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News and reviews

Substance P and fibrotic diseases

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ABSTRACT

Substance P (SP) is an undecapeptide encoding the *tachykinin 1 (TAC1)* gene and belongs to the tachykinin family. SP is widely distributed in the central nervous system and the peripheral nervous system. SP is also produced by nonneuronal cells, such as inflammatory cells and endothelial cells. The biological activities of SP are mainly regulated through the high-affinity neurokinin 1 receptor (NK-1R). The SP/NK-1R system plays an important role in the molecular bases of many human pathophysiologic processes, such as pain, infectious and inflammatory diseases, and cancer. In addition, this system has been implicated in fibrotic diseases and processes such as wound healing, myocardial fibrosis, bowel fibrosis, myelofibrosis, renal fibrosis, and lung fibrosis. Recently, studies have shown that SP plays an important role in liver fibrosis and that NK-1R antagonists can inhibit the progression of fibrosis. NK-1R receptor antagonists could provide clinical solutions for fibrotic diseases. This review summarizes the structure and function of SP and its involvement in fibrotic diseases.

1. Introduction

Human fibrotic diseases constitute a major health problem worldwide because of the large number of patients, the unclear understanding of the pathogenesis of fibrotic processes, and the limited effective treatments. Fibrosis is the hallmark of many chronic inflammatory diseases and cancer, and it is a predictor of organ transplantation failure (Rockey et al., 2015; Eddy, 2014). The progression of fibrosis is a nonspecific final pathway following local inflammation and scarring. In chronic pathological fibrotic responses, connective tissue gradually replaces normal tissue, with uncontrolled deposition of ECM. In addition, the normal progress of ECM degradation is disturbed. This abnormal deposition and decreased degradation of the ECM promotes progression to fibrosis and, ultimately, to end-organ failure (Wynn and Ramalingam, 2012). Although fibrosis is becoming increasingly recognized as a major cause of morbidity and mortality in most chronic inflammatory diseases, few treatment strategies are available that specifically target the pathogenesis of fibrosis. Additionally, the underlying mechanisms of fibrosis are still largely unknown.

The neuropeptide SP has been linked to fibrosis. SP is an undecapeptide that is produced by neuronal and nonneuronal cells, including lymphocytes, macrophages, neutrophils, and dendritic cells. SP was first discovered in 1931 by von Euler and Gaddum (Gaddum, 1931). This newly discovered, water-soluble powder was isolated from the equine brain and intestine and named “substance P” (Gaddum and Schild, 1934). In the early 1970s, the pure form of SP was extracted from bovine hypothalamus, and the amino acid composition was determined (Leeman and Hammerschlag, 1967; Chang et al., 1971).

SP was one of the most extensively studied active substances during the half-century after its discovery. Recent studies have shown that SP plays an important role in fibrosis (Fig. 1). The focus of the current review is to highlight SP and its receptor NK-1R in fibrotic diseases. Our research group verified, for the first time, the involvement of SP in the pathogenesis of liver fibrosis (Peng et al., 2017).

2. Synthesis and receptors of SP

Mammalian SP is a member of the tachykinin family of neuropeptides and is encoded by the *TAC1* gene (Pennefather et al., 2004). In humans, the *TAC* genes consist of seven exons and encode SP, neurokinin A (NKA), neuropeptide K, and neuropeptide-γ (Krause et al., 1987; Nawa et al., 1983). *TAC1* encodes SP/NKA, and TAC3 encodes neurokinin B (NKB). The sequences that encode SP and NKA are contained in exon 3 and exon 6, respectively. Transcription of the TAC1 gene generates four distinct messenger ribonucleic acid (mRNA) isoforms: α, β, γ and δ. These four different types of isoforms differ only in the number of exons. Of the four mRNA isoforms, α and δ give rise to

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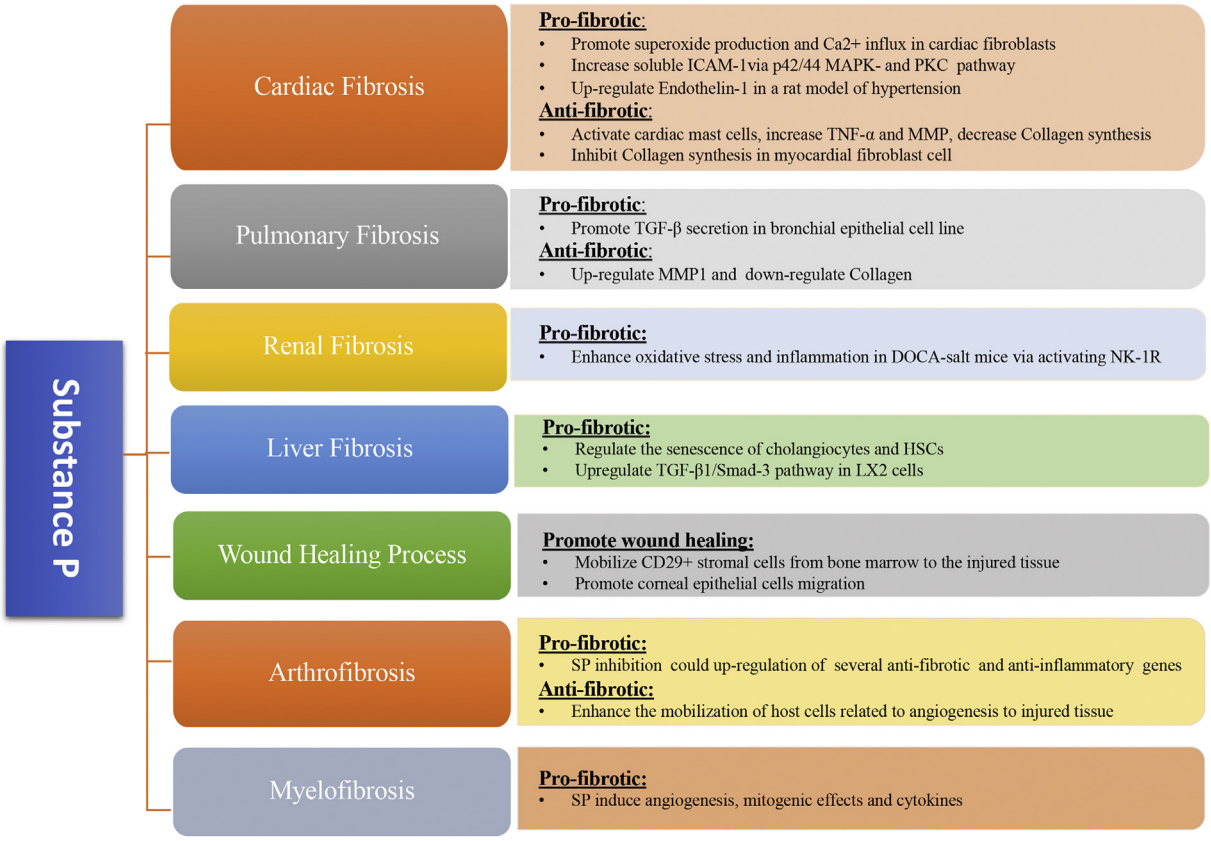

Fig. 1. Substance P and fibrotic diseases.

the SP peptide only, whereas β yields SP and the NKA peptide, and the δ transcript encodes SP, NKA, and neuropeptide-γ, indicating that SP can be expressed without NKA, but the synthesis of NKA is always accompanied by the synthesis of SP (Nawa et al., 1983). After synthesis, SP is packed into vesicles and transported to the central and peripheral endings of primary sensory neurons (Nakanishi, 1987). After release, the actions of tachykinins are terminated by diffusion away from the receptor site or degradation by extracellular peptidases, and the slow nature of these processes accounts for the prolonged effects of these peptides.

The biological actions of SP are mediated by neurokinin receptors, which belong to the rhodopsin-like family of G protein-coupled receptors (Maggi et al., 1993). There are three known types of NK receptors, NK-1R, NK-2R and NK-3R, and the binding affinity of NK-Rs to SP is in the order of NK-1R > NK-2R > NK-3R (Mantyh, 2002). It is obvious that SP binds preferentially to NK-1R. However, NKA and NKB exhibit higher affinity for NK-2R and NK-3R, respectively (Kerdelhué et al., 1997; Stahl, 1999). Stimulation of NK-1R leads to intracellular inositol 1,4,5-triphosphate (IP3) turnover with subsequent elevation of intracellular calcium, phospholipase A2 induces an increase in arachidonic acid mobilization (Garcia et al., 1994), and adenylyl cyclase induces cyclic adenosine monophosphate accumulation (Takeda et al., 1992). However, studies show that stimulation of NK-1R activates adenylyl cyclase, producing cyclic adenosine monophosphate, which activates the calcium ATPase, in turn reducing intracellular calcium levels and promoting the relaxation and dilation of vascular smooth muscle (Maggi, 1995). Further studies are required to clarify the underlying mechanism. It is worth noting that SP can modulate its own release via NK-1R, while NK-1R acts as an autoreceptor. Several studies have demonstrated that this regulation could have negative feedback characteristics due to the blockade of potassium channels or stimulatory effects via the production of IP3 (Harrison and Geppetti, 2001).

3. SP and cardiac fibrosis

In 1981, SP-positive nerve fibers were identified in both atrial and ventricular myocardium (Wharton et al., 1981). SP was also found in sensory nerves that project to coronary arteries and arterioles and in a small population of coronary endothelial cells (Wharton et al., 1981; Reinecke et al., 1980; Dalsgaard et al., 1986; Milner et al., 1989). This specialized localization was beneficial to the release of SP in response to changes in coronary pressure, flow and homeostasis.

SP plays an important role in cardiac fibrosis, where it promotes cardiac fibroblast proliferation through calcium and superoxide anion-mediated mechanisms (Kumaran and Shivakumar, 2002). In addition, SP enhances soluble intercellular cell adhesion molecule-1 release from adult rat cardiac fibroblasts by a p42/44 mitogen activated protein kinase- and protein kinase C-mediated mechanism (Sapna and Shivakumar, 2007). SP can also regulate adverse myocardial remodeling secondary to volume overload by activating cardiac mast cells, leading to increased tumor necrosis factor-α and matrix metalloproteinase activation, with subsequent degradation of the extracellular matrix (Meléndez et al., 2011). Moreover, the action of SP via NK-1R regulated adverse myocardial remodeling in a rat model of hypertension. The results also showed that an NK-1R antagonist effectively prevented the development of cardiac fibrosis (Dehlin et al., 2013). Interestingly, a recent study showed that SP can inhibit collagen synthesis by rat myocardial fibroblasts induced by angiotensin II. In addition, SP could dose-dependently block the progression of myocardial fibrosis, which was expected to be a promising target for the treatment of myocardial fibrosis (Yang et al., 2016). The reason for the different effects of SP on cardiac fibrosis may be that different concentrations of SP were used in the different cell or animal models. Further study should be performed to clarify these controversial outcomes.

4. SP and pulmonary fibrosis

Pulmonary fibrosis is characterized by parenchymal honeycombing, reduced lung compliance, and restricted lung function. The events that initiate pulmonary fibrosis are diverse and include infection, systemic sclerosis and sarcoidosis, and environmental exposure to substances such as silica dust or asbestos (Rockey et al., 2015).

In the lungs, SP is secreted from sensory airway nerves in response to different stimuli, such as allergens (Myers et al., 2002), tobacco smoke (Joad et al., 2004), and ozone exposure (Wu et al., 2003). In 1995, it was reported that SP and NKA can promote human lung fibroblast proliferation and chemotaxis in vitro (Harrison et al., 1995). Furthermore, increased levels of SP-like immunoreactive substances have also been found in bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis (IPF), indicating increased activity of SP-containing nerves. These studies reported that the concentration of SP-like immunoreactive substances is much higher in IPF patients than in healthy nonsmokers (Takeyama et al., 1996). Interestingly, a previous study demonstrated that inhaled SP can induce an enhanced cough response in normal subjects following upper respiratory tract infection (KATSUMATA et al., 1989). It is worth noting that pirfenidone, an antifibrotic drug with anti-inflammatory and antioxidant effects, dramatically decreased SP levels in IPF models (Okazaki et al., 2013). Another study showed that SP directly modulated the release of transforming growth factor-β (TGF-β) from human bronchial epithelial cell lines and that this promotive effect was completely inhibited by an NK-1R antagonist, indicating that SP plays a substantial role in inflammation and lung fibrosis (Yaraee and Ghazanfari, 2009). However, another study showed that SP upregulates matrix metalloproteinase-1 and downregulates collagen in human lung fibroblasts via its highest-affinity receptor, NK-1R, indicating that SP exhibits anti-fibrotic effects (Ramos et al., 2007). These opposing effects require further research.

5. SP and renal fibrosis

Renal fibrosis mostly occurs in association with a wide range of diseases from primary renal injury to systemic diseases (Liu, 2011; Kaissling et al., n.d.) and is a frequent final outcome of almost all progressive chronic kidney diseases. Renal fibrogenesis is considered a failed wound healing process that occurs after various kidney injuries (Renalfibrosis, 2006; Wynn, 2008). A wide range of cell types in the kidneys, including tubular epithelial cells, pericytes, fibroblasts, endothelial cells, vascular smooth muscle cells, mesangial cells and podocytes, as well as infiltrated cells such as lymphocytes and macrophages, are involved in the pathogenesis of renal fibrosis, which can explain the great complexity of this process (Liu, 2011; Wynn, 2008; Boor et al., 2010).

The kidneys and the cardiovascular system are innervated by sensory nerve terminals that contain various neuropeptides, such as calcitonin gene-related peptide (CGRP) and SP, which may play an important role in cardiovascular and renal function (Wimalawansa, 1996). It has been reported that plasma SP levels are significantly higher in deoxycorticosterone (DOCA)-salt–treated mice than in control mice. In addition, blockade of NK-1R attenuates the interstitial monocyte/macrophage infiltration, glomerulosclerosis and tubulointerstitial injury and fibrosis induced by DOCA-salt hypertension, suggesting that SP may contribute to DOCA-salt hypertension-induced renal injury by the activation of NK-1R in mice, leading to enhanced oxidative stress and inflammation in the kidneys (Wang and Wang, 2012).

6. SP and liver fibrosis

Liver fibrosis typically occurs in a wide range of chronic liver diseases, including alcoholic liver diseases, hepatitis B and C, cholestasis and drug-induced liver disease (Borkham-Kamphorst et al., 2014). Liver fibrosis is a reversible phase during the formation of liver cirrhosis and is defined as an increase in the levels of type I and type III collagens and the excessive deposition of extracellular matrix (ECM) in the liver parenchyma (Bataller and Brenner, 2005). Progressive liver fibrosis may result in cirrhosis, hepatic failure, and ultimately, death.

In the liver, multiple cell types, including hepatic stellate cells (HSCs), endothelial cells, bile duct cells, Kupffer cells and immune cells, can orchestrate the cellular and molecular response to different kinds of injury (Rockey, n.d.). However, HSCs are the principal hepatic fibrogenic cells in the production of ECM components, e.g., collagen, fibronectin and hyaluronic acid, in response to persistent liver injury (Lee and Friedman, 2010; Mederacke et al., 2013). Activation of HSCs in response to liver injury is recognized as a central event in the development of liver fibrosis. A number of cytokines and peptides, including interferon-γ (Rockey and Chung, 1994), hepatocyte growth factor (Ueki et al., 1999), interferon-α (Inagaki et al., 2003), adiponectin (Kamada et al., 2003), and stellate cell activation-associated protein, appear to have antiactivation or antifibrogenic effects on stellate cells (Kawada et al., 2001).

The liver is innervated by sympathetic, parasympathetic and peptidergic nerves, which contain both afferent and efferent fibers (Jensen et al., 2013). In 1991, SP nerve fibers were found around portal veins, bile ducts, and hepatic arteries in portal areas, as well as along sinusoids and hepatocytes. Interestingly, these SP-positive nerve endings were localized near HSCs, fibroblasts, myofibroblasts and sinusoids (Ueno et al., 1991). Ying and her colleagues confirmed that SP increases liver fibrosis by differential changes in the senescence of cholangiocytes and HSCs (Wan et al., 2017). These results demonstrated the regulatory effects of the SP/NK-1R axis on liver fibrosis through changes in cellular senescence during cholestatic liver injury. Our previous study also showed that SP can promote HSC proliferation and induce HSC activation via the TGF-β1/Smad3 signaling pathway (Peng et al., 2017). Liver sinusoidal endothelial cells are involved in hepatic regeneration by interacting with HSCs and hepatocytes in a paracrine manner. Dysfunction of endothelial cells could eventually induce the development of critical hepatic disease, including liver fibrosis. Recently, one study reported that SP promotes liver sinusoidal endothelium-mediated hepatic regeneration by regulating nitric oxide/hepatic growth factor, indicating that SP may inhibit liver fibrosis via increased hepatocyte activity (Piao et al., 2019). These contradictory results may relate to the disease course and the different concentrations of SP used in the experiments. Further studies should be performed to elucidate this phenomenon.

7. SP and corneal wound healing

The cornea is highly innervated with sensory nerves that produce several neuropeptides, including SP and CGRP (Müller et al., 2003). SP is reported to play an important role in corneal wound healing. Previous studies showed that SP is expressed in the corneal epithelium and stromal keratocytes and is distributed in corneal nerve endings as well as in tears (Jones and Marfurt, 1998; Yamada et al., 2002; Watanabe et al., 2002). It has been reported that SP increases the synthesis of interleukin-8 both in human corneal epithelial cells and in primary human keratocytes via NK-1R, indicating that SP contributes significantly to corneal wound healing (Tran et al., 2000; Słoniecka et al., 2016). Moreover, SP also promotes the diabetic corneal epithelial wound healing process through NK-1R (Yang et al., 2014). Importantly, studies demonstrated that SP could mobilize $CD29^+$ stromal cells from the bone marrow to the injured tissue and subsequently promote the wound healing process in an alkali burn model in rabbits (Hong et al., 2009). However, topical application of SP showed no effect on promoting the corneal wound healing process in the rabbit model (Kingsley and Marfurt, 1997). It is worth noting that the combined application of SP and insulin-like growth factor-1 (IGF-1) significantly accelerated the migration of corneal epithelial cells and their attachment to extracellular matrix proteins in an organ culture system of the rabbit cornea

(Mannis and Murphy, 1996). In addition, administration of eye drops containing both SP and IGF-1 was shown to promote corneal epithelial wound healing in rabbits (Nakamura et al., 1997). In summary, these studies show the beneficial effect of SP on the induction of corneal epithelial wound healing under experimental and clinical conditions.

8. SP and arthrofibrosis

Arthrofibrosis has been recognized as a complication of injury or trauma and is characterized by the excessive production of scar tissue in a joint (Sanders et al., 2017; Parvataneni et al., n.d.; Vezeridis et al., 2010; Donaldson et al., 2016). The current prevalence rate of this disease is estimated to be between 8% and 12% (Bong and Di Cesare, 2004). The main consequence of arthrofibrosis is the loss of range of motion because of the painful stiffness of proliferated scar tissue (Mohtadi et al., 1991). Multiple cells and cytokines are involved in the etiology of arthrofibrosis. Activation of fibroblast and myofibroblast cells induces the increased production of collagen VI (Zeichen et al., 1999), alpha smooth muscle actin (α-SMA) (Unterhauser et al., 2004) and β-catenin (Krenn et al., 2013), an important aspect of the beginning of arthrofibrosis. Like fibroblasts, profibrotic mast cells and T lymphocytes are also involved in the scarring process in arthrofibrosis (Bosch et al., 2001; Freeman et al., 2010). It has been reported that the proinflammatory cytokine interleukin-18 plays an important role in arthrofibrosis (Brown et al., 2010). In addition, TGF-β and VEGF were found to be associated with fibrosis (Bosch et al., 2001; Freeman et al., 2010). Although enormous progress has been made, the specific mechanisms of pain and scar formation in arthrofibrosis remain unclear.

SP has been considered an injury-inducible factor that is activated early in the wound healing process via regulating the mobilization of $CD29^{+}$ stromal-like cells (Hong et al., 2009). Similar studies also showed that SP plays an important role in immune cell recruitment and tissue regeneration (Kohara et al., 2010; Ko et al., 2012). Kim reported that combined systemic and local delivery of SP would prevent fibrosis and enhance the neovascularization of the injured tissue in a mouse hindlimb ischemia model (Kim et al., 2016). However, another study showed the controversial functions of SP in fibrosis. Then, the inhibition of SP was found to alter the expression of profibrotic genes in a joint contracture rabbit model (Morrey et al., 2017). Further studies should be performed to clarify the mechanism underlying these opposite outcomes of SP in arthrofibrosis.

9. SP and myelofibrosis

Myelofibrosis is an uncommon phenomenon associated with several hematologic disorders, particularly chronic myeloproliferative disorders. Myelofibrosis is characterized by fibrosis, hypercellularity, excessive deposits of extracellular matrix proteins, increased circulating levels of particular cytokines, and neoangiogenesis in the bone marrow (Tefferi, 1970; Barosi, 1999; Rameshwar et al., 1994a; Aguayo et al., 2000). The mechanism of myelofibrosis remains mostly undefined. Immune-mediated mechanisms in the development of myelofibrosis have been widely reported (Kaelin and Spivak, 1986; Colović et al., 2010; Hasselbalch et al., 2010). In addition, several types of cells, including monocytes/macrophages and megakaryocytes, play significant roles in the pathophysiology of myelofibrosis, suggesting that non-immune-mediated mechanisms are also operative (Rameshwar et al., 1994b; Reilly, 2010). Furthermore, some pathological features, such as neoangiogenesis, increased proliferation of fibroblasts, and in most cases, the type of clonal disorder (myeloid vs. lymphoid lineage) do not always depend on immune-mediated mechanisms. A better understanding of the underlying mechanisms requires analyses of the roles of immune cells and their contributions to the molecular aspects that lead to the pathophysiology of myelofibrosis. At present, it is unclear whether fibrosis is secondary to immune dysfunction or vice versa. However, in patients with autoimmune diseases and myelofibrosis, treatment with immunosuppressive therapy resulted in the reversal of fibrosis (Kaelin and Spivak, 1986).

SP, as a proinflammatory cytokine, has been demonstrated to play an important role in the pathophysiology of myelofibrosis. The SP level was increased in the blood of patients with myelofibrosis. Another study also showed that SP immunoreactivity was dramatically increased in the sera of patients with bone marrow fibrosis compared with that in the sera of patients with hematologic disorders but no histologic evidence of fibrosis(Rameshwar et al., 2001). Furthermore, SP promotes myelofibrosis via several mechanisms, such as the induction of angiogenesis, mitogenic effects on fibroblasts, and the induction of fibrogenic cytokines in immune and mesenchymal cells that could stimulate the proliferation of hematopoietic progenitors(Rameshwar, 1997; Fan et al., 1993; Rameshwar et al., 1993; Lotz et al., 1988; Rameshwar and Gascón, 1995). In addition, SP has been found to form a complex with fibronectin, which could protect SP and provide chemical stability to this small peptide(Rameshwar et al., 2001). This observation could provide insight into the development of myelofibrosis. Further evidence strengthening the association of SP with fibronectin is the increase in SP levels in the sera of patients with myelofibrosis (Rameshwar et al., 2001). The pathophysiology of myelofibrosis is complex, involving cellular and humoral interactions as well as the implication of extracellular matrix proteins. Therefore, further studies are required to show a cause-and-effect relationship between the pathophysiology of myelofibrosis and SP levels.

10. SP and other fibrotic diseases

The neuromuscular compartment of the inflamed colon was found to express increased levels of SP fibers. Studies also showed that SP is involved in the control of enteric motility and intercellular communication between myenteric neurons(Liu et al., 2002; Grider et al., 2010). It was found that NK-1R antagonists can reduce colonic inflammation, colonic fibrosis, fibroblast accumulation, and the expression levels of fibrogenic factors in a chronic mouse model of trinitrobenzenesulfonic acid (TNBS)-induced colitis(Koon et al., 2010). In addition, NK-1R knockout mice chronically exposed to TNBS had similar colonic inflammation to WT mice but exhibited reduced colonic fibrosis, fibroblast accumulation, and expression levels of fibrogenic factors. SP also promoted human colonic CCD-18Co fibroblast migration and stimulated collagen synthesis in CCD-18Co fibroblasts in vitro (Koon et al., 2010). Thus, SP, via NK-1R, promotes intestinal fibrogenesis after chronic colitis by stimulating fibrotic responses in fibroblasts(Koon et al., 2010; Sebastiano et al., 1999).

The development of hypertrophic scars is a devastating complication after a deep partial thickness cutaneous injury, such as a burn injury or abrasion. However, the pathophysiology of hypertrophic scar formation has not been fully identified. The clinical observations of increased itching in hypertrophic scars and histologic findings of increased numbers of nerves in hypertrophic scar samples (Zhang & Laato, n.d.; Zhi et al., 2004) indicate that the nervous system may play an important role in hypertrophic scar formation. It has been reported that the number of nerves is higher in hypertrophic scars than in normal scars(Crowe et al., 2010). Another study showed that hypertrophic scar tissue has increased levels of SP and decreased levels of neutral endopeptidase activity, indicating that inhibiting the activity of neutral endopeptidase may be a therapeutic target for regulating inflammatory responses in healing burn wounds and controlling hypertrophic scar formation.

11. Conclusion

SP is ubiquitous throughout the body. After binding to NK-1R, SP plays an important role in fibrotic diseases, including cardiac, pulmonary, renal, and liver fibrosis, arthrofibrosis and wound healing processes. Thus, a profound knowledge of these processes will be the

key to the in-depth understanding and, consequently, improved management of fibrotic diseases. We suggest therapeutic interventions using NK-1R antagonists in human pathologies in which the SP/NK-1R system is upregulated. Accordingly, in the future, the use of NK-1R antagonists should be tested clinically in these pathologies.

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