Table 1. Studies providing empirical evidence for the relationship between KE4 (Event 1499) and KE5 (Event 1500).
+: Severity of Response. References available in main KER page.

Stressor (Reference)	***In vitro*/*in vivo*/*ex vivo***	**Species/Cell line**	**Exposure Conditions**	**KE4 (Event 1499) Activation, T helper (Th) type 2 cells**		**KE5 (Event 1500) Increased, fibroblast proliferation, and myofibroblast differentiation**
Silica particles (SiO_2) (Lo Re et al., 2011)	*In vivo*/*ex vivo*	NMRI, C57BL/6, DBA/2 mice Rag2-/- mice and C57BL/6 wild-type Foxp3-GFP and Foxp3-eGFP/diphtheria toxin receptor (DTR) Depletion of regulatory T cell (DEREG) mice.	2.5 mg/mouse pharyngeal instillation 15 days after instillation, regulatory T cells were purified from Foxp3-GFP transgenic mice. Regulatory T cells were co-culture with mouse lung fibroblast 5, 10, 25, 50, 100 x 10^3 regulatory T cells/well	Increase in expression of PDGF-B and TGF-β1 in purified regulatory T cells PDGF-B: ++ TGF-β1: ++		Fibroblast proliferation 3H-thymidine (48 h co-culture) 5 x 10^3: + 10 x 10^3: + 25 x 10^3: ++ 50 x 10^3: +++ 100 x 10^3: +++
Multi-walled carbon nanotubes (Dong and Ma, 2016)	*In vivo*	Male C57BL/6J mice	40 μg/mouse pharyngeal aspiration. Evaluation: 1, 3, 7, 14 days post-exposure	Increased Th2 cytokines interleukin production IL-4, IL-13, phospho-STAT6 and GATA-3 (mRNA and proteins)		Collagen I deposition
				Day 1+ Day 3 + Day 7: +++ Day 14 +		Day 7: +++
Bleomycin (Cao et al., 2014)	*In vivo*	Male Wistar rats	5 mg/Kg intratracheal instillation Evaluation: 7, 14, 28 days post-exposure	Increased IL-4 content in broncho-alveolar lavage fluid	Increased IFN-γ content in bronchoalveolar lavage fluid	Increased collagen I deposition
				Day 7: +++ Day 14: ++ Day 28: +	Day 7: + Day 14: ++ Day 28: ++	Day 7: + Day 14: ++ Day 28: +++
Wound model and IL-33 (Yin et al., 2013)	*In vivo*	Male BALB/c mice	Skin wounds created on the dorsal skin. Murine recombinant IL-33 (1.0 μg/mouse) intraperitoneal injection once a day from day 0 to day 3 Evaluation: 0 – 14 days post-injury	Alternatively activated macrophages (AAM) increase (vs. PBS) Day 5: ++ mRNA expression of AAM-associated genes increase (vs. PBS) Day 5: ++		% Wound closure increase (vs. PBS): Day 0: Day 3: ++ Day 5: ++ Day 7: ++ Day 10: + Day 14:

						% Reepithelization increase (vs. PBS) Day 1: Day 3: ++ Day 6: ++ Day 14: Collagen deposition increase (vs. PBS) Day 3: Day 5: + Day 7: + Day 14: mRNA expression of extracellular matrix-associated genes increase (vs. PBS) Day 5: ++
IL-4 (Wynes et al., 2004)	*Ex vivo*/*in vitro*	Monolayers of mouse bone marrow-derived macrophages C3H/HeJ mice CCL39 cells	2 ng/ml IL-4 for 26 h (macrophages) CCL39 myofibroblasts were cultured for 24 h with conditioned media from IL-4 treated macrophages	IGF-1 release (IL-4 treated macrophages) +++		CCL39 myofibroblast consumed the macrophage-derived IGF-1 from condition media Caspase-3 activity was reduced in CCL39 myofibroblasts that were protected by macrophage-derived IGF-1 Pro-survival kinases Akt and ERK were activated in CCL39 myofibroblasts by macrophage-derived IGF-1
Radiation (Meziani et al., 2018)	*Ex vivo*/*in vivo*/ Human	Female C57BL/6J mice AMs: Alveolar macrophages IMs: infiltrating macrophages	16 Gray (Gy) single dose locally administered to the whole thorax Evaluation: 0 – 20 weeks post exposure	Differential phenotype of AMs and IMs Day 6: Number of Icam1+ IMs transiently increased on day 6 Week 20: Increased	Activated IMs induced myofibroblastic activation IMs sorted from radiation induced fibrosis tissue 15 weeks post-irradiation were co-cultured with	Week 20: Increased collagen deposition. Increased TGF-β1, PAI-1, and Smad2/3 phosphorylation expressing in lung tissue

				number of CD206+ IMs Week 20: Th1 cytokines decreased and TIMP-1 increased Week 20: IMs expressed Arg-1.	normal fibroblasts: Increased α-SMA and TGF-β1 IMs sorted from normal mouse lung and activated *in vitro* with IL-13/-4 for 24 h: Increased α-SMA expression			
Bleomycin IL-4 and IL-13 (Liu et al., 2011)	*In vivo*/*Ex vivo*/ Human	C57BL/6 mice BALB/c mice GFP-transgenic mice Female fisher 344 rats FIZZ2 knockout mice IL-4 knockout mice IL-4/IL-13 knockout mice STAT6 knockout mice	Bleomycin 2 U/Kg and 10 U/Kg mice Rat alveolar epithelial cells isolated and human primary small airway epithelial cells (PCS-301-010) were treated with 10 ng/ml of rIL-4, rIL-13, rIL-17 or IFN-γ and incubated for 4 h, 8 h Mouse lung fibroblasts were isolated and treated with 2.5 - 100 ng/mL recombinant mouse FIZZ2 for 2, 6, 24 h Evaluation: 0 -21 days post-exposure	FIZZ2 mRNA expression in treated alveolar epithelial cells		Mouse lung fibroblasts treated with FIZZ2		
				IL-4 Treatment: 4 h: ++++ (Rat cells) 8 h: +++ (Rat cells), + (Human cells) IL-13 Treatment: 4 h: ++ (Rat cells) 8 h: ++ (Human cells)		Collagen type I mRNA expression 2 h 10: 25: 6 h 25: +	Abundance of α-SMA protein 24 h 25: + 50: ++ 100: +++	Increased cell proliferation 24 h 10: +++ 25: +++ 50: ++
Bleomycin (Gibbons et al., 2011)	*In vivo*/ Human/ *Ex vivo*	Female C57BL/6 mice	0.05 U intratracheal instillation Evaluation: 0 - 56 days post-exposure	Increase Arg activity and Ym1 expression	Increase Ym1 cells per field	Increased collagen deposition	Increased expression of α-SMA and Col1A1	Increased fibrosis
				Day 25: +++	Day 32: +++	Day 18: ++	Day 25: +++ (α-SMA) ++ (Col1A1)	Day 32: +++

α-SMA: Alpha-smooth muscle actin.
Akt: Protein kinase B.
Arg: Arginase.
Col1A1: Collagen type I alpha 1 chain.
ERK: Extracellular signal-regulated kinase.
FIZZ2: Found in inflammatory zone 2.
Foxp3: Forkhead box p3.
GATA-3: GATA binding protein 3.
GFP: Green fluorescent protein.
Icam1: Intercellular adhesion molecule 1.
IFN-γ: Interferon gamma.
IGF-1: Insulin-like growth factor 1.
IL: Interleukin.
PAI-1: Plasminogen activator inhibitor 1.
PBS: Phosphate-buffered saline.
PDGF-B: Platelet derived growth factor subunit B.
Rag2: Recombination activating 2.
Smad2/3: SMAD family member (Smad)2/3.
STAT6: Signal transducer and activator of transcription 6.
TGF-β: Transforming growth factor beta.
TIMP: Metalloproteinase inhibitor 1.
Ym1: Chitinase-like protein 3.