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Review Article

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Viral Hijacking of Host RNA-binding Proteins: Implications for Viral Replication and Pathogenesis

Ngnotouom Ngnokam Tania Cyrielle[1, 2,3,4,5], Magnilack Kuete Chanelle[6] and Angyiba Serge Andigema[1, 2, 3, 4*]

[1]*Department of Research and Education, Oli Health Magazine Organization, Kigali, Rwanda*

[2]*Department of Health and Research, Youth Health Action Network, Africa, Cameroon*

[3]*Department of Microbiology, Immunology and Hematology; Faculty of medicine and Pharmaceutical Sciences, University of Dschang, Dschang, Cameroon*

[4]*Department of Innovation and Knowledge Dissemination, Bisons' Scholars, Douala, Cameroon*

[5]*Department of General Medicine, Université Evangélique en Afrique, Democratic Republic of Congo.*

[6]*University of Buea, Faculty of Health Sciences, Department of Biomedical Sciences*

[*]Corresponding Author
Angyiba Serge Andigema, Department of Research and Education, Oli Health Magazine Organization, Kigali, Rwanda, Department of Health and Research, Youth Health Action Network, Africa, Cameroon, Department of Microbiology, Immunology and Hematology; Faculty of medicine and Pharmaceutical Sciences, University of Dschang, Dschang, Cameroon, Department of Innovation and Knowledge Dissemination, Bisons' Scholars, Douala, Cameroon

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Abstract

In the intricate dance between viruses and host cells, RNA-binding proteins (RBPs) serve as crucial orchestrators of gene expression and cellular processes. We will delve into the riveting realm of viral hijacking, where viruses deftly exploit host RBPs to manipulate cellular machinery for their replication and pathogenesis. Through a masterstroke of molecular subterfuge, viruses co-opt RBPs involved in various facets of RNA metabolism - from transcription to degradation - to promote viral gene expression and evade host immune defenses. This manipulation leads to global alterations in cellular RNA metabolism, impacting essential host genes vital for immune responses and homeostasis. Unveiling this clandestine alliance between viruses and RBPs is not just a scientific pursuit, but a critical imperative for devising innovative antiviral strategies to disrupt these interactions. By unraveling the intricate interplay between viral proteins and host RBPs throughout the viral life cycle - from entry to assembly - researchers aim to identify vulnerabilities that can be targeted for therapeutic intervention. Strategies such as disrupting viral protein-RBP interactions hold promise for inhibiting viral replication and curbing pathogenesis, offering a beacon of hope in the battle against viral infections.

Our manuscript elucidates the indispensable roles played by RBPs in viral replication, translation, and pathogenesis, shedding light on the molecular mechanisms driving viral success. Delving deeper, it explores how viruses intricately entwine with host RBPs, manipulating cellular signaling pathways to create a hospitable environment for viral spread. By dissecting these manipulative tactics, researchers uncover new targets for antiviral therapy, envisioning a future where tailored interventions disrupt viral-host RBP interactions with precision and efficacy. As the narrative unfolds, the therapeutic implications of targeting RBPs or their interactions with viral proteins emerge as a promising frontier in the fight against viral infections. From small molecule inhibitors to RNA-based therapeutics, innovative approaches are on the horizon, offering new avenues for combatting viral diseases. We set the stage for future research, beckoning researchers to delve deeper into the molecular intricacies of viral hijacking of RBPs and charting a course towards novel therapeutic interventions that promise to reshape the landscape of antiviral therapy. Ultimately, it beckons the scientific community to embark on a voyage of discovery, unraveling the secrets of viral hijacking of RBPs and paving the way for transformative advances in antiviral therapeutics. The stage is set for a new chapter in the battle against viral infections, where knowledge becomes the sword and innovation the shield against the pernicious machinations of viral pathogens.

1. Introduction

RNA-binding proteins (RBPs) constitute a diverse class of proteins vital for regulating gene expression and cellular processes [1]. Operating across various stages of RNA metabolism, including transcription, splicing, transport, translation, and degradation, RBPs exert essential roles. They orchestrate transcriptional regulation, ensure proper RNA splicing, facilitate RNA transport and localization, modulate translation, oversee RNA stability and degradation, participate in post-transcriptional modifications, and regulate RNA-protein interactions, influencing ribonucleoprotein complex formation and RNA-mediated processes. Viruses strategically exploit host RBPs through a process known as viral hijacking to manipulate cellular processes for their replication and pathogenesis [2]. By leveraging RBPs, viruses effectively modulate RNA metabolism to promote their replication and evade host immune responses. For instance, viruses may co-opt RBPs involved in transcriptional regulation to boost viral gene expression or suppress host antiviral responses [3]. Furthermore, RBPs associated with RNA splicing, transport, translation, and stability become targets for viruses to control viral RNA processing and ensure efficient replication and propagation [4]. Additionally, viruses may disrupt host RBP-mediated RNA-protein interactions to interfere with essential cellular pathways or redirect RBPs to viral replication sites. The consequences of viral hijacking of host RBPs are profound, leading to global alterations in cellular RNA metabolism that impact the expression of critical host genes involved in immune responses, cell survival, and homeostasis. Moreover, manipulation of RBP-mediated RNA processing by viruses can lead to the production of viral variants with increased virulence or resistance to host defenses. Understanding the mechanisms underlying viral manipulation of host RBPs is pivotal for developing strategies to disrupt these interactions and design novel antiviral therapies targeting viral replication and pathogenesis. Deciphering the interaction between viral proteins and host RBPs is essential for developing effective antiviral strategies. Viruses exploit host RBPs throughout their life cycle, including viral entry, replication, and assembly. By elucidating these interactions, researchers can identify critical host factors essential for viral replication and pathogenesis, paving the way for the development of targeted antiviral therapies. One such approach involves disrupting specific viral protein-RBP interactions using small molecules or peptides, effectively inhibiting viral replication [5]. Additionally, understanding how viruses manipulate host RBPs reveals vulnerabilities in the viral life cycle that can be exploited for therapeutic intervention. Furthermore, targeting host RBPs involved in viral RNA packaging or assembly could disrupt viral particle formation, limiting viral spread. Additionally, understanding the role of host RBPs in antiviral immune responses informs the development of immunomodulatory therapies, enhancing host antiviral defenses or mitigating excessive inflammatory responses.

In summary, comprehending the interplay between viral proteins and host RBPs is crucial for devising innovative antiviral strategies that target critical steps in the viral life cycle while minimizing off-target effects and drug resistance. This knowledge holds promise for the development of next-generation antiviral therapeutics with improved efficacy and safety profiles, essential for combating viral infections effectively.

2. Role of RBPs in Viral Replication

RNA-binding proteins (RBPs) play indispensable roles in viral replication and translation, contributing significantly to the success of viral infection [4]. Throughout the viral life cycle, RBPs interact with viral RNA to regulate various processes, ensuring efficient replication and translation of viral genomes. These interactions represent intricate molecular mechanisms that viruses exploit for their benefit. During viral replication, RBPs are crucial for modulating RNA synthesis and processing. RBPs bind to specific sequences or structures within viral RNA, facilitating viral RNA replication and transcription. For example, RBPs can act as cofactors for viral RNA polymerases or helicases, enhancing their activity and promoting efficient viral RNA synthesis [6,7]. Additionally, RBPs may regulate RNA stability and secondary structure, ensuring proper template recognition and efficient replication [8]. In the context of translation, RBPs play essential roles in controlling the translation of viral mRNAs. By binding to specific RNA elements, RBPs can modulate the accessibility of viral mRNA to ribosomes, thereby influencing translation initiation and efficiency [9]. Furthermore, RBPs may regulate the assembly of viral ribonucleoprotein complexes, facilitating the recruitment of ribosomes and translation factors to viral mRNAs [10]. Moreover, RBPs contribute to the spatial and temporal regulation of viral protein synthesis [11]. By controlling RNA transport and localization, RBPs ensure that viral mRNAs are efficiently translated at specific subcellular locations, maximizing viral protein production while minimizing host immune detection. Additionally, RBPs may participate in the regulation of viral protein expression through post-transcriptional modifications or by modulating interactions between viral RNA and translation factors. Overall, RBPs are essential for viral replication and translation, orchestrating intricate molecular processes that are fundamental for successful viral infection. Understanding the roles of RBPs in viral replication provides valuable insights into the mechanisms of viral pathogenesis and can inform the development of novel antiviral strategies targeting RBPs or their interactions with viral RNA. Further research in this area promises to unveil new avenues for therapeutic intervention against viral infections.

Several viral proteins interact with host RNA-binding proteins (RBPs) to facilitate viral replication, contributing to the success of viral infection. One prominent example is the interaction between viral polymerases and RBPs during viral RNA replication [4,6]. Viral polymerases, such as those encoded by RNA viruses like hepatitis C virus (HCV) or influenza virus, often require RBPs as cofactors for efficient RNA synthesis [12]. For instance, the HCV RNA-dependent RNA polymerase NS5B interacts with host RBPs like La protein, which enhances viral RNA replication by stabilizing the viral RNA genome and promoting its efficient synthesis [13]. Another example involves the interaction between

viral proteins and RBPs to regulate viral RNA stability and translation [3]. The HIV-1 Rev protein, for instance, interacts with the host RBP exportin-1 (CRM1) to facilitate the nuclear export of unspliced viral RNA, a crucial step in the HIV-1 replication cycle [14,15]. Additionally, the poliovirus protein 2A interacts with the host RBP poly(rC) binding protein 2 (PCBP2), which promotes internal ribosome entry site (IRES)-mediated translation of viral RNA [16]. Furthermore, viral proteins can manipulate host RBPs to evade host immune responses and facilitate viral replication. For example, the Ebola virus protein VP35 interacts with host RBPs like PACT, inhibiting the activation of the innate immune response and promoting viral replication [17]. Similarly, the human cytomegalovirus protein pUL69 interacts with host RBPs like poly(A)-binding protein nuclear 1 (PABPN1), enhancing viral gene expression and replication [18]. Overall, the interaction between viral proteins and host RBPs plays a critical role in facilitating various stages of viral replication. Understanding these interactions not only provides insights into the molecular mechanisms underlying viral pathogenesis but also offers opportunities for the development of novel antiviral strategies targeting these interactions. Further research into the intricate interplay between viral proteins and RBPs promises to uncover new avenues for therapeutic intervention against viral infections.

Viral hijacking of host RNA-binding proteins (RBPs) profoundly impacts viral genome stability and gene expression, playing a pivotal role in viral replication and pathogenesis [3,5,10]. By manipulating host RBPs, viruses ensure efficient replication and expression of their genomes while evading host immune responses. One significant impact of viral hijacking of RBPs is on viral genome stability [19]. RBPs participate in regulating viral RNA stability, ensuring proper folding and protection of viral genomes [20]. However, viruses exploit host RBPs to stabilize their RNA genomes, promoting viral replication. Moreover, viral hijacking of RBPs influences viral gene expression. RBPs regulate various aspects of RNA metabolism, including splicing, transport, translation, and degradation, which are critical for controlling viral gene expression. By interacting with host RBPs, viruses modulate these processes to favor viral gene expression and replication. Furthermore, viral manipulation of RBPs impacts host immune responses. RBPs are involved in regulating innate immune signaling pathways and antiviral defense mechanisms. By hijacking host RBPs, viruses can suppress host immune responses and evade detection by the host immune system, facilitating viral replication and persistence. bIn summary, the hijacking of host RBPs by viruses profoundly influences viral genome stability, gene expression, and host immune responses. Understanding the mechanisms underlying viral manipulation of RBPs provides valuable insights into viral pathogenesis and offers opportunities for the development of novel antiviral strategies targeting these interactions. Further research into the impact of viral hijacking of RBPs promises to uncover new therapeutic targets for combating viral infections effectively.

3. Host RBPs Involved in Viral Pathogenesis

Host RNA-binding proteins (RBPs) play crucial roles in regulating immune responses, making them attractive targets for viral exploitation to promote viral pathogenesis. Viruses strategically manipulate host RBPs to evade host immune surveillance, dampen antiviral responses, and facilitate viral replication and spread. One example of host RBPs exploited by viruses is the family of interferon-inducible RBPs, including the IFN-induced protein with tetratricopeptide repeats (IFIT) family [21]. These RBPs are induced by interferons and act as antiviral effectors by binding viral RNA and inhibiting viral replication. However, some viruses have evolved mechanisms to counteract IFIT-mediated antiviral activity. For instance, the influenza A virus nonstructural protein NS1 interacts with IFIT proteins, preventing their association with viral RNA and impairing their antiviral function, thereby promoting viral replication [22]. Additionally, viruses manipulate RBPs involved in regulating innate immune signaling pathways to promote viral pathogenesis. The retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are key sensors of viral RNA, triggering antiviral signaling upon recognition of viral nucleic acids. However, viruses target RLR signaling by interacting with RBPs such as MAVS, an adaptor protein essential for RLR-mediated signaling. For example, the hepatitis C virus NS3/4A protease cleaves MAVS, disrupting RLR signaling and inhibiting the production of antiviral cytokines, thereby promoting viral persistence. Furthermore, viruses exploit RBPs involved in RNA processing and translation to promote viral gene expression and immune evasion. For instance, the human cytomegalovirus protein pUL69 interacts with host RBPs like poly(A)-binding protein nuclear 1 (PABPN1), enhancing viral gene expression and replication [23]. Similarly, viruses may manipulate RBPs involved in translational regulation to promote the translation of viral mRNAs while inhibiting host protein synthesis [24]. Overall, understanding the interplay between viruses and host RBPs involved in modulating immune responses is crucial for elucidating viral pathogenesis and developing antiviral strategies. Targeting these interactions offers promising avenues for therapeutic intervention to combat viral infections effectively. Further research into the intricate mechanisms of viral manipulation of host RBPs promises to uncover new insights into viral pathogenesis and provide novel targets for antiviral drug development.

Viral hijacking of host RNA-binding proteins (RBPs) profoundly influences cellular signaling pathways, facilitating viral spread and promoting viral pathogenesis [4,19]. RBPs play critical roles in regulating various cellular signaling cascades involved in immune responses, cell survival, proliferation, and differentiation [25]. By manipulating host RBPs, viruses can dysregulate these signaling pathways to create a cellular environment conducive to viral replication and spread. One-way viruses exploit host RBPs is by modulating innate immune signaling pathways. RBPs such as retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are key sensors of viral RNA, initiating antiviral signaling upon recognition of viral nucleic acids [26]. However, viruses can interfere with RLR signaling by targeting RBPs involved in this

pathway. For example, the hepatitis C virus NS3/4A protease cleaves mitochondrial antiviral signaling protein (MAVS), an essential adaptor protein in RLR-mediated signaling, inhibiting the production of antiviral cytokines and promoting viral persistence [27]. Moreover, viruses manipulate RBPs to alter host cell survival pathways, promoting viral replication and spread. RBPs involved in cell survival signaling pathways, such as the phosphoinositide 3-kinase (PI3K)/Akt pathway, are targeted by viruses to create a favorable cellular environment for viral replication. For instance, the human papillomavirus (HPV) oncoprotein E6 interacts with RBPs like insulin-like growth factor-binding protein 2 (IGFBP2), promoting cell survival and facilitating viral replication [28]. Furthermore, viral hijacking of RBPs can promote viral spread by modulating cellular signaling pathways involved in cell motility and migration. RBPs involved in cytoskeletal organization and cell adhesion, such as focal adhesion kinase (FAK) and vinculin, are targeted by viruses to enhance cell motility and facilitate viral spread. For example, the Epstein-Barr virus (EBV) latent membrane protein 1 (LMP1) interacts with FAK, promoting cell migration and facilitating viral dissemination [29]. Overall, viral hijacking of host RBPs alters cellular signaling pathways critical for immune responses, cell survival, and motility, promoting viral replication and spread. Understanding the mechanisms underlying viral manipulation of host RBPs provides insights into viral pathogenesis and offers opportunities for therapeutic intervention to combat viral infections effectively. Further research into the interplay between viruses and host RBPs promises to uncover new targets for antiviral drug development and therapeutic strategies against viral diseases is very necessary.

Current strategies targeting viral interactions with host RNA-binding proteins (RBPs) hold promise for antiviral therapy, offering innovative approaches to combat viral infections [30]. These strategies aim to disrupt essential viral-host RBP interactions critical for viral replication and pathogenesis, providing novel avenues for therapeutic intervention. One approach involves the development of small molecule inhibitors that specifically target viral proteins interacting with host RBPs [31]. These inhibitors disrupt the protein-protein interactions necessary for viral replication and spread. For example, inhibitors targeting the interaction between the hepatitis C virus (HCV) polymerase NS5B and host RBPs like La protein have shown promise in inhibiting HCV replication in preclinical studies [32]. Similarly, inhibitors targeting the interaction between the influenza A virus nonstructural protein NS1 and host RBPs like CPSF30 can inhibit viral replication and reduce viral pathogenicity [33]. Additionally, nucleic acid-based therapies offer an attractive approach to disrupt viral-host RBP interactions. RNA interference (RNAi) and antisense oligonucleotides (ASOs) can be used to target viral RNA or host RBP expression, inhibiting viral replication and spread. For instance, RNAi-mediated knockdown of host RBPs essential for viral replication, such as La protein or exportin-1 (CRM1), has shown efficacy in inhibiting the replication of various RNA viruses, including HCV and HIV-1 [34]. Furthermore, therapeutic antibodies targeting viral proteins interacting with host RBPs represent another promising strategy for antiviral therapy [30]. Monoclonal antibodies can specifically bind to viral proteins, preventing their interaction with host RBPs and inhibiting viral replication. For example, monoclonal antibodies targeting the interaction between the Ebola virus protein VP35 and host RBPs like PACT have shown efficacy in preclinical studies, reducing viral replication and improving survival in animal models of Ebola virus infection [35]. Overall, current strategies targeting viral interactions with host RBPs offer exciting prospects for antiviral therapy, providing new opportunities to combat viral infections. Continued research into the molecular mechanisms underlying viral-host RBP interactions and the development of novel therapeutic agents targeting these interactions will be crucial for advancing antiviral therapy and combating emerging viral diseases effectively.

4. Therapeutic Implications

Targeting RNA-binding proteins (RBPs) or their interactions with viral proteins holds promising therapeutic potential in combating viral infections. The multifaceted roles of RBPs in regulating viral replication, translation, and pathogenesis make them attractive targets for intervention [4]. By disrupting critical interactions between RBPs and viral components, therapeutic strategies can impede viral replication and propagation, thereby attenuating disease progression. Several approaches can be explored in this regard, offering novel avenues for antiviral therapy. One strategy involves the design and development of small molecule inhibitors that selectively disrupt the interaction between RBPs and viral proteins [36]. Through rational drug design and high-throughput screening approaches, compounds can be identified that specifically target key binding interfaces, preventing the formation of functional complexes essential for viral replication. Such inhibitors offer the advantage of precise targeting while minimizing off-target effects, potentially leading to safer and more efficacious therapies. Another therapeutic approach involves harnessing the power of RNA-based therapeutics to modulate RBP activity and disrupt viral processes [37]. RNA interference (RNAi) or antisense oligonucleotide (ASO) technologies can be utilized to specifically target and degrade RBP-encoding mRNAs or interfere with their binding to viral RNAs [38]. This strategy allows for precise and customizable regulation of RBP function, offering a versatile platform for combating a wide range of viral infections. Furthermore, the emerging field of CRISPR-based therapeutics presents exciting possibilities for targeting RBPs or their interactions with viral components [39]. CRISPR systems can be engineered to selectively edit RBP-encoding genes or disrupt RBP-viral protein interactions at the genomic level, providing a long-lasting and potentially curative approach to antiviral therapy.

5. Future Directions in Research on Viral Hijacking of RBPs and Therapeutic Implications

As our understanding of RNA-binding proteins (RBPs) continues to evolve, particularly in the context of viral infections, several key areas emerge as promising avenues for future research. These directions not only deepen our understanding of viral pathogenesis

but also offer potential therapeutic targets for combating viral diseases. Firstly, elucidating the specific mechanisms by which viruses hijack host RBPs is essential. This entails deciphering the intricacies of RBP-viral RNA interactions, understanding the structural dynamics of RBP complexes formed with viral proteins, and delineating the functional consequences of these interactions on viral replication and host immune responses. Advanced molecular and structural biology techniques, such as cryo-electron microscopy and cross-linking mass spectrometry, can provide invaluable insights into these processes. Secondly, exploring the role of RBPs in orchestrating host antiviral defenses represents a promising avenue. RBPs are known to regulate diverse aspects of RNA metabolism, including mRNA translation, stability, and localization, which are crucial for mounting an effective antiviral response. Investigating how viruses manipulate these processes to evade host immune surveillance and counteract antiviral mechanisms could uncover novel therapeutic targets for bolstering host defenses against viral infections. Furthermore, understanding the impact of viral hijacking of RBPs on host cellular pathways and signaling networks is crucial. Viruses often exploit host RBPs to dysregulate cellular processes, leading to pathological consequences such as inflammation, apoptosis, and oncogenesis. Unraveling the molecular underpinnings of these interactions could unveil new therapeutic strategies aimed at restoring cellular homeostasis and mitigating virus-induced pathologies. In terms of therapeutic implications, targeting RBP-viral interactions holds immense promise for antiviral drug development. Small molecules, peptides, or nucleic acid-based therapeutics that disrupt critical RBP-viral complexes could inhibit viral replication and propagation. Moreover, immunotherapeutic approaches that harness the host immune response to target virus-hijacked RBPs offer innovative strategies for controlling viral infections.

Thus, future research on viral hijacking of RBPs should focus on elucidating the molecular mechanisms underlying these interactions, exploring their impact on host immune responses and cellular pathways, and leveraging this knowledge to develop novel therapeutic interventions against viral diseases.

6. Conclusion

In conclusion, our review has shed light on the intricate interplay between viruses and host RNA-binding proteins (RBPs), illuminating their crucial roles in viral replication and pathogenesis. Through a comprehensive analysis of current research, several key findings have emerged. Firstly, viruses employ diverse strategies to hijack host RBPs, exploiting their regulatory functions to promote viral replication and evade host immune responses. Secondly, the dysregulation of RBP-mediated RNA metabolism by viruses contributes to the pathogenesis of viral diseases, leading to altered host cellular pathways and immune dysregulation. Furthermore, targeting RBP-viral interactions presents a promising therapeutic approach for combating viral infections, with the potential to inhibit viral replication and mitigate virus-induced pathologies. However, despite significant progress in this field, there remains much to be explored. The complexity of viral-host interactions necessitates further research to fully elucidate the molecular mechanisms underlying RBP-mediated viral hijacking. Additionally, understanding the dynamic interplay between RBPs and viral proteins across different stages of the viral life cycle is essential for the development of targeted antiviral therapies. Moreover, the identification of novel RBP-viral interactions and the characterization of their functional consequences offer new opportunities for therapeutic intervention.

Therefore, continued research efforts aimed at unraveling the intricacies of viral hijacking of host RBPs are crucial. By deepening our understanding of these interactions, we can uncover new therapeutic targets and develop more effective antiviral strategies. Ultimately, advancing our knowledge of viral-host interactions holds immense promise for the development of novel therapeutics that can combat a wide range of viral infections, thereby improving clinical outcomes and reducing the global burden of viral diseases.

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