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Review Article

Analytical Evaluation of RNA molecules that Impact Crucial Human Reaction Gene as Putative Biomarkers for Illness with Neural Malaria

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Abstract

First of all, The pathophysiology of cerebral malaria infection and severe malaria is a significant issue that impacts the human body. Genes including CD36, IFN-γ, TLR4, and PRR15, which are candidate genes linked to the pathophysiology of malaria, have the ability to interact with host microRNA. It is still unknown how the cerebral malaria infection and host cytokine responses relate to the pathophysiology of malaria and the important miRNAs that serve as biomarkers.The goal of this work was to predict the relationship between host target miRNA response genes and malaria pathogenesis as a potential biomarker for the emergence of cerebral and severe malaria.

Materials and procedures : The host genes uniquely linked to miRNA as putative malaria biomarkers were predicted using two distinct bioinformatics methods, namely Target Scan and miRanda.

Findings : MiR-203a-3p was the predicted result using bioinformatics techniques.1, miR-146, 3p-miR-155, 425-5p, 217, 3p-miR-153, and 455-3p.2, miR-223, miR-143-3p, miR-146-5p, and miR-216a-5p were found to be capable of controlling host genes during the progression of cerebral and severe malaria. In conclusion, utilising bioinformatics methods connected with certain miRNAs like miR-146 and miR-155, the host microRNA was predicted as prospective biomarkers from selected genes CD36, TLR4, IFN-γ, and PRR15. It is important to look at the circulating microRNAs linked to panels of important host genes.

KeyWords : *Malaria, Plasmodium falciparum, Circulating miRNAs, Host genes, Prognostic biomarker*

Introduction

As a result of the blood stage infection, malaria damages the infected host. The host's reactions to the infection and the increased lysis of both infected and uninfected erythrocytes cause illness [1]. When mature stages of the parasite infect erythrocytes, they attach themselves to the cellular endothelium by interacting with human receptors like Endothelial Protein C Receptor (EPCR), Cluster of Differentiation 36 (CD36), and Intracellular Adhesion Molecule-1 (ICAM-1). They can also attach themselves to non-infected erythrocytes to form "rosettes" or to platelets to form agglutinates. An antibody "footprint" left by malaria infection is persistent beyond the illness itself [2]. Strong pro-inflammatory reactions including pyrogenic cytokines, such as interleukin (IL)-1β and tumour necrosis factor alpha (TNF-α), are what produce paroxysmal fever in cases of Plasmodium falciparum infection. While inflammatory reactions, such as interferon gamma (IFN-γ), IL-12, IL-1β, IL-2, and TNF-α all have vital functions in aiding in the removal of parasites; elevated levels of these cytokines in the blood have been linked to malaria immunopathology [3]. Malaria and miRNAs have a dynamic relationship that is yet poorly understood. As a result, certain genes are identified by the authors as potential biomarkers for malaria infection, including CD36, IFN-γ, Toll-like Receptor 4 (TLR4), and Proline Rich 15 (PRR15). These genes are expressed as miRNAs.

miRNA biogenesis

Beginning with pri-miRNAs, the synthesis of miRNA is processed by the cellular nucleases Drosha and Dicer to produce mature miRNAs. When miRNAs bind to complementary sequences in the 3' Untranslated Region (UTR) of their target mRNAs in animals, they primarily inhibit the expression of those genes

by either via mRNA transcript destruction or translational suppression; in animals, two processing steps result in the creation of mature miRNA. PrimormiRNA, the immature miRNA transcripts, are processed into ~70-nucleotide precursors (pre-miRNA) in the first event. This precursor is then cleaved to produce ~21–25 nucleotide mature miRNAs in the second event that follows. Following synthesis, the transcripts of miRNAs are then processed.

MiRNAs in circulation

The invasion of microorganisms (bacteria, viruses, and parasites) in humans is linked to immune system function and gene expression, which is correlated with the severity of disease and the evaluation of medication efficacy [9]. The presence of a pathogenic agent in systemic infections frequently causes a notable alteration in the profile of circulating miRNAs, which makes it easier to employ these molecules as biomarkers of the onset and course of disease. In some circumstances, such viral infections, these modifications in the circulating It has been shown that miRNAs are linked to the targeted cell in both acute and chronic hepatitis C virus infections. In the immune response that follows a malaria infection, parasitic flatworms like Schistosoma japonicum cause a differential expression of circulating miRNAs in the liver and other organs. Numerous miRNA are known to regulate gene expression, susceptibility to infection, stress responses, and metabolism in addition to cell growth and proliferation.

Biomarkers and microRNAs in malaria

It has been demonstrated that host-pathogen interactions affect the content of miRNAs in the host in the cases of bacteria, viruses, and apicomplexan parasites, such as malaria parasites. Crucially, Plasmodium falciparum's cyto-adhesion to host receptors can initiate intracellular signals in target cells and perhaps impact a variety of physiological responses controlled by miRNAs. such is the production of adhesion molecules, vascular inflammation, and bone marrow cell parenchymal injury. Previous research indicates that Plasmodium falciparum may manipulate host miRNAs despite its inability to produce miRNAs. This suggests that these small molecules may be useful in elucidating the molecular mechanisms underlying severe malaria and sickle cell resistance, as well as in determining the extent of vital organ dysfunction linked to parasite sequestration—which is thought to be a critical pathogenic event in Plasmodium falciparum. As a result, miRNAs released from host tissues injured by Plasmodium falciparum sequestration, such as the liver, spleen, brain, or lung, may one day be used as a diagnostic for a severe form of malaria [14]. Infected Red Blood Cells (RBCs) and/or parasite-derived metabolites stimulate the Toll-like receptors (TLRs), which are well studied in relation to malaria. This stimulation results in the release of pro-inflammatory cytokines like IFN-γ, IL-12, and TNF-α, as well as nitric oxide, which are crucial for managing the acute blood-stage infection. Severe malaria, however, might arise from an overactive or dysregulated inflammatory response [15].

Variations in miRNA

Controlling the amount of mRNA and the expression of proteins depends on miRNA binding to mRNA. Single-nucleotide polymorphisms, which may exist in the miRNA target site, have the ability to influence this interaction by eradicating preexisting binding sites or generating new, illegitimate binding sites. Consequently, variations in miRNA polymorphisms might impact gene and protein expression differently and represent an additional kind of genetic diversity that may impact a person's susceptibility to specific illnesses [7]. TLR4 and TLR9 polymorphisms have been linked to higher parasitemia in cases of Plasmodium falciparum infection or mixed infections, as well as susceptibility to malaria [16]. The transcription process may cause these genes to express.

Supplies and Procedures

An overview of this project

Figure 1 shows the procedure for this project. First, the chosen malarial genes were located in the relevant sources. Employing the genes that have been chosen are Homo sapiens. Second, the list of miRNAs connected to linked genes was obtained by entering the gene symbol into the target scan software and submitting it. The NCBI database (www.ncbi.nim.nih.gov) provided the human 3'UTR sequences for the genes.

Forecasting miRNAs

Three distinct algorithms—miRanda, RegRNA, and Target Scan—which are the most popular in the updated version—were employed to study the prediction of miRNAs. Nevertheless, in our work, we just employ Target Scan and miRanda to forecast the correlation between the chosen genes and particular miRNAs. RegRNA, on the other hand, is unable to forecast since the associated genes have an excess of nucleotides. The process of computationally identifying the malaria-related miRNAs .

Scan for targets

Target Scan predicts miRNA target locations shared by orthologous vertebrate 3UTRs [17–19]. Mammals' predictions are ordered according to the expected effectiveness of targeting, which is determined by adding the site's content scores to their probability.Target Scan is thus further described in the section on whole genome alignments. On the other hand, miRanda favours the quantity of Low mirSVR scores, which encompass the entire family of miRNAs. The process of computationally identifying the malaria-related miRNAs

MiRanda

The mirSVR score was found using the miRanda programme. Genes were entered into the "Target mRNA" column. Predictions were then initiated by selecting "go" and "alignment." The resulting prediction included a mirSVR score that encompassed the entire family of miRNAs. Figure 2 depicts the process of computationally identifying the miRNAs implicated in malaria.

Selection criterion for miRNAs

The genes and miRNAs that are associated throughout the prediction processes provide the basis for the miRNA selection criteria. A high negative free energy indicated a higher likelihood of miRNA-mRNA duplex hybridization. A high negative mirSVR score indicated a higher likelihood of target inhibition. A high negative content + score and a high probability of conserved target indicated a good candidate miRNA for target gene inhibition. These were the selection criteria that were applied.

Outcomes

Using bioinformatics methods, we detailed the prediction of CD36, IFN-γ, TNF-α, TLR4, and PRR15 associated with particular miRNAs. The genes' forecasting was defined as follows:

Target scan-based candidate gene prediction

The stages involved in predicting candidate genes (such as CD36, IFN-γ, TLR4, and PRR15) are delineated in the materials and methods section. These steps serve to determine the correlation between the genes and certain miRNAs.Candidate gene prediction with miRanda Determine the relationship between target miRNAs and candidate genes (PRR15, TLR4, IFN-γ, and CD36). We employed the miRanda programme to forecast the presence of a given miRNA.

Production of microRNA candidates

Malaria is an inflammatory disease that starts when innate immune cells, such as monocytes, dendritic cells, and macrophages, recognise parasite toxins like glycophosphatidyl inositol (GPI). This recognition triggers an intracellular signal transduction pathway that leads to the production of pro-inflammatory cytokines like interleukin-12 (IL-12), tumour necrosis factor-alpha (TNF-α), and interferon gamma (IFN-γ). Toll-like receptor 4, a major pathogen recognition receptor (PRR) expressed on the membrane surface of innate immune cells, is genetically encoded by the TLR4 gene. Since there is minimal expression of CD36, its function in cerebral malaria is unknown. on the endothelium cells of the cerebral microvasculature. Cerebral endothelial cells produce ICAM-1 and other adhesion receptors, which may be up-regulated by inflammatory cytokines such tumour necrosis factor (TNF)-α. High concentrations of pro-inflammatory cytokines, like TNF-α, have been linked to severe malaria and a dismal outlook. Hence, the chosen genes (PRR15, TLR4, IFN-γ, and CD36) become potential biomarkers for miR-146 and miR-155 in the malaria degradation pathway, which begins with gene transcription in the nucleus from pri-miRNA to pre-miRNA after Dorsha cuts it, and is exported into the cytoplasm from pre-miRNA to duplex and mature miRNA after dicer cuts it.

CONCLUSION

An infection with malaria boosts the host's immune system. As a result, the genes produced could be used as potential genes for prediction utilising bioinformatics techniques. Using Target Scan, the CD36 was effectively linked to certain miRNAs during the prediction process; however, miRanda did not yield the same results. Moreover, miRanda can predict IFN-γ, whereas Target Scan is useless in doing so. Furthermore, TLR4 was able to foresee with miR-146 alone utilising both bioinformatics programmes. Furthermore, PRR15 was the only candidate gene that could be identified using two target miRNAs, such as miR-146 and miR-155, in bioinformatics techniques. As a result, the candidate miRNAs (miR-146 and miR-155) that were linked to the possible genes (CD36, PRR15, IFN-γ, and TLR4) became biomarkers for malaria infection. In conclusion, this work used bioinformatics techniques with specific miRNAs to predict the host microRNA that associated to severe and cerebral malaria infection as a possible biomarker from selected gene CD36, TLR4, IFN-γ, and PRR15.

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