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Regular paper

Identification of key genes involved in Brg1 mutation-induced cataract using bioinformatics analyses with publicly available microarray data

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Background: **Cataract is a common and frequently occurring disease in the elderly. The Brahma-related gene 1 (Brg1) is believed to be related to the formation of cataract, but its mechanisms still remain unclear. This study aimed to investigate how a Brg1 mutation affects lens development and promotes the formation of cataract in mice. Methods**: **We used mRNA profiles downloaded from the Gene Expression Omnibus (GEO) database to compare the tissue samples of lenses from 4 dominant-negative Brg1(dnBrg1) transgenic mice and 4 wild-type mice. Then, the NetworkAnalyst online tool was employed to screen for the significantly differentially expressed genes (DEGs). Gene Ontology (GO) annotation, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome pathway analysis were examined in DEGs by using Metascape. In addition, we applied the STRING online tool and Cytoscape software to build the protein-protein interaction (PPI) network. Finally, the CytoNCA plug-in was used to choose the central modules from the PPI network. Results**: **323 DEGs were filtered in total, 222 of which were up-regulated genes and enriched in the cell cycle process regulation, mitotic G1-G1/S phase, mRNA splicing, etc., while 101 of which were down-regulated genes and enriched in the organ hydroxy compound transport, synaptic vesicle cycle and neuron migration. Within this network of PPI, we found that the heat shock protein 90 alpha (cytosolic), class B member 1 (*HSP90ab1*), the polymerase (RNA) II (DNA directed) polypeptide E (*Polr2e*), the cell division cycle 20 (*Cdc20*) and the polymerase (RNA) II (DNA directed) polypeptide C (*Polr2c*) had higher connectivity degrees and may interact and influence each other. Conclusions**: **The Brg1 mutation affected expression of various genes in mice, such as *HSP90ab1*, *Polr2e*, *Cdc20,* and *Polr2c*. These genes may have some effects on the occurrence and development of cataract, and may serve as potential therapeutic targets for the cataract treatment.**

Keywords: cataract, Brg-1, gene expression profiling, differentially expressed genes

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Abbreviations: Brg1, Brahma-related gene 1; GEO Gene Expression Omnibus; DEGs, differentially expressed genes; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PCA, principal component analysis; PPI, protein-protein interaction

BACKGROUND

Cataract remains a substantial public health issue in the middle- and low-income developing countries. Total funding for eliminating blindness caused by cataract was estimated at more than $ 57 billion during the years of 2010 to 2020 (He *et al*., 2017). Multiple risk factors have been implicated in the pathogenesis of cataracts, and the main factors are aging, heredity and environment, among which heredity is the most prominent factor contributing to cataract formation (Yonova-Doing *et al*., 2016). Generally, cataract demonstrated multiple inheritance patterns, including autosomal recessive, autosomal dominant, and X-linked recessive, among which autosomal dominant inheritance is the most prominent. Mutations in genes can affect the structure and function of the lens proteins, which may ultimately lead to the development of cataract (Zhu *et al*., 2017).

Brahma-related gene 1 (Brg1, also called Snf2b or Smarca4), involved in transcriptional regulation, is one of the core catalytic subunits of diverse chromatin-remodeling complexes acting in an ATP-dependent manner, and plays a crucial role in early embryonic development of mammals (Bultman *et al*., 2000). Several studies on a point mutation (K798R) in the ATP-binding region of Brg1 have revealed the vital role of Brg1 in tissue differentiation, such as the marrow (Vradii *et al*., 2006), smooth muscle (Zhou *et al*., 2009) and mammary epithelium (Xu *et al*., 2007), which may act through a dominant-negative (DN) mechanism (Peterson *et al*., 1993). According to the literature, Brg1 participates in various aspects of retinal and lens development in the visual system of zebrafish (Gregg *et al*., 2003; Kurita *et al*., 2003; Leung *et al*., 2008). In addition, He *et al*. (He *et al*., 2010) reported that Brg1 is essential for DNase expression, differentiation of lens fiber cells and nucleus degradation of the lens. Brg1 attrition ultimately results in decreased TUNEL-positive nuclei, stagnation of the lens fiber nucleus, and reduced expression of Hsf4 and DNase2b, which are identified as direct and functional targets of Pax6 and Hsf4 (He *et al*., 2016). However, molecular mechanisms leading to cataract by Brg1 mutations still remain unclear.

Gene expression microarray data provides a systematic analysis to characterize gene expression profiles associated with normal or disease states, as well as biological processes (Lovén *et al*., 2012), which enables researchers to simultaneously detect hundreds or thousands of data on gene expression levels (Ueda *et al*., 2003). Based on the microarray analysis, it is reported that Hsf4, Pax6, and Brg1 perform their roles by acting on other targeted genes (He *et al*., 2010). However, the underlying molecular mechanism of Brg1 remains unclear. Therefore, our purpose is to identify potential mechanisms indicating how Brg1 mutation affects the lens development and promotes cataract formation. We downloaded the mRNA profiles

of the lens of 4 *dnBrg1* transgenic mice and 4 wild-type mice from the Gene Expression Omnibus (GEO) database (He *et al.*, 2010), then screened for the differentially expressed genes (DEGs), and performed functional annotation. Furthermore, we constructed a protein-protein interaction (PPI) network for DEGs to conduct modular analysis in order to identify the hub genes.

METHODS

The preprocessing of microarray data

We downloaded the mRNA expression profile of GSE22322 (He *et al.*, 2010) from the GEO microarray database (http://www.ncbi.nlm.nih.gov/geo/) (Barrett *et al.*, 2013), which consisted of eight chips of tissue samples of lenses from 4 *dnBrg1* transgenic mice and 4 wild-type mice. Microarray gene expression profiling was performed by using the [Mouse430A_2] Affymetrix Mouse Genome 430A 2.0 Array platform (Affymetrix, Inc., Santa Clara, CA, USA).

Identification of DEGs

The NetworkAnalyst online tool (Zhou *et al.*, 2019; Xia *et al.*, 2013; Xia *et al.*, 2015) was used to obtain the DEGs between *dnBrg1* transgenic and wild-type samples. DEGs were defined as genes that were less than the adjusted P-value (adj. P) of 0.05 and greater than the |log Fold Change| (|log FC|) of 1.0. Log FC greater than 1.0 was defined as up-regulated genes, and log FC less than 1.0 was defined as down-regulated genes.

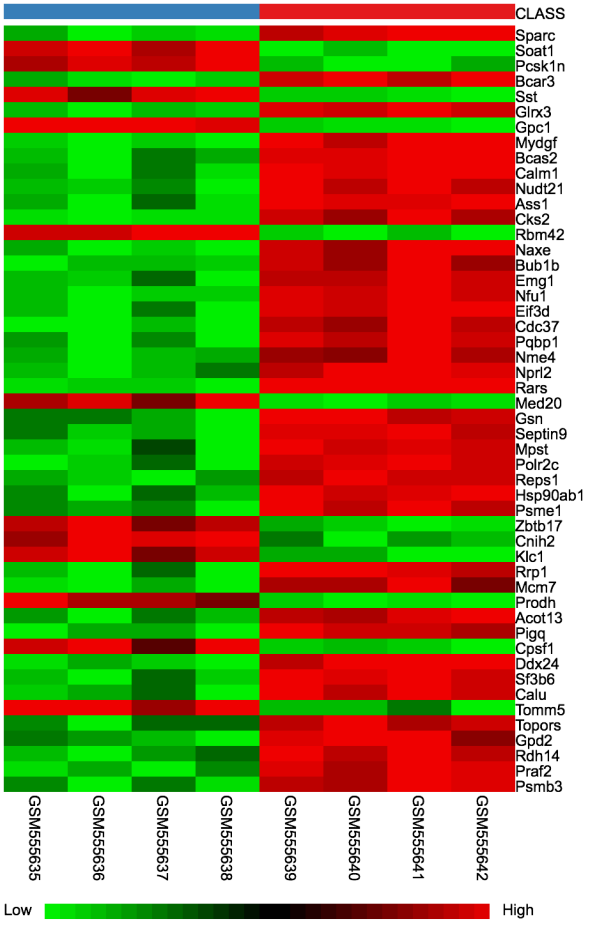

Figure 1. Heat map of the 50 genes from GSE22322.
Gene expression levels was visualized by the heat map, with green indicating low expression, whereas red indicates high expression.

Gene ontology, KEGG and Reactome pathway enrichment analysis

Metascape (http://metascape.org) is a comprehensive web resource that was applied to facilitate data management and analysis. It provided gene-annotation enrichment analysis which was helpful to understand their role in a biological context (Zhou *et al.*, 2019). Gene Ontology (GO) annotation, Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway and Reactome pathway enrichment were accomplished for DEGs by Metascape to perform the enrichment analysis in this study. Similarly, enrichment analysis of core genes was carried out by Metascape and results were considered significant if the *P*-value was less than 0.05.

PPI network analysis

To determine the functional relationship between the DEGs, PPI networks were built through the website of STRING (http://www.string-db.org) (Franceschini *et al.*, 2012). DEG pairs with confidence score larger than 0.4 were retained in a protein-protein interaction network to generate the PPI network, which was visualized by the Cytoscape software (Saito *et al.*, 2012). Then, the CytoHubba (Chin *et al.*, 2014) plug-in of the Cytoscape software was applied to explore the hub genes, generated by degree centrality, maximal clique centrality and betweenness centrality. In this way, the CytoNCA (Tang *et al.*, 2015) plug-in was used to obtain the key nodes within the PPI network by calculating three topological attributes to filter the top 10 hub genes.

RESULTS

Preliminary analysis of the GSE22322 dataset

To assess the DEGs, the public GSE22322 dataset, which contains 8 tissue samples, was taken from the GEO database. The heat map for the filtered DEGs is illustrated in Fig. 1. Supplementary Fig. 1A (at https://ojs.ptbioch.edu.pl/index.php/abp/) presents the principal component analysis (PCA) plot. It showed that the difference between the *dnBrg1* transgenic group and the wild-type group was significant. Supplementary Fig. 1B (at https://ojs.ptbioch.edu.pl/index.php/abp/) displays a volcano plot of all genes in the *dnBrg1* transgenic group when compared to the control group. In total, 323 DEGs were identified after filtration, for their |logFC| was larger than 1.0 and the *P*-value was less than 0.05 in *dnBrg1* transgenic samples when compared to the wild-type samples. Among these DEGs, 222 genes were up-regulated which were more plentiful than the down-regulated 101 genes. The volcano plot depicted distribution of all genes based on the fold change and *P*-value. Blue, red and grey points represented down-regulated, up-regulated and non-regulated genes, respectively (Fig. 1C).

GO and pathway enrichment analysis of the DEGs

We analyzed GO annotation, KEGG and Reactome pathway enrichment by Metascape to explore the pathogenesis of cataract. Figure 2A reveals that the up-regulated genes were particularly enriched in the regulation

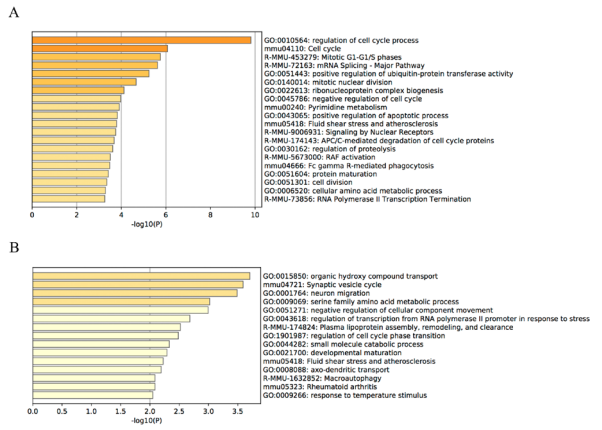

Figure 2. GO function and pathway enrichment of the DEGs (A) The top cluster with their representative enriched terms of up-regulated genes. (B) The top cluster with their representative enriched terms of down-regulated genes.
GO, gene ontology; DEGs, differentially expressed genes.

of cell cycle, mitotic G1-G1/S phase, mRNA splicing, positive regulation of ubiquitin-protein transferase activity and mitotic nuclear division. And the down-regulated genes were particularly enriched in the organ hydroxy compound transport, synaptic vesicle cycle, neuron migration and metabolic process of amino acid from the serine family (Fig. 2B).

PPI network construction and core genes determination

The PPI network was constructed for investigating the relationship of the DEGs. Figure 3A shows the PPI network with 148 edges and 498 nodes constructed by the up-regulated DEGs, as well as the 55 nodes along with 55 edges constructed by the down-regulated DEGs (Fig. 3B). The red nodes in the graph represented higher connectivity degree of the PPT network. Among them, 20 genes were recognized as the hub genes as they had higher connectivity degrees than the other genes in the network. The top four hub genes were heat shock protein 90 alpha (cytosolic), class B member 1 (*HSP90ab1*, degree=30), polymerase (RNA) II (DNA directed) polypeptide E (*Polr2e*, degree=30), cell division cycle 20 (*Cdc20*, degree=29), and polymerase (RNA) II (DNA directed) polypeptide C (*Polr2c*, degree=25) (Fig. 4). GO annotation, KEGG pathway and Reactome pathway gene enhancement were incorporated into the top 10 hub genes, and Fig. 5 shows that these genes were

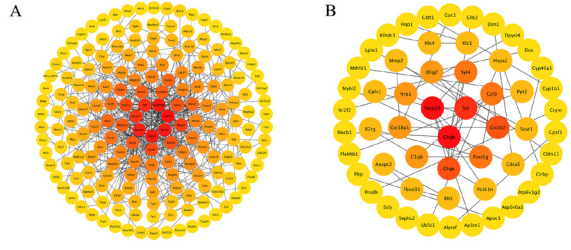

Figure 3. The protein-protein interaction network of the DEGs (A) the PPI network of up-regulated genes. (B) the PPI network of the down-regulated genes.
Circular nodes represent DEGs, connecting lines represent interaction of the DEGs. The red nodes represent a higher connectivity degree of the PPI network. PPI, protein-protein interaction; DEGs, differentially expressed genes.

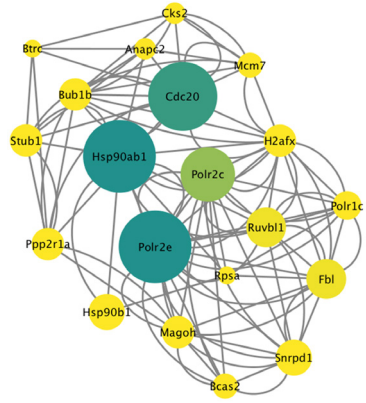

Figure 4. The selected core genes from the PPI network.
The green and big nodes represent top four hub genes (*HSP-90ab1, Polr2e, Cdc20, Polr2c*) from the PPI network. PPI, protein-protein interaction.

primarily associated with the cell cycle, metabolism of RNA, RNA polymerase, ubiquitin-mediated proteolysis, ribonucleoprotein complex biogenesis and protein folding.

DISCUSSION

The aim of this study was to unravel genes involved in the Brg1 transgenic-induced cataract, which was helpful in investigating the pathogenesis of cataract and may provide valuable therapeutic targets for further clinical therapy. Via the NetworkAnalyst online tool, 323 DEGs were identified in the *dnBrg1* transgenic samples, consisting of 222 up-regulated and 101 down-regulated genes when compared to the wild-type samples. Secondly, GO annotation, KEGG and Reactome Pathway enrichment analysis were done by the Metascape online tool, and the up-regulated genes were particularly concentrated in regulation of the cell cycle, mitotic G1-G1/S phase, mRNA splicing, positive regulation of ubiquitin-protein transferase activity, and mitotic nuclear division, while the down-regulated genes were particularly concentrated in the organ hydroxy compound transport, synaptic vesicle cycle, neuron migration, and serine family amino acid metabolic process. Next, the PPI network was obtained on the basis of analysis applying the STRING online tool and Cytoscape software. *HSP90ab1, Polr2e*, *Cdc20* and *Polr2c* were the uppermost four core genes in the PPI network, as their connectivity degree was relatively high. We next analyzed the top 10 hub genes of GO annotation, KEGG and Reactome Pathway via Metascape again, and these hub genes were enriched in the pathways of cell cycle, metabolism of RNA, RNA polymerase, ubiquitin-mediated proteolysis, ribonucleoprotein complex biogenesis and protein folding.

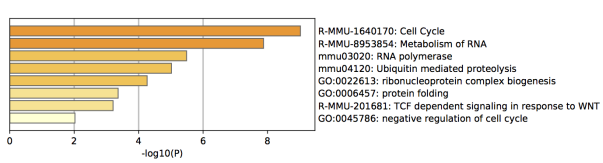

Figure 5. GO function and pathway enrichment of the hub genes.
The top cluster with their representative enriched terms of the hub genes. GO, gene ontology.

HSP90ab1, one of the major isoforms of Heat shock protein 90 (HSP90) chaperones (Schopf *et al*., 2017), is well recognized as a constitutively active molecular chaperone. HSP90 has been reported to be overexpressed in many malignant diseases, and it has been demonstrated that it plays key roles in various diseases as the multifarious client protein, and thus it could be employed as a promising candidate target gene for anticancer drug treatment (Haase & Fitze, 2016). In addition, HSP90 is also expressed in the lens and has the function of balancing the lens homeostasis (Bagchi *et al*., 2002). Furthermore, researchers believe that it is involved in regulating the lens proteasome activity (Wagner & Margolis, 1995), and down regulation of HSP90 plays an important role in aging of the lens epithelial cells (Colitz *et al*., 2006). Moreover, in the rat lens epithelial explants, HSP90 has a protective effect on the TGF-β2-induced apoptosis of lens epithelial cells and TGF-β2-induced EMT up-regulation (Banh *et al*., 2007). In another study of posterior capsule opacification (PCO), it has been demonstrated that HSP90 has a protective effect on residual epithelial cells in the capsular bag, resisting the capsulorhexis-induced stress and participating in monitoring the migration, EMT and proliferation processes of residual epithelial cells in the rat capsular bag via the signaling pathways of EGF receptor and TGF receptor (Li *et al*., 2019). The function of HSP90 has been clarified in PCO, so we hypothesize that *HSP90ab1* also plays a role in the development of cataract.

The *Cdc20*, from the cell cycle proteins' family, is a pivotal element controlling chromosome segregation and normal cell division during mitosis (Kapanidou *et al*., 2017). It is reported that abnormal expression of *Cdc20* could affect mitosis, leading to the overexpression of oncogenes or dysfunction or mutation of tumor suppressor genes, which will subsequently contribute to cancer (Gayyed *et al*., 2016). However, there are limited studies focused on the function of *Cdc20* in the pathogenesis of cataract, and we predict that *Cdc20* may also play a role in the development or formation of cataract.

Interestingly, *Polr2*C and *Polr2E*, two of the core genes identified, belong to RNA polymerase II (*Polr2*). RNA *Polr2*, which can synthesize mRNA and noncoding RNA, is a key regulatory machine determining gene expression, cell fate and organ development (Lynch *et al*., 2018). The RNA *Polr2* is assembled in the cytoplasm, a process in which HSP90 participates, and is then transferred to the nucleus for transcription (Boulon *et al*., 2010). RNA *Polr2* is composed of 12 highly conserved subunits, among which *Polr2*C is the third largest subunit. It has been demonstrated that lack of any of these subunits, including *Polr2C*, would result in failure in *Polr2* assembly, aggregation of the rest of subunits in the cytoplasm, and eventually in failure in transporting *Polr2* to the nucleus (Boulon *et al*., 2010). *Polr2E* encodes one subunit of *Polr2* and is in charge of the biosynthesis of messenger RNA (Jin *et al*., 2011). Many researchers have reported that the *Polr2E* rs3787016 polymorphism is substantially associated with susceptibility to a variety of cancers, such as cancers of the breast, esophagus, liver, prostate, and thyroid. A number of studies has demonstrated that *Polr2E* has an effect on the subunit of *Polr2* which is related to the transcription of most long non-coding RNAs (lncRNAs) (Gong *et al*., 2017). Several lncRNAs have been verified to be involved in the eye development, such as lncRNA MIAT, exerting influence on the differentiation and proliferation of the lens epithelial cells (Gosak *et al*., 2015). The lncRNA KCNQ10T1 is upregulated in cataract lens anterior capsular samples, and KCNQ10T1 inhibits the pyroptosis of human lens epithelial cells (Jin *et al*., 2017). The lncRNA GPX3-AS, lncRNA PLCD3-OT1 and lncRNA H19 participate in the occurrence and development of cataract (Tu *et al*., 2019; Xiang *et al*., 2019; Cheng *et al*., 2019). Nevertheless, the function of RNA polymerase II in the cataract still remains unclear.

Still, our study has some limitations. Firstly, it is possible that the results of animal model in this study might be different from the human patients. Secondly, proper experiments have not yet been conducted to prove our predictions, but these hypotheses will be tested in future experiments. Thirdly, there were too few samples and we need to expand the sample size in the forthcoming work.

CONCLUSION

In conclusion, the bioinformatics analysis identified 323 genes that were differentially expressed between the *dnBrg1* transgenic lenses and wild-type lenses in mice. On this basis, the core genes were screened for, including *HSP90ab1*, *Cdc20*, *Polr2E,* and *Polr2C*, which might relate to the pathogenesis of Brg1 mutation-induced cataract. However, these findings were acquired through bioinformatics analyses and future associated studies will examine these issues in-depth.

Declarations

Ethics approval and consent to participate: Not Applicable Consent for publication: Not Applicable Availability of data and material: Research data are not shared. Competing interests: The authors have no conflicts of interest to declare.

Authors' contributions

Study concept and design: CL, PL; Acquisition of data: All authors; Analysis and interpretation of data: All authors; Drafting of the manuscript: CL, PL; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: All authors. All authors have read and approved the final version of manuscript.

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