RNA-seq profiles of LPS-induced transcriptional changes in LBP-deficient rat and its possible implications for the liver dysregulation during sepsis

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Abstract

Background

Sepsis is an organ dysfunction caused by the dysregulated inflammatory response to infection. LBP binds to LPS, and modulates the inflammatory response. Rare systematic study has been reported to detect the effect of LBP gene during the LPS-induced sepsis. Herein, we explored the RNA sequencing technology to profile the transcriptomic changes in liver tissue between LBP-deficient rats and WT rats at multiple timepoints after LPS administration.

Results

We compared the serum ALT levels using the biochemistry analyzer and proceeded RNA sequencing of liver tissue to search differentially expressed genes and enriched biological processes and pathways between LBP-deficient and WT groups at 0 h, 6 h, and 24 h. In total, 168, 284, and 307 differential expressed genes (DEGs) were identified at 0 h, 6 h, and 24 h respectively, including *Lrp5*, *Cyp7a1*, *Nfkbiz*, *Sigmar1*, *Fabp7*, and *Hao1*, which are related to the inflammatory or lipid-related process. Functional enrichment analysis revealed that inflammatory response to LPS mediated by *Ifng*, *Cxcl10*, *Serpine1*, and *Lbp* was enhanced at 6 h, while lipid-related metabolism associated with *C5*, *Cyp4a1*, and *Eci1* was enriched at 24 h after LPS administration in the WT samples. The inflammatory process was not found when the LBP gene was knocked out, lipid-related metabolic process and PPAR signaling pathway mediated by Dhrs7b and Tysnd1 were significantly activated in LBP-deficient samples.

Conclusions

Our study suggested that the invading LPS may interplay with LBP to activate NF-κB signaling pathway and trigger uncontrolled inflammatory response. However, when inhibiting the activity of NF-κB, lipid-related metabolism would make bacteria removal via the effect on PPAR signaling pathway in the absence of LBP gene. Moreover, we further found the potent implications of targeting the LBP gene may as a biomarker for inflammatory conditions induced by metabolic disorders.

Background

Sepsis is a life-threatening disorder accompanied with organ dysfunction [1], which remains the leading cause of mortality in critically ill patients [2]. Despite years of intensive study and advances in the pathogenesis and supportive care, sepsis is still an enigmatic disease and a horrendous financial burden for the healthcare system [3].

LPS, a major constituent of the outer cell wall of gram-negative (GN) bacteria, is considered to be the most important activator in the pathogenesis of sepsis, of which minute amounts can initiate the

molecular mechanisms of the innate immune response [5, 6]. According to the previous study, the dysregulated inflammatory response initiated by the interaction between lipopolysaccharide-binding protein (LBP) and lipopolysaccharide (LPS) is closely related with the development of sepsis [4]. LBP is a class I acute-phase protein primarily synthesized by hepatocytes [7]. It firstly recognizes LPS released from infecting pathogens by forming a high-affinity complex. The LBP-LPS complex is transfered to cluster of differentiation 14 (CD14) and toll-like receptor (TLR) 4 to trigger the release of inflammatory cytokines [8]. Additionally, increasing evidence indicated that lipid metabolism is correlated with the host's pro-inflammatory status. The inflammatory response is promoted by both obesity and high-fat meals, which may alter the intestinal barrier via affecting the gut microbiota to translocate LPS into the bloodstream [9, 10]. LBP acts catalytically to facilitate binding of LPS to lipoproteins such as very low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein, which also represent an important mechanism in host defense to inactivate with LPS [11, 12]

To date, rare systematic study has been reported to detect the transcriptomic changes in liver tissue to investigate the role of LBP in LPS induced inflammatory response. To this end, we explored the RNA sequencing technology to compare gene expression profiling between LBP-deficient groups and WT groups at 0 h, 6 h, and 24 h after LPS infection, and identified candidate genes, biological processes and signal pathways which functionally related to sepsis, providing new clues for clinical treatment.

Results

Hepatocellular Damage in Normal and LBP-Deficient Rats after LPS-Administration

Inferior vena cava blood was collected from 3 normal and 3 LBP-deficient rats after LPS-induced at 0 h, 6 h, and 24 h respectively, then we analyzed the serum levels of ALT. In the normal groups, the serum ALT level reached a peak at 6 h after LPS administration (Fig. 1), suggesting the most severe liver injury. In contrast, less hepatocellular damage was observed in consistent with the obvious decreases in serum levels of ALT in LBP-deficient samples (Fig. 1).

Mapping and Annotation of RNA Sequencing Reads

The RNA sequencing technique integrated with bioinformatics analysis was used to characterize alteration in liver gene expression between WT and LBP-deficient samples triggered by LPS-induced systemic inflammation, and the analyze steps were sown in Fig. 2A. We obtained about 69.7 million (M) of 150 bp paired-end reads for each sample (ranging from 57.2 to 107.2 million reads) **(Additional file 1)**. After ambiguous mapping (allowing for multi-hits) via STAR-2.5.3a [13], a total of ~ 64.4 M reads for each sample were mapped against the rat reference genome Rattus_norvegicus.Rnor_6.0 (Ensembl, ftp://ftp.ensembl.org/pub/release-96/fasta/rattus_norvegicus) (Fig. 2B, **Additional file 1**). Among the mapped reads, 92.1% of these reads were mapped to exonic regions, 4.5% mapped intergenic regions, and 3.4% mapped intronic regions **(**Fig. 2B**)**.

To evaluate the segregation between WT and LBP-deficient samples during the different time after LPS administration, we conducted the neighbor-joining tree of samples based on the expression of all genes. As shown in Fig. 2C, a clear divergence between the time of LPS-treated (0 h, 6 h, and 24 h) was observed in this tree, and WT and LBP-deficient rats were also defined their respective separate clades, suggesting high fidelity of our RNA-Seq data.

Systemic Administration of Bacterial LPS Induces Global Changes in the Liver Transcriptome

To further characterize the DEGs from our RNA-Seq data, an analysis was performed to screen DEGs with *P*-value less than 0.05 and log2(fold change) higher than 1.5 using DESeq2 R package [14] (Fig. 3). In total, we identified 168, 284 and 307 significantly alternative genes respectively during the time of 0 h, 6 h, and 24 h between the normal and LBP-deficient samples. Then we clustered these DEGs via hierarchical heatmap (Fig. 3A-C) to depict the differential expression gene profile between the normal and $LBP^{-/-}$ rats. The most significantly DEGs with *P*-value < 0.001 and log2(fold change) > 1.5 were labeled in the volcano plots (Fig. 3D-F, **Additional file 2**). Among that, *Lrp5* [15], *Cyp7a1* [16], *Nfkbiz* [17], *Sigmar1* [18], *Fabp7* [19], and *Hao1* [20] (**Additional file 3**) have been reported in inflammatory response and lipid metabolic process, suggesting these genes may play an important role in modulating sepsis-induced system inflammation in WT and LBP-deficient rats after LPS injection.

Gene Annotation and Gene Ontology Analyses of DEGs

To further study of significantly overrepresented gene ontology terms involving these DEGs during 0 h, 6 h, and 24 h after LPS administration, functional annotations were performed with the DAVID Bioinformatics Resources 6.7 (https://david-d.ncifcrf.gov/) respectively [21]. Selecting from the full enrichment data sets (Fig. 4A), we found ten representative terms with the exhibition of strong differential enrichment patterns were mainly related to inflammatory response, immune response and lipid metabolic processes (Fig. 4B**)**. In further, to detect the most associated DEGs during those biological processes between healthy and LBP-deficient groups, we exhibited associated genes evolved in the representative terms and pathways (Fig. 5). Interestingly, we found that in the normal rats, LPS strongly upregulated genes involved in the processes of the inflammatory response and immunomodulation including *Ifng* [22], *Cxcl10* [23], *Serpine1* [24], and *Lbp* [25] (**Additional file 4A-D**) at 6 h after LPS injection, then proceed in lipid metabolic response including *C5* [26], *Cyp4a1* [27], and *Eci1* [28] (**Additional file 4E-G**) at 24 h (Fig. 5A). And the enriched pathways were in accordance with the results of gene ontology (Fig. 5B), which revealed that inflammatory pathways containing the toll-like receptor signaling pathways and natural killer cell-mediated cytotoxicity were enhanced in the normal groups at 6 h and lipid-related metabolism of peroxisome proliferator activated receptor (PPAR) signaling pathway was enriched at 24 h after LPS administration. Conversely, the functional enrichment of DEGs in LBP-deficient groups predominantly activated the lipid metabolic response instead of inflammatory or immunological response during the first two time points, enriching some up-regulated genes such as *Dhrs7b* [29] and *Tysnd1* [30] (**Additional file 4H-I**). And the PPAR signaling pathway was significantly over-represented at

the first two time points, which suggesting modulating inflammation and bacterial killing after LPS challenge with the deficient of the LBP gene [31]. Interestingly, the DEGs both in healthy and $LBP^{-/-}$ groups were over-represented in the processes of lipid metabolic and repeatedly enriched genes of *Eci1*, *Pnpla3* [32], *Apoa5* [33], and *Fabp1* [34] (**Additional file 4J-L**).

A Proposed Model of the Roles of NF-κB and PPAR Signaling Pathways in the WT and LBP-Deficient Rats after LPS Challenge

Based on the biological functions of above-mentioned genes and previous studies of nuclear factor kappa B (NF-κB) and PPAR signaling pathways, we presented a proposed model for the development of sepsis in rats (Fig. 6**)**. At 6 h, the upregulation of *Ifng*, *Cxcl10*, *Serpine1*, and *Lbp* in WT rats trigger NF-κB signaling pathway induced inflammation response after LPS injection. And the activation of NF-κB signaling pathway is responsible for modulating the immune reaction via enhanced biosynthesis of large quantities of pro-inflammatory molecules, including cytokines, adhesion molecules, etc., which are frequently induce sepsis and cause tissue damage when their production is dysregulated and excessive [35, 36].

At 24 h, PPAR signaling pathway was found and may function as bacterial clearance via the formation of NET by highlighted genes of *C5*, *Cyp4a1*, and *Eci1* in SD rats, and enhanced *Dhrs7b* and *Tysnd1* in the $LBP^{-/-}$ rats after LPS administration. Just as reports revealed, PPARs are a large superfamily of nuclear receptors and incorporate three isoforms (PPAR-α, PPAR-β, and PPAR-γ), which are broadly involved in the regulation of metabolism, especially associated with lipid and glucose homeostasis [37, 38]. In the process of activating pathway, PPAR-γ negatively regulates the activity of the transcription factor to inhibit the expression of pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin 12 (IL-12), and adhesion molecules which results in anti-inflammatory outcomes in the setting of sepsis induced by LPS [39].

Together, the proposed model reflects that invading LPS may interplay with LBP to activate NF-κB signaling pathway and trigger uncontrolled inflammatory response. However, when inhibiting the activity of NF-κB, lipid-related metabolism would make bacteria removal via the effect on PPAR signaling pathway in the absence of LBP gene.

Discussion

Potent Alterations of Pathways in LBP-Deficient Rats in Comparison with the Normal Rats after LPS Administration

In this study, we adopted RNA sequencing to confirm that LBP expression level was elevated after LPS treatment in *vivo* (**Additional file 4D**), following the previous research that LBP delivers LPS to CD14 and TLR4 and finally triggers a cascade of events including the translocation of NF-κB to the nucleus and the initiation of the production and release of inflammatory cytokines via the activation of TLR-4 signaling pathway [40].

PPAR-γ stimulated with correlative ligands performed anti-inflammation activity via down-regulating NF-κB actions and subsequently inhibiting the expression of inflammatory mediators, such as TNF-α, IL-12, and adhesion molecules [31]. It could be deemed that the diminished liver inflammation and injury in the normal groups at 24 h may be performed by modulating the inflammatory response through PPAR-γ signaling pathway. Additionally, combined with the enrichment results of functional annotations and pathways, we surmised that given at the time of resuscitation, LBP-deficient rats would reduce liver injury by enhancing bacterial clearance through PPAR-γ signaling pathway, as reported that the activation of PPAR-γ increased the formation of neutrophil extracellular traps (NET) containing neutrophil, histones, and granule proteins, which may potentially propose a protective mechanism of bacterial elimination in the LBP-deficient group [31].

Poor Effects of Anti-inflammatory Therapies during Sepsis

Our findings support that inflammatory response is closely associated with liver injury, which can further demonstrate that dysregulated inflammatory response exerts a crucial part in the development of sepsis [4]. However, during the last decades, the effects of many clinical trials testing anti-inflammatory approaches on patients with sepsis were rather disappointing. Gordon et al. [41] suggested that AZD9773, a polyclonal fragment antibody which has the effect of decreasing the concentration of TNF-α in circulation, was short of clinical benefit. Steven et al. [42] demonstrated that Eritoran did not improve survival among patients with sepsis shock as the antagonist of the MD2-TLR4 receptor for treatment. The administration of a high dose of corticosteroids, anti-inflammatory agents that globally depress the activity of the immune system and reduce the damage from cytokines and neutrophils, also failed to bring about improving outcomes for patients with sepsis [43]. Thus, it can be possible to conclude that the development of sepsis in humans is not merely the modulation of the inflammatory response, more comprehensive exploration concerning complicated molecular mechanisms requires undertaking for the more effective clinical treatment.

The SNPs in LBP and the Potential of LBP as a Biomarker in Clinical Application

The mechanisms mediated by LBP is a crucial player in the production of sepsis and related metabolic disorders, which makes it rational to suppose that single nucleotide polymorphisms (SNPs) within LBP gene might be determinants for interindividual susceptibility. Eckert et al. [44] previously found the rs2232613 polymorphism, leading to the substitution of proline with leucine at position 333 of LBP protein, was associated with a reduced ability to bind LPS or induce cytokines *in vitro*. The phenotype of individuals carrying the rs2232618 (Phe436Leu) had significant relevance with the higher incidence of sepsis and multiple organ dysfunction [45]. Another study also showed that susceptibility to severe sepsis was strongly correlative with a common haplotype from the 5′-flanking region of the LBP gene [46]. Additionally, a foregoing study reported the rs2232592 polymorphism, located in the intron of LBP, were significantly related to type 2 diabetes [47]. Briefly, polymorphisms within the LBP gene might have

an intensive association with sepsis and metabolic risk, which emphasize the immense potential of LBP in clinical application.

It has been performed that the up-regulation of LBP was widely observed in patients with severe infectious diseases [48] and increased circulating LBP-levels are correlative with the severity of sepsis [49], suggesting LBP may serve as a valuable biological marker for diagnosis and prognosis of patients with sepsis. However, previous reports showed LBP provided little clinical favorable information. Compared to other traditional biomarkers, such as procalcitonin and C-reactive protein, LBP has a moderate degree of diagnostic accuracy for sepsis [50]. Similarly, Sakr et al. [48] demonstrated that LBP moderately discriminated patients without infection from patients with severe sepsis.

What worth noting is that although LBP concentrations may weakly correlate with the severity and outcome of sepsis, circulating LBP was elevated when it came to obesity, metabolic syndrome (MetS), and type 2 diabetes in apparently healthy Chinese [51]. According to the investigation concerning the association between LBP levels and 6-year incident MetS, Liu et al. [52] suggested that LBP was positively correlatively with the increased 6-year risks of MetS among middle-aged and older Chinese. Besides, higher LPS or LBP concentrations could be observed than in diabetic subjects in healthy controls [53]. In short, LBP might be a promising biomarker of metabolic endotoxemia, but future prospective studies are still recommended for elucidating the potential biological mechanisms.

Conclusions

Taken together, to the best of our knowledge, we present here the first comprehensive profile of gene expression between the healthy and LBP-deficient rats after LPS-induced at multiple time points using RNA sequencing technology. With all these data surrounding the influence of sepsis evoked by acute administration of LPS, we reported a list of genes that tremendously altered in the liver tissue. Most importantly, we emphasized the modulation of uncontrolled inflammatory response triggered by the NF-κB signaling pathway and bacterial elimination via lipid-related metabolism with the effect of the PPAR signaling pathway, which may as the potential reason for the alleviated inflammatory response and the attenuated liver damage and mortality of rats. And we also exhibited the proposal model to explain the genetic mechanisms in $LBP^{-/-}$ rats after LPS challenge, which may have more biological and clinical implications. However, further and ongoing in vivo studies are still required to confirm the proposed model and the candidate genes to ultimately validate the functional role of these findings.

Methods

Experimental Animals and Tissue Collection

A total of 18 male SD and $LBP^{-/-}$ rats (body weight 230 ± 20 g) were used in this study. SD rats were originally provided by Beijing Vital River Laboratory Animal Technology Co., Ltd., and $LBP^{-/-}$ rats were purchased from Nanjing Biomedical Research Institute of Nanjing University, which had the same genetic

background as SD rats. All animals were housed under standard animal care conditions and had free to access to water and rat chow ad libitum. Thick corn cob padding and nest material was used for enrichment of housing environment. Animals were acclimatized for 7 days before treatment. All procedures were carried out according to the Animal Welfare legislation of China. Animal experiments were approved by the ethics committee of Anhui Medical University. All the treatment were performed under inhalation anesthesia using vaporized isoflurane (Raymain, Shanghai, China). The anesthesia was induced in a chamber and maintained using a face mask with a 0.5L/min oxygen flow mixed with 3% isoflurane. The injection, and operation started when the rat had no more pain reflexes, e.g. no response to clamping the skin using surgical forceps.

SD rats and $LBP^{-/-}$ rats were divided into the control and treated groups respectively (n = 9 per group) and anesthetized. Rats were challenged with a sub-lethal LPS injection (2 mg/kg, intravenous injection, E. coli serotype O55:B05 type, Sigma-Aldrich, St. Louis, USA). Meloxicam (0.2 mg/kg, subcutaneous injection, targetmol,) was administered to achieve the postoperative analgesia. Penicillin was not applied considering no open wound and low possibility of infection within 24 h after LPS administration. At 0 h (n = 3), 6 h (n = 3), and 24 h (n = 3) after LPS administration, rats were sacrificed under 5% isoflurane (Raymain, Shanghai, China). Blood was taken from the inferior vena cava, and the liver tissues were collected, and used for succedent transcriptome sequencing and data analysis. Subsequently, all the rats were euthanatized with 5% isoflurane (Raymain, Shanghai, China).

Phenotypic values were presented as mean ± standard deviation (M ± SD). Statistical comparisons of phenotypic values between the experimental and normal groups were conducted by the Student t-test. The statistical difference was considered as significant at $P < 0.05$ and highly significant at $P < 0.01$.

Liver Enzyme

To investigate the hepatocellular injury in normal and LBP-Deficient rats after LPS-induced, we took venous blood from the cavity and measured the levels of serum alanine transaminase (ALT) using an Automated Chemical Analyzer (Bayer Advia 1650; Leverkusen, Germany).

RNA Extraction and Sequencing

Total RNA was extracted from 100 mg of adipose tissue from three LBP-deficient experimental individuals and three normal individuals using the RiboPure kit (Ambion, Austin, USA) according to the manufacturer's protocol. The RNA integrity was assessed by an Agilent Bioanalyser 2100 and RNA Nano 6000 Lab chip kit (Agilent Technologies, USA). Sequencing libraries were generated using the NEBNext UltraTM Directional RNA Library Prep Kit (Illumina, USA) following the manufacturer’s recommendations, and index codes were added to attribute sequences to each sample. Then the paired-end sequencing of the libraries was constructed on a Hi-Seq 4000 platform (Illumina, USA) via Novogene (Novogene, USA). The resultant data will be deposited at NCBI Sequence Read Archive (SRA) database upon acceptance.

Mapping, Assembling, and Annotation of Sequence Reads

First, the RNA-seq reads were discriminated based on the indexing adaptors. Low-quality reads and those containing ploy-N were then removed from raw data using FastQC v0.11.7 (http://www.bioinformatics.bbsrc.ac.uk/projects/fastqc). Next, the filtered reads were mapped against the chicken reference genome Gallus_gallus-5.0 (Ensembl) using STAR-2.5.3a [13], a fast splice junction mapper for short and long RNA-seq reads to a reference genome using uncompressed suffix arrays. Parameters of STAR were set to only allow unique alignment to the reference genome. Transcripts were assembled and quantified by Stringtie-1.3.3b [54]. In addition, we explored S-MART (http://urgi.versailles.inra.fr/Tools/S-MART) to calculate the distribution of reads mapped to exons, introns and 1 kb upstream/downstream of the annotated genes. To count the number of reads that uniquely mapped to an exon, featureCounts was used with 'gene' as feature and not strand-specific [55]. Since low expressed genes are more vulnerable to measurement errors, we removed low expressed genes whose counts were lower than 2 in 90% samples. And then FPKM (expected number of Fragments Per Kilobase of transcript sequence per Millions base pairs sequenced) of each gene was calculated based on the length of the gene and read count mapped to this gene. FPKM considers the effect of sequencing depth and gene length for the read counts at the same time and is currently the most commonly used method for estimating gene expression levels from RNA-seq data [14].

Hierarchical Clustering

After quality control, we investigated sample heterogeneity between wild- and LBP-deficient liver transcriptome data by performing unsupervised hierarchical cluster analysis. Raw z-scores were firstly calculated from counts of wild- and LBP-deficient samples and then subjected to agglomerative hierarchical clustering analysis based on Ward's method and Euclidean distance. Bioinformatics analysis was performed in R version 3.5.1 and heat map was generated by pheatmap package from CRAN R-project (https://CRAN.R-project.org/package=pheatmap).

Differential Gene Expression Analyses

Differential expression analyses of the $LBP^{-/-}$ experimental and normal groups were performed using the DESeq2 R package [14]. It provides statistical routines for determining DEGs from digital gene expression data using a model based on the negative binomial distribution. The resulting *P*-values were adjusted using the Benjamini and Hochberg's approach for controlling the false discovery rate. Genes with adjusted *P*-value less than 0.05 and log2(fold change) greater than 1.5 were assigned as DEGs.

Gene Ontology and Pathway Enrichment Analyses

DAVID (https://david-d.ncifcrf.gov/) and PANTHER (http://www.pantherdb.org/) were executed to identify over-represented gene ontology (GO) terms and pathways of the DEGs. GO terms with corrected *P*-value less than 0.05 were considered significantly enriched by DEGs. KEGG is a database resource for understanding high-level functions and utilities of the biological system, such as the cell, the organism and the ecosystem, from molecular-level information, especially large-scale molecular datasets generated by genome sequencing and other high-through put experimental technologies

(http://www.genome.jp/kegg/). We used the KOBAS software (http://kobas.cbi.pku.edu.cn) to test the statistical enrichment of DEGs in KEGG pathways.

Abbreviations

LBP: lipopolysaccharide-binding protein; LPS:lipopolysaccharide; DEGs:differentially expressed genes; NF-κB:factor kappa B; PPAR:peroxisome proliferator activated receptor; GN:gram-negative; CD:cluster of differentiation; TLR:toll-like receptor; ALT:alanine transaminase; GO:gene ontology; SNPs:single nucleotide polymorphisms

Declarations

Ethics approval and consent to participate

All the tested animals are raised in compliance with the care and use guidelines of experimental animals established by the Ministry of Agriculture of China. The study was approved by the ethics committee of Anhui Medical University.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analyzed during the current study have been deposited at the GSA repository (https://bigd.big.ac.cn/gsa/browse/CRA002638).

Competing interests

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors’ contributions

HF and YZ designed the experiments and revised and edited the manuscript. ZH and ZS analyzed data and wrote the manuscript. LM, WC, FH, MZ, WX and RX made substantial contributions to the materials collection and data analysis. All authors read and approved the paper.

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Figures

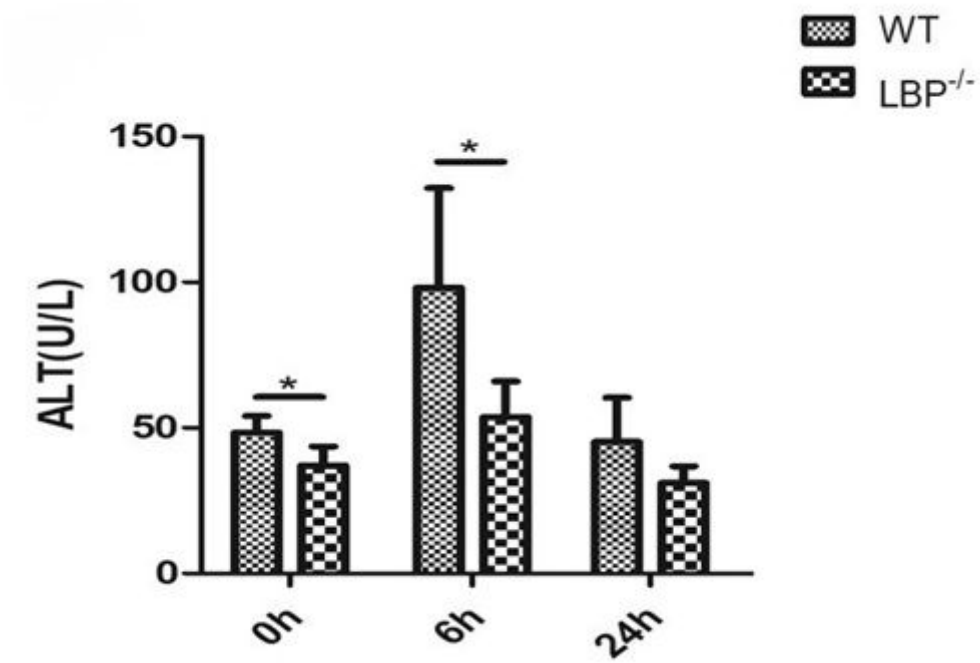

Figure 1

Levels of liver enzymes in wild type and LBP-deficient groups after LPS injection. ALT levels in serum samples collected at 0h, 6h, and 24h after LPS challenge. Serum ALT levels were analyzed as a measure of hepatocellular injury. Data are shown as means and standard deviations (n=3 per group at each time point). *p < 0.05, **p < 0.005, ***p < 0.0005, significantly different from the wild type groups.

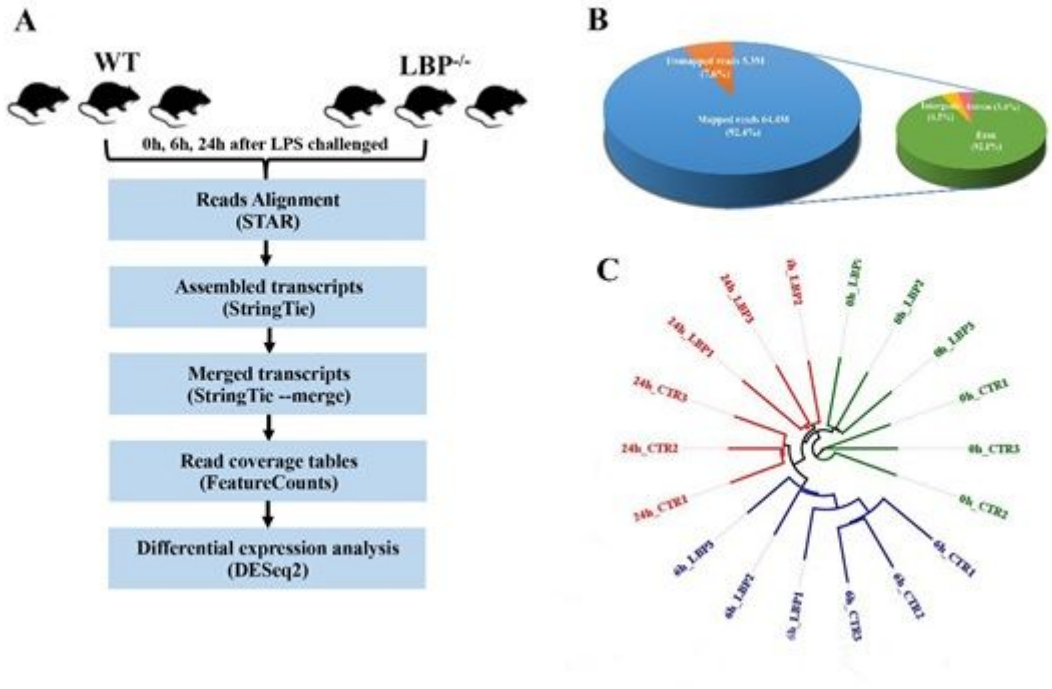

Figure 2

Summary of RNA-Seq data of normal and LBP-deficient rats. (A) RNA-Seq bioinformatic workflow showing analyze steps. (B) A pie chart of average mapping statistics involving RNA-Seq data. (C) Neighbor joining tree of normal and LBP-deficient samples that treated with LPS for the times indicated (0h, 6h, 24h). Each condition has 3 replicates. Logarithm transformed counts from RNA-Seq dataset were computed for sample correlation by Pearson's correlation. CTR: normal rat; LBP: LBP-deficient rat.

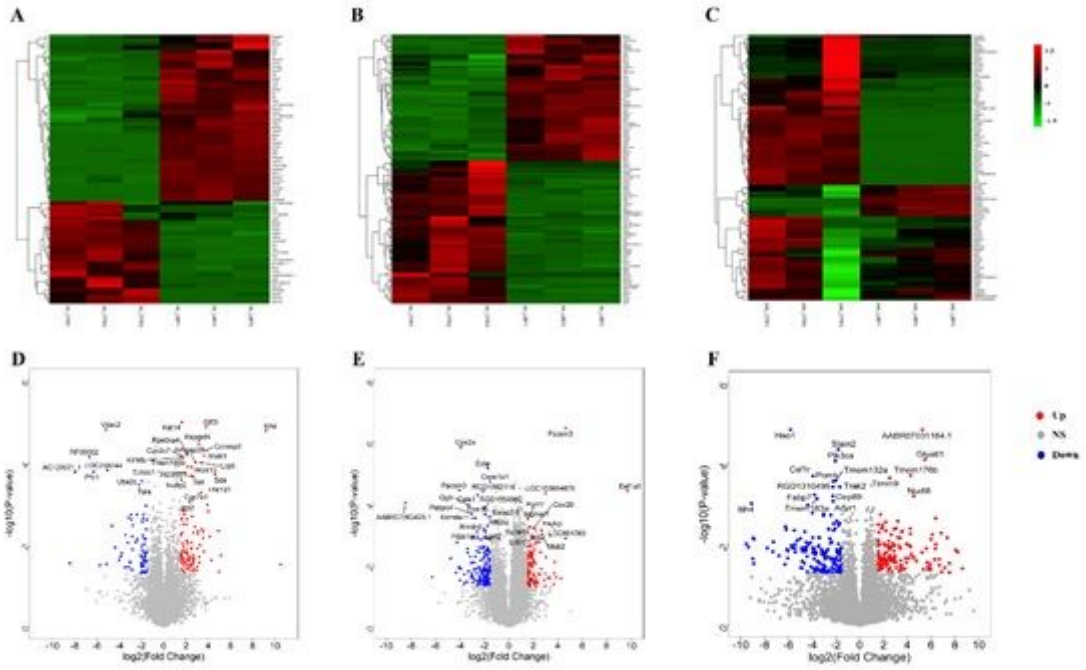

Figure 3

Distinct transcriptional signature between WT and LBP-deficient rats. (A-C) Transcription profiles of significantly differentially expressed genes (DEGs) with log2(Fold Change) larger than 1.5 at P-value < 0.01 at 0h, 6h, 24h respectively. The labeling condition and DEGs were adapted as previous panels. (D-F) The volcano plot of LPS-induced transcriptional changes between normal and LBP-deficient rats with the time of 0h, 6h, 24h respectively. Differential expression genes with log2(Fold Change) larger than 1.5 at P-value < 0.05 were colored with blue (down-regulated) and red (up-regulated).

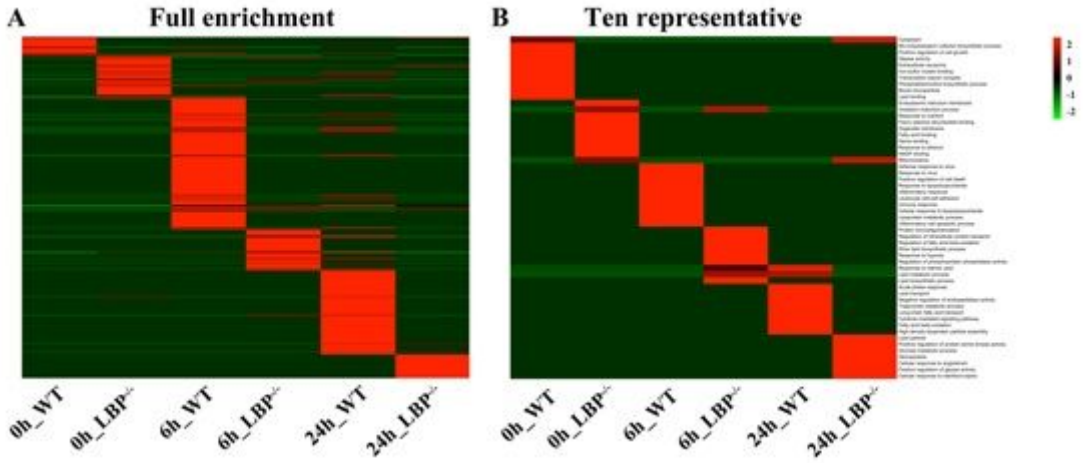

Figure 4

Association of differential genes with functional Gene Ontology (GO) terms. (A) Full enrichment data set heatmap for GO terms from WT and LBP-/- at 0h, 6h, 24h after LPS challenge. (B) Ten representative differentially enriched GO terms.

A

	Category	GO	Terms	Associated genes	*P*-value
WT	8h	GO:0006656	Phosphatidylcholine biosynthetic process	*APOA2, FABP5*	3.5E-02
		GO:0008289	Lipid binding	*APOA2, PACSIN3, FABP5*	4.2E-02
	6h	GO:0051607	Defense response to virus	*IFIT5, IFIT2, IFNAR2, OASL, ZC3HAV1, IFNG, CXCL9, CCAD8, CXCL10*	5.9E-06
		GO:0010942	Positive regulation of cell death	*CDKN1A, GZMBL2, ZC3H12A, GZMB, FAS, BCL2L11*	5.5E-05
		GO:0032496	Response to lipopolysaccharide	*SELP, TNFRSF9, JUN, SOCS1, SERPINE1, IL1RN, CXCL9, LBP, FAS, PCK1, CXCL10*	5.5E-05
		GO:0006954	Inflammatory response	*SELP, NFKBIZ, TNFRSF9, OLR1, C4B, CXCL9, ZC3H12A, FAS, CELA1, CXCL10*	4.4E-04
		GO:0007159	Leukocyte cell-cell adhesion	*SELP, OLR1, TNIP1, NT5E*	8.7E-04
		GO:0006955	Immune response	*RT1-A2, TNFRSF9, GZMBL2, CXCL9, GZMB, FAS, SECTM1B, RT1-BB, CXCL10*	9.9E-04
		GO:0071222	Cellular response to lipopolysaccharide	*SERPINE1, IFNG, ZC3H12A, LBP, ABCA1, CXCL10, ADAM9*	1.7E-03
		GO:0042157	Lipoprotein metabolic process	*OLR1, APOL9A, ABCA1*	1.8E-02
		GO:0006925	Inflammatory cell apoptotic process	*IFNG, FAS*	2.3E-02
		GO:0006953	Acute-phase response	*HSPA8P8, IL1RN, ITIH4, LBP, LOC100911545*	1.9E-04
		GO:0006641	Triglyceride metabolic process	*APOE, APOA5, CYP2E1, SLC22A5*	3.4E-03
	24h	GO:0006635	Fatty acid beta-oxidation	*ECI1, EHHADH, DECR1, CROT*	5.1E-03
		GO:0006629	Lipid metabolic process	*SLC16A1, HNF4A, APOE, IL1RN*	3.0E-02
		GO:0034380	High-density lipoprotein particle assembly	*APOE, APOA5*	5.9E-02
		GO:0006869	Lipid transport	*APOE, APOA5, LBP*	7.4E-02
LBP⁻	0h	GO:0055114	Oxidation-reduction process	*FMO5, CYP4A2, D2HGDH, HSD17B2, GPX4, CYP7A1, CYP2C7, DPYD, CYP8B1, POR*	2.8E-03
		GO:0005504	Fatty acid binding	*ACOX2, CYP4A2, ADH4*	7.8E-03
	6h	GO:0005739	Mitochondrion	*ACOX2, D2HGDH, TRMT1L, SDS, GPX4, ADH4, MRPS10, VDAC2, PTEN, GPT2, ACSF2, POR, LRP5*	4.9E-02
		GO:0055114	Oxidation-reduction process	*CYP4A2, PYCR2, PIR, CYP4F6, FASN, ADH6, NQO1, DHRS7B, DDO, CYP2A3, FDFT1*	1.2E-03
		GO:0031998	Regulation of fatty acid beta-oxidation	*TYSND1, CPT1A*	2.4E-02
		GO:0008611	Ether lipid biosynthetic process	*FASN, DHRS7B*	2.9E-02
		GO:0001666	Response to hypoxia	*CD58, RAMP2, HSP90B1, CLDN3, ANGPTL4*	4.2E-02
		GO:0043666	Regulation of phosphoprotein phosphatase activity	*HSP90B1, BCAN1*	4.7E-02
		GO:0006629	Lipid metabolic process	*APOE, ACLY, MID1IP1*	6.9E-02
		GO:0005739	Mitochondrion	*NADK2, ABCF2, NUDT9, MRPS12, MRPS10, PLGRKT, QARS, LOC100359687, COMT, GLYATL1, FIS1, CYB5A, SCCPDH, CHCHD10, ACSL1, KRAS, PARL, P2RY2, TIMM9, HEBP1, PXMP2, APEX1, MYC*	4.5E-04
		GO:0006006	Glucose metabolic process	*LOC108351137, ONECUT1, MYC, FABP5*	7.5E-03
	24h	GO:1904385	Cellular response to angiotensin	*CYB5A, MYC*	5.9E-02
		GO:0005811	Lipid particle	*SCCPDH, PNPLA5, ANXA2*	6.5E-02
		GO:0035457	Cellular response to interferon-alpha	*MNDA, MYC*	7.6E-02
		GO:0030097	Hemopoiesis	*SGPL1, CD4PIN1, CSF1R*	8.3E-02

B

	Category	ID	Pathways	Associated genes	*P*-value
WT	0h	/	/	/	/
	6h	rno05320	Autoimmune thyroid disease	*RT1-A2, RT1-CE7, GZMBL2, GZMB, FAS, RT1-BB*	8.0E-04
		rno04066	HIF-1 signaling pathway	*EGFR, CDKN1A, PFKFB3, HMOX1, SERPINE1, IFNG*	2.8E-03
		rno04060	Cytokine-cytokine receptor interaction	*IFNAR2, TNFRSF9, IFNG, CXCL9, EDAR, FAS, CXCL10*	1.2E-02
		rno04620	Toll-like receptor signaling pathway	*IFNAR2, JUN, CXCL9, LBP, CXCL10*	1.4E-02
		rno04650	Natural killer cell mediated cytotoxicity	*IFNAR2, GZMBL2, IFNG, GZMB, FAS*	1.4E-02
		rno04152	AMPK signaling pathway	*IRS2, CCND1, PFKFB3, CAB39, PCK1*	3.4E-02
		rno03320	PPAR signaling pathway	*CYP4A1, EHHADH1, APOA5, FABP1, FABP7*	5.0E-03
	24h	rno00071	Fatty acid degradation	*ECI1, CYP4A1, EHHADH, ADH6*	8.6E-03
		rno04060	Cytokine-cytokine receptor interaction	*CCL12, TNFSF10, LIFR, IL2RG, IL1A, CSF1R, ACVR1*	8.9E-03
		rno04931	Insulin resistance	*SREBF1, PTPRF, GFPT1, PIK3CA*	7.7E-02
LBP⁻	0h	rno03320	PPAR signaling pathway	*ACOX2, CYP4A2, RXRA, CYP7A1, CYP8B1*	7.6E-04
		rno00140	Steroid hormone biosynthesis	*HSD17B2, CYP7A1, CYP2C7*	7.1E-02
	6h	rno01100	Metabolic pathways	*CYP4A2, NAGS, N4T1, B3GALT4, ADH6, ACLY, FDFT1, CD38, PTCR2, UGT1A3, CYP4F6, GMPPA, FASN, LOC100912599, PAPSS1, CYP2A3*	1.6E-02
		rno00071	Fatty acid degradation	*CYP4A2, ADH8, CPT1A*	3.8E-02
		rno03320	PPAR signaling pathway	*CYP4A2, CPT1A, ANGPTL4*	9.1E-02
	24h	rno01100	Metabolic pathways	*NADK2, SGPL1, QARS, COMT, PSPH, PNPLA5, GMPS, UMPS, ACSL1, GBE1, DPM3, LOC100912599, UGT2A3, ATG10, AMDI, FUCA1, CYP2C22*	3.2E-02

Figure 5

Associated genes enriched in representative GO terms and pathways. (A) Representative GO terms and related genes involved in WT and LBP-deficient group after LPS injection. (B) Interested pathways enriched from DEGs between WT and LBP-deficient rats.

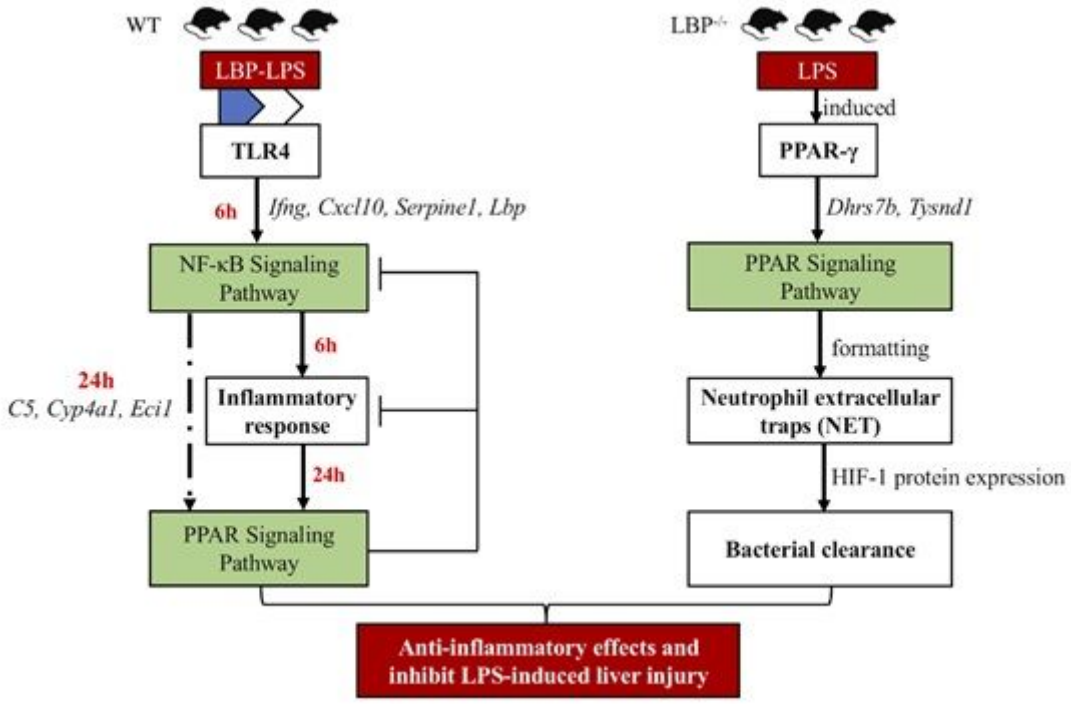

Figure 6

A proposed model of the WT and LBP-deficient rats after LPS administration. The upregulation of Ifng, Cxcl10, Serpine1, and Lbp in WT rats trigger NF-κB signaling pathway induced inflammation response at 6h after LPS injection. While PPAR signaling pathway plays a part in bacterial clearance via the formation of NET by highlighted genes of C5, Cyp4a1, and Eci1 at 24h after LPS administration in SD rats and of Dhrs7b and Tysnd1 in the LBP-/- rats.

Supplementary Files

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- NC3RsARRIVEGuidelinesChecklist2014.docx
- Additionalfiles.docx