Clinical Trial/Experimental Study

Medicine®

OPEN

Identification of hub genes, key pathways, and therapeutic agents in Hutchinson–Gilford Progeria syndrome using bioinformatics analysis

Dengchuan Wang, BSc, MSc[a,*], Shengshuo Liu, BSc[b], Shi Xu, PhD[c,*]

Abstract

Background: Hutchinson–Gilford Progeria syndrome (HGPS) is a rare lethal premature and accelerated aging disease caused by mutations in the lamin A/C gene. Nevertheless, the mechanisms of cellular damage, senescence, and accelerated aging in HGPS are not fully understood. Therefore, we aimed to screen potential key genes, pathways, and therapeutic agents of HGPS by using bioinformatics methods in this study.

Methods: The gene expression profile of GSE113648 and GSE41751 were retrieved from the gene expression omnibus database and analyzed to identify the differentially expressed genes (DEGs) between HGPS and normal controls. Then, gene ontology and the Kyoto encyclopedia of genes and genomes pathway enrichment analysis were carried out. To construct the protein-protein interaction (PPI) network, we used STRING and Cytoscape to make module analysis of these DEGs. Besides, the connectivity map (cMAP) tool was used as well to predict potential drugs.

Results: As a result, 180 upregulated DEGs and 345 downregulated DEGs were identified, which were significantly enriched in pathways in cancer and PI3K-Akt signaling pathway. The top centrality hub genes fibroblast growth factor 2, decorin, matrix metallopeptidase2, and Fos proto-oncogene, AP-1 transcription factor subunit were screened out as the critical genes among the DEGs from the PPI network. Dexibuprofen and parthenolide were predicted to be the possible agents for the treatment of HGPS by cMAP analysis.

Conclusion: This study identified key genes, signal pathways and therapeutic agents, which might help us improve our understanding of the mechanisms of HGPS and identify some new therapeutic agents for HGPS.

Abbreviations: cMAP = connectivity map, DCN = decorin, dDEGs = downregulated DEGs, DEGs = differentially expressed genes, ECM = extracellular matrix, FGF2 = fibroblast growth factor 2, FOS = Fos proto-oncogene, AP-1 transcription factor subunit, GEO = gene expression omnibus, GO = gene ontology, HGPS = Hutchinson–Gilford Progeria syndrome, KEGG = Kyoto encyclopedia of genes and genomes, LMNA = lamin A/C, MMP2 = matrix metallopeptidase2, PPI = protein-protein interaction, uDEGs = upregulated DEGs.

Keywords: bioinformatics, differentially expressed genes, function enrichment analysis, progeria, protein-protein interaction network

1. Introduction

Hutchinson–Gilford progeria syndrome (HGPS, progeria) is an extremely rare premature and accelerated aging disease.[1] HGPS patients generally appear physiological aging including thin skin with hyperpigmented lesions, loss of subcutaneous fat, alopecia, osteoporosis and severe generalized arteriosclerosis, leading to myocardial infarction in most cases, and the mean age of demise was 14.6 years.[2,3] The leading cause of HGPS is the aberrant

Editor: Fumio Tsuji.

The ethical approval was not necessary since the raw data were obtained from the Gene Expression Omnibus database, which is a public functional genomics data repository and is freely available for users.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Office of Medical Ethics, Shenzhen Longhua District Central Hospital, Shenzhen, Guangdong, [b] School of Pharmacy, Henan University, Kaifeng, Henan, China, [c] Department of Burn and Plastic Surgery, Shenzhen Longhua District Central Hospital, Shenzhen, Guangdong, China.

[*] Correspondence: Dengchuan Wang, Office of Medical Ethics, Shenzhen Longhua District Central Hospital, 187 Guanlan Avenue, Longhua District, Shenzhen, Guangdong 518110, China (e-mail: roywon1012@foxmail.com); Shi Xu, Department of Burn and Plastic Surgery, Shenzhen Longhua District Central Hospital, 187 Guanlan Avenue, Longhua District, Shenzhen, Guangdong 518110, China (e-mail: xushi_cn@163.com).

How to cite this article: Wang D, Liu S, Xu S. Identification of hub genes, key pathways, and therapeutic agents in Hutchinson–Gilford Progeria syndrome using bioinformatics analysis. Medicine 2020;99:7(e19022).

Received: 14 August 2019 / Received in final form: 3 December 2019 / Accepted: 4 January 2020

http://dx.doi.org/10.1097/MD.0000000000019022

splicing of the lamin A/C (*LMNA*) gene.[1] Lamin A and lamin C encoded by *LMNA*, are significant components of the nuclear lamina – a proteinaceous meshwork that underlies the inner nuclear membrane. It is necessary for proper nuclear architecture.[4] Due to the mutations in the *LMNA* gene, the proper synthesis and maturation of lamin A are impaired and a truncated unprocessed lamin A protein called progerin is accumulated.[5] Accumulation of progerin that disrupts the integrity of the nuclear lamina affects a whole repertoire of nuclear functions, causing faster cellular senescence, stem cell depletion and the progeroid phenotype, likely being the cause of the progressive nature of the disease.[4,6,7] The cytological hallmark of HGPS involves nuclear morphological abnormalities, mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and chromosomal and telomere aberrations.[4,8,9] HGPS cells have altered cell-cycle regulation and impaired DNA repair mechanisms, a higher apoptosis rate, and quicker cellular senescence.[9] In HGPS, severe epigenetic alterations have been reported, including histone-covalent modifications, histone variants, DNA methylation, chromatin remodelers, chromatin architecture, and miRNAs.[6,10]

Recently, numerous potential treatment strategies for HGPS have been developed, which mainly by interfering with the processing of lamin A in the post-translational level; and thus promote the clearance of progerin, or directly target the HGPS mutation to diminish the progerin-producing alternative splicing of the *LMNA* gene.[11] Farnesyltransferase inhibitors,[12] statins or bisphosphonates,[13] mono-aminopyrimidines[14] have been found to interfere with prelamin A processing. The autophagy pathway is triggered by the administration of rapamycin,[15] sulphoraphane,[16] leading to the lysosomal degradation of progerin. Finally, mitochondrial function and biogenesis have been targeted by drugs with antioxidant effects such as Metformin,[17] methylene blue,[18] which resulted in improved mitochondrial function and reduction of ROS. Hence, HGPS is an excellent model to explore the accelerated aging with these striking features and similar mechanisms of normal aging. However, the mechanisms underlying cellular damage and senescence and accelerated aging in HGPS are incompletely understood.

Along with the development of bioinformatics, high-throughput tools such as microarray and sequencing have been widely used to explore the genetic variations which concerning a variety of disorders, including cancer and aging.[19,20] Mateos et al[21] found that ribose-phosphate pyrophosphokinase 1 was significantly decreased in HGPS cell lines versus healthy parental controls using Next-Generation Sequencing (RNAseq) and High-Resolution Quantitative Proteomics (iTRAQ) techniques. The bioinformatics analysis of the network of interactions of the *LMNA* gene and transcripts showed that particular relevance of epigenetic modifiers and adenosine triphosphate-dependent chromatin remodelers.[22] Ly et al[23] used fibroblast cells from young, middle and aged normal donors as well as from a HGPS patient, and identified 61 differentially expressed genes among the 6000 genes monitored, of which there are 2 major functional groups:

(1) genes involved in cell cycle progression and
(2) genes involved in maintenance and remodeling of the extracellular matrix (ECM).

Mining and analyzing the massive data allow us to screen key genes or pathways associated with the diseases. Therefore, in this study, we aimed to screen relevant data to identify the DEGs that may play a role in HGPS. In addition, we assessed the functions and roles of screened candidate genes. Besides, the agents that maybe likely to rescue HGPS were also predicted and evaluated.

2. Materials and methods

2.1. Datasets and data preprocessing

The gene expression profiles GSE113648 and GSE41751 were obtained from the Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database in the National Center for Biotechnology Information. The former dataset has 4 progenitor lines: 2 HGPS patients and 2 control samples. And the latter one has 2 primary fibroblasts of HGPS patients and 2 healthy age-matched control samples.

The analysis of screening DEGs between HGPS and control samples was analyzed by GEO2R, respectively. Moreover, the threshold for the DEGs was set as P-value $< .01$ and $|\log2\text{foldchange (FC)}| \geq 1$.

2.2. Gene ontology (GO) and pathway enrichment analysis of DEGs

To analyze the functions of DEGs, GO enrichment and Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis were carried out by using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) online tool.[24] $P < .05$ was set as the cut-off point.

2.3. Protein-protein interaction (PPI) network construction and module selection

To investigate the possible hub genes/proteins that might play a significant role in the biological process, all DEGs were imported into STRING (https://string-db.org/)[25] and Cytoscape[26] to create network visualizations. A confidence score $>.4$ was defined as significant in STRING analysis to evaluate the interactive relationships. Then, we use Cytoscape to construct PPI networks and the Molecular Complex Detection (MCODE, a plugin for Cytoscape)[27] to screen the modules of the PPI network. The default parameters were set as follows: degree cut-off = 2, node score cut-off = 2, k-core = 2, and maximum depth = 100.

2.4. Analysis of module and hub genes in the PPI network

The function and pathway enrichment analysis were carried out for DEGs in the modules. To explore key genes in the PPI network, 3 centrality methods: degree, closeness, and subgraph[28] were calculated using a Cytoscape plugin CytoNCA.[29]

2.5. Connectivity map (cMAP) database mining

With the aim of finding potential agents with molecular signatures that might reverse the transcriptional profiles of HGPS, we compared the observed gene expression profiles with the cMAP reference database (http://portals.broadinstitute.org/cmap/).[30] DEGs between HGPS and control samples were used as query terms to submit to cMAP for analysis. The P-value $< .05$ was considered as the cut-off value. Small molecular compounds with negative connectivity enrichment scores were selected as potential therapeutic molecules for the treatment of HGPS.

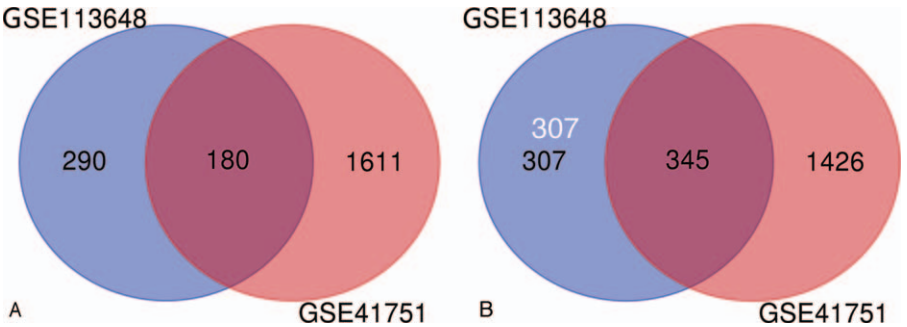

Figure 1. Intersection of the uDEGs (1A) and dDEGs (1B) from GSE113648 and GSE41751 dataset respectively. The intersection included 180 upregulated and 345 downregulated genes. dDEGs = downregulated differentially expressed genes, uDEGs = upregulated differentially expressed genes.

3. Results

3.1. Identification of DEGs

HGPS patients and control samples in GSE113648 and GSE41751 dataset were analyzed to identify DEGs using the $P < .01$ and $|\log2FC| \geq 1$ criteria. Compared with control, a total of 1126 DEGs were identified from GSE113648 dataset, consisting of 472 upregulated DEGs (uDEGs) and 654 downregulated DEGs (dDEGs) in HGPS cells (Table S1, http://links.lww.com/MD/D706). As shown in Supplemental Table 2, http://links.lww.com/MD/D707, 1791 uDEGs and 1771 dDEGs have been generated from GSE41751 dataset. Moreover, 180 uDEGs and 345 dDEGs have been screened out in the intersections, respectively (Fig. 1, Table S3, http://links.lww.com/MD/D708).

3.2. Functional analysis of DEGs

Aiming to evaluate the functions of identified DEGs, we uploaded all DEGs to DAVID to identify significant GO categories and KEGG pathways. GO analysis showed that the DEGs were enriched in biological process, including positive and negative regulation of transcription from RNA polymerase II promoter, cell adhesion, positive regulation of GTPase activity and ECM organization (Table 1). For cellular components, DEGs were enriched in the plasma membrane, cytoplasm, extracellular exosome, extracellular region, and extracellular space (Table 1). Besides, for molecular function, the DEGs were enriched in transcription factor activity, sequence-specific DNA binding, calcium ion binding, protein homodimerization activity, sequence-specific DNA binding, and receptor binding (Table 1).

KEGG pathway analysis indicated that the DEGs were enriched in pathways in cancer, PI3K-Akt signaling pathway, focal adhesion, ECM-receptor interaction, and Ras signaling pathway (Table 2).

3.3. PPI network construction and modules selection

The PPI network of DEGs consisting of 206 nodes and 412 edges was constructed in the STRING database (version 11.0). Then it was visualized through Cytoscape (Fig. 2A). Furthermore, degree ≥10 was set as the cut-off criterion. Based on the STRING database, the DEGs with the highest PPI scores identified by the 3 centrality methods are shown in Table 3. After repeated genes removing, the hub genes (shown in Fig. 2A, highlighted in yellow and shaped in diamond) were obtained using the 3 centrality methods, including fibroblast growth factor 2 (*FGF2*), decorin (*DCN*), matrix metallopeptidase2 (*MMP2*), Fos proto-oncogene, AP-1 transcription factor subunit (*FOS*), syndecan 4, early growth response 1, glial cell-derived neurotrophic factor, fibroblast growth factor receptor 2, syndecan 3, and ADAM metallopeptidase with thrombospondin type 1 motif 5. Among these genes, *FGF2* revealed the highest node degree, which was 28. A significant module was constructed from the PPI network of the DEGs using MCODE, including 11 nodes and 30 edges

Table 1

Gene ontology analysis of the differentially expressed genes (DEGs) associated with Hutchinson–Gilford Progeria syndrome.

Category	Term/functions	Gene count	%	*P*-value
BP	Positive regulation of Transcription from RNA Polymerase II promoter	52	10.0	8.0E-6
	Cell adhesion	50	9.6	3.3E-16
	Negative regulation of Transcription from RNA Polymerase II promoter	40	7.7	4.1E-5
	Positive regulation of GTPase activity	37	7.1	2.5E-6
	Extracellular matrix organization	32	6.1	2.4E-15
CC	Plasma membrane	160	30.7	3.5E-7
	Cytoplasm	160	30.7	3.9E-2
	Extracellular exosome	108	20.7	1.0E-4
	Extracellular region	86	16.5	1.2E-9
	Extracellular space	73	14.0	1.7E-8
MF	Transcription factor activity, Sequence-specific DNA binding	45	8.6	2.7E-4
	Calcium ion binding	36	6.9	3.7E-4
	Protein homodimerization activity	30	5.7	1.9E-2
	Sequence-specific DNA binding	29	5.6	2.9E-4
	receptor binding	23	4.4	1.9E-4

BP = biological process, CC = cellular component, MF = molecular function.

Table 2

Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis of the differentially expressed genes (DEGs) associated with Hutchinson–Gilford Progeria Syndrome.

Pathway ID	Name	Gene count	%	*P*-value
hsa05200	Pathways in cancer	26	5.0	1.9E-4
hsa04151	PI3K-Akt signaling pathway	25	4.8	6.6E-5
hsa04510	Focal adhesion	16	3.1	1.0E-3
hsa04512	ECM-receptor interaction	14	2.7	1.2E-6
hsa04014	Ras signaling pathway	13	2.5	3.4E-2

(Fig. 2B). Biological functional enrichment analysis showed that genes in this module were markedly enriched in glycosaminoglycan (GAG) biosynthetic process, GAG metabolic process, and GAG catabolic process (Table 4). Proteoglycans in cancer and GAG biosynthesis-heparansulfate/heparin were enriched in the KEGG pathway analysis.

3.4. cAMP analysis

The identified DEGs were selected and entered as a query signature in the cMAP database. It shows the top 5 hits with low connectivity scores (−0.863 to −0.738), indicating a high negative correlation with the HGPS signature (Table 5). These compounds may be capable of reversing or counteracting the gene expression pattern observed in HGPS and are thus candidate novel therapies. They were dexibuprofen, parthenolide, lomustine, PNU-0293363, and lincomycin.

4. Discussion

Despite advances in the present study and therapeutics, the molecular mechanisms underlying cellular damage and senescence and accelerated aging in HGPS have not been fully understood. In this study, DEGs in HGPS compared with normal controls were analyzed. The KEGG pathway analysis revealed that the DEGs were obviously enriched in pathways in cancer, PI3K-Akt signaling pathway, focal adhesion, and ECM-receptor interaction. As is known to us, cancer and progeria shared many molecular and cellular mechanisms, particularly in DNA damage. DNA damage has emerged as a significant cause in cancer and many diseases related to aging.[31] HGPS and other premature aging disorders caused by mutations in DNA repair proteins are often characterized by cancer susceptibility.[32,33] PI3K/Akt pathway is a regulator of endothelial senescence.[34,35] Yentrapalli et al[36] reported that inactivation of the PI3K/Akt pathway accompanying premature senescence. The focal adhesion structure is mildly affected in HGPS mouse model and Emery–Dreifuss muscular dystrophy mouse model.[37] Csoka et al[38] compared the gene expression patterns of HGPS fibroblast cells with normal control and found that the most prominent significant differentially genes encode transcription factors and ECM proteins, many of which are known to function in the tissues severely affected in HGPS. HGPS fibroblasts exhibit high expression of ECM proteins and low expression of ECM remodeling enzymes, which can result in aberrant ECM deposition.[4] In addition, changes in ECM composition are caused by inhibition of the Wnt signaling pathway in HGPS.[39,40]

The GO analysis results indicated that the DEGs were enriched in biological process, including positive and negative regulation of transcription from RNA polymerase II promoter, cell adhesion, and positive regulation of GTPase activity. RNA polymerase II Transcription is active in the lamin B deficient nuclear blebs of atypical progeria cells.[41] In Werner syndrome, Werner syndrome protein is possibly a transcriptional activator in RNA polII transcription.[42] In the meantime, Spann et al[43] deemed that disruption of normal lamin organization inhibits RNA polymerase II-dependent transcription. These may indicate that the screened DEGs may act on positive and negative regulation of transcription from RNA polymerase II. Hale et al[37] reported that cell adhesion defects in $Lmna^{L530P/L530P}$ mouse (HGPS mouse model) adult fibroblasts and $Lmna^{-/-}$ mouse (Emery–Dreifuss muscular dystrophy mouse model) embryonic fibroblasts. Ran is a small ras-related GTPase that controls the nucleocytoplasmic exchange of macromolecules across the nuclear envelope.[44] The nuclear levels of Ran GTPase are reduced. And the Ran protein gradient is disrupted in fibroblasts from HGPS patients, which causes a defect in generating nuclear γ-H2AX and DNA damage and ROS.[45,46]

The PPI network was constructed with DEGs, and the top centrality hub genes were obtained: *FGF2*, *DCN*, *MMP2*, and *FOS*. *FGF2* was identified as one of the hub genes with the highest degree of connectivity, the protein encoded by which is a member of the fibroblast growth factor (FGF) family. However, the relation between *FGF2* and progeria has not been reported at present. The biosynthesis of the small proteoglycan decorin decreased in progeroid syndromes.[47] MMP-2 messenger RNA showed a donor age-dependent decrease in HGPS fibroblasts, but levels of secreted protein were unchanged.[48] The levels of proto-oncogene c-fos mRNA expression decreased in HGPS fibroblasts.[49]

Module analysis of the PPI network showed that HGPS was associated with proteoglycans in cancer and GAG processes, such as biosynthesis, metabolic, and catabolic. Several patients with progeroid-like symptoms have been shown to have abnormalities in the biosynthesis of proteoglycans.[50] O-glycosylation, the main type of protein glycosylation, is related to progeria.[51] GAGs are an abundant structural component of the ECM.[52] GAG hyaluronic acid (HA) was found excreted with an excessive amount in progeria patients.[53,54] However, no conclusive evidence of HA being a primary effect in progeria has been found.[55]

To predict the drugs that have the potential to rescue the HGPS biological process, DEGs were submitted to cMAP for analysis. Using this tool, a list of compounds that might reverse the DEGs profiles was screened out, of which 2 compounds (dexibuprofen and parthenolide) are particularly interested in our study. Mouse models that phenotypically recapitulate HGPS show increased activation of Nuclear Factor-kappa B (NF-κB) with a concomitant increase in interleukin-6 at the transcriptional and protein

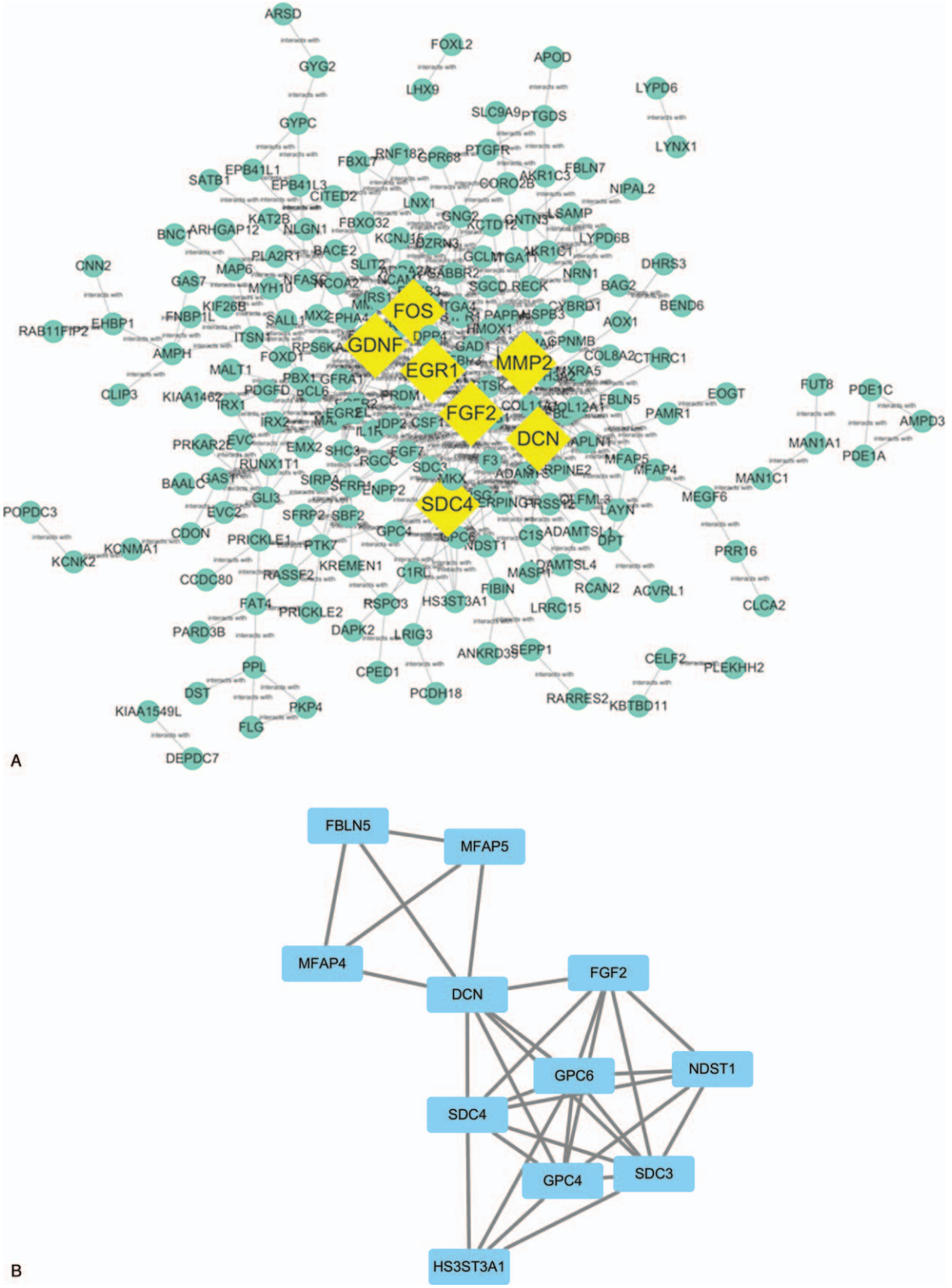

Figure 2. Protein-protein interaction network of DEGs. (A) A total of 203 nodes and 346 interaction associations were identified. The nodes with the highest PPI scores were shaped as the diamond in yellow. (B) The most significant module from the PPI network. DEGs = differentially expressed genes, PPI = protein-protein interaction.

Table 3

The top 10 differentially expressed genes (DEGs) with higher scores, respectively, identified by the 3 centrality methods.

Subgraph		Degree		Closeness	
FGF2	2093.965	FGF2	28	FGF2	0.06858
DCN	1203.585	DCN	22	MMP2	0.06759
MMP2	1137.531	MMP2	21	DCN	0.06741
FOS	776.427	FOS	19	FOS	0.06719
SDC3	492.079	SDC4	13	EGR1	0.06688
SDC4	482.186	EGR1	13	FGFR2	0.06667
ADAMTS5	467.320	GDNF	13	GDNF	0.06667
FGFR2	392.824	FGFR2	12	SDC3	0.06651
EGR1	373.374	SDC3	11	ADAMTS5	0.06641
GDNF	369.072	ADAMTS5	11	SDC4	0.06630

ADAMTS5 = ADAM metallopeptidase with thrombospondin type 1 motif 5, DCN = decorin, EGR1 = early growth response 1, FGF2 = fibroblast growth factor 2, FGFR2 = fibroblast growth factor receptor 2, FOS = Fos proto-oncogene, AP-1 transcription factor subunit, GDNF = glial cell-derived neurotrophic factor, MMP2 = matrix metallopeptidase 2, SDC3 = syndecan 3, SDC4 = syndecan 4.

Table 4

Gene ontology (GO) and the Kyoto encyclopedia of genes and genomes (KEGG) pathway analysis of genes in the selected module.

Category	Term/functions	Gene count	%	*P*-value
BP	Glycosaminoglycan Biosynthetic process	6	0.4	1.9E-11
	Glycosaminoglycan Metabolic process	5	0.3	1.5E-9
	Glycosaminoglycan catabolic process	4	0.2	3.9E-7
	Retinoid metabolic process	4	0.2	5.4E-6
	Extracellular matrix organization	4	0.2	1.8E-4
CC	Lysosomal lumen	5	0.3	9.1E-8
	Golgi lumen	5	0.3	1.5E-7
	Extracellular space	5	0.3	4.3E-3
	Extracellular region	5	0.3	8.3E-3
	Proteinaceous extracellular matrix	3	0.2	9.0E-3
MF	Coreceptor activity involved in the Wnt signaling pathway, planar cell polarity pathway	2	0.1	3.2E-3
	heparan sulfate proteoglycan binding	2	0.1	9.6E-3
PATHWAY	Proteoglycans in cancer	3	0.2	1.2E-2
	Glycosaminoglycan biosynthesis – heparan sulfate/heparin	2	0.1	2.1E-2

BP = biological process, CC = cellular component, MF = molecular function.

levels.[56] JoãoRibas et al[57] reported that HGPS smooth muscle cells showed an exacerbated inflammatory response and an increase of inflammation markers levels. Lovastatin and lonafarnib were able to ameliorate the exacerbated inflammatory response to strain in HGPS smooth muscle cells derived from human induced pluripotent stem cells (iPS-SMCs). Methionine restriction could prolong health span and longevity of 2 short-lived strains of HGPS mice by reducing inflammation and improving the DNA stability of HGPS.[58] Dexibuprofenis a nonsteroidal anti-inflammatory drug, which works by preventing the oxidation of arachidonic acid by inhibiting the enzyme cyclooxygenase.[59] Dexibuprofen may be a potential drug of age-related Alzheimer disease through reducing neuroinflammation.[60] Further studies are required for the validation of Dexibuprofen as a potential compound of treatment of HGPS by anti-inflammatory effects.

Parthenolide is a sesquiterpene lactone found in the medicinal herb Feverfew. Parthenolide exhibits anti-inflammatory activity by inhibiting NF-κB activation. NF-κB altered signaling, which inhibition is an aging intervention strategy, has been causally linked to aging.[61] Parthenolide could effectively inhibit the gene expression mediated by NF-κB and may be useful in preventing the skin photoaging.[62] Parthenolide also inhibits HDAC1 protein without affecting other class I/II HDACs. HDAC

Table 5

The top 5 compounds with high negative correlations with Hutchinson–Gilford Progeria syndrome.

Rank	CMAP name	Mean	N	Enrichment	*P*	Percent non-null
1	Dexibuprofen	-0.432	4	−0.863	.00064	75
2	Parthenolide	-0.225	4	−0.797	.00338	50
3	Lomustine	-0.311	4	−0.794	.00366	50
4	PNU-0293363	-0.259	3	−0.741	.03561	66
5	Lincomycin	-0.479	3	−0.738	.03702	66

inhibitors are new promising drugs in anti-aging research,[63] which can recoverage-associated functional declines, primarily the transcriptional levels of the biosynthetic and metabolic genes decreased.[64] Krishnan et al[65] found that histone H4 acetylation impaired in the *Zmpste24*-deficient (HGPS mouse model) cells, using sodium butyrate (HDAC inhibitor) improved DNA repair and extend the life span of *Zmpste24*$^{-/-}$mouse. Some of HDAC inhibitors have been recently examined in human clinical trials and recommended for the treatment of age-associated diseases.[66]

Overall, dexibuprofen and parthenolide may be the promising drugs for the treatment of HGPS. Nevertheless, little evidence has shown the effect of HGPS or other premature aging disorders. Future validation investigations are needed to test their biological functions.

5. Conclusion

In conclusion, this study provides a preliminary study of the mechanisms underlying HGPS. DEGs were screened out and selected the intersection. Their possible functions were annotated by GO analysis and pathway analysis. The DEGs were mostly enriched in pathways in cancer and PI3K-Akt signaling pathway. Afterward, several key hub genes that may play key roles in HGPS have been screened out by PPI analysis. Using the cMAP tool, dexibuprofen, and parthenolide that might have the potential to reverse the progerin-induced biological process has been predicted. This study may provide a valuable clue for both prevention and treatment research of HGPS. Since HGPS is a rare disease and its incidence is very low, the data obtained is relatively limited in GEO database. Thus, it is necessary to have further studies with larger sample sizes. Our conclusions are based solely on the results of analysis of the gene expression profiles. Therefore, future validation experiments are warranted to examine the results.

Acknowledgments

We would like to thank Dr. Shun Xu for his kindest support and technical assistance.

Author contributions

Dengchuan Wang, Shengshuo Liu, Shi Xu made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. Dengchuan Wang involved in drafting the manuscript or revising it critically for important intellectual content. Dengchuan Wang and Shi Xu gave final approval of the version to be published. Dengchuan Wang, Shengshuo Liu, Shi Xu agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.
Data curation: Shengshuo Liu.
Formal analysis: Dengchuan Wang.

References

[1] Gonzalez JM, Pla D, Perez-Sala D, et al. A-type lamins and Hutchinson-Gilford progeria syndrome: pathogenesis and therapy. Front Biosci (Schol Ed) 2011;3:1133–46.
[2] Hennekam RC. Hutchinson-gilford progeria syndrome: review of the phenotype. Am J Med Genet A 2006;140:2603–24.
[3] Gordon LB, Massaro J, D'Agostino RBSr, et al. Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome. Circulation 2014;130:27–34.
[4] Gonzalo S, Kreienkamp R, Askjaer P. Hutchinson-Gilford Progeria Syndrome: a premature aging disease caused by LMNA gene mutations. Ageing Res Rev 2017;33:18–29.
[5] Dechat T, Pfleghaar K, Sengupta K, et al. Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. Genes Dev 2008;22:832–53.
[6] Arancio W, Pizzolanti G, Genovese SI, et al. Epigenetic involvement in Hutchinson-Gilford Progeria syndrome: a mini-review. Gerontology 2014;60:197–203.
[7] Rodriguez S, Coppedè F, Sagelius H, et al. Increased expression of the Hutchinson–Gilford progeria syndrome truncated lamin A transcript during cell aging. Eur J Hum Genet 2009;17:928–37.
[8] Rivera-Torres J, Acín-Perez R, Cabezas-Sánchez P, et al. Identification of mitochondrial dysfunction in Hutchinson-Gilford progeria syndrome through use of stable isotope labeling with amino acids in cell culture. J Proteomics 2013;91:466–77.
[9] Prokocimer M, Barkan R, Gruenbaum Y. Hutchinson-Gilford progeria syndrome through the lens of transcription. Aging Cell 2013;12:533–43.
[10] Gonzalo S, Kreienkamp R. DNA repair defects and genome instability in Hutchinson-Gilford Progeria Syndrome. Curr Opin Cell Biol 2015;34:75–83.
[11] Strandgren C, Revêchon G, Sola-Carvajal A, et al. Emerging candidate treatment strategies for Hutchinson-Gilford progeria syndrome. Biochem Soc Trans 2017;45:1279–93.
[12] Fong LG, Frost D, Meta M, et al. A protein farnesyltransferase inhibitor ameliorates disease in a mousemodel of progeria. Science 2006;311:1621–3.
[13] Varela I, Pereira S, Ugalde AP, et al. Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. Nat Med 2008;14:767–72.
[14] Blondel S, Egesipe AL, Picardi P, et al. Drug screening on Hutchinson Gilford progeria pluripotent stem cells reveals aminopyrimidines as new modulators of farnesylation. Cell Death Dis 2016;7:e2105.
[15] Cao K, Graziotto JJ, Blair CD, et al. Rapamycin reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson-Gilford progeria syndrome cells. Sci Transl Med 2011;3:ra58.
[16] Gabriel D, Roedl D, Gordon LB, et al. Sulforaphane enhances progerin clearance in Hutchinson-Gilford progeria fibroblasts. Aging Cell 2015;14:78–91.
[17] Park SK, Shin OS. Metformin alleviates ageing cellular phenotypes in Hutchinson-Gilford progeria syndrome dermal fibroblasts. Exp Dermatol 2017;26:889–95.
[18] Xiong ZM, Choi JY, Wang K, et al. Methylene blue alleviates nuclear and mitochondrial abnormalities inprogeria. Aging Cell 2016;15:279–90.
[19] Surrey LF, Luo M, Chang F, et al. The genomic era of clinical oncology: integrated genomic analysis for precision cancer care. Cytogenet Genome Res 2016;150:162–75.
[20] Peters MJ, Joehanes R, Pilling LC, et al. The transcriptional landscape of age in human peripheral blood. Nat Commun 2015;6:8570.
[21] Mateos J, Fafián-Labora J, Morente-López M, et al. Next-generation sequencing and quantitative proteomics of Hutchinson-Gilford progeria syndrome-derived cells point to a role of nucleotide metabolism in premature aging. PLoS One 2018;13:e0205878.
[22] Arancio W. A bioinformatics analysis of lamin-A regulatory network: a perspective on epigenetic involvement in Hutchinson-Gilford progeria syndrome. Rejuvenation Res 2012;15:123–7.
[23] Ly DH, Lockhart DJ, Lerner RA, et al. Mitotic misregulation and human aging. Science 2000;287:2486–92.
[24] Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 2009;4:44–57.
[25] von Mering C, Huynen M, Jaeggi D, et al. STRING: a database of predicted functional associations between proteins. Nucleic Acids Res 2003;31:258–61.
[26] Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003;13:2498–504.
[27] Bader GD, Hogue CW. An automated method for finding molecular complexes in large protein interaction networks. BMC Bioinformatics 2003;4:2.
[28] Jeong H, Mason SP, Barabási AL, et al. Lethality and centrality in protein networks. Nature 2001;411:41–2.

[29] Tang Y, Li M, Wang J, et al. CytoNCA: a cytoscape plugin for centrality analysis and evaluation of protein interaction networks. Biosystems 2015;127:67–72.
[30] Gillbro JM, Merinville E, Olsson M, et al. The use of gene arrays and corresponding connectivity mapping (Cmap) to identify novel anti-ageing ingredients. Int J Cosmet Sci 2015;(Suppl 1):9–14.
[31] Hoeijmakers JH. DNA damage, aging, and cancer. N Engl J Med 2009;361:1475–85.
[32] Kubben N, Misteli T. Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases. Nat Rev Mol Cell Biol 2017;18:595–609.
[33] Stewart CL. Mouse models of the nuclear envelopathies and related diseases. Preface. Curr Top Dev Biol 2014;109:11–3.
[34] Breitschopf K, Zeiher AM, Dimmeler S. Pro-atherogenic factors induce telomerase inactivation in endothelial cells through an Akt-dependent mechanism. FEBS Lett 2001;493:21–5.
[35] Xiao-Hong D, Chang-Qin X, Jian-Hua H, et al. Icariin delays homocysteine-induced endothelial cellular senescence involving activation of the PI3K/AKT-eNOS signaling pathway. Pharm Biol 2013;51:433–40.
[36] Yentrapalli R, Azimzadeh O, Sriharshan A, et al. The PI3K/Akt/mTOR pathway is implicated in the premature senescence of primary human endothelial cells exposed to chronic radiation. PLoS One 2013;8:e70024.
[37] Hale CM, Shrestha AL, Khatau SB, et al. Dysfunctional connections between the nucleus and the actin and microtubule networks in laminopathic models. Biophys J 2008;95:5462–75.
[38] Csoka AB, English SB, Simkevich CP, et al. Genome-scale expression profiling of Hutchinson-Gilford progeria syndrome reveals widespread transcriptional misregulation leading to mesodermal/mesenchymal defects and accelerated atherosclerosis. Aging Cell 2004;3:235–43.
[39] Hernandez L, Roux KJ, Wong ES, et al. Functional coupling between the extracellular matrix and nuclear lamina by Wnt signaling in progeria. Dev Cell 2010;19:413–25.
[40] Vidak S, Foisner R. Molecular insights into the premature aging disease progeria. Histochem Cell Biol 2016;145:401–17.
[41] Bercht Pfleghaar K, Taimen P, Butin-Israeli V, et al. Gene-rich chromosomal regions are preferentially localized in the lamin B deficient nuclear blebs of atypical progeria cells. Nucleus 2015;6:66–76.
[42] Balajee AS, Machwe A, May A, et al. The Werner syndrome protein is involved in RNA polymerase II transcription. Mol Biol Cell 1999;10:2655–68.
[43] Spann TP, Goldman AE, Wang C, et al. Alteration of nuclear lamin organization inhibits RNA polymerase II-dependent transcription. J Cell Biol 2002;156:603–8.
[44] Matchett KB, McFarlane S, Hamilton SE, et al. Ran GTPase in nuclear envelope formation and cancer metastasis. Adv Exp Med Biol 2014;773:323–51.
[45] Datta S, Snow CJ, Paschal BM. A pathway linking oxidative stress and the Ran GTPase system in progeria. Mol Biol Cell 2014;25:1202–15.
[46] Dworak N, Makosa D, Chatterjee M, et al. A nuclear lamina-chromatin-Ran GTPase axis modulates nuclear import and DNA damage signaling. Aging Cell 2019;18:e12851.
[47] Beavan LA, Quentin-Hoffmann E, Schönherr E, et al. Deficient expression of decorin in infantile progeroid patients. J Biol Chem 1993;268:9856–62.
[48] Harten IA, Zahr RS, Lemire JM, et al. Age-dependent loss of MMP-3 in Hutchinson-Gilford progeria syndrome. J Gerontol A Biol Sci Med Sci 2011;66:1201–7.
[49] Winkles JA, O'Connor ML, Friesel R. Altered regulation of platelet-derived growth factor A-chain and c-fos gene expression in senescent progeria fibroblasts. J Cell Physiol 1990;144:313–25.
[50] Quentin-Hoffmann E, Harrach B, Robenek H, et al. Genetic defects in proteoglycan biosynthesis. Padiatr Padol 1993;28:37–41.
[51] Cylwik B, Lipartowska K, Chrostek L, et al. Congenital disorders of glycosylation. Part II. Defects of protein O-glycosylation. Acta Biochim Pol 2013;60:361–8.
[52] Lee DH, Oh JH, Chung JH. Glycosaminoglycan and proteoglycan in skin aging. J Dermatol Sci 2016;83:174–81.
[53] Brown WT. Progeria: a human-disease model of accelerated aging. Am J Clin Nutr 1992;55(6 Suppl):1222S–4S.
[54] Zebrower M, Kieras FJ, Brown WT. Urinary hyaluronic acid elevation in Hutchinson-Gilford progeria syndrome. Mech Ageing Dev 1986;35: 39–46.
[55] Sweeney KJ, Weiss AS. Hyaluronic acid in progeria and the aged phenotype? Gerontology 1992;38:139–52.
[56] Osorio FG, Bárcena C, Soria-Valles C, et al. Nuclear lamina defects cause ATM-dependent NF-κB activation and link accelerated aging to a systemic inflammatory response. Genes Dev 2012;26:2311–24.
[57] Ribas J, Zhang YS, Pitrez PR, et al. Biomechanical strain exacerbates inflammation on a progeria-on-a-chip model. Small 2017;13:10.
[58] Bárcena C, López-Otín C, Kroemer G, et al. Methionine restriction for improving progeria: another autophagy-inducing anti-aging strategy? Autophagy 2019;15:558–9.
[59] Bacchi S, Palumbo P, Sponta A, et al. Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. Antiinflamm Antiallergy Agents Med Chem 2012;11:52–64.
[60] Ettcheto M, Sánchez-López E, Pons L, et al. Dexibuprofen prevents neurodegeneration and cognitive decline in APPswe/PS1dE9 through multiple signaling pathways. Redox Biol 2017;13:345–52.
[61] Osorio FG, Soria-Valles C, Santiago-Fernández O, et al. NF-κB signaling as a driver of ageing. Int Rev Cell Mol Biol 2016;326:133–74.
[62] Tanaka K, Asamitsu K, Uranishi H, et al. Protecting skin photoaging by NF-kappaB inhibitor. Curr Drug Metab 2010;11:431–5.
[63] Pasyukova EG, Vaiserman AM. HDAC inhibitors: a new promising drug class in anti-aging research. Mech Ageing Dev 2017;166:6–15.
[64] Seroude L, Brummel T, Kapahi P, et al. Spatio-temporal analysis of gene expression during aging in Drosophila melanogaster. Aging Cell 2002;1:47–56.
[65] Krishnan V, Chow MZ, Wang Z, et al. Histone H4 lysine 16 hypoacetylation is associated with defective DNA repair and premature senescence in Zmpste24-deficient mice. Proc Natl Acad Sci U S A 2011;108:12325–30.
[66] Vaiserman AM, Pasyukova EG. Epigenetic drugs: a novel anti-aging strategy? Front Genet 2012;3:224.