Babol University of Medical Sciences
IJMCM
International Journal of Molecular and Cellular Medicine
p-ISSN: 2251-9637 e-ISSN: 2251-9645
Cellular and Molecular Biology Research Center

hsa-miR-508-5p as a New Potential Player in Intervertebral Disc Degeneration

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Article type:
Original Article

Received:
2022.08.12
Revised:
2022.11.09
Accepted:
2022.11.28
Pub Online:
2023.01.01

ABSTRACT

Intervertebral disc degeneration (IDD) is widely known as the principal cause of low back pain, diminishing patients' quality of life and imposing a huge economic burden on healthcare systems worldwide. However, the underlying mechanisms of IDD remain to be determined. This study aimed to scrutinize data sets via bioinformatics to identify microRNAs (miRNAs)/genes and pathways associated with IDD. The array profiling of patients with IDD and individuals without IDD was acquired from the Gene Expression Omnibus (GEO) database (viz., GSE19943, GSE63492, and GSE34095). The expression profiles of miRNAs and genes with differential patterns were analyzed using GEO2R. The target genes of the chosen miRNA were then examined, and in silico functional analyses were performed on the signaling pathways and biological processes of the differentially expressed genes. Three human miRNAs were up and downregulated in IDD patients in the examined data sets. Among them, hsa-miR-508-5p had a significant differential expression in the IDD group, and *SEC11A*, *IPO5*, *FN1*, and *MRPS10*, as the targets of hsa-miR-508-5p, were upregulated in the IDD group. Furthermore, extracellular matrix-receptor interactions, focal adhesion, and actin cytoskeleton regulation were important pathways involved in IDD. Our analysis identified hsa-miR-508-5p as a novel miRNA involved in IDD pathogenies. Our findings not only further confirmed the significant role of miRNAs in IDD pathogenesis but also extended the spectrum of the miRNAs and genes involved in IDD. Though, still, further experimental investigations are needed to confirm our findings.

Keywords: Intervertebral disc degeneration, hsa-miR-508-5p, noncoding RNA regulators, low back pain

Cite this article: Gholipour. A. hsa-miR-508-5p as a New Potential Player in Intervertebral Disc Degeneration. *International Journal of Molecular and Cellular Medicine*. 2022; 11(2): 137-149. **DOI:**10.22088/IJMCM.BUMS.11.2.137

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[DOI: 10.22088/IJMCM.BUMS.11.2.137]

Introduction

Intervertebral disc degeneration (IDD) is a pathological condition that can cause not only intractable back pain, the most common orthopedic disease, but also neurological complications. The prevalence of low back pain is on the rise the world over. It affects the quality of life of patients and imposes a huge economic burden on healthcare systems, accounting for approximately 70 billion euros annually worldwide (1). The pathogenesis of IDD is multifactorial, with accumulating evidence indicating the contribution of both genetic and environmental factors to the disease (2, 3).

The nucleus pulposus, considered the core structural component of the intervertebral disc, is harbored between two vertebrae and is composed of the extracellular matrix (ECM) and nucleus pulposus cells (4, 5). The etiology of IDD is associated with an increase in apoptosis and necrosis (2, 6, 7) and irregular inflammatory cytokines (8), deregulating the function of nucleus pulposus cells and leading to ECM degradation (9-11). Nonetheless, the fundamental mechanisms of IDD have yet to be elucidated.

MicroRNAs (miRNAs) constitute a type of small endogenous noncoding regulatory RNA post-transcriptionally regulating gene expression in numerous processes, such as proliferation, apoptosis, and inflammation (12, 13). Recent investigations have demonstrated major alterations in miRNA expression in degenerated tissue (14-16). In this regard, miR-486-5p is significantly lower in degenerated discs than in controls (17), whereas miR-222 is upregulated in human degenerative disc tissue (18). In addition, the inhibition of miR-27a may be an attractive strategy to prevent cell death in degenerative discs (19). Several miRNAs, including miR-199a-5p, miR-574-3p, miR-551a, and miR-640, may be potential candidate markers for predicting IDD (20).

In the present study, we drew upon *in silico* analysis to address the current paucity of research on the molecular mechanisms of IDD and determine new miRNAs and their targets with differential expression levels in IDD.

Materials and Methods

Data sets and differential expression analysis

The data sets examined in the present study were downloaded from the NCBI Gene Expression Omnibus (GEO) database. In total, two expression profiles of miRNAs (viz., GSE19943 and GSE63492) and one expression profile of messenger RNAs (mRNAs) (viz., GSE34095) were downloaded. The GSE19943 samples were obtained from control nucleus pulposus cells and degenerative nucleus pulposus cells. The nondegenerative cells were extracted through the enzymatic digestion of human nucleus pulposus cells obtained from individuals with scoliosis, while the degenerative cells were obtained via the enzymatic digestion of human nucleus pulposus cells collected from individuals with IDD. Moreover, the GSE63492 samples were obtained from nondegenerative and degenerative nucleus pulposus cells. All the control nucleus pulposus specimens were obtained from the intervertebral discs of cadaveric donors with no IDD-related disease, whereas all the degenerative nucleus pulposus samples were acquired from the intervertebral discs of cadaveric donors with intervertebral disc herniation. Additionally, the mRNA samples (viz., GSE34095) were obtained from human degenerative and nondegenerative intervertebral discs, the former from individuals with degenerative disc disease and the latter from adolescents with idiopathic scoliosis. No

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special treatment was administered to the nucleus pulposus cells. The profiles of miRNAs and mRNAs differentially expressed between the normal and degenerated samples were investigated by GEO2R for all the data sets.

Common miRNAs of the two data sets and the target prediction of the chosen miRNA

Differentially expressed miRNAs were obtained from two expression profiles of miRNAs (viz., GSE19943 and GSE63492); subsequently, common miRNAs between the two expression profiles were identified utilizing the Venny 2.1 database. Among them, the miRNA with the most significant differential expression was selected to continue the *in silico* analysis.

Thereafter, the target genes of the chosen miRNA were examined using the TargetScan (http:// www.targetscan.org/vert_80/), miRDB (http://mirdb.org/), and miRTarBase (https://mirtarbase. cuhk.edu. cn/~miRTarBase/miRTarBase_2022/php/index.php) databases, and the common target genes were isolated from the three databases utilizing the Venny 2.1 database.

Afterwards, common genes between the mRNAs with differential expression levels in the GSE34095 expression profile and the target genes of the chosen miRNA were recognized using GEO2R.

Next, the expression values of the selected miRNA and its common target genes were examined in the analyzed miRNA and mRNA data sets using the limma package in the GEO2R database. Moreover, the interactions between mRNAs and long noncoding RNAs (lncRNAs) were investigated using the lncRRIsearch (http:// http://rtools.cbrc.jp/LncRRIsearch) database.

Biological processes and pathway enrichment analyses

For the determination of the function of the target genes of the chosen miRNA in IDD, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and biological process analyses were performed employing the online databases of Enrichr (https://maayanlab.cloud/Enrichr/) and PANTHER (http://www.pantherdb.org/pathway/), respectively.

Results

Differential expression levels of about hundreds of miRNAs and 200 genes in patients with IDD

The differential expression patterns of the miRNAs were scrutinized between the IDD group and the control group. Differential expression levels were observed in 177 miRNAs in the GSE19943 data set and 124 miRNAs in the GSE63492 data set. The results showed that 250 genes had differential expression levels in the patient group in comparison with the control group according to the *in-silico* analysis.

miR- 508- 5p as a novel RNA regulator in IDD

Among the differentially expressed miRNAs obtained by GEO2R, only four miRNAs-namely hsa-miR-518b (GSE19943: logFC=0.58, P=0.61 and GSE63492: logFC=0.88, P=0.11), hsa-miR-486-5p (GSE19943: logFC=0.70, P=0.34 and GSE63492: logFC= -1.64, P=0.0008), hsa-miR-508-5p (GSE19943: logFC= -1.37, P=0.036 and GSE63492: logFC=1.80, P=0.025), and ebv-miR-BART6-3p-were common between both data sets (Figure 1).

The expression of hsa-miR-518b was upregulated in both data sets, while the expression of hsa-miR-486-5p was upregulated in the GSE19943 data set and significantly downregulated in the GSE63492 data set. However, other alterations were not statistically significant based on their logFCs and P-values. In

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addition, the fourth miRNA, ebv-miR-BART6-3p, was not found in human miRNA data; thus, all these three miRNAs (viz., hsa-miR-518b, hsa-miR-486-5p, and ebv-miR-BART6-3p) were omitted from further analysis conducted on hsa-miR-508-5p given its significant logFC and P-value in both data sets.

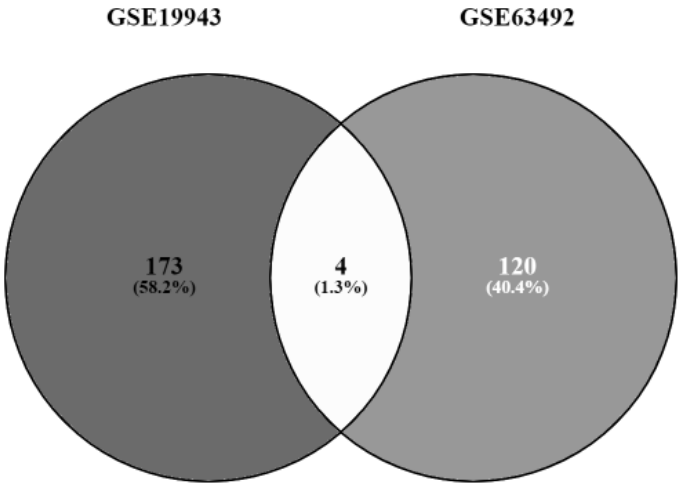

Fig. 1. The figure presents the common miRNAs between two data sets. Four miRNAs were common. Totally, 177 miRNAs were differentially expressed in the GSE19943 data set, and 124 miRNAs with differential expression levels were found in the GSE63492 data set.

The results revealed that hsa-miR-508-5p was downregulated in the patients of the GSE19943 data set and upregulated in the patients of the GSE63492 data set (Figure 2A & B), likely because the nucleus pulposus cells in the GSE19943 data set were obtained from individuals with scoliosis. Therefore, hsa-miR-508-5p, which showed the highest differential expression, was chosen for further analysis owing to its significant logFC and P-value.

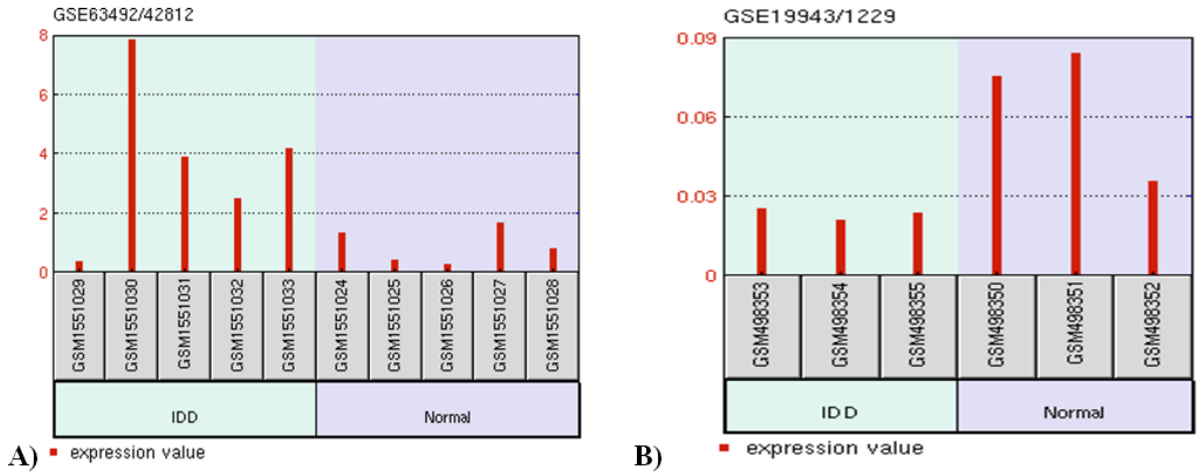

Fig. 2. The image depicts the expression of hsa-miR-508-5p in the patient (IDD) and normal samples. (A) hsa-miR-508-5p was downregulated in the patient group of the GSE19943 data set. (B) hsa-miR-508-5p was upregulated in the patient group of the GSE63492 data set.

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Targeting of some differentially expressed genes by hsa-miR-508-5p

The target genes of hsa-miR-508-5p were examined using the TargetScan, miRDB, and miRTarBase databases. Afterwards, the common candidate genes from the three databases were chosen for further analysis. The analysis via the Venny 2.1 database demonstrated that 243 genes were common between the three databases for hsa-miR-508-5p (Figure 3).

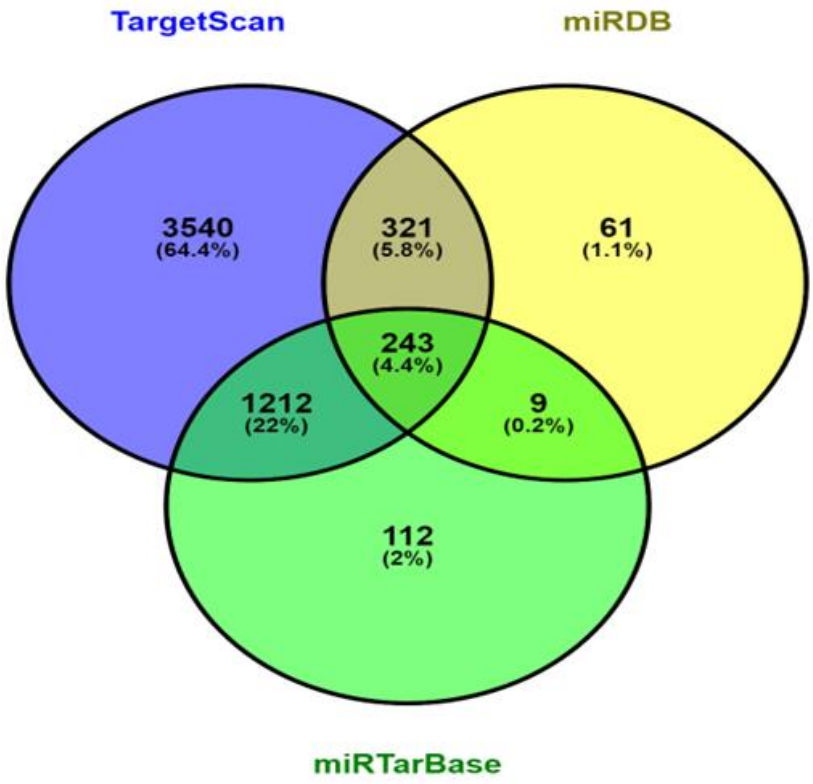

Fig. 3. The image demonstrates the target genes of hsa-miR-508-5p that were common between the three analyzed databases, namely TargetScan, miRDB, and miRTarBase.

In the next stage, the list of the miRNA target genes was compared with the list of the genes that had differential expression levels in the GSE34095 data set. The results demonstrated that four genes-namely, *SEC11A*, *IPO5*, *FN1*, and *MRPS10*-were mutual. Accordingly, *SEC11A* (logFC=0.31, P=0.01), *IPO5* (logFC=0.45, P=0.015), *FN1* (logFC=0.51, P=0.001), and *MRPS10* (logFC=0.29, P=0.004) were considered the targets of hsa-miR-508-5p with differential expression levels in the IDD patients. Furthermore, *SEC11A*, *IPO5*, *FN1*, and MRPS10 exhibited upregulation in the patients with degenerative discs (Figure 4). The interaction between each examined gene and lncRNAs demonstrated that the following lncRNAs-OTX2-AS1, UXT-AS1, PABPC1L2B-AS1, HOXA-AS3, BHLHE40-AS1, and LINC00562-interacted with *SEC11A*. Additionally, *IPO5* interacted with LINC01239, LINC00987, LINC01484, VIPR1-AS1, LINC00562, and LINC01121 lncRNAs. Further, four lncRNAs-namely LINC01239, LINC01215, PABPC1L2B, and SLC25A25-AS1-interacted with *FN1*. Moreover, interactions were between *MRPS10* and PRKAR2A-AS1, SLC25A25-AS1, GABPB1-AS1, LINC00963, and RUNDC3A-AS1 (Table 1).

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Table 1. The list of lncRNAs that interacted with the examined genes.

Genes	lncRNAs
SEC11A	OTX2-AS1, UXT-AS1, PABPC1L2B-AS1, HOXA-AS3, BHLHE40-AS1, LINC00562, LINC00910, LINC01012, SLC7A11-AS1, LINC01484, LINC00473, TMCC1-AS1, BAIAP2-AS1, POT1-AS1
IPO5	LINC01239, LINC00987, LINC01484, VIPR1-AS1, LINC00562, LINC01121, LINC00442, LINC01582, ZNF528-AS1, CDKN2B-AS1, LINC01539
FN1	LINC01239, LINC01215, PABPC1L2B, SLC25A25-AS1,
MRPS10	PRKAR2A-AS1, SLC25A25-AS1, GABPB1-AS1, LINC00963, RUNDC3A-AS1, LINC01012, LINC00649, LINC01531, CPEB1-AS1, LINC01359, LINC00910, LINC01562, LINC01482, LINC00963, LINC00926

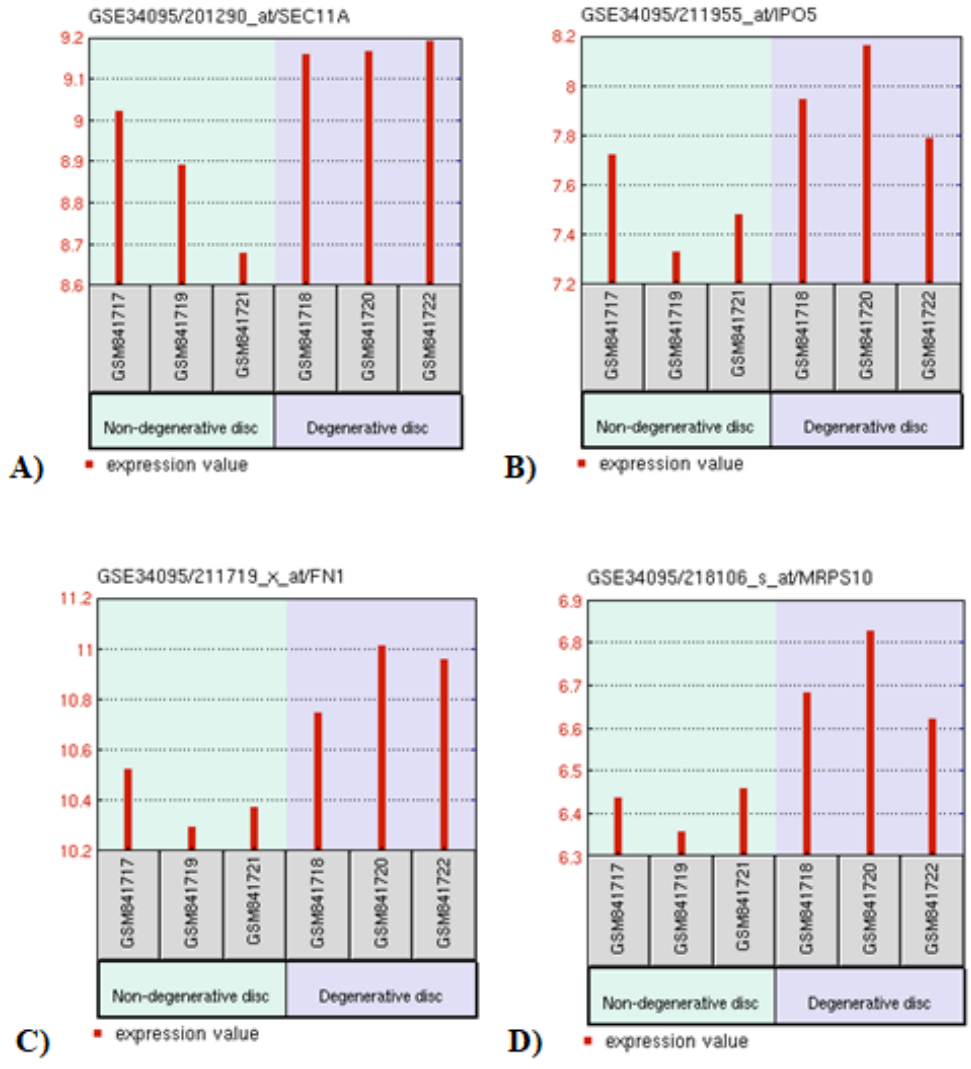

Fig. 4. The image illustrates the expression levels of (A) *SEC11A*, (B) *IPO5*, (C) *FN1*, and (D) *MRPS10* as the common genes among the differentially expressed genes, as well as the hsa-miR-508-5p target genes among the degenerative and nondegenerative discs samples.

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ECM pathway as a critical pathway in functional enrichment analysis

The results of the signaling pathway analysis showed that the genes whose expression patterns differed between the IDD and control groups were targeted by hsa-miR-508-5p and were involved in protein export, ECM-receptor interactions, focal adhesion, and actin cytoskeleton regulation pathways (Figure 5A). Previous studies have revealed that the ECM is one of the significant pathways in disc degeneration (21,22).

The biological process analysis, thereafter, showed that *SEC11A*, *FN1*, *MRPS10*, and *MRPS10* played roles in biological activities such as cellular, developmental, and metabolic processes (Figure 5B).

A)

Index	Name	P-value	Adjusted p-value
1	Protein export	0.004592	0.04724
2	Bacterial invasion of epithelial cells	0.01531	0.04724
3	ECM-receptor interaction	0.01749	0.04724
4	Small cell lung cancer	0.01827	0.04724
5	AGE-RAGE signaling pathway in diabetic complications	0.01985	0.04724
6	Amoebiasis	0.02025	0.04724
7	Yersinia infection	0.02712	0.05424
8	Ribosome	0.03123	0.05459
9	Focal adhesion	0.03960	0.05459
10	Proteoglycans in cancer	0.04038	0.05459
11	Regulation of actin cytoskeleton	0.04290	0.05459
12	Human papillomavirus infection	0.06458	0.07425
13	PI3K-Akt signaling pathway	0.06895	0.07425
14	Pathways in cancer	0.1021	0.1021

B)

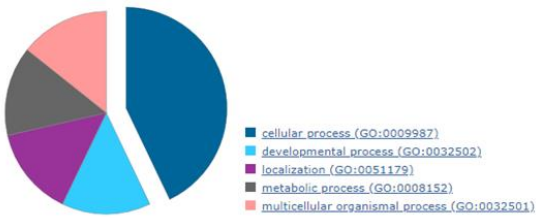

Fig. 5. The image shows the functional analysis. (A) the signaling pathway of the common genes between the differentially expressed genes and the hsa-miR-508-5p target genes and (B) the biological process of the common genes between the differentially expressed genes and the hsa-miR-508-5p target genes.

Discussion

IDD causes the deterioration of the connective tissue between the vertebrae, playing a crucial role in spinal kinematics. Consequently, IDD is deemed one of the major causes of chronic low back pain. The degenerative process is associated with apoptosis, ECM disruption, cell proliferation, and inflammatory responses. The current medical armamentarium lacks therapeutic methods capable of targeting the pathophysiology of disc degeneration since the etiology of this multifactorial disease is not fully understood (23, 24). Several studies have indicated that IDD progression is critically aided by genetic factors (25, 26) such as the polymorphisms of the COL1A1 gene, a key gene encoding collagen I (27).

Notably, miRNAs play a prominent role in regulating many normal physiological and pathophysiological processes, including degenerative disc disease. Prior studies have demonstrated the abnormal expression of miRNAs in the intervertebral disc. Such abnormal expression patterns are implicated in various pathological developments of IDD, such as apoptosis, ECM degradation, cell proliferation, and inflammatory responses (14, 15, 28-30). In the present study, we found that miR-508-5p, miR-518b, and miR-486-5p were differentially expressed in patients with IDD in comparison with healthy controls. Further, miR-508-5p may potentially target *SEC11A*, *IPO5*, *FN1*, and *MRPS10*, which are upregulated in IDD patients.

Wang *et al*. (31) revealed that miR-518b was one of the upregulated miRNAs in IDD patients. Although miR-518b was upregulated in both mRNA data sets analyzed in the current investigation, this differential

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expression failed to constitute statistical significance. Our data analysis showed that miR-486-5p was significantly downregulated in the GSE63492 data set. Consistent with our findings, Chai *et al*. (17) reported that miR-486-5p expression was significantly downregulated in nucleus pulposus cells, and *FOXO1* was a direct target gene of miR-486-5p. Chai *et al*. also showed that overexpressed *FOXO1* aggravated lipopolysaccharide (LPS)-induced injury and antagonized the protection effects of miR-486-5p. Zhang *et al*. (32) found that hsa-miR-486-5p was downregulated in IDD patients and suggested that the expression of *GSK3B* might be coregulated by miR-486-5p and affect IDD development. Furthermore, Ji *et al*. (33) also found that the level of miR-486-5p was significantly lower in IDD samples than in controls.

Previous research has shown that miR-508-5p is not only associated with various cancers by negatively modulating cancer cells but also involved in the pathogenesis of chronic heart failure. Prior investigations have shown that miR-508-5p is crucially involved in disorders characterized by abnormal immune responses and apoptosis (28, 34, 35). Nevertheless, the specific functions and potential regulatory mechanisms of miR-508-5p in various diseases still require further investigation. In the present study, we revealed that the expression of miR-508-5p was significantly changed among patients in both miRNA data sets examined. Our analysis also demonstrated that miR-508-5p was downregulated among the patients of the GSE19943 data set and upregulated among the patients of the GSE63492 data set. In addition, the expression of the predicted target genes of miR-508-5p —namely *SEC11A*, *IPO5*, *FN1*, and *MRPS10*—showed upregulation in our analysis, which is in line with the downregulation of miR-508-5p in IDD patients (GSE19943). One of the reasons for the discrepancy concerning the expression levels of miR-508-5p between the two data sets might be the origin of the cells in the control group: whereas the cells in the GSE19943 data set were obtained from the nucleus pulposus cells of individuals with scoliosis, the cells in the GSE63492 data set were extracted from donors with no IDD-related disease. Interestingly, the GSE34095 data set, employed in the present study for the expression analysis of genes, had the same origin as the control samples of the data set utilized for miRNAs expression, in which miR-508-5p exhibited a reduction.

No studies to date have reported that miR-508-5p can target *SEC11A*, *IPO5*, and *MRPS10*. Li *et al*. (36) concluded that *FN1* was a target gene of miR-508-5p, which can confirm our finding of the upregulation of genes and the downregulation of miR-508-5p in the GSE19943 data set of IDD samples. Therefore, we assume that the downregulation of miR-508-5p might play a role in IDD pathogenesis. Still, the specific functions and potential regulatory mechanisms of miR-508-5p in IDD require further surveys.

Furthermore, our analysis demonstrated that *SEC11A*, *IPO5*, *FN1*, and *MRPS10*, which are involved in different pathways (viz., ECM-receptor interactions, focal adhesion, and actin cytoskeleton regulation), were upregulated in patients with IDD and might be the potential targets of miR-508-5p. The current literature lacks information on the effects and expressions of *SEC11A*, *IPO5*, and *MRPS10* in IDD.

According to previous investigations, the balance between ECM catabolism and anabolism is the foundation of the biomechanical function of disc degeneration, with several studies having demonstrated that miRNAs may be involved in the regulation of the ECM in IDD (37, 38). During IDD development, the ability of intervertebral disc cells to produce the ECM is undermined, leading to macroscopic changes in the intervertebral disc (39). Fibronectin (*FN1*) is acknowledged as an age-related marker protein due to its increased expression at protein and mRNA levels in senescent cells (40). Furthermore, the expression level

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of *FN1*, the major component of the ECM, is reportedly increased in degenerating discs (41). Two studies have demonstrated that the elevated expressions of collagen I (*COL1A1*) and *FN1* are involved in the fibrotic alterations of nucleus pulposus cells in disc degeneration (42, 43). Fibronectin 1 (*FN1*), upregulated in our analysis, was upregulated in punctured mouse tail discs, exhibiting progressive degenerative changes in a previous study (43). The results of another investigation demonstrated *FN1*, *COL1A2*, *SPARC*, *COL3A1*, *CTGF*, *LUM*, *TIMP1*, *THBS2*, *COL5A2*, and *TGFB1* were upregulated in the group with degenerated discs compared with the control group, which may provide new insights into the underlying mechanisms of IDD (44). Chiming in with this finding, our analysis demonstrated *FN1* upregulation in IDD patients. We also found upregulated *SEC11A*, *IPO5*, and *MRPS10* in IDD patients. According to previous research, *SEC11A* encodes the SPC18 protein, one of the subunits of the signal peptidase complex (SPC) (45). Importin-5 is a member of the importin-β family and encoded by the *IPO5* gene (46). Further, Mitochondrial Ribosomal Protein S10 (*MRPS10*) encodes MRPS10, involved in the pathways of mitochondrial translation and organelle biogenesis and maintenance (47).

Likewise, Chen *et al*. (48) reported the upregulation of LINC01121 in patients with IDD compared with controls. The overexpression of LINC01121 is involved in ECM degradation and the secretion of inflammatory cytokines by modulating MMP-16.

Our results demonstrated that not only was *IPO5* expression upregulated among patients with IDD but also *IPO5* interacted with LINC01121. Accordingly, we suggest that miR-508-5p downregulation could lead to *IPO5* upregulation, and its associated lncRNA, LINC01121, could modulate MMP-16. This pathway could interfere with ECM remodeling and cause disc degeneration (Figure 6). Still, the significance and exact regulatory mechanisms of LINC01121 and other introduced lncRNAs in IDD need further investigation.

To the best of our knowledge, the present study is the first investigation to introduce the aforementioned genes, which are potentially involved in the pathogenesis of IDD. Nevertheless, further experimental investigations are needed to confirm our findings.

We suggest that future studies experimentally investigate the expression patterns of miR-508-5p, miR-518b, and miR-486-5p in the nucleus pulposus cells of IDD patients. Further research is also warranted on expression alterations in miR-508-5p target genes in IDD patients' nucleus pulposus cells. Moreover, interactions between miR-508-5p and predicted target genes should be experimentally confirmed via luciferase assays and other approaches.

Limitations

The salient limitation of the present study is its reliance only on bioinformatics methods. Our findings, therefore, need confirmation via experimental analysis.

Conclusion

The underlying pathogenesis of IDD remains poorly understood despite years of investigation. Recently, RNA-based biopharmaceuticals have ushered in a new era of drug discovery and development. The current study utilized miRNA/gene expression profiling to identify molecular pathways involved in IDD and succeeded in detecting miR-508-5p, whose expression patterns differed between patients with IDD and normal controls.

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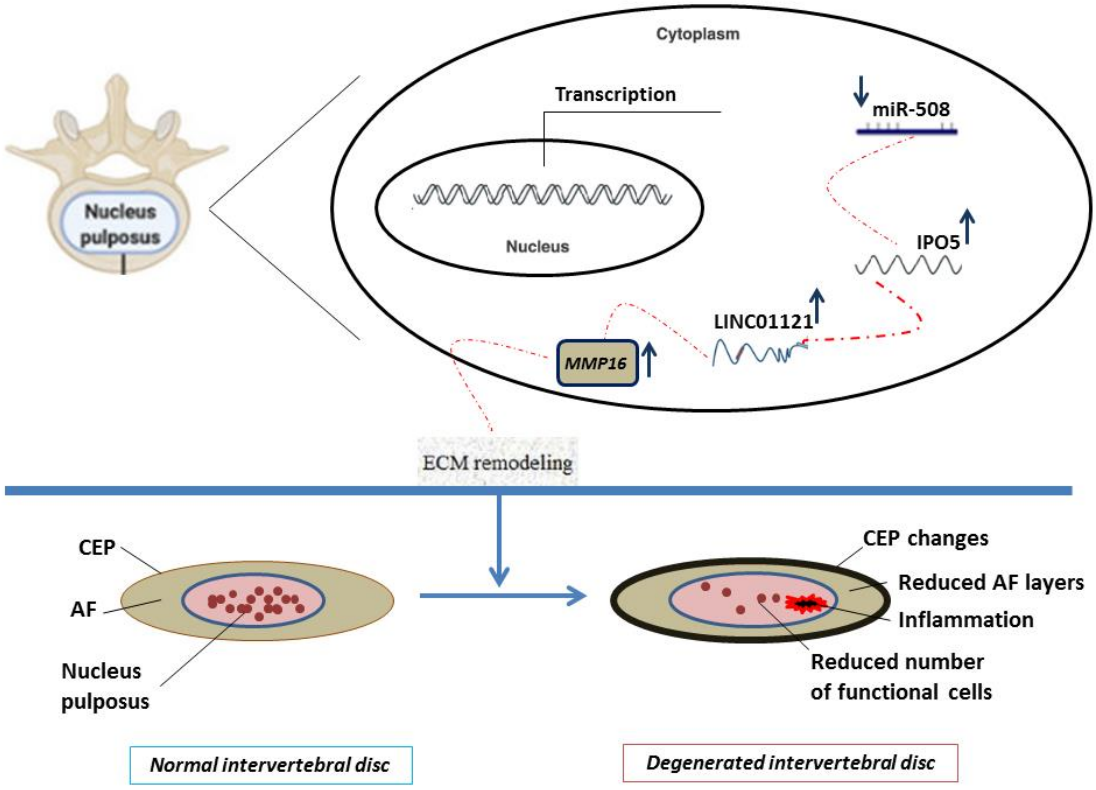

Fig. 6. The image presents a schematic view of the suggested pathway involved in IDD according to our findings. Downregulation in miR-508-5p led to the upregulation of *IPO5*. Its associated lncRNA, LINC01121, modulated MMP-16, which interfered with ECM remodeling. CEP: cartilaginous endplate, AF: annulus fibrosus

We suggest that the expression patterns of *SEC11A*, *IPO5*, *FN1*, and *MRPS10*, introduced herein, as well as the pathways involved, be confirmed by more detailed laboratory studies to help shed light on the exact mechanisms of IDD. Not only do our findings further underscore the significant role of miRNAs in IDD pathogenesis, but also they expand the spectrum of the miRNAs and genes involved in IDD.

Declaration

The study protocol was approved by Bam University of Medical Sciences (IR.MUBAM. REC.1401.003). The data source was a publicly accessible database, and no human contributors were involved directly in the present study. The authors declare no conflicts of interest.

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