Bioinformatics Analysis of Ataxin-3's Transcriptional Regulation in Nervous System Inflammation, Metabolism, and Angiogenesis

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Abstract: Utilizing principles of bioinformatics, this study endeavors to elucidate the role of Ataxin-3 in gene expression regulation and propose novel research avenues to unravel the pathophysiological mechanisms of Spinocerebellar Ataxia Type 3 (SCA3), attributed to the functional impairment and deficiency of Ataxin-3. This study accessed the Gene Expression Omnibus (GEO) database to obtain microarray data (GSE117028) from both normal and *Atxn3* knockout Mouse embryonic fibroblasts (MEFs), aiming to identify differentially expressed genes (DEGs). Tissue expression specificity was analyzed using the BioGPS database. The DAVID 2021 analysis platform is utilized for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. A protein-protein interaction (PPI) network for DEGs was constructed with the STRING database, and PPI data visualization was achieved through the Cytoscape software, with the hub-DEGs identified using the CytoHubba plugin. Enrichment analysis of key differentially expressed proteins and transcriptional regulatory network construction were performed using DAVID 2021 and Cistrome DB databases. Our analysis identified 164 DEGs, which showed pronounced expression specificity in the nervous and immune systems. GO analysis indicated that these DEGs are extensively involved in processes such as multicellular organism development, cell adhesion, and angiogenesis. KEGG analysis highlighted the involvement of DEGs in metabolic processes, immune pathways mediated by cytokines and chemokines, and the IL-17 signaling pathway. PPI network analysis identified six hub proteins: Cxcl1, Cxcl5, Saa3, Eng, Thy1, and Lpl, playing significant roles in the immune-inflammatory pathway. Additionally, transcription factors (TFs) CEBPB, STAT5A, NR3C1, SPI1, and EP300 were found to exert regulatory functions within these pathways. The impairment of Ataxin-3's regulatory function across various signaling pathways is hypothesized to contribute to the pathogenesis of SCA3. These findings suggest that restoring Ataxin-3 function could represent a potential therapeutic strategy for SCA3.

Keywords: Ataxin-3; Inflammation; Metabolism; Angiogenesis; Transcriptional Regulation; Bioinformatics

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1 Introduction

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is recognized as the most prevalent subtype of hereditary ataxia worldwide [1]. Research indicates that the pathogenesis of SCA3 is closely associated with the expansion of CAG repeat sequences in the *ATXN3* gene, leading to the accumulation of mutated Ataxin-3 protein characterized by polyglutamine (PolyQ) chains [2]. This accumulation initiates cytotoxic mechanisms including chronic inflammation of the nervous system, disturbances in protein homeostasis, mitochondrial dysfunction, and transcriptional dysregulation [3, 4].

The Ataxin-3 protein, encoded by the *ATXN3* gene and functioning as a deubiquitinase within the ubiquitin proteasome system (UPS) [5], plays a pivotal role across a

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broad array of biological processes. Its widespread expression throughout the central nervous system and various other tissues is critical for gene transcription regulation, misfolded protein clearance, cytoskeleton integrity maintenance, cell adhesion, macrophage function, DNA repair, stress response, and skeletal muscle development [6–9]. Studies in *Atxn3* knockout mouse models have shown upregulation in genes related to inflammatory immunity and cell adhesion. Additionally, deletion of *Atxn3* in C. elegans has been linked to transcriptional abnormalities impacting genes involved in the ubiquitin proteasome pathway, cellular structure and mobility, and signal transduction, underscoring Ataxin-3's significant role in transcriptional regulation [10]. Ataxin-3's ability to bind DNA and interact with transcription regulatory factors such as CBP, P300, HDAC6, and NCoR has been documented. Transcriptomic analyses in the cerebellum of *Atxn3* transgenic mice have indicated a downregulation of TFs integral to several critical cellular signaling pathways and an upregulation of genes associated with inflammation and cell apoptosis [11].

Despite ongoing uncertainty regarding the contribution of Ataxin-3 function loss to transcriptional dysfunction in SCA3, we conducted comprehensive bioinformatics analyses of microarray data from both normal and *Atxn3* knockout Mouse embryonic fibroblasts (MEFs). Differentially expressed genes (DEGs) displayed pronounced expression specificity in the nervous and immune systems, involving key biological processes including inflammatory responses, angiogenesis, and multicellular organism development. Moreover, these DEGs are enriched in pathways linked to substance metabolism, immune-related inflammation, and synaptic signaling. Significantly, the pivotal differential proteins differentiated within the protein-protein interaction (PPI) network were related to inflammation signaling, lipid metabolism, and angiogenesis, regulated by a diverse array of TFs. These observations provide critical insights into Ataxin-3's potential transcriptional regulatory functions, particularly in inflammation, metabolism, and angiogenesis within the nervous system.

2 Materials and Methods

2.1 Microarray Data

Access the GEO database (https://www.ncbi.nlm.nih.gov/geo/) and download the gene chip: GSE117028. This dataset comprises gene expression profiles of three *Atxn3* wild-type and three *Atxn3* knockout MEFs.

2.2 Identification of DEGs

Utilizing the GEO2R online analysis tool (available at https://www.ncbi.nlm.nih.gov/geo/geo2r/), we identified DEGs within the dataset GSE117028. DEGs were determined using stringent screening criteria: |log2 (Fold Change)| > 1.5 and Benjamini- adjusted P<.01. Download all gene expression data, matrix files, and platform file GPL1261 corresponding to the microarray chip.

2.3 Tissue-specific Gene Expression Analysis

Access the BioGPS database (http://biogps.org/) to examine the expression patterns of each DEG. Highly tissue-specific DEGs are identified based on the following screening criteria: (1) Expression levels in a specific tissue exceeding 10 times the median expression level across tissues; (2) The second highest expression level being less than one-third of the highest expression level.

2.4 Functional Enrichment Analysis

We conducted GO and KEGG enrichment analyses on the DEGs using the Functional Annotation Chart component in DAVID 2021 (https://david.ncifcrf.gov/). GO analysis encompassed the functional annotation of biological processes (BP), molecular functions (MF), and cellular components (CC) mediated by the DEGs, with a stringent threshold set at a Benjamini-adjusted P<.01. KEGG analysis was used to identify the enrichment of DEGs within specific signaling pathways, with a significance threshold of P<.05 and requiring at least three enriched genes for inclusion.

2.5 Construction of PPI Network and Identification of Key Differentially Expressed Proteins

The STRING database (https://cn.string-db.org/) was employed to construct a PPI network based on functional associations. DEGs were projected into the PPI network, utilizing a threshold interaction index > 0.4 as the screening criterion, and the resulting data was downloaded in TSV format. Subsequently, Cytoscape v3.9.1 (https://cytoscape.org/) was utilized to visualize the PPI information. The Maximal Clique Centrality (MCC) algo-

rithm within the Cytohubba plugin was then employed to identify key differentially expressed proteins.

2.6 Functional Enrichment and Transcriptional Network of Key Differentially Expressed Proteins

DAVID 2021 was employed for GO and KEGG enrichment analysis of significant differentially expressed proteins, utilizing a significance threshold of P <.05. The Citrome DB database (http://cistrome.org/db/#/) was utilized to identify TFs corresponding to node genes.

2.7 Statistical Analysis and Data Visualization

Statistical analysis was conducted using the R software package, version 4.1.2. In the DEG analysis and in the GO and KEGG enrichment analysis, t-tests are employed to determine and adjust P-values. The Benjamini method adjusts these P-values, with a threshold of P <.05 considered statistically significant. The Hiplot online plotting platform (https://hiplot-academic.com/) was employed for generating visual graphs.

3 Results

3.1 Identification of DEGs Before and After *Atxn3* Knockout

Using the online analysis tool GEO2R, we identified 164 DEGs including 99 upregulated and 65 downregulated genes. A heatmap was generated (Figure 1).

3.2 The Tissue Specificity of DEGs

BioGPS revealed 71 DEGs in specific tissue or organ systems. The most tissue-specific system identified was the nervous system (42.3%, 30/71), followed by the immune system (22.5%, 16/71), reproductive system (11.3%, 8/71), and digestive system (7.0%, 5/71) (Table 1).

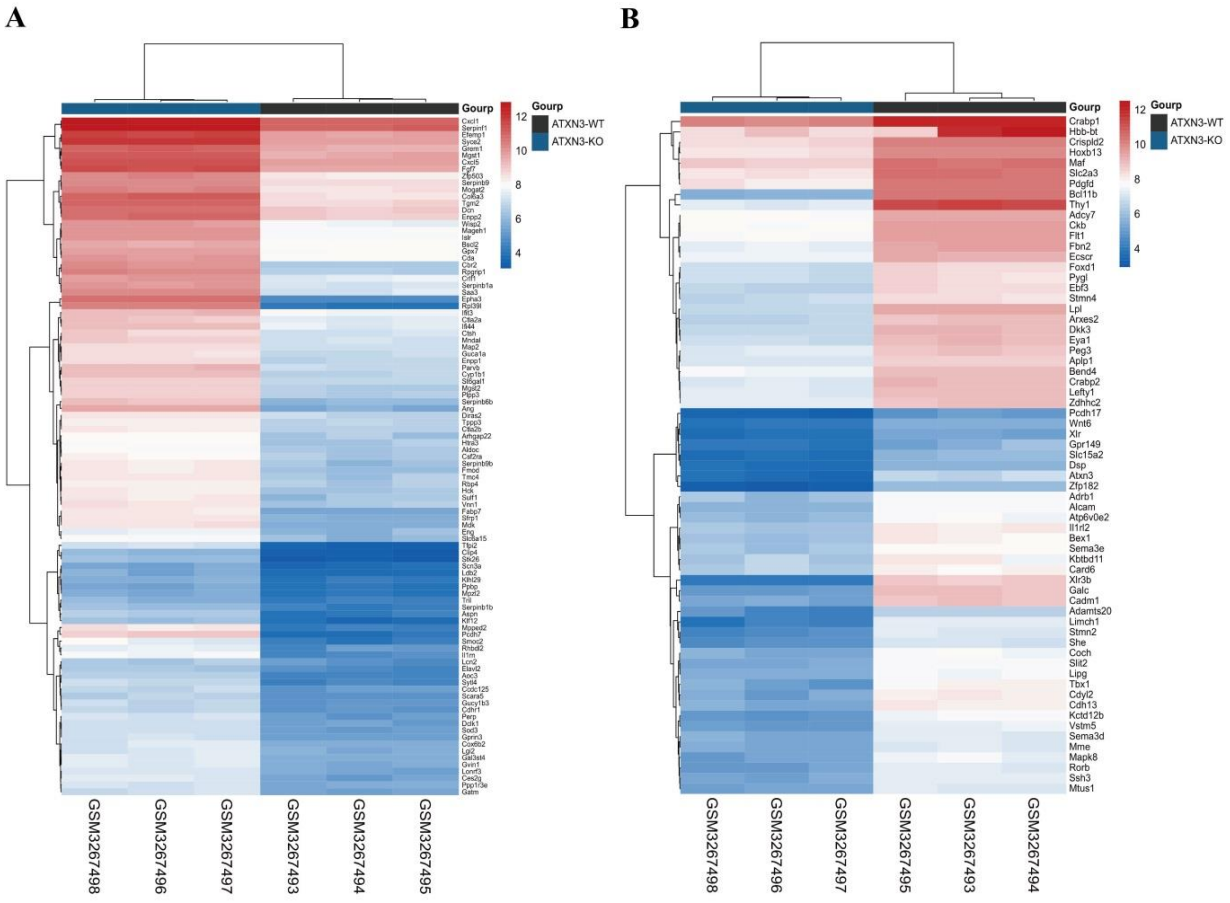

Figure 1 Heatmap of GSE133608 chip. (A) and (B) are heatmaps of up-regulated and down-regulated genes respectively

Table 1 Tissue specificity analysis of DEGs

Tissue/System	DEGs
Skeletal system	Epha3, Sfrp1, Gpx7, Ppbp
Reproductive system	Tfpi2, Serpinb9b, Cox6b2, Fbn2, Crabp1, Flt1, Lefty1, Gpr149
Immune system	Il1rn, Saa3, Serpinb1a, Hck, Gvin1, Lonrf3, Mndal, Cxcl1, Serpinb9, Ifit3, Csf2ra, Ctla2b, Ctsh, Lipg, Ssh3, Card6
Nervous system	Fabp7, Enpp2, Slc6a15, Ldb2, Serpinb1b, Scn3a, Gprin3, Klhl29, Guca1a, Diras2, Aldoc, Map2, Tril, Lgi2, Tppp3, Xlr3b, Thy1, Limch1, Stmn2, Dkk3, Arxes2, Mapk8, Rorb, Adamts20, Atp6v0e2, Ckb, Zdhhc2, Stmn4, Pcdh17, Aplp1
Digestive system	Rhbdl2, Tmc4, Mogat2, Ang, Rbp4
Urinary system	Cda, Pdgfd, Hoxb13, Mme
White adipose tissue	Enpp1
Skeletal muscle system	Grem1
Spleen system	Coch
Salivary gland tissue	Adrb1

3.3 Functional Enrichment Analysis of DEGs

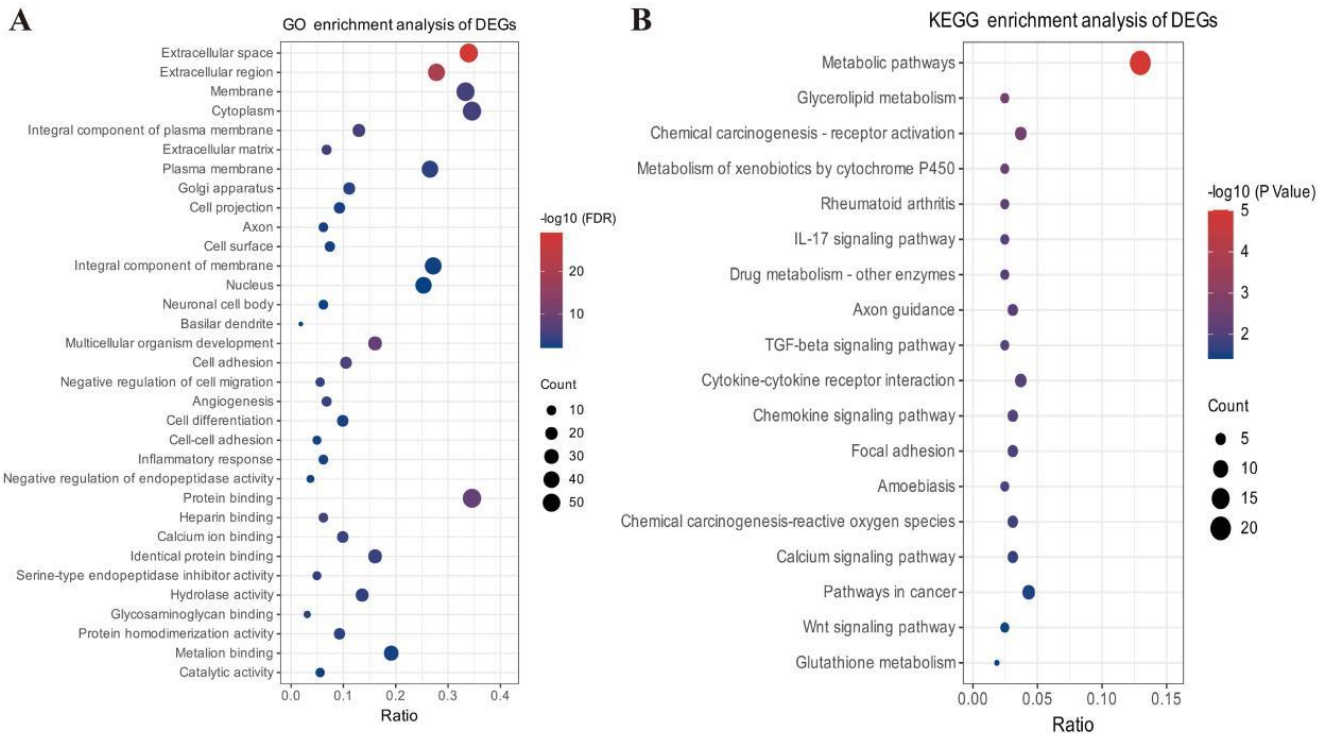

Figure 2 GO (A) and KEGG (B) enrichment analysis of DEGs

Utilizing DAVID 2021 for GO and KEGG enrichment analysis of DEGs, a total of 33 GO terms (comprising 15 CC terms, 8 BP terms, and 10 MF terms) and 18 KEGG pathways were identified. Based on the screening criteria: Benjamini-adjusted P<.01, the DEGs predominantly function in the extracellular space, cell membrane, and cytoplasm. They are involved in BP such as multicellular organism development, cell adhesion and differentiation, vascular regeneration, and inflammatory response. Additionally, they mediate MF such as protein and metal ion binding, as well as proteolytic enzyme activity. KEGG pathway enrichment analysis revealed that the DEGs primarily participate in total metabolic pathways, glyceride and glutathione metabolic pathways, drug metabolic pathways, cytokine receptor interaction signaling pathways, chemokine signaling pathways, and IL-17 signaling pathways. Notably, the extracellular space (p=7.35E-30) and metabolic pathway (P=0.00001) emerged as the most significant functional sites and regulatory pathways for DEGs (Figure 2).

3.4 Construction of PPI Network and Identification of Key Differentially Expressed Proteins

A PPI network was constructed utilizing the STRING database (Figure 3A). Utilizing Cytoscape, a visual PPI network comprising 99 nodes and 127 edges was obtained. The MCC algorithm within the cytoHubba plugin identified six significant differentially expressed proteins: Cxcl1, Cxcl5, Saa3, Eng, Thy1, and Lpl (Figure 3B). Following Ataxin-3 knockout, the expression levels of Cxcl1, Cxcl5, Saa3, and Eng were upregulated, whereas Thy1 and Lpl were downregulated (Figure 1).

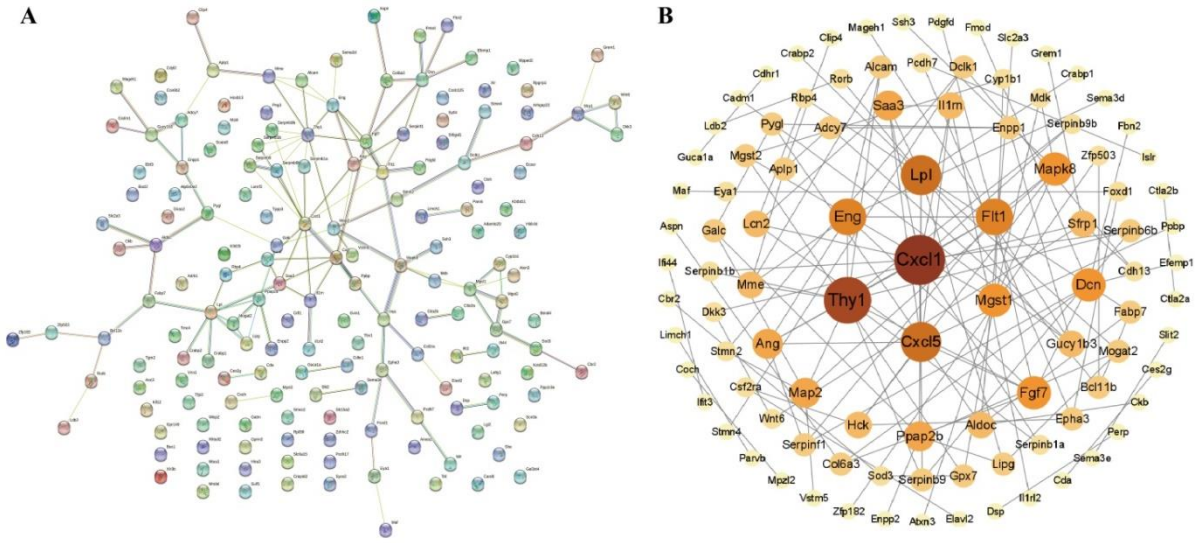

Figure 3 Protein interaction network (A) and visualization (B) of DEGs

3.5 Enrichment Analysis of Key Differentially Expressed Proteins

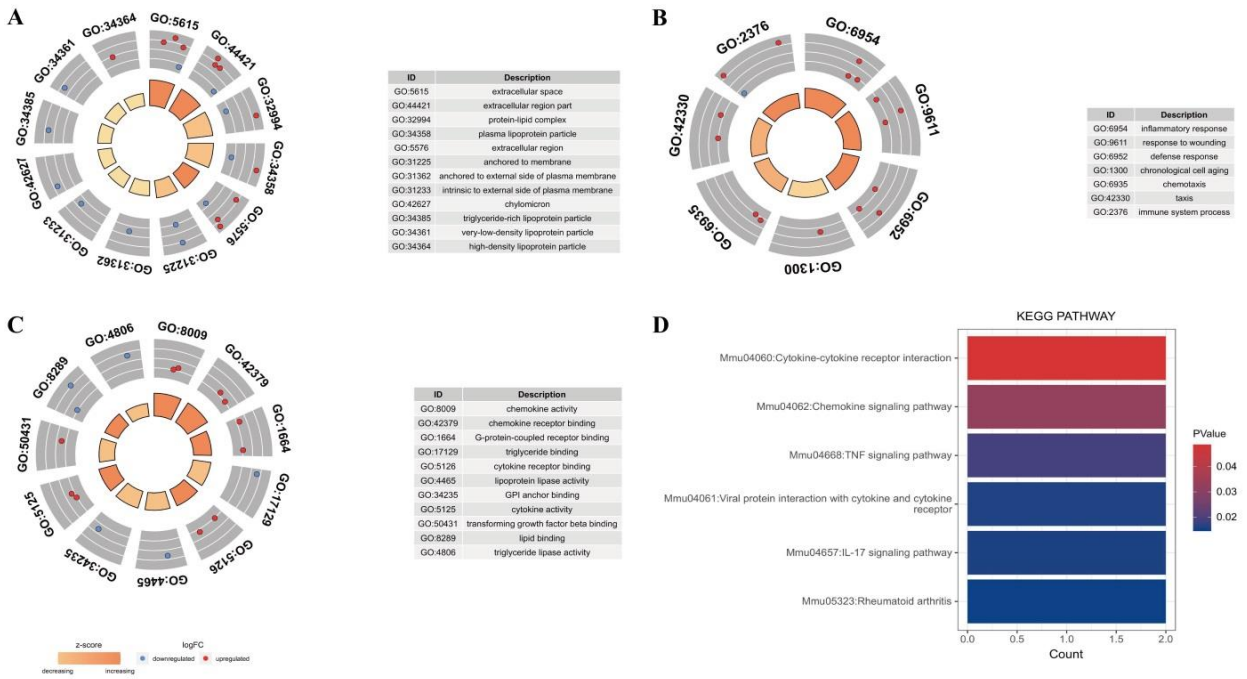

Figure 4 Enrichment analysis of key differential proteins. (A-C) GO function enrichment analysis, including CC (A), BP (B), and MF (C) entries. Red and blue represent key differential proteins that are upregulated and downregulated, respectively. (D) KEGG pathway enrichment analysis

DAVID2021 was utilized for functional enrichment analysis of significant differentially expressed proteins. GO enrichment analysis revealed predominant functionality in extracellular vesicles, plasma lipoproteins, and various cellular locations. The enriched BP primarily involved inflammatory and defense responses against cellular damage. The MF included cytokine/chemokine activation and receptor binding, G protein-coupled receptor binding, and lipid binding (Figure 4A-C). KEGG enrichment analysis revealed predominant participation in rheumatoid arthritis, IL-17, cytokines and their receptors, and chemokine signaling pathways (Figure 4D).

3.6 Construction of Transcription Factor Regulatory Network

The Citrome DB database was utilized to identify TFs corresponding to node genes (Figure 5A-F). The network reveals several key regulators (with a target gene count of ≥ 4), including CEBPB, STAT5A, NR3C1, SPI1, and EP300 (Figure 6).

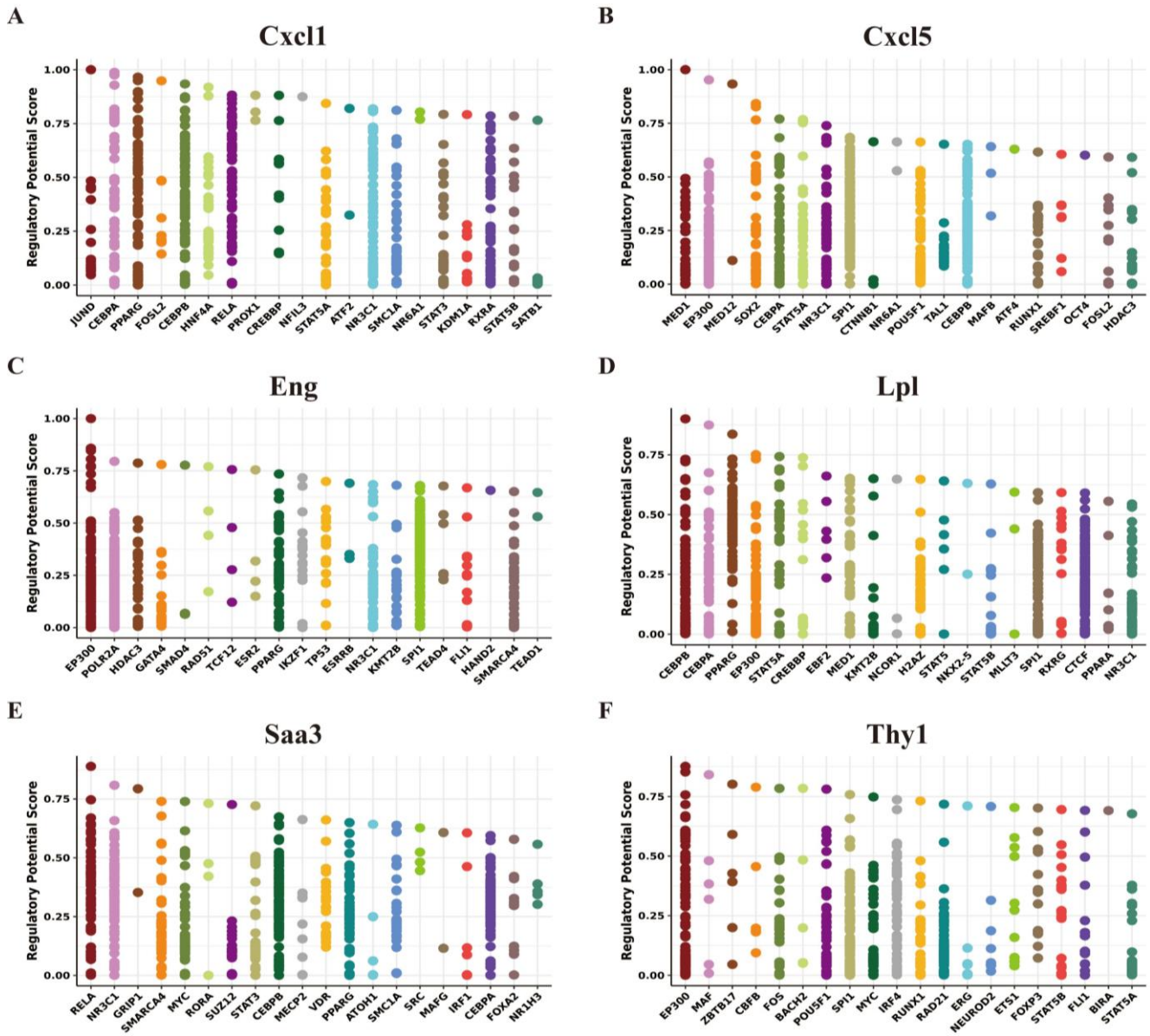

Figure 5 (A-F) The top 20 TFs regulating Cxcl1 (A), Cxcl5 (B), Saa3 (C), Eng (D), Thy1 (E), and Lpl (F) in the Cistrome DB database

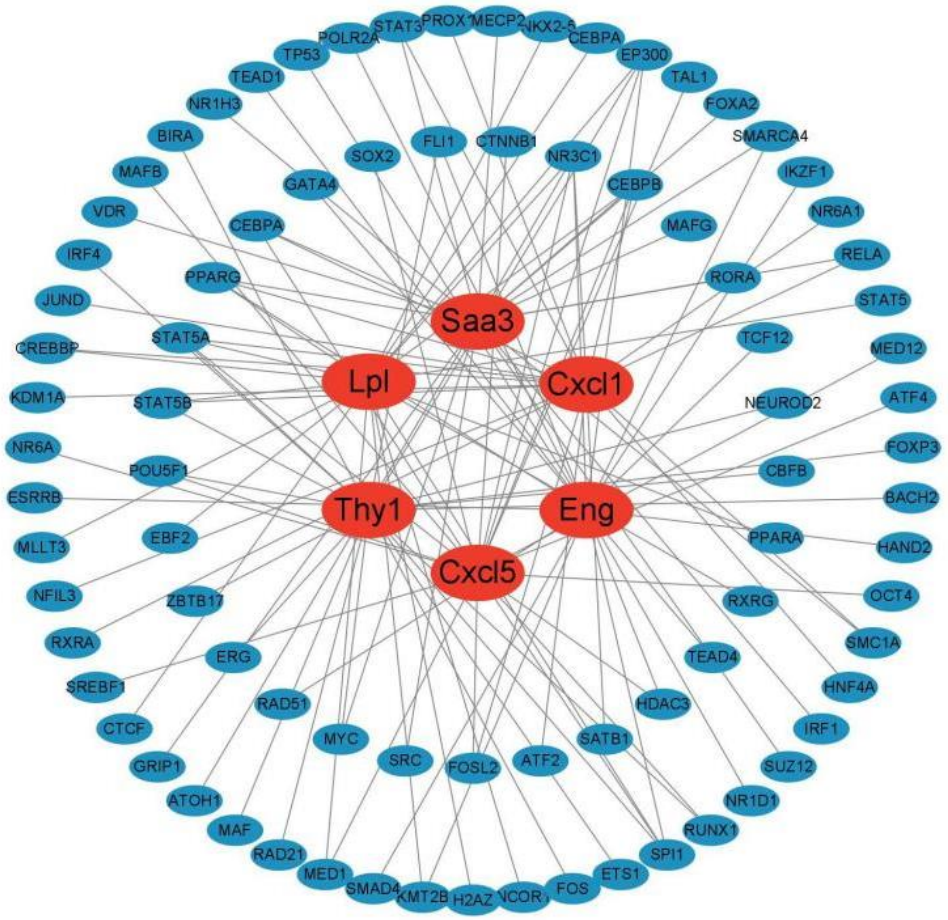

Figure 6 Nodal genes-TFs regulatory network. Red represents nodal genes and blue represents TFs

4 Discussion

SCA3 is a progressive neurodegenerative disorder characterized by the expansion of PolyQ domain mutations within the Ataxin-3 protein. Its pathogenesis is attributed to a complex interplay among multiple factors, mechanisms, and pathways [12]. To further investigate Ataxin-3's role in SCA3 pathogenesis, researchers have developed various Ataxin-3 knockout models. The depletion of endogenous Ataxin-3 in *Drosophila* mirrors the pathological cascades observed in both SCA3 and Huntington's Disease (HD), suggesting a potential neuroprotective function of Ataxin-3 under normal conditions [13]. *Atxn3* knockout mice demonstrate preserved fertility and a normal lifespan, exhibiting elevated ubiquitinated protein accumulation in the brain and reduced exploratory behavior [14, 15]. Conversely, in vitro studies show that the loss of Ataxin-3 in human and murine cell lines leads to significant disruptions and functional impairments of cytoskeletal microtubules and intermediate filaments, resulting in increased apoptosis [16].

In the current study, microarray data of MEFs were extracted from the GEO database. The analysis revealed significant upregulation of DEGs, suggesting Ataxin-3 may function as a transcriptional repressor. These DEGs were predominantly found in the extracellular space, cell membrane, and cytoplasm, and were mainly involved in pathways pertaining to cell adhesion and differentiation. Ataxin-3, identified as a cytoplasmic protein, significantly downregulates genes encoding cell membrane proteins when overexpressed [17]. In contrast, the intracellular depletion of Ataxin-3 leads to a decrease in the expression of cell adhesion molecules, such as Talin and integrin subunits α1, impairing cell-matrix interactions [16]. Thymocyte differentiation antigen-1 (Thy-1), a crucial cell surface glycoprotein that plays roles in cell migration, adhesion, differentiation, and apoptosis, exhibits significantly reduced expression following Ataxin-3 knockout [18]. The interaction between Ataxin-3 and Thy-1 may be essential for the former's intercellular function.

DEGs exhibit marked tissue specificity within the

nervous and immune systems, underscoring Ataxin-3's distinctive roles in these domains. GO/KEGG analyses revealed that DEGs and key differentially expressed proteins participate in immune- and inflammation-related signaling pathways. Chronic inflammation within the nervous system acts as an ancillary factor promoting neurodegeneration progression in SCA3 patients [19]. Furthermore, inflammatory cascade reactions are documented in the brains of mice expressing a stable form of mutant Ataxin-3 [17]. The C-X-C motif chemokine ligand 1 (Cxcl1), a pro-inflammatory agent involved in neutrophil chemotaxis and various neurological conditions, including Alzheimer's disease (AD) [20]. Mutated, amplified Ataxin-3 in SCA3 suppresses tumor necrosis factor-α (TNF-α) while concurrently elevating Cxcl1 levels, indicating Ataxin-3's critical role in modulating the cellular autonomous inflammatory pathway [21]. Additionally, chemokine Cxcl5 plays a significant role in the inflammatory mechanisms of the central nervous system, with its upregulation potentially triggering swift changes in several neuroinflammatory conditions [22]. In AD patients, serum amyloid a (Saa) is significantly increased in the brain, exacerbating neuronal loss through neuroinflammation [23]. These observations imply that increased inflammation-related gene expression in the cerebellum of SCA3 patients might result from the impairment of Ataxin-3's regulatory capacity over inflammation.

KEGG analysis revealed DEG enrichment in glyceride/glutathione metabolic pathways, where the global metabolic pathway emerged as the most significant. Further analysis of transcription and metabolic networks in SCA3 transgenic mice has shown that Ataxin-3-84Q regulates gene expression and drives metabolic remodeling in the brain [24]. Within bone marrow cells, the interaction between Ataxin-3 and the mitochondrial inner membrane protein Mic60 is crucial for mitochondrial oxidative phosphorylation. Disrupting this interaction reduces mitochondrial ROS production. Moreover, mass spectrometry analysis aimed at identifying Ataxin-3's deubiquitination targets revealed specific immune metabolism regulatory factors, such as HIF-1α and LAMTOR1, highlighting Ataxin-3's integral role in immune metabolism [25]. Lipoprotein lipase (Lpl), which catalyzes the hydrolysis of triglycerides in lipoproteins, plays a key role in regulating the energy balance of lipid metabolism, promoting neuronal survival, and facilitating synaptic remodeling. Neuron-specific *Lpl* knockout mice exhibit obesity, cognitive impairment, and anxiety-like behaviors [26]. These findings suggest that a deficiency in Ataxin-3, similar to its mutation, may lead to metabolic changes in SCA3, possibly associated with decreased Lpl levels.

Ataxin-3 may contribute to neurodegeneration through the regulation of angiogenesis. Autopsy specimens from patients with SCA3 have shown the presence of Ataxin-3 aggregates and increased microglial cell proliferation within cerebral blood vessels, resulting in blood-brain barrier disruption [27]. Angiogenesis-related DEGs show significantly upregulated endothelial glycoprotein (ENG/CD105). This transmembrane glycoprotein, predominantly found on endothelial cells that line blood vessels, plays an essential role in angiogenesis and vascular remodeling [28]. Ataxin-3-mediated dysregulation of angiogenesis may worsen SCA3 neuropathology.

Ataxin-3 plays a role in transcriptional regulation through its deubiquitinase activity, thereby affecting gene expression [10]. PolyQ tract expansions impair Ataxin-3 function and disrupt its typical protein interactions, leading to atypical cellular transcription [29]. In our study, we established a network of TFs and identified five central hub TFs. Among these, EP300 (p300), stands out as a multi-domain chromatin regulatory factor with both histone and non-histone acetyltransferase activities [30]. The N-terminal domain of native Ataxin-3 has been shown to inhibit P300-mediated histone acetylation in vitro and reduce transcriptional activity in vivo [31]. Although existing literature does not extensively cover the relationship between CEBPB, STAT5A, NR3C1, SPI1, and Ataxin-3, our findings suggest that the interaction between Ataxin-3 and P300 might modulate the transcription levels of specific genes such as Cxcl5, Eng, Thy1, and Lpl, which may have pathophysiological consequences. Future studies should clarify if Ataxin-3 deficiency-induced transcriptional dysregulation drives SCA3 progression.

5 Conclusion

This study employs bioinformatics approaches to elucidate the pivotal role of Ataxin-3 in modulating the inflammatory, metabolic, and angiogenic processes within the nervous system. The analysis reveals that DEGs form a complex network, with crucial proteins and TFs potentially engaging with Ataxin-3, a factor intimately linked to the etiology of SCA3. Ataxin-3 deficiency may induce pathology similar to polyQ-expanded Ataxin-3, suggesting that the loss of its regulatory functions could significantly impact the pathogenic landscape of SCA3. While

the precise pathological mechanism of Ataxin-3 in SCA3, whether mediated through gain-of-function toxicity or loss-of-normal function, requires further elucidation through experimental and clinical studies, our findings significantly advance the understanding of SCA3 pathogenesis by identifying key molecular interactions within the Ataxin-3 signaling network. These newly identified therapeutic targets should be prioritized for in vivo validation, focusing on functional restoration strategies in future translational studies to develop effective SCA3 treatments.

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Author Contributions

Deng Qing: Data curation; Formal analysis; Methodology; Software; Visualization; Validation; Roles / Writing - original draft.

Gong Ziwei: Data curation; Formal analysis; Software; Validation; Supervision; Writing - review & editing.

Ethics Approval

This study solely utilized publicly available genomic data and did not involve human or animal subjects, hence ethical review was not required.

Availability of Data

The datasets used in this study are available from the GEO database (https://www.ncbi.nlm.nih.gov/geo/).

Declaration of Competing Interest

The authors declare no competing financial interests or personal relationships that could have influenced the reported work in this paper.

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