Recent Trends in Systems Biology of miRNAs and RNAi in Dengue Fever: Diagnosis and Treatment

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Authors' contributions
Mohamed Shahen, Akhtar Hussain Shar and Yonghua Wang conceived the project. Mohamed Shahen, Akhtar Hussain Shar,Abd El-Fatah Abomohra and Yonghua Wang provided critical intellectual input to the manuscript preparation. Mohamed Shahen, Zihu Guo, Akhtar Hussain Shar and Abd El-Fatah Abomohra write the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Systems biology has been emerged as an exciting and rapidly growing area of research. Especially, microRNAs (miRNAs) can react as a particular regulated target for gene expression and different diseases pathway. So far, little is known the distinguished functions for miRNAs have been discovered in numerous dengue fever disease, miRNAs being considered the novel therapeutic targets it has the therapeutic capability to manipulate miRNA expression and functions through miRNA inhibitors in patients of dengue fever. This review article focused on the characterization of miRNAs and RNAi (RNA Interference) role regarding to dengue fever, discussing the available opportunities and complications related with this new therapeutic modality.

INTRODUCTION

Numerous viral pathogenic cycles among humans and insect vectors have been discovered recently. These viruses showed distinctive strategies of quick acclimatization with several hosts abundantly available in the environments. Chang et al.[1] recorded widespread infections of murine typhus, scrub typhus, Q fever and dengue fever in tropical and subtropical areas, which often present initially as acute febrile illnesses of unclear etiology. One of them is a Dengue disease which is excessively prevalent in the

developing countries at an alarming rate.[2] Until now, comprehensive knowledge about the human mosquito cycle on the basis of adaptation mechanism remained poorly elucidated.[3]

Before 2013, dengue was rarely taken into interpretation in the health statistics and was not considered for prior notification in the surveillance system.[4] The approval of a dependable and available express symptomatic test is basic for overseeing such intense febrile sickness in the tropics, and in addition to repaid explorers with its spread to the created world.[5] Infection of dengue virus (DENV) is transmitted by mosquito vectors and more affects about 2.5 billion individuals in tropical and subtropical areas around the world.[2,6,7] DENV is transmitted to people by tainted female of the genus Aedes (especially Aedes albopictus and Aedes aegypti). It belongs to flaviviridae family.[8] DENV have four serotypes and causes severe dengue hemorrhagic fever, dengue shock syndrome and self-limiting dengue.[9] Until now, there is no effective vaccine available against dengue infection, due to the multistrains of DENV.[10] Recently, miRNAs was discussed as an effective targets to suppress DENV.

The development of an effective, less toxic and efficient anti-dengue treatment against all serotypes of viruses needs more scientific knowledge and capital investment.[7] Recently, the efficacy of an improved vaccine against DENV has been initially evaluated in Thailand.[11] However, gene silencing is newly introduced technique, which include growing to tiny RNAs, which are responsible for the adjustment of proteins and DNA in heterochromatic duplication and transposable components through RNAi.[12] During the last decade, several studies have been conducted to assess the proficiency of siRNA for restraining the DENV replication.[13] RNAi is a significant antiviral defense reaction among invertebrates and plants, the target of RNAi is caused down-regulation in mammalian cells as anti-DENV either familiar human miRNAs in response to viral infection.[14] RNAi go about as make preparations for moving toward infection and regulating cellular genes expression. Several studies have proposed RNAi as a favorable candidate for curing flavivirus infections in the harbor host and to control flavivirus transmission by mosquito vector.[13,15] Moreover, it is additionally of significance that by demonstrating the viral replication remained generally unaltered after miRNA and siRNA generation was all around withdrawn through thumping down. Dicer[16] found that numerous infections are persistent to miRNA or little snooping siRNA tweak in host cells. This review will explore the recent trends on the function of miRNAs to innate immune responses, and suppress the replication of dengue virus implications for dengue fever diseases.

Therapy for Dengue Virus

Until now, it has been cloudy how dengue viremia levels contribute to the severity of the disease, after reducing viremia by antiviral drugs to reduce the symptoms of DENV. Several clinical trials were conducted to treat DENV infection and reduce its symptoms, but no licensed medicine could deal with DF so far. However, supportive care with a sedative, the replacement of fluids, and bed rest are recommended in some cases.[17] Pandejpong et al.[18] recommended that a dosage of 1 g Acetaminophen every 8 h for 3 days might be useful against DENV infection, while Loratadine (LRD, ethyl4-(8-chloro-5,6-dihydro-11H-benzo, cyclohepta1,2-b pyridin-11-ylidene)-1-iperidinecarboxylate) is an orally effective medicine[19] that could be used to treat antihistamine and relieve other allergy symptoms.[20] ReDuNing (RDN) is a patented traditional antipyretic-detoxicate Chinese injection medicine that has been widely used as an anti-inflammatory and anti-infectious drug in Chinese clinics[21] Dealing with that severity of dengue demands taking caution toward bodily fluids exchanges, while using proactive therapy for bleeding[22] Liu, et al.[23] reported that RDN is composed of three herbs, Artemisiae annuae L. (Asteraceae), Gardenia jasminoides J.

Ellis (Rubiaceae), and Lonicera japonica Thunb. (Caprifoliaceae). In addition to the aforementioned actions, RDN injection exhibits promising effects against enterovirus 71 in Vero monkey cells.[24]

Recently, miRNAs have received a great attention as diagnostic and therapeutic signatures for DF.25. miRNAs are small (18 –25 base long) noncoding RNAs, which were identified as vital ingredients of immune precision and other biological processes, such as development infection and inflammation.[26] Indeed, miRNAs have a primary function in the early differentiation of B-cells and maintaining the regulatory T-cell lineage. Additionally, they regulate the differentiation of dendritic cells and macrophages via toll-like receptors.[27] However, arguments for the possibility of a major function of miRNAs in controlling target genes of dengue fever were increased in recent years.[28]

Diagnostic Findings of miRNA in Fever

Many human diseases (such as cancer, cardiovascular or neurological disorders) are induced due to ectopic expressions of miRNA.[29] Recently, a number of studies confirmed the vibrant role of miRNAs in successful regulation of diverse biological processes through synergistic effects of multiple miRNAs network in an integrated manner to control an individual gene.[30] Moreover, several other physiological functions (such as development, infection, immune response, inflammation, tumor genesis, and regulating of bone mass) have been suggested to be controlled by miRNAs. Recently, it has been reported that miRNAs are able to regulate the gene expression at post transcriptional level of more than 50% of protein coding genes in humans.[26]

Looking at the synergism of miRNAs is a huge tread for deciding miRNA capacities at a system-wide level. On the others hand, miRNA defenses against hepatitis C virus RNA and decrease replication and infection.[31] miRNAs have founded to play roles in both aiding viruses and defending against them. Mammalian miRNA genes often exist on non-coding region of genes, but they also occur both within exonic regions of protein-coding genes,[16] and alternate exon splicing can also regulate the expression of interionic miRNA genes.[32] Latsoudis et al.[33] reported miR-4520a as a valid target for Familial Mediterranean Fever (FMF) with the relative expression levels. These results show a role of deregulated autophagy in the pathogenesis of FMF. In that context, the up-regulation of hsa-miR-31 and down-regulations of hsa-miR-493, hsamiR-889, hsa-miR-655, hsa-miR-656, hsa-miR-26a-1, hsa-miR-154, hsa-miR-335, hsa-miR-1197, and hsamiR-146a enhance the innate antiviral responses in the cells infected with virus.[34]

miRNA and Dengue

In this study, we efficiently have looked into the unthinking premise of miRNA capacities inside the structure of malady alteration and think about the parts of delegate miRNAs in dengue virus infection. On the premise of previously mentioned writing on this new research topic, it is theorized that miRNAs is one of potentially helpful focuses for the DENV issue and consider the difficulties related with potential new therapeutic methodology. Numerous viral diseases are correlated with miRNA expression, which can provide necessary data about how cellular pathways respond to virus infection.[34] The principal miRNA was found by Victor Ambros and his partners Rosalind Lee and Rhonda Feinbaum in 1993 amid a hereditary screen in the roundworm (Caenorhabditis elegans).[35] In general, miRNA impersonates can be used to actuate the statement of important miRNAs in infection position, while miRNA inhibitors can be conveyed to deny the activity of miRNAs that drive disease progression.[36] Defense of the host against viral invasion require distinctive immune responses, and these responses must be tightly regulated to defend rapid and earlier against infection than the essential effect of the miRNA network and individual miRNA on cellular processes proceeds in the immune system.[37] Supplementary, the miRNAs

encoded by viruses themselves capable to up-regulate or down-regulate expression of miRNAs in host cells.[38] Therefore, studies on joint activation and inhibition of endogenous miRNA fight against DF that includes synergistic and antagonistic effects of the initial cytokines, indeed miRNA have a key role in regulating macrophages via toll-like receptors and regulating the differentiation of dendritic cells. Aadditionally,they play a role in the early differentiation of B cells and maintenance the regulatory T-cell lineage.[37, 39-42]. Therefore. miRNAs were initially discovered in the nematode C. elegans.[29]

RNA Interference and Inhibition of Viruses

Viruses often encode bi-cistronic and poly-cistronic transcripts to increase coding efficiency.[43] RNAi is an energizing field of practical genomics that can silence viral genes, and found these antiviral mechanisms in many eukaryotes, a promising treatment for flavi virus's infections in hosts. However, detailed knowledge for the potential role of RNAi against flaviviruses has obscured. siRNAs and dsRNAs that intercede productive gene silencing in a sequence.[44,45] RNA silencing is a past eukaryotic process concerned in sequence-specific control of gene expression and plays an essential role in many biological processes of gene expression. Until now, it has undergone various studies to identify the RNAi mechanism.

This was the ancient anti-virus technical discovery in Drosophila melanogaster, Caenorhabditis elegans, plants, and humans. Once the virus invades dsRNA as a notice signal and starts RNAi mechanism,it leads to the decay of the catalytic flexible target genes, thus silencing it's the best expression.[46] Procedure of RNAi techniques firstly is the conjunction of dsRNA in the cytoplasm of the cell as a starting point for a series of RNAi sequences. Then Dicer enzyme (DICER), cut dsRNA and create small RNA interference (RNA RNAs siRNAs ~ 21-23bp in length) pool. These RNAs were included siRNAs RNA in argon Experts containing complex silencing (RISC) resulting from RNA, now it is activated RISC. After that, RISC contain siRNA connects with a flexible supplementary goal.

Finally, the activity of RISC endonuclease leads to almost split one site in the middle of the target mRNA region siRNA binding region. Thus, the mRNA is destabilized and self-degrade through natural mechanisms.[7] Discovered small RNA interference to suppress the gene by expelling the corresponding messenger RNA, therefore, anticipating protein combination. siRNAs regulate mRNA degradations of molecules indistinguishable in arrangement to that of corresponding siRNA, which prompted the silencing of the corresponding genes and shutting down protein amalgamation.[47]

Finally, it can be concluded that the RNAi, discovered since 1998, has given new roads to medication revelation and biological research. From that point forward, it has been developing as an intense apparatus to battle the most difficult infections, for example, tumor, hereditary scatters, and the clinical and viral targets. This new innovation has numerous vital issues in the advance towards clinical trials on human.

Role of RNAi in Dengue Fever Therapy

Up to now, RNAi has been used against a few human pathogens including influenza virus, hepatitis C virus, hepatitis B virus, human immunodeficiency virus type 1, polio, and DENV. These viruses are characterized by the presence of ssRNA genomes, which are potential targets for RNAi within the cytoplasm. This functional interaction took place during viral RNA un-coating and replication.[48] Any changes in RNAi pathway may clarify why a few mosquitoes are specific vector of arthropod-borne virus's infections (arboviruses), however, rests are not. The first evidence is the interference Sindbis viruses expressing recombinant part of the RNA to not unrelated inconsequential (DENV-2), with DENV-2 replication in mosquitoes (Aedes egyptian) through a system like the silencing mechanism in plants. The potential evidence include the second intervention C6/36 (dengue fever) infected

cells transport with dsRNA or siRNA derived from the genome arbovirus like me to repeat with a virus.[49]

Mammals have many thousands of Piwi-interaction RNAs genes from producer groups that are repeated units of several types of microRNAs regulation expression to control the various steps in the development of cells and physiology. The important role of RNAi is the defense against viruses in the primary organisms, but in mammals, the mechanism of antiviral defense so far controversial. It is being now conserved mechanism of RNAi in mammals, where their siRNA introduction efficacy silent repetition of viruses.[50] Currently RNAi technique is use widely in many areas and study genetic functions by reverse genetics.[51]

CONCLUSION

DENV are the most important factors transmitted by mosquitoes worldwide causing, viral disease, almost 100 million cases of dangerous DENV each year, resulting in severe and life-threatening conditions. However, we have not completed a comprehensive outlook of all miRNAs expression regulation target genes through virus-human interactions in patients of DENV. A few human miRNAs might show antiviral miRNAs. When some delusive antiviral miRNAs were blocked by locked nucleic acid-modified antisense oligoribonucleotides, the hosts miss carriage to suppress viral replication. Schul et al.[52] found that higher levels of viremia were linked with increased DENV intensity and proposed that lowering viremia may reduce morbidity and the risk of dengue hemorrhagic fever or dengue shock syndrome. Infected mice by dengue showed increased TNF-a, IFN-g and IL-6 levels, which were recognized as triggers for DENV. We have found that reducing some immune parameters in blood through the use of antiviral treatment significantly decreases pro-inflammatory cytokine levels and increases the concentrations of coagulants factors in the blood of the treated patients. These results suggest that lowering pro-inflammatory cytokine parameters through timely antiviral drug treatment may improve the severity of DF symptoms and perhaps decrease the risk of progression

Antiviral RNAi was, for the first time, detailed in Drosophila cell culture.[53] The treatment of dengue infection and different sicknesses utilizing RNA therapeutic approach is cost-effective and hopeful. New techniques have been intended to advance the proficiency and diminish the off-target silencing by the sense strand are of significance for clinical applications later on. The insusceptible reaction to novel RNA duplex caused substantially milder in the resistant reaction.

However, the RNAi approache increases privacy at the expense of low efficiency of gene silencing. Recently, the strand selection theory has been intensively studied, and asymmetry to reduce the thermal load of passengers strand through design algorithms is also seeking to reduce the off-target effects.[54,55]

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