

Review

TWEAK/Fn14 signaling: a promising target in intervertebral disc degeneration

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Summary. Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) is a potent chemo-attractant cytokine with various biological functions, such as stimulation of angiogenesis, induction of proinflammatory cytokines, regulation of cellular proliferation and apoptosis. Therefore, it has also been implicated in several pathological processes, from cancer to inflammatory diseases. Remarkably, TWEAK and its receptors, fibroblast growth factor inducible 14 (Fn14), are also present in intervertebral disc (IVD) tissue, where they play a role in the pathogenesis of IVD degeneration. The interaction of TWEAK with Fn14 is involved in physiological and pathological activities of IVD degeneration patients, which includes apoptosis of endplate chondrocytes, extracellular matrix degradation, reduction in proteoglycan synthesis and so on. The blockade of this interaction results in suppressing overproduction of proinflammatory factors and cell death in *in vivo* or *in vitro* experiments, suggesting that TWEAK/Fn14 signaling may be therapeutically relevant in IVD degeneration, and the targeting of TWEAK or Fn14 has been proposed as a potential therapeutic approach for autoimmune diseases such as Rheumatoid arthritis (RA). In this article, we discuss the biological features of TWEAK/Fn14 signaling and summarize recent advances in our understanding of the role of TWEAK/Fn14 signaling in the pathogenesis and treatment of IVD degeneration. We think that the

blockade of TWEAK/Fn14 signaling may be a promising therapeutic strategy for IVD degeneration in the near future.

Key words: TWEAK, Fn14, Target, Intervertebral disc, Degeneration

Introduction

Degenerative disc disease is a pathologic process of uncertain etiology that may cause acute or chronic low back pain, and IVD degeneration is thought to be the first step in degenerative spinal changes (Boos et al., 2002). The typical radiographic findings in degenerative disc disease include disc space narrowing, osteophyte formation, endplate sclerosis and vacuum disc. Degenerative disc disease can greatly affect the sufferer's quality of life and cause severe chronic pain if left untreated. Back complaints are the leading cause of all visits to orthopedic and neurosurgeons (Okada et al., 2009; Teraguchi et al., 2014). Disc degeneration seems to be related to lower back pain intensity, due to a severe loss of mechanical stability in the spine. Herniated discs are common and are responsible for symptoms in up to 40% of all patients with lower back pain (Deyo, 2007).

An inner gelatinous nucleus pulposus surrounded by an outer annulus arranged in concentric lamellae are the two main components of IVD (Antoniou et al., 1996; Wako et al., 2007), the nucleus pulposus which originates from segmented notochordal tissue is replaced postnatally with an aggrecan-rich extracellular matrix and type II collagen (Antoniou et al., 1996; Wako et al.,

2007). The annulus fibrosus consists of type I collagen and derives from fibrocartilage (Antoniou et al., 1996; Wako et al., 2007). Disc degeneration results from both biochemical and structural changes. There is increasing evidence that several enzymes, cytokines and inflammatory signaling pathways play critical roles in the pathogenesis and etiology of IVD degeneration that leads to loss of aggrecan and distinction between the nucleus and the annulus, changes of lamellar architecture of the annulus fibrosus, annular tears, and formation of osteophytes during the process of degenerative disc disease. It is widely believed that loss of aggrecan reduces the capacity of the nucleus pulposus to attract and bind water, leading to decreased disc height (Priyadarshani et al., 2016). Although the primary cause of lower back pain has not yet been identified, IVD degeneration is considered to be one of the causes of several symptoms (neck pain or low back pain) (Deyo, 2007).

The cytokine tumor necrosis factor-like weak inducer of apoptosis (TWEAK) was initially described as a member of the tumor necrosis factor (TNF) superfamily in 1997, and is primarily expressed as cell surface-associated type II transmembrane protein (Wiley and Winkles, 2003). TWEAK binding to a small, 14kDa cell surface fibroblast growth factor-inducible protein (Fn14) which also belongs to the TNF superfamily acts on responsive cells. TWEAK and Fn14 are expressed in a variety of cell and tissue types, such as human and murine brain, heart, pancreas, colon, small intestine, lung, ovary, prostate, kidney, testis, liver, and spleen (Chicheportiche et al., 1997; Lynch et al., 1999; Polek et al., 2003). TWEAK can be cleaved to generate a soluble factor with many biological activities, including proliferation, migration, differentiation, apoptosis, angiogenesis, and tissue remodeling, besides inflammatory response (Bertin et al., 2013). Fn14 is highly upregulated in the context of tissue injury, regeneration, and inflammatory responses (Campbell et al., 2004). It is widely believed that matrix metalloproteinases (MMPs) such as MMP-1, MMP-3 and MMP-9 are the main players in destruction of cartilage in RA patients, based on their contribution to collagenous matrix degradation at different levels. Initial studies also revealed that MMP-3 play a crucial role in IVD degradation (Haro et al., 2000). There is increasing evidence that cytokines (such as IL-1, IL-6, TNF- α) and inflammatory signaling, including the nuclear factor- κ B (NF- κ B) pathway, may be key factors of the pathogenesis of RA and be involved in the persistent immunologic response (Yamana et al., 2012; Du et al., 2015). TWEAK can promote the production of various inflammatory cytokines in normal human synoviocytes and fibroblasts derived from patients with osteoarthritis and rheumatoid arthritis (Chicheportiche et al., 2002). Furthermore, TWEAK binding to Fn14 can activate the nuclear factor- κ B (NF- κ B) pathway (Brown et al., 2013).

A growing body of evidence supports the thesis that

these TWEAK/Fn14 pathway-induced activities contribute to progressive local tissue damage and maladaptive remodeling when exaggerated and dysregulated in injured and diseased target tissues (Dohi and Burkly, 2012). Initial studies also revealed that TWEAK can target human primary chondrocytes and osteoblast-like cells, in addition to synovial fibroblasts, raising the possibility that TWEAK may play a role in the regulation of IVD degeneration (Perper et al., 2006). Recent studies (Park et al., 2012, 2013) have reported that TWEAK can promote osteoclastogenesis and Th17 differentiation in RA patients, Fn14 and IL-17 were highly expressed in arthritic tissues of collagen-induced arthritis (CIA) mice, and TWEAK promoted IL-17 production synergistically with IL-23 or IL-21. TWEAK and IL-17 concentrations were significantly higher in synovial fluid and serum in RA patients than OA patients. Collectively, these data suggest that TWEAK and the interaction between TWEAK and Fn14 may play a pivotal role in inflammation, vascularization, and degradation of IVD degeneration.

In this article we provide a brief overview of the molecular properties of TWEAK/Fn14 signaling, and summarize recent advances on the role of TWEAK/Fn14 in the pathogenesis and treatment of IVD degeneration.

Biological functions of TWEAK/Fn14 signaling

As a ligand/receptor pair of the TNF superfamily, the TWEAK/Fn14 pathway has emerged as a prominent player in normal and pathological tissue remodeling, and persistent TWEAK/Fn14 signaling has been implicated in the pathogenesis of these and other related diseases. The activation of TWEAK/Fn14 pathway can drive many processes relevant to inflammatory and autoimmune diseases (Dohi and Burkly, 2012). As a matter of fact, TWEAK has been demonstrated to promote bone and cartilage destruction through inhibition of chondrogenesis, osteogenesis and the induced production of MMP-3 (Perper et al., 2006; Xia et al., 2009). Gao et al. (2009) reported that TWEAK induces human kidney cells to express multiple inflammatory mediators, including RANTES, MCP-1, IP-10, MIP-1 α , ICAM-1, and VCAM-1. Cytokine production is mediated through NF- κ B activation, and TWEAK can stimulate chemokines induced migration of human PBMC, particularly monocytes/macrophages. The gene expression of TWEAK/Fn14 increased in tubulointerstitium and glomeruli of patients with lupus nephritis and increased early in kidneys of a mouse lupus model (Chicheportiche et al., 2000; Lu et al., 2011). Moreover, the effects of targeting TWEAK and/or Fn14 in autoimmune diseases of mouse model with anti-TWEAK mAb administration have recently been reported, studies have revealed that disrupting TWEAK/Fn14 interactions may be an innovative kidney-protective approach for the treatment of lupus nephritis and other antibody-induced renal diseases (Xia et al., 2012). Several similar studies complemented these

findings and showed that *in vivo* blockade of TWEAK/Fn14 signaling using blocking monoclonal antibodies or fusion proteins can mitigate collagen-induced arthritis (Kamata et al., 2006). *In vivo* studies using mouse models of RA have shown that the TWEAK/Fn14 signaling pathway is a significant contributor to RA pathogenesis. The TWEAK antibody treatment also resulted in reduced inflammation and reduced cartilage and bone loss according to histological analysis (Wisniacki et al., 2013). Furthermore, the TWEAK antibody-treated mice had reduced synovial angiogenesis and a reduction in the serum levels of inflammatory cytokines and chemokines and the antibody efficiently inhibited joint inflammation and destruction (Cheng et al., 2013). It has been demonstrated that in disc tissues, TWEAK plays a role in MMP-3 upregulation and aggrecan downregulation, resulting in proteoglycan degradation and promotion of disc degeneration (Wako et al., 2007). *In vitro* experiments (Lei et al., 2015) have shown that TWEAK has a biological effect on phenotype of uterine natural killer (uNK) cells as well as the secretion and expression of interferon- γ by uNK cells in goats. Moreover, TWEAK decreases the cytotoxicity of goat uNK cells *in vitro*. More recently, Wen et al (Wen et al., 2015) reported that TWEAK/Fn14 interactions play an important role in the pathogenesis of neuropsychiatric lupus by increasing the accumulation of inflammatory cells in the choroid plexus, disrupting blood brain barrier integrity, and increasing neuronal damage, suggesting a novel target for therapy in this disease. Moreover, Yin et al. (2014) found that TWEAK/Fn14 signaling may contribute to prostate cancer metastasis through the NF- κ B pathway and suggest Fn14 as a candidate therapeutic and imaging target for castrate-resistant prostate cancers. Ogura et al (Ogura et al., 2013) demonstrated that TWEAK suppresses satellite cell self-renewal through activating NF- κ B and repressing Notch signaling.

This evidence suggests that TWEAK/Fn14 signaling can target various immune cell types, which emphasizes its potential in influencing the outcome of a wide range of diseases, including IVD degeneration.

TWEAK/Fn14 signaling in the pathogenesis of IVD degeneration

Cytokine-mediated immunity plays a major role in the pathogenesis of IVD degeneration and other autoimmune diseases. Recently, there has been increasing evidence that TWEAK/Fn14 signaling contributes to the pathogenesis of IVD degeneration due to its properties of regulating tissue responses after acute tissue injury and in contexts of chronic injury and disease, including autoimmunity, chronic inflammation, fibrosis, and malignancy. The degeneration of the IVD is related to a variety of inflammatory mediators, including interleukins, MMP, TNF- α and other cytokines (Podichetty, 2007). Expression of TWEAK and its receptor Fn14 in murine intervertebral disc tissues was

first reported by Wako (2007) the finding suggested that TWEAK plays a role in MMP-3 up-regulation and aggrecan down-regulation in disc tissues, resulting in proteoglycan degradation and promotion of disc degeneration. In other studies, they (Wako et al., 2008; Hirooka et al., 2011) demonstrated that TWEAK induced disc cells to generate MMP-3, as did TNF-alpha and IL-1beta, and MMP-3 activity was detectable in murine disc cells. Introduction of TWEAK resulted in the degradation of disc matrix in organ disc culture, whereas proteoglycan degradation was markedly stimulated in the presence of MMP-3. In addition, TWEAK also induced monocyte chemotactic protein-1 via the NF- κ B pathway. Interestingly, a recent cell culture study by Huh et al. (2010) showed that TWEAK can decrease the mRNA levels of Sox9 and versican and the sGAG amount in human IVD tissues and cells. Numerous studies have demonstrated that cartilage endplate degeneration or calcification and intervertebral facet joints degeneration played important roles in the progress of IVD degeneration (Peng et al., 2001; Hao et al., 2011). We think that TWEAK/Fn14 signaling may have a crucial role in the pathogenesis of intervertebral facet joint degeneration, similar to TWEAK/Fn14 signaling to RA. Therefore, it seems that TWEAK/Fn14 should be added to the increasing list of molecules involved in the pathogenesis of IVD degeneration.

In brief, TWEAK/Fn14 signaling may play a crucial role in the induction and development of systemic autoimmune diseases, and inhibition of the pathway in IVD degeneration appears to be a reasonable proposal at this time.

Therapeutic implications for targeting TWEAK/Fn14 signaling in IVD degeneration

Presently, there is increasing evidence in both humans and in mouse models that TWEAK/Fn14 signaling plays a role in the development and progression of degenerative disc disease. The differences in TWEAK and /or Fn14 expression between patients and healthy controls may suggest the possibility of using anti-TWEAK therapy to treat IVD degeneration patients characterized by high levels of TWEAK. In fact, exciting discoveries regarding the effects of targeting TWEAK or Fn14 in autoimmune diseases have recently been reported. Initial studies revealed that administration of TWEAK mAb and Fn14-fc fusion protein in mouse and human models of arthritis significantly suppressed clinical parameters of arthritis, including levels of inflammatory cytokine, differentiation of osteoblastic and chondrocytic precursors, and so on (Perper et al., 2006; Wako et al., 2007). Indeed, the recent demonstration of the efficacy of targeting the TWEAK/Fn14 pathway in animal models of RA positions TWEAK as an attractive candidate for clinical development. Targeting TWEAK or Fn14 in a mouse CIA model, described by Kamata et al. (2006), effectively inhibited the severity of CIA, including

pannus tissue formation, marked inflammatory cell infiltration, and bone and cartilage destruction. Interestingly, a previous study by Chicheportiche et al. (2002) showed that an anti-hTWEAK mAb, BCB10 not only inhibited the inflammatory response of fibroblasts and synoviocytes but also completely blocked the production of PGE₂, MMP-1, IL-8, IL-6, RANTES and IP-10 induced by hTWEAK. Furthermore, Wisniacki et al. (2013) demonstrated that TWEAK-blocking monoclonal antibody BIIB023 had a favorable safety and tolerability profile in RA patients, levels of serum-soluble TWEAK were suppressed at all dose levels, and at high dose levels, they were suppressed for up to 28 days. Moreover, a recent study confirmed the reciprocal reaction of TWEAK and Fn14 on disc degeneration and suggested that TWEAK has a negative effect on sulfated glycosaminoglycan (sGAG) production via lowering the mRNA expression of sex determining region Y (SRY)-box 9 (Sox9) and versican, and participated in the production of sGAG and other proteoglycan in nucleus pulposus (Huh et al., 2010). Moreover, a recent study reported that an antagonistic anti-TWEAK antibody RG7212 *in vitro* experiment showed antitumor efficacy in multiple diverse tumor models in mice with efficacy associated with tumor Fn14 expression and pathway activation. Expression of Fn14 has been shown to be upregulated in many human cancers, suggesting that RG7212 may provide broad clinical benefits in patients with TWEAK-driven tumors (Yin et al., 2013).

Conclusion

Although much remains to be elucidated regarding the role of TWEAK/Fn14 signaling in IVD degeneration, evidence is now accumulating from *in vivo* and *in vitro* experiments to support the therapeutic potential of TWEAK/Fn14 signaling in IVD degeneration. Understanding TWEAK/Fn14 signaling biological activity, the expression and function of related inflammatory molecules and downstream signaling pathway, could ultimately lead to modulation of TWEAK/Fn14 and its pathway for therapeutic benefit. More and more interest in and understanding of the TWEAK/Fn14 pathway has increased greatly in recent years, which demonstrated that the TWEAK/Fn14 pathway may play a role in the induction of release of pro-inflammatory factors, functional cell apoptosis, IVD degeneration or destruction due to its ability to activate cells of the innate and adaptive immune system. However, much of the data regarding the therapeutic implications of TWEAK/Fn14 pathway have been obtained from mouse models, which may not be applicable to human IVD degeneration. Some of the limitations of animal models of degenerative disc disease are due to the differences between humans and laboratory animals. Some of the findings observed in animal models may not occur in human degenerative disc disease. Accordingly, conclusions drawn from

animal model studies should be restricted to animal models until they are confirmed in human degenerative disc disease, and all these potential deficiencies must be considered. Therefore, further studies in human systems are required to comprehensively explore the therapeutic potential of TWEAK/Fn14 signaling in human degenerative disc disease.

In summary, a thorough understanding of the complexity of TWEAK/Fn14 pathway processing and secretion is essential, so additional studies are required, not only in animals, but in human systems to further illustrate the clear relationship between TWEAK and its receptor Fn14 in various inflammatory, infectious and autoimmune diseases.

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