecular mechanisms underlying ZFP36L1 function, its roles in immune regulation and antiviral responses, and recent advances in the field. Key challenges, including functional redundancy and context-dependent target selection, are discussed, along with future directions for therapeutic targeting of RNA stability pathways.
Keywords: AU-rich elements; mRNA decay; post-transcriptional regulation; RNA-binding proteins; ZFP36L1

INTRODUCTION

Gene expression is regulated through multiple interconnected layers, including transcriptional, post-transcriptional, translational, and post-translational mechanisms. While transcriptional regulation has historically been emphasised, post-transcriptional processes are now recognised as major determinants of protein abundance across mammalian systems (Vogel and Marcotte, 2012; Franks *et al.*, 2017; Hentze *et al.,* 2018; Furlan *et al.,* 2021). These processes enable rapid and reversible modulation of gene expression in response to environmental and physiological stimuli, particularly during dynamic cellular responses such as infection and stress. Recent studies further highlight that RNA-binding proteins (RBPs) act as key regulators of RNA fate, influencing cellular behaviour by coordinating the control of RNA stability and translation.

A central mechanism governing mRNA turnover in eukaryotic cells is AU-rich element (ARE)-mediated decay. AREs are cis-regulatory sequences located within the 3' untranslated regions (3'UTRs) of many short-lived transcripts, particularly those encoding cytokines, growth factors, and proto-oncogenes (Chen and Shyu, 1995; Barreau *et al.* 2005; Planel *et al.,* 2014).

These elements serve as binding platforms for RNA-binding proteins, which determine whether transcripts are stabilised or targeted for degradation (Hasan *et al.,* 2014; Corley *et al.,* 2020). It is estimated that a substantial proportion of inducible transcripts contain AREs, highlighting the widespread influence of this regulatory mechanism on gene expression programmes.

RNA-binding proteins play a central role in post-transcriptional regulation by interacting with target transcripts and modulating their stability, localisation, and translation (Glisovic *et al.,* 2008; Kishore *et al.,* 2010; Harvey *et al.,* 2017). The human genome encodes more than 1,500 RBPs, many of which are involved in essential cellular processes and disease pathogenesis (Gerstberger *et al.,* 2014). In the immune system, RBPs are essential for maintaining appropriate gene expression dynamics, as timely mRNA degradation is required to ensure controlled inflammatory responses (Kafasla *et al.,* 2014). Recent work has demonstrated that selective cytoplasmic mRNA decay is a critical determinant of immune response fidelity, with RBPs orchestrating the degradation of transcripts at multiple stages of RNA metabolism (Ghosh and Jacobson, 2010; Turner and Diaz-Munoz, 2018; Makita *et al.,* 2021).

Among ARE-binding RBPs, the ZFP36 family, also known as the tristetraprolin (TTP) family, plays a critical role in promoting mRNA decay (Sanduja *et al.,* 2011; Makita *et al.,* 2021). This family comprises three main members in humans: ZFP36 (TTP), ZFP36L1, and ZFP36L2, all of which contain conserved tandem CCCH-type zinc finger domains responsible for RNA binding (Blackshear, 2002; Baou *et al.* 2009). These proteins function as post-transcriptional repressors by binding to ARE-containing transcripts and recruiting components of the mRNA decay machinery, including the CCR4–NOT deadenylase complex.

Recent mechanistic studies suggest that these decay processes are highly coordinated and may be initiated co-transcriptionally, linking RNA synthesis directly to its eventual degradation (Makita *et al.,* 2021).

ZFP36L1 has emerged as a multifunctional regulator with roles extending beyond classical cytokine regulation. It is broadly expressed across cell types and regulates transcripts involved in immune signalling, cellular differentiation, and metabolic adaptation (Stumpo *et al.,* 2009). More recent studies indicate that members of the ZFP36 family can directly regulate metabolic gene expression programmes through mRNA stability control, highlighting an expanded role beyond immune regulation (Cai *et al.,* 2022; Cicchetto *et al.,* 2023). In addition, genetic and functional studies have demonstrated that ZFP36L1, together with ZFP36L2, is essential for maintaining immune homeostasis and preventing dysregulated cytokine expression in vivo (Makita *et al.,* 2020; Cook *et al.,* 2022; Zandhuis *et al.,* 2025).

Importantly, ZFP36L1 activity is dynamically controlled by signalling pathways such as the p38 MAPK–MK2 axis, which modulate its phosphorylation state and functional interactions (Stoecklin *et al.,* 2004). This regulatory mechanism allows integration of extracellular signals with post-transcriptional gene control, enabling precise temporal regulation of gene expression during immune activation.

Recent advances in transcriptomic and biochemical approaches have revealed that ZFP36L1 regulates extensive RNA networks, including genes involved in innate immunity and antiviral responses (Hafner *et al.,* 2010). However, its precise functions remain context-dependent, and key questions regarding target specificity, redundancy with other family members, and relevance in disease remain incompletely understood.

This review provides a comprehensive overview of ZFP36L1 as a central regulator of post-transcriptional gene expression, with particular emphasis on its molecular mechanisms, roles in immune regulation and antiviral defence, and emerging insights from recent studies.

Literature included in this review was identified through searches of PubMed, Scopus, and Google Scholar databases. Search terms included "ZFP36L1", "RNA-binding proteins", "AU-rich elements", "mRNA decay", "interferon signalling", "antiviral immunity", and "post-transcriptional regulation". Priority was given to peer-reviewed studies published in recent years, while seminal earlier studies relevant to the molecular mechanisms of ZFP36L1 were also included. Additional articles were identified through citation tracking of relevant publications.

ZFP36L1 and Mechanisms of Post-Transcriptional Regulation

The ZFP36 family of RNA-binding proteins constitutes a central group of post-transcriptional regulators that control mRNA turnover through interaction with AREs. This family includes ZFP36 (tristetraprolin, TTP), ZFP36L1, and ZFP36L2, which share conserved tandem CCCH-type zinc finger domains that enable sequence-specific binding to target transcripts (Blackshear, 2002; Baou *et al.,* 2009). While these proteins recognise similar RNA motifs, increasing evidence indicates that they exhibit both overlapping and context-specific functions depending on cellular state, signalling inputs, and target transcript availability (Makita *et al.,* 2021).

ZFP36L1 is broadly expressed across multiple cell types and regulates diverse gene expression programmes. ZFP36L1 is more constitutively expressed and contributes to basal control of transcript stability, consistent with transcriptome-wide studies demonstrating extensive RNA regulatory networks mediated by ZFP36 family proteins (Mukherjee *et al.,* 2014). More recent work has expanded its functional scope, demonstrating that ZFP36 family proteins regulate not only inflammatory mediators but also metabolic gene networks, highlighting a broader role in coordinating cellular adaptation to external stimuli (Cicchetto *et al.,* 2023). These findings position ZFP36L1 as a regulator of both immune and metabolic homeostasis.

At the molecular level, ZFP36L1 binds to ARE-containing transcripts within the 3′ untranslated region (3′UTR), typically recognising UAUUUAU motifs embedded within U-rich regions. Upon binding, ZFP36L1 recruits the CCR4–NOT deadenylase complex, initiating shortening of the poly(A) tail, which represents the rate-limiting step in mRNA decay (Fabian *et al.* 2011). This is followed by decapping and exonucleolytic degradation via both 5′–3′ and 3′–5′ pathways, resulting in efficient removal of target transcripts.

Recent mechanistic advances have refined this classical model. Emerging evidence suggests that ZFP36L1-mediated mRNA decay is not restricted to the cytoplasm but is functionally linked to transcriptional processes in the nucleus. Studies have shown that ZFP36 family proteins can bind pre-mRNA and "license" transcripts for degradation before they are fully exported to the cytoplasm, indicating that transcript fate may be determined at or near the point of synthesis (Makita *et al.,* 2021). This represents a significant shift from the traditional view of post-transcriptional regulation as a purely cytoplasmic process and highlights a coordinated coupling between transcription and RNA decay.

In addition to promoting mRNA degradation, ZFP36L1 can repress translation independently of transcript decay. This mechanism enables rapid suppression of protein synthesis, providing an immediate regulatory response prior to mRNA turnover. Such dual functionality is particularly important in dynamic biological contexts such as immune activation, where rapid changes in protein expression are required.

Transcriptome-wide approaches, including individual-nucleotide resolution crosslinking and immunoprecipitation (iCLIP) and related techniques, have further expanded understanding of ZFP36L1 target selection. These studies demonstrate that ZFP36L1 binds to hundreds to thousands of transcripts, often forming coordinated RNA regulons that control functionally related gene networks, including signalling pathways such as MAPK, PI3K–AKT, and JAK–STAT (Hafner *et al.,* 2010; Garcia-Moreno *et al.,* 2019)

(Figure 1). This systems-level regulation allows ZFP36L1 to exert broad effects on cellular phenotype beyond individual transcript control.

The activity of ZFP36L1 is tightly regulated by post-translational modifications, particularly phosphorylation. The p38 MAPK–MK2 signalling axis remains a key regulatory pathway, where phosphorylation promotes interaction with 14-3-3 adaptor proteins and reduces mRNA decay activity (Stoecklin *et al.,* 2004) (Figure 1). More recent studies have shown that phosphorylation-dependent regulation also affects interactions with components of the CCR4–NOT complex and modulates RNA-binding dynamics, further refining the temporal control of gene expression (Adachi *et al.,* 2014).

Beyond host mRNA regulation, ZFP36L1 has also been implicated in direct targeting of viral RNA. Recent studies demonstrate that ZFP36L1 can bind viral genomes and promote their degradation via recruitment of cellular exonucleases such as XRN1 and the RNA exosome (Figure 1), thereby functioning as a host restriction factor against RNA viruses (Chiu *et al.,* 2022). This expands the functional repertoire of ZFP36L1 from a regulator of host gene expression to an active participant in antiviral defence.

Collectively, these findings highlight ZFP36L1 as a dynamic and multifunctional regulator of post-transcriptional gene expression. Its ability to integrate RNA binding, decay machinery recruitment, translational repression, and signalling-dependent regulation enables precise control of gene expression programmes across diverse biological contexts. A summary of the key molecular functions and regulatory mechanisms of ZFP36L1 is presented in Table 1.

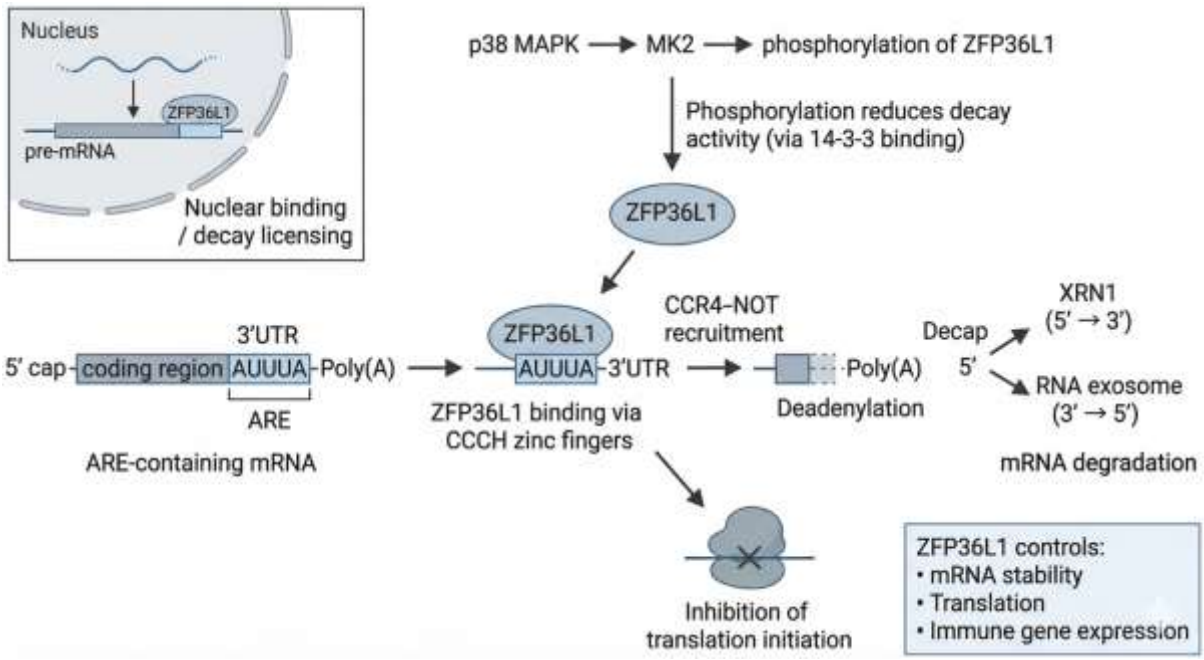

Figure 1: Mechanistic overview of ZFP36L1-mediated post-transcriptional regulation of mRNA. ZFP36L1 binds AU-rich element (ARE)-containing transcripts within the 3'UTR via its tandem CCCH-type zinc finger domains. Upon binding, ZFP36L1 recruits the CCR4–NOT deadenylase complex, leading to poly(A) tail shortening (deadenylation). This is followed by decapping and 5'–3' exonucleolytic degradation mediated by XRN1, and 3'–5' degradation via the RNA exosome (Figure created using Biorender.com further edited in Microsoft PowerPoint).

In addition to promoting mRNA decay, ZFP36L1 can repress translation independently of transcript degradation. Its activity is dynamically regulated by phosphorylation via the p38 MAPK–MK2 pathway, which promotes its interaction with 14-3-3 proteins and reduces its mRNA decay activity (Lin *et al.,* 2012). Emerging evidence also suggests that ZFP36L1 may bind transcripts in the nucleus, influencing RNA fate before export (Matsuura *et al.,* 2020). Collectively, these mechanisms enable precise temporal control of gene expression.

Table 1: Key Functions and Mechanisms of ZFP36L1

Function	Mechanism	Biological Context	Key References
mRNA decay	CCR4–NOT recruitment	Cytokine regulation	Fabian *et al.,* (2011)
Nuclear decay licensing	Pre-mRNA binding	Immune regulation	Makita *et al.,* (2021)
RNA regulon control	CLIP-defined targets	Signalling networks	Hafner *et al.* (2010); Garcia-Moreno *et al.* (2019)
Metabolic regulation	Decay of metabolic transcripts	Growth factor signalling	Cicchetto *et al.* (2023)
Translational repression	Ribosome inhibition	Rapid response control	Mukherjee *et al.* (2014)
Antiviral activity	Viral RNA degradation (XRN1/exosome)	RNA virus infection	Chiu *et al.* (2022)
Signal integration	MK2 phosphorylation	Stress/inflammation	Adachi *et al.* (2014)

ZFP36L1 in Immune Regulation

ZFP36L1 plays a central role in immune regulation by controlling the stability and translation of transcripts encoding cytokines, signalling molecules, and transcription factors. While transcriptional activation initiates immune responses, post-transcriptional mechanisms are essential for shaping their magnitude, duration, and resolution. Many immune-related transcripts contain AREs within their 3′ untranslated regions (3′UTRs), rendering them susceptible to regulation by ZFP36 family proteins (Chen & Shyu, 1995; Barreau *et al.,* 2005).

A key function of ZFP36L1 in the immune system is the regulation of inflammatory gene expression through targeted mRNA decay. By binding to ARE-containing transcripts, ZFP36L1 promotes their degradation and limits excessive cytokine production. This function is particularly important during the resolution phase of inflammation, where sustained expression of cytokines such as tumour necrosis factor (TNF), interleukin-6 (IL-6), and granulocyte–macrophage colony-stimulating factor (GM-CSF) can result in tissue damage (Hodson *et al.,* 2010; Turner & Díaz-Muñoz, 2018). While ZFP36 is often considered the dominant regulator of TNF mRNA, ZFP36L1 contributes to overlapping regulatory networks that ensure robustness and redundancy in cytokine control.

Recent studies have expanded this classical view by demonstrating that ZFP36L1 is not merely a suppressor of inflammatory transcripts but a regulator of immune response kinetics and quality. In T lymphocytes, ZFP36L1, together with ZFP36L2, controls T cell activation thresholds and maintains immune homeostasis by limiting inappropriate cytokine production, including interferon-gamma (IFNγ) (Hodson *et al.,* 2010; Turner & Díaz-Muñoz, 2018). Loss of ZFP36L1 function in this context results in dysregulated immune activation and systemic inflammation, highlighting its essential role in maintaining immune balance.

In innate immunity, ZFP36L1 operates downstream of pattern recognition receptor (PRR) signalling pathways, including Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs). Activation of these pathways induces rapid transcription of inflammatory mediators; however, ZFP36L1-mediated mRNA decay acts as a post-transcriptional checkpoint that limits excessive activation of NF-κB and MAPK signalling pathways (Turner & Díaz-Muñoz, 2018). This ensures that inflammatory responses are appropriately scaled and do not persist beyond their functional requirement.

Beyond innate immune signalling, ZFP36L1 plays a critical role in shaping adaptive immune responses. Recent work demonstrates that ZFP36L1 functions as a regulator of T cell receptor (TCR) signal strength, influencing clonal expansion and differentiation of $CD8^+$ T cells (Petkau *et al.,* 2024). By modulating the stability of transcripts involved in activation and effector function, ZFP36L1 contributes to the fine-tuning of adaptive immunity, ensuring that T cell responses are proportional to antigenic stimulation.

An emerging area of interest is the role of ZFP36L1 in interferon-mediated responses (Lin *et al.,* 2025). While interferon signalling is essential for antiviral defence, excessive or prolonged activation can lead to immunopathology (Cameron *et al.,* 2007). ZFP36L1 contributes to the regulation of interferon-stimulated genes (ISGs) by modulating the stability of their transcripts, thereby acting as a feedback regulator that limits the duration of interferon responses (Hafner *et al.,* 2010; García-Moreno *et al.,* 2021). More recent evidence indicates that ZFP36L1 may also influence interferon-driven immune environments by regulating cytokine networks that shape immune cell recruitment and activation (Li *et al.,* 2026).

In addition to its role in classical immune pathways, ZFP36L1 has been implicated in the regulation of immune checkpoint molecules. Recent studies demonstrate that ZFP36L1 enhances interferon-gamma-induced expression of programmed death-ligand 1 (PD-L1) through post-transcriptional mechanisms, linking RNA stability control to immune evasion pathways (Zhang *et al.,* 2023). This finding expands the functional scope of ZFP36L1 beyond inflammation and antiviral defence to include regulation of tumour–immune interactions.

The activity of ZFP36L1 is dynamically regulated by signalling pathways that modulate its phosphorylation status (Adachi *et al.,* 2014). During early immune activation, phosphorylation via the p38 MAPK–MK2 pathway reduces its mRNA decay activity, allowing transient stabilisation of inflammatory transcripts (Stoecklin *et al.,* 2004).

As signalling subsides, dephosphorylation restores its repressive function, promoting resolution of the immune response. This reversible regulation provides a mechanism for temporal control of gene expression, ensuring that immune responses are both effective and self-limiting.

Collectively, these findings position ZFP36L1 as a key regulator of immune response dynamics rather than a simple suppressor of gene expression. By integrating signalling pathways with post-transcriptional control of mRNA stability, ZFP36L1 shapes both the amplitude and duration of immune responses across innate and adaptive systems. A summary of the major immune-related functions of ZFP36L1 is provided in Table 2.

Table 2. Major immune-related functions of ZFP36L1

Immune Context	Target Transcripts	Functional Outcome	Key References
Inflammation	TNF, IL-6, GM-CSF	Resolution of inflammation	Hodson *et al.* (2010)
Innate immunity	NF-κB pathway genes	Limitation of signalling amplitude	Makita *et al.* (2021)
Interferon response	ISGs	Temporal control of antiviral signalling	Hafner *et al.* (2010)
T cell activation	TCR signalling genes	Control of activation thresholds	Petkau *et al.* (2024)
Immune homeostasis	IFNγ, cytokine networks	Prevention of immune dysregulation	Cook *et al.* (2022)
Immune checkpoints	PD-L1	Regulation of tumour immunity	Zhang *et al.* (2023)

ZFP36L1 in Antiviral Defence

ZFP36L1 has emerged as an important component of host antiviral defence through its ability to regulate both host and viral RNA stability. As an RNA-binding protein that recognises AREs, ZFP36L1 is uniquely positioned to influence viral replication and host antiviral responses at the post-transcriptional level. Recent studies have demonstrated that ZFP36L1 functions as a host restriction factor against multiple RNA viruses, acting through both direct targeting of viral RNA and indirect modulation of host antiviral pathways (Lin *et al.,* 2020; Lin *et al.,* 2025).

One of the primary antiviral mechanisms of ZFP36L1 involves direct binding to viral RNA transcripts, leading to inhibition of viral gene expression. In influenza A virus (IAV) infection, ZFP36L1 has been shown to bind viral mRNAs encoding haemagglutinin (HA), matrix (M), and non-structural protein 1 (NS1), resulting in translational repression and reduced viral replication (Lin *et al.,* 2020). Importantly, mutation of the CCCH-type zinc finger domains abolishes both RNA binding and antiviral activity, confirming that RNA recognition is essential for its function. This highlights a mechanism whereby ZFP36L1 directly interferes with viral protein synthesis, thereby limiting viral propagation.

Beyond translational repression, ZFP36L1 also promotes viral RNA degradation through canonical mRNA decay pathways. Recent evidence indicates that ZFP36L1 can recruit cellular exonucleases, including the 5′–3′ exonuclease XRN1 and components of the RNA exosome, to degrade viral RNA (Lin *et al.,* 2025; Chiu *et al.,* 2022). This dual engagement of decay pathways enables efficient clearance of viral transcripts and represents a conserved antiviral strategy employed by host RNA-binding proteins. Such mechanisms are particularly relevant for positive-sense RNA viruses, where viral genomes and transcripts are accessible in the cytoplasm.

ZFP36L1-mediated antiviral activity is not limited to influenza viruses. Studies have demonstrated its inhibitory effects on flaviviruses, including dengue virus (DENV) and Japanese encephalitis virus (JEV), where it targets viral RNA for degradation and suppresses viral replication (Lin *et al.,* 2025). More recently, ZFP36L1 has been implicated in restricting other RNA viruses, including emerging and zoonotic pathogens, suggesting a broader role as a general antiviral effector.

Importantly, ZFP36L1 also exerts antiviral effects indirectly through modulation of host gene expression. By regulating the stability of transcripts encoding ISGs and inflammatory mediators, ZFP36L1 contributes to the fine-tuning of antiviral responses. This regulatory function ensures that antiviral signalling is sufficiently robust to control infection while preventing excessive or prolonged interferon responses that can lead to immunopathology (Hafner *et al.,* 2010; García-Moreno *et al.,* 2021). In this context, ZFP36L1 acts as a feedback regulator, shaping the kinetics of interferon responses during viral infection.

Recent studies have further highlighted the relevance of ZFP36L1 in coronavirus biology. Experimental evidence indicates that ZFP36L1 can suppress replication of human coronavirus OC43, supporting its role as a host restriction factor against coronaviruses (Momin *et al.,* 2023). Although the precise mechanisms remain to be fully defined, ZFP36L1 likely targets viral RNA or host factors required for replication, consistent with its established roles in RNA regulation. These findings are particularly relevant given the importance of RNA-binding proteins in controlling coronavirus replication and host responses.

In addition to RNA targeting, ZFP36L1 may influence viral infection through interactions with viral proteins (Lin *et al.,* 2020). Recent work suggests that ZFP36L1 can interact with viral nucleoproteins, potentially interfering with viral RNA stability and replication complex formation (Hirano *et al.,* 2025). This expands the functional repertoire of ZFP36L1 beyond RNA decay to include modulation of virus–host protein interactions.

An emerging concept is that ZFP36L1 operates as part of a broader network of RNA-binding proteins that collectively regulate antiviral defence. Members of the CCCH-type zinc finger protein family, including ZAP, MCPIP1, and PARP12, have been shown to restrict viral replication through similar mechanisms involving RNA binding, decay, and translational repression (Hentze et al., 2018; Corley et al., 2020). Within this network, ZFP36L1 contributes to a coordinated antiviral response that targets both viral and host transcripts.

Despite these advances, several questions remain regarding the precise role of ZFP36L1 in antiviral immunity. For example, the extent to which ZFP36L1 selectively targets viral RNA versus host transcripts during infection remains unclear. In addition, the interplay between ZFP36L1-mediated RNA decay and interferon signalling pathways requires further investigation, particularly in physiologically relevant systems (García-Moreno et al., 2021; Makita et al., 2021).

Collectively, current evidence supports a model in which ZFP36L1 functions as a multifunctional antiviral regulator. Through direct targeting of viral RNA, recruitment of RNA decay machinery, and modulation of host immune responses, ZFP36L1 contributes to the control of viral infection at multiple levels. A summary of the antiviral mechanisms of ZFP36L1 is presented in Figure 2.

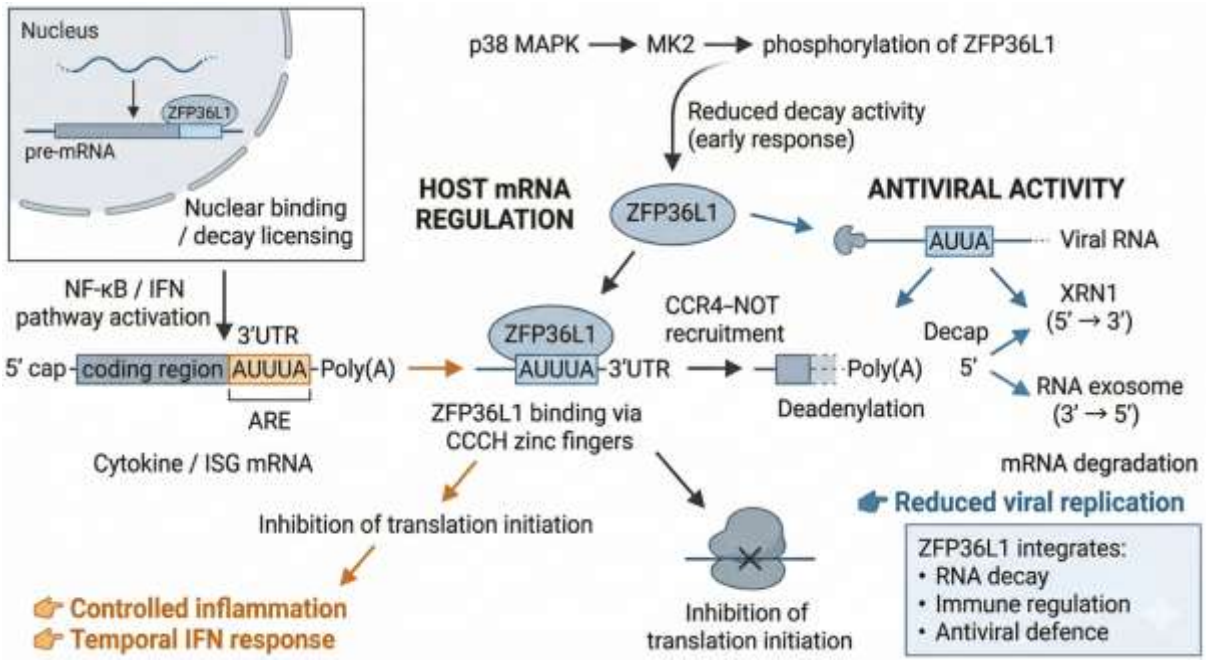

Figure 2: Conceptual model illustrating the role of ZFP36L1 in coordinating antiviral defence and immune regulation. ZFP36L1 binds AU-rich element (ARE)-containing host transcripts and viral RNAs via its CCCH-type zinc finger domains. In host cells, ZFP36L1 promotes degradation of cytokine and ISG mRNAs through recruitment of the CCR4–NOT deadenylase complex, leading to deadenylation, decapping, and exonucleolytic decay. This process contributes to the temporal regulation of inflammatory and interferon responses (Figure created using Biorender.com further edited in Microsoft PowerPoint).

In parallel, ZFP36L1 directly targets viral RNA transcripts, resulting in translational repression and degradation via cellular exonucleases such as XRN1 and the RNA exosome (Chiu *et al.,* 2022). ZFP36L1 activity is regulated by phosphorylation through the p38 MAPK–MK2 pathway, which transiently inhibits its mRNA decay function during early immune activation (Stoecklin et al., 2004; Makita et al., 2021). Collectively, these mechanisms position ZFP36L1 as a central regulator that integrates RNA stability control with antiviral defence and immune homeostasis.

Recent Advances in ZFP36L1 Biology

Recent years have seen significant advances in understanding the biological functions of ZFP36L1, driven by the application of high-throughput transcriptomic approaches, improved biochemical techniques, and the increasing recognition of RNA-binding proteins as key regulators of cellular processes (Hafner *et al.,* 2010; Hentze *et al.*, 2018; Garcia-Moreno *et al.,* 2019). These studies have expanded the role of ZFP36L1 beyond classical ARE-mediated mRNA decay to include regulation of complex RNA networks, immune cell function, and antiviral defence (Makita *et al.,* 2021).

One major advancement has been the use of transcriptome-wide RNA-binding approaches, such as crosslinking and immunoprecipitation (CLIP)-based methods, to define the global target repertoire of ZFP36L1. These studies reveal that ZFP36L1 binds to hundreds to thousands of transcripts, often forming coordinated RNA regulons that control functionally related gene networks (Hafner *et al.,* 2010; Garcia-Moreno *et al.,* 2019).

More recent analyses have demonstrated that these RNA regulons extend beyond inflammatory mediators to include genes involved in metabolism, cell cycle regulation, and signal transduction, highlighting a broader systems-level role for ZFP36L1 in cellular homeostasis (Cicchetto *et al.,* 2023).

Another key development is the emerging concept that mRNA decay can be coupled to transcription. Recent work indicates that ZFP36 family proteins, including ZFP36L1, may bind nascent transcripts in the nucleus and "license" them for degradation prior to cytoplasmic export (Makita *et al.,* 2021). This finding challenges the traditional view of post-transcriptional regulation as a purely cytoplasmic process and suggests that RNA fate decisions may be established early during gene expression. Such coupling provides a mechanism for tightly coordinated control of gene expression programmes.

Advances in immunology have also highlighted previously unappreciated roles for ZFP36L1 in regulating immune cell function. ZFP36L1 and ZFP36L2 are critical for maintaining T cell homeostasis and controlling cytokine production, including IFNγ, thereby preventing excessive immune activation (Hodson *et al.,* 2010; Turner & Díaz-Muñoz, 2018). In addition, ZFP36L1 has been shown to regulate T cell receptor (TCR) signal strength and influence $CD8^+$ T cell differentiation, underscoring its role in shaping adaptive immune responses (Petkau *et al.,* 2024).

In parallel, growing evidence supports a role for ZFP36L1 in modulating interferon signalling and antiviral responses. Transcriptomic analyses have identified ISGs as potential targets of ZFP36L1-mediated regulation, suggesting that RNA stability control contributes to the temporal dynamics of antiviral responses (García-Moreno *et al.,* 2021). More recent work indicates that ZFP36L1 may influence interferon-driven immune environments by regulating cytokine networks that control immune cell recruitment and activation (Li *et al.,* 2026). These findings highlight a broader role for ZFP36L1 in orchestrating host defence beyond direct antiviral activity.

Another notable advancement is the identification of ZFP36L1 as a regulator of immune checkpoint pathways. Recent studies demonstrate that ZFP36L1 enhances interferon-gamma-induced expression of programmed death-ligand 1 (PD-L1) through post-transcriptional mechanisms, linking RNA stability control to tumour immune evasion (Zhang *et al.,* 2023). This expands the functional relevance of ZFP36L1 into cancer immunology and suggests potential therapeutic implications.

Progress has also been made in understanding the antiviral functions of ZFP36L1. Recent studies demonstrate that ZFP36L1 can directly bind viral RNA and promote its degradation through recruitment of cellular exonucleases, including XRN1 and the RNA exosome (Chiu *et al.,* 2022; Lin *et al.,* 2025). In addition, ZFP36L1 has been shown to suppress replication of RNA viruses, including influenza virus and human coronavirus OC43, supporting its role as a host restriction factor (Lin *et al.,* 2020; Momin *et al.,* 2023). These findings highlight a conserved antiviral mechanism involving RNA recognition and decay.

Finally, recent work has begun to uncover the broader regulatory networks in which ZFP36L1 operates. Rather than acting in isolation, ZFP36L1 functions as part of a network of RNA-binding proteins that collectively regulate gene expression. Interactions with other RBPs and components of the RNA decay machinery enable coordinated control of transcript stability, suggesting that ZFP36L1 contributes to a larger post-transcriptional regulatory landscape.

Collectively, these advances have transformed the understanding of ZFP36L1 from a classical mRNA decay factor to a multifunctional regulator of RNA biology. Its roles now encompass regulation of RNA networks, immune responses, antiviral defence, and disease-related pathways.

Challenges and Knowledge Gaps in ZFP36L1 Biology

Despite substantial progress in understanding the role of ZFP36L1 in post-transcriptional gene regulation, several key challenges and unresolved questions remain. These limitations highlight gaps in current knowledge and underscore the need for further investigation to fully define the biological and therapeutic relevance of ZFP36L1.

One of the major challenges in the field is the issue of functional redundancy within the ZFP36 family. ZFP36, ZFP36L1, and ZFP36L2 share similar RNA-binding domains and recognise overlapping ARE motifs, making it difficult to distinguish their individual contributions to mRNA regulation. While genetic studies have demonstrated non-redundant roles in specific developmental contexts, particularly in immune cell maturation, many transcriptomic studies do not adequately resolve the relative contributions of each family member (Hodson *et al.,* 2010; Turner & Díaz-Muñoz, 2018). As a result, attribution of specific regulatory functions to ZFP36L1 alone remains uncertain in many experimental systems.

A second limitation relates to the interpretation of transcriptome-wide binding data. Techniques such as CLIP-seq and iCLIP have revealed extensive binding of ZFP36L1 to large numbers of transcripts; however, RNA binding does not necessarily equate to functional regulation. Many studies report hundreds or thousands of potential targets without demonstrating direct effects on mRNA stability or protein expression (Hafner *et al.,* 2010; Garcia-Moreno *et al.,* 2019). This creates ambiguity regarding which interactions are biologically meaningful. Functional validation of targets, particularly in physiologically relevant systems, remains a critical gap.

Another important challenge is the context-dependent nature of ZFP36L1 activity. The effects of ZFP36L1 on mRNA stability can vary depending on cell type, activation state, and signalling environment. For example, phosphorylation of ZFP36L1 via the p38 MAPK–MK2 pathway can transiently inhibit its mRNA decay activity, allowing stabilisation of transcripts during early immune activation (Stoecklin *et al.,* 2004). However, the extent to which this regulatory mechanism operates across different tissues and

disease contexts is not fully understood. Moreover, the balance between mRNA decay and translational repression mediated by ZFP36L1 remains poorly defined.

A further unresolved issue concerns the relationship between ZFP36L1-mediated RNA decay and interferon signalling pathways. While several studies suggest that ZFP36L1 regulates ISGs, the extent to which it directly modulates antiviral signalling versus indirectly shaping cytokine environments remains unclear (García-Moreno *et al.,* 2021). In addition, it is not well established whether ZFP36L1 preferentially targets specific subsets of ISGs or broadly influences interferon responses. This represents an important gap, particularly in the context of viral infection and immune regulation.

In the antiviral field, a significant limitation is the lack of comprehensive in vivo validation. Although in vitro studies demonstrate that ZFP36L1 can restrict viral replication through RNA binding and degradation, there is limited evidence from animal models or primary human systems confirming its role as a bona fide antiviral effector. Furthermore, the extent to which ZFP36L1 directly targets viral RNA versus modulating host antiviral pathways remains unresolved. This distinction is critical for understanding its mechanism of action and potential as a therapeutic target.

Another emerging but underexplored area is the interaction between ZFP36L1 and other RNA-binding proteins (RBPs). ZFP36L1 operates within a broader network of RBPs, including proteins such as ZAP, MCPIP1, and members of the AUF1 and HuR families, which also regulate mRNA stability. However, the extent to which these proteins cooperate, compete, or function sequentially on shared transcripts is poorly understood. Dissecting these interactions is essential for developing a systems-level understanding of post-transcriptional regulation.

Recent studies proposing nuclear roles for ZFP36L1 in "decay licensing" raise additional questions. While evidence suggests that ZFP36 family proteins may bind transcripts co-transcriptionally and influence RNA fate prior to export, the mechanistic basis and physiological relevance of this process remain to be fully established (Makita *et al.,* 2021). It is unclear whether this represents a general mechanism or is restricted to specific gene classes or cellular conditions.

From a translational perspective, there are also challenges in targeting ZFP36L1 for therapeutic applications. Given its broad role in regulating multiple transcripts, modulation of ZFP36L1 activity could have widespread effects on gene expression, raising concerns about specificity and potential off-target consequences (Sanduja *et al.,* 2011; Loh *et al*., 2020). Furthermore, the dual role of ZFP36L1 in both limiting inflammation and supporting antiviral defence complicates its therapeutic targeting, as inhibition or activation may have context-dependent outcomes (Makita *et al.,* 2021; Moore *et al.,* 2018).

Finally, a major limitation in the current literature is the lack of integration between transcriptomic, proteomic, and functional data. Many studies focus on changes in mRNA abundance without assessing corresponding protein levels or biological outcomes (Vogel & Marcotte, 2012; Franks *et al.,* 2017). Given that ZFP36L1 can regulate both mRNA stability and translation, comprehensive multi-omics approaches are required to fully capture its functional impact (Hentze *et al.,* 2018; Otsuka *et al.,* 2020).

In summary, while significant progress has been made in defining the role of ZFP36L1, key challenges remain in understanding its specificity, regulatory mechanisms, and functional relevance in physiological and disease contexts. Addressing these gaps will be essential for advancing the field and harnessing ZFP36L1 as a potential target for therapeutic intervention.

Future Perspectives

Advancing the understanding of ZFP36L1 biology will require a shift from descriptive studies of RNA binding toward mechanistic and functional interrogation in physiologically relevant systems. One of the most immediate priorities is the development of approaches that can distinguish direct functional targets of ZFP36L1 from transcripts that are merely bound without measurable regulatory consequence. Integrating CLIP-based binding data with transcript stability assays, ribosome profiling, and quantitative proteomics will be essential to define the subset of transcripts that are truly regulated at both the RNA and protein levels (Hafner *et al.,* 2010; Garcia-Moreno *et al.,* 2019).

Another important direction involves resolving functional specificity within the ZFP36 family. Given the overlapping RNA-binding motifs of ZFP36, ZFP36L1, and ZFP36L2, future studies should employ combinatorial genetic approaches, including conditional knockouts and CRISPR-based perturbation systems, to dissect their individual and cooperative roles (Hodson *et al.,* 2010; Turner & Díaz-Muñoz, 2018). Single-cell transcriptomic analyses combined with perturbation experiments may provide additional insight into how these proteins regulate gene expression in specific cellular contexts, particularly within heterogeneous immune populations (Cook *et al.,* 2022; Makita *et al.,* 2021).

Further work is also required to clarify the relationship between ZFP36L1 and interferon signalling pathways. While existing evidence suggests that ZFP36L1 modulates interferon-stimulated gene expression, it remains unclear whether this regulation is selective or global, and how it influences antiviral outcomes in different tissues (Hafner *et al.,* 2010; García-Moreno *et al.,* 2021). Time-resolved studies examining mRNA decay kinetics during interferon stimulation and viral infection will be particularly informative in defining the role of ZFP36L1 in shaping the temporal dynamics of antiviral responses.

The emerging evidence for direct antiviral activity of ZFP36L1 presents an important opportunity for future research. Key questions include whether ZFP36L1 preferentially targets specific classes of viral RNA, how viral sequence or structural features influence recognition, and whether viruses have evolved mechanisms to evade or counteract ZFP36L1-mediated restriction (Lin *et al.,* 2020; Chiu *et al.,* 2022; Momin

et al., 2023). Addressing these questions will require the use of physiologically relevant infection models, including primary human cells and in vivo systems, to validate findings from in vitro studies.

Another promising area is the investigation of ZFP36L1 within networks of RNA-binding proteins. Rather than acting in isolation, ZFP36L1 likely functions as part of a coordinated regulatory system involving other RBPs such as ZAP, HuR, and AUF1 (Hentze *et al.,* 2018; Corley *et al.,* 2020). Future studies should aim to map these interactions and determine whether RBPs act cooperatively, competitively, or sequentially on shared targets. Systems-level approaches integrating RNA–protein interaction networks with functional assays will be critical for understanding the complexity of post-transcriptional regulation.

The proposed nuclear roles of ZFP36L1 in decay licensing also warrant further investigation. Determining whether ZFP36L1 binds nascent transcripts in a gene-specific manner and how this influences downstream RNA stability will require advanced imaging techniques and high-resolution transcriptomic analyses (Makita *et al.,* 2021). Clarifying these mechanisms could redefine current models of gene expression regulation by linking transcription and RNA decay more directly (Eisen *et al.,* 2020).

From a translational perspective, ZFP36L1 represents a potential target for therapeutic intervention in diseases characterised by dysregulated gene expression, including inflammatory disorders, viral infections, and cancer. However, its broad regulatory functions present a challenge for therapeutic targeting (Hentze *et al.,* 2018; Makita *et al*., 2021). Future strategies may focus on modulating specific interactions, such as disrupting binding to particular transcripts or altering post-translational modifications that control activity, rather than globally inhibiting or enhancing ZFP36L1 function.

In addition, the role of ZFP36L1 in immune checkpoint regulation, particularly its influence on programmed death-ligand 1 (PD-L1) expression, suggests potential relevance in cancer immunotherapy (Zhang *et al.,* 2023). Understanding how ZFP36L1 integrates interferon signalling with immune checkpoint pathways could provide new avenues for enhancing anti-tumour immune responses.

Finally, future studies should prioritise multi-omics integration, combining transcriptomic, proteomic, and functional datasets to provide a comprehensive view of ZFP36L1 activity. Given its ability to regulate both mRNA stability and translation, such integrative approaches are essential to fully capture its impact on cellular phenotypes.

In summary, advancing the field will require a combination of mechanistic, systems-level, and translational approaches. Addressing these challenges will not only improve understanding of ZFP36L1 biology but also uncover new opportunities for targeting post-transcriptional regulation in disease.

CONCLUSION

ZFP36L1 is a central regulator of post-transcriptional gene expression, functioning through AU-rich element-mediated mRNA decay and translational repression. Its ability to control the stability of transcripts involved in inflammation, immune signalling, and antiviral responses highlights its importance in maintaining cellular homeostasis.

Recent advances have expanded the functional scope of ZFP36L1 beyond classical mRNA decay, revealing roles in RNA regulon control, immune cell regulation, and direct antiviral activity. Despite these developments, key questions remain regarding its target specificity, regulatory mechanisms, and functional relevance in physiological systems.

Overall, ZFP36L1 represents a critical link between RNA biology and immune regulation, and further investigation of its mechanisms may provide new insights into the control of gene expression in health and disease.

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