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Exploring the Biomarkers of Clinical Diagnosis by Analyzing the Tissue Specificity and Commonality of Echinococcosis Based on The Pathogenic Modules in Echinococcosis

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Abstract

Hydatid disease caused by echinococcus multilocularis is a latent zoonotic parasitic disease. It is not easy to be discovered and diagnosed, but it can seriously threaten the health of the patient and even lead to death. Therefore, exploring its key biomarkers and its pathogenic mechanism are essential. Based on disease-related co-expression modules, we showed the relationships between pivot regulators and echinococcosis, including transcription factors (SMADC7, EP300 and TRP53, etc.) and miRNAs (miR-132-3p, miR-384-5p and miR-20b-5p, etc.). Functional enrichment analysis showed that they can regulate a series of symptoms and complications of echinococcosis by mediating functions and pathways such as antimicrobial humoral immune response mediated by antimicrobial peptide, regulation of MAP kinase activity and acute inflammatory response. In addition, we validated the reliability of results through the label-free differential protein analysis. We found that most of the disease-causing genes were tissue-specific, while the five genes APOA1, F2, SERPING1, APOH, and CLU have tissue commonality, which identified as key biomarkers for clinical diagnosis. In general, our work not only clarifies the tissue specificity and commonality of echinococcosis, but also clarifies the key biomarker for clinical diagnosis, which providing medical scientists with a solid theoretical foundation for more in-depth research.

Keywords: echinococcosis, pathogenic modules, tissue specificity and commonality, biomarkers

Introduction

The echinococcosis caused by echinococcus multilocularis (Em) infection is prevalent in animal husbandry areas around the world, becoming an invisible killer lurking in patients (Arminanzas et al, 2015), host, and then move to the appropriate tissue for development. This process can cause a series of The infection process is mainly caused by a large amount of invasive insect eggs that invade the patient's tissue barrier and resist the early inflammatory reaction and immune response of thereactions in the human body. In addition to the positive response to invasion, there are also cytokines, insulin signaling pathways and other physiological responses that favor parasite survival and development (Hemer et al, 2014 ; Ni et al, 2012). In the resistance response, activation of the immune response is the most significant body response involving macrophages, lymphocytes, B

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cells, T cells, eosinophils and chemokines, and is a member of almost the entire immune system (Gottstein et al, 2010). However, during chronic infection, the TGF-β/Smad signaling pathway is activated, thereby regulating Th17/Treg balance during E. coli infection. Its involvement in regulated immune tolerance and tissue inflammation promotes long-term survival of Em in the host (Pang et al, 2014 ; Wang et al, 2013). This is a sign that the parasite has successfully invaded the host organism.

In addition, high expression of tumor necrosis factor-α (TNF-α) and tumor suppressor gene p53 may regulate apoptosis and oxidative stress during Em infection. This may inhibit the host's immune function and lead to clinical signs of hepatomegaly, and is therefore used in strategies for designing interventions and medications (Yang et al, 2012 ; Cheng et al, 2015 ; Zhang et al, 2013). *Sako Y et al.* showed that cathepsin B-like cysteine peptidase (EmCBP1 and EmCBP2) may play a key role in protein digestion of parasite nutrition and parasite-host interactions, thereby promoting the survival of Em. And development (Sako et al, 2011). Together, these studies have shown that echinococcosis caused by Em is a complex infectious disease with multiple factors, multiple steps and multiple tissues, from immune insecticide to immunosuppression, and even creates conditions for survival and development of parasites. Therefore, attention to the different stages of the host organism during the parasite invasion process, the response of different tissues has become the key to exploring the pathogenesis of echinococcosis. To further explore the pathogenesis of Em invasion, we analyzed the tissue specificity and commonality of echinococcosis based on multifactor-driven disease-causing module theory and differential protein results from different tissues.

First, based on the differentially expressed genes of patients with echinococcosis infected with Em, we extracted 13 functional co-expression modules. Considering the functions and pathways modules involved in, 10 modules were identified as pathogenic modules, which involved in parasitic symbiosis, immune inflammation, sputum metabolism, cytokines and other functions associated with echinococcosis. Especially, modules 2, 3, 5, 6, and 9 which mainly involved in immune inflammation, sputum metabolism, vascular development and parasitic symbiosis. Then, we identified pivot regulators for these pathogenic modules, including transcription factors (TFs) and ncRNAs. Finally, we have not only validated the reliability of these results, but also indicated the tissue specificity and commonality of e echinococcosis-related genes, which is important for the classification of echinococcosis, and tissue commonality provides us with key biomarks for clinical diagnosis. Overall, this study not only revealed the pathogenesis of echinococcosis caused by Em infection, but also identified the molecular typing and biomarks of echinococcosis. This not only provides a number of candidate molecules for biologists to perform validation analysis, but also provides theoretical guidance for clinicians to perform accurate diagnosis and treatment.

Results

Differential expression analysis and exploring co-expression modules

In order to further explore the pathogenesis of echinococcosis, we performed differential expression analysis on the expression profiles of echinococcosis patients (1, 2, 3, 6 months of infection) and normal subjects. The results of functional enrichment (Figure 1) showed that 807

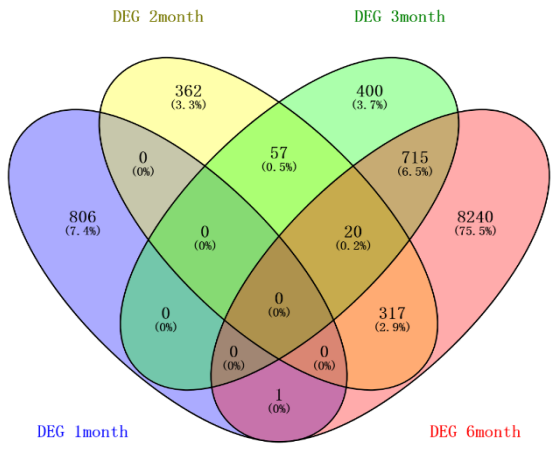

Figure 1. **Comparison of differentially expressed genes in patients with echinococcosis infection at 1, 2, 3, and 6 months**

differentially expressed (DE) genes were predominantly immune responses in the first month of infection.

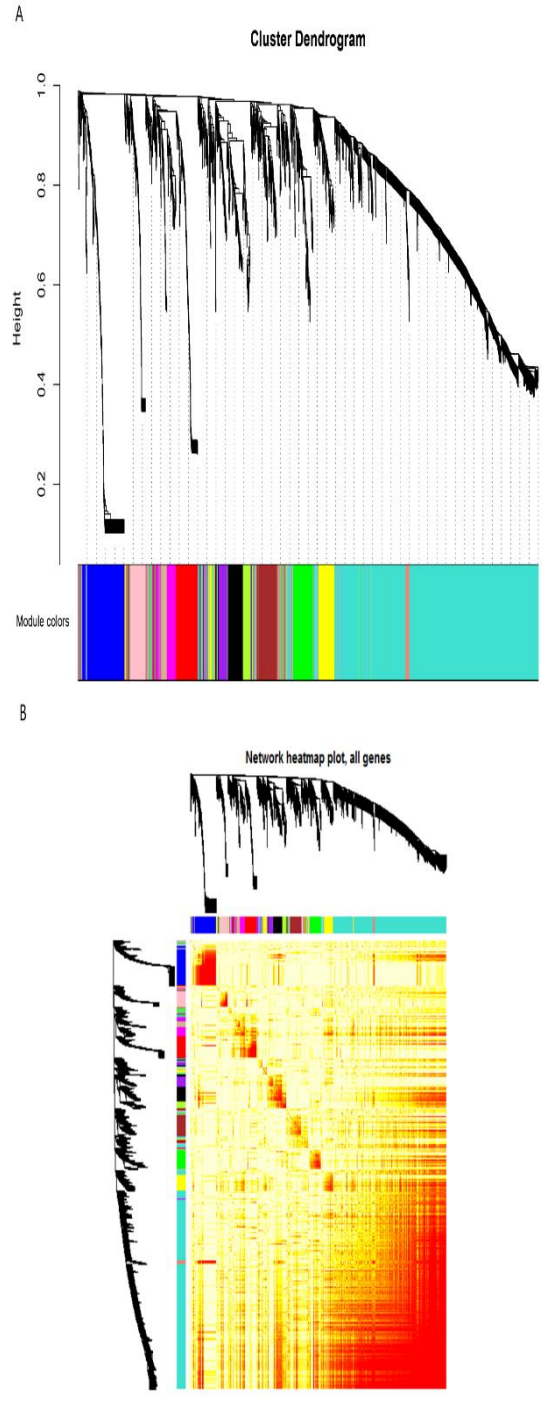

Figure 2. **14 co-expression function modules**

From the second month onwards, patients began to develop immunosuppression, which was explained in 756 differential genes. And with the infection time increases, more and more gene differentially expressed in patients, and the physiological response in the body becomes more and more disordered.

In particular, the number of genes significantly differentially expressed rapidly increased from 1192 to 9293 in the third month to the sixth month, and various symptoms and complications that lurk in the patient rapidly erupted. In addition, we performed global differential expression analysis, and identified 14 DE genes co-expression modules (Figure 2). Considering the effectiveness of modules, 13 modules with the size < 300 were retained for further analysis.

Identification of pathogenic modules

The function of the gene and the pathways involved are important pathways for regulating biochemical reactions and disease manifestations. In order to reveal the mechanism of function of the functional module, we perform functional and pathways enrichment analysis on 13 core modules. The results (Figure 3) showed that 10 modules were significantly involved in echinococcosis-related functions and signaling pathways and were identified as core modules (Figure 4). Module 1 participated in antimicrobial humoral immune response mediated by antimicrobial peptide and other biological processes related to antibacterial immunity. Module 2 participated in blood circulation, sputum metabolism, immune inflammation-related functions and pathways such as vascular process in circulatory system, purine ribonucleotide metabolic process, Inflammatory mediator regulation of TRP channels, cytokine-mediated signaling pathway.

Module 3 and 5 were also involved in functions such as acute inflammatory response, positive regulation of p38 MAPK cascade, activation of immune response and modulation of growth of symbiont involved in interaction with host. In particular, module 6 and 9 were involved in various protein kinases, cytokines, blood circulation, sputum metabolism, immunity related pathways, for example regulation of ERK1 and ERK2 cascade,

cofactor metabolic process, tumor necrosis factor superfamily cytokine production, purine nucleoside monophosphate metabolic process and angiogenesis. Other modules were also involved to varying degrees in regulating the changes in a range of functions and pathways caused by parasite invading. In general, the infection of Em mediates these pathogenic modules, which in turn regulate a range of biochemical reactions, creating opportunities for survival and development of the parasite and causing serious damage to the host. Considering the overall effect of the 13 modules, we constructed a disease-related functional network (Figure 5).

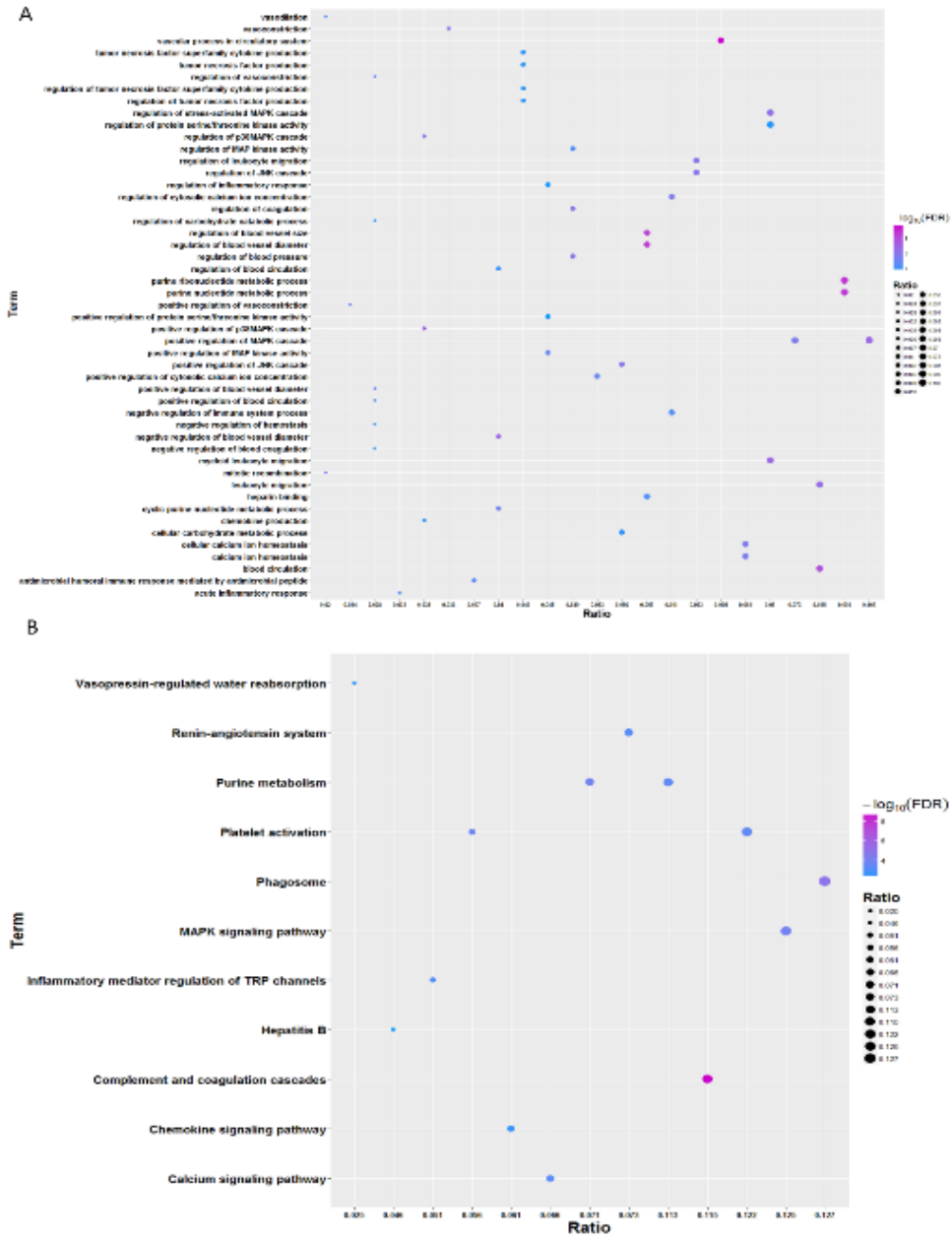

Figure 3. **Functions and path enrichment results of 13 core modules**

Identifying pivot regulators for pathogenic modules

The transcription and post-transcriptional regulation of genes has long been recognized as an important regulator of disease, and the expression of genes in disease-causing modules is also regulated by many regulators such as TFs and ncRNAs. Here, we identified 51 transcription factors and 113 ncRNAs that significantly regulated disease-causing modules based on pivotal analysis (Figure 6). For example, SMAD7, EP300, TRP53, miR-132-3p, miR-384-5p and miR-20b-5p. These ranscription factors and ncRNAs were identified as regulators of echinococcosis. In addition, some of these regulators also have regulatory effects on multiple pathogenic modules, which means they may serve as potential biomarkers or therapeutic targets for echinococcosis.

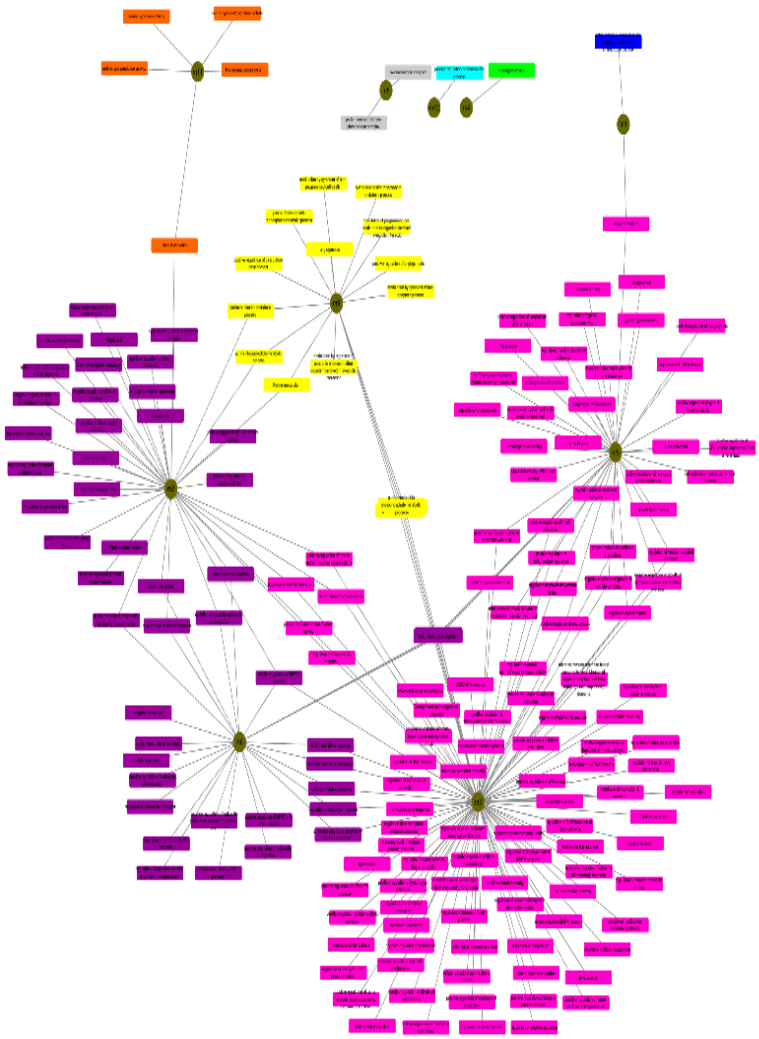

Figure 4. **Identification of pathogenic modules based on function and pathway**

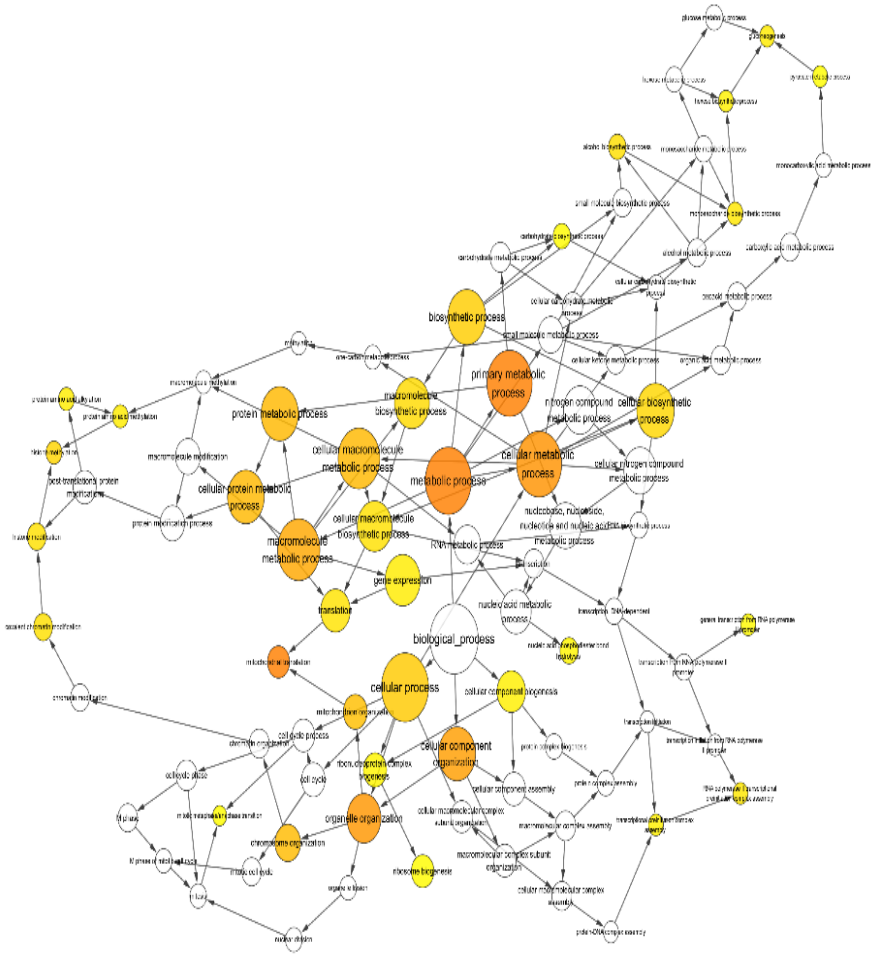

Figure 5. **Hydatidosis related function netw**

Analysis of tissue specificity and commonality of gene expression

To verify the reliability of the above analysis, we collected liver and plasma samples from 5 echinococcosis patients and plasma samples from 5 normal individuals for proteomic analysis. The results of the differential protein analysis (Figure 7) indicated that there were significantly differentially expressed genes in all modules, meaning that the disease-causing module theory is quite scientific and suitable for the exploration of human echinococcosis. Moreover, in these module genes, it was observed that there was only one gene differentially expressed in the lesion area and the marginal area, but there were 32 genes differentially expressed in the lesion area and the distal area (Figure 8). In addition, in the blood, there are 12 genes differentially expressed, which shows significant tissue specificity. It may have important guiding significance for the molecular

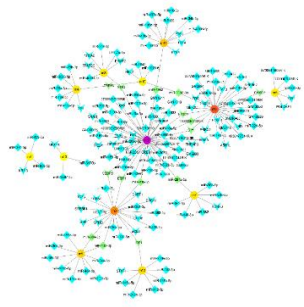

Figure 6. Module regulators prediction results for TF and ncRNA

typing of echinococcosis. Combined with proteomic analysis, we not only explored the tissue specificity of echinococcosis, but also the tissue commonality. For exampleAPOA1, F2, SERPING1, APOH and CLU were the pathogenic module genes identified both in the liver and in blood, suggesting that echinococcosis has tissue commonality in molecular biology, and so we identified them as key biomarkers for echinococcosis to guide clinicians in accurate diagnosis.

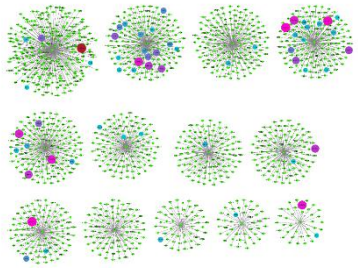

Figure 7. Differential quantitative protein mapping to pathogenic modules

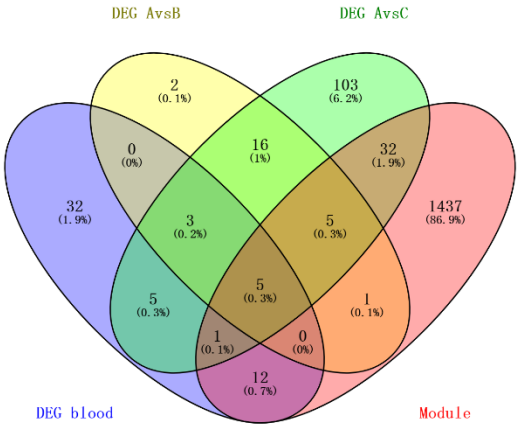

Figure 8. Comparison of differential protein and pathogenic module genes in different tissues

Discussion

At present, the echinococcosis caused by echinococcus multilocularis infection is mostly limited to one-sided research. We still know very little about its overall and in-depth pathogenesis. Therefore, in order to systematically understand the pathogenesis of echinococcosis, we conducted a series of experiments and analyses. First, mice with different infection times showed significant differences in gene expression. These differences suggested the changes in the body's physiological response: from actively resisting the invasion of pathogens to passively accepting the parasitization of Em, and finally creating conditions for its survival and development, which seriously damages the life and health of the host. Second, the disease-related genes co-expression modules involved in various functions and pathways associated with echinococcosis, leading to the body's corresponding symptoms. There were up to five modules participate in immune-related functions and pathways, for example antimicrobial humoral immune response mediated by antimicrobial peptide and acute inflammatory response, immunoglobulin mediated immune response. Studies have shown that echinococcus multilocularis infects the human body as a foreign pathogen, often causing a strong immune response and inflammatory response in patients. However, these parasites secrete a range of cytokines that inhibit these immune responses and increase their survival. Studies by *Lechner CJ et al.* have shown that echinococcus multilocularis regulates the proinflammatory immune response mediated by lL 17 cytokines, which promoting tissue invasive growth of parasites and their persistence in human hosts (Lechner et al, 2012). *Mejri et al.* showed that the metabolites of Echinococcus multilocularis metacestode contains cysteine protease that digesting eosinophil chemotactic factor which is a CC pro-inflammatory chemokine (Mejri et al, 2009). This cysteine protease can lead to the inactivation of the corresponding chemokine, and the lack of eosinophils may be an important cause of inflammatory response in patients. In addition, the mutual regulation of the TGF-β/Smad signaling pathway during chronic infection also shows that echinococcosis multilocularis can regulates the pro-inflammatory immune response, achieving host immune tolerance and tissue inflammation, which in turn promotes long-term survival of echinococcosis multilocularis in the host. There were three modules enriched in blood circulation, vascular development, sputum metabolism and

parasitic symbiosis regulation. For example, purine ribonucleotide metabolic process, positive regulation of vasculature development and modulation by symbiont of host apoptotic process. It is well known that echinococcus multilocularis are mainly transferred to various organs of the body through blood circulation and infiltration and diffusion, which is related to adhesion molecules (Paul et al, 2004). On the other hand, parasites may promote various metabolisms of the host, especially sputum metabolism and metabolism of carbohydrates to obtain nutrients and promote their growth and development (Suchail et al, 1998 ; Kepron and Novak,2002; McManus and Smyth, 1982). Then, we identified transcription factors and ncRNAs that significantly regulated the disease-related genes co-expression modules. For example, miR-132-3p is thought to be involved in inflammation and cell migration and invasion, which may be an important explanation for the inflammatory response and parasitic adhesion of echinococcus multilocularis infection (Marques-Rocha et al, 2016; Kim et al, 2017). SMAD7 is thought to be involved in the interaction of TGF-β and Smad signaling pathways in chronic infection processes, thereby regulating immune tolerance and tissue inflammation, promoting long-term survival of Em in the host and liver fibrosis of the host (Hosseini-Esfahani et al, 2016). These key regulators together mediate the pathogenic module, which plays an important regulatory role in the invasion and development of echinococcus multilocularis, and even in the process of causing host echinococcosis.

In addition, we performed systematic protein quantification experiments and analysis to verify the reliability of the conclusions. We found that most of the disease-causing genes are tissue-specific, while the five genes APOA1, F2, SERPING1, APOH, and CLU have tissue commonality. The five genes are differentially expressed both in the liver of the echinococcosis and in the blood of the patient, suggesting that these five genes can be used as biomarks for clinical diagnosis. APOA1 is associated with metabolism and inflammation (Digre et al, 2016; Pontarollo et al, 2017), which means that parasites can regulate host metabolism and pro-inflammatory immunity to survive. Factor II (F2) plays a role in maintaining vascular integrity and antimicrobial activity during development and postnatal life (Colobran et al, 2014). SERPING1 is thought to be associated with vascular disease (Liu et al, 2015; Firinu et al, 2013; Zhu et al, 2018), but its pathogenesis with echinococcosis remains poorly understood. Apolipoprotein H (apoH) is involved in a series of physiological reactions such as lipoprotein metabolism, coagulation and production of antiphospholipid autoantibodies (Iwaniec et al, 2017; Haight et al, 2018), which may mean that echinococcus multilocularis infection regulates the host's coagulation response and facilitates its metastasis. And infiltration. CLU is a secreted chaperone protein under stress conditions that has been shown to be associated with cell death, insulin resistance, tumor progression, and neurodegenerative diseases (Seo et al, 2018; Brehm and Spiliotis,2008). The invasion of echinococcus multilocularis may activate CLU to participate in the regulation of various physiological responses such as insulin resistance in order to achieve the purpose of adapting to the host's internal environment (Barrett et al, 2013). These key biomarks are differentially expressed in the liver and blood of patients with echinococcosis. The expression of these molecules in the blood of patients during clinical tests can be used as an important criterion for diagnosis. In summary, this study studied the pathogenesis of echinococcosis by constructing a systemic disease-causing module theory, and verified it by protein quantitative experiments. The verification experiment not only confirms the objectivity and scientificity of the module theory, but also provides important evidence for the tissue specificity and commonality of the pathogenic genes of echinococcosis. Its tissue specificity reflects the different ways and effects of echinococcus multilocularis infection on different tissues and organs, and tissue commonality provides us with important biomarks for clinical diagnosis.

Materials and Methods

Data recourse

The expression microarray dataset (GSE24376) were collected from the NCBI Gene

Expression Omnibus (GEO), referring to liver samples from 12 normal and 12 Em.Leuckart-infected mice. In addition, with the consent of the

volunteers, we collected liver and plasma samples from 5 patients and plasma samples from 5 healthy individuals. These liver samples were divided into lesion area (A), marginal region (B) and distal region (C, closing to normal liver tissue). We added 1 groups of pool samples to eliminate the differences between individuals. All samples were subjected to the same treatment and quantified using a protein-unlabeled quantification technique called Label-free.

Identification of differentially expressed genes

The expression microarray dataset downloaded from GEO was divided into 4 groups according to the infection time, and each group had 3 diseases and 3 healthy samples. The differentially expressed (DE) genes of the four groups were identified, respectively. First, background correction and normalization were performed with the backgroundCorrect function of the R language limma package. Then, the control probes and the low expression probes were filtered out by the quantile normalization of normalizeBetweenArrays function. Finally, the differentially expressed genes of the four groups were identified using the lmFit and eBayes functions of the R language limma package, with the default parameters (p value < 0.05).

Similarly, the expression microarray dataset was divided into disease group (12 disease samples) and control group (12 healthy samples) and the disease-related DE genes were identified. And In addition, protein quantitative data was also analyzed with the lmFit and eBayes functions of the limma package.

Mining co-expression module

We first extracted the interactor of echinococcosis-related DE genes in mouse from the String database (score > 900). These DE genes and their interactors were considered to be echinococcosis-related genes. Then, based on the expression data of these genes, we performed weighted gene co-expression network analysis with the R language package WGCNA. Finally, 14 co-

expression modules were identified as functional modules. Considering the effectiveness of modules, 13 modules with the size < 300 were retained for further analysis.

Pivot analysis

Pivot analysis is intended to find pivot nodes significantly regulated modules. A regulator was defined as core regulators, if the regulators interacted with at least 2 genes and the number of interactors significant enriched for each module (hypergeometric tests, P value < 0.01). NcRNA-associated interactions in mouse were exacted form RAID 2.0 database (score > 0.5), involving 2310 ncRNAs, 80343 interaction relationships. Transcription factor-target entries in mouse were exacted from the TRRUST v2 database, a total of 827 TFs and 7,057 interactions.

Functional and pathways enrichment analysis

The Go functional and the KEGG pathways enrichment analysis were performed with the R language Clusterprofile package (p value < 0.05). In addition, the functional and pathways analysis of the integrated module network was performed with the BinGO application in Cytoscape.

Conflicts of Interest: The authors declare no conflict of interest.

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