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Original Article

Molecular biological characteristics: common and different profiles between the dental pulp stem cells and periodontal ligament stem cells

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Abstract: Dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) are two most common dental stem cell resources for tissue engineering or stem cell therapy for many conditions. However, the molecular biological characteristics of DPSCs and PDLSCs are still unclear. In this study, we tried to explore the common and different profiles of molecular characteristics between the DPSCs and PDLSCs based on the analysis of gene-expression microarray data from Gene Expression Omnibus (GEO) database using database for annotation, visualization and integrated discovery (DAVID). The results showed that many differentially expressed genes between the human DPSCs and PDLSCs were related to neural system, skeleton system, teeth and cardiovascular system development. The different molecular expression patterns between the DPSCs and PDLSCs also implied that DPSCs may be more suitable cell resources for the treatment of neural, cardiovascular and odontogenesis related disease, whereas PDLSCs may be more suitable cell resources for the treatment of periodontal ligament, cementum and alveolar bone related disease.

Keywords: Molecular biological characteristics, dental pulp stem cells, periodontal ligament stem cells

Introduction

Dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) are two most common dental stem cells, and considered to be derived from cranial neural crest cells, and can differentiate into several mesenchymal cells (MSCs) lineages, including osteoblasts, adipocytes, chondrocytes and neuron both *in vitro* and *in vivo* [1-4]. Although DPSCs and PDLSCs exhibit several common multi-differentiation potentials, differences have been reported among different stem cell types. Although DPSCs have been used as a promising cell type for bone tissue engineering, previous studies showed that DPSCs appeared to be more committed to odontogenic capability [5, 6]. In addition, PDLSCs are more likely to generate a cementum/periodontal ligament (PDL)-like structure, and show the best regenerating capacity of periodontal ligament, cementum and alveolar bone [7]. These findings implied that DPSCs and PDLSCs may have many differences in their biological characterisitics and functions, and these differences may due to genetic backgrounds or molecular characterisitcs. In this study, we tried to explore the common and different profiles of molecular biological characteristics between the DPSCs and PDLSCs using the gene-expression microarray data from Gene Expression Omnibus (GEO) database.

Materials and methods

Obtaining gene expression profiles of DPSCs and PDLSCs from the GEO database

GEO is a public functional genomics data repository that stores curated gene expression datasets, as well as original series and platform records. Enter search terms could locate experiments of interest. Dataset records also contain additional resources including cluster tools and differential expression queries for further analysis [8]. In this study, we obtained gene expression profiles of human DPSCs and PDLSCs from

Table 1. Differentially expressed genes between the human DPSCs and PDLSCs are enriched into neural system related subgroups based on "Biological Process" GO term

GO Term	*P* Value	Genes
Nervous system development	1.88E-08	SLC5A3, NRG3, S100A8, FGF9, PLPPR5, POSTN, NAP1L2, KANK1, WNT2, EDNRB, BRINP1, DAB1, UNC5B, SCRG1, TIAM1, SEMA7A, MAPT, SEMA3E, RSPO2, SPON2, NEGR1, DLG2, PTPRK, WNT10A, EGR3, SGK1, TNIK, STX3, CNTN6, CRTAC1, KIF5C, GRIN2A, PADI2, THY1, CTNNA2, AMIGO2, PRKCQ, CHRDL1, CBLN2, RELN, CNTN3, GAP43, WNT5A, IRX3, PLXNC1, IRX5, SPOCK2, KCNA1, CLU, COL3A1, CTNND2, BEX1, SPOCK1, CLDN11, DTNBP1, CDH4, CRMP1, ALDH1A3, MSI1, ACAN, TNN, SPP1, PARD6B, NES, TRPC4, GLRB, NOS1, GABRA4, GDPD5, GAS7, SHANK2, PROM1, EPHA5, SLC4A10, PPP1R9A, SRPX2, WDR62, SFRP2, ITGA8, SALL1, MAP2, LRRN1, MYO16, ATP8A2, GFRA1, SCN8A, RGS9, BMPR1B, BMP7, HDAC9, SYT17
Neurogenesis	7.99E-07	NRG3, S100A8, PLPPR5, POSTN, NAP1L2, KANK1, WNT2, EDNRB, BRINP1, DAB1, UNC5B, TIAM1, SEMA7A, MAPT, SEMA3E, RSPO2, SPON2, NEGR1, PTPRK, WNT10A, SGK1, TNIK, STX3, CRTAC1, CNTN6, KIF5C, GRIN2A, THY1, CTNNA2, PRKCQ, RELN, GAP43, WNT5A, IRX3, PLXNC1, IRX5, KCNA1, CLU, COL3A1, CTNND2, SPOCK1, DTNBP1, CDH4, CRMP1, TNN, SPP1, PARD6B, TRPC4, NOS1, GDPD5, PROM1, EPHA5, PPP1R9A, SLC4A10, WDR62, SFRP2, SALL1, MAP2, LRRN1, ATP8A2, BMP7, HDAC9, BMPR1B, SYT17
Neuron differentiation	3.92E-06	PLPPR5, POSTN, NAP1L2, KANK1, WNT2, EDNRB, BRINP1, DAB1, UNC5B, TIAM1, SEMA7A, MAPT, SEMA3E, RSPO2, SPON2, NEGR1, WNT10A, PTPRK, SGK1, TNIK, STX3, CRTAC1, CNTN6, KIF5C, THY1, CTNNA2, PRKCQ, RELN, GAP43, WNT5A, IRX3, PLXNC1, IRX5, CTNND2, SPOCK1, CDH4, DTNBP1, CRMP1, TNN, SPP1, PARD6B, GDPD5, EPHA5, PROM1, PPP1R9A, SLC4A10, SFRP2, SALL1, MAP2, LRRN1, ATP8A2, BMP7, HDAC9, BMPR1B, SYT17
Generation of neurons	4.18E-06	NRG3, PLPPR5, POSTN, NAP1L2, KANK1, WNT2, EDNRB, BRINP1, DAB1, UNC5B, TIAM1, SEMA7A, MAPT, SEMA3E, RSPO2, SPON2, NEGR1, PTPRK, WNT10A, SGK1, TNIK, STX3, CRTAC1, CNTN6, KIF5C, THY1, CTNNA2, PRKCQ, RELN, GAP43, WNT5A, IRX3, PLXNC1, IRX5, KCNA1, COL3A1, CTNND2, SPOCK1, CDH4, DTNBP1, CRMP1, TNN, SPP1, PARD6B, NOS1, GDPD5, PROM1, EPHA5, PPP1R9A, SLC4A10, SFRP2, SALL1, MAP2, LRRN1, ATP8A2, BMP7, HDAC9, BMPR1B, SYT17
Neuron projection development	7.13E-06	WNT5A, PLXNC1, CTNND2, PLPPR5, SPOCK1, POSTN, DTNBP1, CDH4, KANK1, DAB1, UNC5B, TIAM1, CRMP1, SEMA7A, MAPT, SEMA3E, TNN, SPON2, NEGR1, SPP1, PARD6B, PTPRK, SGK1, STX3, TNIK, CRTAC1, KIF5C, GDPD5, CTNNA2, THY1, EPHA5, PRKCQ, PPP1R9A, MAP2, LRRN1, ATP8A2, RELN, BMPR1B, BMP7, SYT17, GAP43
Neuron development	3.17E-05	WNT5A, PLXNC1, IRX5, CTNND2, PLPPR5, SPOCK1, POSTN, DTNBP1, CDH4, KANK1, EDNRB, DAB1, UNC5B, TIAM1, CRMP1, SEMA7A, MAPT, SEMA3E, TNN, SPON2, NEGR1, SPP1, PARD6B, PTPRK, SGK1, STX3, TNIK, CRTAC1, KIF5C, GDPD5, CTNNA2, THY1, EPHA5, PRKCQ, PPP1R9A, SLC4A10, MAP2, LRRN1, ATP8A2, RELN, BMPR1B, BMP7, SYT17, GAP43
Axon development	4.59E-05	WNT5A, PLXNC1, CDH4, DAB1, UNC5B, CRMP1, TIAM1, MAPT, SEMA7A, SEMA3E, TNN, SPON2, SPP1, PARD6B, CRTAC1, KIF5C, CTNNA2, THY1, EPHA5, PRKCQ, LRRN1, ATP8A2, RELN, BMP7, BMPR1B, GAP43
Regulation of nervous system development	2.54E-04	WNT5A, IRX3, PLXNC1, NRG3, COL3A1, PLPPR5, SPOCK1, NAP1L2, CDH4, KANK1, WNT2, EDNRB, BRINP1, DAB1, TIAM1, CRMP1, SEMA7A, MAPT, SEMA3E, NEGR1, SPP1, TNIK, NOS1, GDPD5, THY1, AMIGO2, PPP1R9A, CBLN2, SRPX2, SFRP2, LRRN1, ATP8A2, RELN, BMP7, SYT17
Regulation of neuron differentiation	6.65E-04	WNT5A, IRX3, PLXNC1, PLPPR5, SPOCK1, NAP1L2, CDH4, KANK1, EDNRB, BRINP1, DAB1, TIAM1, CRMP1, MAPT, SEMA7A, SEMA3E, NEGR1, SPP1, TNIK, GDPD5, THY1, PPP1R9A, SFRP2, ATP8A2, RELN, BMP7, SYT17
Negative regulation of neurogenesis	0.001827	WNT5A, IRX3, NRG3, COL3A1, SPOCK1, KANK1, THY1, EDNRB, BRINP1, DAB1, CRMP1, SEMA7A, SEMA3E, BMP7, SPP1
Positive regulation of nervous system development	0.001948	WNT5A, IRX3, PLPPR5, GDPD5, NAP1L2, CDH4, WNT2, AMIGO2, BRINP1, PPP1R9A, DAB1, CBLN2, SRPX2, TIAM1, MAPT, SEMA7A, LRRN1, ATP8A2, RELN, BMP7, NEGR1, SYT17
Positive regulation of neuron differentiation	0.002523	WNT5A, IRX3, PLPPR5, GDPD5, NAP1L2, CDH4, BRINP1, PPP1R9A, DAB1, TIAM1, MAPT, SEMA7A, ATP8A2, RELN, BMP7, NEGR1, SYT17
Negative regulation of nervous system development	0.003616	WNT5A, IRX3, NRG3, COL3A1, SPOCK1, KANK1, THY1, EDNRB, BRINP1, DAB1, CRMP1, SEMA7A, SEMA3E, BMP7, SPP1
Negative regulation of neuron differentiation	0.005549	WNT5A, EDNRB, IRX3, DAB1, CRMP1, SEMA7A, SEMA3E, SPOCK1, BMP7, KANK1, SPP1, THY1
Positive regulation of neurogenesis	0.009342	WNT5A, IRX3, PLPPR5, GDPD5, NAP1L2, CDH4, WNT2, BRINP1, PPP1R9A, DAB1, TIAM1, MAPT, SEMA7A, ATP8A2, RELN, BMP7, NEGR1, SYT17

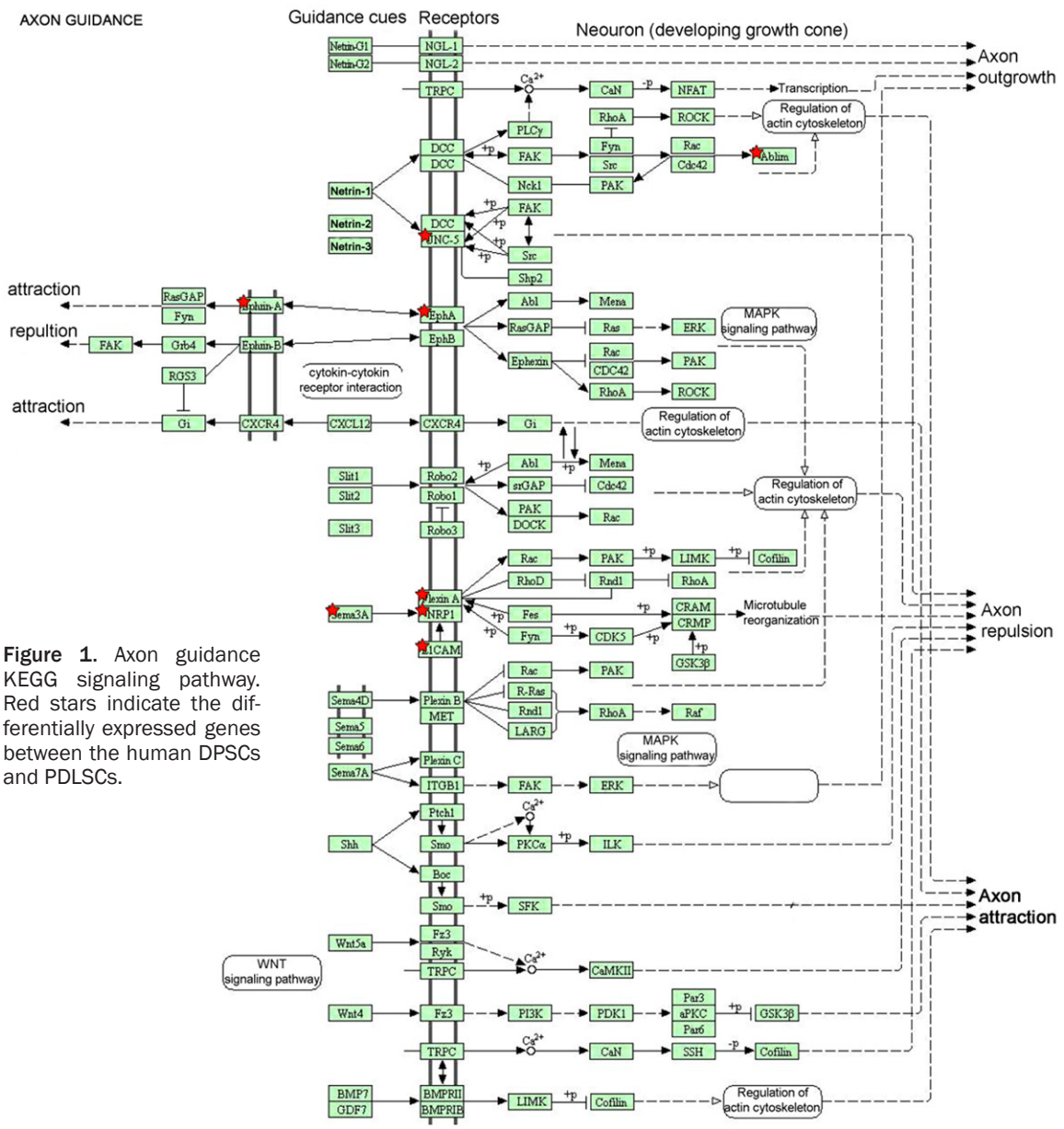

Figure 1. Axon guidance KEGG signaling pathway. Red stars indicate the differentially expressed genes between the human DPSCs and PDLSCs.

the GEO database. The first step was to enter the GEO website: http://www.ncbi.nlm.nih.gov/gds/. Then entered the sentence "periodontal ligament and dental pulp" to start search. The datasets (Title: Comparative gene expression analysis of the human periodontal ligament and dental pulp in the human permanent teeth. Series Accession number: GSE50639) was chosen. In this datasets, DPSCs and PDLSCs were obtained from the human permanent teeth. The total RNA from the DPSCs and PDLSCs were used for cDNA microarray analysis, and the detailed information about this datasets was described by Kim S in the on-line webpage (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE50639). The GEO2R software (GEO own data analysis tools) was used to obtained the genes that differentially expressed between the DPSCs and PDLSCs. The genes' expression values also were obtained.

Bioinformatic analysis for genes that differentially expressed between the DPSCs and PDLSCs

The on-line database for annotation, visualization and integrated discovery (DAVID) is a useful tool for analysis of large gene list, and can

Table 2. Differentially expressed genes between the human DPSCs and PDLSCs are enriched into skeleton system related subgroups based on "Biological Process" GO term

GO Term	*P* Value	Genes
Skeletal system development	4.73E-07	WNT5A, RBP4, IRX5, FGF9, MMP9, COL3A1, ACP5, POSTN, CHAD, MSX2, TYMS, DSPP, RSPO2, ACAN, COL12A1, SLC9B2, COL11A2, LOXL2, COL11A1, COL10A1, EFEMP1, MMP13, SIGLEC15, PTHLH, RDH10, DHRS3, SFRP2, SCIN, RASSF2, BMPR1B, BMP7, PHEX
Ossification	1.13E-06	WNT5A, ASPN, FGF9, MMP9, ITGA11, IGSF10, MSX2, DSPP, GPC3, SEMA7A, RSPO2, COL6A1, COL11A2, COL11A1, SPP1, COL10A1, DMP1, MMP13, PTHLH, CTSK, CHRDL1, SFRP2, RASSF2, BMPR1B, PHEX, BMP7
Biomineral tissue development	2.88E-06	ASPN, ODAM, DMP1, MMP13, MSX2, AMBN, DSPP, WDR72, MMP20, GPC3, RSPO2, BMPR1B, BMP7, PHEX, SPP1
Cartilage development	5.95E-06	WNT5A, FGF9, EFEMP1, MMP13, PTHLH, MSX2, TYMS, SFRP2, RSPO2, SCIN, ACAN, BMPR1B, BMP7, COL11A2, LOXL2, COL11A1, COL10A1
Chondrocyte differentiation	2.85E-04	PTHLH, MSX2, SFRP2, FGF9, EFEMP1, ACAN, BMPR1B, COL11A2, LOXL2, COL11A1
Skeletal system morphogenesis	0.00135	IRX5, ACP5, MMP13, CHAD, MSX2, RDH10, DHRS3, SFRP2, ACAN, BMPR1B, BMP7, COL11A2, COL11A1, COL10A1
Chondrocyte development	0.002462	MSX2, SFRP2, ACAN, BMPR1B, COL11A1
Osteoblast differentiation	0.015907	PTHLH, MSX2, SFRP2, FGF9, SEMA7A, RSPO2, ITGA11, COL6A1, BMPR1B, BMP7, SPP1
Regulation of cartilage development	0.016392	WNT5A, PTHLH, SCIN, EFEMP1, BMPR1B, LOXL2
Regulation of chondrocyte differentiation	0.021716	PTHLH, SCIN, EFEMP1, BMPR1B, LOXL2
Bone remodeling	0.022015	CTSK, RASSF2, ACP5, SIGLEC15, DCSTAMP, SPP1
Bone development	0.024195	MSX2, DHRS3, SFRP2, ACP5, SLC9B2, BMPR1B, MMP13, SIGLEC15, COL10A1, CHAD

provide a comprehensive set of functional annotation tools for investigators to understand biological meaning behind large list of genes [9]. In this study, we used the DAVID to systematically explore the common and different profiles of molecular biological characteristics between the DPSCs and PDLSCs. We firstly entered the on-line DAVID website: https://david.ncifcrf.gov/. Then input the name of these four hundred and fifty differentially expressed genes obtained from the GEO database, and chose the "official gene symbol" as the gene identifier type, and "Homo sapiens" as annotations to start the analysis.

Results

Some genes that differentially expressed between the DPSCs and PDLSCs were related to neural system

Dental stem cells are considered to be derived from neural crest cells, and DPSCs were showed to be powerful cell resources for treatment of neural disease. These differentially expressed genes between the DPSCs and PDLSCs could be enriched into many subgroups based on the analysis of DAVID. For Gene Ontology (GO) term "biological process, (BP)". Many of these subgroups were related to neural system (**Table 1**), such as nervous system development, neurogenesis, neuron differentiation. For KEGG pathway, seven genes, EPHA5, ABLIM2, PLXNC1, UNC5B, SEMA7A, SEMA3E and MET were enriched into "axon guidance" pathway (**Figure 1**). Although many genes may exhibit different function under different condition, many of these differentially expressed genes, such as BMP7, NEGR1, GDPD5 that could positively regulate the nervous system development, exhibited higher expression level in DPSCs.

Some genes that differentially expressed between the DPSCs and PDLSCs were related to skeleton system

DPSCs and PDLSCs were used as cell resources for bone and cartilage tissue engineering. In this study, with the analysis of DAVID database, these differentially expressed genes between the DPSCs and PDLSCs could be enriched into many skeleton system-related subgroups (**Table 2**) based on the biological process GO term. To our surprise, some chondrogenic marker genes, such as ACAN, exhibited higher expression level in PDLSCs.

Some genes that differentially expressed between the DPSCs and PDLSCs were related to teeth development

DPSCs and PDLSCs have different function during the developmental process of teeth. These

Table 3. Differentially expressed genes between the human DPSCs and PDLSCs are enriched into teeth development related subgroups based on "Biological Process" GO term

GO Term	*P* Value	Genes
Odontogenesis	3.48E-04	ASPN, DLX3, MSX2, WNT10A, ODAM, MMP20, WDR72, AMBN, DMP1, RSPO2, BMP7
Tooth mineralization	0.001788	ASPN, MSX2, MMP20, WDR72, DMP1
Regulation of odontogenesis	0.002462	ASPN, WNT10A, MMP20, DMP1, RSPO2
Regulation of odontogenesis of dentin-containing tooth	0.00299	WNT10A, MMP20, DMP1, RSPO2
Regulation of enamel mineralization	0.089722	MMP20, DMP1
Osteoclast fusion	0.089722	CD109, DCSTAMP
Spinal cord motor neuron migration	0.089722	DAB1, RELN
Negative regulation of odontogenesis	0.089722	ASPN, RSPO2

Table 4. Differentially expressed genes between the human DPSCs and PDLSCs are enriched into cardiovascular system related subgroups based on "Biological Process" GO term

GO Term	*P* Value	Genes
Cardiovascular system development	0.007607	WNT5A, RBP4, FGF9, COL3A1, CXCL8, ANPEP, CXADR, MSX2, WNT2, APLNR, GPC3, UNC5B, SORBS2, FAP, SEMA3E, ACAN, TGFA, IL1B, TMEM100, LOXL2, COL11A1, SCG2, EGR3, KCNK2, COL5A1, THY1, DLX3, PROK2, MYO18B, DHRS3, SRPX2, SFRP2, SALL1, BMP7, HDAC9
Circulatory system development	0.007607	WNT5A, RBP4, FGF9, COL3A1, CXCL8, ANPEP, CXADR, MSX2, WNT2, APLNR, GPC3, UNC5B, SORBS2, FAP, SEMA3E, ACAN, TGFA, IL1B, TMEM100, LOXL2, COL11A1, SCG2, EGR3, KCNK2, COL5A1, THY1, DLX3, PROK2, MYO18B, DHRS3, SRPX2, SFRP2, SALL1, BMP7, HDAC9
Blood vessel morphogenesis	0.021148	WNT5A, EGR3, FGF9, COL3A1, CXCL8, ANPEP, THY1, PROK2, MYO18B, SRPX2, UNC5B, SFRP2, FAP, SEMA3E, TGFA, IL1B, TMEM100, HDAC9, LOXL2, SCG2
Cardiac muscle tissue development	0.02999	WNT5A, WNT2, RBP4, MYO18B, SORBS2, FGF9, BMP7, CXADR, COL11A1, KCNK2
Regulation of cardiac muscle tissue growth	0.090872	WNT2, RBP4, FGF9, KCNK2

differentially expressed genes between the DPSCs and PDLSCs could be enriched into many teeth development related subgroups (**Table 3**) based on the biological process GO term, and several dentin development related genes, such as Dlx3 and DMP1, exhibited higher expression level in DPSCs.

Some genes that differentially expressed between the DPSCs and PDLSCs were related to cardiovascular system

Cardiac neural crest cell is one type of neural crest cells. In this study, these differentially expressed genes between the DPSCs and PDLSCs could be enriched into many cardiovascular system related subgroups (**Table 4**) based on the biological process GO term. For KEGG pathway, SGK1, FGF9, COL3A1, MET, ITGA11, KITLG, ITGA4, COL5A1, CHAD, ITGA8, COL6A3, COL6A2, COL6A1, RELN, TNN, PRKAA2, COL11A2, COL11A1 and SPP1 are enriched into "PI3K-Akt" signaling pathway (**Figure 2**), a pathway that plays crucial role in the cardiocascular system development [10, 11]. Many genes, such as Msx2 and MYO18B, that could positively regulate cardiovascular development, exhibited higher expression level in DPSCs.

Discussion

DPSCs and PDLSCs could serve as easily accessible adult MSCs resources for clinical applications, including tissue engineering and stem cell therapy for teeth, bone, neuro and cardiovascule related diseases [2, 12-14]. However, the molecular biological characteristics of DPSCs and PDLSCs have not been clearly depicted. An elaborate comparison of common and different molecular profiles between the DPSCs and PDLSCs could offer some useful clues for expanding the application range of DPSCs and PDLSCs, choosing suitable cell resources for different condition. In this study, our findings showed that many differentially expressed between the DPSCs and PDLSCs were related to neural system, one possible cause may due to DPSCs and PDLSCs derived from the neural crest cells. The findings also implied that DPSCs and PDLSCs, especially DPSCs exhibited higher expression level in genes that could positively regulate the development of nervous system,

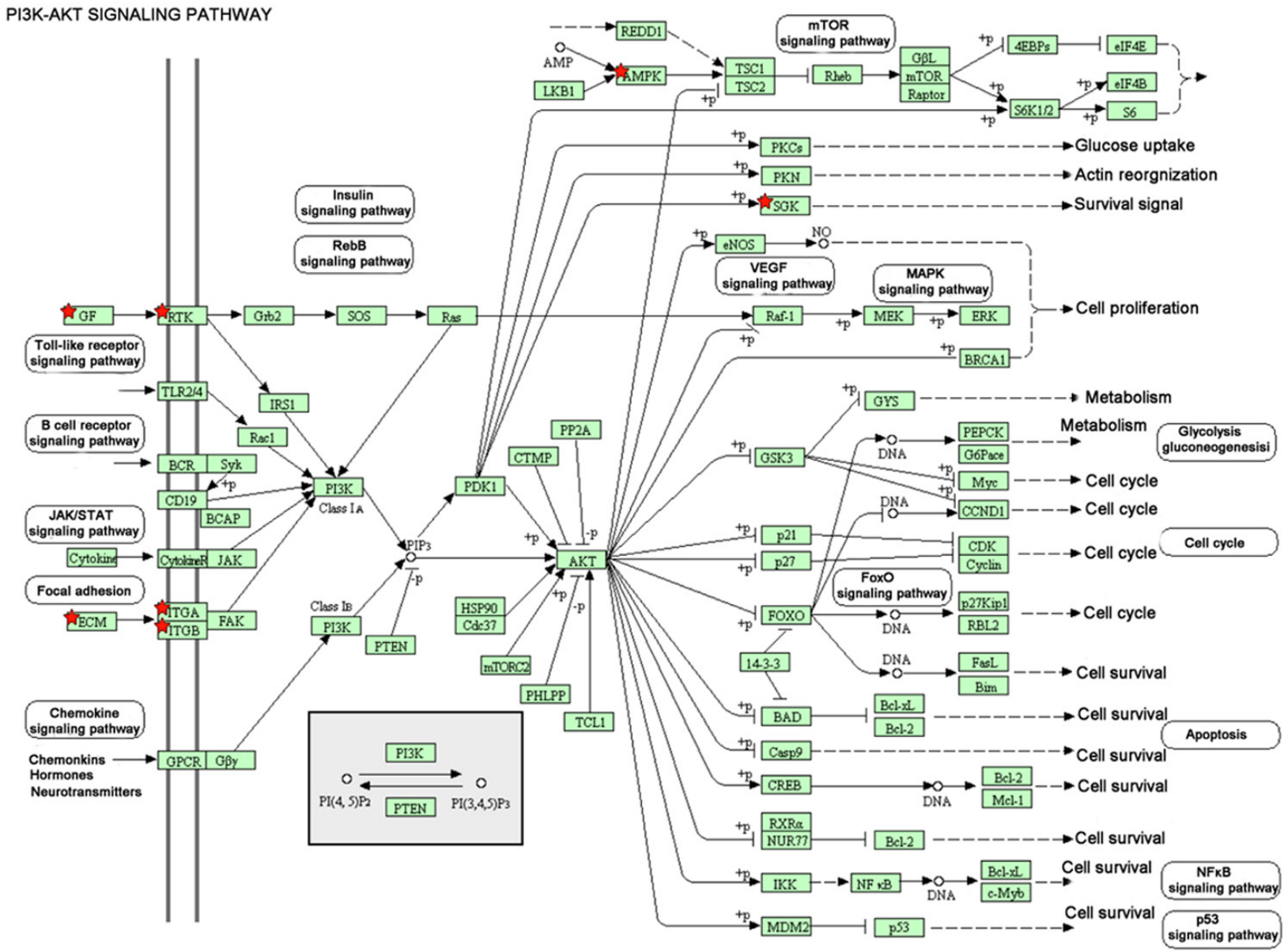

Figure 2. PI3K-Akt KEGG signaling pathway. Red stars indicate differentially expressed genes between the human DPSCs and PDLSCs.

may be useful cell resources for neuro related disease. Previous studies also demonstrated that both DPSCs and PDLSCs could differentiate into neurons, and in-vivo transplantation of DPSCs could repair spinal cord injury or therapy Parkinson disease [15-17].

DPSCs and PDLSCs, which is more suitable for bone or dentin regeneration is still no definite conclusion. Previous studies showed that DPSCs appear to be more committed to odontogenic capability [6]. In addition, PDLSCs are more likely to generate a cementum/PDL-like structure, and showed the best regenerating capacity of periodontal ligament, cementum and alveolar bone [7]. In this study, the findings showed that several dentin development-related genes, such as Dlx3 and DMP1, exhibited higher expression level in DPSCs when compared to PDLSCs [18]. It may also confirmed that DPSCs may be more committed to odontogenic capability. Although DPSCs and PDLSCs could differentiated into chondrocyte under suitable condition *in vitro*, these two cells have not been widely used for cartilage regeneration. In this study, the findings showed that PDLSCs exhibited higher expression level of ACAN, a chondrogenic marker. It implied that PDLSCs have stronger matrix formation ability, but whether PDLSCs are more suitable for cartilage regeneration should be investigated in future functional experiment.

Cardiac neural crest cells and cranial neural crest cells are two types of neural crest cells. In this study, the finds showed that many genes, such as Msx2 and MYO18B, that could positively regulate cardiovascular development, exhibited higher expression level in DPSCs [19]. It implied that DPSCs may be suitable cell resources for treatment of cardiovascular disease. Previous studies also showed that conditioned medium of DPSCs from human exfoliated deciduous teeth reduces cardiac injury following ischemia-reperfusion [20]. In addition, human DPSCs could improve left ventricular function, induce angiogenesis, and reduce infarct size in rats with acute myocardial infarction [21].

In summary, our findings showed that there were many differentially expressed genes between the human DPSCs and PDLSCs, and these genes were related to neural system, skeleton system, teeth and cardiovascular system development. The different molecular expression patterns between the DPSCs and PDLSCs also implied that DPSCs may be more suitable cell resources for treatment of neuro, cardiovascule and odontogenesis related disease, whereas PDLSCs may be more suitable cell resources for treatment of periodontal ligament, cementum and alveolar bone related disease.

Disclosure of conflict of interest

None.

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