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Review

The role of IL-1β and TNF-α in intervertebral disc degeneration

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ABSTRACT

Low back pain (LBP), a prevalent and costly disease around the world, is predominantly caused by intervertebral disc (IVD) degeneration (IDD). LBP also presents a substantial burden to public health and the economy. IDD is mainly caused by aging, trauma, genetic susceptibility, and other factors. It is closely associated with changes in tissue structure and function, including progressive destruction of the extracellular matrix (ECM), enhanced senescence, disc cell death, and impairment of tissue biomechanical function. The inflammatory process, exacerbated by cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), are considered to be the key mediators of IDD and LBP. IL-1β and TNF-α are the most important proinflammatory cytokines, as they have powerful proinflammatory activities and can promote the secretion of a variety of proinflammatory mediators. They are also upregulated in the degenerative IVDs, and they are closely related to various pathological IDD processes, including inflammatory response, matrix destruction, cellular senescence, autophagy, apoptosis, pyroptosis, and proliferation. Therefore, anti-IL-1β and anti-TNF-α therapies may have the potential to alleviate disc degeneration and LBP. In this paper, we reviewed the expression pattern and signal transduction pathways of IL-1β and TNF-α, and we primarily focused on their similar and different roles in IDD. Because IL-1β and TNF-α inhibition have the potential to alleviate IDD, an in-depth understanding of the role of IL-1β and TNF-α in IDD will benefit the development of new treatment methods for disc degeneration with IL-1β and TNF-α at the core.

1. Introduction

Low back pain (LBP) is a chronic, highly prevalent and costly medical problem [1]. According to reports, the total costs associated with LBP reach $100–200 billion per year in the United States [1,2]. LBP also ranks highest among 291 disorders in the Global Burden of Disease 2010 Study in terms of overall disability [3]. LBP has become the second most common medical cause affecting quality of life, and it causes a substantial social and economic burden [4]. Of LBP's many possible causes, intervertebral disc degeneration (IDD) is the most common [5,6]. IDD is the basis of multiple musculoskeletal and spine diseases, such as structural instability, disc herniation, spinal stenosis, radiculopathy, and myelopathy. The etiology of IDD is multifactorial, including genetic causes (e.g., polymorphism in genes encoding aggrecan and collagen I, IX, and XI), lifestyle factors (e.g., occupational type, smoking, drinking, lack of physical activity, and night shift work), and aging [7–9]. The development of IDD is characterized by cellular and biochemical changes in the intervertebral disc microenvironment, which lead to progressive functional and structural impairment. The major pathological features of IDD include the production of pro-inflammatory mediators, progressive loss of the extracellular matrix (ECM), increased cell senescence and death, altered healthy disc cell phenotype, and decreased active cell numbers [7,10–12]. These changes further lead to the destruction of normal intervertebral disc function.

Inflammatory processes, exacerbated by TNF-α and IL-1β, are believed to be critical events during IDD [13]. IL-1β is a crucial member of the IL-1 family, which has gained much attention because of its significant role in inflammation-related diseases. IL-1β has strong proinflammatory activity, inducing various proinflammatory mediators, such as cytokines and chemokines [14,15]. IL-1β has a variety of functions. It exerts multiple effects on various kinds of cells and eventually results in extensive inflammatory events. Systemically, IL-1β signaling results in an acute phase response, hypotension, vasodilatation, and fever. Locally, the results of IL-1 signaling lead to the upregulation of adhesion molecules, which promote lymphocyte recruitment. Subsequently, the immune cells are activated and inflammation is further amplified. In addition to playing a critical role in innate immune responses, IL-1β also participates in adaptive immune responses by affecting Th17 and Th1-induced immune responses. Abnormal IL-1β signal transduction has been reported to cause heritable auto-inflammatory disorders, such as

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familial Mediterranean fever. Furthermore, it is also associated with common diseases, such as type 2 diabetes, gout, and cardiovascular diseases [14,16–18]. Interestingly, a previous study has shown that the IL-1β level in degenerative intervertebral discs (IVDs) is significantly increased [19], and IL-1β participates in multiple pathological processes of IDD [13]. Conversely, IL-1β suppression has been reported to prevent disc degeneration [20,21].

Similar to IL-1β, TNF-α is a pleiotropic proinflammatory cytokine belonging to the TNF superfamily of ligands. TNF-α is well known for its proinflammatory activity [22–24], and it has been linked to multiple diseases [22]. Dysregulation of TNF-α is linked with a wide range of pathological conditions, such as infection, autoimmune disease [25,26], cancer [23], atherosclerosis [27], Alzheimer's disease [28], and inflammatory bowel disease [29]. TNF-α also plays diverse roles in modulating several developmental and immunological processes, including inflammation, differentiation, lipid metabolism, and apoptosis [30–32]. Virtually all components of the human immune system have been reported to have a functional relationship with TNF-α [33]. Interestingly, puncture combined with TNF-α treatment has been discovered to increase pain-related behavior in disc degeneration [34]. After injecting TNF-α into IVDs in a porcine model, degenerative features appeared, including annulus fissures, nucleus pulposus (NP) matrix degradation, cell clustering, and vascularization. These results suggest that TNF-α could be a crucial driver of IDD [35]. Therefore, we summarized current knowledge about the expression profile and signal transduction pathways of IL-β and TNF-α, and we primarily focused on their similar and different roles in IDD.

2. Expression patterns of IL-1β and TNF-α in IVDs

IL-1β and TNF-α are mainly produced and secreted by immune cells, but they are also secreted by IVD cells [36,37]. Low levels of TNF-α and IL-1β are found within non-degenerative disc cells, suggesting that IL-1β and TNF-α participate in the reconstruction of IVD tissues [37–39]. Interestingly, the expression of TNF-α and IL-1β in degenerated IVDs was higher than expression in non-degenerative IVDs, which was also shown by immunohistochemistry [37,40,41]. Moreover, the expression level of TNF-α and IL-1β present a positive correlation with age and disc degeneration degree [36,37,41–43]. Compared with pain-free scoliosis patients, IL-1β and TNF-α level are significantly upregulated in lumbar disc herniation patients suffering from chronic LBP [44,45]. Additionally, the distribution of IL-1β and TNF-α in IVDs is also related to tissue type. A higher level of TNF-α was observed in nucleus pulposus cells compared to annulus fibrosus cells (AFCs) [42]. Also, TNF receptor 1 (TNFR1), TNF receptor 2 (TNFR2), TNF-α-converting enzyme (TACE), and IL-1 receptor type I (IL-1RI) are found to be expressed in NP tissues. Collectively, IL-1β and TNF-α are highly expressed in degenerated IVDs, and their overexpression may be a causative factor in IDD.

3. IL-1β signal transduction pathways

The expression of IL-1β requires the inflammasome. Inflammasome complexes include Nod-like receptor protein 12 (NLRP12), NRLP7, NRLP6, NLRP4, NLRP3, NLRP2, and NLRP1 [46]. Among them, the NLRP3 inflammasome is most widely studied, and consists of three components: NLRP3 sensor, adaptor protein apoptosis-associated speck-like (ASC) protein, and procaspase-1 [47–49]. A variety of stimuli can trigger the NLRP3 inflammasome. These stimuli belong to danger-associated molecular patterns (DAMPs) of exogenous and endogenous origin (reactive oxygen species [ROS], extracellular ATP, monosodium urate crystals, cholesterol, silica, asbestos, or amyloid beta plaques) [50–56] or belong to pathogen-associated molecular patterns (PAMPs) that are produced during infection (bacterial, viral, protozoan, or fungal) [57–60]. IL-1β is initially produced as proIL-1β, a biologically inactive precursor peptide. When exposed to stimulation, the NLRP3 inflammasome is activated, promoting caspase-1 activation, which then cleaves proIL-1β into mIL-1β and IL-1β N-terminal peptide [61,62] (Fig. 1).

IL-1β works by activating the IL-1 receptor on responsive cells. According to a previous study, IL-1β receptor is a heterodimeric complex. It consists of IL-1 receptor accessory protein (IL-1RAcP) and IL-1 receptor type I (IL-1RI). IL-1RI exists widely on the cell surface, containing an intracellular domain and three extracellular immunoglobulin domains, of which Toll-like/IL-1 receptor (TIR) domain is the most notable [63]. IL-1RAcP is a co-receptor necessary for IL-1/IL-1RI complex signal transduction [64]. In the signal transduction process, the IL-1RI extracellular immunoglobulin domain binds IL-1β, forming an obligate heterodimer (Fig. 1). Then, the TIR domain recruits IL-1RAcP to form IL-1β/IL-1RI/IL-1RAcP complexes. Next, the complexes bind an adapter protein, myeloid differentiation factor 88 (MyD88), recruiting IL-1R associated kinase (IRAK) 4. After that, IRAK1 is phosphorylated by IRAK4, which subsequently interacts with TRAF6. Interestingly, TRAF6 signaling can be divided into two predominant pathways (Fig. 1). TRAF6 activates transforming growth factor-β-activated kinase 1 (TAK1) and TAK1-binding protein 2 (TAB2), and thereby leads to nuclear factor-kappaB (NF-κB) nuclear translocation. Furthermore, TRAF6 activates the MAPK and c-JNK pathways, thus contributing to the activation of activator protein-1 (AP-1). Finally, the activated AP-1 and NF-κB mediate the expression of multiple genes [65].

4. TNF-α signal transduction pathways

TNF-α is primarily produced as transmembrane TNF-α (tmTNF-α), a type II transmembrane protein arranged in stable homotrimers [66]. Then, the metalloprotease TNF-α-converting enzyme (TACE) cleaves tmTNF-α into sTNF-α (a soluble form) (Fig. 2) [66–68]. TmTNF-α and sTNF-α are both biologically active [22–24,69,70]. TNF-α elicits its effects via two distinct receptors: TNFR1 and TNFR2. TNFR 1 can be activated either by tmTNF-α or sTNF-α, while TNFR2 is activated mainly by sTNF-α [71]. TNFR1 appears to be the core mediator in TNF-α signal transduction due to its constitutive expression in most cell types. Conversely, TNFR2 mainly exists in immune cells and can be highly regulated, revealing it to be capable of regulating immune function [72]. The TNFR1 and TNFR2 extracellular domains can be cleaved and released from the surface of the cell into soluble forms, neutralizing the role of TNF-α [73]. TNF-α has a high affinity with TNFR1 and TNFR2. The tmTNF-α could bind to both receptors, while sTNF-α interacts with TNFR1 only. TNF-α activates TNFR1 and forms two different TNF signal complexes: complex I has an anti-apoptotic effect, while complex II induces apoptosis (Fig. 2). TNFR2 activation, however, is considered anti-apoptotic due to the absence of an intracellular death domain. However, recent evidence shows that TNFR2 can lead to interaction between TNFR1 and TNFR2 signaling via its induction of TNF receptor-associated factor 2 (TRAF2) destruction (Fig. 2).

4.1. TNFR1-dependent pathways

It has been discovered that a cytoplasmic death domain (DD) exists in TNFR1. When there is no ligand, the interaction between DD and silencer of death domain (SODD) can inactivate TNFR1 [74]. Conversely, under tmTNF-α and sTNF-α stimulation, the TNFR1/SODD complex releases SODD, and thus TNFR1 becomes activated. Then, TNFR1 can bind TNF receptor-associated death domain (TRADD), recruiting other adaptor proteins, including TNF receptor-associated factor 2 (TRAF2), receptor-interacting protein-1 (RIP-1), cellular inhibitor of apoptosis protein (cIAP) 1, and cIAP2, to form complex I [75–77]. Subsequently, this complex activates MAPK kinase kinase-3 (MEKK-3) [78], which leads to inhibitor of κB (IκB) kinase (IKK) activation. Next, IκB is phosphorylated by IKK and undergoes degradation. NF-κB is thereby released, entering the nucleus and triggering the transcription of many genes [79,80]. Additionally, stimulation of TNFR1 is able to trigger apoptosis signaling kinase-1 (ASK-1), which is linked to

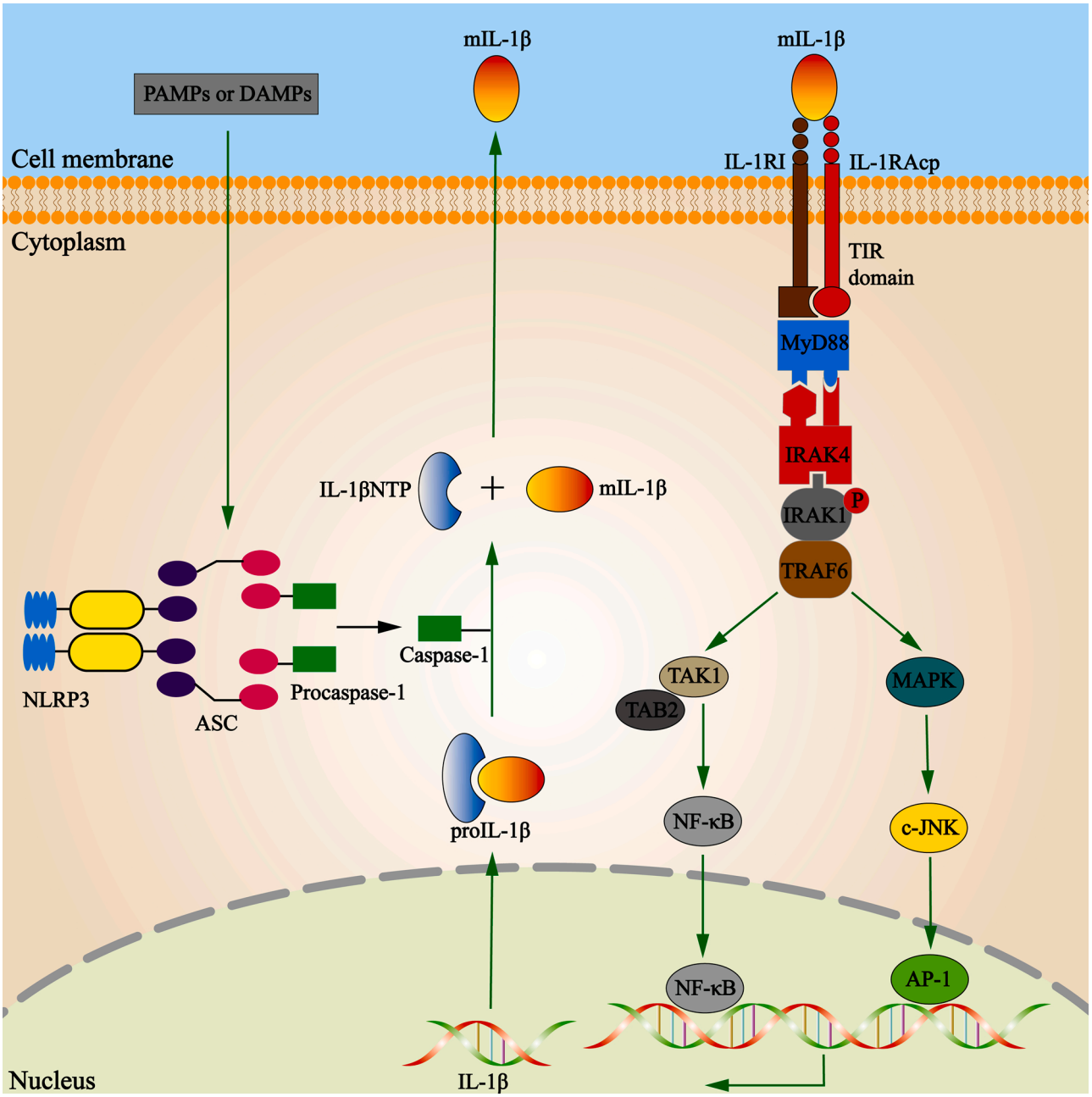

Fig. 1. The production of IL-1β and its transduction signaling pathways. Initially, IL-1β is synthesized as proIL-1β. Next, it is cleaved by caspase-1 into mIL-1β (active form) via the NLRP3 inflammasome, which is composed of NLRP3 sensor, ASC protein, and Procaspase-1. The mIL-1β can bind to IL-1RI, and then IL-1RI recruits IL-1RAcP as its co-receptor. The established mIL-1β/IL-1RI/IL-1RAcP complexes then interact with adapter molecules, such as MyD88, IRAK4, IRAK1, and TRAF6. Subsequently, the activated TRAF6 triggers traget gene transcription via activating the TAK1/TAB2/NF-κB or MAPK/c-JNK/AP-1 pathways.

TRAF2. Then, ASK-1 and MEK 4/6 interact with each other. The activation of MEK 4/6 results in c-JNK and subsequently p38 MAPK activation [81,82]. Through this pathway, AP-1 is activated and multiple genes are transcribed. Furthermore, TNFR1 could regulate cell survival through another pathway (Fig. 2). In some cases, complex I is internalized, after which TNFR1 releases a complex that includes TRADD, TRAF2, and RIP-1. Next, Fas-associated DD protein (FADD) and TRADD bind together, contributing to the recruitment of pro-caspase 8, which in turn results in complex II formation. Interestingly, complex II could transform pro-caspase 8 into caspase 8, activating caspase 3 and mediating apoptosis [83,84]. Collectively, TNF-α induces a variety of signaling pathways through activating TNFR1, a process that involves a variety of cellular effects.

4.2. *TNFR2-dependent pathways*

There is no death domain in the TNFR2 intracellular region, and thus, it cannot combine with TRADD. However, it can interplay with TRAF2 directly to recruit TRAF3, TRAF1, cIAP1, and cIAP2 (Fig. 2). Therefore, TNFR2 and TNFR1 have some common signaling effects, such as AP-1 and NF-κB activation, indicating that there is crosstalk between the TNFR1 and TNFR2 pathways [85,86]. TNFR2 has also been found to interact with endothelial/epithelial tyrosine kinase (Etk), which can subsequently activate vascular endothelial growth factor receptor 2 (VEGFR2), contributing to phosphatidylinositol 3-kinase (PI3K)/Akt pathway activation. Activation of the (PI3K)/Akt pathway could regulate various biological actions, including cell adhesion, survival, apoptosis, proliferation, and migration [87]. In general, signal

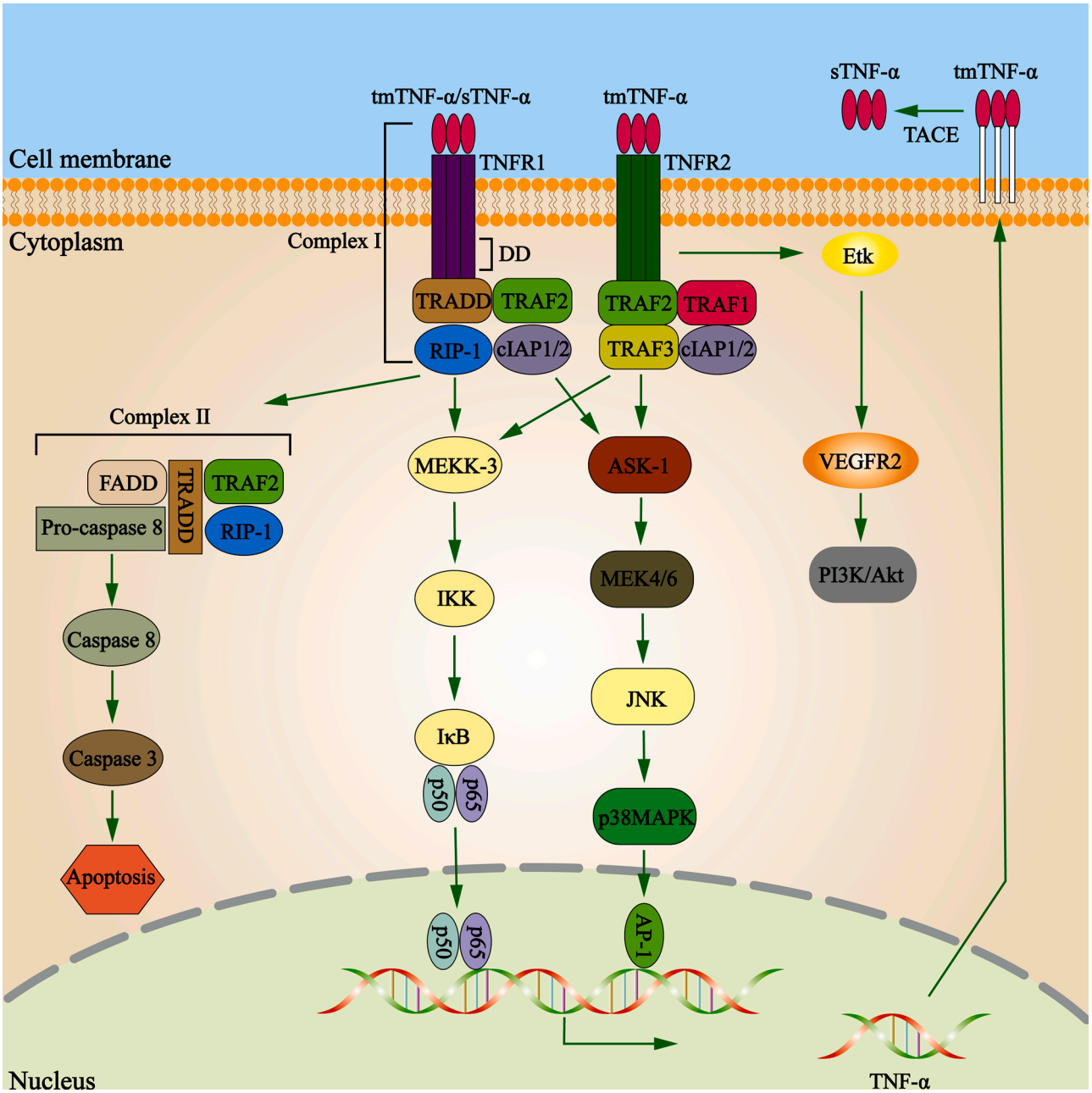

Fig. 2. TNF-α production and transduction signaling pathways. TNF-α is primarily secreted as a type II transmembrane protein arranged in stable homotrimers, known as tmTNF-α. The tmTNF-α can be cleaved into sTNF-α by TACE. TNF-α works via two distinct receptors: TNFR1 and TNFR2. After binding with tmTNF-α/sTNF-α, TNFR1 separates itself from the inhibitory SODD protein. Next, TRAF2, TRADD, cIAP1/2, and RIP-1 are recruited to form complex I. Complex I activates MEKK-3 and IKK, as well as promoting nuclear translocation of NF-κB, leading to transcription of mulatiple target genes. Furthermore, complex I activates ASK-1 and interacts with MEK4/6, which subsequently triggers AP-1 via the JNK or p38 MAPK signaling pathway to promote gene transcription. Under certain conditions, complex I is internalized and then converted to complex II. Complex II is composed of FADD, TRADD, TRAF2, RIP-1, and pro-caspase 8. Complex II can mediate the transfer of pro-caspase 8 into caspase 8, which subesequently activates caspase 3 and induces apoptosis. When binding with tmTNF-α, TNFR2 recruits TRAF3, TRAF2, cIAP1/2, and TRAF1 to establish a complex that also activates NF-κB and AP-1. Additionally, activation of TNFR2 can activate Etk, which subsequently transactivates VEGFR2, leading to the activation of the PI3K/Akt pathway.

transduction through TNFR2 is considered to have significant proinflammatory and survival-promoting effects.

5. Main roles of IL-1β in IDD

It is well known that inflammatory responses, ECM degradation, cellular senescence, apoptosis, pyroptosis, oxidative stress, and cell proliferation participate in the onset and development of disc degeneration [6,88–90]. Several studies have reported that IL-1β is closely linked to these processes (Fig. 3), which will be thoroughly described below.

5.1. IL-1β amplifies inflammatory responses

Inflammation is considered to be a crucial factor in the process of disc degeneration [91]. Meanwhile, a growing number of studies suggest that IL-1β is involved in the inflammatory response during disc degeneration. In bovine mesenchymal stem cells (MSCs), IL-1β exposure

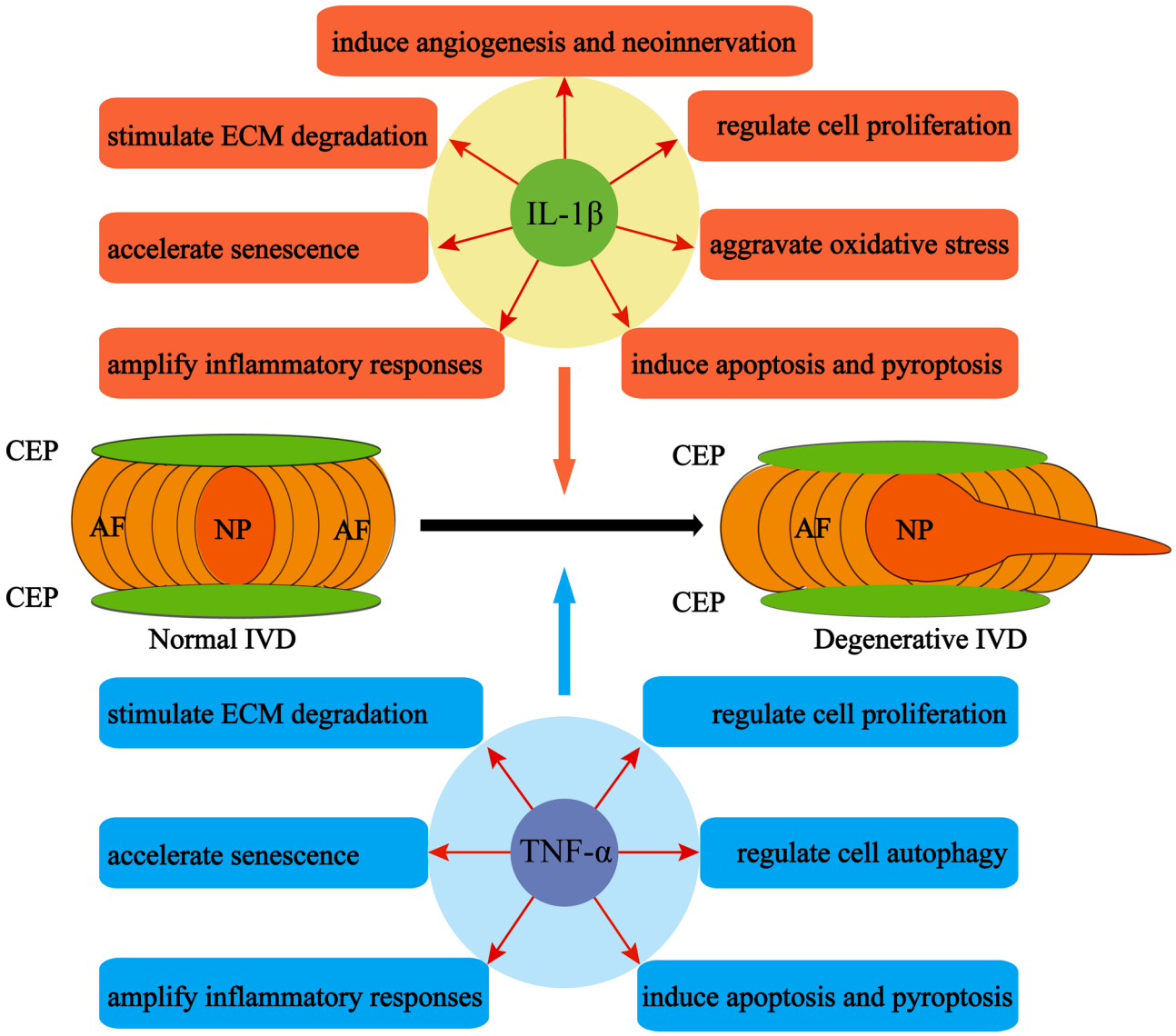

Fig. 3. IL-1β and TNF-α are involved in multiple pathological processes of intervertebral disc degeneration.

increased monocyte chemoattractant protein-1, IL-6, IL-8, and prostaglandin E2 production [92]. Another study has shown that exposing human AF and NP cells to IL-1β dramatically enhances IL-8 and IL-6 levels [93,94] and upregulates inflammatory molecules, including inducible nitric oxide synthase, nitric oxide, prostaglandin E2, cyclooxygenase-2, and TNF-α [95–97]. Additionally, the binding of IL-6 and its soluble receptor could in turn promote IL-1β-induced catabolism of proteoglycan [98], suggesting the presence of a positive feedback loop within IL-1β and IL-6 to further amplify the inflammatory response in IVDs. IL-17 is a strong proinflammatory cytokine largely secreted by Th17 cells that is reported to play a proinflammatory role in IDD immune pathogenesis [99]. IL-17 is significantly increased in more severely degenerated human discs, and it has been reported that exposing degenerated disc cells to IL-1β stimulates IL-17 production [100]. Therefore, IL-1β may be a key promoter of inflammatory cascade events by inducing IL-6, IL-8, and IL-17 production.

IL-1β can also modulate chemokine production in discs. IL-1β induces human NP cells (HNPCs) to dramatically upregulate chemokine C-C Motif ligand 3 (CCL3), CCL7, and C-X-C motif chemokine ligand 8 (CXCL8) expression. This suggests that NPCs are critical sources of various chemokines, and therefore have paracrine or autocrine responses [101]. IL-1β is also found to induce the production of CCL2, a critical chemokine-attracting monocyte, in human AFCs, [102]. Furthermore, both IL-1β and CCL5, a macrophage and eosinophil chemoattractant, are clearly elevated in disc samples from patients with painful IDD, and the expression of CCL5 is markedly related to IL-1β [103]. In addition, human degenerative AFCs or NPCs under IL-1β stimulation also promote CCL5 production in a concentration-dependent manner [104]. Collectively, IL-1β-induced CCL2, CCL3, CCL5, CCL7, and CXCL8 upregulation are responsible for inflammation amplification in IDD.

Dysregulated NLRP3 inflammasome activation has been previously reported to participate in diverse disorders, including osteoarthritis [105], neurodegenerative diseases [106], metabolic syndromes [107], cancer [108], infections [109], injury [110], autoimmune diseases [111], and inflammatory diseases [112]. The NLRP3 inflammasome activation/IL-1β inflammatory response axis was also reported to play a vital role in IDD [113,114]. Chen and colleagues [115] first found that IL-1β could promote its own production by enhancing NLRP3 inflammasome activation. They also found an IL-1β/NF-κB-NLRP3 inflammasome activation positive feedback loop in IL-1β-treated NPCs, and that melatonin could disrupt this loop both *in vitro* and *in vivo*. Brand et al. [116] found that the activated inflammasome could promote IL-1β secretion in NPCs, and that the inflammatory response was not initiated

when acidification was the stimulus. In another study, Piezo1 was found to accelerate the production of IL-1β by activating NLRP3 through the Ca^{2+}/NF-κB pathway, which may represent a novel aspect of IDD pathogenesis [117]. Additionally, a recent study suggested that *Propionibacterium acnes* (*P. acnes*) may act as a new pathogenic factor for IDD [118]. IL-1β was found to be the key component in responses to *P. acnes*. Meanwhile, in the *P. acnes*-infected NP tissues, the number of NLRP3-positive cells was dramatically increased [119]. The results of Zhang et al. [120] showed that NLRP3 inflammasome was involved in the maintenance of pain in rats with lumbar disc herniation, and the selective inhibitor of IKK-β, Bay11-7082, could suppress mechanical allodynia and thermal hyperalgesia by blocking NLRP3 inflammasome and NF-κB activation. Additionally, Song et al. [113] observed that compared with idiopathic scoliosis, the NLRP3 inflammasome was significantly activated in NPCs collected from patients with degenerative disc disease. They also suggested that advanced glycation end products (AGEs) could promote IDD by activating the NLRP3 inflammasome and inducing IL-1β secretion in NP cells [113].

IL-1β is closely related to mechanical loading and associated with chronic inflammation, which are involved in the vicious circle of IDD. Abnormal mechanical loading has been considered as a pivotal causative factor for IDD [121]. Interestingly, IL-1β treatment was discovered to sensitize AFCs to mechanical loading [122]. Such enhanced responsiveness to mechanical load during IL-1β stimulation may affect IDD progression. Another study suggested that IL-1β and cyclic tensile strain act synergistically to induce proinflammatory and catabolic molecules within the annulus fibrosus, contributing to AF structural weakening [123]. Additionally, static and dynamic compression was found to mediate different IVD responses [124]. Static compression was found to play a catabolic role on the disc, while dynamic compression may benefit the anabolic response of the disc. Both loading conditions lead to significant upregulation of IL-1β and TNF-α expression and histologic changes within the discs [124].

5.2. IL-1β stimulates ECM degradation

In healthy intervertebral discs, due to the complex regulation of growth factors and catabolic cytokines, the synthesis and decomposition rate of ECM is in balance. When ECM catabolism exceeds anabolism, IDD develops [125]. Matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs) are the essential enzymes leading to ECM loss. Studies have shown that multiple kinds of ADAMTSs and MMPs are upregulated in degenerated IVDs, and they are closely related to the destruction of ECM and the IDD progress [126,127].

MMPs, a vast family of zinc-containing and calcium-dependent endopeptidases, have been defined as the most critical enzymes causing ECM degradation [128]. Recently, a lot of evidence has shown that IL-1β could promote the expression of MMPs in discs. Shi et al. [129] suggested that IL-1β could induce MMP-1 production. In another study, IL-1β stimulation triggered a dramatic increase in MMP-1 and MMP-3 in human AFCs [130]. Additionally, Zhan et al. [131] discovered that IL-1β stimulation enhanced the production of catabolic enzymes (MMP-10, MMP-9, and MMP-3), but it decreased the expression of aggrecan and collagen II. Fang et al. [132] demonstrated that IL-1β could induce MMP1, MMP3, MMP13, and ADAMTS4 production. Moreover, mice without the natural inhibitor of IL-1R show an apparent increase in MMP-3 and MMP-7, and display similar characteristic features linked to human disc degeneration [133]. Conversely, NF-κB inhibition could significantly reduce these enzymes [134]. A new activator of sirtuin-1 (sirt1), 1,4-dihydropyridine (DHP), was found to inhibit IL-1β-mediated MMP-3 and ADAMTS-5 increase [135]. Hyperbaric oxygen could decrease MMP-3 level through blocking p38 MAPK signaling in degenerated HNPCs [136]. Moreover, the extracellular signal-regulated kinase (ERK) inhibitor, U0126, can dramatically block the secretion of MMP-3 and MMP-13 in IL-1β-treated rat AFCs, suggesting that ERK is associated with IL-1β-induced MMP production [137]. Therefore, IL-1β might act as a contributor to disc MMP synthesis, and its suppression may be a powerful method to prevent matrix degradation and thereby alleviate disc degeneration.

IL-1β is also reported to promote ADAMTs expression in discs [138,139]. IL-1R antagonist knockout shows typical characteristics of human disc degeneration, including increased ADAMTS-4 expression and degradation of proteoglycans [133]. Co-culture of HNPCs with IL-1β can activate NF-κB as well as MAPK signaling pathways, resulting in an increase in ADAMTS-4 [140]. In addition to ADAMTS-4, IL-1β is also able to modulate the expression of ADAMTS-5. A study by Wang et al. [141] discovered that IL-1β treatment upregulates syndecan-4 (SDC4) production as well as SDC4 promoter activity through NF-κB activation, thus promoting the synthesis of ADAMTS-5 and aggrecan destruction in HNPCs. Conversely, psoralen can significantly reduce the production of ADAMTS-5 in rat lumbar IVD chondrocytes, indicating its ability to alleviate IL-1β-induced IDD [142]. Taken together, these findings indicate that IL-1β can regulate ADAMTS-4 and ADAMTS-5 production in intervertebral discs, thus contributing to the loss of ECM and development of IDD.

5.3. IL-1β accelerates cellular senescence

Maintaining normal cell viability is critical to maintaining the physiological characteristics of discs. However, IVD cells gradually undergo senescence with aging and degeneration. Senescence associated β-galactosidase (SA-β-Gal) was recognized as a reliable marker of cell senescence [143], and cellular senescence can be divided into two different types: stress-induced premature senescence and replicative senescence [144]. A growing body of studies are indicating that IL-1 is associated with stress-induced premature senescence [145]. Yang et al. [146] found that β-gal was significantly increased in IL-1β-stimulated HNPCs. Li et al. [147] and Chen et al. [148] demonstrated that IL-1β promoted IDD progression, with markedly increased expressions of p16, p53, and SA-β-Gal. Compared with the control group, SA-β-Gal-positive cells markedly increased after human chondrocytes were exposed to IL-1β. However, co-incubation of IL-1β with Rg3 significantly suppressed SA-β-Gal production [149]. Furthermore, it has been reported that chondrocytes stimulated with IL-1β exhibit characteristics of senescent phenotypes, which include increased SA-β-Gal activity, altered cellular morphology, cell growth arrest, and telomere erosion [150]. Mechanistically, the expression of senescent phenotypes is partly related to caveolin 1 increase, and the activation of p38 MAPK as well as P53/P21/retinoblastoma (RB) pathways [150]. Additionally, it was discovered that an increase in senescent disc cells reduced the self-renewal abilities of IVD cells, and it produced more matrix-degrading enzymes and inflammatory cytokines, leading to the deterioration of the disc microenvironment. Therefore, cellular senescence is considered a potential initiator of IDD.

5.4. IL-1β induces apoptosis and pyroptosis of IVD cells

Apoptosis, a mechanism of cellular self-destruction, participates in many biological events, including tissue homeostasis, the removal of unwanted cells, and developmental sculpturing. Under normal physiological conditions, apoptosis plays an essential role in maintaining tissue homeostasis. However, excessive apoptosis causes a dramatic decrease of disc cells, leading to IDD [151].

IL-1β has been discovered to mediate apoptosis in NPCs and AFCs, a process that is closely correlated with IDD [138,152]. A study by Wang et al. [95] suggested that IL-1β promoted the production of pro-apoptotic proteins, including cleaved-caspase 3 and Bax, and decreased the production of anti-apoptotic contents in NPCs. Jiang et al. [153] discovered that IL-1β stimulation dramatically enhanced caspase-3 activity, cell apoptosis ratio, and production of cleaved PARP, Bax, caspase-3, and cleaved caspase-3, but reduced Bcl-2 level in rat

NPCs. Additionally, serum deprivation can enhance apoptotic incidence and the activity of caspase-3. Interestingly, IL-1β treatment markedly enhanced the impact of serum deprivation on cells [154]. Under IL-1β stimulation, many rabbit NPCs display apoptosis and related morphological features. However, oxygenase-1 significantly blocks IL-1β-mediated apoptosis by suppressing NF-κB, and promotes autophagy via enhancing Beclin-1/PI3KC3 complex formation [155]. In the study by Yang et al. [156], IL-1β significantly enhanced the apoptotic ratio of rat NPCs through a mitochondrial pathway, which can be suppressed by 17β-estradiol. Similar to these findings, Wang et al. [157] discovered that IL-1β stimulation results in a dramatic increase in the apoptotic rate in rat AFCs through increasing caspase-3 activity, which is also suppressed by 17β-estradiol. Moreover, flow cytometry and TUNEL assay found that insulin-like growth factor-1 significantly reduced IL-1β-induced apoptosis when combined with IL-1β treatment [158]. However, TUNEL is not specific for apoptosis.

IL-1β is associated with pyroptosis, which is also revealed by TUNEL staining. Pyroptosis is a newly discovered form of inflammatory programmed cell death that is related to IL-1β secretion [159]. The pyroptosis process is proinflammatory and triggered by the NLRP3 inflammasome [160,161], which depends on the formation of ASC oligomers known as pyroptosomes [162]. When caspase-1 is activated by the inflammasome, the maturation of IL-1β is accelerated, and the gasdermin-N domain (GSDMD) is cleaved to the N-terminal gasdermin-N domain (GSDMD-N) and the C-terminal gasdermin-C domain (GSDMD-C). Then, GSDMD-N can puncture the cell membrane, thereby triggering pyroptosis [163,164]. Additionally, pyroptosis is found to be associated with the proinflammatory process of *P. acnes*-mediated IDD [119]. Elevated levels of NLRP3, IL-1β, caspase-5, caspase-1, and GSDMD were discovered within NPCs after co-culturing with *P. acnes* [119]. Collectively, all of these findings indicate that IL-1β plays an essential role in IVD cell apoptosis and pyroptosis.

5.5. IL-1β regulates the proliferation of IVD cells

The appearance of cell clusters is one of the most important features of disc degeneration, especially in the damaged area [165]. NPCs are the most critical cells in discs. Their abnormal proliferation is considered to be the reason for the formation of cell clusters, which are closely associated with IDD [166]. Previous studies have found a variety of factors that can modulate NP cell proliferation, such as thymosin beta-4 [167], IGF-1 [168], and leptin [169]. Similarly, IL-1β can also regulate the proliferation of NPCs. Wang et al. [170] found that IL-1β stimulation significantly suppressed NPCs proliferation. In contrast, Li et al. [147] suggested that IL-1β dramatically inhibited cell proliferation and telomerase activity and promoted G0/1 cell cycle arrest. Also, a study by Wei et al. [171] demonstrated that 17β-estradiol prevented IL-1β-induced cell death and enhanced cell proliferation. Bai et al. [172] demonstrated that silencing of human triggering receptor expressed on myeloid cells-2 (TREM2) was a potential treatment approach for human degenerated NPCs, showing promise in inhibiting apoptosis, promoting cell proliferation, and blocking the production of IL-6, IL-1β, and TNF-α. Moreover, the proliferation of IL-1β-stimulated NPCs was enhanced under BMSCs and TSG-6 treatment, and the TLR2/NF-κB pathway was suppressed by bone marrow stromal cells (BMSCs) and TSG-6 [173]. Collectively, these studies show that NP cell proliferation modulated by IL-1β is responsible for IDD development.

5.6. IL-1β aggravates oxidative stress

Recently, increasing research has focused on the relationship between IL-1β and oxidative stress in discs. In an aerobic environment, oxygen takes part in redox reactions to produce reactive oxygen species (ROS). Under physiological conditions, ROS are beneficial to disc cells. However, the overaccumulation of ROS can cause oxidative stress, leading to the progression of IDD [174,175]. Furthermore, it has been reported that the responsiveness of disc cells to apoptosis is dramatically enhanced under oxidative stress, resulting in the destruction of ECM and the development of IDD [176]. Vertebral bone marrow plays a key role in metabolic exchange and nutritional supply for intervertebral discs. Interestingly, IL-1β was discovered to dramatically increase the intracellular ROS in mice vertebral BMSCs [177]. Conversely, fullerol nanoparticles could prevent IL-1β-mediated ROS production [177]. Sirtuin2 prevented NP degradation via restraining oxidative stress by inhibiting the p53/p21 pathway [146]. Honokiol, a low molecular weight natural product, could inhibit H2O2-induced oxidative stress by suppressing the TXNIP/NLRP3/caspase-1/IL-1β signaling axis [178]. Celastrol and aspirin could reduce IL-1β-induced or lipopolysaccharide (LPS)-induced oxidative stress in NPCs [179,180]. Moreover, stimulation of bovine NPCs with resveratrol could also inhibit IL-1β-induced oxidative stress [181]. Additionally, Mathy-Hartert et al. discovered that bovine chondrocytes incubated with IL-1β significantly reduced the production of superoxide dismutase as well as catalase [182], which form the first line of cellular ROS defense [183]. This indicates that IL-1β can inhibit the antioxidant abilities of discs. Overall, the above results indicate that IL-1β-induced oxidative stress may play an important role in IDD.

5.7. IL-1β promotes angiogenesis and neoinnervation

Discs are the largest aneural and avascular tissue in body. Normal neoinnervation and angiogenesis are critical for tissue repair and regeneration. However, in the process of IDD, the discs gradually become vascularized and innervated. A variety of studies indicated that neoinnervation and angiogenesis were dramatically enhanced in degenerative discs, and they were positively correlated with IDD severity [184,185]. This indicates that neoinnervation and angiogenesis may play essential roles in IDD progression. Previous studies have reported that overexpression of vascular endothelial growth factor (VEGF), the most important pro-angiogenic factor, leads to IDD [186]. Similarly, overexpression of neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), also accelerates IDD [187,188]. Interestingly, recent evidence indicates that IL-1β plays a role in the upregulation of VEGF, NGF, and BDNF expression within discs. Under hypoxic conditions, IL-1β increased the production of VEGF in disc cells, while treatment with IL-1β antibody reduced VEGF production [189,190]. In IDD patients' NPCs, the levels of VEGF, BDNF, and NGF were markedly elevated under IL-1β stimulation, and IL-1β concentration shows a positive correlation with the expression level of these factors [191]. In addition, IL-1β-stimulated human AFCs also exhibit a significant increase in NGF and BDNF [192]. Conversely, high molecular weight hyaluronic acid hydrogels have been discovered to reduce IL-1β-mediated NGF and BDNF by inhibiting the IL-1R1/MyD88 pathway in bovine NPCs [193]. Collectively, IL-1β promotes angiogenesis and neoinnervation by inducing VEGF, NGF, and BDNF production.

6. Main roles of TNF-α in IDD

TNF-α is a pleiotropic cytokine that is also involved in multiple pathological changes of disc degeneration (Fig. 3), which are thoroughly described below.

6.1. TNF-α amplifies inflammatory responses

TNF-α could induce IVDs to produce a variety of proinflammatory cytokines, thus further amplifying the inflammatory response in discs. Previous studies have shown that TNF-α stimulation promotes IL-8 and IL-6 production in human AFCs [194]. When stimulated with TNF-α, the level of Substance P (SP) increased, which subsequently induced IL-1β, IL-6, and IL-8 expression [195,196]. TNF-α can also stimulate AFCs to produce IL-17, which is related to IDD severity [100]. In addition, in AF

and NP cells from patients with IDD surgery, both IL-17 and TNF-α can induce the secretion of inflammation mediators, including IL-6, NO, and PGE2. IL-17 and TNF-α also upregulate the level of intercellular adhesion molecule (ICAM-1) in these cells [197]. Conversely, IL-38 significantly decreased the TNF-α-stimulated expression of IL-1β, COX-2, and IL-6 in HNPCs [198].

TNF-α can also modulate the production of various chemokines in discs. A study from Liu et al. [199] found that the gene expression level of CCL3, CCL20, CXCL2, and CXCL5 are increased in disc cells under TNF-α stimulation. In accordance with this, TNF-α-treated IVDs markedly increase CCL5 production, which is closely linked to the severity of degeneration and pain [104]. Additionally, Wang et al. [200] demonstrated that CCL3, which is also closely correlated with degeneration severity, is significantly induced through the NF-κB and MAPK signaling pathways during TNF-α exposure. Additionally, exposing human AFCs to TNF-α showed a dramatic enhancement in CCL2 expression [102]. Moreover, upregulation or downregulation of nicotinamide phosphoribosyl transferase (NAMPT) was found to control TNF-α-induced matrix destruction via regulating NLRP3 inflammasome activity, whereas melatonin could inhibit TNF-α-mediated matrix destruction by reducing NLRP3 inflammasome activity within NPCs [201].

TNF-α is also closely associated with mechanical loading. Mechanical loading can trigger TNF-α expression and histologic changes in the discs [124], and TNF-α can penetrate healthy discs under dynamic loading, promoting the production of other proinflammatory cytokines, and changing disc mechanical behavior [202]. Overall, TNF-α is considered to participate in amplifying inflammation responses during IDD development.

6.2. TNF-α stimulates ECM degradation

Recently, there has been much evidence indicating that TNF-α could stimulate the expression of multiple MMPs and ADAMTSs. TNF-α induces the expression of these enzymes mostly through the NF-κB/MAPK signaling pathways. It was found that TNF-α dramatically increased the production of MMP-1, MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5 in ex vivo HNPCs, leading to aggrecan and collagen degradation [203]. Yang et al. [204] found that TNF-α stimulation remarkably elevated MMP-3 and ADAMTS5 levels, whereas the collagen II levels decreased. Li et al. [147] demonstrated that TNF-α dramatically enhanced protein and gene expression of MMP-13, MMP-3, and ADAMTS-4, but decreased the production of collagen II and aggrecan. Wang et al. [205] thought TNF-α was critical for maintaining ADAMTS7 level during inflammation in NPCs. Furthermore, in organ culture models, TNF-α treatment can inhibit the expression of various types of collagen, aggrecan, and fibromodulin, and increase the production of MMPs as well as pain-associated molecule nerve growth factor (NGF) [206]. Moreover, when normal AFCs are stimulated with TNF-α, MMP-1 production was also enhanced [207]. In addition, exposing NPCs to TNF-α increases PHD2 level, which can interact with NF-κB to induce ADAMTS-5, MMP-13, and MMP-3 transcription [208]. Similarly, PHD3 is also involved in the activation of NF-κB and production of ADAMTS-5 and MMP-13 induced by TNF-α [209].

Conversely, LIM mineralization protein-1 can inhibit NF-κB p65 nuclear translocation in NPCs, thereby suppressing TNF-α-triggered MMP-3 and MMP-13 expression [210]. BMP-7 can block NF-κB pathway activation as well as the production of ADAMTS-4 and ADAMTS-5 mediated by TNF-α [211,212]. Furthermore, Kletsas et al. [213] discovered that TNF-α-mediated enhancement of MMP-3 secretion is blocked by p38 MAPK inhibitor in bovine NPCs. Huang et al. [201] found that melatonin could suppress TNF-α-mediated ECM destruction by inhibiting NLRP3 inflammasome activity, which is related to the MAPK and NF-κB pathway in NPCs. Wang et al. [214] discovered that in HNPCs, resveratrol (RSV) alleviated MMP-3 expression mediated by TNF-α through regulating autophagy by the AMPK/SIRT1 signaling pathway. Additionally, TNF-α induces Wnt5a expression, increasing ECM in a Sox9-dependent manner by activating JNK-AP1 (JunB) signaling, and inhibiting TNF-α-mediated production of MMPs by the NF-κB pathway [215]. These findings all support the idea that TNF-α is a critical causative factor in ECM degeneration.

6.3. TNF-α accelerates cellular senescence

TNF-α is also found to promote premature senescence in NPCs. Purmessur et al. [216] discovered that TNF-α could induce cell senescence along with pro-catabolic and anti-anabolic cellular activities in a bovine organ culture model. Another study from Li et al. [147] demonstrated that TNF-α treatment markedly increased SA-β-Gal activity, upregulated production of senescence markers (p53 and p16), and increased G0/1 cell cycle arrest. Similarly, Xie et al. [217] found that TNF-α enhanced NPC senescence, which was confirmed by the enhancement in SA-β-Gal activity as well as senescence marker (p53 and p16) production. They found that estrogenic protein-1 could suppress the impact of TNF-α on cell senescence. In addition, in cartilage endplate stem cells (CESCs), TNF-α also caused cell senescence, while rapamycin-mediated autophagy prevented TNF-α-mediated cell senescence in CESCs [218]. Additionally, Li et al. [219] found that 17beta-estradiol could alleviate TNF-α-mediated rat NPC senescence by interacting with the ROS/NF-κB pathway. Additionally, 17beta-estradiol treatment dramatically enhanced cell proliferation potency, but decreased SA-β-Gal activity and the senescence markers (p16 and p53) produced in TNF-α-stimulated NPCs [219]. Moreover, silencing LncRNA TUG1 could protect HNPCs from TNF-α-mediated senescence by inhibiting the Wnt/β-catenin pathway, which could provide the basis for future IDD therapy [220]. Furthermore, overexpression of zinc metallopeptidase STE24, which is associated with aging and premature cell senescence, suppressed the pro-senescence effects of TGFβ/NF-κB in NPCs upon TNF-α treatment [221].

6.4. TNF-α induces apoptosis and pyroptosis of IVD cells

Recently, there has been much evidence demonstrating that TNF-α is involved in disc cell apoptosis. TNF-α binds to TNF receptors, controlling the JNK/ERK-MAPK and NF-κB signaling pathways in NPCs during IDD, upregulating pro-apoptotic protein and downregulating anti-apoptotic protein, thereby leading to cell apoptosis [222]. Yu et al. [223] found that TNF-α stimulation markedly increased caspase-3 activity, apoptosis ratio, the production of Bcl-2, caspase-3 and Bax, and NF-κB pathway activity. In both degenerative human AFCs and NPCs isolated from patients undergoing spinal operations, TNF-α markedly enhances the apoptotic rate as well as the expression of caspase 3 and p53 [224]. Similarly, when rabbit NPCs are exposed to TNF-α, many disc cells suffer apoptosis and exhibit related morphological features. However, hepatocyte growth factor pretreatment could inhibit this process, which was confirmed by caspase-3 activity and TUNEL assay [225]. Additionally, overexpression of miR-532-5p in NPCs could suppress TNF-α-mediated increase of apoptosis and activation of apoptosis-related proteins, such as caspase-3, caspase-8 and caspase-9 [226]. Knockout of miR-494 was found to protect NPCs from apoptosis induced by TNF-α via cytochrome C apoptotic signaling-mediated JunD [227]. MiR-499a-5p could alleviate TNF-α-mediated NPC apoptosis as well as the imbalance between ECM catabolism and anabolism by downregulating SOX4. Furthermore, it was reported that the JAG2/Notch2 axis could also inhibit TNF-α-mediated apoptosis by blocking RIP1-FADD-caspase-8 complex formation [228]. Moreover, BMP-7 and insulin-like growth factor-1 (IGF-1) were discovered to suppress TNF-α-mediated NPC apoptosis through flow cytometry, caspase-3 activity testing, and TUNEL assay [229,230]. However, TUNEL is not specific for apoptosis.

TNF-α is also involved in pyroptosis, which also is revealed by TUNEL staining. The typical inflammasome activation pathway requires initiation events involving the binding of proinflammatory cytokines to their receptors, such as TNF-α binding to TNF-α receptors, or by

triggering a pattern recognition receptor (PRR) [46,231,232]. Such binding triggered the MyD88-induced activation of NF-κB, thereby resulting in increased pro-IL-1β and NLRP3 [46]. Under stimulation by PAMPs or DAMPs, the inflammasome complexes are assembled, which lead to further activation of caspase 1, cleavage of IL-1β, and pyroptosis. Moreover, reactive oxygen species (ROS) could also mediate NPCs pyroptosis through the NLRP3/PYCARD pathway, and perform negative regulation by increasing autophagy and transcription factor nuclear factor erythroid 2-like 2 (NFE2L2) [233].

6.5. TNF-α regulates the proliferation of IVD cells

TNF-α is considered to be associated with the proliferation and viability of NPCs. When exposing HNPCs to TNF-α, the cell number and viability significantly increased, and the cyclin B1 levels were markedly upregulated, indicating cell proliferation enhancement [234]. The results of Chen et al. [235] demonstrated that TNF-α led to apoptosis of some NPCs in the early stage, and later promoted the proliferation of surviving cells. In contrast, the results of Lin et al.'s study [236] showed that TNF-α treatment dramatically inhibited HNPC viability and increased IL-1β level in a time-dependent manner. Similarly, Li et al. [147] demonstrated that TNF-α significantly decreased cell proliferation and telomerase activity and promoted G0/1 cell cycle arrest. Additionally, Cheng et al. [237] found that stimulation with a relatively high concentration of TNF-α (50–200 ng/mL) induced nucleus pulposus mesenchymal stem cell (NPMSC) apoptosis. In contrast, a low concentration (0.1–10 ng/mL) enhanced NPMSC migration and proliferation, but suppressed their differentiation. In terms of underlying mechanisms, the proliferation of HNPCs induced by TNF-α is related to JNK, NF-κB, and p38 MAPK signaling pathways [234]. Recently, Notch signaling was also found to promote disc cell proliferation [238]. Wang et al. [239] demonstrated that in rat NPCs, TNF-α stimulation enhanced the production of Notch1 and Notch2 receptors, ligands, and target genes. Meanwhile, Notch2 levels in degenerative IVD tissues are richer than in non-degenerated tissues [239]. Moreover, Chen et al. [240] found that acute exposure to TNF-α enhanced NPC proliferation by activating the UPR/XBP1 pathway. Additionally, silencing LncRNA TUG1 also promotes cell proliferation, and protects HNPCs from TNF-α-mediated apoptosis by inhibiting the Wnt/β-catenin pathway [220]. Taken together, these findings demonstrate that NPC proliferation regulated by TNF-α also participates in the pathological process of IDD.

6.6. TNF-α regulates autophagy

Autophagy primarily plays a cytoprotective role, but it can also cause cell death. In the process of autophagy, autophagosome-dependent lysosomes degrade a variety of cytoplasmic contents, damaged or excessive organelles, and abnormal protein aggregates. Recently, a growing body of evidence has indicated that autophagy plays a pivotal role in IDD [176]. However, the exact function of autophagy in IDD remains controversial and needs to be further investigated. Some reports suggest that autophagy has a protective role [241,242], while others indicate that autophagy induces IDD progression [243,244].

The relationship between autophagy and TNF-α in disc cells has attracted much attention. Compared to healthy discs, the levels of autophagy-related genes, including beclin 1, cathepsin B, presenilin 1, ATG8, and ATG12, are markedly increased in degenerative discs [245]. Moreover, exposing human AFCs to TNF-α dramatically increases autophagy-related genes, including p62, damage-regulated autophagy modulator 1, WIPI49, and PIM-2 [245]. This result indicates that TNF-α is an important promoter of AFC autophagy. Additionally, acute exposure to TNF-α triggered a protein kinase RNA-like ER kinase/eukaryotic translation initiation factor 2α (PERK/eIF2α) pathway of unfolded protein response and activated autophagy, while interference in the PERK/eIF2α pathway suppressed autophagy in NPCs [246]. Moreover, moracin M could inhibit LPS-mediated PI3K and Akt phosphorylation, increase the production of autophagy-related proteins, and suppress TNF-α production in LPS-treated NPCs [247]. Estrogen can alleviate IDD by suppressing TNF-α production and promoting autophagy [248]. RSV reduced TNF-α-induced MMP-3 production in HNPCs by triggering autophagy via the AMPK/SIRT1 pathway [214]. In addition, rapamycin-induced autophagy upregulates Nrf2/Keap1 signaling and the production of antioxidant contents, thus reducing ROS, decreasing the estrogenic differentiation of cartilage endplate stem cells (CESCs), inhibiting cell senescence, and ultimately protecting cartilage endplates (CEPs) from TNF-α-mediated degeneration [218]. Collectively, the above results indicate that TNF-α-related autophagy plays a pivotal role in IDD.

7. Conclusion and future directions

IDD is a widespread pathogenic process leading to LBP, which seriously affects quality of life. However, the precise mechanisms of IDD molecular pathogenesis remain unclear. Most previous studies indicated that disc degeneration is a complicated process with multiple interacting factors. Also, emerging evidence has indicated that a variety of cytokines play vital roles in IDD, such as IL-1β, TNF-α, IL-6, and IL-17. In particular, IL-1β and TNF-α are found to be highly expressed in degenerative IVDs, and extensive studies have hinted at the functional roles of IL-1β and TNF-α in IDD, as well as shedding new light on their clinical use as potential therapeutic targets. However, functional studies of IL-1β and TNF-α are still limited, with most previous studies demonstrating that IL-1β and TNF-α are involved in IDD progression and initiation by regulating inflammatory response, IVD cellular proliferation, senescence, apoptosis, pyroptosis, autophagy, ECM destruction, and oxidative stress. Therefore, ideal IDD therapy may be achieved by targeting these functions of TNF-α and IL-1β in the future. Recently, clinical trials have indicated that inhibiting IL-1β and TNF-α has considerable prospects in inflammatory disease therapy. Thus, more translational works are critically needed to maximize the clinical potential of IL-1β and TNF-α in IDD. Additionally, more effort is expected to be devoted to the research of IDD-related cytokines, which will expand knowledge of molecular pathogenesis and offer novel ideas for the development of cytokine-based therapy for IDD in the future.

Authors' contributions

YJW, MXC and JBL conceived the idea. YJW collected the related references and wrote the manuscript. YJW and JGX drawn the figures. ZZ, JBL and SKZ supervised and revised the manuscript. All authors agree with the content of the manuscript.

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