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ORIGINAL ARTICLE

The expression pattern of ACTBL2 in thymoma reveals its potential therapeutic target efficacy

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Summary

Purpose: *Thymoma is a thymic epithelial tumor characterized by the presence of epithelial cells and lymphocytes in the thymus. Although the incidence of thymoma is not high, we know very little about its treatment mechanism. Therefore, this study was intended to explore its potential targets and provide a new approach for perfect targeted therapy.*

Methods: *We identified a series of non-coding (nc) RNAs (including BCL11A, miR-3977, miR-4460 and miR-542-3p) and TF (FAM185A, MGAM2, SEC14L4, ACTBL2), and predicted transcription factors (including AHR, ATF4, CEBPA and DDIT3) that have significant regulatory effects on the module by difference analysis, co-expression analysis, enrichment analysis of thymoma gene expression profiling and using hypergeometric test to calculate the potential regulatory effects of multiple factors on the module.*

Results: *We obtained 15 modules from the thymoma dysfunction modules and found that the module genes are involved in a variety of immune-related biological functions. For example, neutrophil activation involved in immune response, neutrophil mediated immunity and response to extracellular stimulus indicate that neutrophil-mediated regulation plays an important regulatory role in the thymoma disorder module.*

Conclusion: *Overall, a dysfunction module for thymoma was identified, and significant pivotal regulators in the module were used as important components of thymoma molecular dysregulation, of which ACTBL2 could serve as a potential therapeutic target in thymoma, which provides an effective theoretical reference for subsequent researchers.*

Key words: *thymoma, core gene, therapeutic target, pivotal regulator, dysfunction module*

Introduction

Thymoma is a primary mediastinal tumor, a kind of typical cancer with non-neoplastic lymphocytes [1]. It is characterized by differentiation into thymic epithelial cells [2], and also manifests as oppressive symptoms or anterior mediastinal mass [3]. It is a rare epithelial mediastinal tumor, usually associated with a local and intrathoracic recurrence of a certain tendency [4], but it accounts for 1% of all adult malignancies. In addition to thymoma, it also includes thymic carcinoma and thymic carcinoid tumors caused by thymoma [5]. Thymoma shows great variability in histological, biological and genetic characteristics [6], which seriously affects the health of young people and continues to be a difficulty that needs to overcome [7]. Among human tumors, thymoma is known for its association with paraneoplastic autoimmune diseases such as myasthenia gravis [8]. The lack of knowledge of the syndrome is often considered a common variant immunodeficiency [9]. In addition, thymoma can also cause autoimmune neuromuscular disease [10] because thymoma is associated with a unique paraneoplastic syndrome, such as myasthenia gravis, hypogammaglobulinemia, and pure red cell aplasia. Therefore, the rarity of this tumor masks the best treatment for this disease to some extent [10-12].

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Therefore, information about its surgical outcome and possible prognostic factors is also limited [13]. Surgical removal of thymoma is a preferred treatment because it is safe and effective. Besides, it can availably reduce recurrence rate and increase survival rate [14-16]. At present, the treatment of thymoma is mainly based on multi-disciplinary anti-tumor strategy consisting of surgery, chemotherapy and radiation therapy [17]. Although the effect is very good, the side effects are large, so looking for thymoma biomarkers provides a superior strategy for targeted therapy [18,19].

Updated advances in the treatment of thymoma are usually based on the Masaoka clinical staging system. There are not many studies on the characters of molecular pathology of thymoma, but some authors have made some progress. They have found some specific biological targets for targeted therapy. Among them, the malignant degree of thymoma is related to the epithelial mesenchymal transition (EMT) mechanism that E-cadherin participated in [20]. In addition, it has been reported that PTEN is a type of tumor suppressor gene that expresses protein phosphatase activity and lipid phosphatase activity, which can inhibit the proliferation of mesenchymal cells and promote their apoptosis. Therefore, the activation or inhibition targeting tumor markers will become a new treatment mode.

Here we presented a new combination of cyber disease-related dysfunction modules and conducted a series of comprehensive analyses of thymoma-related data to explore the possibilities for the function and pathways that key factors involved in to reduce tumor invasiveness and identify that ACTBL2 are the potential target for the treatment of thymoma. The comprehensive strategy based on this dysfunction module not only helps explore the relevant situation of thymoma progression, but also provides a new idea for biologists to design further experiments.

Methods

Data resource

From gene expression profiling data of the The Cancer Genome Atlas (TCGA) database [21], the data expression profile of thymoma which was derived contained two normal samples and two primary tumor samples. The disease expression profiles of 119 samples of primary tumors were established, and a total of 1369 differential genes were obtained by differential analysis.

Co-expression analysis

To explore the synergistic expression of the disorder genes, we built a gene expression profile matrix for co-expression network analysis (WGCNA) on these genes [22]. WGCNA is a systematic biology method used to describe the pattern of gene association among different samples. It can be used not only to identify synergistic changes in gene sets with high interconnection, but also to link the relationship between gene expression behavior and sample phenotype. Therefore, we initially use the correlation coefficient weighting value, that is, taking the N-th power of the gene correlation coefficient and calculating the correlation coefficient (Pearson Coefficient) between any two genes. Since the nodes in the network are subject to scale-free networks, their characteristics are consistent with the expression relationship between genes, and the algorithm is more biologically significant than other algorithms. Then, a hierarchical clustering tree is constructed by correlation coefficients between genes, and different branches of the clustering tree represent different gene modules, that is, different colors represent different modules.

Function and pathway enrichment analysis

Function and pathway are considered as important channels for studying molecular mechanisms for we use the Cluster profile package for each functional module gene of thymoma [23] to proceed Go function ($p<0.05$) and KEGG Pathway ($p<0.05$) enrichment analysis. Moreover, we screened the functions and pathways associated with thymoma progression and mapped the bubbles for display.

Adjustment factor of function module

431937 ncRNA-mRNA interaction pairs of 5431 ncRNAs were downloaded in the RAID 2.0 database. According to Raid Pivot data, Pivot analysis was performed to find the regulatory module, and ncRNA-mRNA (protein) data with p value less than 0.01 in thymoma was screened. Finally, 207 ncRNAs were obtained involving 213 interaction pairs. Secondly, in the context of transcription factor (TF) Pivot data, pivot analysis (point of the control module) was performed with p value less than 0.01 to get 23 transcription factors and 23 target pairs.

Results

Co-expression behavior of genes associated with dysfunction of thymoma

First, in order to systematically study the mechanism of action associated with thymoma dysfunction in patient samples, we conducted extensive analytical studies due to 1369 differential genes of thymoma as well as expression matrix of their interacting genes in patient samples. Then, on the base of weighted gene co-expression network analysis (WGCNA), we observed that these genes exhibited significant group co-expression in disease samples. Therefore, by identifying the co-expression panel as a module, we obtained that there are 15 functional disorder modules in thymoma (Figure 1A,1B). Based on the functional disorder

module, the crucial genes of each module were identified, and 14 core genes including FAM185A, MGAM2, SEC14L4, and ACTBL2 were obtained. Based on the module and co-expression data, it can be found that these core genes are associated with thymoma, which represents the regulation mechanism mediating the occurrence and development of thymoma dysfunction.

Function and pathway analysis of pathogenic modules

Studying the functions and pathways that genes are involved in is an important means of identifying pathogenesis mediating. To investigate the possible dysfunction of modular gene dysfunction, we performed GO function and KEGG pathway enrichment analysis on 1369 genes of 15 modules (Figure 2). We collected a wealth of GO terms and got a total of 1889 cell composition entries, 2811 molecular functional terms, and 14510 biological processes. Based on functional analysis, we observed that relevant functional modules tend to enrich multiple disease-related functions. For example, neutrophil activation involved in immune response, neutrophil mediated immune and response to extracellular stimulus. On the other hand, 927 KEGG pathway enrichment results reflect that the functional module genes mainly joined in cAMP signaling pathway, Neuroactive

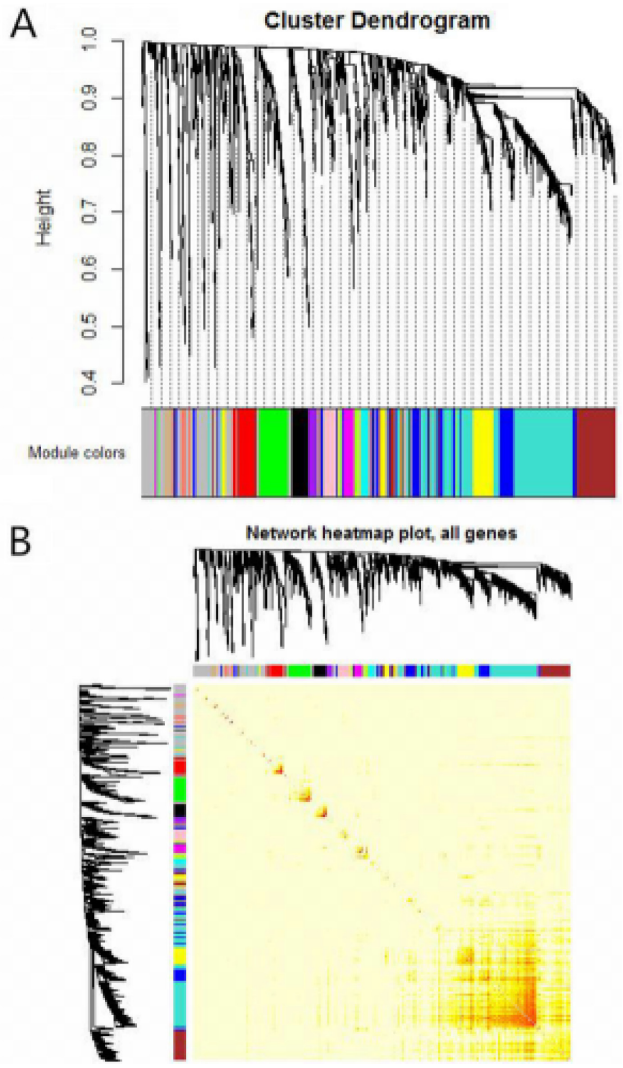

Figure 1. Clustered modules related genes in thymoma were performed according to the synergistic expression relationship. The genes related to thymoma are clustered into modules. **A:** 15 modules were clustered based on the synergistic expression relationship of differential genes, and one color represents one module. **B:** Heat map of the expression of the module gene in the sample. The related genes in thymoma visually present a phenomenon of group expression in disease samples.

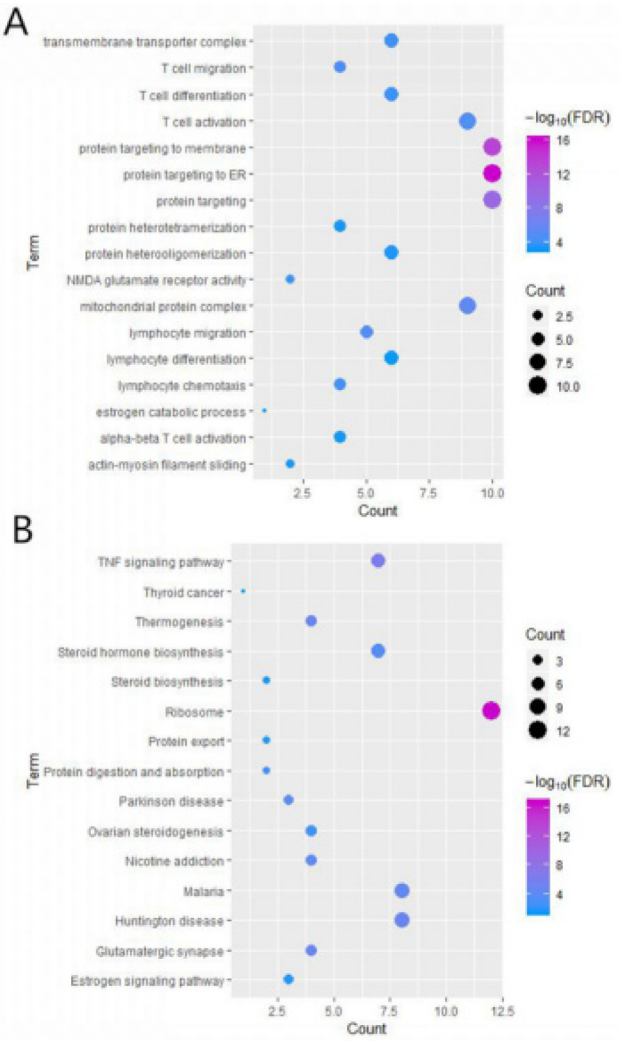

Figure 2. Function and pathway in module genes identified thymoma dysfunction modules. **A:** GO function of module genes enrichment analysis excerpt. The deeper the color, the stronger the enrichment. The larger the circle, the greater the proportion of module gene that accounts for entry gene of the GO function. **B:** Enrichment analysis excerpt of module gene KEGG pathway. The deeper the color, the stronger the enrichment. The larger the circle, the greater the proportion of the module gene accounts for the entry gene of the KEGG pathway.

ligand-receptor interaction and MicroRNAs in cancer. These signaling pathways have been shown to have to do with the development and progression of thymoma. Given that the functional and pathway results of modular gene enrichment have a close relationship with thymoma, we identified these 15 modules as dysfunction modules.

ncRNA mediating dysfunction modules

The transcription and post-transcriptional regulation of genes has long been recognized as a key factor regulating the occurrence and development of diseases, and ncRNA is considered as an important regulator of it. Scientific prediction of ncRNAs towards adjustment dysfunctional module genes is beneficial for us to delve into the regulatory mechanisms of thymoma. To this end, we performed a pivotal analysis due to the targeted relationship between ncRNA and genes to explore ncRNA regulatory molecules that cause dysfunction of the module. The predicted results showed that 207 ncRNAs had significant regulatory effects on the module, involving 213 ncRNA-Module target pairs (Figure 3). These ncRNAs refer to genetic alterations as well as to thymoma pathogenesis in varying degrees. In addition, statistical analysis of the results revealed that BCL11A, miR-3977, miR-4460, and miR-542-3p respectively targeted up to two dysfunction modules, which had significant regulatory effects on thymoma. Other ncRNAs also regulated multiple dysfunction modules to different extents, having potential effects on thymoma.

The key regulatory role of transcription factors in dysfunction modules

Many studies have shown that the dysregulation of transcription factors may lead to various diseases. Similarly, the occurrence of thymoma is also inseparable from the dysregulation of transcription factors, which also reflected on the regulation of transcription factors on dysfunction modules. Therefore, we performed pivotal analysis and prediction according to the regulatory relationship of transcription factors. We learned about a total of 23 transcription factors having significant transcriptional regulation effect on the thymoma dysfunction module, involving 23 TF-Module regulatory pairs (Figure 4). AHR, ATF4, CEBPA and DDIT3 had a significant regulatory effect on a dysfunction module from statistical analysis of these transcription factor regulatory pairs. These transcription factors may mediate dysfunction modules to regulate molecular dysregulation of thymoma and play a key role in the pathogenesis of thymo-

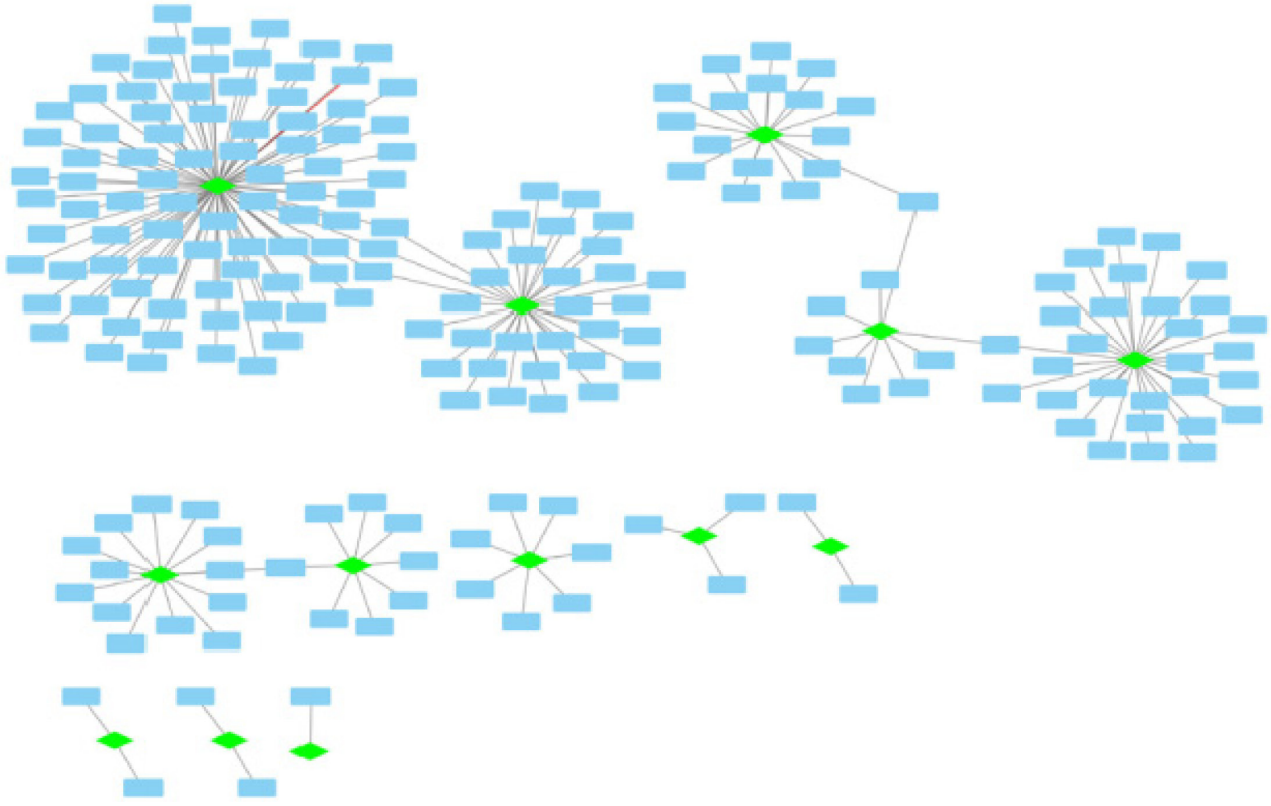

Figure 3. ncRNA Pivot regulated thymoma-related module genes. The quadrilateral represents the module and the rectangle represents the ncRNA of the regulatin module genes.

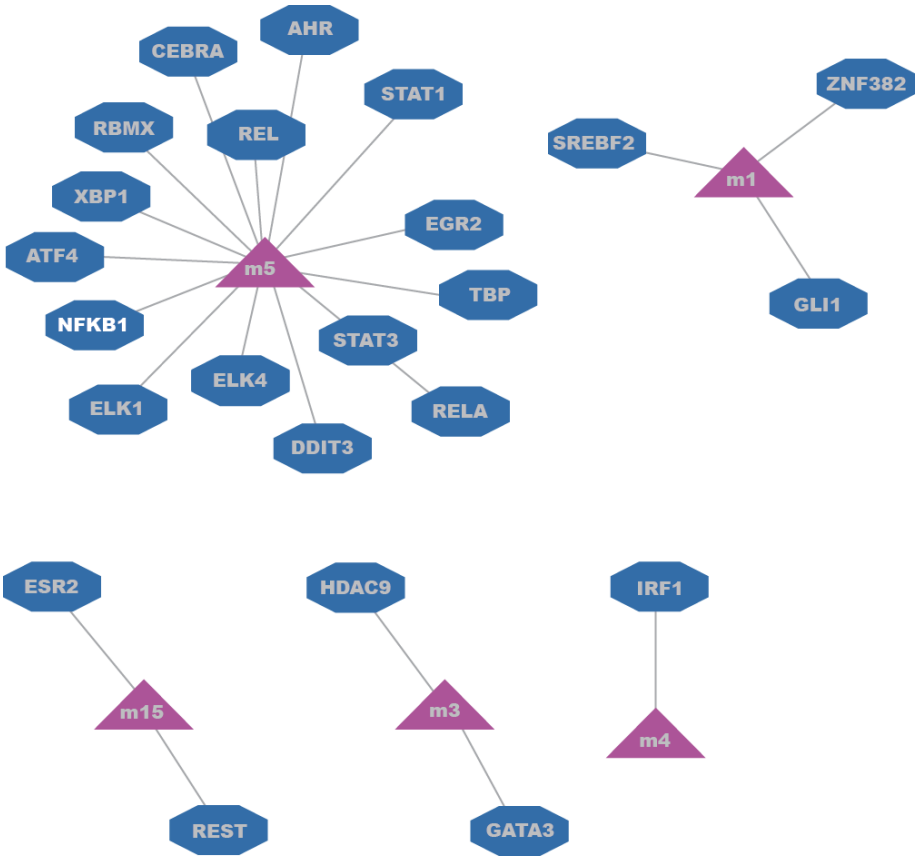

Figure 4. The regulatory role of thymoma transcription factors on dysfunction modules. The corresponding modules also have regulatory impact. Triangles represent modules, and hexagons represent the transcription factors of the modules they belong to.

ma. In general, an in-depth study of the regulation of these pivot regulators on dysfunction modules will benefit us to fully understand the underlying pathogenesis of thymoma. These pivot regulators can also be used as candidates for further experimental studies by other biologists.

Discussion

Thymoma is a rare mediastinal tumor. Mediastinal tumor in cystic thymoma is mainly characterized by cystic formation [24]. 28% to 66% of thymomas presented with chest symptoms as the first manifestation, and 40% of patients with thymoma have one or more paraneoplastic syndromes, including myasthenia gravis, pure red blood cell hypoplasia, and globulinemia [25]. The classification of thymoma is the focus aimed at raising the reproducibility of diagnosis [26,27]. According to the histological classification system of WHO thymic epithelial tumors, thymic epithelial tumors are stratified into six categories: type A, type AB, type B1, type B2, type B3 and thymic carcinoma [28]. Although thymoma is the most common cancer in the anterior mediastinum, distant metastases and local recurrences are found at various stages. So far, the causal mechanism driving thymoma progression has been unclear as yet [29]. In this regard, we have integrated a series of analytical methods to look into the molecular disorder mechanism of thymoma. Based on the co-expression network, 15 functional modules are identified by the combination with the cohesiveness of the functional cluster [30]. They regulate each other, meanwhile, through enrichment and pivotal regulator analysis, we found that dysfunction modules regulated by transcription factors and ncRNAs as pivot regulators can link to a range of functions and pathways, leading to the development and progression of thymoma. In view of the enrichment analysis results, the module genes are involved in neutrophil activation, neutrophil mediated immune reaction, and response to extracellular stimuli and other signaling pathways. Recent studies have found that epithelial tumors always have many mixed mature T cells (thymocytes), suggesting that there are some specific autoantigen expressions in thymoma, including T cell selective expression or autoimmunity [31]. At the same time, the acetylcholine receptor (AChR) subunit expressed by thymic epithelial cells (TEC) has

an epitope. Autoimmune helper T cells, including non-neoplastic immature T cells containing the CD3 (low) CD4(+)CD8(+) phenotype, can maintain the function of cortical epithelial cells [32]. This function has a pathogenic relationship with myasthenia gravis [33], which also demonstrates that thymic tumors are associated with immunodeficiency and autoimmune diseases [34], which also provides new ideas about looking for the potential targets.

In order to identify potential therapeutic targets in thymoma we firstly identified factors that regulate these dysfunction modules related to ncRNA (including BCL11A, miR-3977, miR-4460, and miR-542-3p, etc.). The study of Wang et al [35] found that the expansion of BCL11A further affects the local invasion or compression of primary mediastinal (thymus) large B-cell lymphoma (PMBCL), which proves that BCL11A is closely related to the occurrence and development of thymoma. In addition, specific miRNA expression characteristics are associated with tumor classification as predictors of lymph node metastasis [36]. Moreover, miRNAs have been testified to be potent biomarkers in malignant tumors [37]. In human cancer cells when tyrosine kinase is transformed into fibroblasts or overexpressed, miR-542-3p is significantly down-regulated, indicating that down-regulation of miR-542-3p is strongly linked with tumor progression [38].

Subsequently, we identified transcription factors that regulate these dysfunction modules AHR, ATF4, CEBPA, and DDIT3. These transcription factors affected obviously the module, and it is of great importance for studying the function and signaling pathway of the module genes participated in through transcription factors to confirm the pathogenesis of thymoma. Related studies have reported that hypoxia-inducible factor-1α (HIF-1α) and aryl hydrocarbon receptor nuclear transporter (ARNT) are two basic helical loop helix/PAS family transcription factors. During angiogenesis and tumor growth, HIF-1α binded to ARNT so that the expression of various genes such as vascular endothelial growth factor (VEGF) [39] was induced. That impact on late T cells up growth and T-substance by the activation of AHR contributes to the susceptibility of thymoma Noch 1 induction. AHR activation can alleviate the downstream effects on thymocyte up growth and disease progression, so it has important implications for the development of thymoma [40]. In addition, activation of the transcription factor ATF 4 is an important mediator of metabolism, oxidative homeostasis and cell survival. Effectively inhibiting ATF 4 serves as a valid method to inhibit tumor growth and vascularization, therefore it is also a potential therapeutic target in thymoma [41]. Recently, studies have also shown that DDIT3 engaged in TRX-1 mediated endoplasmic reticulum and mitochondrial pathways, affects brain damage of myasthenia gravis (MG) upon thymoma invasion [42].

Finally, we used the co-expression as a reference to identify the core genes of each module based on the functional disorder module, and obtained 14 core genes including FAM185A, MGAM2, SEC14L4, and ACTBL2. Among them, ACTBL2 acts as an actin-related protein (ARP) 2/3 building complex, responsible for the mechanical transport of nascent cells and the mobilization assembly of the main component actin [43]. The actin ring is essential for osteoclastic bone resorption, and the actin-related protein 2/3 complex is a key regulator of actin polymerization [44], thus illustrating the ACTBL2 has an important impact on the thymoma-induced myasthenia gravis. Secondly, the results suggest that TDP-43 may contribute to metabolism and mitochondrial function by interacting with mitochondrial proteins [45], further demonstrating that ACTBL2 is involved in neutrophil activation in thymoma and its mediating immune response, which is a critical therapeutic target in thymoma.

Therefore, based on data mining and combined with modular research methods, this study conducted a series of comprehensive and systematic analysis to identify thymoma-related molecular processes and determined ACTBL2 is a crucial therapeutic target in thymoma. This also offers a new research tool for the exploration of the pathogenesis of thymoma, and a potential molecular target for the diagnosis and treatment of this disease.

Conflict of interests

The authors declare no conflict of interests.

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