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Organ-specific host differential gene expression analysis in systemic candidiasis: A systems biology approach

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ABSTRACT

Patients admitted to the hospital with coronavirus disease (COVID-19) are at risk for acquiring mycotic infections in particular Candidemia. *Candida albicans* (*C. albicans*) constitutes an important component of the human mycobiome and the most common cause of invasive fungal infections. Invasive yeast infections are gaining interest among the scientific community as a consequence of complications associated with severe COVID-19 infections. Early identification and surveillance for *Candida* infections is critical for decreasing the COVID-19 mortality. Our current study attempted to understand the molecular-level interactions between the human genes in different organs during systematic candidiasis. Our research findings have shed light on the molecular events that occur during Candidiasis in organs such as the kidney, liver, and spleen. The differentially expressed genes (up and down-regulated) in each organ will aid in designing organ-specific therapeutic protocols for systemic candidiasis. We observed organ-specific immune responses such as the development of the acute phase response in the liver; TGF-pathway and genes involved in lymphocyte activation, and leukocyte proliferation in the kidney. We have also observed that in the kidney, filament production, up-regulation of iron acquisition mechanisms, and metabolic adaptability are aided by the late initiation of innate defense mechanisms, which is likely related to the low number of resident immune cells and the sluggish recruitment of new effector cells. Our findings point to major pathways that play essential roles in specific organs during systemic candidiasis. The hub genes discovered in the study can be used to develop novel drugs for clinical management of Candidiasis.

1. Introduction

COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 which has resulted in the present pandemic affecting over 200 million people and leading to the death of several million humans. Hypoxia, immune suppression, host iron depletion, hyperglycemia leading to diabetes mellitus, and prolonged hospitalization have all been linked to COVID-19 infection. These clinical symptoms make it easier for opportunistic fungal infections to infect COVID-19 affected individuals. COVID-19 patients may be more susceptible to fungal co-infections due to the interventions such as corticosteroid therapy and mechanical ventilation. The most commonly reported fungal infections in patients with COVID-19 include aspergillosis, invasive candidiasis, and mucormycosis [1,2].

Patients with COVID-19 who developed Candidemia were less likely to have specific underlying illnesses and procedures usually associated with Candidemia and more likely to have acute risk factors associated with COVID-19 treatment, such as immune-suppressing medications [3]. *C. albicans* is an emerging fungus that can cause catastrophic infection outbreaks in healthcare institutions. Commensal *Candida* species are found on human skin, gastrointestinal, and genital tracts [4]. It has often spread in tertiary health care institutions that cater to persons with serious medical problems. However, outbreaks of *Candida* have been observed in COVID-19 units of acute care hospitals since the start of the epidemic. During the COVID-19 pandemic, modifications in standard infection control methods, such as the restricted supply of gloves and gowns, reuse or prolonged use of these items, and changes in cleaning and disinfection practices, may have contributed to these outbreaks. As healthcare facilities and health authorities respond to COVID-19, screening for *Candida* colonisation, an essential aspect of containment efforts, is unfortunately limited [5]. COVID-19 patients are more likely to develop candidiasis, particularly denture wearers with prosthetic stomatitis who require mechanical ventilation. *C. albicans* infections in COVID-19 patients have very high probability to increase the morbidity and mortality. Thus, the early diagnosis of *C. albicans* associated infections in COVID-19 patients is vital to improve the

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treatment methods and reduce the mortality rate [6,7].

Patients with Candidemia typically have an initial septic illness that is indistinguishable from bacteremia, but they can also have a more indolent course characterised by a fever of unclear etiology. Intravascular catheters, parenteral hyper-alimentation, and broad-spectrum antibiotics are major risk factors for Candidemia. Patients with pyrexia of unknown origin with the risk of acquiring fungal infections particularly those treated with broad-spectrum antibiotics may be given empirical antifungal medications. The clinical picture in *C. albicans* sepsis and Non *C. albicans* (NAC) sepsis is identical. On the other hand, NAC is frequently less sensitive to Fluconazole than *C. albicans* and may require a higher dosage to treat clinically [8]. Candidemia can result in a serious, life-threatening condition and therapy is normally initiated as soon as an infection is diagnosed. Finding the source of the infection and if feasible, removing it before starting therapy with medication is part of the treatment. Although *Candida* infections of the mucosal surfaces (mouth and oesophagus) are normally straightforward to cure, Candidemia can be difficult to treat, especially if the infection is invasive and spread to other parts like eye, brain and kidneys [9].

The drug resistance exerted by *Candida* strains has become a significant concern worldwide. The existing treatment strategies are limited, and there is an urgent need to understand the disease pathology at the molecular level. New drug targets need to be developed to combat *Candida* as there is an alarming increase in reported infections globally [10]. A study on the murine model to understand the immune response against the fungal infection revealed that the pathological consequence varies in different organs. Although the kidney is considered the primary target organ, the murine model of systematic candidiasis displayed a decline in fungal load over time in the liver and spleen during the timeline. There is a significant up-regulation in the host immune response-related genes in the liver, suggesting the considerable requirement for controlling the fungal load in the liver. In contrast, it is observed to have a delayed transcriptional immune response in the kidney [11].

For the present study, we employed systems biology approaches to understand the molecular-level interactions between the genes expressed during *Candida* infections in the kidney, liver and spleen. Gene network analysis has generated interest among biomedical researchers and has become one of scientifically acceptable method to understand the molecular-level interactions between the genes during various disease conditions [12–21]. The schematic workflow of the present study is given in Fig. 1. The differentially expressed gene data set

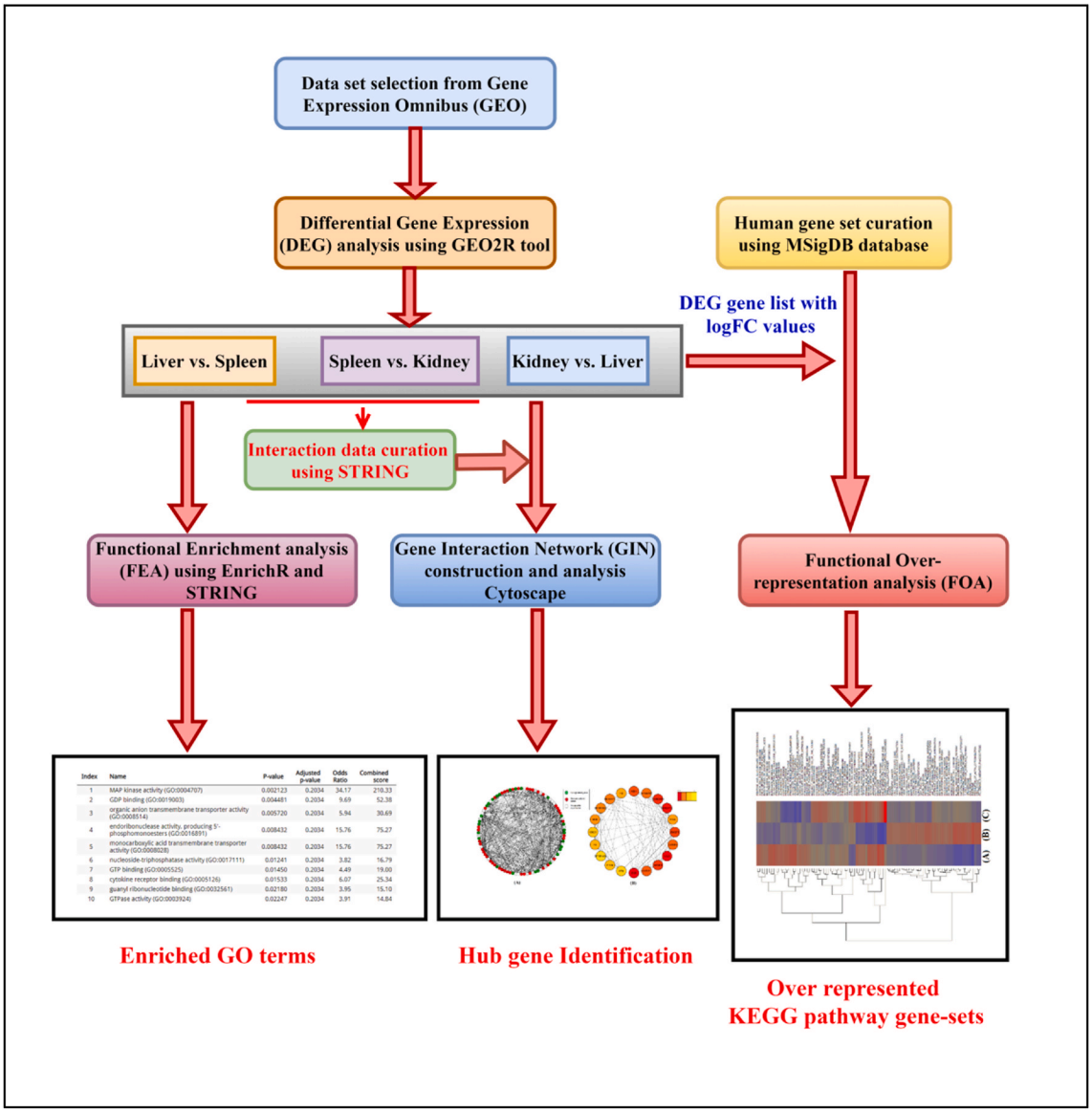

Fig. 1. Systematic workflow of organ specific differential gene expression analysis during the candidiasis.

was curated from the gene expression study with the accession number GSE83682 where the gene expression of the kidney, liver and spleen were compared at different time duration [11]. The experimental study dealt with the organ-specific differences in host pathogen interactions by the gene expression profiling of murine kidney, liver and spleen and determined the fungal transcriptome. Here in our analysis, we have selected the transcriptome data of the kidney, liver and spleen transcriptome data at 8 h time slots out of three-time slots (8 h, 12 h and 24 h). It takes at least a few days for significant levels of antibodies or immune cells to be generated and transported to the site of infection. However, the period of manifestation of antibodies may be underestimated since the initial antibodies generated are instantly complexed with the microbe, and no free antibodies are left unless excess antibodies are present. We attempted to understand the early-stage molecular events in each organ, which will enhance the early detection to ensure effective treatment strategies. The comparison of each organ's data set of differentially expressed genes to find inter-organ differences revealed by transcriptional data sets obtained from each individual organ. The approach will aid in enhancing the comprehensive diagnostic intervention using histopathology, direct microscopic examination or PCR-based assays. The gene interaction network analysis of differentially expressed genes in three different organs provided us with the molecular level interactions between the genes and their associated partners in various molecular functions during the infection. The top 100 differently expressed genes from each set of compared datasets between kidney vs liver, liver vs spleen and spleen vs kidney were further filtered based on the logP values. This study aimed to understand the role of differently expressed genes in human immune response and the essential regulatory genes to enhance further treatment options against candidiasis. The results obtained from the study would be helpful for researchers to understand better the molecular-level interaction between differentially expressed genes and the role of these genes in the host immune system against systematic candidiasis. The genes reported in this study have an important role during the Candidiasis and they can be exploited as potential drug targets for new drug discovery.

2. Materials and methods

2.1. Differentially expressed gene curation

The micro-array dataset with accession number GSE83682 at 8 hh was curated from the GEO database (https://www.ncbi.nlm.nih.gov/geo/), and differential gene expression analysis was performed using the GEO2R tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/) [22]. The data consists of three-time slots 8 h, 24 h, and 36 h; as our focus is on the early stages of infection, we choose 8 h for our analysis. The gene expressions in the liver, spleen and kidney after the intravenous injection with the *C. albicans* were used to analyse the differentially expressed genes after 8 h. Three different comparisons were carried out: kidney vs liver, liver vs spleen and spleen vs kidney. The differentially expressed genes for each study were identified based on the fold change (FC) values as up-regulated and down-regulated genes at the given condition.

2.2. Functional over-representation analysis (FOA) of gene groups

Gene sets are characterised by various criteria, such as participation in specific biological pathways or co-expression under certain conditions. These gene sets are grouped in collections called gene set databases. MSigDB, GeneSigDB, and GeneSetDB are the three gene set databases created exclusively for gene set analysis. These gene set collections enable researchers to examine the activity of groups of biologically related genes rather than single genes to discover which of these groups is important to a trait of interest. Gene sets were curated from the MsigDB database (https://www.gsea-msigdb.org/gsea/msigdb/index.jsp). The MsigDB database hosts the annotated gene sets, which can be used for gene set enrichment analysis [23]. The differential expressed genes in each case were used to predict the top enriched gene sets at each condition. We have used the FOA method previously developed to understand the role of differentially expressed genes in *Mycobacterium tuberculosis* virulence and host-pathogen interactions [24,25]. For each gene set, the FOA score will be assigned by adding the gene logFC values divided by the square root of the number of genes in the gene set. The process will be repeated over 1,00,000 times, and the sampling distribution's mean and standard deviation will be used to correct the original FOA scores.

2.3. Protein-protein interaction data curation

The top 100 genes from each dataset were used to understand the role of differential genes in host-pathogen interaction during the *C. albicans* infection in the liver, spleen and kidney. The genes were collected based on the "(-Log10 (P-value))", which consists of both up-regulated and down-regulated genes. The genes were further used to collect the interaction data using the STRING database (https://string-db.org/) at low confidence scores (above 0.15) [26]. The obtained gene network consisted of 91 genes with 400 edges in the case of differentially expressed genes in the kidney, followed by 94 genes with 505 edges and 93 genes with 650 edges in the spleen and liver, respectively. We further performed the functional enrichment analysis using the STRING analysis tool and collected the crucial pathways, Gene Ontology terms enriched in kidney, liver and spleen during the *C. albicans* infection.

2.4. Gene interaction network construction and analysis

The interaction data was used to construct the network using the Cytoscape tool [27]. Cytoscape gives the user an integrated visualisation of biological networks by providing different tools for analysis. NetworkAnalyzer tool was used to calculate the topological parameters of each gene in the network [28]. To identify the hub genes in the network Cytoscape-Cytohubba tool was used [29].

3. Results and discussion

Gene expression data of the kidney, liver and spleen were compared to understand the variation in organ-specific gene expressions during the infection of *C. albicans*. The statistical significance of the expression data of three datasets has been provided in **Supplementary File S1**. Based on the log2FC (between $>+1$ and $-1<$) and the p-value (<0.05) the differentially expressed genes were filtered. We filtered the top 100 differentially expressed genes based on the -log10 (P-value) **(Supplementary File S2)**. The 100 genes were subsequently used to construct and analyse the gene interaction network. The differentially expressed genes (up-regulated and down-regulated) for each dataset from three comparisons were further used for the FOA analysis.

3.1. Comparison of differential gene expressions in liver vs spleen

Among the 100 differently expressed genes during the comparison of liver vs spleen, 35 genes have displayed significant up-regulation, and 65 genes have shown significant down-regulation. The top 10 differentially expressed genes for both up-regulated and down-regulated genes are provided in Table 1. We observed that the innate immune factors are rapidly elevated in the liver during the fungal reaction, suggesting probable phagocytosis, which may assist in explaining the organ's notable absence of filamentation. The diverse microenvironment most likely drives the varied expression of the cell wall and cell surface modifying enzymes in the different organs. This, in turn, may cause structural changes that impact interaction with immune cells, thereby contributing to the unique course of infections in the liver.

The top five up-regulated genes include *FCMR, COCH, CD79B,*

Table 1
List of top 10 up- and down-regulated differentially expressed genes in Liver when compared with Spleen.

Gene Name	Log (FC)	-log10(P-value)	Protein
Top 10 up-regulated genes			
FCMR	6.189	12.641	Fas apoptotic inhibitory molecule 3
COCH	5.629	12.31	Cochlin
CD79B	5.3	11.658	B-cell antigen receptor complex-associated protein beta chain
SATB1	5.22	12.593	DNA-binding protein SATB1
POU2AF1	5.008	11.375	POU domain class 2-associating factor 1
FCRLA	4.943	11.934	Fc receptor-like A
MFGE8	4.571	13.644	Lactadherin
NAPSA	4.461	11.268	Napsin-A
FCRLA	4.43	12.167	Fc receptor-like A
CCR6	4.3	11.737	C–C chemokine receptor type 6
Top 10 down-regulated genes			
SLC22A1	−6.667	11.746	Solute carrier family 22 member 1
ACAA1B	−6.424	12.467	3-ketoacyl-CoA thiolase B, peroxisomal
GJB2	−6.252	11.34	Gap junction beta-2 protein
CDO1	−6.226	12.71	Cysteine dioxy genase type 1
UGT3A2	−5.948	11.24	UDP-glucuronosyltransferase 3A2
ASS1	−5.741	11.066	Argininosuccinate synthase
HGD	−5.725	11.795	Homogentisate 1,2-dioxygenase
CES1D	−5.65	11.159	Carboxy lesterase 1D
UGT1A10	−5.441	11.451	UDP-glucuronosyl transferase 1A10

SATB1 and *POU2AF1*. *FCMR* was expressed in high levels by the B-cells and was found to enhance the B-cell meditated homeostasis. It is also reported that *FCMR* is necessary for B-cell differentiation and homeostasis, auto-reactive B-cell prevention, and the immune response against the invading antigens [30]. *COCH* codes for the extracellular matrix protein Cochlin. Cochlin is mainly expressed in the inner ear and is found in very low levels in other body parts such as the Liver, Kidney, cerebellum and eye [31]. Cochlin plays an important role in the positive regulation of innate immune response against pathogenic responses [32]. The gene *CD79B* codes for an immunoglobulin-associated beta--protein (IGβ) and is required for B-lymphocyte development. A recent study has reported that spontaneous mutation in the *CD79B* gene leads to a condition where a stop codon will be generated, and the B-cell development will be intercepted [33]. *SATB1* codes for the special AT-rich sequence binding protein (SATB1) and plays a crucial role in cellular processes such as cell differentiation, proliferation and apoptosis. SATB1 protein undergoes post-translational modifications, which determine the interaction between SATB1 and other co-activators and co-repressors, which induces the regulation of gene transcription [34]. *POU2AF1* codes for the POU domain class 2-associating factor 1 expresses mainly in lymphocytes. A recent study on the human airway epithelium has reported that the *POU2AF1* gene acts as a potential regulator of the host defence genes [35]. The polymorphism of *POU2AF1* is reported to have a role in B-cell maturation and defective immune responses against antigens [36]. These results indicate that the top up-regulated genes in the liver, compared with the spleen, are essential for B-cell differentiation and maturation along with developing an immune response against the infection.

The genes *SLC22A1, ACAA1B, GJB2, CDO1* and *UGT3A2* are the top five down-regulated genes. The gene *SLC22A1* codes for a solute carrier family 22 member-1 protein, also known as human organic cation transporter-1, was observed to be down-regulated in the liver. It plays a critical role in the uptake of drugs by the target cells and is mainly found in liver cells. The down-regulation of *SLC22A1* was reported to have an impact on the uptake of the cationic drugs by the healthy hepatocytes [37]. The gene *ACAA1B* is one of the key proteins in the peroxisome proliferator-activated receptors (PPAR) signaling pathway. The PPAR proteins play an important role in the clearance of circulating lipids by regulating gene expression associated with the lipid metabolism in the liver. A recent report has shown that during dysbacteriosis, the PPAR signaling pathway is influenced by the inflammatory response and energy metabolism [38]. The gene *GJB2* codes for the Gap junction protein β-2, also known as the connexin-26, found throughout body cells. A mutation in the *GJB2* gene was reported to have a critical role in fungal infection caused by *Trichophyton rubrum* [39]. The gene *CDO1* is expressed abundantly in the adult liver and plays an important role in amino acid cysteine catabolism to sulfate. It plays a key role in maintaining the hepatic concentration of intracellular free cysteine levels. Being an important factor in maintaining cysteine levels, the *CDO1* gene was reported as the potential biomarker of various diseases [40,41]. *UGT3A2* gene is found in the thymus, kidney and testis and its abundance is less in the liver and gastrointestinal tract. The low expression of the *UGT3A2* gene in organs associated with drug metabolism was reported to have a major role in protecting the organs from external stress such as pathogenic invasion and drug metabolism [42]. Thus, we observed that the top-down-regulated genes in the liver were relevant concerning drug metabolism and maintenance of the infection.

The 100 differentially expressed genes were further used to retrieve the interacting partners using the STRING database. Out of 100 genes, the STRING database consists of interaction data for only 94 genes. A total of 505 functional interactions between the 94 differentially expressed genes (DEG) in the liver were used for the interaction network construction and analysis. We have also performed the hub gene analysis and identified the genes with the highest number of direct interactions (Fig. 2). The results signify that the nodes *SYK, CYFIP2, NCKAP1L, VAV1, ARHGAP4, APBB1IP, FGA, ABI1, WASF2, WASF1* and *CYFIP1* have more than 10 direct interactions. The five genes *CYFIP2, NCKAP1L, VAV1, ARHGAP4,* and *APBB1IP,* showed significant up-regulation in our DEG analysis. We further performed functional enrichment analysis to understand the gene ontology terms associated with the DEGs in the liver **(Supplementary file S3; Sheet 1)**.

3.2. Comparison of differential gene expressions in kidney vs liver

Among the 100 differently expressed genes during the comparison of kidney vs liver, 15 genes have displayed significant up-regulation, and 15 genes have shown significant down-regulation. The top 10 differentially expressed genes for both up-regulated and down-regulated genes are provided in Table 2. Our results indicate that both host responses and fungal adaptation during disseminated candidiasis are organ-specific at the transcriptional level. In the kidney, the late onset of innate defense mechanisms, likely due to the comparatively low number of resident immune cells and slow recruitment of other effector cells, facilitates fungal proliferation accompanied by filament formation, up-regulation of iron acquisition mechanisms, and metabolic adaptation. Failure to control fungal growth likely drives the observed exacerbated induction of pro-inflammatory responses, thereby contributing to immunopathology.

The top five up-regulated genes include *PCK1, HGD, ACY1, SLC6A13* and *COL4A*. The gene *PCK1* codes for the cytosolic isozyme of phosphoenolpyruvate carboxykinase. It is one of the first rate-limiting enzymes in the gluconeogenesis pathways and is important in maintaining blood glucose levels. *PCK1* has been implicated in several physiological and pathological processes, including glucose and lipid metabolism, diabetes, and cancer. Nonetheless, the relationship between *PCK1* and the aging process and the exact processes by which PCK1 affects aging are yet unknown. *PCK1* deficiency considerably reduced the replicative lifetime (RLS) in *Saccharomyces cerevisiae* (*S. cerevisiae)*, but *PCK1* overexpression greatly increased RLS [43,44]. The *Hgd* gene codes for the protein Homogentisate 1, 2-dioxygenase, which is important for step four of the sub-pathway of the L-phenylalanine degradation pathway that synthesises acetoacetate and fumarate from L-phenylalanine. The high concentrations of acetoacetate lead to the clinical condition known as ketoacidosis. During the infection, *C. albicans* produces high pyruvate levels, which can induce localised tissue ketosis or ketoacidosis.

Ketosis can potentially affect the defensive function of human neutrophil myeloperoxidase activity. It is considered one of the

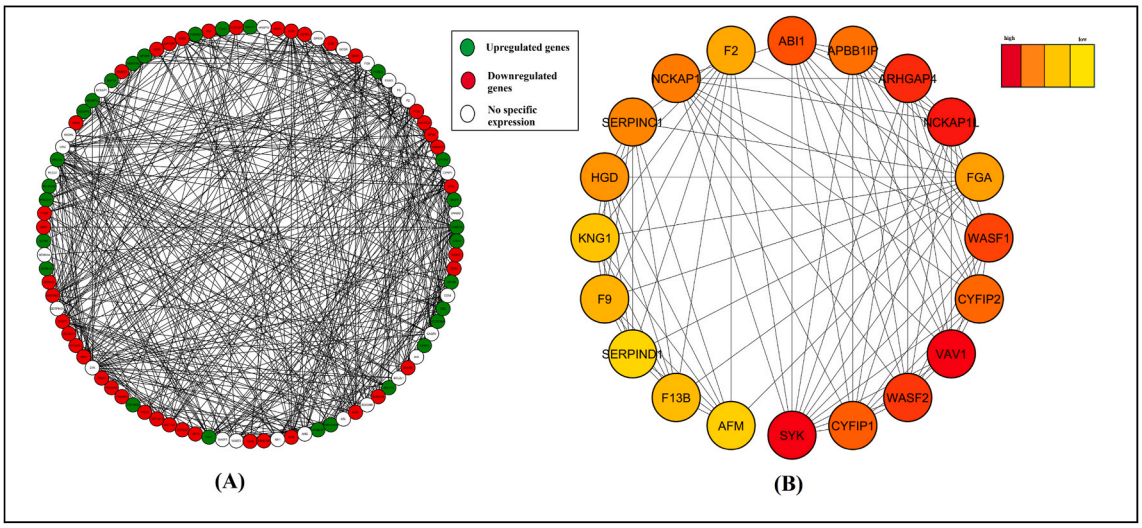

Fig. 2. Gene Interaction network analysis of differentially expressed genes during the comparison of Liver vs. Spleen. A) The DEGs with functional partner genes are used for construction interaction network. The up-regulated genes are highlighted in Green color and down-regulated genes are given in Red color. Genes with no specific expression are the functional partners of the DEGs. B) The key regulatory genes of the network (hub genes) are identified and are highlighted using the number of direct interactions.

Table 2
List of top 10 up and down-regulated differentially expressed genes in Kidney when compared with Liver.

Gene Name	Log (FC)	-log10(P-value)	Protein
Top 10 up-regulated genes			
PCK1	6.012	9.504	Phosphoenolpyruvate carboxykinase, cytosolic [GTP]
HGD	5.476	11.638	Homogentisate 1,2-dioxygenase
ACY1	4.216	12.553	Aminoacylase-1
SLC6A13	3.179	9.401	Sodium- and chloride-dependent GABA transporter 2
COL4A3	2.501	8.742	Collagen alpha-3(IV) chain
SGK1	2.228	7.667	Serine/threonine-protein kinase Sgk1
SLC16A13	1.966	9.673	Monocarboxylate transporter 13
C8A	1.815	8.285	Complement component C8 alpha chain
AUTS2	1.684	7.214	Autism susceptibility gene 2 protein
LONRF3	1.64	8.872	LON peptidase N-terminal domain and RING finger protein 3
Top 10 down-regulated genes			
CCL21A	−4.884	9.006	C–C motif chemokine 21a
PTPRC	−4.114	8.24	Receptor-type tyrosine-protein phosphatase C
GPR18	−3.897	9.663	N-arachidonyl glycine receptor
MCM7	−2.265	5.678	DNA replication licensing factor MCM7
HEATR1	−2.241	7.172	HEAT repeat-containing protein 1
ZFP318	−2.027	8.406	Zinc finger protein 318
NCAPH	−1.642	4.764	Condensin-2 complex subunit H2
AIF1	−1.578	8.613	Allograft inflammatory factor 1
H2AFY	−1.532	6.435	Core histone macro-H2A.1
AI467606	−1.519	10.874	transmembrane protein C16orf54 homolog

virulence mechanisms displayed by the virulent *Candida* spp. Ketoacidosis is a severe metabolic disorder commonly seen in diabetic patients, but it is also reported in some pathological conditions such as COVID-19 [45,46]. Upregulation of the *HGD* gene may be a host strategy to combat localised ketosis caused by *C. albicans*. The gene *Acy1* codes for mammalian amnoacyclas-1, which has a critical role in the breakdown of N-acetylated amino acids during intracellular protein catabolism. *ACY1* gene is most abundantly expressed in the kidney tubular epithelium [47]. Studies have shown that the expression of *ACY1* can influence the cellular localisation and functionality of the gene *Sphk1*.

The inhibition of the *ACY1* gene can affect the functionality of the *Sphk1* gene in the proliferation and anti-apoptosis process [48]. The gene *SLC6A13* codes for the GABA promotor 2 (GAT-2). During pathogenic infection, GABA promotes Th17 cell differentiation and interleukin-17 (IL-17). GAT-2 inhibits GABA signaling by facilitating GABA translocation from the extracellular to intracellular space. Although the significance of GAT-2 in T-cell mediated response is still unknown, studies have shown that GAT-2 loss impairs T-cell development and peripheral T-cell homeostasis. The deletion of the *SLC6A13* gene impairs the GABA uptake and GABA shunt pathway in Th17 cells [49]. The *COL4A* gene encodes Collagen Alpha-1(IV) Chain protein. These proteins are found throughout the body as part of the basement membrane, which forms a protective covering around blood vessels in the extracellular matrix. Collagen proteins are glycoproteins with multiple functions such as cellular morphogenesis, cell signaling, tissue repair and cell migration. Most human pathogens associated with the respiratory, gastrointestinal, or urogenital tracts and the central nervous system can adhere and degrade the collagen to invade the host tissue [50].

The top down-regulated genes are *Ccl21a, Ptprc, Gpr18, Mcm7, Heatr1, AI467606, H2afy, Aif1, Ncaph* and *Zfp318*. The gene *CCL21* codes for C–C Motif chemokine Ligand 21 protein. It is a known antimicrobial gene belonging to CC cytokine genes clustered on the p-arm of chromosome 9. Cytokines are a family of secreted proteins involved in immunoregulatory and inflammatory processes. During Candida infection, these chemotactic cytokines mediate the recruitment of leukocytes into the infected tissues and play a major role in the acute inflammatory response [51]. Downregulation of *CCL21* might be an important strategy employed by *C. albicans* for immune evasion. The gene *PTPRC* encodes for the protein tyrosine phosphatase receptor type C. It belongs to the protein tyrosine phosphatase family, which regulates cellular processes such as cell growth, differentiation, mitosis and oncogenic transformation. The other important functions associated with PTP proteins are T and B-cell antigen receptor signaling regulation. These proteins function either through direct interaction with the components of antigen receptor complexes or by activating Src family kinases that are required for antigen receptor signaling [52]. G protein-coupled receptor 18 is encoded by the *GPR18* gene in humans. The pathophysiological role of *GPR18* is, however, poorly understood. It's also thought to play a part in the phospholipase C-activating G-protein coupled signaling pathway's positive regulation of Rho protein signaling; and positive regulation of cytosolic calcium ion concentration. According to a study on the functional role of *GPR18*, it also acts upstream of T-cell

differentiation, negatively regulates leukocyte chemotaxis, and negatively regulates tumor necrosis factor production [53,54]. The gene MCM7 encodes for the DNA replication licensing factor MCM7. It is one of the important components of the MCM2-7 complex (MCM complex) that play an important role in DNA replication and elongation in eukaryotic cells. It is reported as the key marker protein with a high proliferation rate in various cancers [55]. A report on the role of yeast infections and cancer development has reported that *C. albicans* can promote cancer through several plausible mechanisms [55].

The gene *HEATR1* codes for the uncharacterised protein HEAT repeat contacting 1. It is predicted to have a role in ribosome biogenesis and other cellular pathways. The role of *HEATR1* in cellular functions is largely unknown. Ribosomal biogenesis perturbation leads to the activation of p53 tumor suppressor protein promoting processes such as cell cycle arrest, apoptosis and senescence. The down-regulation of HEATR1 leads to the destruction of nucleolar structure and activates the ribosomal biogenesis stress pathway RPL5/RPL11 dependent stabilisation and activation of p53. It plays an important role in p53-dependent cell cycle checkpoint activation with implications for human pathologies, including cancer [56]. Thus, it is apparent that the top-down-regulated genes in the kidney majorly interfere with signaling pathways responsible for cell proliferation and immune responses.

Out of 100 genes, the STRING database consists of interaction data for only 91 genes. A total of 400 functional interactions between the 91 DEG in the kidney were used for the interaction network construction and analysis. We also performed hub gene analysis and identified the genes with the highest number of direct interactions (Fig. 3). From the results, it is observed that the nodes MCM7, CDC6, GINS2, MCM5, NCAPH, LIG1, NCAPG, TOPBP1, ORC6, ORC2, ORC3 and DDX39A have more than 10 direct interactions. Among them, the genes *MCM7* and *NCAPH* have shown significant down-regulation in our DEG analysis. We further performed functional enrichment analysis to understand the gene ontology terms associated with the DEGs in the kidney **(Supplementary file S3; Sheet 2)**.

3.3. Comparison of differential gene expressions in spleen vs kidney

Among the 100 differently expressed genes during the comparison of spleen vs kidney, eight genes have displayed significant up-regulation, and 91 genes have shown significant down-regulation. The top 10 differentially expressed genes for both up-regulated and down-regulated genes are provided in Table 3.

The top five up-regulated genes include *GSTM6, TIMD2, SERPINC1, NR1I3* and *KNGL*. The gene *GSTM6* encodes for the glutathione S-transferase Mu 6 protein, which may play a role in disrupting microbial biofilms. Candida spp. grows in various clinical settings, such as surface-associated biofilm that can be difficult to eliminate. Biofilm communities and associated cells aggregate and generate a protective extracellular matrix, impacting the host's ability to respond to infection [57]. Glutathione helps in the disruption of biofilm in Gram-negative nosocomial pathogens and plays a critical role in the treatment against wounds that can reduce morbidity and mortality in weakened and critically ill patients. It was also reported that glutathione enhances the drug efficacy of antibiotics used in the treatment [58].

TIMD2 encodes for T-cell immunoglobulin and mucin domain-containing protein 2, plays an important role in iron homeostasis, and

Table 3
List of top 10 up- and down-regulated differentially expressed genes in Spleen when compared with Kidney.

Gene Name	LogFC	-log10(P-value)	Protein
Up-regulated genes			
GSTM6	3.588	11.121	Antithrombin-III
TIMD2	3.367	11.868	T-cell immunoglobulin and mucin domain-containing protein 2
SERPINC1	3.086	11.285	Antithrombin-III
NR1I3	2.92	11.134	Nuclear receptor subfamily 1 group I member 3
KNG1	2.869	12.107	Bradykinin
TLCD2	2.824	11.666	Kininogen-1
UGT2B35	2.446	11.414	UDP-glucuronosyltransferase
UGT1A9	2.078	11.948	UDP-glucuronosyltransferase 1A9
Top 10 down-regulated genes			
SLC34A1	−7.71	13.001	Sodium-dependent phosphate transport protein 2A
UMOD	−7.652	14.288	Uromodulin
KLK1B26	−7.495	12.003	Kallikrein 1-related peptidase b26
NAPSA	−7.282	12.768	Napsin-A
CDH16	−7.269	13.656	Cadherin-16
ANGPTL7	−7.268	12.245	Angiopoietin-related protein 7
NAPSA	−7.136	12.923	Napsin-A
FXYD2	−7.027	13.757	Sodium/potassium-transporting ATPase subunit gamma
MIOX	−6.856	12.012	Inositol oxygenase

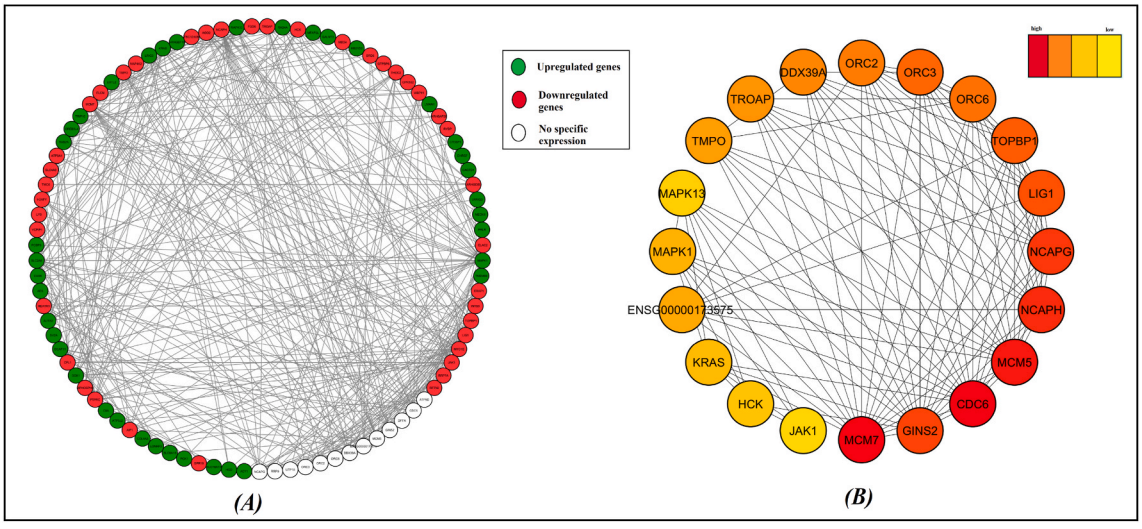

Fig. 3. Gene Interaction network analysis of differentially expressed genes during the comparison of Kidney vs. Liver. A) The DEG with functional partner genes are used for construction interaction network. The up-regulated genes are highlighted in Green color and down-regulated genes are given in Red color. Genes with no specific expression are the functional partners of the DEGs. B) The key regulatory genes of the network (hub genes) are identified and are highlighted using the number of direct interactions.

mediates iron-contacting ferritin uptake via an endocytic pathway, trafficking to endosomes and subsequently to lysosomes [59,60]. It was also reported to have a role in regulating T-cell function, enhancing T-cell activation [61]. The gene *SERPINC1* encodes for the protein antithrombin-III and is a Serpin superfamily member that functions as a protease inhibitor. Serpin family proteins are serine protease inhibitors distributed broadly among the eukaryotic organisms. A study published in 2015 reported that once *C. albicans* invade the host, the serum constituents of the host interact with the *C. albicans* cell surface in the bloodstream. Especially, the *C. albicans* hyphae surface proteins are induced with 10% of human serum proteins involved in complement and coagulation pathways, some of them are observed to be Serpin proteins [62]. *NR1I3* codes for the protein nuclear receptor subfamily 1 group I member 3. The protein belongs to the nuclear receptor superfamily and is involved in xenobiotic and endobiotic metabolic control. Xenobiotics are chemical compounds not part of a live organism's regular metabolism.

As a defensive strategy against host reactions, some species, such as fungus, bacteria, and even plants produce xenobiotics. The human microbiome has a direct xenobiotic-metabolising capacity, but it can also impact the expression of host metabolising genes and host enzyme activity [63,64]. The gene *kng1* encodes for the protein kininogen-1. Kininogen alternately splices into two products high molecular weight and low molecular weight kininogen. High molecular weight kininogen has an important role in procoagulant, pro-inflammatory and antimicrobial functions [65]. The kinins, vasoactive and pro-inflammatory peptides related to bradykinin, are frequently engaged in the human host's defence against microbial infections. Recent research has discovered that *C. albicans* may bind to the proteinaceous kinin precursor, high molecular weight kininogen, and activate the kinin-forming cascade on the cell surface [66]. Thus, we observed that genes with direct effector functions against microbial infections had been up-regulated in the spleen.

The top five down-regulated genes are *SLC34A1, UMOD, KLK1B26, NAPSA* and *CDH16*. *SLC34A1* gene codes for sodium-dependent phosphate transport protein 2 A, a type II sodium phosphate co-transporter family member. Pathogens usually receive all inorganic nutrients from the host during infection. As a result, infections produce various importers responsible for absorbing nutrients such as metals and inorganic phosphates (Pi). These nutrients, while necessary can be harmful if ingested in excess. Variations in intracellular Pi levels cause large changes in cellular metal concentration in *C. albicans* and *S. cerevisiae*. In a more immediate sense, Pi and inorganic polyphosphate interact with intracellular metals and can effectively encapsulate them, a function that has been shown to reduce heavy metal toxicity in various organisms. The gene *UMOD* encodes for uromodulin protein that functions as a receptor for cytokines (IL-1, IL-2) and TNF binding and endocytosis [67]. It also plays a role in the facilitation of neutrophil migration across the renal epithelia. In the urine, it can help with colloid osmotic pressure, slowing the transit of positively charged electrolytes, preventing urinary tract infections, and preventing the production of supersaturated salt liquids and salt crystals [66]. The gene *KLK1B26* encodes for the protein kallikrein 1-related peptidase b26 that cleaves Met-Lys and Arg-Ser bonds in kininogen to release Lys-bradykinin. REN-2 prorenin is cleaved at a dibasic location by the prorenin-converting enzyme, resulting in mature renin. Renin is an important hormone in blood pressure control and fluid-electrolyte equilibrium. Renin-expressing cells can also be found outside the kidney, although their role remains unknown. B-1 lymphocytes that express renin may play unnoticed functions in the organism's defence against pathogens. The capacity of renin-bearing lymphocytes to control infections, which is boosted by the presence of renin, adds a new, previously unknown dimension to renin-expressing cells' defensive role, connecting endocrine regulation of circulatory homeostasis with immunological control of infections to ensure survival [68]. Downregulation of genes that have important roles in pathogen defence may aid in advancing systemic candidiasis.

The 100 genes were then used to search the STRING database for identifying the interacting partners of the DEGs. Only 93 genes out of 100 DEGs have shown interactions in the STRING database. A total of 650 functional interactions between the 93 DEGs were used for gene interaction network construction and analysis. We further performed the hub gene identification, and the genes with the maximum number of direct interactions were highlighted in Fig. 4. From the results, it is observed that 53 nodes have more than 10 direct interactions. The five genes *EGFR, EGF, UMOD, SPP1* and *PLAU* have shown significant up-regulation in our DEG analysis. The functional enrichment analysis has provided the enriched Gene Ontology terms associated with the DEGs **(Supplementary file S3; Sheet 3)**.

3.4. Functional over-representation analysis

The gene sets curated from MsigDB were used to analyse the three data sets' functionally over-represented pathways, and the top enriched pathways are given in Fig. 5. There are 186 pathways enriched in three datasets. The enriched pathways, along with the FOA scores, are provided in **Supplementary File S4.** In our results, we observed differences in immune responses in various organs, and organ-specific host-pathogen interactions are anticipated to occur and contribute to the varied course of infection in murine organs. Understanding these distinctions is critical for knowing the pathogenicity of potentially fatal systemic *C. albicans* infections. A time-course transcriptional study of liver, spleen, and kidney samples from mice infected intravenously with *C. albicans* revealed not only a delayed immune response in the kidney relative to the liver and spleen but also qualitative variations in these organs' responses. Notably, genes related to organ function were down-regulated in all organs, most likely due to organ dysfunction and over-expression of genes involved in immune responses. These alterations were temporary in the spleen and liver but grew over time in the kidney, which is consistent with the progression of fungal load.

The top five positively enriched pathways in the Kidney, when compared with the liver, are related to peroxisome, drug metabolism, cytochrome P450, oxidative phosphorylation, glycolysis, gluconeogenesis and PPAR signaling pathway, whereas the pathways associated with ribosome, natural killer cell-mediated cytotoxicity, B-cell receptor signaling pathway, primary immunodeficiency and hematopoietic cell lineage showed significant negative enrichment. in contrast, the top five enriched pathways in the liver when compared with spleen were ribosome, B-cell receptor signaling pathway, hematopoietic cell lineage, regulation of actin cytoskeleton and cell cycle, whereas the pathways of drug metabolism, cytochrome P450, PPAR signaling pathway, peroxisome, complement and coagulation cascades and primary bile acid biosynthesis are observed with negative FOA scores. In spleen, compared with kidney, the top five positively enriched pathways are complement and coagulation cascades, primary bile acid biosynthesis, drug metabolism cytochrome P450, retinol metabolism and steroid hormone biosynthesis; negatively enriched pathways are oxidative phosphorylation, cardiac muscle contraction, Parkinson's disease, TCA cycle, glycolysis and gluconeogenesis pathways.

The kidney's transcriptional alterations were characterised by late activation of pro-inflammatory pathways, which is consistent with the organ's reported delayed immune cell recruitment. The rising or persistent fungal load, which leads to continuing immunological activation, can explain some of the gradual elevations of pro-inflammatory pathways in the kidney during infection. Fungal growth is also linked to increasing kidney injury, as evidenced by the over-expression of wound-healing genes and the down-regulation of genes involved in "renal system functions," "transport processes," and "ion homeostasis" identified in our observations. In the kidney, fungal proliferation is facilitated by filament formation, up-regulation of iron acquisition mechanisms, and metabolic adaptation due to the late onset of innate defense mechanisms, which is likely due to the low number of resident immune cells and slow recruitment of additional effector cells. Failure to limit fungal

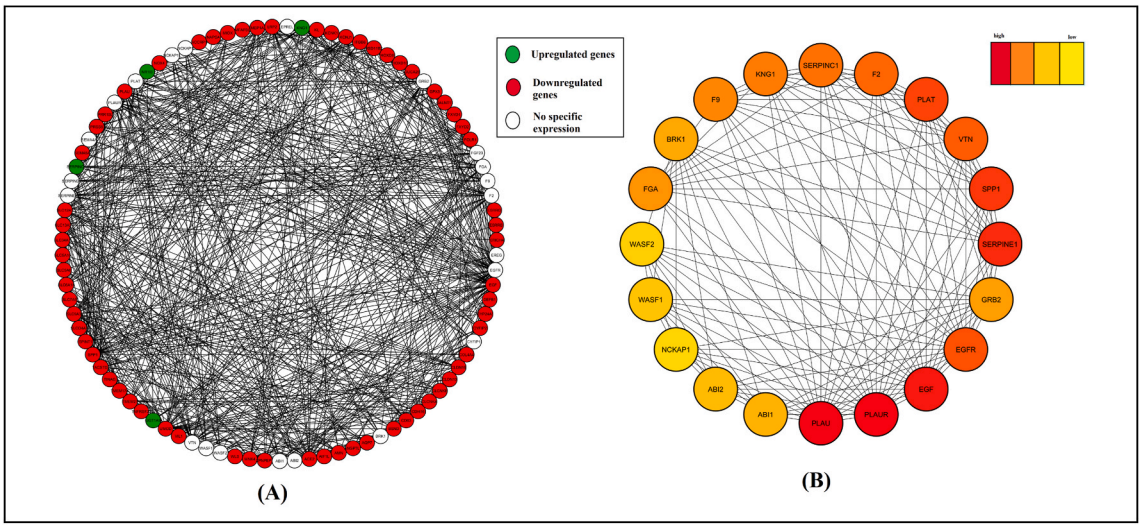

Fig. 4. Gene Interaction network analysis of differentially expressed genes during the comparison of Spleen vs. Kidney. A) The DEGs with functional partner genes are used for construction interaction network. The up-regulated genes are highlighted in Green color and down-regulated genes are given in Red color. Genes with no specific expression are the functional partners of the DEGs. B) The key regulatory genes of the network (hub genes) are identified and are highlighted using the number of direct interactions.

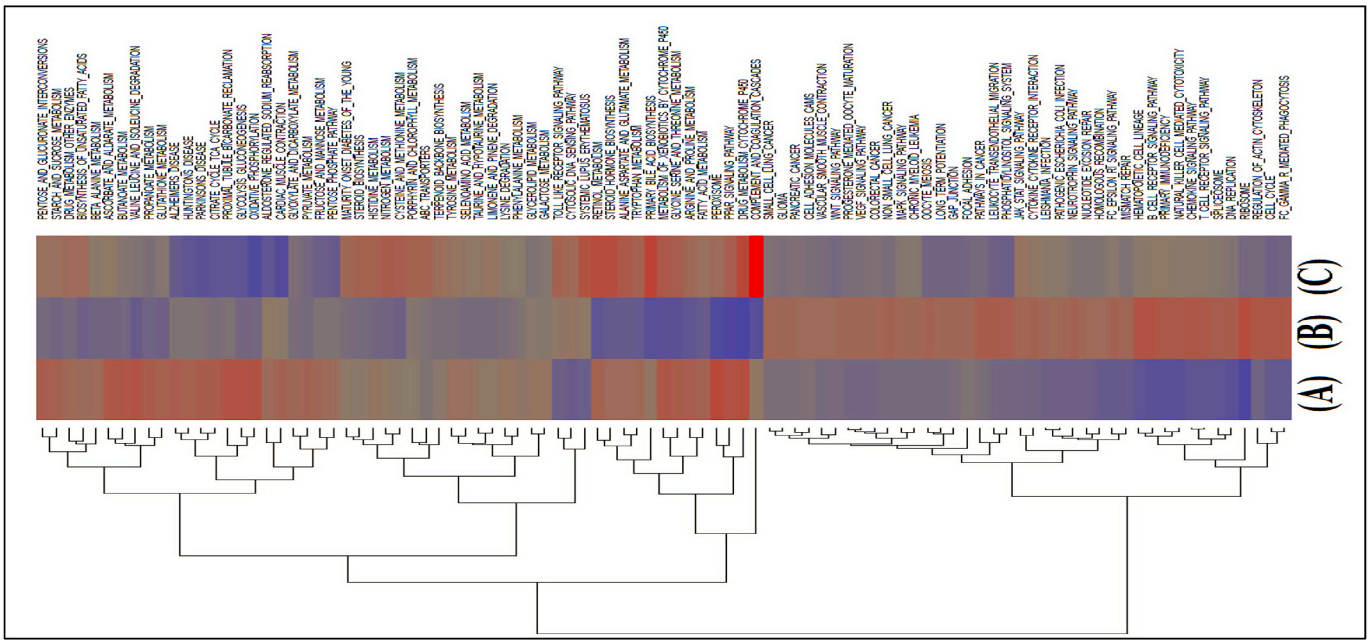

Fig. 5. The comparison of functional over representation of gene sets using significant differences in the differentially expressed genes: (A) Kidney vs. Liver (B) Liver vs. Spleen and (C) Spleen vs. Kidney respectively. We consider the gene sets with at least three genes and the FOA score between >+3 and <-3 are considered positively and negatively enriched respectively. The positively enriched pathways were given in red color and negatively expressed genes were in blue color. The pathways enriched neither positive nor negative (+3 <FOA score > −3) were given in ash color.

growth is most likely to blame for the elevated production of pro-inflammatory responses, which contributes to immune pathology [69]. TLR and NLR signaling pathways, which are part of the innate immune response, were stimulated to a greater extent in the liver. in the liver, on the other hand, innate immune factors are rapidly elevated, and the fungal reaction implies probable phagocytosis, which might explain the organ's notable absence of filamentation [70]. The moderate and temporary generation of pro-inflammatory cytokines in the spleen during systemic candidiasis is consistent with the lack of substantial activation of genes linked with pro-inflammatory responses. Systemic responses, such as the acute phase response, were activated in the liver, and genes implicated in complement activation were elevated. The sudden elevation of complement activation might point to the liver's participation in the systemic immune response during continuing candidiasis, irrespective of local pathogen management, and explain why metabolic liver function genes are expressed. *C. albicans's* transcriptional profile revealed a starving response, probably due to fast growth and hypha production [71,72].

Differentially expressed metabolic genes in the liver, on the other hand, showed catabolic activities and glucose transport. Some of *C. albicans's* organ-specific metabolic changes may be a reaction to organ-specific nutrient supply. The development of the acute phase response in the liver and the TGF-pathway and genes involved with lymphocyte activation and leukocyte proliferation in the kidney were

examples of organ-specific immune responses. The spleen's principal activities as a secondary lymphoid organ are related to leukocyte activation and proliferation. As a result, transiently decreased expression of these genes might be interpreted as decreased expression of genes with organ-specific activities. The transient nature of these changes may thus reflect spleen's successful regulation of fungal development. Genes related to liver function were also down-regulated in the liver.

4. Conclusions

The results obtained from our study provide valuable insights on the molecular-level events during Candidiasis infection in various organs such as the kidney, liver and spleen. The top differentially expressed genes (both up-regulated and down-regulated) observed in each organ will help in developing organ-specific treatment strategies for systemic candidiasis. Our results suggest the key pathways that play critical roles in different organs during systemic candidiasis. The interaction network revealed a dense network of interactions between the genes and their functional partners. The functional enrichment analysis revealed the associated genes' roles in several critical pathways in each organ. The kidneys' sensitivity to murine candidiasis has been attributed to the organ's unique immune system. Neutrophils and macrophages are more abundant in the liver and spleen than in the kidneys as reported in previous experimental studies.

Furthermore in Candidiasis, unlike the spleen and liver, there is a delay in leukocyte migration to kidneys. The early neutrophil buildup is protective, and mononuclear phagocytes can directly kill *C. albicans in vitro* and *in vivo.* Because kidney-resident macrophages and inflammatory monocytes are essential for fungal clearance, the delay in the early phagocytic response in the kidney appears significant for infection progression. Thus, during systemic *C. albicans* infection, the immune response, fungal clearance, and clinical outcomes varied greatly in various organs. The top five up-regulated genes in the liver include *FCMR, COCH, CD79B, SATB1, POU2AF1,* and they are observed to have a role in B-cell homeostasis, positive regulation of innate immune response against pathogenic responses. Whereas the genes *PCK1, HGD, ACY1, SLC6A13,* and *COL4A* have shown significant up-regulation in the kidney are observed to have up-regulation of iron acquisition mechanisms and metabolic adaptability is aided by the late initiation of innate defense mechanisms. In spleen, the genes *GSTM6, TIMD2, SERPINC1 NR1I3,* and *KNGL* were observed to have significant upregulation and are mainly associated with disruption of microbial biofilm, iron homeostasis and regulation of xenobiotic and endobiotic metabolism. Our findings will aid in better understanding the differentially expressed genes and the corresponding pathways function in each organ during *Candida* infection. The genes found to have essential roles during Candidemia can be exploited as prospective therapeutic targets and in devising new anti-*Candida* strategies.

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CRediT authorship contribution statement

Sravan Kumar Miryala: Writing – original draft, Methodology, Investigation. **Anand Anbarasu:** Writing – review & editing, Validation, Data curation, Conceptualization. **Sudha Ramaiah:** Writing – review & editing, Supervision, Software, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.micpath.2022.105677.

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