Review article

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# Platelet-rich plasma in discogenic pain: therapeutic potential of multifactorial action

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Intervertebral disc degeneration (IVDD) is one of the leading causes of chronic low back pain and disability. The key pathogenetic mechanism of IVDD is chronic inflammation, which leads to extracellular matrix catabolism and the death of disc cells. It has been established that these changes are based on the activation of pro-inflammatory signaling cascades, particularly NF-κB, MAPK, and JAK/STAT pathways, as well as the induction of caspase-dependent apoptosis.

**Objective:** To summarize the current understanding of the molecular signaling pathways involved in degenerative processes within the intervertebral disc, and to elucidate the mechanisms of action of platelet-rich plasma (PRP) components capable of modulating these pathways.

**Materials and methods:** A comprehensive analysis of contemporary experimental and clinical studies was performed to evaluate the effects of the main growth factors present in PRP (TGF-β, PDGF, IGF-1, FGF, CTGF, EGF, HGF) on signaling pathways in intervertebral disc cells associated with catabolism, apoptosis, and inflammation.

**Results:** PRP-derived factors exert their effects predominantly through activation of the Smad, PI3K/AKT, MAPK, and JAK/STAT pathways while attenuating NF-κB activity, leading to decreased levels of pro-inflammatory cytokines (IL-1β, TNF-α) and metalloproteinases (MMPs, ADAMTS). These effects are accompanied by enhanced expression of type II collagen and aggrecan, stabilization of the extracellular matrix, restoration of tissue homeostasis and increased cell proliferation.

**Conclusions:** PRP therapy demonstrates considerable potential as a pathogenetically oriented regenerative strategy for the treatment of IVDD. Its efficacy arises from a multimodal influence on inflammatory, catabolic, and apoptotic pathways. Further clinical research is warranted to standardize treatment protocols and confirm the long-term therapeutic effectiveness of PRP.

**Keywords:** *intervertebral disc; degeneration; platelet-rich plasma; growth factors; NF-κB; signaling pathways; regeneration.*

## Introduction

Intervertebral disc degeneration (IVDD) is a major cause of chronic low back pain and one of the most common reasons for disability worldwide (affecting more than 600 million people), leading to significant social and economic burdens. Discogenic pain arises as a result of inflammation within the intervertebral disc (IVD), which activates nociceptive receptors and triggers pain signal transmission to the central nervous system. Inflammation of the IVD is accompanied by the accumulation of pro-inflammatory cytokines such as TNF-α (tumor necrosis factor-α), IL-1β (interleukin 1β), IL-6 (interleukin-6), prostaglandins (PGE2, PGI2), bradykinin, and matrix metalloproteinases (MMPs). The main nociceptors involved in discogenic pain include transient receptor potential vanilloid 1 (TRPV1), which are activated by inflammation, heat, and acidic pH; ASIC3 (acid-sensing ion channel 3), which responds to pH reduction during degeneration; and P2X3 (ATP receptor), which is activated under mechanical stress [1]. Prolonged exposure to pain mediators leads to nociceptor sensitization and a lowered activation threshold, resulting in pain even from minimal stimuli. The transmission of pain signals to the thalamus occurs via the spinothalamic tract, forming both sensory (localization and intensity) and emotional aspects of pain perception (through the limbic system, contributing to the affective-emotional component of pain perception). When pain becomes chronic, the spinal cord and brain adapt to constant stimulation, characterized by increased expression of NMDA-receptors (enhancing pain signaling) and decreased activity of inhibitory neurons, such as gamma-aminobutyric acid (GABA) and glycine [2]. Thus, discogenic pain represents a complex mechanism encompassing both peripheral (inflammatory and nociceptor activation) and central pain signal transmission processes.

Initially, pro-inflammatory cytokines are produced predominantly by resident disc cells. Nucleus pulposus (NP) cells, annulus fibrosus (AF) cells, and senescent cells produce pro-inflammatory cytokines in response to mechanical or oxidative stress and other external stressors [3]. These cytokines spread through the disc tissue via exocytosis, membrane vesicles, and diffusion. The intervertebral disc is normally poorly innervated and vascularized; however, during degeneration, neovascularization and the ingrowth of nociceptive nerve endings into the annulus fibrosus and vertebral endplates occur [4]. In healthy discs, immune cells are absent, but neovascularization allows immune cell infiltration. Infiltrated M1-type macrophages activate TNF-α, IL-1β, and IL-6 receptors. TNF-α, in turn, activates NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), which promotes the expression of pro-inflammatory cytokine genes. Consequently, the inflammatory process within the IVD can become self-amplifying and capable of persisting even after resolution of the initial trigger has resolved. NF-κB activation is accompanied by the progression of catabolic processes, with increased synthesis of metalloproteinases and aggrecanases (ADAMTS) that degrade key extracellular matrix components such as aggrecan and collagen type II. As a result of catabolic pathway activation in IVD cells, anabolic signaling pathways (TGF-β and PI3K/Akt — phosphoinositide 3-kinase/RAC-alpha serine/threonine-protein kinase), which are responsible for maintaining collagen and proteoglycan synthesis, lose their capacity to sustain matrix homeostasis [3].

A wide range of conservative methods aimed at reducing discogenic pain has been tested for its therapy. Currently, as an alternative to symptomatic procedures, new therapeutic options are being explored that target the inhibition of signaling pathways involved in degenerative processes and the activation of anabolic mechanisms. Therapeutic strategies aimed at modulating these pathways have the potential to slow down or halt the degenerative process. Autologous platelet-rich plasma (PRP) is considered a promising approach for regenerative treatment.

Growth factors released from platelets are believed to play an essential role in reducing inflammation and can also induce cellular proliferation and matrix remodeling. The most relevant growth factors present in PRP include transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), connective tissue growth factor (CTGF), epidermal growth factor (EGF), and hepatocyte growth factor (HGF). It is known that IVD cells express receptors for EGF, IGF, HGF, CTGF, PDGF, FGF, and TGF. These receptors play a key role in maintaining disc homeostasis, regulating cell proliferation and differentiation, and responding to tissue injury. The expression and activation of these receptors are critical for preserving the structure and function of the IVD, as well as its capacity for recovery following damage [5, 6].

Randomized controlled trials investigating the effects of PRP on IVD cells following direct injection into the nucleus pulposus have demonstrated pain reduction, improved functionality, and long-lasting therapeutic outcomes. A relevant current objective is to further investigate the mechanisms underlying catabolic activation in IVD cells, as well as the molecular pathways through which PRP components may inhibit degenerative processes in the disc [7].

**Objective:** To summarize current knowledge on the molecular signaling pathways involved in degenerative processes of the intervertebral disc, as well as the mechanisms of action of platelet-rich plasma components capable of modulating these processes.

### *Signaling pathways involved in degenerative processes of the intervertebral disc*

#### *NF-κB signaling pathway – a catabolic activator in intervertebral disc degeneration*

The NF-κB signaling pathway in IVD tissues plays a crucial role in regulating inflammatory processes and cellular responses to stress stimuli. Activation of NF-κB in NP and AF cells is associated with enhanced inflammation, extracellular matrix degradation, apoptosis induction, and the progression of IVDD [8]. The main activators of NF-κB include cytokines TNF-α and IL-1β, mechanical and oxidative stress, hypoxia, microbial lipopolysaccharides (LPS), and viral infection [9–12].

Signal transduction from ligands to receptors via adaptor proteins activates the IKK complex (IKKα, IKKβ, IKKγ), followed by deactivation of the inhibitor IκB, which normally retains NF-κB in an inactive state within the cytoplasm. As a result of IκB phosphorylation and degradation, NF-κB is released. The liberated NF-κB p65/p50 dimer translocates to the nucleus, where it regulates the transcription of proinflammatory (TNF-α, IL-1β, IL-6) and catabolic (MMP-3, MMP-9, MMP-13, ADAMTS-4, ADAMTS-5) genes [9]. Activation of NF-κB also enhances the expression of inflammatory mediators such as iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase-2), whose activity products—namely nitric oxide (NO) and prostaglandins—inhibit aggrecan expression in the NP. Furthermore, NF-κB contributes to the destructive processes in the IVD by activating hypoxia-inducible factor HIF-2α. The target genes of activated HIF-2α include MMP-13 and ADAMTS-4, which regulate the metabolism of type II collagen and aggrecan (***Fig. 1***) [13, 14].

The major pathways mediating the proinflammatory response in IVD cells under various stimuli are illustrated in ***Fig. 1***. Bacterial pathogens activate Toll-like receptors (TLR2/4) or intracellular NOD receptors, initiating a signaling cascade via MyD88, IRAK, and TRAF6 to IKK, which subsequently activates the transcription factor NF-κB. Cytokines IL-1β and TNF-α induce NF-κB activation through the IL-1R (MyD88-dependent) and TNFR1 (TRADD/RIPK1-mediated) pathways. Viral components are recognized by TLR3/7/9, triggering NF-κB activation and an interferon-mediated response.

Mechanical loading is sensed by TRPV4 channels and integrins, which activate FAK, MAPK, and PI3K/Akt pathways that potentiate NF-κB activation. Oxidative stress, characterized by excessive accumulation of reactive oxygen species (ROS), activates the MAPK p38/JNK/ERK signaling cascade, leading to the activation of the transcription factor AP-1 and subsequent upregulation of IL-6, IL-8, COX-2, iNOS, and MMPs.

*This article contains some figures that are displayed in color online but in black and white in the print edition*

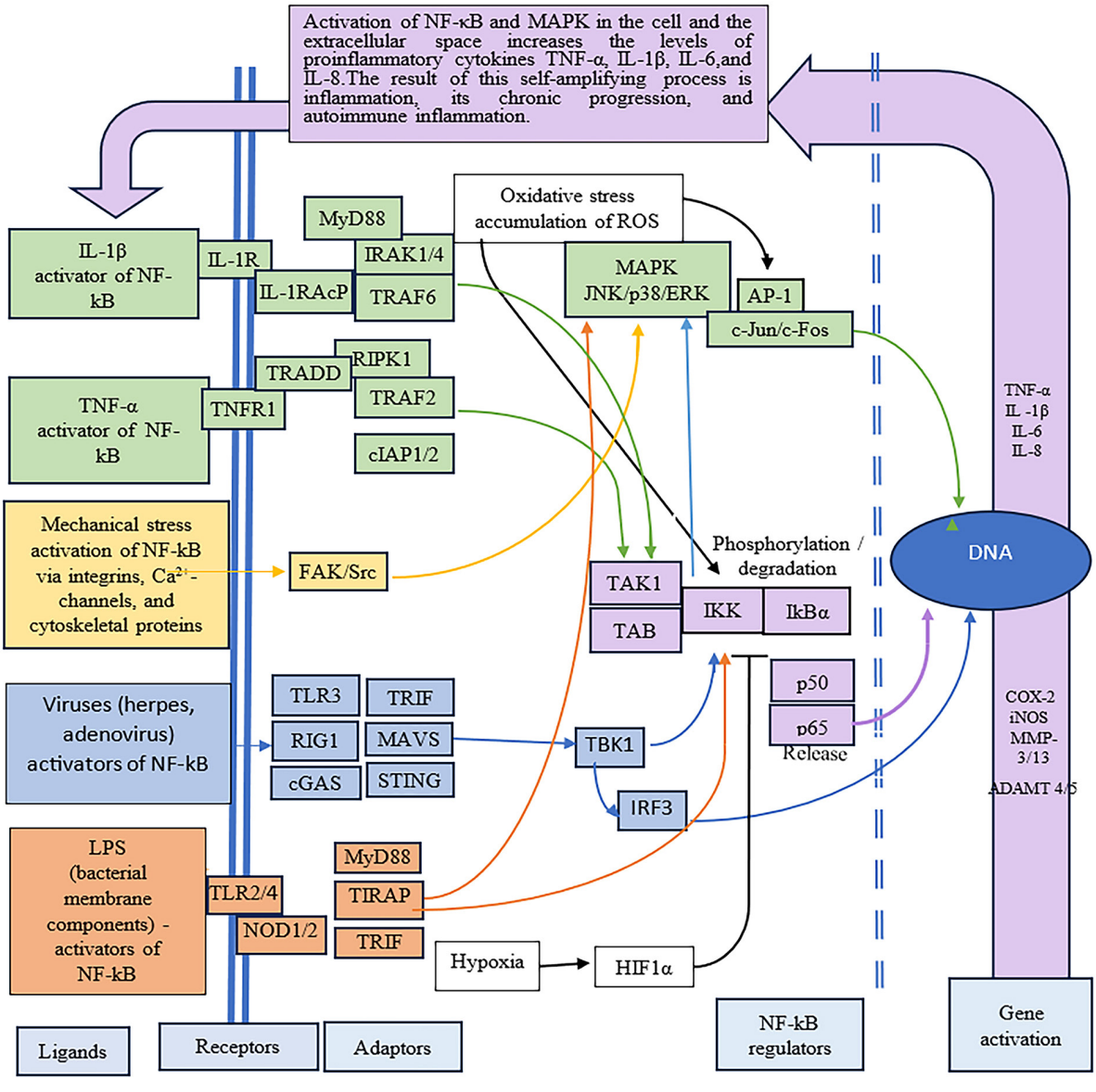


***Fig. 1.*** Major signaling pathways of NF-κB activation in intervertebral disc cells under the influence of proinflammatory cytokines (TNF-α, IL-1β), bacterial components (LPS), mechanical stress, hypoxia, and oxidative damage (based on KEGG PATHWAY Database for NF-κB signaling pathway (map04064), MAPK signaling pathway (map04010), Toll-like receptor signaling pathway (map04620), HIF-1 signaling pathway (map04066), TNF signaling pathway (map04668) [67]) (explanation provided in the text)

ROS promote phosphorylation of IKK and degradation of IκBα, resulting in NF-κB translocation to the nucleus and stimulation of proinflammatory gene expression. Through NLRP3 involvement, ROS activate caspase-1, driving the maturation of IL-1β and IL-18 and amplifying sterile inflammation.

Hypoxia—reduced oxygen availability in IVD tissues—activates hypoxia-inducible factors (HIFs), while HIF-1α stabilizes NF-κB, enhancing the transcription of proinflammatory genes.

All these pathways converge at the level of the IKK complex and NF-κB, leading to increased expression of IL-1β, IL-6, TNF-α, MMPs, and ADAMTS, which in turn drive chronic inflammation, matrix degradation, and progression of degenerative changes within the intervertebral disc.

***IL-1β*** is one of the key proinflammatory cytokines and plays a crucial role in IVD degeneration. It binds to the IL-1R1 receptor on the surface of NP and AF cells. This complex activates the adaptor protein MyD88, initiating downstream signaling cascades (see ***Fig. 1***). The subsequent effects are mediated through several interconnected mechanisms and pathways (NF-κB, MAPK, JAK/STAT), which collectively promote inflammation, matrix degradation, and cellular dysfunction [12].

***TNF-α*** is another major inflammatory cytokine that activates the NF-κB pathway through TNF receptors. The signal is further transduced via TRADD to the TNFR-associated signaling complex and TRAFs [15].

***LPS***—components of the outer membrane of Gram-negative bacteria—are potent inducers of the

inflammatory response in IVD cells. They activate the NF-κB signaling pathway through interaction with Toll-like receptors, particularly TLR4, via the adaptor protein MyD88, which is shared by both TLR and IL-1R pathways [16].

***Viral infection*** has been recognized as another factor capable of NF-κB activation. Viral signaling involves induction of immune and inflammatory responses. Viruses trigger the NF-κB pathway through various pathogen recognition receptors and associated molecules (TLRs, RIG-I, MDA5). Cellular receptors recognize viral ligands, including dsRNA, ssRNA, viral DNA, capsid proteins, and surface glycoproteins. Signals from activated receptors are transmitted via adaptor molecules such as MyD88, TRIF, and MAVS, leading to NF-κB activation and enhanced transcription of proinflammatory genes. NF-κB activation in response to viral exposure may sustain chronic inflammation in the IVD, which, upon reaching a critical threshold, can induce apoptosis of disc cells [17–19].

***Oxidative stress*** plays a pivotal role in degenerative processes within the IVD, primarily through mechanisms mediated by reactive oxygen species (ROS) [20]. In IVD cells, mitochondria represent the main source of ROS. Elevated ROS levels induce mitochondrial dysfunction and DNA damage, resulting in apoptosis of NP and AF cells. ROS further promote inflammation, extracellular matrix (ECM) degradation, and apoptosis through the MAPK (particularly p38 and JNK) and NF-κB signaling pathways [21–23].

***Hypoxia,*** characterized by reduced oxygen availability in IVD tissues (especially within the NP), stimulates the expression of HIF-1α and HIF-2α. The transcriptional activity of HIF-1α/2α induces proinflammatory activation via upregulation of COX-2, iNOS, and the cytokine IL-1β. Moreover, HIF-1α stabilizes NF-κB, enhancing the transcription of proinflammatory and catabolic genes. Under chronic or dysregulated hypoxic conditions, persistent HIF activation leads to cellular dysfunction and sustained inflammation in the IVD, ultimately contributing to the progression of degenerative changes [24].

***Mechanical loading acts as an activator of the inflammatory process via NF-κB signaling.*** It is well established that intervertebral disc (IVD) cells convert mechanical stress into biological signals integrated into cellular responses through the regulation of gene transcription. Abnormal mechanical loading enhances catabolic activity in nucleus pulposus (NP) cells through the NF-κB signaling pathway. A key role in this process is played by Piezo1, a mechanosensitive transmembrane cation channel (encoded by the FAM38A gene), which facilitates nonselective permeation of $Ca^{2+}$, $Mg^{2+}$, and $Mn^{2+}$ ions, activates the NF-κB signaling cascade, increases IL-1β expression in annulus fibrosus (AF) cells, promotes the formation of a proinflammatory microenvironment within AF tissue, and accelerates IVD degeneration [25].

***Differences in NF-κB signaling between nucleus pulposus chondrocytes and annulus fibrosus fibroblasts.*** A characteristic feature of NF-κB activation in NP cells is their greater sensitivity to oxidative stress and inflammatory stimuli. In NP cells, NF-κB is activated by proinflammatory cytokines (IL-1β, TNF-α), hypoxia, oxidative and osmotic stress, and dehydration. This activation enhances the expression of MMPs and ADAMTS, leading to degradation of aggrecan and type II collagen. The upregulation of inflammatory processes also increases the expression of proinflammatory cytokines IL-6 and IL-8, as well as COX-2, which stimulates prostaglandin synthesis. Under conditions of prolonged inflammation, NF-κB activation may induce apoptosis of NP cells [26, 27].

In contrast, the primary stimulus of NF-κB signaling in AF fibroblasts is mechanical stress (stretching and shear loading). NF-κB activation in AF cells leads to increased production of type I collagen—the main structural component of the AF. AF fibroblasts are also sensitive to proinflammatory cytokines such as IL-1β and TNF-α. In these cells, extracellular matrix (ECM) degradation is less pronounced compared to NP cells. AF fibroblasts exhibit a higher degree of adaptation to mechanical stress through ECM remodeling, primarily by synthesizing type I collagen. In AF cells, NF-κB plays a protective role by promoting fibrotic remodeling; however, under conditions of chronic activation, it may contribute to fibrotic sclerosis [26].

***The MAPK signaling pathway — an activator of degenerative processes in the intervertebral disc***

The mitogen-activated protein kinase (MAPK) signaling pathway plays an important role in IVD degeneration. MAPK signaling comprises the ERK (extracellular signal-regulated kinase), JNK (c-Jun N-terminal kinase) and p38 subpathways. The MAPK/p38 and MAPK/JNK subpathways are principally involved in the activation of inflammatory responses and induction of metalloproteinase synthesis. [28] Inflammatory activation mediated by MAPK signaling is triggered via TNFR, IL-1R, Toll-like receptors, integrins and viral recognition receptors. [29–33] Extracellular stimuli are relayed through MAPK cascades to activate the MAPK transcription factor AP-1 (c-Fos/c-Jun), which in turn drives transcription of catabolic enzymes such as MMP-3, MMP-13, ADAMTS-4 and ADAMTS-5 that are responsible for ECM degradation. The inflammatory response is further amplified through increased transcription of proinflammatory cytokines including IL-1β and TNF-α [34, 35]. MAPK signaling, particularly the p38 MAPK axis, potentiates proinflammatory processes and apoptosis in part by modulatory cross-talk with the catabolic NF-κB pathway (see ***Fig. 1***). [36, 37]

***PRP-derived factors — activators of anabolism and inhibitors of catabolic processes in the intervertebral disc***

Growth factors contained in PRP act in a synergistic manner by engaging multiple intracellular signaling pathways that regulate inflammation, cell death, and extracellular matrix metabolism. These factors contribute to the reduction of proinflammatory cytokine production, suppression of metalloproteinase activity, attenuation of apoptosis in NP cells, and stimulation of the synthesis of key matrix components such as type II collagen and aggrecan. This multifactorial influence not only slows the progression of degenerative changes but also promotes endogenous repair processes within the disc tissue. Collectively, these effects position PRP as a promising bioactive therapeutic strategy, particularly at early stages of IVDD, when residual elements of cellular and matrix homeostasis can still be modulated to reverse the pathological process (***Fig. 2***).

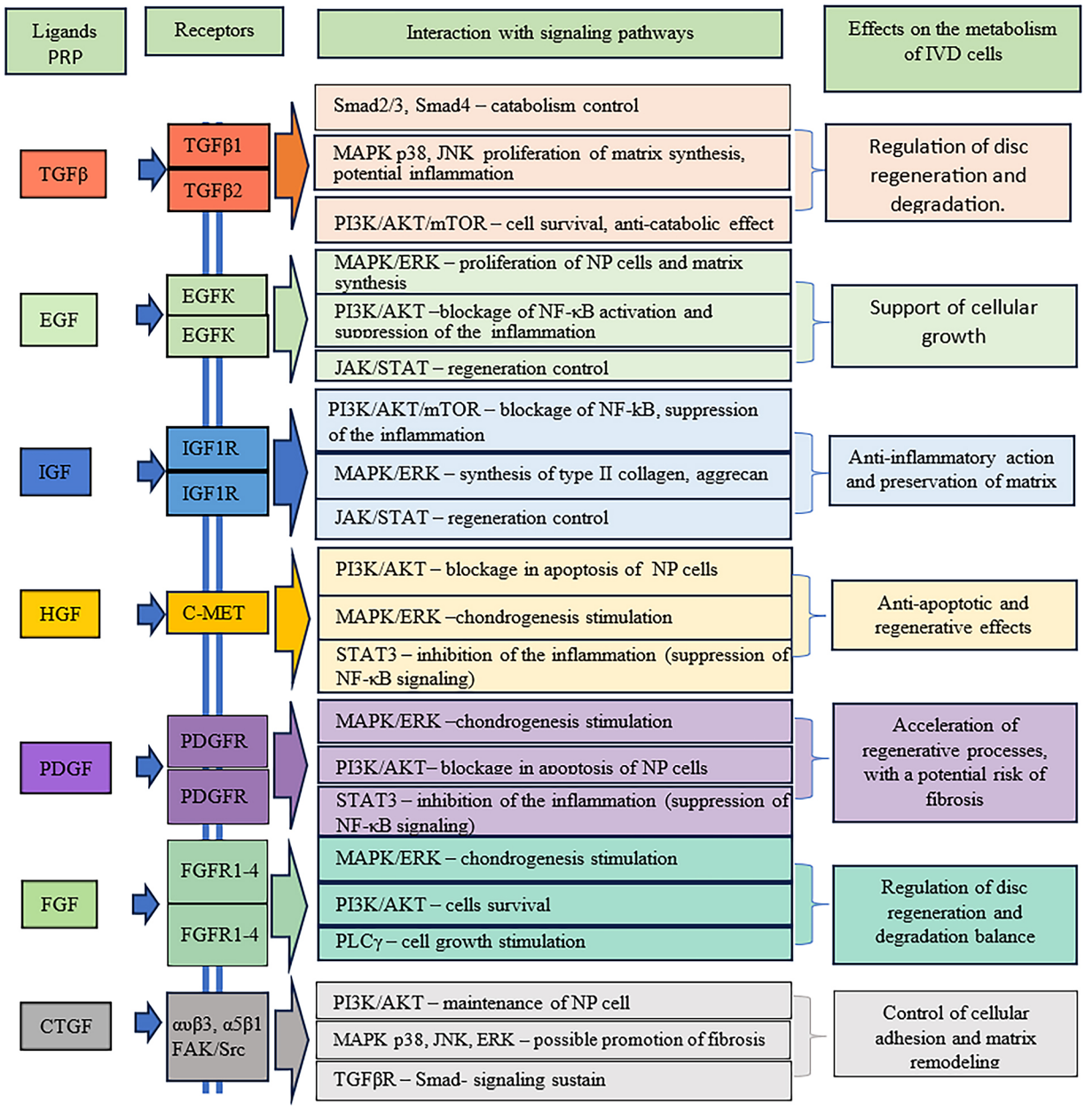


***Fig. 2.*** The main signaling pathways activated by PRP-derived factors: TGF-β/Smad, MAPK/ERK, PI3K/AKT/mTOR, JAK/STAT, Wnt/β-catenin, and HIF-1 (according to the KEGG PATHWAY Database [67])

***Figure 2*** illustrates the molecular interactions between PRP ligands (TGF-β, EGF, IGF-1, HGF, PDGF, FGF, CTGF) and their corresponding receptors (TGFβR, EGFR, IGF1R, c-MET, PDGFR, FGFR, αVβ3), which lead to the activation of intracellular signaling cascades such as Smad, MAPK/ERK, PI3K/AKT/mTOR, JAK/STAT, and PLCγ. The activation of these pathways is accompanied by the suppression of the pro-inflammatory factor NF-κB, inhibition of apoptosis, stimulation of chondrogenesis, cell proliferation, and synthesis of extracellular matrix components (type II collagen, aggrecan). These effects indicate the complex homeostatic influence of PRP on intervertebral disc tissue and substantiate its use as a pathogenetically oriented regenerative therapy for IVDD.

***TGF-β – a key growth factor in PRP***

1. TGF-β is a crucial regulator that suppresses inflammatory processes and maintains the structure of the IVD, counteracting degenerative changes. The concentration of TGF-β in PRP varies depending on the preparation method and the individual characteristics of the donor. On average, TGF-β levels range from 10–50 ng/mL in activated PRP fractions, although some samples may show significantly higher or lower concentrations [38, 39].

The primary effects of TGF-β are mediated through the Smad signaling pathway. The interaction of TGF-β with the TGFBR receptor triggers the phosphorylation of Smad2 and Smad3, which subsequently form a complex with Smad4. The Smad2/3/4 complex

indirectly suppresses NF-κB transcriptional activity the transcriptional activity of NF-κB — through induction of IκB expression and/or modulation of shared transcriptional cofactors (p300/CBP) — thereby reducing its ability to activate the expression of pro-inflammatory cytokine genes such as IL-1β, IL-6, and TNF-α, and consequently decreasing inflammation and degeneration within the IVD. The complex is then translocated into the cell nucleus, where it activates the expression of genes responsible for suppressing inflammation and supporting the structure of the extracellular matrix of the disc [40].

2. TGF-β activates the PI3K/AKT pathway. The PI3K/AKT pathway operates independently of Smad signaling but is often activated in parallel through TGFBR1 and ShcA/p85 [41]. Following TGF-β receptor activation, the adaptor proteins ShcA or p85 stimulate PI3K and initiate a downstream cascade leading to AKT activation. The downstream effects of AKT activation in the context of IVD degeneration include enhanced cell survival and anti-apoptotic activity via the inhibition of pro-apoptotic factors (such as BAD) and activation of anti-apoptotic proteins (Bcl-2). An important aspect of metabolic regulation is that AKT modulates glucose uptake and metabolism, thereby promoting the synthesis of extracellular matrix (ECM) components, including collagen and aggrecan [42].

3. TGF-β also activates the MAPK/ERK signaling pathway (mitogen-activated protein kinases), which can interact with NF-$\kappa B$ and modulate its transcriptional activity, thus influencing inflammatory responses. Under certain conditions, the MAPK/ERK pathway may exert a protective or even anti-inflammatory role by reducing the expression of pro-inflammatory genes (see ***Fig. 2***) [41].

4. Through the Rho/ROCK signaling pathway, TGF-β regulates cytoskeletal structural rearrangements and supports the maintenance of the extracellular matrix. This stabilizes disc tissue, reduces structural damage, and indirectly attenuates the inflammatory response [42].

The TGF-β, NF-$\kappa B$, MAPK, PI3K/AKT, and Rho/ROCK signaling pathways interact to form a complex regulatory network that enables TGF-β to control inflammatory processes, cell apoptosis, and the structural integrity of the IVD. The TGF-β pathway is crucial for maintaining ECM homeostasis and facilitating anabolic processes within the disc [43].

***PDGF*** exerts its effects through the activation of several intracellular signaling pathways. The primary action of PDGF in IVDD is mediated by its binding to PDGFR-α and PDGFR-β receptors, which belong to the receptor tyrosine kinase family. Ligand binding induces dimerization and autophosphorylation of tyrosine residues within the intracellular domain of the receptor, enabling the recruitment of signaling proteins and initiating multiple downstream signaling cascades. In particular, the MAPK/ERK pathway triggers mitogen-mediated cell proliferation, while the PI3K/AKT pathway promotes cell survival and inhibits apoptosis. STAT3 is activated via JAK- or Src-dependent pathways and regulates the expression of genes associated with inflammation, angiogenesis, and tissue remodeling. As a result, there is stimulation of IVD cells proliferation and enhanced synthesis of ECM components, including type I/II collagen and aggrecan [40].

The concentration of PDGF in PRP ranges from 10 to 50 ng/mL, depending on the individual characteristics of the sample and preparation conditions; however, in samples with extremely high platelet counts, PDGF levels may exceed 100 ng/mL [43].

PDGF signaling via PRP, when monitored at optimal concentrations, can promote reparative processes and prevent degenerative changes within IVD tissue [44, 45].

***FGF*** interacts with specific receptors (FGFR1–FGFR4), and the activation of this signaling pathway stimulates the proliferation of nucleus pulposus and fibrocartilage cells. The major pathways activated by FGF include MAPK/ERK, PI3K/AKT, and JAK/STAT [46]. The key transcription factor regulating the expression of chondrocyte-specific genes, such as type II collagen and aggrecan, is Sox9 [47]. By stimulating tissue inhibitors of metalloproteinases (TIMP), FGF decreases their activity, thereby suppressing ECM degradation [48]. Furthermore, FGF downregulates the expression of proinflammatory cytokines (e.g., IL-1β and TNF-α), which play a critical role in disc degeneration, and inhibits the NF-κB signaling pathway. Through suppression of inflammatory signaling, FGF promotes angiogenesis, improving the delivery of nutrients and regenerative factors. It has been demonstrated that PRP preparations containing a high concentration of FGF can be administered via intradiscal injections to stimulate tissue regeneration. This approach reduces pain associated with degenerative changes and slows the progression of degeneration. However, the use of FGF requires precise dosing and monitoring, as its concentration in PRP may vary depending on the preparation method and platelet count, ranging from 20 to 200 pg/mL [49].

***IGF-1,*** a key component of PRP, plays an essential role in tissue repair and regeneration, particularly in degenerative processes of the IVD. Its binding to the IGF-1 receptor (IGF-1R) activates the latter, initiating intracellular signaling cascades that are crucial for cell growth, survival, and recovery. IGF-1 primarily transmits signals through the PI3K/AKT pathway, which promotes cell survival by inhibiting apoptosis and stimulating matrix synthesis, including the production of proteoglycans and type II collagen. This pathway also provides protection against oxidative stress and cellular senescence. The concentration of IGF-1 in PRP may vary depending on the preparation technique and platelet yield (ranging from 70 to 250 ng/mL). When PRP is used therapeutically, it is essential to determine the IGF-1 content in the preparation to ensure reproducibility and treatment efficacy [50, 51].

***CTGF*** (connective tissue growth factor) is a bioactive protein that plays a significant role in tissue repair and regeneration, especially in degenerative conditions of the IVD [52]. It binds to TGF-β receptors, enhancing the activation of Smad2/3, thereby inhibiting IKK and IκB-α. As a result, NF-κB remains in the cytoplasm and does not activate pro-inflammatory genes such as TNF-α and IL-1β [53]. CTGF also activates the MAPK/ERK signaling pathway, promoting cell proliferation and survival, as well as PI3K and Akt, which enhance cell viability by suppressing apoptosis in disc cells. Indirectly, CTGF modulates the NF-κB pathway and activates the Wnt (Wingless-related Integration Site) signaling pathway, which regulates cellular proliferation, differentiation, and

matrix homeostasis in the IVD. Through its interaction with vascular endothelial growth factor (VEGF), CTGF also modulates angiogenesis. By activating these pathways, CTGF contributes to inflammation regulation, tissue regeneration, and the maintenance of disc homeostasis, while preventing cell death—making it a pivotal factor in the therapeutic effects of PRP [54–56]. The concentration of CTGF in PRP may vary substantially depending on the preparation method and donor platelet count (20–300 ng/mL) [56].

***EGF*** plays a crucial role in tissue repair and regeneration, particularly in IVDD. It binds to the epidermal growth factor receptor (EGFR), a transmembrane receptor that undergoes dimerization, autophosphorylation, and initiation of intracellular signaling cascades. Studies have shown that EGF activates the MAPK/ERK signaling pathway, leading to the formation of the AP-1 complex, which regulates the expression of genes responsible for cell proliferation and the synthesis of extracellular matrix components [57]. Activation of the PI3K/AKT and JAK/STAT pathways supports anti-apoptotic processes, collagen and proteoglycan synthesis, thereby promoting the restoration of IVDD structure. Despite the controversial nature of EGF activity in the context of IVD (due to the avascular nature of the disc), it contributes to angiogenesis, which may improve nutrient delivery to the disc, and modulates inflammatory responses by suppressing the synthesis of pro-inflammatory cytokines IL-1β and TNF-α. Within PRP, EGF helps create a microenvironment favorable for disc repair and reduction of degenerative processes. It acts synergistically with other growth factors present in PRP (TGF-β, PDGF, and IGF-1) [57].

The concentration of EGF in PRP depends on the preparation method and individual sample characteristics, typically ranging from ~100 to 300 pg/mL in non-activated PRP [59].

***HGF*** binds to the tyrosine kinase receptor MET, expressed on the surface of target NP and AF cells. Activation of the MET receptor triggers downstream signaling pathways essential for cell recovery and survival. The key activated signaling cascades include PI3K/AKT, which promotes cell survival and reduces apoptosis; RAS/MAPK, which stimulates cell proliferation and enhances tissue repair; and the STAT pathway, which regulates anti-inflammatory responses and supports the expression of genes involved in tissue regeneration. The Wnt pathway contributes to cell differentiation and matrix synthesis [60]. Protection of disc tissue by HGF occurs through suppression of TNF-α and IL-1β cytokine activity. Moreover, HGF promotes the synthesis of ECM components, including collagen and proteoglycans. Controlled modulation of matrix metalloproteinase (MMP) activity and inhibition of their tissue inhibitors allows for ECM remodeling. HGF also induces angiogenesis in surrounding tissues, enhancing nutrient and oxygen delivery to the IVD and thereby potentially improving its regenerative capacity. Its antifibrotic effect is based on the ability to inhibit TGF-β activity [61, 62].

The concentration of HGF in PRP may vary depending on the preparation protocol and other factors. Studies have demonstrated HGF levels of approximately 377.7–386.3 pg/mL in PRP samples, which reflects variations in platelet activation protocols and growth factor release [63].

Clinical research data on PRP application indicate its therapeutic potential. A systematic review and meta-analysis covering 10 studies involving intradiscal PRP injections in patients with vertebrogenic and discogenic pain [64] demonstrated positive effects on pain reduction and spinal function improvement. Similar beneficial outcomes have been reported in other studies, including the work of S. Kawabata et al. [65], emphasizing the importance of a critical approach to data interpretation and caution in drawing clinical conclusions [66].

## Conclusions

Platelet-rich plasma is a multifunctional biological agent capable of modulating degenerative processes in IVDD. IVD cells express receptors for key growth factors present in PRP (TGF-β, PDGF, IGF-1, FGF, CTGF, EGF, HGF). The interaction of these ligands with their corresponding receptors (TGFβR, PDGFR, IGF1R, FGFR, EGFR, c-Met) activates several intracellular signaling cascades (Smad, PI3K/AKT, MAPK, JAK/STAT, etc.), which collectively inhibit the catabolic factor NF-κB and trigger anabolic processes. This leads to enhanced synthesis of extracellular matrix components (collagen, aggrecan), increased cell survival, and reduced inflammation within disc tissues. Specifically, TGF-β via the Smad cascade suppresses the expression of pro-inflammatory cytokines and promotes matrix synthesis; PDGF and IGF-1 activate the PI3K/AKT and MAPK pathways to enhance proliferation and protect cells from apoptosis. FGF and EGF engage the ERK/MAPK and JAK/STAT pathways, stimulating disc cell regeneration, while HGF complements the actions of other factors by reducing inflammation and fibrosis and supporting matrix synthesis through activation of the MET receptor and AKT/MAPK pathways.

Thus, at the current stage of scientific understanding, PRP is considered a pathogenetically justified therapeutic approach for influencing discogenic pain associated with degenerative changes of the IVD. However, PRP should not be regarded as a universal treatment modality for treating all forms of degeneration. To substantiate the long-term efficacy and safety of this method, large-scale randomized controlled trials are required, considering the clinical forms of pathology, inclusion criteria, PRP dosing, injection techniques, and standardized efficacy outcomes.

## Disclosure

*Conflict of interest*

The authors declare no conflict of interest.

*Ethical Standards*

This article is a literature review; therefore, ethical approval was not required.

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