

Table 1. Studies providing empirical evidence for the relationship between KE5 (Event 1500) and KE6 (Event 68). +: Severity of Response. References available in main KER page.

Stressor (Reference)	<i>In vitro/in vivo/ex vivo</i>	Species/Cell line	Exposure Conditions	KE5 (Event 1500) Increased, fibroblast proliferation, and myofibroblast differentiation				KE6 (Event 68) Accumulation, Collagen
				Exudate macrophages (ExM) increased in DTR+ lungs	Accumulation of ExM and Ly-6C ^{high} monocytes in DTR+ lungs	Immunophenotype of ExM and Ly6C ^{high} monocytes in DTR+ mice		
Diphtheria toxin (Osterholzer et al., 2013)	<i>In vivo</i>	C57BL/6 mice wild-type Diphtheria toxin receptor (DTR) + mice DTR ⁺ /CCR2 ^{-/-} mice	10.0 µg/kg intraperitoneal injection once/day, 14 days Evaluation: 7, 14, and 21, days after onset of treatment	Exudate macrophages (ExM) increased in DTR+ lungs	Accumulation of ExM and Ly-6C ^{high} monocytes in DTR+ lungs	Immunophenotype of ExM and Ly6C ^{high} monocytes in DTR+ mice	Lung collagen content in DTR+ mice	
				Day 7: +++ Day 14: +++ Day 21: ++				Day 14: ++
Silicon dioxide (SiO ₂) (Fang et al., 2018)	<i>In vivo</i>	Stock TEK-GFP 287 Sato/JNju (Tie2-GFP) mice	0.5 g/Kg intratracheal instillation Evaluation: 28 days post-exposure	Day 28: GFP localized with α-SMA/Acta2 in lung tissue			Day 28: Sirius red staining (marks collagen I and III) co-localized with GFP signal.	
	<i>In vitro</i>	Mouse microvascular lung cells	50 µg/cm ² for 6, 12, 24, 48 h	Increase protein expression of mesenchymal markers (Col1A1, Acta2)	Decrease protein expression of endothelial markers (Cdh5, PECAM1)	Increase cell proliferation and migration		
				6 h: 12 h: + 24 h: ++ 48 h: +++	6 h: 12 h: + 24 h: + 48 h: ++	6 h: 12 h: 24 h: + 48 h: ++		
Human	Lung sections from patients	Patients with silicosis				Day 28: Decrease Tie2-GFP and HECTD1 expression		
Multi-walled carbon nanotubes (Dong et al., 2017)	<i>In vivo</i>	Male C57BL/6J wild-type mice B6.129S4-Timp1tm1Pd ^s /J (Timp1 Knockout) mice	40 µg/mouse pharyngeal aspiration Evaluation: 1, 3, 7, 14 days post-exposure	Timp1 mRNA and protein levels increased in lung, BALF and serum	Increase FN1 protein expression in lungs	Increase FSP protein expression in lungs	Increase Ki67 and PCNA expression levels in lungs	Collagen deposition (Masson's trichrome)

				Day 1: +++ Day 3: +++ Day 7: ++ Day 14: +	Day 1: ++ Day 3: +++ Day 7: +++ Day 14: +	Day 1: + Day 3: +++ Day 7: +++ Day 14: ++	Day 1: + Day 3: ++ Day 7: +++ Day 14: ++	
				Day 7: Increase in the levels of Hsp47, vimentin, α -SMA, PDGFR- β , CD63, integrin β 1, p-Erk1/2, and genes involved in cell cycle regulation (wild-type and Timp1 knockout)			Day 7: Mice Timp1Knockout showed a significant reduction of fibrosis as compared to wild-type	
CeO ₂ nanoparticles (Ma et al. 2017)	<i>In vivo</i>	Male Sprague-Dawley rats	0.15-7 mg/Kg intratracheal instillation Evaluation: 1 – 28 days post-exposure	Increased soluble collagen in BALF		Increased α -SMA expression in lung tissue	Increases hydroxyproline content in lung tissue	
				3.5 mg/Kg Day 3: + Day 28: +++				3.5mg/Kg Day 1: +++ Day 3: ++ Day 28: ++
	<i>Ex vivo</i>	Alveolar Macrophages Fibroblasts ATII cells	Isolated from CeO ₂ exposed rats 1 - 28 days post-exposure	Increased TGF- β 1 (Macrophages)	Decreased proliferation (Fibroblasts)	Increased α -SMA (Fibroblasts & ATII)		
				3.5mg/Kg CeO ₂ Day 1: ++ Day 3: ++ Day 10: ++ Day 28: +	Day 28 0.15mg/kg: + 1mg/kg: ++ 3.5mg/kg: +++ 7 mg/Kg: +++	Day 3 (ATII) 3.5mg/kg: +++ Day 28 (Fibroblasts) +++		
Bleomycin (Hu et al., 2015)	<i>In vivo</i>	Notch1 conditional knockout (CKO) and wild-type mice	2 U/kg endotracheal injection (wild-type & CKO mice) Evaluation: 7 – 28 days post-exposure	Increased protein expression Jagged-1 and Notch1 in wild-type mouse lungs	Increased expression mRNA α -SMA and Col1, Notch1 protein in isolated wild-type lung fibroblasts	Increased percentage of α -SMA+ cells in lungs	Increased hydroxyproline content in lung tissue	

				Jagged1 Day 7: ++ Day 14: ++ Day 21: + Day 28: + Notch1 Day 7: ++ Day 14: + Day 21: ---- Day 28: ----	Day 14 α -SMA (protein & mRNA): +++ Col1 (protein & mRNA): +++ Notch1(protein):	Day 14 Wild-type mice: +++ CKO mice: +	Day 28 CKO mice showed a significant attenuation of collagen deposition as compared to wild-type
Bleomycin TGF- β (Blaauboer et al., 2014)	<i>In vivo</i>	Female C57BL/6 mice	30 μ l (1.25 U/ml in phosphate-buffered saline) Bleomycin intratracheal instillation. Evaluation: 1 – 5 weeks post-exposure.	Increased α -SMA protein level on histological staining in lungs		New collagen formation and gene expression	Extracellular matrix proteins Increased protein level on histological staining in lungs
				Week 1: ++ Week 2: +++ Week 3: +	Gene expression of ELN, type V collagen and TNC highly correlated to new collagen formation		
	<i>In vitro</i>	Primary normal human lung fibroblast Human fetal lung fibroblast	1, 2, 4, 10 ng/mL TGF- β Evaluation: 24, 48 h	Increased mRNA expression 24 h	Increased ELN, COL5A1 mRNA expression 24 h	Increased mRNA expression 48 h, ELN coated surface	

									(10 ng/ml TGF-β)	
				ACTA 1: 2: + 5: ++ 10: +++	COL1A1 1: + 2: ++ 5: ++ 10: +++	ELN 1: + 2: ++ 5: +++ 10: ++++	COL5A1 1: 2: + 5: ++ 10: +++	TNC 1: 2: + 5: + 10: +++	+++ (ACTA2 COL1A1 ELN)	
Radiation (Judge et al., 2015)	Study population/ <i>In vivo/In vitro</i>	Lung biopsies from patients with thoracic radiation for cancer treatment C57BL/6 mice Primary human lung fibroblast	5 Gray (Gy) total body plus 10 Gy thoracic radiation (mice). Evaluation: 12-26 weeks post-exposure 3, 7 Gy (primary human lung fibroblasts) Evaluation: 5 days post-exposure	Increased LDH expression	Increased extracellular acidification and lactate production (Fibroblasts)	Increased α-SMA protein expression, soluble collagen I, Col1A1, and Col3A1 mRNA levels (Fibroblasts)	TGF-β1 activation (Fibroblasts)	Increased collagen fibers deposition trichrome stain		
				Lung biopsies: ++++	Acidification 3 Gy:++ 7 Gy:+++	Soluble Collagen 3 Gy: 7 Gy: +++ Col1A1 7 Gy: +++ Col3A1 7 Gy: +++	3 Gy: +++ 7 Gy: ++++	Lung biopsies: +++		
Copper oxide nanoparticles (Lai et al., 2018)	<i>In vivo</i>	C57BL/6 mice	1, 2.5, 5, 10 mg/Kg intranasal instillation Evaluation: 7, 14, 28 days post-exposure	Increased mRNA levels of CCL-2, CCL-3, IL-4, IL-10, IFN-α, TGF-β1 at day 14.	Cell apoptosis in lung tissue	Increased TGF-β1 content in BALF on day 14	Increased α-SMA on day 28	Increased collagen-I and hydroxyproline content on day 28		

				5: +++	Day 14: 1: + 2.5: ++ 5: +++ 5mg/kg: Day 7: ++ Day 14: +++ Day 28: +++	2.5: +++ 5: ++++	2.5: ++ 5: ++++	2.5: ++ 5: +++	
Cadmium chloride (CdCl ₂) (Li et al., 2017)	<i>In vivo</i>	C57BL/6 vimentin knockout mice C57BL/6 wild-type mice	0.009, 0.018 mg/Kg intratracheal instillation (once / 2 days; 8 weeks) Evaluation: weeks 1, 2, 4, 8 of exposure.	Increased α -SMA in lung tissue (0.009 mg/Kg)			Increased (0.009 mg/Kg)		
				Week 4: +++			Subepithelial thickness Week 4: ++ Airway resistance Week 4: ++ Collagen-I staining Week 4: +++ Picrosirius red Week 4: +++ Collagen content (Sircol assay) Week 1: Week 2: ++ Week 4: ++ Week 8: +++		
	<i>In vitro</i>	Primary human fibroblast	5, 10, 20 μ M for 3 h. Allowed to recover for 3, 24, 48, 72 h.	Increased α -SMA			Increased		
				10 μ M CdCl ₂ for 3 h followed by recovery 3 h: 24 h: 48 h: + 72 h: ++			Soluble collagen (48 h recovery) 5: 10: +++ 20: ++++		
				20 μ M CdCl ₂ for 3 h followed by recovery 3 h: + 24 h: + 48 h: ++			Soluble collagen (20 μ M CdCl ₂) 3 h: 24 h: ++++		

				72 h: ++	48 h: ++++ 72 h: ++++ Fibronectin and Collagen I (10 and 20 μ M CdCl ₂) 3 h: + 24 h: ++ 48 h: +++ 72 h: +++
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Acta2: Actin alpha 2.

Arg: Arginase.

BALF: Bronchoalveolar lavage fluid.

CCL: C-C motif chemokine ligand.

CCR: C-C motif chemokine receptor.

CD: Cluster of differentiation.

Cdh5: Cadherin 5.

Col1: Collagen type I.

COL1A1: Collagen type 1 alpha 1 chain.

Col3A1: Collagen type III alpha 1 chain.

COL5A1: Collagen type V alpha 1 chain.

ELN: Elastin.

ERK: Extracellular signal-regulated kinase.

FN1: Fibronectin 1.

FSP: Fibroblast-specific protein-1.

GFP: Green fluorescent protein.

HECTD1: HECT Domain E3 ubiquitin-protein ligase 1.

Hsp: Heat Shock protein.

IFN: Interferon.

IL: Interleukin.

iNOS: Inducible nitric oxide synthase.

LDH: Lactate dehydrogenase.

Notch1: Neurogenic locus notch homolog protein 1.

PECAM1: Platelet and endothelial cell adhesion molecule 1.

PCNA: Proliferating cell nuclear antigen.

PDGFR- β : Platelet derived growth factor receptor beta.

SMA: Smooth muscle actin.

TGF: Transforming growth factor beta.

Timp1: TIMP metalloproteinase inhibitor 1.

TNC: Tenascin C.