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THE ROLE OF VIRAL NON-CODING RNAS IN IMMUNE EVASION AND HOST GENE REGULATION

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ABSTRACT

The varied threats viruses pose to host's defensive mechanisms underscores the need for understanding its multifunctional approaches used in tricking the host. Among such approaches used by viruses is its derivation of non-coding RNAs which are critical in fine tuning host cellular defence organization and consequently regulating host gene processes. The v-ncRNAs non-immunogenicity feature provides an appealing medium for viral pathogens in the virus-host conflict. Viruses' limited genome size functionally relays important genomic sequences which are necessary for their replication and survival. This review aims to examine DNA and RNA viruses' shared strategy and the targeted host cell pathways crucial in facilitating v-ncRNAs prolonged life cycle.

KEYWORDS: Immune evasion, miRNA mimicry, viral circRNA, viral non-coding RNA.

1. INTRODUCTION

The virus-host adaptiveness for survival has endured an ongoing debacle on the parasitic yet scientifically useful observation of the evolutionary relationship. The continuous adaptiveness of viruses towards evading host's defences is an indicator of willed existence within a viable host. On the other hand, the equally evolutionary mechanisms adopted by hosts to repel viral adaptive strategies suggests an un-enticing appeal for the pathogen. Hence the existence of a constant biological evolution model of survival.

The virus, in its fashioned approach, penetrates the host after attaching itself to the cell surface. This is achieved by membrane fusion and endocytosis.[1] On entering the host, its capsid is uncoated and released as a naked viral genome for replication and establishment of gene expression.[2] The viral genome's expression of Non-Coding RNAs (ncRNAs) towards viral evasiveness is rationed accordingly as dictated by the size-limited genome.[3][4] RNA viruses exhibit a high degree of recombination event and mutation rate[5], with ncRNAs produced expressing a high correlative index with viral activities.[6]

NcRNAs and viral induced ncRNAs (v-ncRNA) functions as translation, gene expressiveness and RNA splicing regulators, in its interactions with the host's pathway.[7] Despite its heterogeneous nature in conformity and cellular function[8], ncRNAs are generally divided into two groups. Long non-coding RNA (lncRNA) and small non-coding RNA (sncRNA).[9]

LncRNAs are generally over 200 nucleotides (nt) long[10], and function as gene regulators as well as scaffold and enhancer RNAs.[11] They're able to regulate gene expression by limiting the bioavailability of microRNAs (miRNAs) in their interactions with other RNAs.[12] MiRNAs are specialized sncRNA usually between 18 to 25 nt in length[13], whose role is primarily to post-transcript gene regulations by binding with messenger RNAs (mRNAs).[14] LncRNAs are able to repress or regulate gene expressions regulating miRNAs bioavailability through the recruitment of RNA-induced silencing complexes to recognize and destabilize target mRNAs.[15]

V-ncRNAs play an active role in ncRNAs interaction with host's cell pathways. By triggering the connective interaction through conveying channels, v-ncRNAs are able to regulate gene expressions, thereby evading immune responses, and facilitating their life cycle. This study aims to observe the evasion strategies by specifically targeting v-ncRNAs adaptive mechanisms, and its role in Host Gene regulations.

2. Viral Immune Evasion Strategies

NcRNAs play a critical role in fighting against viral infections. LncRNAs are particularly instrumental in inducing antiviral functions thereby inhibiting viral pathogenic activities.[16] This necessitates the presumptive processes of virus requiring evolving modulation mechanisms to evade host's innate and adaptive immune strategies.[17]

The absence of ncRNAs in major histocompatibility complexes (MHC) makes it non-immunogenic to adaptive immune complexes.[18] This presents an opportuned outlook for attacking viruses to utilize. By producing v-ncRNAs, viruses are able to sneak past innate responses and other specific and induced responses associated with halting viral pathogenic activities.[19] This results in the influence of host cell functions by controlling gene expressions and host cell regulation.[20]

Pattern recognition receptors (PRRs) are programmed to detect viral RNAs and foreign activities.[21][22] Such PRRs include Toll-like receptors (TLRs), protein kinase R (PKR), and retinoic acid-inducible gene-1 (RIG-1).[23]

Viral induced RNAs however act as a trap to evade detection. Examples include Epstein-Barr virus (EBV)-encoded small RNAs (EBERs), adenoviral I and II (VAI and VAII), and HIV's trans-activatiin response RNA (TAR).[24] These viral-derived double stranded RNAs (dsRNA) induces the activation of dsRNA dependent PKR and TLRs.[25] Type I interferon (IFN) response is eventually activated as a result of the PKR and TLRs activation.[26] IFNs are antiviral signalling proteins produced in response to viral infections.[27]

Virus-derived IFN production automatically aids inhibition of antiviral responses.[28] Thus, IFN signaling is an important target for virus-derived lncRNAs aimed at regulating the response pathway.[29] Viral genome on partial degradation produces viral non-coding subgenomic flavivirus RNAs (sfRNAs).[30] The produced sfRNAs are active immune evasive agents.>[31] Variants like sfRNA1 and sfRNA2 target signal transducers and activators of transcription (STAT)2 pathways in order to inhibit IFN production.[32]

Cytokines and chemokines secretion are also evasive mechanisms used by v-ncRNAs against the immune system.[33] EBV encoded miRNAs such as ebv-miR-BART6-3p binds to RIG1 mRNA to produce an impaired antiviral cytokine type 1 IFN.[34] The EBV encoded miRNAs also induce production of impaired proinflammatory cytokine interleukin(IL)-6.[35] This is achieved by the association of EBV encoded miRNAs with host-derived miR-197. On association, they act on IL-6 mRNA to produce the impaired cytokine IL-6.[36]

V-ncRNAs also influence the processing and presentation of MHC-restricted antigen.[37] CTSB mRNA, a target for ebv-miR-BART2, influences the interference of MHC-I antigen processing by ebv-miR-BART2.[38] Also, ebv-miR-BHRF1-3, in targeting transmembrane transporter (TAP)2, blocks peptide transport to MHC-I.[39]

Antisense proteins (ASP) are suppressed by HIV-1-derived ncRNAs.[40] During chronic infections, ASP induces the cytotoxic T lymphocytes (CTL) CD8 T cell responses to curb attack.[41] By suppressing ASP, the HIV-1 meditated ncRNAs inhibits the activation and functioning of CD7 T cell.[42]

The ebola RNA virus produces miRNA-like small RNAs. The ebola encoded miRNA EBOV-miR-1-5p, inhibits importin-α5 expression.[43] Importin-α5 plays a crucial role in transporting nuclear localization signals (NLS) containing proteins from cytoplasm to nucleus.[44] By interfering with communication and transportation channels, v-ncRNAs are able to evade detection, making it a potent immune evasive mechanism.[45]

3. Viral Non-Coding RNAs Transcriptional Weapon Function

V-ncRNAs are able to interact with different host cell pathways. They show a high degree of copy numbers in infected cells.[46] Their modulation strategies include viral gene expression and host gene expression.[47] Viral replication and proliferation and cell transformation are other cell survival strategies used by viruses.[48][49][50]

However, in an attempt to fight against viral infections, host cells are able to regulate their ncRNAs expression which leads to the activation of defense mechanisms.[51]

3.1. Regulation of Host and Viral Gene Expression

The hijacking of the host's transcriptional machinery ensures that host RNA polymerase II (RNAP) II and RNAP III synthesize viral mRNAs.[52] Single positive/negative stranded (+ss/-ss) viral RNAs also encodes RNA-dependent RNA polymerase (RdRp).[53] This can also be equally performed by double stranded (ds) viral RNAs.

The degradation of a unique viral mature sequence also leads to the generation of v-ncRNAs through host cell machinery processing of this sequence.[54] Through the host cell's defence mechanism, RNases exoribonuclease 1 (XRN1) degrades flavivirus RNA.[55] The flavivirus, through the process, produces large amounts of sfRNAs.[56] This is possible because of the alteration of XRN1 process during the degradation attempt on flavivirus RNA, making it possible for specific RNA structures to alter XRN1 activity.

Recent studies also indicate the physiologic roles played by discarded sequences during splicing.[57] The discarded stable intrinsic sequence RNAs (sisRNAs) suit viruses with dimension limited genomes.[58] Herpes simplex virus 1 (HSV-1) produces latency associated transcript (LAT) ncRNA in high quantities during latency phase.[59][60] The excised introns act as sisRNAs after a high accumulation around infected cells.[61]

LAT ncRNA which is produced by HSV, modified the expressive chromatin structure of lytic genes, thereby silencing operation of the HSV lytic cycle.[62]

Subgenomic v-ncRNAs are also produced by different

negative strand RNA viruses. By interacting with viral RNAP, processes from mRNA synthesis to viral genome replications are regulated.[63] Some of these viruses include vestibular stomatitis virus (VSV) and influenza A virus (IAV).[64]

As sighted above with little examples, viruses develop varied transcriptional mechanisms on hijacking responses acting as guard against its infections, thereby promoting replication and other viral related activities.

3.2. Host Cell Survival

The survival strategy of viruses includes the survival of the host cell for continued viral propagation and preservation. Hence, it continuously influences host cell survival by blocking cell death responses and interventions.

MivaRNAI-138, an adenovirus VA associated RNA beta (RNAb) can inhibit TIA-1 mRNA.[65] T-cell intracellular antigen-1 (TIA-1) mRNA, as an RNA binding protein is a proponent in apoptosis activation can be inhibited by adenovirus virus-associated (VA) RNAs.[66] TIA-1 regulates mRNA stability, splicing and translation.[67] MivaRNAI-138 is a TIA-1 derived RNA that targets cellular genes involved in DNA repairs, gene expressions and cell growth.[68]

HSV-1 and HSV-2 coded LAT also exert anti-apoptotic influence to maintain latency.[69] HSV-1 down regulates transforming growth factor-beta 1 (TGF-β1) and SMAD3 expressions.[70] SMAD3 plays an important role in transmitting signals within the TGF-β signaling pathway.[71] The protein which is usually encoded by SMAD3 gene transmits a signal to the nucleus from the cell surface.[72] TGF-β1 is usually involved in immune regulation, extracellular matrix (ECM) and cell growth regulation.[73] The multifunctional cytokine is also involved in several other functions across diverse biological processes.[74]

HSV-2 induced LAT, through LAT encoded miRNAs, inhibits apoptosis.[75] The miRNAs such as miR-H3, miR-H4-3p, miR-H4-5p, miR-H24 and miR-H19 provide protection against actinomycin D influenced (ActD) apoptosis.[76] ActD, which is an antineoplastic agent, binds to guanine residues thereby inhibiting DNA-dependent RNAP and RNA synthesis.[77]

While v-miRNAs generally target different sites, they all play crucial roles in maintaining the viral life cycle. V-miRNAs convergence may also occur on similar targets without a form of co-dependence in their operational matrix. The diverse operations of viral related activities have aided its adaptiveness and sustainability efficiency in host cells.

3.3. Efficiency of Viral Infection Regulation

On hijacking translational machinery, viruses reinforce its infectious command by replicating itself as well as disrupting and suppressing immune response activities. Viral sisRNAs expression inhibits apoptosis, making identification of sisRNAs consistent among a few viral pathogenic infections. Citomegalovirus (CMV), EBV, human immunodeficiency virus (HIV) are some of the pathogenic viruses that induce the expression of sisRNAs.[78]

V-ncRNAs are manifested through nuclear polyadenylated (PAN) RNAs in kaposi's sarcoma-associated herpesvirus (KSHV) infested human B cells.[79] PAN RNA represents KSHV during its interaction with jumonji domain-containing protein 3 (JMJD3) and ubiquitously transcribed tetratricopeptide (UTX).[80] JMJD3 and UTC are both histone demethylase which are responsible for methyl groups removal from histone H3 lysine 27 (H3k27me2/3). This effectively silences the gene.[81] The binding of PAN RNA to KSHV latency-associated nuclear antigen (LANA) could also lead to the reactivation of virus from latency phase.[82]

Human cytomegalovirus (HCMV) encoded miRNAs on derivation from the UL gene region of the viral genome, may down regulate major immediate-early genes.[83] Mitogen-activated protein kinases (MAPKs) may also be regulated by hcmv-miR-UL.[84] Extracellular signals are relayed by MAPKs to intracellular responses, which is how MAPKs regulate cellular programs.[85] Hcmv-miR-UL70 influences epithelial cell migration by regulating MAPK signaling and gap junction pathways.[86] Downregulation of IE72 by hcmv-miR-UL112 leads to latency which is achieved through the reduction in expression of replication related viral genes.[87]

Hcmv-miR-UL112 also upregulated MAPK pathways or cell growth related genes, leading to proliferation of endothelial cells.[88] Related genes upregulated by hcmv-miR-UL112 include TSPYL2, FXYD2, TAOK2, ST7L and TP73.[89]

Ring finger protein 38 (RNF38) and NF-κB inhibitor-interacting Ras-like protein 2 (NKIRAS2) are also a target for ebv-miR-BART8-3p and ebv-miR-BART13.[90] RNF38 is an E3 ubiquitin ligase protein which is encoded by RNF38 gene, while NKIRAS2 protein is involved in regulating NF-κB signaling activities.[91] RNF38 uses ubiquitin to modify other proteins in order to degrade or change their functions.[92] The NF-κB signaling pathway plays a critical role in immune response as well as other cellular processes. NKIRAS2 helps to modulate NF-κB signaling activities.[93] By hijacking these proteins, ebv-miR variants are able to modify other proteins with the aid of RNF38 along critical signaling pathways such as NF-κB by influencing NKIRAS2.

Mitogen-activated protein kinase kinase kinase 2 enzyme (MAP3k2) is a target for ebv-miR-18-5p which suppresses MAPK signaling towards the regulation of lytic viral replication.[94] The protein coding gene is

primarily functioned to encode MAP3k2, making it a key component of the mitogen-activated protein (MAP) kinase signaling pathway.[95]

By targeting and hijacking critical host cells components, viruses are able to sustain an efficient regulation of the host's critical response channels, promoting persistent activities and infections.

3.4. Cell Transformation

Cell transformation is a causative effect of viral infection. It involves phenotypical changes such as cell immortalization, contact inhibition loss and anchorage-independent cell growth.[96] Therefore the deregulation of protein gene expression leads to cellular transformation with consequential cell cycle alterations.[97]

The correlation between viral infections and host ncRNAs transformative expressions have been observed in a number of studies. Mechanistic target of rapamycin (mTOR) signaling is a key inductive transformation pathway target for KSHV.[98] MTOR is activated when an inhibitory factor cytosolic arginine sensor for MTORC1 subunit1 (CASTOR1) has been targeted by KSHV. Leading to a transformative expression of phenotypic induction.[99]

The transformative influence leads to the initiation and progression of viral activities in host cells. V-ncRNAs such as hsa-miR-20b, -miR-34a, -miR-218, -miR-29a and -miR-146a which are regulated by HPV18 E6/E7 have all been observed to have had this effect on hijacking host cells ncRNAs, with all having an active involvement in HPV related cervical cancer initiation and progression.[100]

4. V-ncRNA Host Mimicry

Viral hijack manipulative mechanism ensures sequential function and order of hijacked targets is maintained. Leading to a perfect mimicry of host cells functional sequence. Hence, viral miRNAs are downloaded from the seed sequence of the host's miRNAs. Leading to an orderly structure that is tweaked in command in favour of viruses.

Kshv-miR-K12-11 which is associated with different cancers as a multifunctional miRNA operates identically to the hsa-miR-155.[101]

Such similarities have been observed between negatively regulating cell cycle and viral physiological activities to balance pro-proliferative and pro-survival functions of oncogenes with kshv-miR-K6-5p and hsa-miR-15/16 as examples.[102]

Retroviruses have also been indicated to show similar expressive traits of mimicry of other retroviruses.[103] The sfv-miR-S4-3p of the simian foamy virus (SFV) mimics the sequence of cellular hsa-miR-155 of the bovine leukemia virus (BLV).[104]

The mimicry advantage of v-ncRNAs have ensured an ongoing survival by adapting to the host's responses using the host's response mechanisms, its own generative responses to its hijacked commands when a balance is needed, as well as copied sequence from other retroviruses which all contributes to viral adaptiveness and evolution.

5. Viral Circular RNA

The circular RNAs (circRNAs) are considered to function as sponges of miRNAs which regulates gene expression at post transcript level.[105] Unlike the typically linear RNA, circRNAs are characteristically structured by its closed loop. The cerebellar degeneration-related 1 antisense RNA (CDR1as) binds hsa-miR-7 in order to prevent other molecules from binding to it.[106] This function which is termed as “sponge” give the circRNAs the functional sponge characteristic.[107]

The presence of viral circRNAs have been indicated to have been encoded in EBV and KSHV.[108] The circRNAs are encoded by derived viral genes by back-splicing mechanism[109], leading to apoptosis and reduced invasiveness.[110]

While the presence of circRNAs have been observed to play tumorigenic functions in cells such as EBV-infected cells, its absence in lymphoblastoid cell line which is obtained with B95-8 EBV strains indicate its non-mandatory status for EBV genome maintenance in cell culture.[111] CircRNAs have however become the subject of many studies as a result of its transcription regulation which could play a contributive role in understanding viral oncogenesis.

6.0 CONCLUSION

Viral non-coding RNAs are instrumental in immune evasiveness of viral pathogens on host cell pathways. By hijacking and mimicking communication channels, viruses are able to regulate host expressions for their benefit. The activation of v-ncRNAs enables viruses to sneak past innate responses, with viruses taking advantage of ncRNAs absence in MHC. This non-immunogenic nature results in viral control of host gene regulation and expression.

The viral derived ncRNAs also function as scaffold and enhancer RNAs which aids the inhibition of host gene expressions. V-ncRNAs can be divided into lncRNA and sncRNA. This division is based on size, with lncRNAs usually over 200 nt long, while sncRNAs are usually less than 200 nt. MiRNAs are however a specialized form of sncRNA, usually between 18 to 25 nt long, and function primarily as post-transcript gene regulations.

Generally, v-ncRNAs function as post-transcript translators, gene expression controllers and RNA splicing regulators which enhances cell transformation as a result of viral invasion. The cell transformation is a

form of hijacked effect of the virus on gene regulatory mechanisms. Its control of the related communication channel limits the host's responses against the attack thereby enabling its sustainability and life cycle.

The discussed viral non-coding RNAs derivatives in this study, and their various evasion strategies which also includes mimicry and control of cell pathways highlights the importance of further studies in examining viral structural components, and its biological enabler in order to isolate genomic features responsible for its easy transitional relationship with the host.

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