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REVIEW **Open Access**

The regulatory role of the BDNF/TrkB pathway in organ and tissue fibrosis

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Summary. Fibrosis across diverse organ systems is one of the leading causes of morbidity and mortality by inducing progressive architectural remodeling and organ dysfunction. Brain-derived neurotrophic factor (BDNF) and its receptor tyrosine kinase receptor B (TrkB) play crucial roles in regulating neural survival, development, function and plasticity in the central and the peripheral nervous system. Previous studies demonstrated that the BDNF/TrkB pathway is widely distributed in different cell types such as neuron, epithelial cell, hepatocyte, and cardiomyocyte. Recently, there is increasing recognition that BDNF and TrkB are also expressed in fibroblasts in different organs. Moreover, growing evidence was obtained regarding the functional roles of BDNF/TrkB signaling in organ and tissue fibrosis. Thus, this review summarizes the basic molecular characteristics of the BDNF/TrkB cascade and the findings of the crucial roles and therapeutic value in organ and tissue fibrosis including pulmonary fibrosis, hepatic fibrosis, renal fibrosis, cardiac fibrosis, bladder fibrosis and skin fibrosis. Small molecule BDNF mimetic and BDNF-related non-coding RNAs are also discussed for developing new therapeutic approaches for fibrotic disorders.

Key words: BDNF/TrkB, Noncoding RNA, Organ fibrosis, Tissue fibrosis

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Introduction

Fibrosis is a reparative or reactive consequence that can occur in both organs (eg. lung, liver, kidney, and heart) and tissues. A variety of etiological conditions leads to chronic tissue injury, scar tissue formation, and eventually organ dysfunction and death. Fibrotic disease is usually characterized by excessive deposition of extracellular matrix (ECM) components (Rockey et al., 2015). Previous studies thought that fibrosis was irreversible and thereby to identify and eradicate the pathological stimulus was the only measurement of halting the progression of fibrosis. However, emerging evidence suggests that fibrosis is reversible depending on the organ involved, and the nature and chronicity of the injurious stimulus (Horowitz and Thannickal, 2019). Moreover, targeting transforming growth factor-β (TGF-β) signaling has been validated as an effective therapy for fibrosis (Li et al., 2021). To date, two drugs have received FDA approval for treatment of fibrosis. Pirfenidone (a TGF-β inhibitor) is an orally active small molecule drug, which can reduce collagen synthesis, down-regulate the production of a variety of cytokines, inhibit fibroblast proliferation and stimulate cytokines. Pirfenidone has been shown to be effective in various fibrotic conditions, including those of the lung, kidney, and liver. In addition, nidanib (a tyrosine kinase receptor B, TrkB, inhibitor) is approved for treatment of idiopathic pulmonary fibrosis (IPF). Although these two drugs can slow fibrotic disease progression, most compounds tested in clinical trials received no positive data on primary end points. Therefore, further exploration pathological mechanisms of fibrosis and screening of new drug targets is warranted (Mora et al.,

Abbreviations. ASM, airway smooth muscle; BDNF, brain-derived neurotrophic factor; CF, cystic fibrosis; circRNA, circular RNA; 7,8-DHF, 7,8-dihydroxyflavone; ECM, extracellular matrix; EMT, epithelial to mesenchymal transition; ERK, extracellular regulated protein kinases; IPF, idiopathic pulmonary fibrosis; lncRNA, long non-coding RNA; miRNA, microRNA; NT, neurotrophin; TGF-β, transform growth factor-β; 7,8,3-THF, 7,8,3-trihydroxyflavone; TrkB, tyrosine kinase receptor B.

2017).

Neurotrophins (NTs) are a family of proteins that regulate neuron differentiation, survival, dendritic pruning, innervation pattern, synaptic function, and plasticity in the central and peripheral nervous systems. In mammals, there are four classical types of NTs including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3, and NT-4. Among them, BDNF is the most studied because of its high expression in the brain. BDNF participates in many biological activities by binding to its high affinity TrkB receptor (Numakawa et al., 2018). However, several NTs including BDNF and their receptors (particularly TrkB) have been demonstrated to be expressed in non-neuronal tissues, including lung, heart, liver and kidney, etc. More and more attention has been paid to the relationship between BDNF/TrkB and organ/tissue fibrosis. Hence, we summarize current knowledge of modulators of the BDNF/TrkB pathway and their regulation in organ and tissue fibrosis (list in Table 1).

Regulators of BDNF/TrkB

Agonist and antagonist of TrkB

Many compounds were screened from the natural library and some of them have been demonstrated as selective agonists of TrkB receptor, including 7,8-dihydroxyflavone (7,8-DHF), 7,8,3-trihydroxyflavone (7,8,3-THF), deoxygedunin, LM22A-4, demethylasterriquinone B1 (DMAQ-B1), amitriptyline, and deprenyl. Among them, 7,8-DHF has been most commonly used in about two hundreds preclinical studies as a BDNF mimetic and TrkB agonist (Emili et al., 2020). A large number of studies have documented that 7,8-DHF has good performance in many BDNF-implicated human disorders such as Parkinson's disease (Sconce et al., 2015), Alzheimer's disease (Chen et al., 2018), traumatic brain injury (Wu et al., 2014), and obesity (Chan et al., 2015). The promising roles of 7,8-DHF in body and brain disorders have been discussed lately (Emili et al., 2020; Paul et al., 2021). In contrast, although 7,8,3-THF has 2–3 times higher potency for stimulating TrkB phosphorylation than 7,8-DHF, only a few studies focused on the pharmacological role of 7,8,3-THF. In detail, Shi and Luo uncovered that 7,8,3-THF had a profound neuroprotective effect on neuronal growth, as well as protecting against local anesthetic-induced neurotoxicity in spinal cord dorsal root ganglion (DRG) neurons. They demonstrated that 7,8,3-THF promoted neurite growth in neonatal DRG neuron culture in a concentration-dependent manner (Shi and Luo, 2016). Yu et al. found that 7,8,3-THF protected spiral ganglion neurons from degeneration (Yu et al., 2012, 2013). Another study reported that 7,8,3-THF mitigated retinal oxidative stress and promoted retinal ganglion cell growth (Han et al., 2018). However, BDNF was found to be more effective than 7,8,3-THF in preserving the auditory nerve in deafened guinea pigs (Vink et al., 2020). Theoretically, 7,8,3-THF has more potent effects than BDNF because it has better pharmacokinetic and pharmacodynamic properties. However, Vink et al. reported no protective role in preserving the auditory nerve in deafened guinea pigs (Vink et al., 2020), which is in contrast to previous studies (Yu et al., 2013). By comparing these studies, we speculated that the difference may be associated with methodology such as the delivery method and diffusion of 7,8,3-THF.

Deoxygedunin was reported to have potent neurotrophic activity (Jang et al., 2010). It was able to promote axon regeneration in cut peripheral nerves (English et al., 2013), and protect nigrostriatal

Table 1. Relationship between BDNF/TrkB and organ/tissue fibrosis.

Organ/ Tissue	BDNF Expression	Effects	Mechanisms	References
Pulmonary	Increased	BDNF/TrkB promoted lung fibrosis	Promoted epithelial to mesenchymal transition and activated Twist-Snail axis	Chaudhuri et al., 2005; Cherubini et al., 2017; Smit et al., 2009
Airway	Increased	Lead to airway fibrosis and allergic airway inflammation in asthma	Participated in ECM composition and regulated airway hyper-responsiveness	Freeman et al., 2017; Britt et al., 2019
Liver	Increased	Decreased hepatic elasticity and protected against diet-induced NASH	Activated the mechanisms of catabolism and inhibited gluconeogenesis by binding to hepatocytes and reduced membrane TrkB-T1 protein	Girard et al., 2020; Shu et al., 2019; Xiong et al., 2020
Kidney	Decreased	Protected against diabetic renal fibrosis and renal dysfunction	Target of miR-365	Zhao et al., 2021
Heart	Decreased	Decreased BDNF is associated with cardiac interstitial and perivascular fibrosis	Regulated cardiomyocyte apoptosis, NO production, and oxidative stress	Agrimi et al., 2019; Zeng et al., 2017; Sefidgari-Abrasi et al., 2021
Bladder	Increased	Promoted the activation of astrocytes and microglias and aggravated neuro-inflammation and mechanical pain in cyclophosphamide-induced cystitis	Regulated p38/JNK pathway	Ding et al., 2020
Skin	Not available	Promoted angiogenesis; stimulated dermal fibroblast contraction; attenuated TNF-α-induced skin aging	By a direct effect on endothelial cells, inhibiting oxidative stress and MAPKs/Akt pathways	Blais et al., 2013; Palazzo et al., 2012; Choi et al., 2017

dopaminergic neurons against 6-OHDA and MPTP-induced neurotoxicity in rodents (Nie et al., 2015). In addition, Nguyen et al. reported that LM22A-4 exerts its effects via indirect transactivation of Trk receptors (Nguyen et al., 2019). Lately, another TrkB agonist, LMDS-1, was uncovered to have better effects than 7,8-DHF in Alzheimer's disease (Fan et al., 2020).

However, there are also contradictory results found in the literature. Studies reported that current available small-molecule TrkB agonists including 7,8-DHF, deoxygedunin, LM22A-4, demethylasterriquinone B1 (DMAQ-B1), amitriptyline, and deprenyl were unable to activated TrkB in a cell assay (Boltaev et al., 2017). In this study, neither 7,8-DHF nor LM22A-4 induced dose-dependent Akt or extracellular regulated protein kinases (ERK) activation in cortical neurons. It was proposed that the discrepancies may result from the methodological nature. Previous studies mainly used Western blot to detect protein levels of phosphorylation of TrkB and downstream Akt or ERK signals. In contrast, quantitative ELISA assay was used in studies by Boltaev et al. Therefore, more solid evidence is needed to confirm whether these small-molecule agonists are suitable for investigating effects and mechanisms of BDNF/TrkB axis. It is well recognized that several TrkB agonists have been discovered, however, their levels of efficacy are not consistent. Sometime they show different pharmacological effects. This phenomenon is probably due to the selectivity of TrkB and regulatory mechanisms of these compounds. For example, amitriptyline is a selective agonist of TrkB which directly binds TrkA and TrkB and triggers their dimerization and activation (Jang et al., 2009; Zhang et al., 2020). Moreover, deprenyl, a selective monoamine oxidase B (MAO-B) inhibitor, activated TrkB and downstream PI3K signals. However, it should be pointed out that the phosphorylation of TrkB by deprenyl is observed later than that by BDNF, and the mechanism of TrkB activation by deprenyl is different from that by BDNF (Nakaso et al., 2006). Taken together, the specificity and mechamisms are main factors determining the different pharmacological performance of these agonists. Moreover, a fully human agonist antibody to TrkB (ZEB85) was synthesized to mimic BDNF function with better biophysical properties. They used a function-based cell screening approach to select activated antibodies of TrkB receptor from a combined human short-chain variable fragment antibody library (Merkouris et al., 2018). Lately, the efficacy of another TrkB agonistic antibody AS86 in Alzheimer's disease has been demonstrated (Wang et al., 2020). There new progresses may provide new tools for activating TrkB receptor.

In previous studies, cyclotraxin-B was firstly employed as a highly potent TrkB inhibitor (Cazorla et al., 2010). Nowadays, the widely used antagonists of TrkB receptor are ANA-12 and K252a. ANA-12 directly and selectively binds to TrkB and inhibited downstream signals of TrkB without affecting TrkA and TrkC functions. Moreover, ANA-12 has been suggested to produce both anti-anxiety and anti-depression effects (Cazorla et al., 2011). Additionally, K252a is another widely used selective antagonist of TrkB receptor (Hashikawa et al., 2017). However, K252a inhibited not only TrkB but also TrkA (Dai et al., 2017). Better specific antagonists for TrkB are still anticipated for investigating the specific role of the BDNF/TrkB pathway in future studies.

Noncoding RNAs related to BDNF

As we all know, non-coding RNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) play vital roles in cardiac development and the pathogenesis of cardiovascular diseases (Ooi and Bernardo, 2020). The relationship between BDNF and miRNAs in neurodegenerative diseases and ischemic stroke has been summarized recently (Eyileten et al., 2021). A group of miRNAs have been uncovered related to BDNF in cardiac diseases such as miR-1, -376b-5p, -18a, -124, -195. BDNF is a known target of miR-1. For example, Brandenburger et al. claimed that there is a strong interaction between miR-1 and the 3'UTR of BDNF by luciferase assay, which negatively regulated BDNF protein levels (Brandenburger et al., 2014). Moreover, it was reported that cardiac over-expression of miR-1 caused behavioral abnormalities by inhibiting BDNF protein expression in the hippocampus (Ma et al., 2015). MiR-376b-5p was another upstream regulator of BDNF, which was significantly increased in ischemic myocardium and downregulation of miR-376b-5p leading to an increment of its target protein expression of BDNF (Pan et al., 2012). Increased miR-18a together with decreased BDNF was found in MI, inhibition of miR-18a alleviated MI injury by targeting BDNF (Lin et al., 2019). In contrast, BDNF also regulated miRNA expression. Descamps et al. found that BDNF promoted embryonic stem cell-endothelial differentiation acting by upregulating miR-214 (Descamps et al., 2018). Our previous study found that BDNF inhibited miR-195 expression in ischemic cardiomyocytes (Hang et al., 2016). Another previous study reported that miR-10b, miR-155, and miR-191 are also regulators of BDNF (Varendi et al., 2014). Hippocampus miR-191a-5p negatively regulates BDNF expression and is associated with cognitive impairment caused by paradoxical sleep deprivation (Mohammadipoor-Ghasemabad et al., 2019). Even so, no direct evidence was acquired between BDNF and miRNAs in cardiac fibrosis. Therefore, it is interesting to further clarify the reciprocal regulation between fibrosis-associated miRNAs and BDNF.

LncRNA MALAT1 increased BDNF expression and promoted proliferation and migration of Schwann cells by sponging miR-129-5p. At the same time, blocking BDNF reversed the effect of MALAT1 overexpression on Schwann cell proliferation and migration (Wu et al., 2020). Similarly, another lncRNA BC083743 promoted

Schwann cell proliferation and the axon regeneration after sciatic nerve compression via miR-103-3p/BDNF (Gao et al., 2020). LncRNA MIR155HG protected chronic unpredictable mild stress-induced depression mice by regulating the miR-155/BDNF axis (Huan et al., 2021). Besides, a recent study found that lncRNA KCNQ1OT1 inhibited ketamine-induced neural injury by regulating miR-206/BDNF axis (Yao et al., 2020).

Except the abovementioned lncRNAs, BDNF antisense RNA (BDNF-AS, also known as BDNF-OS) is also a lncRNA, which was originally discovered as a naturally occurring RNA antisense against BDNF. BDNF-AS was expressed in various cell types including neurons, cancer cells, and cardiomyocytes, which functioned inversely as BDNF. The majority of previous studies focused on the role of BDNF-AS in neurons and cancer. Studies suggested that BDNF-AS was dysregulated and closely associated with neuronal disorders and various types of cancer. In detail, in an *in vitro* DRG neurotoxicity model established by local anesthetic, bupivacaine, BDNF-AS was significantly upregulated in a dose- and time-dependent manner. In DRG neurons, siRNA-mediated downregulation of BDNF-AS promoted the growth of neuronal processes and reduced neuronal apoptosis (Zhang et al., 2016). Similarly, BDNF-AS was significantly increased by oxygen and glucose deprivation (OGD) exposure in retinal ganglion cells (RGCs). BDNF-AS promoted ischemic injury of RGCs by suppressing BDNF and that inhibition of BDNF-AS attenuated ischemic injury (Xu et al., 2016). The expression of BDNF-AS was significantly increased in an acute spinal cord injury rat model and hypoxia cellular model. BDNF-AS acted as a competitive endogenous RNA. Downregulation of BDNF-AS significantly reduced neuronal apoptosis by targeting the miR-130b-5p/PRDM5 axis (Zhang et al., 2018a). In addition, BDNF-AS level was found significantly decreased in several cancer cells including cervical cancer (Zhang et al., 2018b), prostate cancer (Li et al., 2018), oesophageal cancer (Zhao et al., 2018), non-small lung cancer (Shen et al., 2017) and retinoblastoma (Shang et al., 2018). Meanwhile, low BDNF-AS level was suggested to be correlated with shorter overall survival among cancer patients. Overexpression of BDNF-AS produced anti-cancer actions on proliferation and migration. In contrast, the relationship between BDNF-AS and cardiomyocytes is largely unknown. A recent study by Zhao et al reported that inhibition of lncRNA BDNF-AS rescues cell death and apoptosis of murine cardiomyocyte subjected to hypoxia/reoxygenation injury (Zhao et al., 2017). Nevertheless, *in vivo* evidence and concrete mechanisms of BDNF-AS in cardiac function remain to be elucidated. Based on the above findings, the following questions are waiting to be answered. First, whether BDNF-AS has a functional role in organ fibrosis. Second, if BDNF-AS has potential impact on organ fibrosis, what is the performance after being treated with BDNF agonists/antagonists? Third, whether circulating BDNF-AS is associated with the progression of organ fibrosis, and could be used as a novel early warning biomarker. Much work needs to be done to clarify these issues.

Furthermore, recent studies uncovered several circRNAs associated with BDNF. For instance, circRNA DLGAP4 (circDLGAP4) produced neuroprotective effects against Parkinson's disease by targeting the miR-134-5p/CREB pathway, thereby influence the expression of CREB and its target gene BDNF (Feng et al., 2020). Another study reported that circHIPK3 promoted non-small-cell lung cancer progression by targeting the miR-107/BDNF pathway (Hong et al., 2020). Another recent study reported the role of circRIMS2 in vascular cognitive impairment (VCI) by regulating BDNF. They found that the serum expression of circriMS2 and BDNF was markedly reduced in patients with VCI, whereas the expression of miR-186 was increased. Aerobic exercise improved VCI and inhibited neuronal apoptosis by the circRIMS2/miR-186/BDNF pathway (Niu et al., 2021).

As we know, many studies suggest that circRNA and lncRNA are potential biomarkers for the diagnosis and evaluation of treatment in diseases. As mentioned in the review, several studies have found that circRNA might influence the progression of different diseases by regulating BDNF. Meanwhile, serum BDNF was used as relatively reliable evidence to evaluate the clinical utility and potential function of circRNAs (Shi et al., 2021). LncRNAs have similar effects to cirRNAs, moreover, lncRNA is also regulated by BDNF. It was suggested that lncRNAs might be an important regulator of gene expression cascade triggered by BDNF (Aliperti and Donizetti, 2016). Of course, the reciprocal regulation mechanisms of lncRNA/circRNA and BDNF need further investigation.

BDNF polymorphism

The BDNF gene is localized on chromosome 11 band p13 (Maisonpierre et al., 1991), which comprises 11 exons and 9 functional promoters (Pruunsild et al., 2007). The BDNF gene has several polymorphism sites, such as C270T (rs56164415), Val66Met, and rs2030324 etc (Toh et al., 2018). Among them, Val66Met is one of the most studied. Many studies have documented that Val66Met polymorphism is closely associated with many neurodegenerative disorders including depression, schizophrenia, epilepsy, and Parkinson disease (Hwang et al., 2006; Altmann et al., 2016; Skibinska et al., 2018; Sidhu et al., 2019). Furthermore, it has been concluded that BDNF polymorphism is a novel potential diagnostic and therapeutic target of these diseases (Shen et al., 2018). However, the relationship between BDNF polymorphism and organ/tissue fibrosis remain unclear.

Mechanism of fibrosis

Organ failure caused by fibrosis of solid organs such as heart, liver, lung and kidney is the leading cause of

disability and death in patients. Fibrosis is not a disease, but a result of tissue repair response, which becomes maladjusted after many types of tissue injury, especially during chronic inflammatory diseases. In the early stages of the disease, inflammation and vascular changes, as well as an increase in reactive oxygen species, play a key role. After inflammation subsides, fibrosis and scarring are formed in the later stage (Ramming et al., 2015). The formation of fibrotic tissue is determined by the excessive accumulation of ECM components such as collagen and fibronectin, which is actually a normal and important stage in the repair of all organs (Wynn and Ramalingam, 2012). Pro-fibrotic factors includes, angiotensin type II (Ang II), platelet derived grow factor (PDGF) and connective tissue grow factor (CTGF), etc. When a tissue is injured, local tissue fibroblasts are activated, and their contractile capacity, secretion of inflammatory mediators and synthesis of ECM components are increased. Together, these changes initiate a wound-healing response. Nowadays, it is well recognized that fibrosis is a double-edged sword. Schematically, fibrosis includes reparative fibrosis and reactive fibrosis according to different pathogenic mechanisms. On the one hand, wound healing is effective when the injury is minor or non-repetitive, resulting in only a transient increase in the deposition of ECM components, which promotes the repair of functional tissue structure. However, on the other hand, when the injury is repetitive or severe, the ECM component continues to accumulate, which can lead to tissue structure destruction, organ dysfunction, and ultimately organ failure (Henderson et al., 2020). Recent studies have shown that mitochondrial function and cellular metabolism are novel key therapeutic targets of fibrosis in many organ types. In addition, some pathways, such as TGF-β, are metabolic regulators. Thus, reversal of metabolic changes has emerged as a promising strategy to reduce fibrosis (Gibb et al., 2020; Zhao et al., 2020).

BDNF/TrkB and fibrosis in the respiratory system

BDNF/TrkB and lung fibrosis

Emerging evidence implicates NT signaling pathways in both physiology and pathological processes of lungs. Early studies examined BDNF concentrations in sputa and found it was elevated in IPF patients. In contrast, BDNF was not elevated in induced sputum or serum of subjects with chronic persistent cough (Chaudhuri et al., 2005). It was demonstrated that the activation of the BDNF/TrkB signaling pathway participated in epithelial to mesenchymal transition (EMT) in primary fibroblasts isolated from IPF lung (Cherubini et al., 2017). They proposed that inhibition of BDNF/TrkB axis might prevent EMT-dependent lung fibrosis (Cherubini et al., 2017). Besides, TrkB signaling was found to activate a Twist-Snail axis, which is critically involved in EMT-like transformation, tumorigenesis, and metastasis (Smit et al., 2009). Moreover, NT4/5 was found to enhance the proliferation of alveolar Type II cells and promote the proliferation of primary human and murine lung fibroblasts, through TrkB and protein kinase B-dependent pathways (Avcuoglu et al., 2011). It is widely accepted that pulmonary hypertension (PH) often complicates the course of pulmonary fibrosis. In the pulmonary fibrosis patients, the development of PH secondary to pulmonary fibrosis is a leading determinant of mortality (Ruffenach et al., 2020). Therefore, there might be a casual relationship between BDNF/TrkB and PH. It was found that expressions of BDNF and TrkB were dramatically increased in both hypoxic mouse lungs, and arteries of patients suffering from idiopathic pulmonary arterial hypertension. They also found that BDNF/TrkB promoted proliferation of pulmonary arterial smooth muscle cells by activating ERK and early growth response factor 1 (Kwapiszewska et al., 2012). Similarly, another study found that enhanced BDNF/TrkB signaling increased survival and proliferation of pulmonary artery smooth muscle cells and reduced apoptosis after hypoxia. In addition, human pulmonary artery endothelial cells regulate the expression and secretion of BDNF through hypoxia-inducible factor 1 pathway in response to hypoxia (Helan et al., 2014). Therefore, the BDNF/TrkB pathway may play an important role in the pathogenesis of hypoxia-induced pulmonary vascular disease (Hartman et al., 2015).

BDNF/TrkB and pulmonary tuberculosis

Tuberculosis is associated with significant increases in the synthesis of inflammatory and anti-inflammatory cytokines in discrete brain regions such as hypothalamus, hippocampal formation, and cerebellum, accompanied by significant changes in the synthesis of neurotransmitters. In addition, as the infection progressed, histopathology revealed neurodegeneration and neuronal death, p38, JNK activation, and decreased BDNF levels (Lara-Espinosa et al., 2020).

BDNF/TrkB and airway fibrosis

There is now increasing evidence that airway smooth muscle (ASM) is a significant source of NTs including BDNF. It was found that ASM-derived BDNF is a factor in the composition of ECM protein and its dysregulation leading to airway fibrosis in asthma. Exogenous BDNF significantly increased ECM production and deposition, characterized by increasing collagen-I/-III expression and the activity of matrix metalloproteinases (Freeman et al., 2017). Furthermore, it was reported that smooth muscle-specific deletion of BDNF reduced airway hyperresponsiveness and blunted airway fibrosis but did not significantly alter airway inflammation (Britt et al., 2019). Nevertheless, the

sources, targets and mechanisms of BDNF in airway fibrosis are still under investigation.

BDNF/TrkB and cystic fibrosis

Cystic fibrosis (CF) is a progressive genetic disease that causes persistent lung infections and limits the ability to breathe over time. CF is involved in chronic inflammation and decreased pulmonary function, which increases caloric demand. Studies have assessed the concentrations of BDNF, neuropeptide Y (NPY) and leptin in CF patients to explore the potential clinical correlates. They found that BDNF/NPY ratio was associated with leptin, and BDNF/leptin ratio was correlated with NPY (Nowak et al., 2020).

BDNF/TrkB and hepatic fibrosis

In an early study, both mRNA and protein expression of TrkB were found to express in mouse liver and play critical roles in maintaining the innervation and the hepatic haematopoietic function (Garcia-Suarez et al., 2006). The expression of BDNF and TrkB receptor in liver of rats suffering from bile duct ligation was related to bile duct proliferation, suggesting that BDNF plays a role in bile duct remodeling during cholestasis (Vivacqua et al., 2014). Recently, several studies documented that BDNF is associated with addiction and withdraw of alcohol. It was proposed that BDNF levels were correlated to liver stiffness values according to fibrosis risk categories in alcohol use disorder (Girard et al., 2020). Shu et al. focused on the association of serum BDNF level and its gene polymorphism with liver function classification in patients with hepatitis B virus (HBV)-induced liver cirrhosis. They found that AA genotype at rs6265 of BDNF gene is a negative factor for liver cirrhosis, meanwhile serum BDNF plays a key role in the grading and early diagnosis of liver function in patients with HBV-induced liver cirrhosis (Shu et al., 2019). Another study found that the lack of heterogeneous nuclear ribonucleoprotein U stimulated the expression of a truncated subtype of TrkB (TrkB-T1), which promoted inflammatory signaling and stress-induced cell death in hepatocytes. BDNF treatment protected against diet-induced nonalcoholic steatohepatitis by reducing membrane TrkB-T1 protein (Xiong et al., 2020).

BDNF/TrkB and renal fibrosis

To date, only a few studies have focused on the role of BDNF in kidney function. A previous *in vitro* study suggested that BDNF/TrkB dependently up-regulated actin polymerization in podocytes by regulating miR-132/134. They found that BDNF mediated TrkB activation has a stabilizing effect on podocyte homeostasis and has a rescue effect in different podocyte injury models (Li et al., 2015). Besides, another study demonstrated that BDNF was essential for the development, morphology, and function of glomeruli. The expression of BDNF and KIM-1 is highly correlated in the urine cells of chronic kidney disease (CKD) patients, which is a potential biomarker of CKD (Endlich et al., 2018). In a very recent study, it was found that protein expression of BDNF was inhibited in a diabetic nephropathy model. Meanwhile, miR-365 aggravated renal fibrosis and inflammation of by targeting the BDNF/TrkB signal axis, which suggested an association between BDNF/TrkB and renal fibrosis (Zhao et al., 2021). However, the role of BDNF/TrkB in other renal fibrotic models remains unclear. In addition, because BDNF is the target of many miRNAs, whether these miRNAs have similar effects on renal function is unknown.

BDNF/TrkB and cardiac fibrosis

A recent study observed that the combination of psychosocial stress and obesity induced cardiac apoptosis and fibrosis as well as hippocampal dysfunction and decreased BDNF and TrkB levels in both the hippocampus and myocardium (Agrimi et al., 2019). Moreover, in a cecal ligation and puncture-induced septic rat model, cardiac BDNF was reduced along with impaired cardiac function, increased cardiac fibrosis, elevated cardiomyocyte apoptosis, reduced NO production, and increased oxidative stress (Zeng et al., 2017). Lately, studies have uncovered that concurrent administration of L. plantarum and inulin significantly increased BDNF and TrkB levels and inhibited cardiac interstitial and perivascular fibrosis in diabetic rats (Sefidgari-Abrasi et al., 2021). Nevertheless, the direct effects of BDNF/TrkB on cardiac fibrosis remain not fully understood. In particular, the potential role of BDNF/TrkB in cardiac fibroblasts as well as crosstalk with other cell types such as cardiomyocytes after different pathological stimuli is worth investigating in future studies.

BDNF/TrkB and bladder fibrosis

Chronic cystitis causes bladder fibrosis and severely affects the patients' quality of life. The upregulation of the NTs and fibrosis factor TGF-β were significantly associated with clinical symptoms, including bladder volume and pain. Causal relationship was found between NTS and TGF-β in the pathogenesis of severe ketamine-associated cystitis (KC), leading to bladder hypersensitivity and fibrosis in patients with severe KC (Jhang et al., 2019). It was suggested that BDNF promoted the activation of astrocytes and microglias through the TrkB-p38/JNK signaling pathway, and aggravate neuroinflammation and mechanical pain in cystitis induced by cyclophosphamide. Meanwhile, antagonizing TrkB receptors by ANA-12 could attenuate mechanical allodynia, restrain activation of astrocytes and microglia and alleviate neuroinflammation (Ding et al., 2020).

BDNF/TrkB and skin fibrosis

In an early study, BDNF together with other NTs including NGF, NT-3, and GDNF were found to be expressed in the epidermis. In addition, they found that NTs might participate in the regulation of skin microvasculature through the release and promoted angiogenesis by a direct effect on endothelial cells. In this study, BDNF was expressed by human umbilical vein endothelial cells but not in fibroblasts (Blais et al., 2013). In contrast, further studies reported that dermal fibroblasts and dermal myofibroblasts synthesized and released all NTs and expressed both the high affinity receptors, TrkA, TrkB, and TrkC, and the low affinity receptor p75NTR. Meanwhile, BDNF was suggested to stimulate dermal fibroblast contraction *in vitro* (Palazzo et al., 2012). Besides, BDNF mimetic 7,8-DHF attenuated TNF-α-induced skin aging by inhibiting oxidative stress and MAPKs/Akt pathways (Choi et al., 2017). Nevertheless, whether the above role of 7,8-DHF was TrkB dependent remains elusive.

Conclusions and future directions

Current findings suggest that the BDNF/TrkB pathway plays an important role in several fibrotic processes (summarized in Fig. 1). Importantly, it should be seriously considered that activation or inhibition of the BDNF/TrkB pathway may even play opposing roles in different organs. However, the concrete mechanism of this difference is not fully understood. We speculate the following points might be considered. First, the expression of BDNF/TrkB in fibrosis is inconsistent in different organs. For example, BDNF expression was decreased in diabetic renal fibrosis but highly expressed in IPF. Second, diverse downstream signals are regulated by BDNF/TrkB in different organs, which may affect the fibrotic signaling network. Third, the regulators of BDNF/TrkB (eg. miRNA, lncRNA, cicrRNA) also affected its activity in fibrotic disorders. So, how to specifically control BDNF/TrkB in certain target organ is very important. Meanwhile, more studies are necessary to validate the potential role of BDNF/TrkB in fibrosis of other organs or tissues, which could fully uncover the regulatory map of BDNF/TrkB. It should also focus on the potential adverse effects (for example in the myocardium and kidney) when treating lung fibrosis by inhibiting the BDNF/TrkB pathway. Small molecule compounds such as 7,8-DHF, 7,8,3-THF and non-coding RNAs could be investigated to fully clarify the regulatory network governed by BDNF. We noticed that novel low molecule BDNF mimetic named GSB-106 was synthesized in very recent studies (Gudasheva et al., 2021). In summary, targeting BDNF/TrkB may be a promising therapeutic strategy for the treatment of organ and tissue fibrosis, but more research in this field is needed in order to pave the way towards the delivery of effective antifibrotic therapies in clincal treatment.

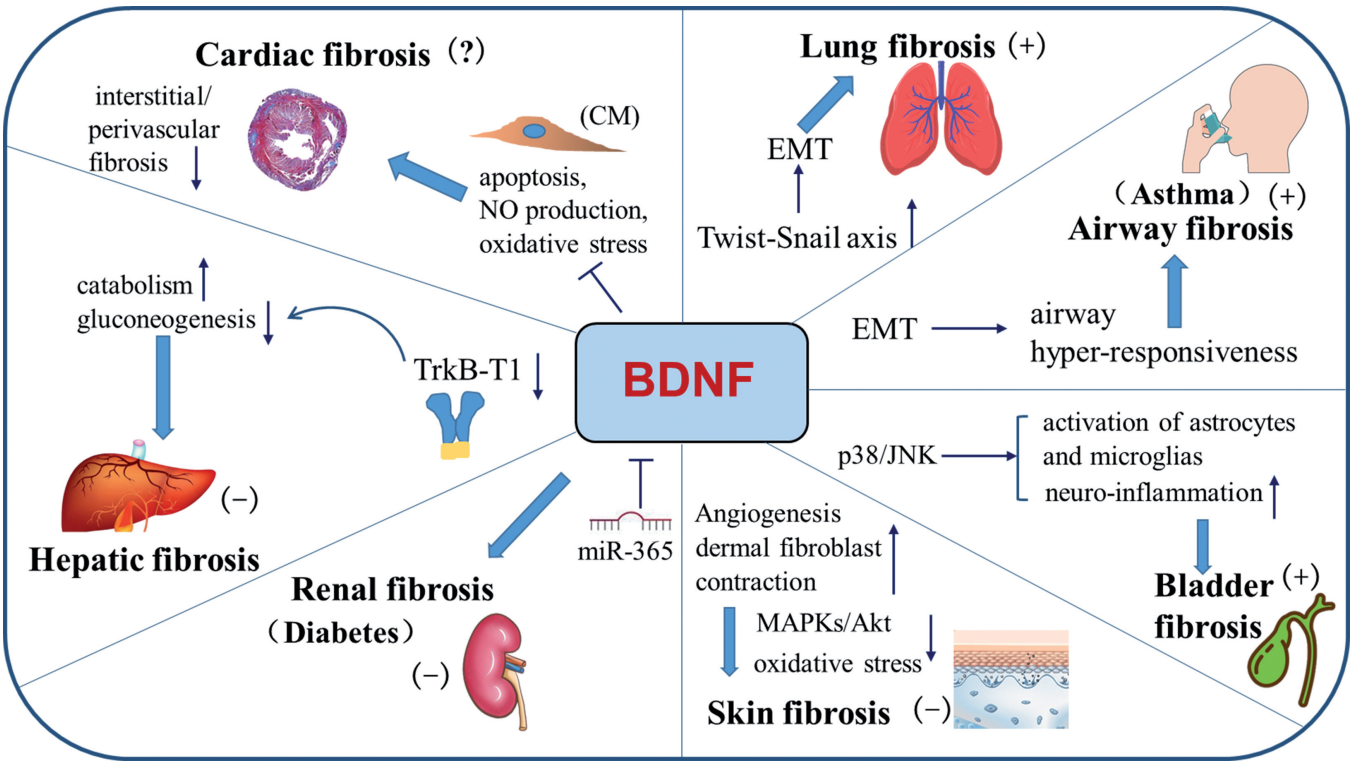

Fig. 1. Schematic diagram of BDNF/TrkB pathway in organ and tissue fibrosis. (+) indicates promoting fibrosis; (-) indicates inhibiting fibrosis.

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