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RESEARCH ARTICLE

Identification of Novel Drug Targets and Immune Response Biomarkers in HCMV-Infected Hosts

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Abstract: Human cytomegalovirus (HCMV) is a well known hallmark of increasing morbidity and mortality in humans with acquired impairment in innate and adaptive immunity indicating high seroprevalence rate of 83%. This study aims to identify novel drug targets as disease biomarkers in HCMV-infected hosts. Thereby datasets were collected from NCBI SRA Database and were further analyzed through RNA-seq pipeline to identify differentially expressed genes between HCMV-infected hosts and healthy individuals. Subsequently functional enrichment analysis of highly significant genes was performed through enrichR. RNA-seq analysis identified 1974 differentially expressed genes in HCMV-infected hosts including 678 over-modulated and 1028 down-modulated genes. Nevertheless, present DGE analysis study has reported novel drug targets including 5 protein-coding genes (RRAGD, SPINK1, NAP1L2, PKIG and LXN) and 2 pseudogenes (EEF1A1P38, WFDC21P). Additionally dysregulated genes have been found to be highly enriched in immune system related biological processes mainly Toll-like receptor signaling pathway, NOD-like receptor signaling pathway, PI3K-Akt signaling pathway, TNF signaling pathway and IL-17 signaling pathway indicating positive correlation between dysregulated immune-system mechanisms and HCMV replication. Hence this study has proposed novel therapeutic targets for early detection and treatment of HCMV infection that would positively influence public health. However wet laboratory explorations are required to ensure safety and efficacy of proposed drug targets.

Keywords: Human cytomegalovirus, novel drug, Immune response biomarkers, RNA-seq., Gene expression.

INTRODUCTION

Cytomegalovirus is an infectious virus that belongs to the order Herpesvirales. Herpesvirales is the order of anti-double-stranded DNA viruses that have a large number of animal hosts [1]. Cytomegalovirus belongs to the family of Herpesviridae and subfamily of Betaherpesvirinae that contains enveloped, linear double-stranded DNA viruses. The members of Herpesviridae family are also known as herpesviruses [2]. Humans and other species that belong to the order primates serve as a natural host for cytomegalovirus [3]. A total of eleven species are present in Cytomegalovirus genus including human betaherpesvirus 5 which is the species that infects humans [4]. Cytomegalovirus scientifically known as the human herpesvirus 5 (HHV-5) has a genome size of approximately 236 kbp (kilobase pair) which is the largest genome of any identified human virus [5][6]. The merlin strain of Cytomegalovirus which is discussed in this study contains 173 genes. Out of these 173, 168 genes are protein-coding genes and 5 are non-protein-coding genes (Martí-Carreras &Maes, 2019). The merlin strain of the Human Cytomegalovirus (HCMV) comprises a total of 168 proteins [7].

The exact prevalence rate of HCMV worldwide is difficult to determine because most of the time it goes undiagnosed and depends upon various factors including geographical region, population demographics, and access to healthcare [8][9]. Once infected with HCMV, the host body retains this virus for life. Most individuals do not find out about the presence of HCMV in their body as it rarely affects healthy individuals [10]. After the primary infection just like other herpesviruses, HCMV remains dormant in the body for life. HCMV alternates between the lytic and latent cycles of infection. However, a latent infection may not cause symptoms again but it may periodically reactivate and cause symptoms (*Herpes Simplex Virus (HSV) Infections - Infections*, n.d.). In a vast number of cases, the host immune response retains the virus in a latent stage therefore HCMV can reactivate in an inflammatory context, hence resulting in sequential lytic/latent viral cycles throughout life [11]. Cytomegalovirus affects various human organs and tissues of the human body. In case of an immunocompromised individual, a long term infection of cytomegalovirus correlates with chronic inflammation which influences the development of cardiovascular diseases and various types of cancer.

Individuals with a healthy immune system might not even experience the symptoms of HCMV infection or rarely experience noticeable symptoms [12]. They often have CMV mononucleosis which can lead to several symptoms including fatigue, muscle aches, headache, sore throat, and swollen lymph nodes [13][14]. Individuals having congenital (present at birth) HCMV means that the virus passed from mother to the fetus and infants who got infected shortly after birth merely through breastfeeding can experience symptoms related

to a number of diseases including anemia, jaundice, hepatomegaly, microcephaly, hearing loss, seizures, rash [15][16][17].Immunocompromised individuals including organ, bone marrow or stem cell transplant recipients, individuals with acquired immunodeficiency syndrome (AIDS), or pregnant females can experience symptoms related to diseases including pneumonitis, gastritis or colitis, esophagitis, colorectal cancer (CRC), gastric cancer (GC), idiopathic thrombocytopenic purpura (ITP), prostate cancer, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), autoimmune connective tissue disease, breast cancer, and retinitis [18][19].

The available antiviral therapies against HCMV-related diseases include ganciclovir, foscarnet, cidofovir, letermovir, maribavir, and other antibody therapies [20]. Nanotechnology, an in vitro antiviral therapy that serves as a low-cost procedure against HCMV also emerged. In nanotechnology, polyanioniccarbosilanedendrimers have proved their promising activity to fight against HCMV. These polyanioniccarbosilanedendrimers have the ability to inhibit the viral infection either by themselves or enhance the activity of ganciclovirtreatment [21]. However, there is no commercial product based on polyanioniccarbosilanedendrimers that is approved for the treatment of HCMV infections. Besides, additional studies and research should be performed to evaluate the safety and efficacy of nanoparticles in human trials [22].

Ganciclovir, a competitive inhibitor of deoxyguanosine, has a greater acquisition in HCMV-infected cells and therefore, proving that the antiviral activity of ganciclovir is better than acyclovir [23]. Foscarnet and cidofovir both are used as second-line drugs in the instance of resistance to ganciclovir [24]. Foscarnet reversibly inhibits viral DNA polymerases. Induction therapy with foscarnet helped CMV retinitis patients and their optical symptoms initially diminished but recurred soon after the treatment stopped [29]. Cidofovir competitively inhibits DNA elongation [25] and is helpful for treating colitis. Antiviral drugs can improve the symptoms of severe and refractory ITP [26], however, the apparent toxic effects and limitations of these aforementioned drugs should also be contemplated. The most common toxicity connected with ganciclovir is Neutropenia, whereas kidney toxicity is associated with foscarnet. Similarly, renal toxicity is linked with cidofovir[27]. Moreover, Ganciclovir or valganciclovir are not available in developing countries due to their high cost and no availability of HCMV tests [28].

The already discovered antiviral therapies have disadvantages including poor bioavailability, severe toxicity, and an emerging resistance to antiviral drugs. Moreover, HCMV is a virus which is difficult to eradicate due to the fact that it establishes latency throughout life in the host's cells after the initial infection [29]. The available antiviral therapies only stop the lytic virus replication and cannot eradicate latent reservoirs of virus. Various solutions emerged to target the HCMV latent reservoir however translational research about the discovered therapies for targeting the HCMV latent reservoir are still underway to determine whether they are suitable to be used in the clinic [30].
Therefore, considering the limitations and shortcomings of previously identified drugs and therapies, the need for a proper antiviral therapy for HCMV still exists. The already discovered treatments either only help with the symptoms of HCMV or have too many side effects to be used effectively. Moreover, novel therapeutic biomarkers need to be identified as the virus can cause dysregulation in gene expression profile [31]. With RNA-sequencing, the upregulated or downregulated genes can be revealed which were involved in the infection caused by the HCMV.

In this study, the HCMV interactions with the human as host are examined through RNA-sequencing and functional enrichment analysis in order to better understand the viral infection through elucidation of immune response generated as a result of this infection. Moreover, this way novel therapeutic biomarkers can be identified that are less prone to drug resistance and can be targeted by small molecule inhibitors. Furthermore, for future prospects this will lead to the invention of novel HCMV antiviral therapies.

MATERIALS AND METHODS

Overview of the Study

In this study, dysregulated genes were identified through the RNA-seq analysis pipeline. These genes were then further analyzed by performing functional enrichment analysis to elucidate various molecular functionalities and characteristics of those genes. The RNA-seq study design is illustrated in **Figure 1**.

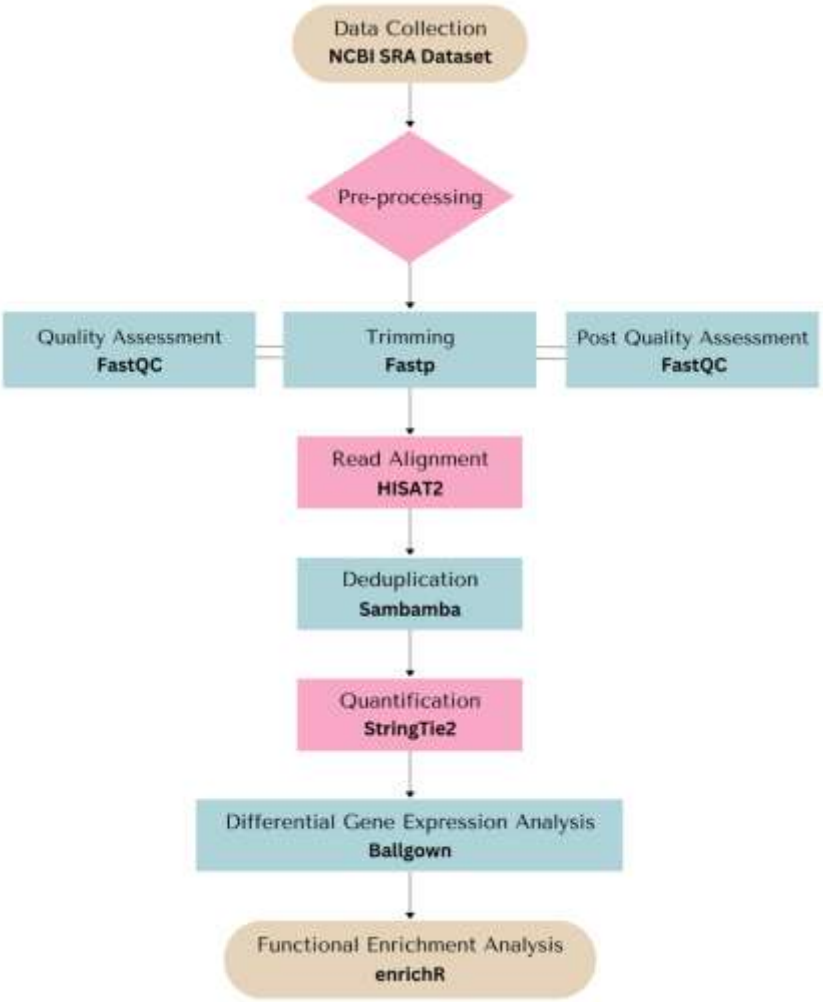

Figure 1. Overview of RNA-Seq Workflow Study

Data Retrieval, Pre-processing, and Read Alignment

In this study, the RNA-Sequencing data was obtained from the NCBI SRA Database (Accession ID: PRJNA435668) and it was collected on the basis of HCMV positive patients and healthy individuals samples. Sequence Read Archive (SRA) is an international public repository that contains next-generation sequence data [32]. The obtained data was single-ended (sequenced using IlluminaHiseq 2500 platform) and it contained 3 samples from control individuals and 6 samples from HCMV positive individuals.

The adopted RNA-seq data was prepared to remove the contaminated adapter sequences, low base quality, primers contents, and duplicates. Therefore, quality assessment and trimming was performed on these raw reads using the FastQC and Fastp tool respectively in order to get rid of the contaminated sequences. FastQC was utilized to analyze the quality of raw reads in terms of per base sequence quality, GC content, sequence length distribution, per base N content, sequence duplication levels, adapter content and overrepresented sequences [33]. The Fastp tool set at parameters i.e -i for raw FASTQ sample, -o for output, -w for multicore processing were used to eliminate PCR artifacts and low quality reads, which in turn helped in accumulating optimal results in downstream analysis.

Read Quantification and Differential Gene Expression Analysis

The statistically and biologically significant genes identified from the differentially expressed genes on the basis of threshold of p-value < 0.05 and 1.5 <LogFC< -1.5 were used to obtain the up and down regulated genes. Additionally, the substantial DEGs were depicted through a volcano plot.

Functional Enrichment Analysis

Functional enrichment analysis (gene ontology (GO) and KEGG pathways) was performed on the dysregulated genes using the enrichR 3.1 package in R 4.2.2 [34]. Moreover, upregulated and downregulated genes were examined independently. Furthermore, plotEnrich() function was used to generate the bar plots of GO terms (biological process,

molecular function, and cellular component) and KEGG pathways. Nevertheless, these enrichment terms were grouped with respect to least p-value.

RESULTS AND OBSERVATIONS:

Identification of Dysregulated Genes

A total of 9 samples (HCMV infected=6, healthy =3) from gene expression profiling identified 1974 dysregulated genes (up and downregulated) in HCMV infected individuals. It was discovered that 678 genes were overexpressed (upregulated) with fold change value > 1.5 and P-value < 0.05 whereas 1028 genes were underexpressed (downregulated) having fold change value < -1.5 and P-value < 0.05 in HCMV. The significant biological and statistical genes areillustrated in **Figure 2**. Moreover, on the basis of logFC values, the top ten upregulated genes are represented in **Table 1** including HERC5, RRAGD, SPINK1, RSAD2, HERC6, IFI44, NAP1L2, ENPP4, OASL, and IDO1 whereas the top ten downregulated genes are given in the **Table 2** including THBS2, TUBB, EEF1A1P38, ACTA2, WFDC21P, PKIG, RHOC, LXN, HGF, and ALDH1A1.

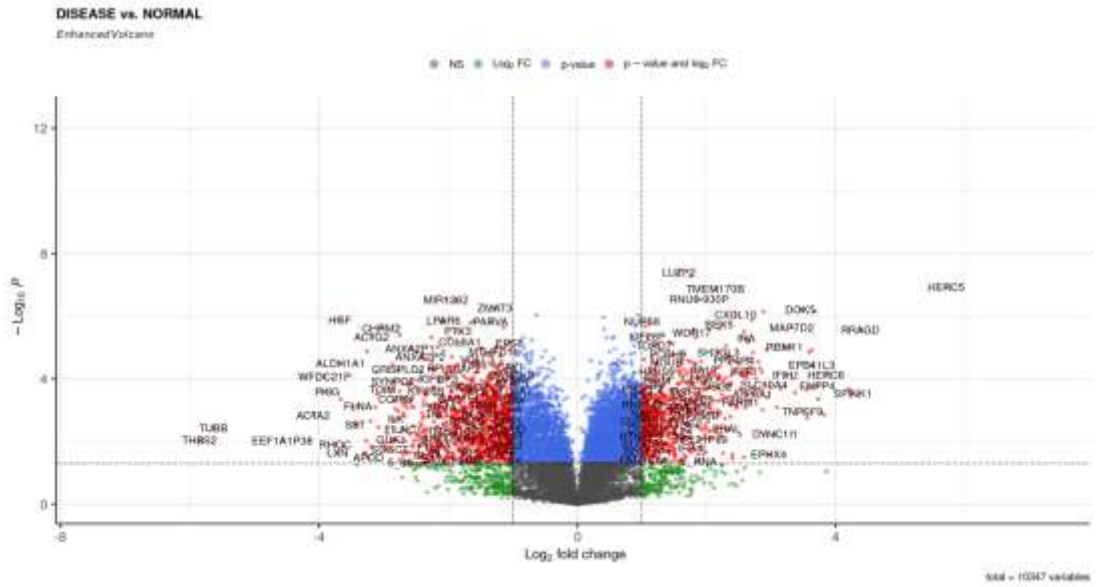

Figure 2. Enhanced Volcano Plot Depicting Differentially Expressed Genes Involved in HCMV. The x-axis represents the biologically significant genes with respect to Log2FC (cutoff: +1.5) whereas the y-axis represents the statistically significant genes on the basis of Log10P value (cutoff < 0.05). These upregulated and down regulated genes are represented with red dots.

Table 1. Top 10 Upregulated Genes in HCMV

Genes	P-value	LogFC	Expression
HERC5	1.17E-07	5.70941433	Overexpression
RRAGD	2.77E-06	4.3799649	Overexpression
SPINK1	0.00029759	4.26408829	Overexpression
RSAD2	0.00020705	4.20970831	Overexpression
HERC6	7.33E-05	3.85301576	Overexpression
IFI44	0.00138262	3.82133868	Overexpression
NAP1L2	0.00043791	3.73269252	Overexpression
ENPP4	0.00016359	3.71307917	Overexpression
OASL	6.87E-07	3.68202739	Overexpression
IDO1	1.21E-05	3.63127339	Overexpression

Table 2. Top 10 Downregulated Genes in HCMV

Genes	P-value	LogFC	Expression
THBS2	0.00907058	-5.8449201	Underexpression
TUBB	0.00364885	-5.6342398	Underexpression
EEF1A1P38	0.00939799	-4.5639922	Underexpression
ACTA2	0.00145352	-4.0905769	Underexpression
WFDC21P	8.34E-05	-3.9152003	Underexpression
PKIG	0.00025526	-3.8734015	Underexpression
RHOC	0.01268618	-3.7466077	Underexpression
LXN	0.02294569	-3.7139885	Underexpression
HGF	1.30E-06	-3.6747725	Underexpression
ALDH1A1	3.17E-05	-3.6669841	Underexpression

GO Term Analysis of Dysregulated Genes

The enrichR package in R was utilized to analyze the dysregulated genes with respect to the GO terms and KEGG pathways. Through GO term analysis, the Biological Process (BP), Cellular Component (CC), and Molecular Function (MF) of dysregulated genes affected by HCMV were discovered. GO biological processes of upregulatedgenesincluding defense response to virus, negative regulation of viral genome replication, regulation of nuclease activity, antiviral innate immunity response were involved in the disruption of immune response, replication of herpesvirus, dysregulation of inflammatory cytokines,symptomatic disease in immunocompromised transplant recipients, chronic villitis and disruption of syncytiotrophoblasts in congenital HCMV [35][36] (**Figure 3**). However, the biological processes of downregulated genes including extracellular matrix organization, regulation of smooth muscle cell proliferation, homotypic cell to cell adhesion, platelet aggregation were associated with spine disc disorders, haemostaticdysregulations, disrupted immunological surveillance of tissues [37][38][39] (**Figure 4**). The upregulated genes were enriched in cellular components including bicellular tight junction, cytoskeleton, neuron projection, cyclin-dependent protein kinase holoenzyme complex which highlighted the dysregulation in neuron projection and how it caused disruption of immune-neural-synaptic axis, and disruption of cell proliferation. [40][41](**Figure 5**). Whereas, cellular components in which the downregulated genes were enriched include secretory granule lumen, microfibril, focal adhesion, cell substrate junction which depicted that dysregulation of cellular components, disrupted neutrophil-mediated inflammatory response, tumor progression and metastasis [42] (**Figure 6**). GO term MF analysis for upregulated genes discovered multiple enriched functions including Wnt-activated receptor activity, CXCR3 chemokine receptor binding, olfactory receptor binding which resulted in the progression of cancer, bone diseases, neurodegenerative diseases, leukocyte trafficking and homing[43][44] (**Figure 7**). GO term MF analysis for downregulated genes identified various enriched functions including chemokine activity,CXCR chemokine receptor binding, cytokine activity, tumor necrosis factor-activated receptor activity which implies their involvement in cellular differentiation and survival, homeostasis disruption, interference in embryogenesis &inflammatory responses, cancer types, and tissue damage[45][46][47](**Figure 8**).

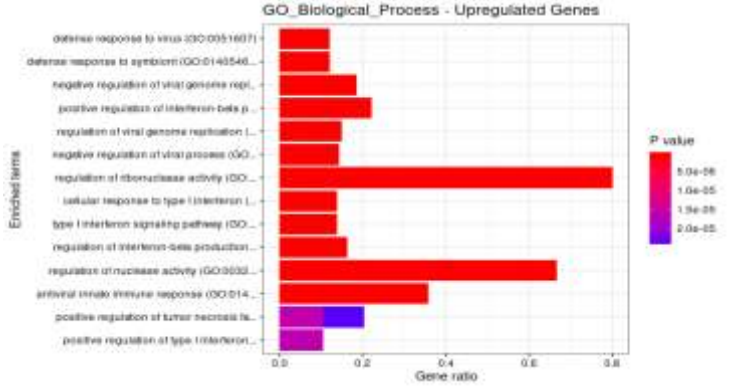

Figure 3.GO biological process (BP) analysis of significantly upregulated genes. Gene ratio and enrichment terms are illustrated in x-axis and y-axis respectively. However the bar plot is sorted with respect to least P-value (shown in colors).

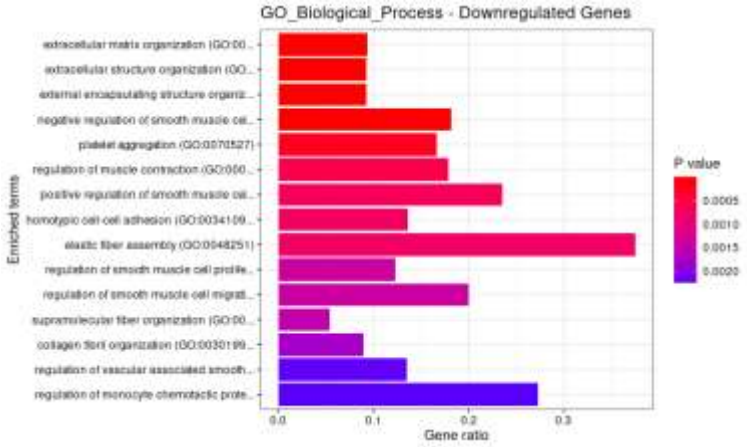

Figure 4. GO biological process (BP) analysis of significantly downregulated genes. Gene ratio and enrichment terms are illustrated in x-axis and y-axis respectively. However the bar plot is sorted with respect to least P-value (shown in colors).

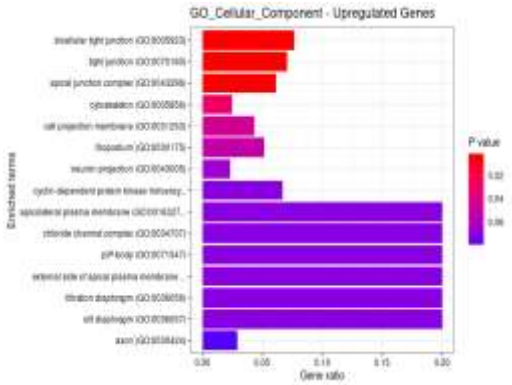

Figure 5.GO cellular component (CC) analysis of significantly upregulated genes. Gene ratio and enrichment terms are illustrated in x-axis and y-axis respectively. However the bar plot is sorted with respect to least P-value (shown in colors).

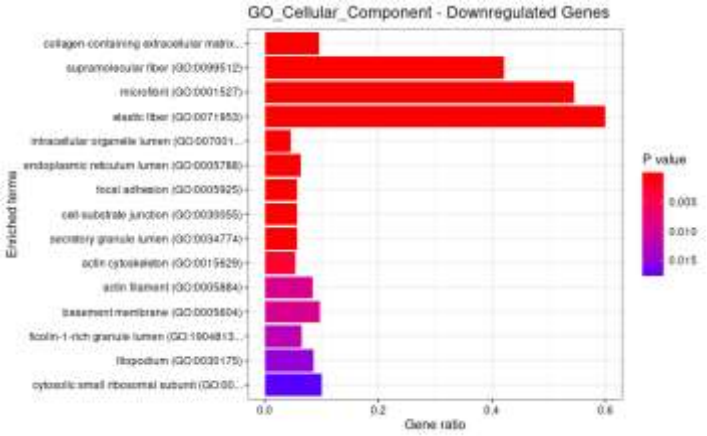

Figure 6.GO cellular component (CC) analysis of significantly downregulated genes. Gene ratio and enrichment terms are illustrated in x-axis and y-axis respectively. However the bar plot is sorted with respect to least P-value (shown in colors).

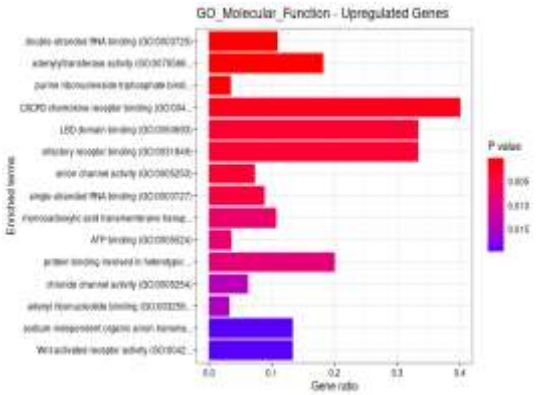

Figure 7.GO molecular function (MF) analysis of significantly upregulated genes. Gene ratio and enrichment terms are illustrated in x-axis and y-axis respectively. However the bar plot is sorted with respect to least P-value (shown in colors).

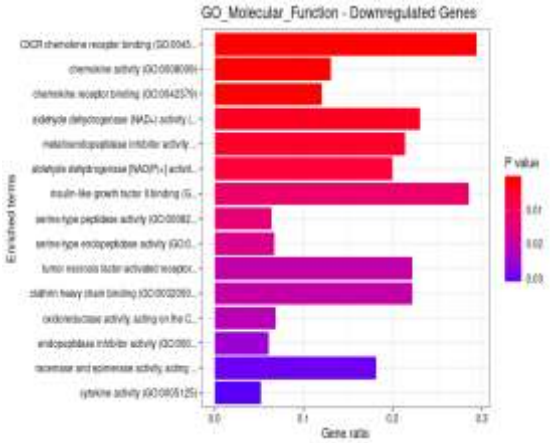

Figure 8.GO molecular function (MF) analysis of significantly downregulated genes. Gene ratio and enrichment terms are illustrated in x-axis and y-axis respectively. However the bar plot is sorted with respect to least P-value (shown in colors).

KEGG Pathway Analysis of Dysregulated Genes

Enrich R package was employed to identify the disrupted biological pathways as a result of dysregulation of genes. It was revealed that various biological pathways were disturbed due to the overexpression and underexpression of the DEGs. Upregulated genes such as CXCL10, OCLN, RSAD2, OAS1, DDX58, OAS2, IFNB1, OAS3, IFIT1, TLR3, CCNE2, CCNE1, CXCL11, CCL28, CXCL14, BIRC3 were found to be enriched with Hepatitis C, Hepatitis B, Cytokine-cytokine receptor interaction, RIG-I-like receptor signaling pathway, PI3K-Akt signaling pathway, Toll-like receptor nod-like receptor signaling pathways (**Figure 9**). Therefore, the overexpression of the aforementioned upregulated genes was found to be associated with the infection caused by HCMV because of their involvement in the aforesaid signaling pathways. However, the downregulated genes that were found to be enriched in the PI3K-Akt signaling pathway, TNF signaling pathway, ECM-receptor interaction, focal adhesion, regulation of actin cytoskeleton pathways include genes such as CHRM2, CDKN1A, LAMA2, ANGPT1, LAMA4, TNC, THBS2, EREG, FGF7, G6PC3, COL4A2, LPAR6, CREB3L1, CDC37, GNB2, PCK2, CXCL12, TMSB4X, ACTG1 (**Figure 10**). Consequently, the underexpression of these genes in the aforementioned pathways is critically involved with the infection of HCMV. Biological pathways play a crucial role in maintaining homeostasis and regulating the functions of the human body and therefore are responsible for various processes such as energy production, DNA replication, apoptosis, cellular communication, protein synthesis and immune response [48]. Hence, their dysregulation can lead to a variety of diseases therefore it is necessary to understand the mechanisms and regulation of these pathways in order to develop effective therapies for HCMV.

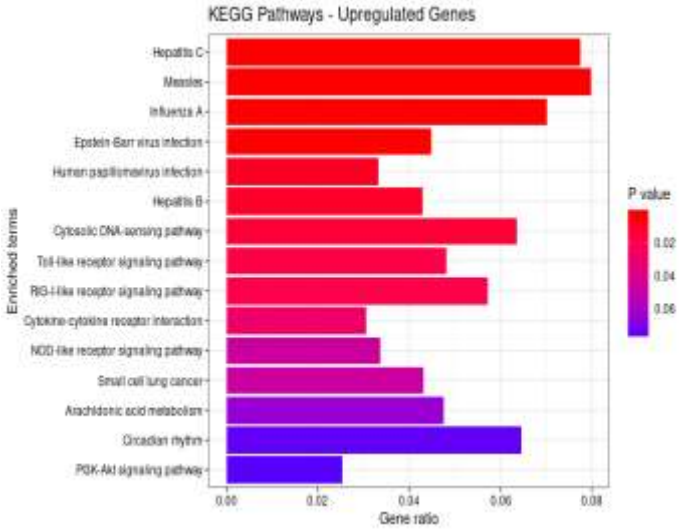

Figure 9.KEGG Pathway analysis of significantly upregulated genes. Gene ratio and enrichment terms are illustrated in x-axis and y-axis respectively. However the bar plot is sorted with respect to least P-value (shown in colors).

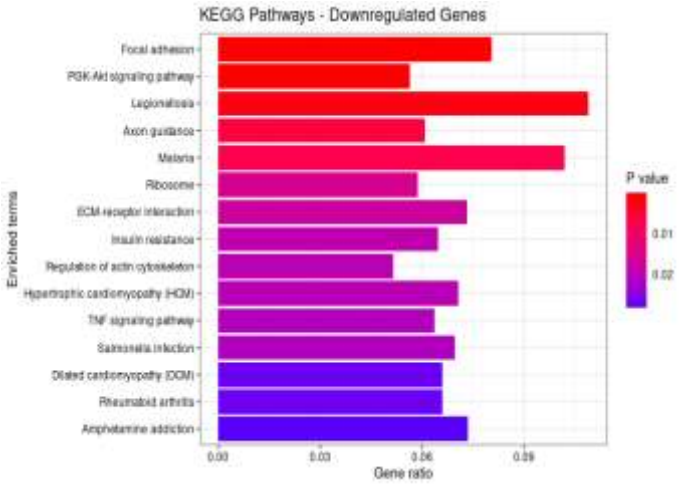

Figure 10.KEGG Pathway analysis of significantly downregulated genes. Gene ratio and enrichment terms are illustrated in x-axis and y-axis respectively. However the bar plot is sorted with respect to least P-value (shown in colors).

DISCUSSION

Human cytomegalovirus (HCMV) is a highly prevalent virus that causes herpesvirus infection in humans with a wide range of severity ranging from asymptomatic to fever and fatigue to severe organ dysfunction in immunocompromised patients [49]. WHO estimated seroprevalence of 83% in the general population indicating high seroprevalence of 90% in the Eastern Mediterranean region and lowest estimate of 66% in the European region [50]. Cytomegalovirus is controlled by immune response howeverver compromised immune system causes high level replication of HCMV leading to organ malfunctioning with a high prevalence rate of 60% in developed countries and 90% in underdeveloped countries [49]. Several malignancies have been reported due to cytomegalovirus including adults, anemia, jaundice, hepatomegaly in infants and muscle aches, swollen lymph nodes, pneumonitis, gastritis, esophagitis and various cancers in immunocompromised patients [51]. Currently numerous antiviral therapies particularly ganciclovir, foscarnet, cidofovir, letermovir and maribavir have been widely used as a treatment measure against HCMV infection however they exhibited several shortcomings including drug resistance and toxicity. Therefore novel antiviral biomarkers are required to be unveiled to develop efficient and safe antiviral therapy.

DGE analysis revealed 1974 highly significant dysregulated genes in HCMV patients as compared to healthy individuals. However, out of 1974 dysregulated genes 678 upregulated genes and 1028 downregulated genes were identified. The top 10 dysregulated genes in terms of high biological and statistical significance included upregulated genes (HERC5, RRAGD, SPINK1, RSAD2, HERC6, IFI44, NAP1L2, ENPP4, OASL, and IDO1) and downregulated genes (THBS2, TUBB, EEF1A1P38, ACTA2, WFDC21P, PKIG, RHOC, LXN, HGF, and ALDH1A1).

Predicted upregulated gene HERC5 together with HECT E3 ubiquitin ligase has been observed to be

involved in the regulation of interferon-stimulated gene 15 (ISG15) signaling in response to viral infections that in turn identifies and combats viral pathogens however high concentration of HERC5 has addressed the outbreak of HCMV infection elucidating increased recruitment of immune genes to infectious cells [52]. RRAGD is a monomeric guanine nucleotide-binding protein, or G protein that acts as molecular switch in several cell processes and signaling pathways therefore dysregulation of RRAGD would lead to infection susceptibility. Additionally, the antiviral role of RRGAD has been identified in Kaposi's Sarcoma Herpesvirus and Epstein-Barr Virus Infections implying that HCMV infection leads to upregulation of RRGAD resulting in activation of inflammatory cytokines responses [53]. SPINK1 (serine peptidase inhibitor, Kazal type 1) was found to be over-expressed in haemochromatosis-related HCC caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) that demonstrated its potential as a diagnostic marker for viral infections [54]. RSAD2 (radical S-adenosyl methionine domain containing 2) is an interferon stimulated gene that showed overexpression upon HCMV and type I/II IFN signaling through the JAK/STAT pathway elucidating its antiviral activity against several viruses including influenza virus, hepatitis C virus, human cytomegalovirus and HIV-1 [55]. HERC6 is well known E3 ligase that regulates signaling cascade of ubiquitin-like protein ISG15 in response to viral infections caused by human cytomegalovirus (HCMV) and hepatitis C virus (HCV) however prolonged infections ultimately undermine the expression of ISG15 at the transcriptional level [56]. Type I interferon, IFN-α/β induces antiviral responses by activating a signaling cascade that leads to the expression of thousands of interferon-stimulated genes (ISGs) including IFI44. IFI44 (Interferon induced protein 44) is an interferon-stimulated gene which is stimulated by IFN-α/β and has been identified as a known hallmark of viral infections caused by several viruses particularly HCMV indicating its elevated expression in HCMV-infected fetal astrocytes [57]. NAP1L2 is an intronless gene that belongs to nucleosome assembly protein family and is involved in the regulation of neuronal cell proliferation nevertheless overexpression of NAP1L2 has been reported in adult T lymphocytes that implies its antiviral role against viral infections [58]. ENPP4 was found to be upregulated in primary fibroblast cell culture over infection with HCMV (AD169 strain) at 18 h time point demonstrating its potential role in diagnostics and prognostics of HCMV [70]. OASL (oligoadenylatesynthetase-like) has been known for its antiviral activity on binding to RIG-I that leads to RIG-I signaling and enhances the anti-viral IFN response [59]. Another study has confirmed OASL as an antiviral response gene indicating its overexpression upon HCMV infection [60]. IDO1 (Indoleamine 2, 3-dioxygenase 1) has been addressed as immunoregulatory factor that regulates immune response however HCMV infection blocks the interferon gamma-induced IDO1 dependent immune regulation hence reports dysregulation of aforementioned immunoregulatory factor over HCMV infection [61].

Underexpressed THBS2 (Thrombospondin 2) belongs to the thrombospondin family and is responsible for cell-to-cell mediated and cell-to-matrix interactions. Additionally THBS2 has been observed to be underexpressed over human cytomegalovirus and human herpesvirus 6 coinfection of dermal fibroblasts indicating its key role in HCMV diagnosis and prognosis [62]. TUBB is one of the ten β-tubulin encoding genes and is highly expressed in the developing central nervous system for proper functioning of the complex structural brain [63]. However downregulation of neurodevelopmental gene expression has been reported in iPSC-derived cerebral organoids upon infection by human cytomegalovirus [64]. EEF1A1P38 is a pseudogene which is not functionally characterized yet however it is derived from the protein coding gene EEF1A1. It has been reported that deregulation of EEF1A leads to oncogenesis, apoptosis and viral infection [65]. Expression profiling of cells infected with the AD169 strain of HCMV demonstrated that statistically significant adhesion-related gene ACTA2 was down modulated across late stages of infection indicating its potential role in viral replication [66]. Though WFDC21P is a pseudogene, it has been observed in several malignancies including gastric cancer and down syndrome. Expression analysis suggests that WFDC21P (WAP four-disulfide core domain 21, pseudogene) may impact IFN response by modulating STAT3 eliciting its potential role against viral infection [67]. PKIG (CAMP-Dependent Protein Kinase Inhibitor Gamma) belongs to a member of the protein kinase inhibitor (PKIs) family genes representing antitumoral LKIs with antiviral properties against cancer or inflammatory processes [68]. Downregulation of Rho small GTPases especially RhoC proteins in HCMV infected glioblastoma cells has elicited decreased proliferation rate preventing malignant glioma from worsening that suggest potential involvement of RhoC in human glioblastoma cells during HCMV infection [69]. Knockdown OF tumor suppressor gene LXN has conferred resistance to docetaxel among prostate cancer cells while overexpression of LXN showed reduced docetaxel resistance besides its indirect involvement in inducing IFN-associated inflammatory responses [70]. It was notably observed that several growth factors including HGF contributed to angiogenesis (AG) and wound healing (WH) over HCMV infection suggesting that transplant vascular sclerosis (TVS) and chronic rejection (CR) of solid organ transplants takes place due to dysregulated expression of HCMV-induced growth factors [71]. ALDH1A1 (Homo sapiens aldehyde dehydrogenase 1 family, member A1) has been observed to be upregulated upon HCMV infection

indicating that dysregulation of ALDH1A1 is associated with infection outbreak [72].

KEGG Pathways identified that dysregulation of genes resulted in deregulation of crucial biological pathways which are essential for the survival of HCMV. Upregulated pathways included Toll-like receptor signaling pathway, RIG-I-like receptor signaling pathway, Cytokine-cytokine receptor interaction, NOD-like receptor signaling pathway, NF-kappa B signaling pathway and PI3K-Akt signaling pathway. Toll-like receptor signaling pathway is induced by Toll-like receptors (TLRs) which are known as primary pathogen sensors due to their crucial roles in activation of the innate immune system against invading pathogens. Upon HCMV infection, activation of TLRs stimulates the upregulation of several transcription factors majorly AP-1 and NF-κB that in turn regulate the expression of type I IFNs and inflammatory cytokines (IRF3 and IRF7) [73]. Regulatory NLRs (Nod-like receptors) are known as cytoplasmic recognition receptors that specifically recognize "non-self-components" and modulate pro-inflammatory pathways by activating host innate immune responses to viruses particularly induce IFN and NF-κB signaling over HCMV infection. Thus overexpression of NOD2 upon HCMV infection has been observed to inhibit virus replication through antiviral and pro-inflammatory cytokine production however immune response was lost over NOD2 knock down [74]. Overexpression of PI3K-Akt Pathway (intracellular signal transduction pathway) has been observed during HCMV entry in CD34+ cells and its antiviral strategy has been believed to promote metabolism, cell survival, proliferation, and angiogenesis following extracellular signals [74]. Downregulated genes were found to be highly enriched in several biological pathways including focal adhesion, PI3K-Akt signaling pathway, ECM-receptor interaction, Regulation of actin cytoskeleton, TNF signaling pathway and IL-17 signaling pathway. The extracellular matrix (ECM)-cell adhesion modulates several signal transduction pathways in response to HCMV infection however ECM-receptor interaction is mediated by integrins which regulate human cytomegalovirus entry through a highly conserved disintegrin-like domain [75]. The TNF-α (Tumor Necrosis Factor Alpha) signaling pathway is essential for physiological and pathological processes majorly apoptosis, inflammation and stimulation of immune responses against viral infection. TNF-α is responsible for inhibition of viral DNA and RNA replication however HCMV inhibits TNF-α signaling pathway by targeting the 55-Kilodalton TNF-α receptor that results in down-modulation of TNF signaling [74]. IL-17 (Interleukin-17) is pleiotropic cytokine that is involved in the activation of protective immune responses against a wide range of viruses indicating that IL-17-targeted immunotherapy may prove as a promising therapeutic strategy against HCMV infection [75].

In this study we have addressed the positive correlation of aforementioned dysregulated genes with HCMV-induced infection suggesting their significance as a HCMV biomarker and target candidate for the efficient development of therapeutic compounds. A total of 5 protein-coding genes (RRAGD, SPINK1, NAP1L2, PKIG and LXN) and 2 pseudogenes (EEF1A1P38, WFDC21P) were not previously seen in HCMV cases but other viral infections however expression profiling of our proposed study has confirmed their role in inducing HCMV therefore aforestated were considered novel targets against HCMV. Additionally biological processes especially Toll-like receptor signaling pathway, PI3K-Akt signaling pathway, TNF signaling pathway and IL-17 signaling pathways have been unveiled demonstrating immune response mechanisms as a result of HCMV-host cell interactions. Thus potential candidate genes against HCMV have been discovered for the development of efficient therapeutics.

CONCLUSION

Expression profiling has revealed a total of 1974 dysregulated genes including 678 upregulated genes and 1028 downregulated genes in HCMV patients. Interestingly novel protein coding genes including RRAGD, SPINK1, NAP1L2, PKIG, LXN and pseudogenes particularly EEF1A1P38, WFDC21P have been predicted in this study suggesting their role as a disease biomarkers. KEGG Pathway analysis has identified several dysregulated biological processes particularly Toll-like receptor signaling pathway, NOD-like receptor signaling pathway, PI3K-Akt signaling pathway, TNF signaling pathway and IL-17 signaling pathway in response to dysregulated genes upon HCMV Infection. Unraveling the innate immune response mechanisms evaded by HCMV-host cell interactions provides insight into viral pathogenesis and cellular innate immunity mechanisms. Furthermore, the proposed study contributes to the discovery of novel efficient treatments against HCMV, however considering significant morbidity and mortality in immunocompromised patients further investigations are still required.

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