The Potential Role of Cytokines in Diabetic Intervertebral Disc Degeneration

Sunlong Li¹,²,³,*, Chongan Huang¹,²,³,*, Jian Xiao¹,²,³, Yuhao Wu¹,²,³, Zengjie Zhang⁵,⁶,⁷, Yifei Zhou¹,²,³, Naifeng Tian¹,²,³, Yaosen Wu¹,²,³, Xiangyang Wang¹,²,³*, Xiaolei Zhang¹,²,³,⁴*

¹Department of Orthopaedics, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China. ²Key Laboratory of Orthopaedics of Zhejiang Province, Wenzhou, Zhejiang, China. ³The Second School of Medicine, Wenzhou Medical University, Wenzhou, Zhejiang, China. ⁴Chinese Orthopaedic Regenerative Medicine Society, Hangzhou, Zhejiang, China. ⁵Department of Orthopedic Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China. ⁶Orthopedics Research Institute of Zhejiang University, Hangzhou, Zhejiang, China. ⁷Key Laboratory of Motor System Disease Research and Precision Therapy of Zhejiang Province, Hangzhou, Zhejiang, China

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ABSTRACT: Intervertebral disc degeneration (IVDD) is a major cause of low back pain. Diabetes mellitus is a chronic inflammatory disease that may cause or aggravate IVDD; however, the mechanism by which diabetes induce IVDD is currently unclear. Compared to non-diabetic individuals, diabetic patients have higher levels of plasma cytokines, especially TNF-α, IL-1 β, IL-5, IL-6, IL-7, IL-10, and IL-18. Due to the crucial role of cytokines in the process of intervertebral disc degeneration, we hypothesized that elevation of these cytokines in plasma of diabetic patients may be involved in the process of diabetes-induced IVDD. In this review, changes in plasma cytokine levels in diabetic patients were summarized and the potential role of elevated cytokines in diabetes-induced IVDD was discussed. Results showed that some cytokines such as TNF-α and IL-1 β may accelerate the development of IVDD, while others such as IL-10 is supposed to prevent its development. Apoptosis, senescence, and extracellular matrix metabolism were found to be regulated by these cytokines in IVDD. Further studies are required to validate the cytokines targeted strategy for diabetic IVDD therapy.

Key words: intervertebral disc degeneration (IVDD), Diabetes, cytokines

Globally, low back pain (LBP) is a common chronic disease that is associated with a significant financial burden [1]. Approximately 40% of the global population suffers from LBP during their lifetime [2]. In the US, it has been reported that from 1996 to 2013, low back and neck pain-associated treatment costs increased by an estimated $87.6 billion. Among the Chinese people, LBP is the leading cause of disability [3, 4]. The potential causes of LBP involve the pathological changes of the spinal column, including intervertebral disc and facet joints. Intervertebral disc degeneration (IVDD), which has a high global incidence, is a major risk factor for low back pain [5]. Clinically, IVDD is a complicated disease that is caused by multiple factors, including age, genetic and environmental factors. It is characterized by biochemical and cellular changes in the disc tissue [6-9]. Occupational habits such as heavy lifting and lifestyle habits like lack of exercises and driving cars for extended periods of time contribute to IVDD development [10]. Moreover, smoking and trauma are associated with the pathogenesis of IVDD [8-11]. However, the mechanisms involved in IVDD have not been clearly established.

*Correspondence should be addressed to: Dr. Xiaolei Zhang (Email: zhangxiaolei@wmu.edu.cn) or Dr. Xiangyang Wang (Email: xiangyangwang@wmu.edu.cn). Department of Orthopaedics, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, West Xueyuan Road, Wenzhou, Zhejiang, China. #These authors contributed equally to this work.

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The pathogenesis of intervertebral disc degeneration

The intervertebral disc (IVD), an elegant structure, is composed of nucleus pulposus (NP), annulus fibrosus (AF) and cartilage endplate (CEP). The gelatinous nucleus pulposus, which is predominantly composed of Type II collagen (Col II) and proteoglycans with a high-water content, is the major component of IVD. It is important in counteracting physiological stress due to human activities [12]. In addition, nucleus pulposus is important in stabilization and biomechanical maintenance of the disc. Nucleus pulposus cell necrosis and apoptosis is highly associated with degeneration of intervertebral discs [13]. The loss of nucleus pulposus impairs the balance between extracellular matrix (ECM) synthesis and degradation, leading to IVDD development. Clinically, IVDD is a degenerative disease that is mainly common among the elderly. Thus, studies have investigated the relationship between senescence and IVDD [14, 15]. Consistent with these studies, we found that nucleus pulposus cell senescence accelerated IVDD progression, which was ameliorated when NP cell senescence was inhibited [16, 17]. Therefore, NP cell apoptosis and senescence is involved in IVDD. Annulus fibrosus, a component of the intervertebral disc tissue, is a thick and dense structure, including the inner and outer annulus. It protects the nucleus pulposus by alleviating nucleus pulposus and vertebral body stress. During IVDD, collagen II levels gradually decrease, leading to annular disruption and IVDD progression [18]. The nucleus pulposus and annulus fibrosus play a significant role in IVDD progression. Moreover, the cartilage endplate is involved in IVDD progression. Due to its restrictive blood supply effects, the endplate is crucial in disc degeneration [19, 20]. Cartilage endplate apoptosis and senescence blocks blood nutrition supply and initiates IVDD [20]. IVDD is a complicated pathological process that involves various factors, such as nutrition, cell senescence, apoptosis, inflammation, cytokines and extracellular matrix degradation of the disc tissue. The definite etiology and pathophysiology of IVDD should be further investigated.

Association between diabetes mellitus and intervertebral disc degeneration

Diabetes mellitus, which is associated with elevated blood glucose levels, is a chronic disease. It results from insulin deficiency and insulin resistance and is classified as type 1 diabetes (T1D) or type 2 diabetes (T2D). In 2013, the estimated overall prevalence of diabetes was 10.9% while that of prediabetes was 35.7% among adults in China [21]. Diabetes mellitus-associated complications, including neuropathy, nephropathy and cardiovascular diseases, significantly decrease the quality of life and increase mortality rates [22]. There is an association between diabetes mellitus and IVDD. First, Sakellaridis reported a significant increase in lumbar disc surgery incidences among diabetes mellitus patients [23]. In Finland, a study involving 638 diabetic and 32510 non-diabetic individuals revealed that herniated disc incidences in diabetic patients were significantly higher than in non-diabetic patients [24]. In Asia, a 4-year case follow-up study in Japan showed that diabetes was closely associated with upper lumbar disc degeneration (OR=6.83; 95% CI, 1.07 -- 133.7) [25]. A retrospective study reported that being an immune disease with an early onset time and difficult glucose control, T1D results in early IVDD [26]. Don-Kyu Kim et al. [27] documented that T2D is significantly associated with degenerative lumbar spine disorders, therefore, they postulated that diabetes is a predisposing factor for lumbar spine disorders. In our previous study, to exclude the effects of other interfering factors, we used animal models to evaluate the effects of diabetes on IVDD alone. We established that nucleus pulposus cell senescence and apoptosis in STZ-induced diabetic rats were markedly increased while the extracellular matrix was degraded, leading to IVDD [28]. It has also been suggested that T1D contributes to IVDD by promoting aggrecan degradation and apoptosis [29, 30]. In a previous study, T2D induced by leptin receptor-deficient knockout (db/db) led to IVDD by elevating MMP3 levels and promoting cell apoptosis [31]. In vivo and in vitro studies have supported the hypothesis that diabetes is a major risk factor for IVDD. Therefore, we defined diabetes-induced IVDD as Diabetic Intervertebral Disc Degeneration (DB-IVDD). Although clinical and animal studies have confirmed that diabetes can cause or worsen IVDD, the exact pathomechanisms have not been conclusively determined. Given the increasing diabetes incidences, it is important to investigate the potential pathomechanisms of diabetes-induced IVDD.

Mechanisms of diabetes-induced intervertebral disc degeneration

Apoptosis, senescence, advanced glycation end products (AGEs) accumulation, microvascular damage, changes in the extracellular matrix (ECM) and direct impairment by hyperglycemia have been associated with diabetes-induced IVDD. Cell death and ECM degradation are major mechanisms of IVDD, including diabetes-induced IVDD. Cell death, a functional biological process required for cellular development, is classified as apoptosis, necrosis or autophagy [32]. Cell death modulation is associated with various diseases and highly contributes to IVDD [33]. The main intervertebral disc
components are collagen II and aggrecans. Due to intrinsic regulation by growth and catabolic factors, anabolism and catabolism of ECM are in equilibrium [18]. When the balance is broken, IVDD development is initiated. Studies have principally focused on regulation of apoptosis, the autophagic pathway and ECM degradation in IVDD, including in diabetes-induced IVDD.

High glucose, reactive oxygen species (ROS), accumulation of AGEs, inflammation and obesity are major factors that contribute to diabetes-induced IVDD [34, 35]. Diabetes-induced degenerative changes have been associated with decreased endplate porosity, increased thickness, and accumulation of advanced glycation end products (AGEs) [36]. In STZ-induced diabetic rats, AGEs accumulation in the nucleus pulposus accelerated disc degeneration by upregulating the levels of matrix degrading enzymes (MMP-2) [35]. In addition, AGEs accumulation in NP may promote disc degeneration-associated inflammation by disturbing the extracellular matrix via NLRP3 inflammasome activation [37]. An experimental study also suggested that AGEs induce AF cells apoptosis, which may provide a theoretical basis for diabetic IVD degeneration [38]. Chronic ingestion of AGEs has a significant effect of IVDD [39]. Mechanistically, AGEs may also enhance endochondral ossification in intervertebral discs, thereby aggravating IVDD. Endplate cartilage calcification plays a significant role in accelerating disc degeneration by blocking nutritional supply [40].

Elevated blood glucose levels, a major characteristic of diabetes mellitus-related disease, have a direct or indirect influence on disc degeneration. High glucose upregulates ROS levels, which promotes the apoptosis of NP as well as CEP cells and enhances the catabolic activities of the ECM, aggravating IVDD [41, 42]. The pathogenesis of IVDD is tightly associated with ROS [43]. ROS modulates homeostasis through various signaling pathways, including the nuclear factor-κ B (NF-κ B) pathway, the mitogen-activated protein kinases (MAPKS) pathway, and the PI3K/AKT pathway [44]. Hyperglycemia-induced ROS promotes NP cell apoptosis through the mitochondrial apoptosis pathway [45]. The death of notochordal cells through the mitochondrial apoptosis and death receptor pathways marks the induction of IVDD [46]. Senescence, a cellular state that is characterized by cell cycle arrest, can be accelerated by oxygen free radicals’ accumulation. The p53/p21 and p16/pRB pathways are the two major pathways that modulate the senescent state. These two pathways are modulated by various factors, including oxidative stress and inflammation [47]. ROS-induced mitochondrial dysfunction and oxidative stress contributes to disc cell senescence, thereby promoting IVDD. High glucose affects the viability of nucleus pulposus cells and matrix degrading enzymes [48]. Moreover, high glucose significantly modulates the expressions of ECM-related proteins, including TIMPs downregulation and MMPs overexpression (1, 3, 13), resulting in rapid IVDD and fibrosis. Collagen II and proteoglycans were found to be suppressed in high glucose treated NP cells [36, 41]. Since the endplate cartilage is the main route for nutrition supply, cartilage endplate degeneration can block nutrition supply [49]. Nutritional deprivation leads to cell death and ECM degradation, which triggers IVDD [49]. Excess apoptosis and calcification of cartilaginous endplate cells accelerates cartilage endplate degeneration [20]. During IVDD, ROS is the main stimuli for cartilage endplate apoptosis and calcification [20]. Autophagy is a complicated process whose main function is to degrade damaged organelles and useless proteins [50]. Animal model studies reported that autophagy was enhanced by high blood glucose, which can be seen as a protective measure against apoptosis and senescence. Metformin protects nucleus pulposus cells from apoptosis and senescence by stimulating autophagy [16, 51]. The silent mating type information regulator 2 homolog1 (sirt1), an NAD+ dependent histone deacetylase is associated with various aging-related diseases and plays an important role in cellular senescence as well as disc cell apoptosis. Non-restriction of calories in the nucleus pulposus due to high glucose degrades sirt1 activities, which enhances disc cell apoptosis [52].

Diabetes mellitus is a chronic inflammatory disease. Inflammation plays an important role in IVDD pathogenesis [53]. In addition, circulating levels of acute-phase proteins as well as some cytokines have been shown to be elevated in diabetes patients [54, 55]. Hyperglycemia impairs β cell functions and directly or indirectly activates immune responses, thereby inducing the changes in levels of circulating cytokines and other proteins [54]. Vascular ingrowth in the nucleus pulposus is a vital pathological phenomenon of IVDD [56, 57]. LA Binch et al. [58] stated that cytokine secretion, particularly IL-1β, during IVDD progression facilitates vascular ingrowth, via which cytokines can exert their effectiveness, implying that vascular ingrowth suppression may be a potential therapeutic strategy [59]. However, the effects of dysregulated cytokine levels in DB-IVDD have not been conclusively determined.

Potential roles of elevated cytokines in DB-IVDD

In this section, we elucidate on some cytokines that are differentially expressed between diabetic and healthy individuals (Table 1). Studies have reported that IL-6 is significantly elevated in both T1D and T2D (Table 1) and is a proven risk factor and an independent predictor for
Due to IL-6-induced HS-CRP production, plasma IL-1β levels have been shown to be elevated in T1D and T2D [55, 63]. However, recent studies have reported that differences in IL-1β levels between T2D and healthy people are not significant (p>0.05; Table 1) [60, 61]. Compared to healthy people, IL-10, an anti-inflammatory factor released to ameliorate inflammation, is elevated in T1D and T2D patients (Table 1) [64, 65]. Levels of IL-18, a cytokine in the interleukin-1 family that is involved in the development and progression of diet-induced cardiac dysfunctions, are elevated in T2D patients (Table 1) [66]. In addition, compared to healthy individuals, plasma TNF-α levels are significantly elevated in both types of diabetes patients (Table 1). As a pro-inflammatory cytokine, TNF-α may have an important role in IVDD [60]. Moreover, TNF-α levels are also increased in diabetes (Table 1), where it may enhance the production of inflammatory factors by T cells. Compared to healthy individuals, hepatocyte growth factor (HGF) and vascular endothelial growth factor receptor (VEGFR-1/2) levels are higher in diabetic patients (Table 1) [67]. In pre-diabetics, IL-5 and IL-7 levels were found to be elevated, compared to controls (Table 1). Elevations of IL-7 in T1D is a risk factor for diabetic nephropathy [68], which has potential associations with IL-5 [69]. Various factors have been attributed to the development of diabetic nephropathy, which may share similar mechanisms with IVDD [70]. Therefore, IL-5 and IL-7 may have a potential impact on IVDD.

Table 1. Plasma concentrations of some cytokines in diabetic patients and healthy individuals.

| Cytokine | Control | T1D | T2D | Prediabetes | p    | Reference |
|----------|---------|-----|-----|-------------|------|-----------|
| IL-1β (pg/ml) | 3.2 | 6.4 | 0.0104 | 55 |
| IL-1α (pg/ml) | 0.47±0.79 | 0.57±0.93 | 0.1959 | 60 |
| IL-2 (pg/ml) | 4.2 | 7.6 | 0.0087 | 55 |
| IL-2R (pg/ml) | 50.8±7.269 | 121.4±22.75 | 0.049 | 67 |
| IL-4 (pg/ml) | 9.37±2.98 | 12.42±2.86 | 0.32 | 68 |
| IL-5 (pg/ml) | 0.40±0.11 | 1.19±0.26 | 0.01 | 68 |
| IL-6 (pg/ml) | 1.9±0.6 | 5.0±1.3 | <0.02 | 62 |
| IL-10 (pg/ml) | 2.8 | 7.1 | 0.0034 | 55 |
| IL-12 (pg/ml) | 1.43±0.38 | 2.85±0.53 | 0.01 | 68 |
| IL-12 (pg/ml) | 7.6 | 33.4 | <0.05 | 65 |
| IL-16 (pg/ml) | 1.76±0.94 | 3.02±2.27 | 0.0163 | 64 |
| IL-18 (pg/ml) | 105.2±20.43 | 112.2±21.62 | 0.08198 | 67 |
| IFN-α (pg/ml) | 34.75±4.82 | 88.47±12.13 | 0.0073 | 67 |
| IFN-γ (pg/ml) | 4.23±0.489 | 4.84±4.84 | 0.72 | 67 |
| TNF-α (pg/ml) | 2.24±0.45 | 3.57±0.59 | 0.21 | 68 |
| TNF-α (pg/ml) | 11.3 | 24.2 | <0.05 | 55 |
| TNF-α (pg/ml) | 1.79±1.28 | 2.03±1.51 | <0.0094 | 60 |
| TNF-α (pg/ml) | 2383 | 2646.5 | <0.001 | 134 |
| HGF (pg/ml) | 589.1±47.02 | 863.1±126.9 | 0.045 | 67 |
| VEGFR-1 (pg/ml) | 643.8 | 2044 | 0.0001 | 67 |
| VEGFR-2 (pg/ml) | 7103 | 19190 | 0.0005 | 67 |
| sIL-6R (pg/ml) | 35040 | 35370 | 0.13 | 135 |
| sIL-6Ra (pg/ml) | 45900 | 65900 | 0.032 | 67 |

Data are displayed as median (IQR) or mean ±SEM. T1D: type 1 diabetes mellitus. T2D: type 2 diabetes mellitus.

Cytokines are important regulators of diabetes mellitus and IVDD [71]. As degeneration proceeds, elevated inflammatory cytokine levels accelerate the process of IVDD by enhancing aggrecan as well as collagen degradation and promoting phenotypic changes of disc cells [5]. Moreover, inflammatory cytokines can induce the death of disc cells and ECM degradation, thereby contributing to IVDD [53]. Diabetes is a chronic inflammatory disease that is associated with alterations in various inflammatory factors [72]. Several cytokines are elevated in diabetes patients, where they accelerate IVDD. Therefore, we summarized some of the elevated cytokines in diabetes and briefly discussed the mechanisms through which these cytokines accelerate IVDD in diabetics.

**TNF-α in DB-IVDD**

Tumor necrosis factor (TNF-α), an important member of the TNF superfamily of ligands, secreted by macrophages, T cells and some non-immune cells, is
a pro-inflammatory cytokine. As previously mentioned, TNF-α is elevated in type 1 and 2 diabetes patients. Bachmeier reported that degenerative and herniated human IVD tissues have higher TNF-α levels, compared to non-degenerative IVD tissues [73]. Through cell apoptosis, senescence, autophagy, ECM degradation and inflammation, elevated TNF-α plays a significant role in DB-IVDD progression [74]. Evidence supports the hypothesis that TNF-α is involved in IVD cell apoptosis. TNF-α elevates the apoptotic rate and up-regulates p53 as well as cleaved-caspase 3 levels in various cells. [75]. Cytochrome C, which is involved in apoptosis, is also associated with TNF-α-induced IVDD [76]. TNF-α enhances apoptosis in IVDD by activating JNK/ERK-MAPK and NF-κB signaling pathways [77]. In addition, autophagy is involved in TNF-α-induced IVDD, as a catabolic mechanism against cell stress. Annulus fibrosus (AF) plays an important role in IVDD. After treatment with TNF-α, autophagy-related proteins, such as autophagy modulator p62 and WIP149, in AF cells were increased, suggesting that TNF-α activates autophagy but, at the same time, blocks the autophagy flux [78]. Using mice models, Risbud found that systemic TNF-α elevation was not enough to promote complete disc degeneration; however, it caused spontaneous disc herniation [79]. Cheng Wang showed that TNF-α stimulated NP and AF cells to synthesize many pro-inflammatory cytokines, such as IL-6, IL-8, IL-1β, IL-8 and IL-17, thereby amplifying inflammatory responses in inflammation-induced IVDD [74]. Given that ECM degradation is tightly associated with DB-IVDD progression, TNF-α also promotes ECM degradation by inducing the production of various enzymes such as MMPs and ADAMTs, which are responsible for ECM degradation. [74, 80, 81] we believe that TNF-α plays a facilitating role in DB-IVDD.

**IL-1β in DB-IVDD**

IL-1β is a pro-inflammatory cytokine whose overproduction exerts deleterious effects on peripheral insulin signaling and β-cell functions [82]. IL-1β is a critical effector molecule in non-obese diabetic (NOD) mice models of T1D, and it’s also an important inflammatory mediator of type II diabetes [83, 84]. Inflammatory responses are induced by overexpression of inflammatory cytokines, mainly IL-1β, and are highly involved in IVDD progression [85]. IL-1 stimulates the production of several metalloproteinases, leading to connective tissue breakdown and suppression of proteoglycan as well as type II collagen levels, thereby exerting a global negative effect on articular cartilage. In addition, IL-1 exerts direct and indirect stimulatory effects on osteoclast maturation, and therefore, participates in the development of bony erosions in arthritis [86]. Qiu-Hui Pan demonstrated that disc cells pre-treated with IL-1β increased their apoptotic rates in response to FasL in vitro [87]. Risbud MV et al. [88] concluded that IL-1β regulates SDC4 expressions, which play a key role in the pathogenesis of degenerative disc diseases by promoting aggrecan degradation via ADAMTS-5 in the nucleus pulposus. In our previous study, we found that IL-1β induced the expressions of senescence-associated secreted phenotype (SASP) factors, which might influence the microenvironment in NP tissues and lead to local dysfunctions [89]. Cao Yang reported that reactive oxygen species (ROS) induced NF-κB pathway activation promotes NLRP3 inflammasome activation and IL-1β release, both of which enhances NP degeneration [90]. Therefore, specifically elevated IL-1β in diabetes may promote the occurrence of DB-IVDD.

**IL-5 in DB-IVDD**

IL-5 was first discovered as a "T-cell replacing factor" that is secreted by T cells to stimulate antibody production by B cells [91]. The major biological function of IL-5 is to promote eosinophil activation, proliferation and migration. It exerts its effects on target cells via the IL-5 receptor (IL-5R), which is composed of a unique α chain (IL-5R to CD125) and the common cytokine β-chain, which is essential for IL-5 signal transduction [92]. Immune responses in NP tissues lead to chronic inflammation and consistent pain in patients. Plasma IL-5 levels have been shown to be elevated in prediabetes patients, compared to healthy volunteers. However, the significance of IL-5 in IVDD has not been conclusively determined. As previously reported, JAK2 and STATs are indispensable in IL-5 dependent signaling transduction in B cells, Th2 cells and eosinophils [93]. JAK2 and STATs signaling pathways are also involved in IVDD progression [94], suggesting that IL-5 participates in IVDD (including DB-IVDD) via the JAK2/STATs signaling pathway. Moreover, Ras GTPase extracellular signaling pathways are involved in IL-5 dependent cell death, proliferation and differentiation of eosinophils [93, 95]. Ras is also associated with extracellular matrix degradation in the chondrocytes, suggesting that IL-5 influences Collagen II and MMPs levels in intervertebral disc tissues in IVDD [96, 97]. Polarization of helper T lymphocytes (Th2) may be involved in IVDD via phenotypic shifts of macrophages [98], and IL-5-induced eosinophils can activate macrophages [99], suggesting that IL-5 influences IVDD progression through various immune responses in the disc tissue. Thus, the significance of IL-5 in DB-IVDD should be investigated.
IL-6 in DB-IVDD

IL-6, a 25kDa protein, has a characteristic structure that is made up of four long α-helices arranged in an up-up-down-down topology. It is a cytokine that promotes B cell maturation into antibody producing cells [100]. IL-6 plays a great role in various physiological functions as well as in immune regulation [101]. Moreover, it stimulates osteoclast formation and promotes bone resorption [102]. Signal transduction is activated by IL-6 via IL-6R and sIL-6R, which contains the signal-transducing component (gp130). Binding of IL-6 to the IL-6R/gp130 complex primarily signals through JAK/STAT, Ras and PI3K pathways and its function varies from growth and differentiation of B- and T- cells to acute-phase protein induction [53]. Many stimuli that activate IL-6 are associated with oxidative stress and damage [103]. IL-6 levels in circulating blood were found to be elevated in acute hyperglycemia, high fat meals, physical activity and before/after surgery [104]. Plasma IL-6 levels were found to be elevated in type 1 and 2 diabetes and were associated with T2D development [60]. Moreover, IL-6 was highly expressed in degenerative discs, causing low back pain and presenting both pro-inflammatory and anti-inflammatory functions [105, 106]. It regulates inflammatory responses by downregulating the levels of pro-inflammatory cytokines and upregulating anti-inflammatory molecules, including IL-1 receptor antagonist protein, TNF-soluble receptor and extrahepatic protease inhibitors [107]. Inhibition of STAT alleviates the effects of IL-6 in the intervertebral disc, therefore, the IL-6/JAK/STAT3 pathway is a potential therapeutic target for IVDD [108]. IL-6 suppresses H2O2-induced cell death by elevating prohibiting levels, which is involved in cell apoptosis and senescence [109]. Moreover, IL-6 promotes the expressions of proteins involved in IVDD, including COX-2 and MMP13. Higher ratios of IL-6/IL-10 plasma levels augments the risk of causing symptomatic lumbar osteoarthritis and IVDD [105]. Therefore, IL-6 plays a complex role in DB-IVDD progression.

IL-7 in DB-IVDD

IL-7 is a member of the common γ chain (γc-CD132) cytokine family, which includes IL-2, IL-4, IL-9, IL-15 and IL-21 [110]. In pre-diabetics and T1D, IL-7 levels were increased, compared to the control group. IL-7 stimulates Janus kinase (JAK) and STAT signaling pathways, which subsequently activate the PI3K/Akt pathway to facilitate target gene transcriptions [110]. Even though IL-7 is rarely reported in IVDD, IL-5, IL-6, IL-7, IL-8 and MCP-2 were established to be significantly elevated in injured-IVD, compared to non-injury-IVD [111]. Senescence contributes to the development of various degenerative diseases, including osteoarthritis and IVDD [112, 113]. In cord blood cells, IL-7 increased telomere length and hTERT gene expressions [114], suggesting that it may also protect against cellular senescence in other degenerative diseases. Elevated IL-7 enhances MMP-13 production in osteoarthritis patients, which has a significant effect in degenerative diseases [115]. It has been reported that IL-7 has comparable pathological characteristics in osteoarthritis and IVDD. However, the significance of IL-7 in IVDD is unknown. The JAK/STAT signaling pathway may be mechanistically involved in IL-7-related IVD degeneration. This is because, IL-7 stimulates the secretion of S100A4, which has been verified to be elevated in osteoarthritis and upregulates the expressions of MMP13 by activating the JAK/STAT pathway [116]. In addition, IL-7 can be stimulated by other cytokines, such as IL-1 and IL-6, and combine with other cytokines like TNF-α and IL-6 to exert its effects in IVDD [117]. However, the specific roles of IL-7 in DB-IVDD have not been conclusively determined.

IL-10 in DB-IVDD

Interleukin-10, which is secreted by type 2 T-helper (Th2) cell clones, belongs to the IL-10 family of cytokines, including IL-19, IL-20, IL-22, IL-24, and IL-26 [118]. IL-10, an anti-inflammatory cytokine, is a protective factor in various tissues, including the articular cartilage and disc tissues. It inhibits innate and acquired immune responses by suppressing the activities of monocytes and the development of activated T-cells. Moreover, IL-10 modulates the functions and differentiation of various immune cells, such as B-cells, NK-cells, granulocytes and some related cells [119]. Elevated plasma IL-10 levels have been documented in type 1 and 2 diabetes patients as well as in degenerated intervertebral discs [64, 105]. In addition, IL-10 levels were up-regulated in rheumatoid arthritis and osteoarthritis models. This cytokine exerts anti-inflammatory, anti-catabolic as well as anti-apoptotic effects in chondrocytes, and is a potential target for curing arthritis [120]. The common characteristic of IVDD and osteoarthritis involves degradation of the extracellular matrix by regulating MMPs and other degrading enzymes to accelerate cell apoptosis [53, 121, 122]. Clinically, IL-10 inhibits the catabolic effects of pro-inflammatory cytokines by down-regulating MMPs and pro-inflammatory COX-2 [123]. IL-10 antagonizes matrix degrading enzymes and affects cartilage matrix gene expressions triggered by pro-inflammatory cytokines, such as TNF-α [123-125]. Behrendt reported that IL-10 significantly reduced the expressions of ADAMTS-4, MMP-3, and MMP-13, which were closely associated...
with ECM degradation, suggesting that IL10 has protective effects on chondrocytes [126]. Apoptosis significantly contributes to osteoarthritis and IVDD pathogenesis [33, 127]. IL-10 inhibits cell apoptosis by suppressing activated caspase-3 levels and the ratio of bax/bcl-2 to ameliorate the process of osteoarthritis. Moreover, it inhibits TNF-α-induced mitochondrial dependent apoptosis by increasing bcl-2 and down-regulating cleaved-caspase3 levels [123, 126]. Therefore, IL-10 has a significant role in interrelations between diabetes mellitus and IVDD.

IL-18 in DB-IVDD

IL-18, a member of the IL-1 superfamily with a similar structure to IL-1β, is a highly regulated inflammatory cytokine that is cleaved by intracellular protease caspase-1 to generate a biologically active molecule. IL-18 has been reported to be elevated in inflammatory diseases and conditions such as, T2D, obesity, Alzheimer's disease, and ischemic heart disease [70, 128]. However, the function of elevated IL-18 in diabetes-induced IVDD remains unknown. T2D, obesity, and stress can promote the release of IL-18 from microglia. Moreover, IL-18 seems to increase ROS production in cells. The ROS in turn activates caspase-1 and inflammasome system leading to further production of IL-18 and neuronal apoptosis [129]. It has been shown that IL-18 can increase the protein level of anti-apoptotic BCL-2 and BCL-XI, which are protective transmembrane proteins that inhibit the mitochondrial pathway of apoptosis in neurons [130]. A previous study revealed that IL-18 released from pyroptotic NPCs caused degeneration of the surrounding normal NPCs, thereby accelerating IVD degeneration [131]. IL-18 may also influence the endplate vascular endothelial cells, hence alter the environment around NP cells, AF cells, and endplate chondrocytes. The major pathological changes associated with IVDD include cartilage endplate degeneration and nucleus pulposus senescence or apoptosis. Calcification of the endplate cartilage is the major cause of endplate degeneration [20]. IL-18 can also induce inflammatory responses in synoviocytes and chondrocytes, and increase the expression of inflammatory factors, such as TNF-α, PGE2, and COX-2. In this way, it contributes to the cartilage degeneration and osteoarthritis [132]. Furthermore, studies have shown that IL-18 degrades the disc matrix and is elevated in serum of patients with IVD degeneration. Elsewhere, IL-18 up-regulated the expression of MMP13 and down-regulated the expression of...
of anabolic factors such as Collagen II and SOX6 in human nucleus pulposus [133]. Therefore, IL-18 may play an important role in diabetes-induced IVDD, although the detailed mechanisms need to be further investigated.

It remains unclear how elevated cytokines in diabetes contribute to disc degeneration. Further research is advocated to reveal the mechanisms and develop novel treatments for disc degeneration targeting these cytokines.

**Conclusion**

Diabetes has been reported to induce intervertebral disc degeneration. As the increasing prevalence of diabetes, diabetes induced IVDD is becoming a burning issue. However, the mechanisms involved in diabetes-induced IVDD have not been clearly illustrated. Inflammation, one of the main characteristics of diabetes, is the main pathogenic factor for various kinds of diseases, including IVDD. Herein, we summarized cytokines that are specifically elevated in diabetic condition, also we discussed the role of these cytokines in IVDD, including ECM metabolism, apoptosis, senescence as well as vascular ingrowth (Fig. 1). IL-1β and TNF-α have been reported to aggravate IVDD; therefore, inhibition of them is considered to be effective therapy for IVDD. However, other elevated cytokines such as IL-5, IL-6, IL-7, IL-10 and IL-18 may play different roles in IVDD, whose effects on IVDD are yet to be determined.

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**References**

[1] Hartvigsen J, Hancock MJ, Kongsted A, Louw Q, Ferreira ML, Genevay S, et al. (2018). What low back pain is and why we need to pay attention. Lancet, 391:2356-2367.

[2] Buchbinder R, van Tulder M, Oberg B, Costa LM, Wooff A, Schoene M, et al. (2018). Low back pain: a call for action. Lancet, 393:2384-2388.

[3] Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. (2019). Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet, 394:1145-1158.

[4] Wu D, Wong P, Guo C, Tam LS, Gu J (2021). Pattern and trend of five major musculoskeletal disorders in China from 1990 to 2017: findings from the Global Burden of Disease Study 2017. BMC Med, 19:34.

[5] Lan T, Shiyu H, Shen Z, Yan B, Chen J (2021). New insights into the interplay between miRNAs and autophagy in the aging of intervertebral discs. Ageing Res Rev, 65:101227.

[6] Weber KT, Jacobsen TD, Maidhof R, Virojanaporn J, Overby C, Bloom O, et al. (2015). Developments in intervertebral disc disease research: pathophysiology, mechanobiology, and therapeutics. Curr Rev Musculoskelet Med, 8:18-31.

[7] Frapin L, Clout J, Delplace V, Fusellier M, Guicheux J, Le Visage C (2019). Lessons learned from intervertebral disc pathophysiology to guide rational design of sequential delivery systems for therapeutic biological factors. Adv Drug Deliv Rev, 149-150:49-71.

[8] Ganko R, Rao PJ, Phan K, Mobbs RJ (2015). Can bacterial infection by low virulent organisms be a plausible cause for symptomatic disc degeneration? A systematic review. Spine (Phila Pa 1976), 40:E587-592.

[9] Kong JG, Park JB, Lee D, Park EY (2015). Effect of high glucose on stress-induced senescence of nucleus pulposus cells of adult rats. Asian Spine J, 9:155-161.

[10] Maher C, Underwood M, Buchbinder R (2017). Non-specific low back pain. Lancet, 389:736-747.

[11] Okada E, Daimon K, Fujisawa H, Nishikawa Y, Nojiri K, Watanabe M, et al. (2019). Ten-year Longitudinal Follow-up MRI Study of Age-related Changes in Thoracic Intervertebral Discs in Asymptomatic Subjects. Spine (Phila Pa 1976), 44:E1317-E1324.

[12] Yang B, O'Connell GD (2019). Intervertebral disc swelling maintains strain homeostasis throughout the annulus fibrosus: A finite element analysis of healthy and degenerated discs. Acta Biomater, 100:61-74.

[13] Li Z, Chen X, Xu D, Li S, Chan MTV, Wu WKK (2019). Circular RNAs in nucleus pulposus cell function and intervertebral disc degeneration. Cell Prolif, 52:e12704.

[14] Zhang Y, Yang B, Wang J, Cheng F, Shi K, Ying L, et al. (2020). Cell Senescence: A Nonnegligible Cell State under Survival Stress in Pathology of Intervertebral Disc Degeneration. Oxid Med Cell Longev, 2020:9503562.

[15] Yang S, Zhang F, Ma J, Ding W (2020). Intervertebral disc ageing and degeneration: The antiapoptotic effect of oestrogen. Ageing Res Rev, 57:100978.

[16] Chen D, Xia D, Pan Z, Xu D, Zhou Y, Wu Y, et al. (2016). Metformin protects against apoptosis and senescence in nucleus pulposus cells and ameliorates disc degeneration in vivo. Cell Death Dis, 7:e2441.

[17] Chen J, Xie JJ, Jin MY, Gu YT, Wu CC, Guo WJ, et al. (2018). Sirt6 overexpression suppresses senescence and apoptosis of nucleus pulposus cells by inducing autophagy in a model of intervertebral disc degeneration. Cell Death Dis, 9:56.

[18] Wang WJ, Yu XH, Wang C, Yang W, He WS, Zhang SJ, et al. (2015). MMPs and ADAMTSs in intervertebral disc degeneration. Clin Chim Acta,
[19] Fournier DE, Kiser PK, Shoemaker JK, Battle MC, Seguin CA (2020). Vascularization of the human intervertebral disc: A scoping review. JOR Spine, 3: e1123.

[20] Han Y, Li X, Yan M, Yang M, Wang S, Pan J, et al. (2019). Oxidative damage induces apoptosis and promotes calcification in disc cartilage endplate cell through ROS/MAPK/NF-kappaB pathway: Implications for disc degeneration. Biochem Biophys Res Commun, 516:1026-1032.

[21] Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, et al. (2017). Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. JAMA, 317:2515-2523.

[22] Chatterjee S, Khunti K, Davies MJ (2017). Type 2 diabetes. Lancet, 389:2239-2251.

[23] Sakellaris N (2006). The influence of diabetes mellitus on lumbar intervertebral disc herniation. Surg Neurol, 66:152-154.

[24] Kivimaki M, Vahtera J, Pentti J, Virtanen M, Elovainio M, Hemingway H (2007). Increased sickness absence in diabetic patients: what is the role of co-morbid conditions? Diabet Med, 24:1043-1048.

[25] Teraguchi M, Yoshimura N, Hashizume H, Yamada H, Oka H, Minamidi A, et al. (2017). Progression, incidence, and risk factors for intervertebral disc degeneration in a longitudinal population-based cohort: the Wakayama Spine Study. Osteoarthritis Cartilage, 25:1122-1131.

[26] Chen R, Liang X, Huang T, Zhong W, Luo X (2020). Effects of type 1 diabetes mellitus on lumbar disc degeneration: a retrospective study of 118 patients. J Orthop Surg Res, 15:280.

[27] Park CH, Min KB, Min JY, Kim DH, Seo KM, Kim DK (2021). Strong association of type 2 diabetes with degenerative lumbar spine disorders. Sci Rep, 11:16472.

[28] Jiang L, Zhang X, Zheng X, Ru A, Ni X, Wu Y, et al. (2013). Apoptosis, senescence, and autophagy in rat nucleus pulposus cells: Implications for diabetic intervertebral disc degeneration. J Orthop Res, 31:692-702.

[29] Won HY, Park JB, Park EY, Riew KD (2009). Effect of hyperglycemia on apoptosis of notochordal cells and intervertebral disc degeneration in diabetic rats. J Neurosurg Spine, 11:741-748.

[30] Russo F, Ambrosio L, Ngo K, Vadala G, Denaro V, Fan Y, et al. (2019). The Role of Type 1 Diabetes in Intervertebral Disc Degeneration. Spine (Phila Pa 1976), 44:1177-1185.

[31] Li X, Liu X, Wang Y, Cao F, Chen Z, Hu Z, et al. (2020). Intervertebral disc degeneration in mice with type II diabetes induced by leptin receptor deficiency. BMC Musculoskelet Disord, 21:77.

[32] Kroemer G, Galluzzi L, Vandenabeele P, Abrams J, Alnemri ES, Baehrecke EH, et al. (2009). Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. Cell Death Differ, 16:3-11.

[33] Zhang XB, Hu YC, Cheng P, Zhou HY, Chen XY, Wu D, et al. (2021). Targeted therapy for intervertebral disc degeneration: inhibiting apoptosis is a promising treatment strategy. Int J Med Sci, 18:2799-2813.

[34] Yao M, Zhang J, Li Z, Guo S, Zhou X, Zhang W (2020). Marein protects human nucleus pulposus cells against high glucose-induced injury and extracellular matrix degradation at least partly by inhibition of ROS/NF-kappaB pathway. Int Immunopharmacol, 80:106126.

[35] Tsai TT, Ho NY, Lin YT, Lai PL, Fu TS, Niu CC, et al. (2014). Advanced glycation end products in degenerative nucleus pulposus with diabetes. J Orthop Res, 32:238-244.

[36] Fields AJ, Berg-Johansen B, Metz LN, Miller S, La B, Liebenberg EC, et al. (2015). Alterations in intervertebral disc composition, matrix homeostasis and biomechanical behavior in the UCD-T2DM rat model of type 2 diabetes. J Orthop Res, 33:738-746.

[37] Song Y, Wang Y, Zhang Y, Geng W, Liu W, Gao Y, et al. (2017). Advanced glycation end products regulate anabolic and catabolic activities via NLRP3-inflammasome activation in human nucleus pulposus cells. J Cell Mol Med, 21:1373-1387.

[38] Hu Y, Shao Z, Cai X, Liu Y, Shen M, Yao Y, et al. (2019). Mitochondrial Pathway Is Involved in Advanced Glycation End Products-Induced Apoptosis of Rabbit Anulus Fibrosus Cells. Spine (Phila Pa 1976), 44:E585-E595.

[39] Illien-Junker S, Lu Y, Qureshi SA, Hecht AC, Cai W, Vlassara H, et al. (2015). Chronic ingestion of advanced glycation end products induces degenerative spinal changes and hypertrophy in aging pre-diabetic mice. PLoS One, 10:e0116625.

[40] Illien-Junker S, Torre OM, Kindschuh WF, Chen X, Laudier DM, Iatridis JC (2016). AGES induce ectopic endochondral ossification in intervertebral discs. Eur Cell Mater, 32:257-270.

[41] Cheng X, Ni B, Zhang F, Hu Y, Zhao J (2016). High Glucose-Induced Oxidative Stress Mediates Apoptosis and Extracellular Matrix Metabolism Imbalances Possibly via p38 MAPK Activation in Rat Nucleus Pulposus Cells. J Diabetes Res, 2016:3765173.

[42] Cheng X, Ni B, Zhang F, Hu Y, Zhao J (2016). High Glucose-Induced Oxidative Stress Mediates Apoptosis and Extracellular Matrix Metabolism Imbalances Possibly via p38 MAPK Activation in Rat Nucleus Pulposus Cells. J Diabetes Res, 2016:3765173.

[43] Jiang Z, Lu W, Zeng Q, Li D, Ding L, Wu J (2018). High glucose-induced excessive reactive oxygen species promote apoptosis through mitochondrial damage in rat cartilage endplate cells. J Orthop Res, 36:2476-2483.

[44] Zheng J, Zhang J, Zhang X, Guo Z, Wu W, Chen Z, et al. (2021). Reactive Oxygen Species Mediate Low Back Pain by Upregulating Substance P in Intervertebral Disc Degeneration. Oxid Med Cell Longev, 2021:6681815.

[45] Davalli P, Mitic T, Caporalì A, Lauriola A, D’Arca D (2016). ROS, Cell Senescence, and Novel Molecular Mechanisms in Aging and Age-Related Diseases. Oxid Med Cell Longev, 2016:3565127.

[46] Chen JW, Ni BB, Li B, Yang YH, Jiang SD, Jiang LS (2014). The responses of autophagy and apoptosis to oxidative stress in nucleus pulposus cells: implications
for disc degeneration. Cell Physiol Biochem, 34:1175-1189.

[46] Park JB, Byun CH, Park EY (2015). Rat Notochordal Cells Undergo Premature Stress-Induced Senescence by High Glucose. Asian Spine J, 9:495-502.

[47] de Almeida A, Ribeiro TP, de Medeiros IA (2017). Aging: Molecular Pathways and Implications on the Cardiovascular System. Oxid Med Cell Longev, 2017:7941563.

[48] Park EY, Park JB (2013). Dose- and time-dependent effect of high glucose concentration on viability of notochordal cells and expression of matrix degrading and fibrotic enzymes. Int Orthop, 37:1179-1186.

[49] Zhu Q, Gao X, Levene HB, Brown MD, Gu W (2016). Influences of Nutrition Supply and Pathways on the Degenerative Patterns in Human Intervertebral Disc. Spine (Phila Pa 1976), 41:568-576.

[50] Chang NC (2020). Autophagy and Stem Cells: Self-Eating for Self-Renewal. Front Cell Dev Biol, 8:138.

[51] Liao Z, Li S, Lu S, Liu H, Li G, Ma L, et al. (2021). Metformin facilitates mesenchymal stem cell-derived extracellular nanovesicle release and optimizes therapeutic efficacy in intervertebral disc degeneration. Biomaterials, 274:120850.

[52] Zhang Z, Lin J, Nisar M, Chen T, Xu T, Zheng G, et al. (2019). The Sirt1/P53 Axis in Diabetic Intervertebral Disc Degeneration Pathogenesis and Therapeutics. Oxid Med Cell Longev, 2019:7959573.

[53] Risbud MV, Shapiro IM (2014). Role of cytokines in intervertebral disc degeneration: pain and disc content. Nat Rev Rheumatol, 10:44-56.

[54] Donath MY, Shoelson SE (2011). Type 2 diabetes as an inflammatory disease. Nat Rev Immunol, 11:98-107.

[55] Alnek K, Kisand K, Heilman K, Peet A, Varik K, Uibo E (2013). Changes of transforming growth factor and counterregulatory responses to exercise in children with type 1 diabetes and healthy controls. Pediatr Diabetes, 7:16-24.

[56] Flower L, Gray R, Pinkney J, Mohamed-Ali V (2003). Stimulation of interleukin-6 release by interleukin-1beta from isolated human adipocytes. Cytokine, 21:32-37.

[57] Barry JC, Shakibakho S, Durrer C, Simtchouk S, Jawanda KK, Cheung ST, et al. (2016). Hyperresponsiveness to the anti-inflammatory action of interleukin-10 in type 2 diabetes. Sci Rep, 6:21244.

[58] Malik A, Morya RK, Bhadada SK, Rana S (2018). Type 1 diabetes mellitus: Complex interplay of oxidative stress, cytokines, gastrointestinal motility and small intestinal bacterial overgrowth. Eur J Clin Invest, 48:e13021.

[59] Carbone S, Lee PJ, Mauro AG, Mezzaroma E, Buzzetti R, Van Tassell B, et al. (2017). Interleukin-18 mediates cardiac dysfunction induced by western diet independent of obesity and hyperglycemia in the mouse. Nutr Diabetes, 7:e258.

[60] Capone F, Guerriero E, Colonna G, Maio P, Mangia A, Marfella R, et al. (2015). The Cytokine Profile in Patients with Hepatocellular Carcinoma and Type 2 Diabetes. PLoS One, 10:e0134594.

[61] Lucas R, Parikh SJ, Sridhar S, Guo DH, Bhagatwala J, Dong Y, et al. (2013). Cytokine profiling of young overweight and obese female African American adults with prediabetes. Cytokine, 64:310-315.

[62] Fukui M, Tanaka M, Hamaguchi M, Senmaru T, Sakabe K, Shiraishi E, et al. (2009). Eosinophil count is positively correlated with albumin excretion rate in men with type 2 diabetes. Clin J Am Soc Nephrol, 4:1761-1765.

[63] Musilli C, Pacconi S, Pala L, Gerlini G, Ledda F, Mugelli A, et al. (2011). Characterization of circulating and monocyte-derived dendritic cells in obese and diabetic patients. Mol Immunol, 49:234-238.

[64] Zhong J, Gong Q, Mima A (2017). Inflammatory cytokines and inflammation markers as biomarkers for the action of thiazolidinediones in Type 2 diabetes mellitus patients and healthy volunteers. Br J Clin Pharmacol, 62:391-402.

[65] Galassetti PR, Iwanaga K, Crisostomo M, Zaldivar FP, Larson J, Pescatello A (2006). Inflammatory cytokine, growth factor and counterregulatory responses to exercise in children with type 1 diabetes and healthy controls. Pediatr Diabetes, 7:16-24.

[66] Flower L, Gray R, Pinkney J, Mohamed-Ali V (2003). Stimulation of interleukin-6 release by interleukin-1beta from isolated human adipocytes. Cytokine, 21:32-37.

[67] Barry JC, Shakibakho S, Durrer C, Simtchouk S, Jawanda KK, Cheung ST, et al. (2016). Hyperresponsiveness to the anti-inflammatory action of interleukin-10 in type 2 diabetes. Sci Rep, 6:21244.

[68] Malik A, Morya RK, Bhadada SK, Rana S (2018). Type 1 diabetes mellitus: Complex interplay of oxidative stress, cytokines, gastrointestinal motility and small intestinal bacterial overgrowth. Eur J Clin Invest, 48:e13021.

[69] Carbone S, Lee PJ, Mauro AG, Mezzaroma E, Buzzetti R, Van Tassell B, et al. (2017). Interleukin-18 mediates cardiac dysfunction induced by western diet independent of obesity and hyperglycemia in the mouse. Nutr Diabetes, 7:e258.

[70] Capone F, Guerriero E, Colonna G, Maio P, Mangia A, Marfella R, et al. (2015). The Cytokine Profile in Patients with Hepatocellular Carcinoma and Type 2 Diabetes. PLoS One, 10:e0134594.

[71] Lucas R, Parikh SJ, Sridhar S, Guo DH, Bhagatwala J, Dong Y, et al. (2013). Cytokine profiling of young overweight and obese female African American adults with prediabetes. Cytokine, 64:310-315.

[72] Fukui M, Tanaka M, Hamaguchi M, Senmaru T, Sakabe K, Shiraishi E, et al. (2009). Eosinophil count is positively correlated with albumin excretion rate in men with type 2 diabetes. Clin J Am Soc Nephrol, 4:1761-1765.

[73] Musilli C, Pacconi S, Pala L, Gerlini G, Ledda F, Mugelli A, et al. (2011). Characterization of circulating and monocyte-derived dendritic cells in obese and diabetic patients. Mol Immunol, 49:234-238.
distribution of TNF-alpha, TNF-alpha-receptors, and the activating TNF-alpha-converting enzyme suggests activation of the TNF-alpha system in the aging intervertebral disc. Ann N Y Acad Sci, 1096:44-54.

[86] Gabay C, Lamacchia C, Palmer G (2010). IL-1 pathways in inflammation and human diseases. Nat Rev Reumumatol, 6:232-241.

Wang Y, Che M, Xin J, Zheng Z, Li J, Zhang S (2020). The role of IL-1beta and TNF-alpha in intervertebral disc degeneration. Biomed Pharmacother, 131:110660.

[87] Cui LY, Liu SL, Ding Y, Huang DS, Ma RF, Huang WG, et al. (2007). IL-1beta sensitizes rat intervertebral disc cells to Fas ligand mediated apoptosis in vitro. Acta Pharmacol Sin, 28:1671-1676.

Liu H, Yang SD, Xu Y, Ning SH, Wang T, Yang DL, et al. (2017). Protective role of 17beta-estradiol on tumor necrosis factor-alpha-induced apoptosis in human nucleus pulposus cells. Mol Med Rep, 16:1093-1100.

[88] Wang J, Markova D, Anderson DG, Zheng Z, Shapiro IM, Risbud MV (2011). TNF-alpha and IL-1beta promote a disintegrin-like and metalloprotease with thrombospondin type 1 motif-5-mediated aggrecan degradation through syndecan-4 in intervertebral disc. J Biol Chem, 286:39738-39749.

Wang T, Li P, Ma X, Tian P, Han C, Zang J, et al. (2015). MicroRNA-494 inhibition protects nucleus pulposus cells from TNF-alpha-induced apoptosis by targeting JundD. Biochimie, 115:1-7.

[89] Shao Z, Wang B, Shi Y, Xie C, Huang C, Chen B, et al. (2021). Senolytic agent Quercetin ameliorates intervertebral disc degeneration via the Nrf2/NF-kappaB axis. Osteoarthritis Cartilage, 29:413-422.

Zhang J, Wang X, Liu H, Li Z, Chen F, Wang H, et al. (2019). TNF-alpha enhances apoptosis by promoting chop expression in nucleus pulposus cells: role of the MAPK and NF-kappaB pathways. J Orthop Res, 37:697-705.

[90] Zhao K, An R, Xiang Q, Li G, Wang K, Song Y, et al. (2021). Acid-sensing ion channels regulate nucleus pulposus cell inflammation and pyroptosis via the NLRP3 inflammasome in intervertebral disc degeneration. Cell Prolif, 54:e12941.

Gruber HE, Hoelscher GL, Ingrum JA, Bethea S, Hanley EN, Jr. (2015). Autophagy in the Degenerating Human Intervertebral Disc: In Vivo Molecular and Morphological Evidence, and Induction of Autophagy in Cultured Anulus Cells Exposed to Proinflammatory Cytokines-Implications for Disc Degeneration. Spine (Phila Pa 1976), 40:773-782.

[91] Takats K, Tominaga A, Hamaoka T (1980). Antigen-induced T cell-replacing factor (TRF). I. Functional characterization of a TRF-producing helper T cell subset and genetic studies on TRF production. J Immunol, 124:2414-2422.

Gorth DJ, Shapiro IM, Risbud MV (2018). Transgenic mice overexpressing human TNF-alpha experience early onset spontaneous intervertebral disc herniation in the absence of overt degeneration. Cell Death Dis, 10:7.

[92] Takaki S, Tominaga A, Hamaoka T, Mita S, Sonoda E, Yamaguchi N, et al. (1990). Molecular cloning and expression of the murine interleukin-5 receptor. EMBO J, 9:4367-4374.

Martirosyan NL, Patel AA, Carotenuto A, Kalani MY, Belykh E, Walker CT, et al. (2016). Genetic Alterations in Intervertebral Disc Disease. Front Surg, 3:59.

[93] Takatsu K (2011). Interleukin-5 and IL-5 receptor in health and diseases. Proc Jpn Acad Ser B Phys Biol Sci, 87:463-485.

Wang L, Yang M, Zhang C, Huang F (2020). The protective effects of dehydrocostus lactone against TNF-alpha-induced degeneration of extracellular matrix (ECM) in SW1353 cells. Aging (Albany NY), 12:17137-17149.

[94] Hu B, Wang J, Wu X, Chen Y, Yuan W, Chen H (2017). Interleukin-17 upregulates vascular endothelial growth factor by activating the JAK/STAT pathway in nucleus pulposus cells. Joint Bone Spine, 84:327-334.

[95] Willebrand R, Dietschmann A, Nitschke L, Krappmann S, Voehringer D (2018). Murine proinflammatory cytokines, JAK/STAT and Ras and reactive oxygen species in nucleus pulposus cell inflammation and matrix (ECM) in SW1353 cells. Aging (Albany NY), 12:17137-17149.

Su D, Coudriet GM, Hyun Kim D, Lu Y, Perdomo G, Qu S, et al. (2009). FoxO1 links insulin resistance to proinflammatory cytokine IL-1beta production in macrophages. Diabetes, 58:2624-2633.

[96] Ahmad R, Sylvester J, Ahmad M, Zafarullah M (2011). Involvement of H-Ras and reactive oxygen species in proinflammatory cytokine-induced matrix metalloproteinase-13 expression in human articular chondrocytes. Arch Biochem Biophys, 507:350-355.

Cailleau C, Diu-Hercend A, Ruuth E, Westwood R, Carnaud C (1997). Treatment with neutralizing antibodies specific for IL-1beta prevents cyclophosphamide-induced diabetes in nonobese diabetic mice. Diabetes, 46:937-940.

[97] Chen H, Shao X, Li L, Zheng C, Xu X, Hong X, et al. (2017). Electroacupuncture serum inhibits TNFalphamediated chondrocyte inflammation via the RasRafMEK1/2ERK1/2 signaling pathway. Mol Med Rep, 16:5807-5814.

Masters SL, Dunne A, Subramanian SL, Hull RL, Tannahill GM, Sharp FA, et al. (2010). Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1beta in type 2 diabetes. Nat Immunol, 11:897-904.

[98] Yao Y, Xue H, Chen X, Cao Y, Yu J, Jiang X, et al. (2017). Polarization of Helper T Lymphocytes Maybe Involved in the Pathogenesis of Lumbar Disc Herniation. Iran J Allergy Asthma Immunol, 16:347-357.

Chen F, Jiang G, Liu H, Li Z, Pei Y, Wang H, et al. (2020). Melatonin alleviates intervertebral disc degeneration by disrupting the IL-1beta/NF-kappaB-NLRP3 inflammasome positive feedback loop. Bone Res, 8:10.
the Genesis of Fibrosis. Front Immunol, 6:597.

Hirano T, Taga T, Nakano N, Yasukawa K, Kashiwamura S, Shimizu K, et al. (1985). Purification to homogeneity and characterization of human B-cell differentiation factor (BCDF or BSFp-2). Proc Natl Acad Sci U S A, 82:5490-5494.

[101] Rogeri PS, Gasparini SO, Martins GL, Costa LKF, Araujo CC, Lugaresi R, et al. (2020). Crosstalk Between Skeletal Muscle and Immune System: Which Roles Do IL-6 and Glutamine Play? Front Physiol, 11:582528.

Mihara M, Hashizume M, Yoshida H, Suzuki M, Shina M (2012). IL-6/IL-6 receptor system and its role in physiological and pathological conditions. Clin Sci (Lond), 122:143-159.

[103] Akira S, Kishimoto T (1992). IL-6 and NF-IL6 in acute-phase response and viral infection. Immunol Rev, 127:25-50.

Devaraj S, Venugopal SK, Singh U, Jialal I (2005). Hyperglycemia induces monocyte release of interleukin-6 via induction of protein kinase c- {alpha} and -{beta}. Diabetes, 54:85-91.

Huang X, Chen F, Zhao J, Wang D, Jing S, Li H, et al. (2017). Interleukin 6 (IL-6) and IL-10 Promoter Region Polymorphisms Are Associated with Risk of Lumbar Disc Herniation in a Northern Chinese Han Population. Genet Test Mol Biomarkers, 21:17-23.

Andrade P, Hoogland G, Garcia MA, Steinbusch HW, Daemen MA, Visser-Vandewalle V (2013). Elevated IL-1beta and IL-6 levels in lumbar herniated discs in patients with sciatic pain. Eur Spine J, 22:714-720.

Tilg H, Trehu E, Atkins MB, Dinarello CA, Mier JW (1994). Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. Blood, 83:113-118.

Suzuki S, Fujita N, Fujii T, Watanabe K, Yagi M, Tsuji Y, et al. (1985). Purification of S100A4 by activating the receptor expression: intelligent design. Nat Rev Immunol, 30:426-431.

Mazzucchelli R, Durum SK (2007). Interleukin-7 receptor expression: intelligent design. Nat Rev Immunol, 7:144-154.

Alkhattib B, Rosenzweig DH, Krock E, Roughley PJ, Beckman L, Steffen T, et al. (2014). Acute mechanical injury of the human intervertebral disc: link to degeneration and pain. Eur Cell Mater, 28:98-110; discussion 110-111.

Munoz-Espin D, Serrano M (2014). Cellular senescence: from physiology to pathology. Nat Rev Mol Cell Biol, 15:482-496.

Wang F, Cai F, Shi R, Wang XH, Wu XT (2016). Aging and age related stresses: a senescence mechanism of intervertebral disc degeneration. Osteoarthritis Cartilage, 24:398-408.

[104] Brazvzan B, Farahzadi R, Mohammadi SM, Montazer Saheb S, Shanehbandi D, Schmied L, et al. (2016). Key Immune Cell Cytokines Affect the Telomere Activity of Cord Blood Cells In vitro. Adv Pharm Bull, 6:153-161.

[105] Long D, Blake S, Song XY, Lark M, Loeser RF (2008). Human articular chondrocytes produce IL-7 and respond to IL-7 with increased production of matrix metalloproteinase-13. Arthritis Res Ther, 10:R23.

[106] Yammani RR, Long D, Loeser RF (2009). Interleukin-7 stimulates secretion of S100A4 by activating the JAK/STAT signaling pathway in human articular chondrocytes. Arthritis Rheum, 60:792-800.

[107] van Rooen JA, Lafeber FP (2008). Role of interleukin-7 in degenerative and inflammatory joint diseases. Arthritis Res Ther, 10:107.

[108] Volk H, Asadullah K, Gallagher G, Sabat R, Grutz G (2001). IL-10 and its homologs: important immune mediators and emerging immunotherapeutic targets. Trends Immunol, 22:414-417.

[109] Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A (2001). Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol, 19:683-765.

[110] Mollazadeh H, Cicero AFG, Blesso CN, Pirro M, Majeed M, Sahebkar A (2019). Immune modulation by curcumin: The role of interleukin-10. Crit Rev Food Sci Nutr, 59:89-101.

[111] Wang T, He C (2018). Pro-inflammatory cytokines: The link between obesity and osteoarthritis. Cytokine Growth Factor Rev, 44:38-50.

[112] Tateiwa D, Yoshikawa H, Kaito T (2019). Cartilage and Bone Destruction in Arthritis: Pathogenesis and Treatment Strategy: A Literature Review. Cells, 8.

[113] Schulze-Tanzil G, Zreiqat H, Sabat R, Kohl B, Halder A, Muller RD, et al. (2009). Interleukin-10 and articular cartilage: experimental therapeutical approaches in cartilage disorders. Curr Gene Ther, 9:306-315.

[114] Muller RD, John T, Kohl B, Oberholzer A, Gust T, Hostmann A, et al. (2008). IL-10 overexpression differentially affects cartilage matrix gene expression in response to TNF-alpha in human articular chondrocytes in vitro. Cytokine, 44:377-385.

[115] Behrendt P, Hafelein K, Preusse-Prange A, Bayer A, Seekamp A, Kurz B (2017). IL-10 ameliorates TNF-alpha induced meniscal degeneration in mature meniscal tissue in vitro. BMC Musculoskeletal Disord, 18:197.

[116] Behrendt P, Preusse-Prange A, Kluter T, Haake M, Rolauffs B, Grodzinsky AJ, et al. (2016). IL-10 reduces apoptosis and extracellular matrix degradation after injurious compression of mature articular cartilage. Osteoarthritis Cartilage, 24:1981-1988.

[117] Hvang HS, Kim HA (2015). Chondrocyte Apoptosis in the Pathogenesis of Osteoarthritis. Int J Mol Sci, 16:26035-26054.

[118] Mallat Z, Corbaz A, Scoazec A, Besnard S, Leschege G, Chvatchko Y, et al. (2001). Expression of interleukin-18 in human atherosclerotic plaques and relation to
plaque instability. Circulation, 104:1598-1603.

[129] Ojala JO, Sutinen EM (2017). The Role of Interleukin-18, Oxidative Stress and Metabolic Syndrome in Alzheimer's Disease. J Clin Med, 6.

[130] Sutinen EM, Pirttila T, Anderson G, Salminen A, Ojala JO (2012). Pro-inflammatory interleukin-18 increases Alzheimer’s disease-associated amyloid-beta production in human neuron-like cells. J Neuroinflammation, 9:199.

[131] Tang G, Han X, Lin Z, Qian H, Chen B, Zhou C, et al. (2021). Propionibacterium acnes Accelerates Intervertebral Disc Degeneration by Inducing Pyroptosis of Nucleus Pulposus Cells via the ROS-NLRP3 Pathway. Oxid Med Cell Longev, 2021:4657014.

[132] Fu Z, Liu P, Yang D, Wang F, Yuan L, Lin Z, et al. (2012). Interleukin-18-induced inflammatory responses in synoviocytes and chondrocytes from osteoarthritic patients. Int J Mol Med, 30:805-810.

[133] Ye S, Ju B, Wang H, Lee KB (2016). Bone morphogenetic protein-2 provokes interleukin-18-induced human intervertebral disc degeneration. Bone Joint Res, 5:412-418.

[134] Anekstein Y, Smorgick Y, Lotan R, Agar G, Shalmon E, Floman Y, et al. (2010). Diabetes mellitus as a risk factor for the development of lumbar spinal stenosis. Isr Med Assoc J, 12:16-20.

[135] Mohamed-Ali V, Armstrong L, Clarke D, Bolton CH, Pinkney JH (2001). Evidence for the regulation of levels of plasma adhesion molecules by proinflammatory cytokines and their soluble receptors in type 1 diabetes. J Intern Med, 250:415-421.