Des-Arg<sup>10</sup>-kallidin Engagement of the B1 Receptor Stimulates Type I Collagen Synthesis via Stabilization of Connective Tissue Growth Factor mRNA

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Expression of the kinin B1 receptor is up-regulated in chronic inflammatory and fibrotic disorders; however, little is known about its role in fibrogenesis. We examined human embryonic lung fibroblasts that constitutively express the B1 receptor and report that engagement of the B1 receptor by des-Arg<sup>10</sup>-kallidin stabilized connective tissue growth factor (CTGF) mRNA, stimulated an increase in α1(I) collagen mRNA, and stimulated type I collagen production. These events were not observed in B2 receptor-activated fibroblasts. In addition, B1 receptor activation by des-Arg<sup>10</sup>-kallidin induced a rise in cytosolic Ca<sup>2+</sup> that is consistent with B1 receptor pharmacology. Our results show that the des-Arg<sup>10</sup>-kallidin-stimulated increase in α1(I) collagen mRNA was time- and dose-dependent, with a peak response observed at 20 h with 100 nM des-Arg<sup>10</sup>-kallidin. The increase in CTGF mRNA was also time- and dose-dependent, with a peak response observed at 4 h with 100 nM des-Arg<sup>10</sup>-kallidin. The increase in CTGF mRNA was blocked by the B1 receptor antagonist des-Arg<sup>10</sup>-Leu<sup>9</sup>-kallidin. Inhibition of protein synthesis by cycloheximide did not block the des-Arg<sup>10</sup>-kallidin-induced increase in CTGF mRNA. These results suggest that engagement of the kinin B1 receptor contributes to fibrogenesis through increased expression of CTGF.

Kinins are involved in the regulation of a variety of physiological and cellular functions, including smooth muscle tone, pain perception, inflammation, and cellular proliferation (1, 2). Molecular biological and pharmacological studies have identified two G-protein-coupled kinin receptors, B1 and B2 (3–5). Activation of the B1 receptor induces cellular and physiological responses that often mimic the responses observed following activation of the B2 receptor. For instance, both receptors activate nuclear factor κB in fibroblasts (6), modulate vascular tone (7), and activate phospholipase C in mesangial cells (8). However, receptor-specific physiological responses induced by the kinin receptors are demonstrated in the kinin-mediated bronchoconstriction of asthmatic airways. The B2 receptor agonists bradykinin (BK) (9) and kallidin (Lys-BK) are potent bronchoconstrictors (9), whereas the B1 receptor agonist des-Arg<sup>10</sup>-kallidin does not induce bronchoconstriction (10).

The B2 receptor, the classical bradykinin receptor, is widely expressed and binds both BK and kallidin with high affinity. In wound repair, activation of the B2 receptor induces a variety of effects, including increased neutrophil proliferation, stimulation of macrophage spreading, release of histamine from mast cells, synthesis of platelet-activating factor and prostaglandins in endothelial cells, release of tachykinin and acetylcholine from sensory nerve endings, increased microvascular permeability, and fibroblast proliferation (2).

Early studies described the B1 receptor as an inducible receptor whose expression is up-regulated following exposure to interleukin-1β or other pro-inflammatory agents (11). A recent study has identified expression of the B1 receptor by immunohistochemistry in transbronchial biopsies from patients with sarcoidosis or progressive systemic sclerosis, whereas expression of the B1 receptor was undetectable in normal subjects (12). Activation of the B1 receptor induces relaxation or contraction of various smooth muscle cell preparations, mediates chronic pain, and may be involved in chronic inflammation (1). Recent studies have demonstrated the expression of the B1 receptor in apparently healthy renal (13), intestinal (14), ocular (15), stomach (16), and pulmonary (17) tissues; however, the role of the B1 receptor in homeostasis and wound repair is not understood. Activation of the B1 receptor stimulates proangiogenesis in fibroblasts, release of tumor necrosis factor α and interleukin-1β from macrophages, and prostaglandin and platelet-activating factor synthesis in endothelial cells (1).

Recently, it was proposed that TGF-β stimulates fibrogenesis and proliferation in fibroblasts via a mechanism that requires de novo synthesis of a secondary factor, which has been identified as connective tissue growth factor (CTGF) (18). CTGF, a member of the CCN family, is a cysteine-rich, heparin-binding, 349-amino acid protein (19). Other members of the CCN family include Fisp12/BIGM2 (mouse ortholog of CTGF) (20), Cyr61 (and the chick ortholog Cef10) (21), Nov (human and Xenopus orthologs) (22), Elm-1 (23), CTGF-L (24), and WISP-3 (25). CCN proteins possess a secretory signal peptide and four distinct protein modules: an insulin-like growth factor-binding domain, a von Willebrand factor type C repeat, a

The abbreviations used are: BK, bradykinin; TGF-β, transforming growth factor β; CTGF, connective tissue growth factor; TPA, 12-O-tetradecanoylphorbol-13-acetate; FBS, fetal bovine serum; DMEM, Dulbecco’s modified Eagle’s medium; MLEC, mink lung epithelial cell; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GM-CSF, granulocyte-macrophage colony-stimulating factor; CHX, cycloheximide.
thrombospondin type 1 repeat, and a C-terminal module. CTGF-L does not contain the C-terminal domain. The CCN family is further distinguished by the high degree of amino acid homology (50–90%) and conservation of 38 cysteine residues. TGF-β (but not epidermal growth factor, fibroblast growth factor, or platelet-derived growth factor) stimulates CTGF transcription in normal rat kidney fibroblasts (26). In adult mammals, CTGF is expressed in high levels during wound repair and at sites of connective tissue formation in a variety of fibrotic disorders (27, 28). CTGF is expressed in lung fibroblasts and has been suggested to play a role in the pathogenesis of lung fibrosis (29).

Our goal was to examine B1 receptor-induced fibrogenesis. Using a human embryonic lung fibroblast cell line, we report that des-Arg10-kallidin, upon binding to the B1 receptor, activates an increase in cytosolic Ca2+ with a different fluorescence signature using fura-2 than the B2 receptor and specifically induces dose- and time-dependent increases in α1(I) collagen mRNA and CTGF mRNA. The increase in steady-state CTGF mRNA levels involves stabilization of the message through a mechanism that is cycloheximide-insensitive and 12-O-tetradecanoylphorbol-13-acetate (TPA)-sensitive. The data suggest that the B1 receptor has a distinct function in the pathophysiology of fibrotic lung diseases.

MATERIALS AND METHODS

Tissue Culture—Human embryonic lung fibroblasts (IMR-90, Institute for Medical Research, Camden, NJ) were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 0.5 g/100 ml sodium bicarbonate, 10% (v/v) fetal bovine serum (FBS), 100 units/ml penicillin, 10 μg/ml streptomycin, 0.1 mm sodium pyruvate, and 0.1% nonessential amino acids. Cell numbers were determined by triplicate cell counts with an electronic particle counter (Coulter Counter ZM). Northern Blotting—Confluent IMR-90 fibroblast cultures were incubated in DMEM supplemented with 0.4% FBS for 24 h. The culture medium was supplemented with protease inhibitors (captopril (10 μM), phosphoramidon (1 μM), and N-2-mercaptoethyl-3-guanidinoethylthiopropanoic acid (1 μM)) and stimulated as indicated. Total cellular RNA was isolated by the single-step method employing guanidine thiocyanate/phenol/chloroform extraction as described by Chomczynski and Sacchi (30). RNA was quantified by absorbance at 260 nm. Purity was determined by absorbance at 280 and 310 nm. RNA (10 μg) was electrophoresed through a 6% formaldehyde-containing 1% agarose gel and blotted onto a nylon membrane. The filter was exposed to x-ray film for autoradiography at several different times to ensure that the bands could be visualized. The probe is a 1.5-kilobase pair fragment of rat α1(I) collagen cDNA that specifically hybridizes to α1(I) collagen mRNA. The CTGF probe is a 586-base pair polymerase chain reaction product generated with the forward primer ggctgatgtgacccgcg and the reverse primer acag-586-base pair polymerase chain reaction product generated with the forward primer ggctgatgtgacccgcg and the reverse primer acag-gag-3gacatgtgcagt-3

RESULTS

Embryonic human lung fibroblasts (IMR-90) constitutively express both the B1 and B2 receptors (36). Since activation of the B1 or B2 receptor activates phospholipase C and induces a rise in cytosolic Ca2+ in a number of cell types (37, 38), we monitored cytosolic Ca2+ levels in kinin-stimulated fibroblasts. To activate the B2 receptor, we employed BK or kallidin, both of which are nearly indistinguishable pharmacologically and physiologically. To activate the B1 receptor, we used des-Arg10-kallidin (39). We found that activation of the B1 receptor by des-Arg10-kallidin induced a dose-dependent increase in cytosolic Ca2+ in human lung fibroblasts (Fig. 1). Increases in cytosolic Ca2+ were detected at the threshold concentration of 1 nm des-Arg10-kallidin. The maximal increase in cytosolic Ca2+ induced by des-Arg10-kallidin was observed at 100 nm (EC50 = 1.9 nm; r2 = 0.9871). Activation of the B2 receptor induced an increase in cytosolic Ca2+ that was a dose-dependent (EC50 = 0.7 nm r2 = 0.9763) (data not shown). To examine the pharmacology of the kinin receptors, we monitored cytosolic Ca2+ concentrations in kinin-stimulated fibroblasts. In fibroblasts stimulated with the B1 receptor agonist des-Arg10-kallidin, the cytosolic Ca2+ increased gradually and returned to base-line levels (Fig. 2A). The B1 receptor antagonist des-Arg10,Leu9-kallidin did not induce an increase in cytosolic Ca2+.
Ca$^{2+}$, but did block the increase in cytosolic Ca$^{2+}$ stimulated by des-Arg$^{10}$-kallidin. However, the kallidin-stimulated increase in cytosolic Ca$^{2+}$ was not affected by des-Arg$^{10}$,Leu$^{9}$-kallidin (Fig. 2B). In fibroblasts stimulated with 1 nM kallidin, cytosolic Ca$^{2+}$ levels increased sharply and remained elevated (Fig. 2C). The B2 receptor-specific antagonist (HOE 140) did not stimulate an increase in cytosolic Ca$^{2+}$ or interfere with the Ca$^{2+}$ movement induced by des-Arg$^{10}$-kallidin. Conversely, the kallidin-stimulated increase in cytosolic Ca$^{2+}$ was blocked by 1 nM HOE 140 (Fig. 2D). We conclude that des-Arg$^{10}$-kallidin stimulates an increase in cytosolic Ca$^{2+}$ via exclusive engagement of the B1 receptor.

To study the effect of kinin receptor activation on the production of type I collagen, fibroblasts were stimulated with the B1 receptor agonist des-Arg$^{10}$-kallidin, the B2 receptor agonist BK, or TGF-β (Fig. 3). BK did not stimulate type I collagen production, whereas des-Arg$^{10}$-kallidin stimulated an increase in type I collagen production. As previously reported, TGF-β is a potent stimulus of type I collagen production (36). Type I collagen is composed of two α1(I) collagen peptides and one α2(I) collagen peptide. Presented in Fig. 3 are radiolabeled α1(I) and α2(I) collagen peptides resolved by polyacrylamide gel electrophoresis. We determined that des-Arg$^{10}$-kallidin stimulated an increase in both α1(I) and α2(I) collagen peptides proportionally.

We examined the modulation of steady-state α1(I) collagen mRNA levels by kinins. BK did not stimulate an increase in α1(I) collagen mRNA. However, in fibroblasts stimulated with des-Arg$^{10}$-kallidin, there was an increase in α1(I) collagen mRNA (Fig. 4A). Variations in RNA loading were monitored by expression of GAPDH mRNA. A narrow dose-response relationship was found for the des-Arg$^{10}$-kallidin-stimulated increase in α1(I) collagen mRNA (Fig. 4B). At concentrations <1 nM des-Arg$^{10}$-kallidin, we did not detect any changes in α1(I) collagen mRNA. Maximal stimulation occurred at concentrations >10 nM. Kinetic studies detected increases in α1(I) collagen mRNA beginning at 4 h, with a maximum response at 24 h (Fig. 4C). In contrast, neither des-Arg$^{10}$-kallidin nor kallidin induced an increase in fibronectin mRNA (data not shown).

TGF-β mediates increases in collagen synthesis induced by other G-protein-coupled receptor agonists, including angiotensin II (40) and thromboxane (41). We determined the amount of active TGF-β present in the culture medium from untreated and des-Arg$^{10}$-kallidin-treated fibroblasts using the bioassay in which MLEC growth was inhibited in a dose-dependent manner by active TGF-β. The medium from des-Arg$^{10}$-kallidin-stimulated fibroblasts was added to MLEC cultures, and [3H]thymidine incorporation was monitored (Table I). The medium from untreated des-Arg$^{10}$-kallidin-stimulated fibroblasts contained small but similar amounts of TGF-β. The values were interpolated from a TGF-β inhibition standard curve. The amount of active TGF-β in the medium from des-Arg$^{10}$-kallidin-stimulated fibroblasts (0.38 ± 0.053 ng/ml) was not statistically different from the control values (p > 0.05). Des-Arg$^{10}$-kallidin (1 µM) did not alter MLEC growth, nor did the presence of des-Arg$^{10}$-kallidin (1 µM) alter TGF-β-mediated growth inhibition (data not shown).

To determine whether des-Arg$^{10}$-kallidin amplifies the TGF-β signaling mechanism, we employed the luciferase reporter pSTP-LUX, which is activated by TGF-β via Smad signaling (42). In fibroblasts that were transiently transfected with pSTP-LUX, TGF-β stimulated transcription from pSTP-LUX, as indicated by increased luciferase activity. Des-Arg$^{10}$-kallidin did not stimulate an increase in luciferase activity. In cultures stimulated with both TGF-β and des-Arg$^{10}$-kallidin, the luciferase activity was comparable to the luciferase activity in cultures stimulated with TGF-β alone (Fig. 5). We conclude that the des-Arg$^{10}$-kallidin-stimulated increase in α1(I) collagen mRNA is mediated through a mechanism that does not increase the amount of active TGF-β or amplify the intracellular signal generated by TGF-β. At this time, we do not exclude the possibility that des-Arg$^{10}$-kallidin amplifies non-SMAD-mediated TGF-β signaling.

In human lung fibroblasts, des-Arg$^{10}$-kallidin stimulates
steady-state levels of CTGF mRNA (Fig. 6A). TGF-β stimulates extracellular matrix protein synthesis and proliferation in fibroblasts through de novo synthesis of CTGF (26), we examined the effects of kinins on the increase in CTGF mRNA. As with α1(I) collagen mRNA, the des-Arg10-kallidin-stimulated increase in CTGF mRNA was dose-dependent (Fig. 6B). For the dose-response studies, fibroblasts were stimulated with des-Arg10-kallidin ranging from 10⁻⁶ to 10⁻⁷ M for 24 h. The location of the ribosomal RNA (28 S) is indicated.

**Table I**

| Culture                          | TGF-β content (ng/ml ± S.D.) |
|----------------------------------|------------------------------|
| Control                          | 0.30 ± 0.062 (n = 10)        |
| Des-Arg10-kallidin-stimulated    | 0.38 ± 0.053 (n = 10)        |

proliferation (36) and increased levels of α1(I) collagen mRNA (Fig. 4A). Since TGF-β stimulates extracellular matrix protein synthesis and proliferation in fibroblasts through de novo synthesis of CTGF (26), we examined the effects of kinins on the steady-state levels of CTGF mRNA (Fig. 6A). TGF-β stimulated an increase in CTGF mRNA, and activation of the B2 receptor did not induce a change in CTGF mRNA levels. In contrast, activation of the B1 receptor by des-Arg10-kallidin stimulated an increase in CTGF mRNA. As with α1(I) collagen mRNA, the des-Arg10-kallidin-stimulated increase in CTGF mRNA was dose-dependent (Fig. 6B). For the dose-response studies, fibroblasts were stimulated with des-Arg10-kallidin ranging from 10⁻⁶ to 10⁻⁷ M for 20 h. The medium was removed, and fibroblasts were stimulated with des-Arg10-kallidin and PMA for 4 h. Total RNA was harvested and Northern-blotted as described under “Results.” B, fibroblasts were stimulated with concentrations of des-Arg10-kallidin ranging from 10⁻⁶ to 10⁻⁷ M for 20 h. The medium was removed, and fibroblasts were stimulated with des-Arg10-kallidin and PMA for 24 h. Total RNA was harvested and Northern-blotted as described under “Results.” The cultures were stimulated with 100 nM des-Arg10-kallidin (DAK) or 100 nM BK or were unstimulated (Control) for 20 h. The location of the ribosomal RNA (28 S) is indicated. Results are representative of three independent experiments. C, fibroblasts were stimulated with 100 nM des-Arg10-kallidin. Total RNA was isolated at the indicated times. Results are representative of three independent experiments.

**DISCUSSION**

In vivo, the B1 receptor is detected in low abundance in normal tissues and is up-regulated following exposure to proinflammatory agents via nuclear factor κB activation. In the studies presented here, we utilized human embryonic lung fibroblasts that constitutively express the B1 receptor. Our results do not require up-regulation of B1 receptor number since treatment with actinomycin D or CHX does not inhibit the des-Arg10-kallidin-induced increase in CTGF mRNA. Since...
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Fig. 6. CTGF mRNA levels in kinin-stimulated fibroblasts. Confluent IMR-90 fibroblasts were incubated in DMEM supplemented with 0.4% FBS for 24 h. Following stimulation, total RNA was harvested and Northern-blotted (10 μg/lane) with probes for CTGF and GAPDH as described under "Results." A, the cultures were stimulated with 100 nM des-Arg<sup>10</sup>-kallidin (DAK), 100 nM kallidin (K), or 1 ng/ml TGF-β or were unstimulated (Control) for 4 h as indicated. Location of the ribosomal RNA (18 S) is indicated. Results are representative of three independent experiments. B, des-Arg<sup>10</sup>-kallidin stimulated a dose-dependent increase in CTGF mRNA. The cultures were stimulated with des-Arg<sup>10</sup>-kallidin (ranging from 10<sup>-11</sup> to 10<sup>-6</sup> M) for 4 h. Results are representative of three independent experiments. C, confluent IMR-90 fibroblasts were stimulated with 100 nM des-Arg<sup>10</sup>-kallidin for the indicated time points. Results are representative of three independent experiments.

Fig. 7. Modulators of des-Arg<sup>10</sup>-kallidin-stimulated increases in CTGF mRNA. Confluent IMR-90 fibroblasts were incubated in DMEM supplemented with 0.4% FBS for 24 h. Following stimulation, total RNA was harvested and Northern-blotted (10 μg/lane) with probes for CTGF and GAPDH as described under "Results." A, the B1 receptor antagonist attenuated the des-Arg<sup>10</sup>-kallidin-stimulated increase in CTGF mRNA. The fibroblasts were incubated with 1 μM des-Arg<sup>10</sup>-Leu<sup>9</sup>-kallidin (DALK) for 10 min and then stimulated with 100 nM des-Arg<sup>10</sup>-kallidin (DAK) or 1 ng/ml TGF-β for 4 h as indicated. Results are representative of three independent experiments. B, the cultures were pretreated with actinomycin D (5 μg/ml) for 10 min and then stimulated with 100 nM des-Arg<sup>10</sup>-kallidin or 1 ng/ml TGF-β or unstimulated for 4 h. Results are representative of three independent experiments. C, the cultures were pretreated with 1 μM cycloheximide for 30 min and then stimulated with 100 nM des-Arg<sup>10</sup>-kallidin or 1 ng/ml TGF-β or were unstimulated for 6 h. Results are representative of three independent experiments. D, the cultures were pretreated with 100 nM TPA for 10 min and then stimulated with 100 nM des-Arg<sup>10</sup>-kallidin or 1 ng/ml TGF-β or were unstimulated for 4 h. Results are representative of three independent experiments.

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Each of these agents prevents de novo synthesis of the B1 receptor, it appears that the number of receptors constitutively expressed by the fibroblasts is sufficient for signaling.

Exogenous administration of B1 and B2 receptor agonists in vivo and in vitro generates responses that appear qualitatively similar. For example, both the B1 and B2 receptors mediate pain perception (45); both receptors activate phospholipase C in mesangial cells (46); and both receptors stimulate mitogenesis (47), release of histamine from mast cells (48), and release of substance P and neurokinin A from sensory neurons (49), processes that can be considered anti-fibrotic. Our data demonstrate that activation of the B2 receptor does not stimulate collagen or CTGF synthesis. However, activation of the B1 receptor by des-Arg<sup>10</sup>-kallidin stimulates type I collagen protein synthesis, increases α(1) collagen mRNA, and stabilizes CTGF mRNA. TGF-β and now des-Arg<sup>10</sup>-kallidin are the only known stimulators of CTGF production.

The rate of mRNA degradation is determined, for the most part, by the activity of destabilizing sequences, although stabilizing sequences have been reported (50). Destabilizing sequences have been found in the 5′-untranslated region (51) and in the coding sequences (52). However, cytokine mRNA degradation is mediated through increased exonuclease activity, which appears to be regulated through adenine/uridine-rich elements found in the 3′-untranslated region (53). GM-CSF mRNA stabilization is well characterized. The GM-CSF 3′-untranslated region contains several elements consisting of core AUUUA pentamers. Proteins bind to AUUUA pentamers and appear to recruit other proteins, resulting in increased exonuclease activity. Inhibition of protein synthesis by CHX induces an increase in GM-CSF mRNA stability, presumably by inhibiting synthesis of destabilizing proteins (54).

The CTGF 3′-untranslated region (996 nucleotides) contains three AUUUA pentamers that potentially bind proteins involved in message destabilization. Each AUUUA pentamer forms the core for nonamers that are highly homologous to UUAUUU(U/A)(U/A), which is reported to destabilize mRNA (55).

The mechanism that induces stabilization of GM-CSF mRNA appears to be distinct from the mechanism that stabilizes CTGF mRNA. In the studies presented here, CHX induces an increase in CTGF mRNA levels at 6 h. The CHX-induced increase in CTGF mRNA is not sensitive to inhibition of transcription by actinomycin D (data not shown), suggesting that CHX induces an increase in CTGF mRNA stability by inhibiting synthesis of destabilizing proteins. CHX could inhibit specific RNases; however, GAPDH mRNA was not altered by CHX. Co-stimulation with CHX and des-Arg<sup>10</sup>-kallidin further increased the amount of CTGF mRNA, suggesting that the mech-
anisms by which CHX and des-Arg10-kallidin induced an increase in CTGF mRNA are distinct. Furthermore, TPA differentially regulates the stabilization of CTGF mRNA and GM-CSF mRNA. Human lung fibroblasts (WI38) exposed to TPA for 10 min exhibit increased GM-CSF mRNA stability (44). In our system, TPA did not stabilize CTGF mRNA. In fact, TPA attenuated the B1 receptor-mediated stabilization of CTGF mRNA. It is possible that the divergent TPA effects are cell type-specific. The data presented are consistent with the interpretation that CTGF mRNA is destabilized through labile destabilizing protein(s) that binds to the AUUUA elements and that recruits RNases and other cytoplasmic proteins. CHX blocks synthesis of the putative destabilizing protein(s), thus attenuating destabilization. Des-Arg10-kallidin induces stabilization of CTGF mRNA through post-translational modifications of the existing destabilizing proteins. The des-Arg10-kallidin-mediated post-translational modifications may reduce the RNA binding affinity of the destabilizing proteins or sterically hinder the complex formation of destabilizing proteins with other cytosolic proteins. The net result of stimulation with des-Arg10-kallidin is an increase in message stability.

Activation of the B2 receptor by BK and kallidin is an integral part of the early events of wound repair, mediating such processes as edema, pain perception, and release or synthesis of pro-inflammatory factors (3). When the possible contribution of the B2 receptor to fibrogenesis was examined, it was found that activation of the B2 receptor does not stimulate an increase in type I collagen production (36). Now it appears that the B1 receptor system plays a distinct role in wound repair, causing a rise in cytosolic Ca2+, stabilizing CTGF mRNA, stimulating an increase in α(I) collagen mRNA, and stimulating collagen production. The potential pathophysiological role of the B1 receptor in the development of fibrosis is intriguing. The B1 receptor is up-regulated at sites of inflammation and appears to be refractory to desensitization (1). These characteristics, together with the pro-fibrotic effects reported here, suggest that activation of the B1 receptor may contribute to the excess collagen deposition associated with chronic inflammatory conditions such as asthma and pulmonary fibrosis.
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