Research Article
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Zika virus therapeutics: drug targets and repurposing medicine from the human genome

Abstract

Zika viral infection is caused by an emerging mosquito-borne virus, the Zika virus (ZIKV) and threatens to become a global pandemic. While not life threatening, the Zika Virus Disease (ZVD) is suspected to be associated with severe neurological disorders including Guillain-Barré syndrome and microcephaly. Currently, no known cure or diagnostic tests for ZVD are available. The host cell molecular targets are unknown for ZIKV. The ZIKV is related to various other mosquito borne viruses including the Chikungunya, Dengue, Japanese encephalitis, Spondweni, Yellow fever and West Nile viruses. The host cell targets are known for most of these viruses. All of these viruses harbor common protein motifs and domains, raising the possibility of shared molecular targets in the host genome. To facilitate target(s) discovery for the ZIKV therapy, the disease- and protein- knowledge databases were datamined for Zika-related viruses. An initial database of 251 genes was established. Additional filtering using variants associated with the Zika-related viruses and neurological disease phenotypes, identified 55 putative candidate ZIKV targets. These encompass druggable proteins including adhesion molecules, chemokines, enzymes, interleukins, receptors and transporters. Genes linked to Guillain-Barré syndrome and microcephaly was among the Zika candidate genes. The protein expression of the candidate genes was detected in diverse body fluids. Drug bank datamining of these candidate targets identified seventy-nine FDA-approved drugs of the class antineoplastics, anti diabetic, anti-inflammatory, antivirals, antibiotics, statins and neutraceuticals. The database of genes from the study provides a framework for diagnosis and therapy of the ZVD. The FDA- approved list of drugs, if verified, may offer a repurposing use for the treatment of the ZVD.

Keywords: antivirals, druggable targets, Flavivirus, genomics, single strand RNA, proteome, secretome, zika virus

Volume 3 Issue 3 - 2016

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Received: February 20, 2016 | **Published:** March 03, 2016

Introduction

The Zika virus (ZIKV) infection threatens to become a global pandemic.[1] Originally identified in Uganda in 1964,[2–5] the virus later spread to South East Asia,[6–8] to the Pacific region[9,10] and more recently to Brazil in the Americas.[11–13] Within the last month, the World Health Organization has declared the neurological conditions associated with the infection as a Global Public Health Emergency (WHO report, 5 February 2016). *The US Center for Disease Control (CDC) recently announced guidelines for pregnant women and for prevention of sexual transmission during the Zika outbreak.*[14,15] The ZIKV is a member of the virus family *Flaviviridae* and the genus Flavivirus. It is related to the dengue, yellow fever, Japanese encephalitis and West Nile viruses, and is most closely related to the Spondweni virus.[16,17] The ZIKV is primarily transmitted by the female mosquitoes *Aedes aegypti*.[18] Various other arboreal mosquito species in the Aedes genus, such as *A. africanus, A. apicoargenteus, A. furcifer, A. hensilli, A. luteocephalus* and *A. vittatus* also act as the vector.[18] The ZVD symptoms include fever, rash, arthralgia and conjunctivitis in infected individuals. While these are non life-threatening, the neurological disorders suspected to be associated with the ZVD, Guillain-Barré syndrome and microcephaly[19–24] are causes for major concern. A causal link between the ZIKV and these disorders is still to be proven. Biomarkers are urgently needed to verify the association of the ZIKV infection with these disorders. Further, possible sexual transmission has recently been reported and the ZIKV was detected in both the semen and urine samples in this study.[25]

Host cell molecular targets are attractive for therapy of infectious diseases.[26–31] A key advantage of host cell targets is that therapeutics may already exist based on some of these targets, which can be explored for repurposing of medicine. In series of recent studies, various FDA- approved drugs were identified for repurposing for the treatment of the Ebola hemorrhagic fever.[32–34] The protein similarity of the Zika-related viruses suggests that common molecular targets may exist in the host genome.[16,17,35–37] Hence, efforts were undertaken to identify molecular targets for the Zika-related viruses. A database of 251 genes associated with Zika-related viruses was established. These results led to the prediction of 55 Zika candidate genes encompassing druggable targets. Seventy-nine FDA-approved drugs emerged from these studies and may provide a repurposing opportunity.

Methods

Knowledge databases

Datamining for Zika-related viruses was performed using disease-oriented databases MalaCards[38] and DisGeNET.[39] The protein-related information was obtained from the UniProtKB.[40] A working database of Zika-related genes was established by combining the output from these three databases. Additional filtering using disease and virus phenotypes, protein motifs and domains and polymorphic variants generated a database of candidate Zika-associated genes.

Batch analysis

Comprehensive bioinformatics analysis of the database of genes

was performed using the GeneALaCart tool from the LifeMap GeneCards Suite.[38,41] The GeneAnalytics Gene Analysis tool was used to categorize results into lists of matched tissues, cells, diseases, pathways, compounds and gene ontology (GO) terms to enhance gene set interpretation. Associations between genes and diseases/phenotypes based on shared pathways, interaction networks and paralogy relations were inferred using the VarElect NGS Phenotyper of the GeneCards Suite. VarElect utilizes the Deep LifeMap Knowledgebase to infer direct, as well as indirect, links between genes and phenotypes. Indirect association between genes and disease are based on shared pathways and interaction networks analysis.

Drug knowledgebase datamining

Multiple drug bank-related tools including The Human Metabolome Database-HMDB[42] the International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification-NC-IUPHAR,[43] Pharmacogenomics Knowledgebase-PharmaGkB,[44] Drug bank[45] and Federal Drug Administration (FDA) were used to identify approved drugs.

Other bioinformatics analyses

Protein expression of the candidate genes was investigated using the Multi Omics Protein Expression Database, MOPED [46], the Human Proteome Map,[47] and the Proteomics DB.[48] Genome-wide association was verified using the NCBI Phenome-Genome Integrator, PheGenI,[49] and the Genome-Wide Association Studies Catalogue.[50] Protein motifs and domains were verified using the Prosite-Expasy.[51] The Human Genome Nomenclature Committee (HUGO) was used to verify the gene symbols used in the database.

Results

Motifs and domains of the Zika-related viruses

Currently, the molecular targets for the ZIKV are unknown. The ZIKV belongs to *Flaviviridae* and the genus Flavivirus, and is thus related to the Chikungunya, Dengue, Japanese encephalitis, Spondweni, Yellow fever and West Nile viruses. Like other flaviviruses, ZIKV has a nonsegmented, single-stranded, positive-sense RNA genome. The ZIKV is most closely related to the Spondweni virus. Motifs and domains analysis by UniProt and Prosyte proteomics tools demonstrated shared protein structural motifs across these viruses (Supplemental Table S1). Motifs such as Peptidase S7, Helicase ATP-binding, Helicase C-terminal, mRNA cap 0-1 NS5-type MT, RdRp catalytic|DEAH box are shared across these viruses. A nuclear localization signal is shared between the Chikungunya, Yellow fever and the Zika viruses. The Zika and the Spondweni viruses share the FLAVIVIRUS_NS2B motif. These results suggested that common molecular host cell targets might utilize shared protein motifs' function in the ZIKV. Hence efforts were undertaken to develop a database of host cell targets for the Zika-related viruses, which could provide a starting point for ZIKV target discovery.

Database of Zika-related genes

The disease-oriented databases (MalaCards, DisGeNET) and protein knowledgebase (UniProtKB) were datamined for Chikungunya, Dengue, Japanese encephalitis, Spondweni, Yellow fever and West Nile viruses. Host cell targets were identified for these viruses (Figure 1 & Supplemental Table S2). An initial database of Zika-related genes (N=251) comprising common targets from these three tools was generated. This database was further filtered by variant analysis (VarElect Tool for the GeneCards Suite). Specific queries were introduced to Identify putative candidate genes for the Zika virus ("aedes mosquito" +Flaviviridae"+"single strand RNA"). In view of the strongly postulated association of the ZIKV with microcephaly and the Guillain–Barré syndrome, these two queries provided additional filtering of the database. These efforts led to the establishment of a smaller database of 55 genes (candidate Zika genes). The candidate genes encompassed RNA helicases and Arbovirus-related genes. Phenotypic association with antivirals, virus attachment and entry, RNA virus infection and virus replication function were associated with the candidate genes. The NGS phenotyper tool from the VarElect tool also identified expression of candidate genes mRNA expression in Zika target tissues[52] such as epidermal keratinocytes, dermal fibroblasts and immature dendritic cells (Supplemental Table S3). These results suggested that the database of 55 Zika candidate genes might provide a starting point for target discovery for therapy and diagnosis of ZVD. Hence a comprehensive bioinformatics analysis was undertaken with this set of genes.

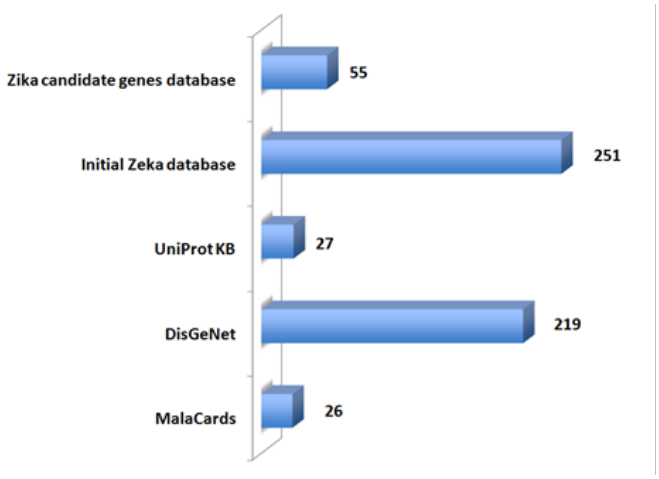

Figure 1 Datamining of the disease and protein knowledge bases.

Disease-oriented databases (MalaCards and DisGeNET) and UniProtKB were queried for Zika-related viruses (Chikungunya virus, Dengue virus, Japanese encephalitis virus, Spondweni virus, West Nile virus, Yellow fever virus and Zika virus), duplicates removed and the total number of genes associated with the viruses is shown. The initial working database was filtered by using the query ("aedes mosquito" 37 +*Flaviviridae* 18+"single strand RNA") and candidate Zika genes were identified.

Protein classes of the Zika candidate genes

The candidate genes were batch analyzed using the GeneALaCart tool and UniProt, and the GO tool was used to cluster the genes into classes of proteins (Figure 2 & Supplemental Table S4). Druggable classes of proteins including adhesion molecules, enzymes, receptors and transporters were identified as putative targets for the ZIKV. Further, antigens, cytokines, chemokines and interferons were identified among the ZIKV candidate genes. Gene Ontology-based biologic processes involved with the candidate genes included defense response to virus, interferon and cytokine signaling and immune response. Major pathways involved included viral (Influenza A, Hepatitis C); NF-Kappa B/AKT signaling; apoptosis; inflammation; Toll- like receptor and TNF signaling. These results raise a possibility that the candidate genes may encompass drug therapy and diagnostic targets for the ZVD. Hence the candidate genes' protein expression was next investigated.

Citation: Narayanan R. Zika virus therapeutics: drug targets and repurposing medicine from the human genome. *MOJ Proteomics Bioinform.* 2016;3(3):52–56. DOI: 10.15406/mojpb.2016.03.00084

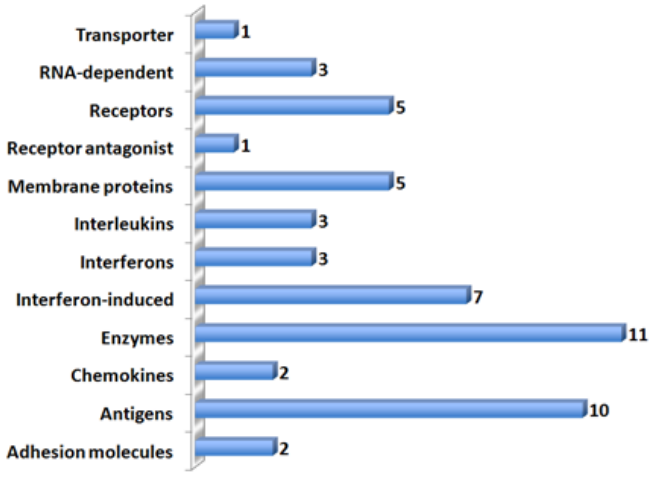

Figure 2 Zika candidate protein classes.

The Zika candidate genes were clustered into protein classes using the GeneALaCart tool (Gene Ontology and UniProt). The numbers indicate the proteins for each class.

The Zika candidate proteins in body fluids

Currently no diagnostic markers are available for ZVD. The ZIKV genome can be detected using the Reverse-Transcriptase Polymerase Chain Reaction method. Measurement of the host cell proteins could provide an approach to monitor response to therapy for drug and vaccines development. To facilitate such biomarkers discovery, the candidate genes were subjected to protein expression analysis in diverse body fluids. Candidate genes' protein expression was detected in ascites, bile, cerumen, cerebrospinal fluid, milk, pancreatic juice, plasma, saliva, serum, semen, synovial fluid and urine using the proteomics tools (MOPED, Proteomics DB and the Human Proteome Map). Key tissues for the ZIKV infection such as skin, spinal cord and uterus also showed expression of candidate genes (Supplemental Table S5). These results provide a framework for rapid verification and marker development potential for the diagnosis and therapy of ZVD.

Involvement in multiple diseases

In order to develop a rationale for repurposed medicine for ZVD, the candidate genes were analyzed for their involvement in other diseases. Genetic association (GWAS) as well as disease phenotype association was seen with the candidate genes in numerous diseases including autoimmune diseases, cancer, coronary disease, diabetes, infectious diseases (viral and parasitic) and neurological diseases (Figure 3 & Supplemental Table S6). The candidate genes were associated with A) microcephaly (CD40 antigen ligand |CD40LG; eIF-2A protein kinase| EIF2AK2; lymphocyte antigen DRB1| HLA-DRB1; interleukin-1 beta| IL1B; type II interleukin-1 receptor antagonist| IL1RN; minisatellite binding protein 1|MSBP1; protein tyrosine phosphatase, non-receptor type 11|PTPN11; PTP synthase| PTS; Proto-oncogene c-RAF| RAF1 and thrombopoietin| THPO) and B) Guillain-Barré syndrome (chemokine (C-C motif) receptor 5 |CCR5; CD40 antigen ligand| CD40LG; lymphocyte antigen DRB1| HLA-DRB1 and TNF-alpha|TNF). In view of the strongly suspected association of ZVD with these two disorders, these putative targets offer a basis for genome to phenome association studies.

Repurposed drugs for ZVD

Identification of druggable targets such as CCR5, FURIN, KRAS, VCAM1 and VEGFA and the association of the candidate genes in other diseases raised a possibility that FDA-approved drugs may already exist for some of these targets. Hence, Drug bank mining was undertaken for the candidate genes (Supplemental Table S7). Seventy-nine FDA-approved drugs and nutraceuticals used for indications such as blood disorders, cancer, cardiac diseases, diabetes, infections (viral and bacterial) and inflammation were identified. This list of approved drugs provides a basis for rapid verification in the laboratory and in the clinic.

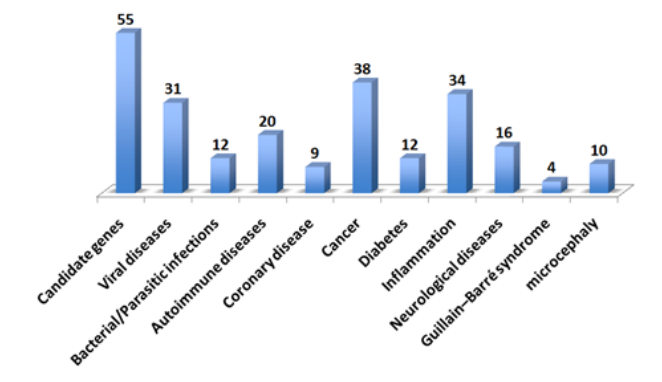

Figure 3 Zika candidate genes in multiple diseases.

The candidate genes were classified into classes of diseases using the MalaCards, Novoseek disorders, UniProt and Human Genome Nomenclature Committee disorders tools. The numbers indicate the proteins for each class.

Discussion

Diagnosis and treatment of ZVD urgently requires molecular targets. While vaccines are the expected approach for an infectious disease such as ZVD, in view of the time course required for regulatory approval of new vaccines, repurposing existing FDA-approved drugs is an attractive option. The protein sequence homology across the Zika-related viruses (Chikungunya, Dengue, Japanese encephalitis, Spondweni, Yellow fever, West Nile and Zika) provided a framework for molecular targets identification for this group of viruses.

The Zika candidate genes encompassed 1) interferon-stimulated genes (2',5'-oligo A synthetase 1 |OAS1, Interferon-induced 15kDa protein |ISG15, interferon-stimulated gene 20kDa protein|ISG20, and Myxovirus resistance protein 1 |MX1); 2) Small-inducible cytokine B10 | CXCL10, inflammatory antiviral chemokine (C-C motif) receptor 5| CCL5; 3) pathogen-associated molecular patterns targets (Toll-like receptor 3|TLR3, RNA helicase RIG-I| DDX58); 4) Dibasic-processing enzyme |FURIN; and 5) epididymis secretory protein Li 39| PPIB. In addition cytokines/interferons, transporters, HLA class I/II histocompatibility antigens were among the candidate genes.

In a recent study[52] using a Zika virus-infected cell culture model, several Zika targets were discovered. These authors showed that the ZIKV infection induced the transcription of CXCl10, TLR-3, RIG-I and IFIH1 genes, as well as several interferon-stimulated genes, including OAS1/2, ISG15 and MX1. The ZIKV candidate genes generated in the current study encompass these targets, thus verifying the validity of the approaches taken to develop a working database of Zika candidate genes.

The candidate genes included genes shown to be associated with microcephaly and the Guillain-Barré syndrome. It is currently unclear whether ZVD is associated with these two disorders. Limited epidemiological evidence however, is beginning to emerge.[19–23] The markers identified in the current study offer a means to evaluate the

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genetic link between these disorders and the ZIKV infection. Twelve of the candidate genes (EIF2AK2, IL6, IFIH1, MAVS, LTA, IFITM3, MX1, TMEM173, TLR3, TNF, CXCL10, DDX58) were associated with increased susceptibility to virus infection. These candidate genes offer a potential to verify susceptibility/risk factor assessment for the ZIKV infection. The identification of a druggable class of proteins (adhesion molecules, enzymes, receptors, transporters) and secreted proteins (milk, saliva and urine) among the candidate Zika genes should facilitate drug discovery and biomarker development for non-invasive diagnostics.

Seventy-nine FDA-approved drugs and nutraceuticals used as medicine for the treatment of cancer, cardiac diseases, diabetes, inflammation, infections (antivirals) and immune function disorders were identified in this study. Safety and tolerance information for these drugs is available from the FDA database. These drugs provide a valuable approach to combat the ZVD by repurposing medicines. It would be informative to perform an epidemiological study with patients under treatment with these drugs for susceptibility/resistance to the ZIKV infection.

The drugs identified in the study using bioinformatics approaches provide a framework for rapid verification in the laboratory. The availability of a cell culture model[52] for ZIKV infection should facilitate lead drugs discovery. Efforts are underway in various laboratories to develop animal models for the ZIKV infection. The lead drugs can be readily tested once the model becomes available. In the interim, epidemiological data should provide additional insight into the usefulness of the lead drugs for potential therapeutics for the ZVD. An added advantage of the drugs discovered in the current study is their potential usefulness for other Zika-related virus diseases as many of the host cell targets are shared across these viruses.

Conclusion

The shared protein homology across the Zika-related viruses led to the development of a database of putative candidate genes for the ZIKV. The drug targets and the identification of FDA-approved drugs with potential for repurposing that emerged from this study, may hasten development of effective treatment options for the Zika and related viruses.

Note: A strong association of the ZIKV infection and Guillain-Barré syndrome is recently shown in a case controlled study.[52]

Acknowledgements

This work was supported in part by the Genomics of Cancer Fund, Florida Atlantic University Foundation. I thank Jeanine Narayanan for editorial assistance.

Conflict of interest

The author declares no conflict of interest.

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Citation: Narayanan R. Zika virus therapeutics: drug targets and repurposing medicine from the human genome. *MOJ Proteomics Bioinform*. 2016;3(3):52–56. DOI: 10.15406/mojpb.2016.03.00084