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COMPUTATIONAL ANALYSIS OF LIVER INFLAMMATION ASSOCIATED GENES IN HUMAN (HOMO SAPIENS) AND PHYLOGENY WITH CHIMPANZEE

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Abstract

This study applies computational approaches to explore and characterize genes associated with liver inflammation in humans. Five key genes were analyzed: mitogen-activated protein kinase 1 (MAPK1), integrin subunit alpha 2 (ITGA2), cyclin-dependent kinase 2 (CDK2), interleukin 6 (IL6), and 2'-5'-oligoadenylate synthetase 2 (OAS2). The workflow included sequence retrieval from NCBI, chromosomal localization, gene structure analysis, motif identification, protein–protein interaction (PPI) mapping, and gene ontology annotation. Results indicated that the studied genes are dispersed across different chromosomes and play crucial roles in biological pathways linked to liver inflammation. PPI analysis highlighted ITGA2 as a hub gene with strong interaction connectivity. Gene ontology suggested that IL6 and OAS2 contribute significantly to antiviral defense mechanisms. Phylogenetic analysis showed a close relationship between OAS2-Hs and OAS2-Pt, whereas MAPK1-Hs displayed greater divergence. Expression profiling revealed that CDK2 is markedly upregulated in the telencephalon region. Overall, these findings provide new insights into the molecular mechanisms of liver inflammation and identify potential biomarkers for early diagnosis and therapeutic intervention, though experimental validation remains essential to support these computational predictions.

INTRODUCTION

The liver is a vital organ responsible for multiple physiological functions, including detoxification, metabolism, and immune regulation. Liver inflammation, a hallmark of hepatic disorders such as hepatitis, non-alcoholic fatty liver disease (NAFLD), and cirrhosis, represents a complex interplay of immune responses, oxidative stress, and genetic predisposition (Zhang et al., 2022). Chronic inflammation of the liver contributes significantly to global morbidity and mortality, being a

precursor to fibrosis and hepatocellular carcinoma (HCC) (Ringelhan et al., 2018). Understanding the molecular and genetic mechanisms underlying liver inflammation is essential for identifying potential biomarkers and therapeutic targets.

Recent advances in genomics and computational biology have provided unprecedented opportunities to analyze genes associated with inflammatory responses at a systems level (Li et al., 2021). Computational analyses, such as comparative genomics and phylogenetic inference, enable the identification of evolutionarily conserved genes and pathways that govern inflammatory mechanisms. In particular, transcriptomic and proteomic datasets have revealed that genes involved in cytokine signaling, immune activation, and apoptosis are key regulators of hepatic inflammation (Cai et al., 2020).

Humans (Homo sapiens) share approximately 98–99% of their genome with chimpanzees (Pan troglodytes), yet exhibit significant differences in disease susceptibility and immune responses (Varki & Altheide, 2005). Comparative genomic studies between humans and chimpanzees have highlighted subtle sequence variations and gene expression differences that may contribute to differential inflammatory and immune phenotypes (Blekhman et al., 2008). Investigating the phylogenetic relationships of liver inflammation-associated genes between these two species could therefore provide critical insights into the evolutionary divergence of immune regulation and inflammatory processes.

Computational approaches such as multiple sequence alignment, phylogenetic tree construction, and functional annotation can elucidate conserved domains and evolutionary patterns of genes implicated in liver inflammation. By integrating bioinformatics tools, such as BLAST, MEGA, and STRING, it becomes possible to predict functional networks and evolutionary trajectories of inflammation-associated genes (Tamura et al., 2021). Such analyses may help to identify conserved genetic elements that are crucial to the pathophysiology of liver inflammation across primates (Kim et al., 2017; Mansouri et al., 2018; Yang et al., 2018).

The present study aims to perform a computational analysis of liver inflammation-associated genes in humans and to explore their phylogenetic relationship with chimpanzee orthologs. Specifically,

we analyze gene conservation, sequence divergence, and evolutionary relationships to better understand the molecular evolution of liver inflammation mechanisms. This comparative approach not only enhances our understanding of hepatic immune evolution but also provides a foundation for translational research in liver disease therapeutics.

MATERIALS AND METHODS

Sequence Retrieval

A search of the GeneBank database was conducted to identify genes associated with liver inflammation in Homo sapiens. Five candidate genes reported in previous studies were selected for analysis. Genomic sequences, protein length, chromosomal positions, and start–end coordinates of each gene were retrieved through the National Center for Biotechnology Information (NCBI). The molecular weight and isoelectric point of the corresponding proteins were calculated using the ExPASy Compute pI/Mw tool (https://web.expasy.org/computepi/). Protein sequence datasets for the identified liver inflammation-related genes were then generated for subsequent analysis and characterization (**Table 1**).

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Table 1: Genes characteristics.

Sr #	Gene Symbol	Description	Gene ID	CH #	Start&End position of each gene on genome	gDNA length	Protein length	CDS length	Acc.# Gene NC	pI	Mw
1	MAPK1	mitogen-activated protein kinase 1	5594	22	21759657..21867680,	108023	360 aa	1,083 nt	NC_000022.11	6.50	41389.71
2	ITGA2	integrin subunit alpha 2	3673	5	52989352..53094779	105427		3,546 nt	NC_000005.10	5.10	12929 6.38
3	CDK2	cyclin dependent kinase 2	1017	12	55966830..55972789	5959	298 aa	897 nt	NC_000012.12	8.80	3392 9.53
4	IL6	interleukin 6	3569	7	22727200..22731998	4798	212 aa	639 nt	NC_000007.14	6.17	23718.22
5	OAS2	2'-5'-oligoadenylate synthetase 2	4939	12	112978519..113011723	33204	687 aa	2,064 nt	NC_000012.12	8.29	78786.58

Chromosomal mapping

For chromosomal mapping, a map chart file was generated containing gene symbols, chromosome numbers, gene positions, and chromosome lengths. This file was then used as the input for visualization with the MapChart bioinformatics tool (http://www.biometris.wur.nl/UK/Software/MapChart/download) (Voorrips, 2002). The analysis illustrated the chromosomal locations of each gene associated with liver inflammation.

Gene structure and Motif analysis

The coding sequences and genomic information for all selected genes were retrieved from the NCBI database. Gene structure prediction was performed using WebScipio, which provides high-quality annotations based on protein queries (https://www.webscipio.org/) (Odronitz et al., 2008).

For motif analysis, the sequences of the five genes were analyzed using the MEME Suite server (version 4.11.2) to identify motif positions and widths. The analysis parameters were set as follows: number of repetitions, any; average protein sequence length, 309.5; maximum number of motifs, 5; and motif width ranging between 6 and 60 residues (Cao et al., 2021).

Protein-protein association

Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) Ver. 11.0 (https://string-db.org/cgi/input.pl) was used to analyze protein-protein association networks (Kim et al. 2021). STRING programme was used to input the amino acid sequence, and the protein-protein analysis result was downloaded to reflect the gene-gene interaction and visualized via cytoscape.

Gene ontology (GO Analysis)

Gene Ontology (GO) analysis was performed using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) tool

(https://david.ncifcrf.gov/tools.jsp) (Huang et al., 2009; Shao et al., 2009; Jiao et al., 2012). The set of gene symbols associated with liver inflammation was provided as input for annotation. The functional annotation tool categorized the genes into biological processes (roles of genes or gene products in biological pathways), molecular functions (biochemical activities of gene products), cellular components (locations within the cell where gene products are active), and other functional ontology classes.

Phylogenetic Analysis

For the phylogenetic analysis of Homo sapiens and Pan troglodytes, amino acid sequences were utilized. Molecular evolutionary assessments were carried out using MEGA X software (Kumar, Stecher, Li, Knyaz, and Tamura, 2018), while tree annotation and visualization were performed through the Interactive Tree of Life (iTOL) platform (https://itol.embl.de/upload.cgi). The phylogenetic tree was generated in a circular layout, with related sequences clustered together (Kalpan-Levy et al., 2012). The evolutionary relationship between Homo sapiens and Pan troglodytes was inferred using the Neighbor-Joining method implemented in MEGA.

Gene expression analysis

Transcriptional profiling was carried out to investigate the potential functions of five genes linked to diabetes mellitus across different human organs. Gene expression data were obtained from the Expression Atlas database (https://www.ebi.ac.uk/gxa/home), where RNA-seq datasets provided FPKM values (Cook et al., 2019). The data were further analyzed using the Heatmapper tool (http://www.heatmapper.ca/) for visualization (Babicki et al., 2016). The dataset included RNA-seq results from two independent experiments, reporting expression values in either FPKM or TPM, specifically focusing on genes associated with liver inflammation in Homo sapiens (Gonzalez et al., 2018).

RESULTS

Physiochemical properties

Four genes proteins were showed acidic in nature (pI<7). While one genes (OAS2) protein showed basic in nature (pI>7) with isoelectric point (pI=8.29) and molecular weight (Mw=41975.60), while SSTR2 protein showed was highly basic in nature than other selected genes with isoelectric point (pI=6.81) and molecular weight (Mw=78786.58) in human (**Table 1**).

Chromosomal mapping

Chromosome mapping revealed that liver inflammation related genes were randomly distributed on chromosomes in human (Homo sapiens). The results showed that chromosome#2, 7 and 22 consisted only one gene. ITGA2 gene (Gene position on chromosome=150.574558), IL6 (22.727200), and MAPK1 (21.759657), located on ch2, chr7, and chr22 respectively. While chromosome chr12 (CDK2= 55.966830, and OAS2 112.978519) consisted two genes (**Figure 1**).

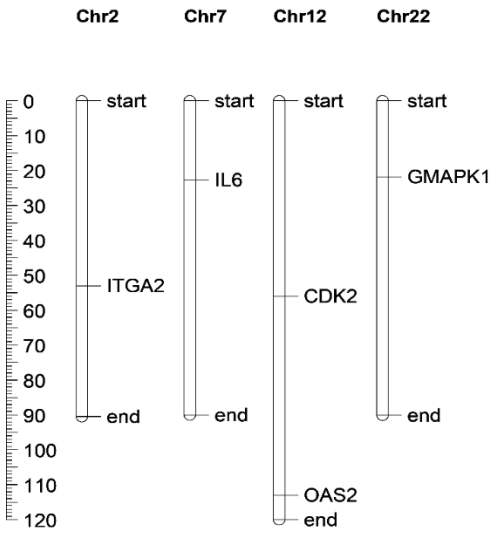

Figure 1: Chromosomal mapping.

Gene structure analysis

Web sci-pio server used as genes structure identification, there were five genes structures analyzed in human (H. sapiens). Red segment showed the gap region while red thin line indicated mismatch and blue line for sequence shift. In human, there was no mismatch or gape region found in all selected genes. ITGA2 genes (Exons: 28, Introns: 12) had greater the number of exons as compared to other genes, while IL6 gene showed only four exons with three introns. Additionally, all five genes associated with liver inflammation related genes with exon and intron showed in **Figure 2**.

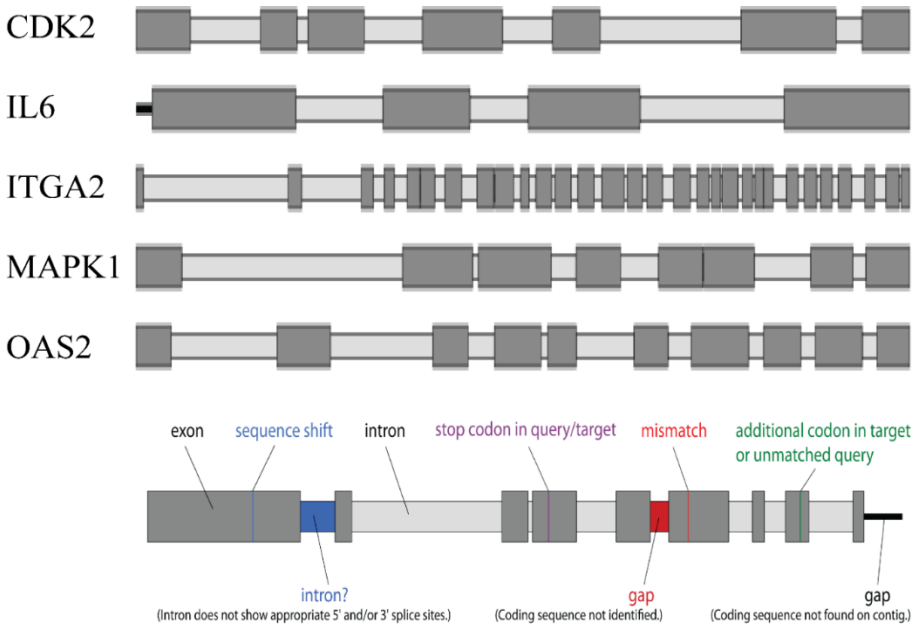

Figure 2: Gene structures.

Motifs analysis

This analysis depicted the motif location, motif consensus and graphical representation of motif. Conserved motifs are involved in liver inflammation in human. Top 5 motifs were predicted; all have same frequency #2 (number of sites contributing to the construction of the motif). Motif 1 was most prominent out of top 5 motifs. Motif analysis revealed that top 5 motif located on three genes. In human, motif-1 was located OAS2 genes had width (amino acids residue) 47 with E-value = 2.2e-

010. Motif-2 was located on two genes (MAPK1 and CDK2) had width 50 with E-value = 1.0e-008. Motif-3 was located on OAS2 gene had width 36 with E-value = 2.8e-005. Motif-4 was located on two genes (MAPK1 and CDK2) had width 48 with E-value = 2.3e-003. Motif-5 was located on OAS2 gene had width 21 with E-value = 2.8e-002 (**Figure 3**).

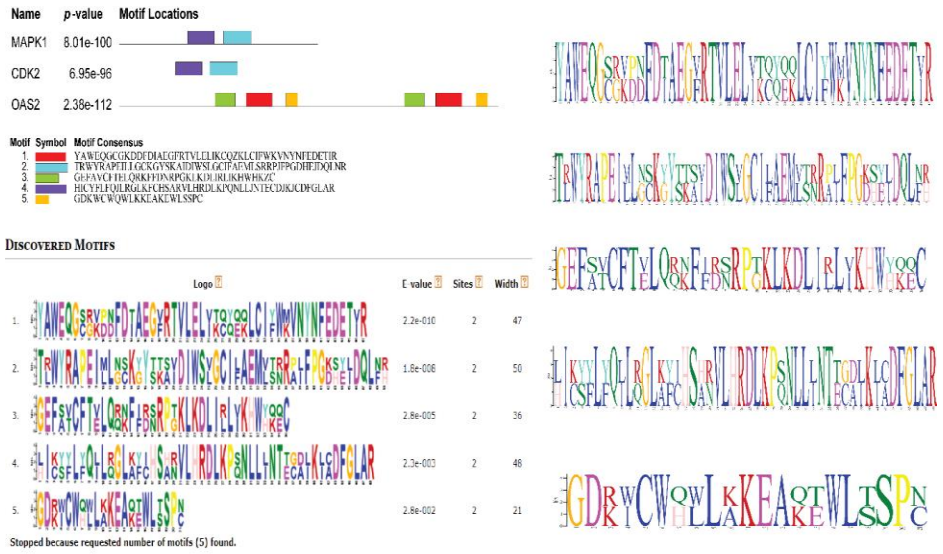

Figure 3: Motif analysis showing the motif location, motif consensus, gene frequency motif logo in Human performed by using MEME.

Protein-protein interaction

Protein control biological function solely or by association with other proteins. IL6 gene visualized by Cytoscape, revealed the protein-protein interaction. ITGA2 showed first shell of interaction with ten predicted functional partners that were ITGB1, ITGB3, FN1, ITGB2, GP6, ITGB6, COL3A1, COL1A1, COL1A2, and ITGB5 genes (Filled nods) with predicted 3D structure in human (Figure). ITGA2 gene had high degree of interaction with all prediction partners except MUC1and ADPGK gene with bitscore value 2343.9 than other genes (STRING). Empty nodes indicated unpredicted 3D structure while filled structure indicated predicted 3D structure available at PDB (data-base). Thickness of line showed degree of interaction of one gene with others (**Figure 4**).

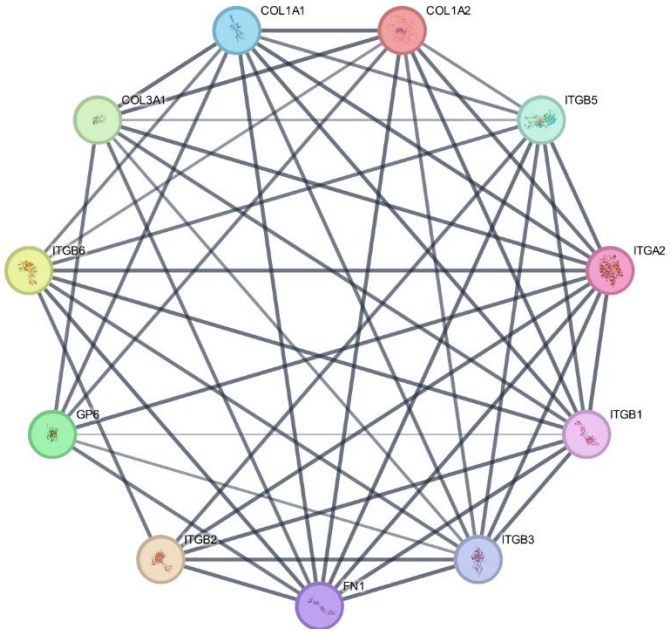

Figure 4: Protein-Protein interaction of Human visualized *via* Cytoscape.

Integrin alpha-2 (Alpha-2/beta-1) is the receptor for the protein laminin the protein collagen, collagen C-propeptides, fibronectin, and E-cadherin. It identifies the proline-hydroxylated motif G-F-P-G-E-R in protein. It is in charge of platelet and other cell attachment to collagen peptides regulating collagen and collagenase enzyme transcription, generating force, and organising freshly combined extracellular matrix. (Microbial Infection) Integrin ITGA2:ITGB1 serves as a binding protein on human echoviruses 1 and 8.

Gene ontology

Functional characteristics associated with proteins were determined by Gene Ontology annotation analysis. Gene Ontology results revealed liver inflammation genes annotation. The result revealed that two genes (IL6, MAPK1) involved in GO term for Endoplasmic reticulum lumen followed by cellular compartment with PV value=0.058246. There were three genes (OAS2, CDK2, MAPK1)

involved in ATP binding followed by Molecular Function with PV value=0.034271. While two genes (IL6, OAS2) in defense response to virus followed by biological process with PV value=0.047379. Gene annotation discrepancy in H. sapiens (Human) showed in **Table 2**.

Table 2. Gene annotation discrepancy in Human.

Category	ID	Term	Gene Count	P-value
CC	GO:0005788	Endoplasmic reticulum lumen	IL6, MAPK1	0.058246
CC	GO:0005925	Focal adhesion	ITGA2, MAPK1	0.080745
MF	GO:0005524	ATP binding	OAS2, CDK2, MAPK1	0.034271
MF	GO:0106310	protein serine kinase activity	CDK2, MAPK1	0.073715
MF	GO:0004674~	protein serine/threonine kinase activity	CDK2, MAPK1	0.076842
BP	GO:0048661	positive regulation of smooth muscle cell proliferation	IL6, ITGA2	0.010902
BP	GO:0045727	positive regulation of translation	IL6, ITGA2	0.016319
BP	GO:0032760	positive regulation of tumor necrosis factor production	IL6, OAS2	0.022511
BP	GO:0018105	peptidyl-serine	CDK2, MAPK1	0.031448

		phosphorylation		
BP	GO:0051607	defense response to virus	IL6, OAS2	0.047379
BP	GO:0006468	protein phosphorylation	CDK2, MAPK1	0.074068
BP	GO:0008284	positive regulation of cell population proliferation	IL6, CDK2	0.098694
KEEG	hsa04151	PI3K-Akt signaling pathway	IL6, ITGA2, CDK2, MAPK1	2.64E-04
KEEG	hsa05160	Hepatitis C	OAS2, CDK2, MAPK1	0.00188369
KEEG	hsa05161	Hepatitis B	IL6, CDK2, MAPK1	0.00197876

Phylogenetic Analysis

The evolutionary link between these genes in Human and Chimpanzee was expressed through phylogeny, which was found by constructing a phylogenetic tree. Protein sequence of liver inflammation associated genes belonging to different families was used to construct phylogenetic tree and to measure the evolutionary relationship between Human and Chimpanzee liver inflammation associated genes.

Phylogenetic tree showed that human and chimpanzee had much closest phylogeny. Phylogenetic tree divided into 3 clades (marked as color), amino acid conservation of clade1 (marked as blue) of liver inflammation genes appeared very close to clade-2 (green) than other clade, while OSA2 –Hs

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showed more phylogeny with OSA2 –Pt gene sequences and showed larger diversity with MAPK1-Hs Clade-3 showed by red color (**Figure 5**).

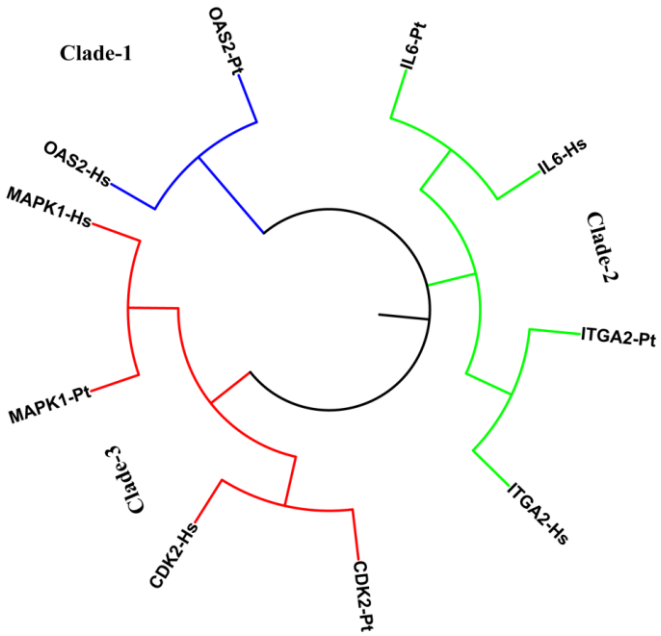

Figure 5: Phylogenetic tree of human (Hs) and chimpanzee species (Pt).

Gene expression analysis

Heat mapper was used to analyze liver inflammation associated genes in several organs showed in (figure) of H.sapeins (Bakhtiarizadeh et al. 2018). In heat map red colour showed up regulation and green colour to down regulation. Results revealed that CDK2 gene showed up-regulation in telencephalon (high expression) while down-regulation (low expression) in brain fragment (**Figure 6**).

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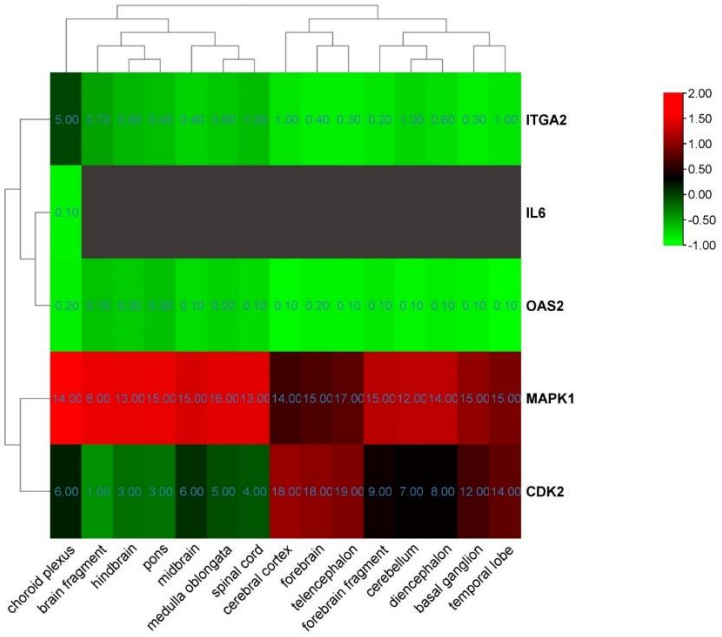

Figure 6: Gene expression analysis: red color indicated up-regulation in gene expression, green color indicated the down-regulation, black color indicated no change (human).

DISCUSSION

In recent years, considerable research has focused on elucidating the mechanisms underlying the progression of HBV-induced liver inflammation to hepatocellular carcinoma (HCC) (Li et al., 2019; Ligat et al., 2019; Liu et al., 2018). Despite these efforts, the precise processes driving liver inflammation remain insufficiently explored. Most studies have investigated only one or two specific genes, without systematically examining differential gene expression across varying inflammation grades. The present study is the first to comprehensively employ bioinformatics approaches—including gene mapping, structural analysis, and motif analysis, in addition to Gene Ontology (GO), protein–protein interaction (PPI), and KEGG pathway analysis—to identify genes involved in hepatic inflammation.

Zhao et al. (2022) performed GO and KEGG enrichment analyses to highlight key biological activities and pathways potentially contributing to enhanced antimicrobial responses in liver tissues

with higher inflammatory grades. KEGG pathway analysis revealed that upregulated differentially expressed genes (DEGs) were enriched in conditions such as graft-versus-host disease, rheumatoid arthritis, parasitic infections, influenza A, type 1 diabetes mellitus, hematopoietic cell lineage, allograft rejection, natural killer cell-mediated cytotoxicity, and cytosolic DNA-sensing pathways. Our findings were consistent with these results, as three genes (IL6, OAS2, and MAPK1) out of the five identified DEGs were also linked to influenza A. Moreover, EP300, PCNA, CDKN2A, CDK2, MTOR, IL6, ITGA2, OAS2, TGFB1, and MAPK1 emerged as hub genes with high centrality, suggesting that they may play crucial roles in the pathogenesis of hepatic inflammation. These genes could serve as potential biomarkers for monitoring the progression of liver inflammation (Zhao et al., 2022). Nevertheless, the current study has certain limitations, particularly the absence of experimental validation. Further investigations are needed to confirm the involvement of these candidate genes in hepatic inflammation.

Chronic inflammation represents a major cause of morbidity and mortality in developed countries, being closely associated with conditions such as cardiovascular disease, diabetes, non-alcoholic fatty liver disease (NAFLD), and autoimmune as well as neurodegenerative disorders (Roth et al., 2018). Obesity, similar to other chronic conditions, is characterized by elevated circulating levels of pro-inflammatory mediators (de Heredia et al., 2012). Persistent low-grade inflammation, arising from both local and systemic immune responses, can disrupt metabolic homeostasis within affected tissues. Thus, clarifying the molecular pathways that connect immune regulation with systemic and tissue-specific metabolic balance is essential for the prevention and treatment of chronic metabolic disorders. Identifying reliable biomarkers reflecting these pathways is equally critical.

Although tissue-specific inflammatory markers have been suggested for several diseases, their diagnostic reliability and clinical applicability remain limited. To address this gap, Jolanda et al. (2021) developed a strategy to interrogate large-scale databases (GO and Human Protein Atlas) for overlapping liver- and adipose-specific genes with known inflammation-related genes. Overlapping genes/proteins were prioritized based on their historical application as circulating biomarkers in clinical studies, using the Clarivate Analytics database. This approach was validated with murine

gene expression data and human biomarker literature related to tissue-driven low-grade inflammation. As a result, 18 biomarkers were identified—16 associated with hepatic inflammation and 2 with adipose tissue inflammation—providing valuable insights into inflammation-specific molecular signatures.

CONCLUSION

The present study demonstrated that the identified genes are distributed across different chromosomes and participate in key biological processes associated with liver inflammation. A total of five inflammation-related genes in humans were selected for computational analysis. Among these, ITGA2 was identified as a hub gene with a high level of interaction, suggesting its potential role in the regulatory network of liver inflammation. Gene Ontology analysis indicated that specific genes, particularly IL6 and OAS2, are likely involved in antiviral defense mechanisms in humans. Phylogenetic analysis revealed that the nucleotide sequence of OAS2-Hs exhibited greater diversity compared with MAPK1-Hs. These findings highlight candidate genes that may be critical for understanding the molecular basis of liver inflammation. However, further experimental studies are necessary to validate these results and to enhance the screening of human liver inflammation–associated genes.

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