The roles and perspectives of microRNAs as biomarkers for intervertebral disc degeneration

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Abstract

MicroRNAs (miRNAs) are highly conserved molecules that regulate protein levels post-transcriptionally. Aberrant miRNA expression presents in various musculoskeletal disorders, such as osteoporosis, osteoarthritis and rheumatoid arthritis. The expression levels of miRNAs are characterized by endogenous properties and tissue specificity. This raises the possibility that miRNAs could serve as useful clinical biomarkers in the diagnosis of certain diseases. Intervertebral disc degeneration (IDD) is one of the major causes of back pain, and a process characterized by a cascade of molecular, cellular, biochemical and structural changes. The presence of dysregulated miRNA expression in patients with disc degeneration diseases indicates that miRNAs may play a vital role in the pathogenesis of IDD. Here, we provide an introduction of the roles of miRNAs in the process of IDD, and the prospective application of miRNAs as biomarkers for IDD. Copyright © 2017 John Wiley & Sons, Ltd.

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Keywords intervertebral disc degeneration; microRNA; biomarker; NP cell apoptosis; NP cell proliferation; ECM metabolism

1. Introduction

Back pain is one of the most common orthopaedic diseases; it severely affects the health of human beings and causes tremendous economic burden to the whole society. Although the pathogenesis of back pain is complex and has not been fully elucidated yet, a cell-mediated degenerative process, intervertebral disc degeneration (IDD) is considered as one of the main causes for back pain (Freemont, 2009). IDD starts early, so that 20% of people have mild disc degeneration in their teens, and it becomes more severe with aging (Boos et al., 2002; Miller et al., 1988). The pathogenesis of IDD is complicated and affected by multiple factors, including genetic inheritance, age, inadequate metabolite transport and loading history. This may weaken discs and cause structural failure and functional impairment (Roberts et al., 2006). IDD further leads to spinal stenosis, spinal segmental instability, osteophyte formation, disc herniation, and compression of spinal cord and nerve root that may cause back and sciatic pain (Mehra et al., 2012). Currently, the clinical diagnosis of IDD is mainly based on imaging modalities such as magnetic resonance imaging (MRI). Normally the degradation of aggrecan is one of the early signs of IDD, and this extracellular matrix (ECM) alteration reduced the capacity to bind water and osmotic pressure, which causes inflammation during the process of degeneration. In the late stages of IDD, it is characterized by loss of disc height, annular tears and rim lesions, and osteophyte formation. MRI is sensitive to detect the alteration of water content and collagen concentration and orientation, while it is not sensitive to detect the alteration of proteoglycans (specifically aggrecan; Mwale et al., 2008). MRI-based images therefore provide information about the intermediate or late states in IDD instead of the early degenerative status. However, early diagnostic methods of IDD are desired in order to prevent and/or delay the degeneration process at the early stages, so that invasive surgical operations may be avoided. Thus, it is essential to seek for a more precise and efficient method for the early diagnosis of IDD.

MicroRNAs (MiRNAs) are a type of small non-coding RNA molecule of 20–22 nucleotides in length, which play important roles in a number of physiological processes, such as individual development (Ying et al., 2013), organ formation (Joglekar et al., 2009; Khoshgoo et al., 2013), tumorigenesis (Lawrie, 2013; Papaconstantinou et al., 2012; Zhan et al., 2013), and cell proliferation,
differentiation and apoptosis (Luo et al., 2013; Mathieu and Ruohola-Baker, 2013). Due to the prominent and extensive functions of the miRNA, the miRNA dysexpression or the combinational alteration between miRNA and its target genes will contribute to certain diseases, such as cancer (Tilghman et al., 2013), autoimmune diseases (Buckland, 2010) and bone-related diseases (Moore and Xiao, 2013). Interestingly, some miRNAs, such as miR-155 (Wang et al., 2011a), miR-146a (Zhao et al., 2014a) and miR-377 (Tsririmonaki et al., 2013), are present in intervertebral disc (IVD), and their dysregulation in IDD might serve as potential biomarkers for the early diagnosis of IDD. However, the expression pattern and the precise cellular and molecular mechanisms of the miRNAs in human disc degeneration have not been elucidated, even though there are some recent reports on the regulatory roles of miRNAs in the field of other musculoskeletal disorders, such as osteoporosis (Seeliger et al., 2014; van Wijnen et al., 2013), osteoarthritis (Abouheif et al., 2010; Miyaki et al., 2010; Okuhara et al., 2012) and rheumatoid arthritis (Murata et al., 2010; Nakasa et al., 2008). In this review, we will provide an introduction on the regulatory roles of miRNAs in IDD and highlight the potential application of miRNAs as biomarkers for early diagnosis of IDD.

2. IDD and pathogenesis

The IVD sandwiches between vertebras as ‘shock absorbers’ of the spine (Le Maitre et al., 2007b). There are three integral parts to form the normal IVD, and include the outer lamellae annulus fibrosus (AF), the inner nucleus pulposus (NP) surrounded by AF, and the cartilage endplates (CEP; Freemont, 2009). Normal IVD fills with a large amount of ECM and a few cells, which only account for 1% of the volume of IVD (Roberts et al., 2006).

In the process of IDD, the anabolism and catabolism of the ECM become disturbed, resulting in the loss of proteoglycans (mainly aggrecan) and decrease of water content in the NP (Le Maitre et al., 2007b; Urban et al., 2004). Loss of the PG content is generally regarded as a sign for early stages of disc degeneration, and leads to NP dehydration and fibrosis and decreases the expansion pressure (Zhu et al., 2014). In ageing and degeneration, collagen catabolism also increases in the AF, which contributes to the loss of tensile strength and damage in CEPs. In the meantime, the decrease of aggrecan content causes inability to maintain the IVD hydration and load absorption (Sandy, 2001; Urban and McMullin, 1988). Subsequently, growth factors and cytokines and other large molecules penetrate into the disc due to the decrease of osmolality, which leads to inflammation in the early stages of IDD and further accelerates the degeneration progression (Cs-Szabo et al., 2002; Sandy, 2001). The ECM within the IVD is degraded by catabolic factors that include the matrix metalloproteinases (MMPs), ADAM metallopeptidase with thrombospondin motifs (ADAMTSs; Le Maitre et al., 2004; Wang et al., 2011b), cathepsin (Gruber et al., 2011) and high-temperature-requirement serine protease A1 (HTRA1; Tiaden et al., 2012). Additionally, immunological factors have been reported in the pathogenesis of IDD. Interleukin (IL)-1 is one of the most predominant cytokines (Le Maitre et al., 2007a) upregulated in disc degeneration, which leads to increased expression of matrix-degrading proteases (MMP3, MMP13, ADAMTS-4) and decreased expression levels of matrix genes (aggrecan, collagen I and II, SOX6; Le Maitre et al., 2005, 2007b; Sakai and Grad, 2014). Some other inflammatory factors are also involved in the degeneration process, which include IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, tumour necrosis factor-α (TNF-α), and interferon-γ. In IDD, the increased expression of these inflammatory factors induces further downstream mediator synthesis, such as nitric oxide and prostaglandin 2 (Wuertz and Haglund, 2013). Recently, several studies have demonstrated that excessive apoptosis of NP cells and abnormal NP cell proliferation also contribute to the process of IDD (Jiang et al., 2014; Liu et al., 2013; Yu et al., 2013). NP cell apoptosis is a crucial type of IVD cell death, and the loss of NP cell numbers results in the reduction of ECM synthesis, which disturbs the balance between the catabolism and anabolism of ECM macromolecules and leads to IDD (Ding et al., 2013), and the inflammatory factors will induce the apoptosis of NP cells such as IL-1 and TNF-α (Le Maitre et al., 2007a). Moreover, the inflammation along with ECM degradation contributes to the tissue destruction of IVD. It has been reported that Fas ligand (FasL) was expressed remarkably and mediated the apoptosis of NP cells in IDD processes (Kaneyama et al., 2008). However, the underlying cellular and molecular mechanisms of NP cell apoptosis in IDD are still unclear that. Thus, it is very important to

Figure 1. Schematic process of the intervertebral disc degeneration (IDD). Diagram shows how intervertebral disc (IVD) tissue is influenced by aging, environmental, mechanical and hereditary factors, many of which are pathogenic factors and initiate IDD.

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MicroRNAs in IDD

3. miRNAs in IDD

Increasing evidence indicates that IDD is associated with some small molecules, including miRNAs. The expression of miRNAs is significantly different in human subjects with IDD compared with the healthy control group (Ohrt-Nissen et al., 2013; Zhao et al., 2014a). Currently, there is very limited information on miRNAs in the samples from patients with IDD. The most common approach is miRNA array technology. Moreover, bioinformatics analysis is used to predict the target of certain miRNAs for further functional verification. MiRNA array technology and bioinformatics analysis showed 51 miRNAs were dysregulated in the NP tissue of patients with IDD that might modulate some vital signalling pathways involved in IDD. These include the phosphoinositide 3-kinase (PI3K)/Akt, mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR; ErbB) and Wnt pathways (Zhao et al., 2014a). However, further function validation of these 51 miRNAs was not performed, and the role of the miRNA in the regulation of IDD still needs to be elucidated. Interestingly, in human degenerative lumbar discs, 10 miRNAs were found to be expressed much higher in the NP compared with AF (Ohrt-Nissen et al., 2013). Besides, the article further confirmed that miRNAs were expressed differently between NP cells and AF cells. This suggested the miRNA signalling pattern might be different between the NP and AF. These studies have demonstrated that abnormal miRNAs expression present in the progress of IDD with clinical samples, which provides evidence that miRNAs might play critical roles in the pathophysiology of IDD. However, the miRNA profiles are initial screening results, and the pathophysiological mechanisms of these miRNAs remain unknown and need to be further investigated.

Although few studies have revealed the detailed roles of miRNAs in IDD, some miRNAs have been found to be able to regulate NP cells (Figure 2; Table 1). Given NP cells are the main cells in IVD and synthesize ECM components to maintain the IVD structural stability from mechanical loads, it is generally considered that abnormal NP cell proliferation and excessive apoptosis of NP cells are critical mechanisms for IDD (Ma et al., 2015). MiR-10b is expressed in many cell types and plays important roles in cell proliferation (Bourguignon et al., 2010; Ma et al., 2007; Sasayama et al., 2009). MiR-10b is not only overexpressed in cancer tissues, but also significantly

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**Table 1.** MiRNAs reported to be involved in the process of IDD

<table>
<thead>
<tr>
<th>MiRNA</th>
<th>Target</th>
<th>Expression</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-155</td>
<td>FADD, caspase-3</td>
<td>Downregulated</td>
<td>miR-155 is involved in the Fas–Fas signalling pathway to mediate the apoptosis of NP cells (Wang et al., 2011a)</td>
</tr>
<tr>
<td>miR-27a</td>
<td>PI3CD</td>
<td>Upregulated</td>
<td>miR-27a regulates the PI3K/Akt signalling pathway to mediate the apoptosis of NP cells (Ji et al., 2015)</td>
</tr>
<tr>
<td>miR-10b</td>
<td>HOXD10</td>
<td>Upregulated</td>
<td>miR-10b promotes NP cell proliferation by modulating the RhoC-Akt signalling pathway (Yu et al., 2013)</td>
</tr>
<tr>
<td>miR-21</td>
<td>PTEN</td>
<td>Upregulated</td>
<td>miR-21 stimulates NP cell proliferation and Akt signalling pathway activation (Ji et al., 2015)</td>
</tr>
<tr>
<td>miR-184</td>
<td>GAS1</td>
<td>Upregulated</td>
<td>miR-184 negatively regulates GAS1 to mediate Akt pathway and modulate NP cell proliferation during IDD (Liu et al., 2016)</td>
</tr>
<tr>
<td>miR-377</td>
<td>ADAMTS5</td>
<td>Downregulated</td>
<td>miR-377 inhibits ADAMTS5 to reduce the aggrecan degradation in human NP cells by mediating the PKCε signalling (Tsirimonaki et al., 2013)</td>
</tr>
<tr>
<td>miR-146a</td>
<td>FADD, IL-1β, IL-6, TNF, MMP-16</td>
<td>Downregulated</td>
<td>miR-146a plays an important role in the anti-inflammatory and anti-catabolic process of IDD (Liu et al., 2015)</td>
</tr>
<tr>
<td>miR-494</td>
<td>JunD</td>
<td>Upregulated</td>
<td>miR-494 plays a critical role in TNF-α-induced apoptosis of NP cells (Wang et al., 2015)</td>
</tr>
<tr>
<td>miR-93</td>
<td>MMP3</td>
<td>Downregulated</td>
<td>miR-93 regulates MMP3 negatively and contributes to development of IDD (Jing and Jiang, 2015)</td>
</tr>
<tr>
<td>miR-100</td>
<td>FGR1</td>
<td>Upregulated</td>
<td>miR-100 increases MMP13 expression levels in disc and contributes to development of IDD (Wang et al., 2015)</td>
</tr>
<tr>
<td>miR-193a-3p</td>
<td>MMP14</td>
<td>Downregulated</td>
<td>miR-193a-3p is associated with IDD by targeting MMP14 and positively regulates type II collagen expression (Ji et al., 2015)</td>
</tr>
<tr>
<td>miR-98</td>
<td>STAT3</td>
<td>Downregulated</td>
<td>miR-98 regulates the pathogenesis in IDD through mediating IL-6/STAT3 signalling pathway (Ji et al., 2009)</td>
</tr>
</tbody>
</table>

IDD, intervertebral disc degeneration; NP, nucleus pulposus.
upregulated in the human degenerative NP tissue compared with idiopathic scoliosis patients’ NP tissues. Moreover, the expression levels of miR-10b are positively associated with the grades of IDD. MiR-10b directly targets homeobox D10 (HOXD10) 3’-UTR and increases ras homologue family member C (RhoC) expression. RhoC has been known to be involved in cell proliferation and negatively regulated by HOXD10. The RhoC-mediated cell proliferation subsequently activates Akt phosphorylation (Bourguignon et al., 2010; Nakayama et al., 2013). Additionally, knockdown of RhoC and repression of Akt activation impeded miR-10b-induced NP cell proliferation (Yu et al., 2013). These findings suggest that aberrant upregulated miR-10b promotes abnormal NP cell proliferation during IDD through modulating the RhoC-Akt signalling pathway, and inhibition of miR-10b might be a novel therapeutic target for the RhoC-Akt signalling pathway, such as cell growth, proliferation, migration and apoptosis.

Moreover, the expression levels of miR-10b are positively associated with the grades of IDD. MiR-10b directly targets homeobox D10 (HOXD10). The expression levels of miR-10b are positively associated with idiopathic scoliosis patients compared with healthy controls, which has been demonstrated that the expression of miR-155 is significantly increased in the degenerated NP tissues, which functions as a suppressor of the activation of the PI3K/Akt signalling pathway (Cheng et al., 2009), and the apoptosis of NP cells was increased assessed by the cleaved caspase-3 immunohistochemistry assay and the Annexin V/PI assay. Thus, besides the miRNAs mentioned above, miR-27a is another crucial regulator that plays an important role in the apoptosis of human NP cells by targeting the PI3K/Akt gene and mediating the PI3K/Akt signalling pathway (Liu et al., 2013). In addition, it has been demonstrated that the expression of miR-494 is significantly increased in the degenerated NP tissues and regulates TNF-α-induced NP cell apoptosis. TNF-α is a key proinflammatory cytokine, and plays an important role in the apoptosis of NP cells in IDD (Wang et al., 2015). The knockout of miR-494 upregulates the level of jun D proto-oncogene (JunD) expression and suppresses the apoptosis of NP cells, which suggests that JunD protects the NP cells from TNF-α-induced apoptosis and is regulated negatively by miR-494 (Wang et al., 2015). Meanwhile, miRNAs also play critical roles of regulating the ECM degeneration through the pathway of ADAMTSs and MMPs. The expression levels of most ADAMTSs and MMPs members are positively associated with the disc degeneration degree. The decreased cleavage of aggrecan in human NP cells is modulated by the protein kinase C epsilon isoform (PKCε) signalling, which plays an important role in pathological ECM remodelling. A recent study has shown that activation of PKCε promoted the expression level of miR-377 in human NP cells. Notably, miR-377 negatively regulates the expression of gene ADAMTS5 so that increased expression of miR-377 decreased ADAMTS5 expression and reduced cleavage of aggrecan (Tsurimokichi et al., 2013). Although this research failed to compare the expression of miR-377 between patients with IDD and controls, it provides evidence that regulation of PKCε and miR-377 could be a novel therapeutic strategy to decelerate IDD. MiR-93 was identified to directly target MMP3 gene in NP cells. The expression level of miR-93 is significantly decreased in degenerative NP tissues, which

Additionally, there are several miRNAs identified to be involved in the apoptosis of NP cells. It has been proved that Fasl is expressed from NP cells and induces apoptosis in immunocytes to maintain the immune privilege of human disc (Liu et al., 2013), and upregulated FasL in NP cells elevates the Fas expression of vascular endothelial cells and the FasL-Fas network plays vital roles in cell apoptosis (Sun et al., 2013). MiR-155 has been reported to be downregulated and target the 3’-UTR of Fas associated via death domain (FADD) and caspase-3 directly in human NP cells. As FADD and caspase-3 are two key proteins in the FasL-Fas signalling pathway, which is regarded as one of the most essential pathways of cell apoptosis, it is shown that depression of miR-155 accelerates Fas-mediated apoptosis of NP cells in human IDD. Various cellular processes are regulated by the PI3K/Akt signalling pathway, such as cell growth, proliferation, migration and apoptosis. It has been shown that miR-27a is remarkably upregulated in degenerative NP cells compared with control NP cells. After being transfected with miR-27a in vitro cell culture, the expression levels of phosphatidylinositol-3-OH kinase (PIK3CD) were decreased, which functions as a suppressor of the activation of the PI3K/Akt signalling pathway (Cheng et al., 2009), and the apoptosis of NP cells was increased assessed by the cleaved caspase-3 immunohistochemistry assay and the Annexin V/PI assay. Thus, besides the miRNAs mentioned above, miR-27a is another crucial regulator that plays an important role in the apoptosis of human NP cells by targeting the PI3K/Akt gene and mediating the PI3K/Akt signalling pathway (Liu et al., 2013). In addition, it has been demonstrated that the expression of miR-494 is significantly increased in the degenerated NP tissues and regulates TNF-α-induced NP cell apoptosis. TNF-α is a key proinflammatory cytokine, and plays an important role in the apoptosis of NP cells in IDD (Wang et al., 2015). The knockout of miR-494 upregulates the level of jun D proto-oncogene (JunD) expression and suppresses the apoptosis of NP cells, which suggests that JunD protects the NP cells from TNF-α-induced apoptosis and is regulated negatively by miR-494 (Wang et al., 2015). Meanwhile, miRNAs also play critical roles of regulating the ECM degeneration through the pathway of ADAMTSs and MMPs. The expression levels of most ADAMTSs and MMPs members are positively associated with the disc degeneration degree. The decreased cleavage of aggrecan in human NP cells is modulated by the protein kinase C epsilon isoform (PKCε) signalling, which plays an important role in pathological ECM remodelling. A recent study has shown that activation of PKCε promoted the expression level of miR-377 in human NP cells. Notably, miR-377 negatively regulates the expression of gene ADAMTS5 so that increased expression of miR-377 decreased ADAMTS5 expression and reduced cleavage of aggrecan (Tsurimokichi et al., 2013). Although this research failed to compare the expression of miR-377 between patients with IDD and controls, it provides evidence that regulation of PKCε and miR-377 could be a novel therapeutic strategy to decelerate IDD. MiR-93 was identified to directly target MMP3 gene in NP cells. The expression level of miR-93 is significantly decreased in degenerative NP tissues, which
induces MMP3 expression and results in degradation of type II collagen and aggrecan (Jing and Jiang, 2015). This finding indicates that downregulated miR-93 directly contributes to disruption of type II collagen and aggrecan in the degeneration of disc. MMP13 has been found to be an enzyme-degraded proteoglycan and collagen for promoting IDD (Fosang et al., 1996), and fibroblast growth factor 2 (FGF2) and fibroblast growth factor receptor 1 (FGFR1) binding complex mediate the expression of MMP13 (Yan et al., 2012). Another member of FGFRs, FGFR3, binds to FGF2 competed with FGFR1 so that negatively regulates MMP13 expression (Ellman et al., 2013). Recently, miR-100 and FGFR1 have been shown to express at dramatically increased levels in patients with IDD compared with healthy controls, and miR-100 targets to 3'-UTR of FGFR3 mRNA leading to inhibition of FGFR3 translation and increase of MMP13 levels in disc (Wang et al., 2015). Thus, miR-100 is another important regulator involved in the pathology of ECM degradation in IDD. Ji et al. (2015) have identified 28 IDD-specific miRNAs that were expressed differentially in patients with IDD compared with normal controls via state-of-the-art next generation sequencing (NGS) platforms. Specially, miR-193a-3p has been found to be significantly downregulated in patients with IDD, and the type II collagen level is inversely relative to the expression of miR-193a-3p. Besides bioinformatics target prediction showed that MMP14 might be a putative target of miR-193a-3p, and the results of luciferase reporter assays and Western blotting confirmed that MMP14 is targeted by miR-193a-3p directly, and the expression level of MMP14 is expressed dramatically higher in 128 patients with IDD than that in 116 healthy controls. Knockdown of MMP14 increased type II collagen expression, which indicates that MMP14 plays an important role in degenerating type II collagen. These findings have demonstrated that miR-193a-3p is associated with IDD by targeting MMP14 and positively regulates type II collagen expression (Ji et al., 2015). Ji et al. (2015) also identified that miR-98 plays an important role in the pathogenesis of IDD. Similar to miR-193a-3p, miR-98 is also significantly downregulated expressed in patients with IDD versus normal controls, and accelerates type II collagen expression in NP cells. However, miR-98 is proved to target IL-6 and signal transducer and activator of transcription 3 (STAT3). Recently, IL-6 has been found to act as a key regulator in the pathogenesis in IDD and contributes to activate STAT3 expression. It has been reported that STAT3 activation promotes the expression of B-cell CLL/lymphoma 2 (Bcl-2), myeloid cell leukemia 1 (Mcl-1), cyclin D1 and MMP2, leading to reduce type II collagen (Yu et al., 2009). Therefore, miR-98 regulates the pathogenesis in IDD through mediating IL-6/STAT3 signalling pathway. Moreover, the expression level of miR-146a is upregulated remarkably in the degenerative disc (Zhao et al., 2014a), which has been found to target the apoptosis-related gene FADD in the immune response of T lymphocytes (Curtale et al., 2010), inflammation-associated gene such as IL-1β, IL-6 and TNF in human gingival fibroblasts (HGFs; Xie et al., 2013), and catabolism-related gene MMP-16 in glia cells (Xia et al., 2009). Recently, it was further confirmed that miR-146a is essential in the pathogenesis of IDD, which was discovered to regulate the anti-inflammatory and anti-catabolic process of IDD by suppressing IL-1-mediated ECM degrading enzymes MMPs and ADAMTS secretion and PG loss (Gu et al., 2015). To date, the research of miRNAs in human IVD tissue is still at an early stage, and the precise role of miRNAs in the pathogenesis of IDD remains to be elucidated (Liu et al., 2014).

4. Perspectives

Numerous studies have demonstrated that alterations in miRNA expression are strongly linked to various kinds of human diseases, including cancers (Adams et al., 2014), cardiovascular diseases (Latronico and Condorelli, 2009), inflammatory and autoimmune diseases (Zeng et al., 2014), and musculoskeletal disorders (Lian et al., 2012; Moore and Xiao, 2013). It has been reported that miRNAs have stable property and tissue-specificity, and might therefore be used as biomarkers for blood-based diagnosis of diseases (Chen et al., 2008; Mitchell et al., 2008). Up to date, over 100 miRNAs have been identified to be associated with the aetiology and pathology of diseases (Zeng et al., 2014). For instance, miR-21 was upregulated in many cancers, including colon, lung, breast and liver cancers (Lee and Dutta, 2009). The increased expression of miR-21 promoted tumour cell proliferation, migration and invasion (Meng et al., 2007). Additionally, miR-208 was identified to be a cardiac-specific miRNA that regulates stress-dependent cardiomyocyte growth and gene expression (van Rooij et al., 2007). Furthermore, circulating miRNAs have emerged in several autoimmune diseases. The level of miR-126 was increased in CD4+ T-cells and contributes to activating T-cells and B-cells through elevating the CD11a and CD70 gene expression in systemic lupus erythematosus (SLE; Zhao et al., 2011). It has been revealed that miRNAs in the human immune system not only regulate the T/B-cell differentiation, development, neutrophils and monocyte proliferation, but also affect the secretion of inflammatory cytokines (Zeng et al., 2014). Therefore, miRNAs have been involved in many diseases, and have the potential of regulating disease progression and diagnosis; the detection of miRNAs could be a potential approach for the early diagnosis of specific diseases.

Intervertebral disc degeneration is a progressive process and generally identified in the intermediate and late stages, thus there is an urgent need for the discovery of novel biomarkers for non-invasive early detection for IDD. miRNAs not only play an important role in regulating signalling pathways of chondrocytes and NP cells development, but also have a strong impact on the catabolism of the major matrix components in the IVD, which is in the early phase. In consideration of the important role of miRNAs in the pathogenesis of IDD,
the miRNAs in the blood and tissue might provide some indication for the early diagnosis of ID. Given the remarkably stable preservation in the blood and the potential diagnostic properties, including easy access, high stability, tissue specificity and significant sensitivity, specifically, the miRNAs in blood (circulating miRNAs) could be useful as biomarkers for the detection of ID. Finally, manipulation of expression of miRNAs in disc cells might provide an alternative approach for treatment of ID.

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Conflict of interest

Each author declares that there is no conflict of interest regarding the publication of this work.

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