Supplemental Material

Table S1. Antibody list used for Western blotting and immunofluorescence staining.

Antibody	Add on	Use/ Dilution	Blocking/ Dilution buffer	Source	MW [kDa]	Manufacturer
Anti-Actin	1A4	IF 1:200	PBS-T			Santa Cruz
Anti-α-Tubulin		WB 1:1000	1% BSA In TBS-T	Mouse	50	Sigma Aldrich, Munich, Germany
Anti-AKT		WB 1:1000	5% BSA in TBS-T	Rabbit	60	Cell Signaling Technology Danvers, MA, USA
Anti-Caspase-3		WB 1:1000	5% NFDM in TBS-T	Rabbit	17, 19, 35	Cell Signaling Technology, Beverly, MA, USA
Anti-GAPDH	D16H11	WB 1:1000	5% BSA in TBS-T	Rabbit	37	Cell Signaling Technology Danvers, MA, USA
Anti-p38		WB 1:1000	5% BSA in TBS-T	Rabbit	43	Cell Signaling Technology Danvers, MA, USA
Anti-RIP3		WB 1:1000	5% BSA in TBS-T	Rabbit	53	BioRAD, Munich, Germany
Anti-TNF alpha		WB 1:700	3% NFDM in TBS-T	Rabbit	25	Abcam, Cambridge, UK
Anti-phospho-AKT	Ser473	WB 1:1000	5% BSA in TBS-T	Rabbit	60	Cell Signaling Technology Danvers, MA, USA
Anti-phospho-p38	Thr180/ Tyr182	WB 1:1000	5% BSA in TBS-T	Rabbit	43	Cell Signaling Technology Danvers, MA, USA
Anti-phospho RIP3	Ser232	WB 1:1000	5% NFDM in TBS-T	Rabbit	53	Abcam, Cambridge, UK

Anti-Vimentin		IF 1:200	2% BSA in PBS-T	Rabbit	57	Thermo Fisher Scientific, Waltham, MA, USA
Anti-Mouse	HRP	WB 1:5,000	1% BSA in TBS-T	Donkey		Abcam, Cambridge, UK
Anti-Rabbit	HRP	WB 1:10,000	1% BSA in TBS-T	Donkey		GE Healthcare, Munich, Germany
Anti-Mouse IgG	DyLight 550	IF 1:200	PBS-T	Goat		Thermo Fisher Scientific, Waltham, MA, USA
Anti-Rabbit IgG (H+L)	DyLight 288	IF 1:200	PBS-T			Thermo Fisher Scientific, Waltham, MA, USA

BSA, bovine serum albumin; HRP, horse radish peroxidase; IF, Immunofluorescence; MW, molecular weight NFDM, non-fat dry milk; PBS-T , phosphate-buffered saline with Tween20; TBS-T, Tris-buffered saline with 0.1% Tween20; WB, Western blot

Table S2. Gene expression analysis using TaqMan assays from Applied Biosystems.

Gene/TaqMan probe	Assay ID
Acta2	Mm00725412_s1
FN1	Mm01256744_m1
Ccl2	Mm00441242_m1
Ccl7	Mm00443113_m1
Clec4e	Mm01183703_m1
Col1a1	Mm00801666_g1
GAPDH	Mm99999915_g1
Ifi44	Mm00505670_m1
Irg1	Mm01224532_m1
Oasl2	Mm01201449_m1
Tgtp2	Mm00786926_s1
TNFα	Mm00443258_m1

Acta2; actin, alpha 2, smooth muscle, aorta (alias: α-SMA); FN1, fibronectin 1; Ccl, C-C motif chemokine ligand; Clec4e, C-type lectin domain family 4 member e; Col1a1, collagen, type I, alpha 1; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; Ifi44, interferon-induced protein 44; Irg1, immunoresponsive gene 1; Oasl2, 2'-5' oligoadenylate synthetase-like 2; Tgtp2, T cell specific GTPase 2; TNFα, tumor necrosis factor α.

Table S3. Antibody list used for flow cytometry analysis.

Antibody	Labeling	Host	Volume	Manufacturer
Anti-mouse-CD74	FITC	Rat	3 µl	BD Bioscience, Heidelberg, Germany
Anti-mouse-CXCR2	PE	Rat	3 µl	R&D, Minneapolis, MN, USA
Anti-mouse-CXCR4	FITC	Rat	3 µl	R&D, Minneapolis, MN, USA
Anti-mouse-TLR2	FITC	Rat	3 µl	R&D, Minneapolis, MN, USA
Anti-mouse-TLR4	PE	Rat	3 µl	R&D, Minneapolis, MN, USA
Anti-mouse-TNFRI	FITC	Hamster	1 µl	Abcam, Cambridge, UK
Anti-hamster IgG	FITC	Hamster	0.2 µl	Abcam, Cambridge, UK
Anti-rat-IgG2B	FITC	Rat	3 µl	BD Bioscience, Heidelberg, Germany
Anti-rat IgG2A	PE	Rat	3 µl	R&D, Minneapolis, MN, USA
Anti-rat Ig2B	FITC	Rat	3 µl	R&D, Minneapolis, MN, USA

FITC, Fluorescein isothiocyanate; PE, Phycoerythrin

Table S4. Effect Size.

		Comparison	d (Effect Size)
Figure 1B	α-SMA	Day0 vs. Day5	16.65
	Col1a1	Day0 vs. Day5	7.44
	Fibronectin 1	Day0 vs. Day5	1.61
Figure 1C	Ctrl vs. sCD74 treatment alone	Ctrl vs. 0.04 nmol/L sCD74	0.21
		Ctrl vs. 0.16 nmol/L sCD74	0.51
		Ctrl vs. 8 nmol/L sCD74	1.02
		Ctrl vs. 16 nmol/L sCD74	1.05
		Ctrl vs. 40 nmol/L sCD74	1.05
	MIF vs. sCD74/MIF Cotreatment	MIF vs. 0.04 nmol/L sCD74 + MIF	0.92
		MIF vs. 0.16 nmol/L sCD74 + MIF	1.11
		MIF vs. 8 nmol/L sCD74 + MIF	2.33
		MIF vs. 16 nmol/L sCD74 + MIF	3.30
		MIF vs. 40 nmol/L sCD74 + MIF	3.27
	sCD74 treatment vs. sCD74/MIF cotreatment	0nmol/L sCD74 (Control) vs. 0.04 nmol/L sCD74 + MIF	0.11
		0.04 nmol/L sCD74 vs. 0.04 nmol/L sCD74 + MIF	0.91
		0.16 nmol/L sCD74 vs. 0.16 nmol/L sCD74 + MIF	1.52
		8 nmol/L sCD74 vs. 8 nmol/L sCD74 + MIF	1.16
		16 nmol/L sCD74 vs. 16 nmol/L sCD74 + MIF	3.27
		40 nmol/L sCD74 vs. 40 nmol/L sCD74 + MIF	1.86
Figure 1D	Effects within CMs	Ctrl vs. MIF	0.18
		Ctrl vs. sCD74	0.44
		Ctrl vs. sCD74/MIF	0.81
		MIF vs. sCD74/MIF	0.66
		sCD74 vs. sCD74/MIF	0.04
	Effects in CMs vs. MyoFBs	Control	0.00
		MIF	0.05
		sCD74	0.55
		sCD74/MIF	3.14
Figure 2A	Cleaved Caspase 3 level at 10h	Ctrl vs. MIF	0.63
		Ctrl vs. sCD74	3.05
		Ctrl vs. sCD74/MIF	0.53
		MIF vs. sCD74/MIF	0.07
		sCD74 vs. sCD74/MIF	0.21
Figure 2C	Phosphorylated RIP3 level at 10h	Ctrl vs. MIF	2.34
		Ctrl vs. sCD74	0.51
		Ctrl vs. sCD74/MIF	1.88
		MIF vs. sCD74/MIF	1.52
		sCD74 vs. sCD74/MIF	1.73
Figure 2E		Ctrl vs. MIF	0.29

	Effects within the DMSO group	Ctrl vs. sCD74	0.42
		Ctrl vs. sCD74/MIF	3.50
		MIF vs. sCD74/MIF	2.72
		sCD74 vs. sCD74/MIF	3.83
	Effects within the Nec1s group	Ctrl vs. MIF	1.81
		Ctrl vs. sCD74	1.38
		Ctrl vs. sCD74/MIF	3.39
		MIF vs. sCD74/MIF	0.59
		sCD74 vs. sCD74/MIF	1.56
	Effects in DMSO vs. Nec1s group	Control	0.02
		MIF	0.94
		sCD74	0.72
		sCD74/MIF	2.29
Figure 3B	Ifi44 mRNA	Ctrl vs. MIF	1.20
		Ctrl vs. sCD74	2.01
		Ctrl vs. sCD74/MIF	2.50
		MIF vs. sCD74/MIF	2.11
		sCD74 vs. sCD74/MIF	1.01
Figure 3C	Irg1 mRNA	Ctrl vs. MIF	1.26
		Ctrl vs. sCD74	1.36
		Ctrl vs. sCD74/MIF	2.11
		MIF vs. sCD74/MIF	0.69
		sCD74 vs. sCD74/MIF	1.10
Figure 3D	Clec4e mRNA	Ctrl vs. MIF	0.96
		Ctrl vs. sCD74	0.99
		Ctrl vs. sCD74/MIF	2.36
		MIF vs. sCD74/MIF	0.86
		sCD74 vs. sCD74/MIF	1.59
Figure 4A	Phosphorylated AKT level at 0.5h	Ctrl vs. MIF	8.31
		Ctrl vs. sCD74	2.21
		Ctrl vs. sCD74/MIF	0.58
		MIF vs. sCD74/MIF	2.23
		sCD74 vs. sCD74/MIF	0.45
Figure 4B	Phosphorylated AKT level at 10h	Ctrl vs. MIF	1.18
		Ctrl vs. sCD74	0.95
		Ctrl vs. sCD74/MIF	0.64
		MIF vs. sCD74/MIF	1.32
		sCD74 vs. sCD74/MIF	1.02
Figure 4E	Phosphorylated p38 level at 0.5h	Ctrl vs. MIF	0.14
		Ctrl vs. sCD74	0.20
		Ctrl vs. sCD74/MIF	0.09
		MIF vs. sCD74/MIF	0.16
		sCD74 vs. sCD74/MIF	0.03
Figure 4F	Phosphorylated p38 level at 10h	Ctrl vs. MIF	2.34
		Ctrl vs. sCD74	0.51
		Ctrl vs. sCD74/MIF	1.88
		MIF vs. sCD74/MIF	1.52

		sCD74 vs. sCD74/MIF	1.73
Figure 5A	Effect of sCD74/MIF on Cd74-/-	Ctrl vs. MIF	0.43
		Ctrl vs. sCD74	0.12
		Ctrl vs. sCD74/MIF	0.94
		MIF vs. sCD74/MIF	0.66
		sCD74 vs. sCD74/MIF	1.02
Figure 5B	Effect of sCD74/MIF on WT	Ctrl vs. MIF	0.11
		Ctrl vs. sCD74	1.05
		Ctrl vs. sCD74/MIF	3.91
		MIF vs. sCD74/MIF	3.27
		sCD74 vs. sCD74/MIF	1.86
Figure 5C	Effect of sCD74/MIF in Cd74-/- vs. WT	Control	0.00
		MIF	0.41
		sCD74	0.94
		sCD74/MIF	1.56
Figure 5D	Effect of sCD74/MIF on SB225002-pretreated WT	Ctrl vs. MIF	0.24
		Ctrl vs. sCD74	1.11
		Ctrl vs. sCD74/MIF	2.71
		MIF vs. sCD74/MIF	2.05
		sCD74 vs. sCD74/MIF	1.77
Figure 5E	Effect of sCD74/MIF on DMSO-pretreated WT	Ctrl vs. MIF	0.23
		Ctrl vs. sCD74	0.58
		Ctrl vs. sCD74/MIF	3.42
		MIF vs. sCD74/MIF	5.59
		sCD74 vs. sCD74/MIF	2.83
Figure 5F	Effect of sCD74/MIF in WT+SB225002 vs. WT+DMSO	Control	0.36
		MIF	0.12
		sCD74	0.58
		sCD74/MIF	1.10
Figure 5G	Effect of sCD74/MIF on AMD3100-pretreated WT	Ctrl vs. MIF	1.95
		Ctrl vs. sCD74	0.88
		Ctrl vs. sCD74/MIF	4.06
		MIF vs. sCD74/MIF	0.86
		sCD74 vs. sCD74/MIF	2.09
Figure 5H	Effect of sCD74/MIF on ddH2O-pretreated WT	Ctrl vs. MIF	0.30
		Ctrl vs. sCD74	0.32
		Ctrl vs. sCD74/MIF	4.33
		MIF vs. sCD74/MIF	3.87
		sCD74 vs. sCD74/MIF	1.93
Figure 5I	Effect of sCD74/MIF in WT+AMD3100 vs. WT+ddH2O	Control	0.57
		MIF	1.99
		sCD74	0.57
		sCD74/MIF	0.96
Figure 6A	human MIF ELISA	Healthy vs.CHD	3.35
		Healthy vs. HF	2.43
		CHD vs. HF	1.52
Figure 6B	human sCD74 ELISA	Healthy vs.CHD	0.32

		Healthy vs. HF	0.11
		CHD vs. HF	0.54
Figure 6C	sCD74/MIF ratio	Healthy vs.CHD	1.02
		Healthy vs. HF	1.12
		CHD vs. HF	0.69
Suppl. Figure 2A	α-SMA	Ctrl vs. MIF	0.66
		Ctrl vs. sCD74	0.04
		Ctrl vs. sCD74/MIF	0.10
		MIF vs. sCD74/MIF	0.37
		sCD74 vs. sCD74/MIF	0.08
	Col1a1	Ctrl vs. MIF	0.53
		Ctrl vs. sCD74	0.25
		Ctrl vs. sCD74/MIF	0.97
		MIF vs. sCD74/MIF	0.50
		sCD74 vs. sCD74/MIF	0.68
	Fibronectin 1	Ctrl vs. MIF	0.87
		Ctrl vs. sCD74	2.10
		Ctrl vs. sCD74/MIF	0.83
		MIF vs. sCD74/MIF	0.15
		sCD74 vs. sCD74/MIF	0.02
Suppl. Figure 5A	TNFα mRNA	Ctrl vs. MIF	0.70
		Ctrl vs. sCD74	0.39
		Ctrl vs. sCD74/MIF	0.81
		MIF vs. sCD74/MIF	0.05
		sCD74 vs. sCD74/MIF	1.05
Suppl. Figure 5B	soluble TNFα	Ctrl vs. MIF	0.23
		Ctrl vs. sCD74	0.29
		Ctrl vs. sCD74/MIF	0.38
		MIF vs. sCD74/MIF	0.62
		sCD74 vs. sCD74/MIF	0.67
Suppl. Figure 5D	Intracellular TNFα at 10h	Ctrl vs. MIF	0.60
		Ctrl vs. sCD74	1.36
		Ctrl vs. sCD74/MIF	1.19
		MIF vs. sCD74/MIF	0.09
		sCD74 vs. sCD74/MIF	0.12
Suppl. Figure 5E	Effects within the donor group after 6h	Ctrl vs. MIF	0.16
		Ctrl vs. sCD74	0.49
		Ctrl vs. sCD74/MIF	1.76
	Effects within the recipient group after 6h	Ctrl vs. MIF	0.06
		Ctrl vs. sCD74	0.44
		Ctrl vs. sCD74/MIF	0.61
	Effect of sCD74/MIF in donor vs. recipient group	Ctrl vs. MIF	0.04
		Ctrl vs. sCD74	0.12
		Ctrl vs. sCD74/MIF	1.00
Suppl. Figure 5F	Effects within the donor group after 10h	Ctrl vs. MIF	1.95
		Ctrl vs. sCD74	1.35
		Ctrl vs. sCD74/MIF	2.99

	Effects within the recipient group after 10h	Ctrl vs. MIF	0.07
		Ctrl vs. sCD74	0.29
		Ctrl vs. sCD74/MIF	1.75
	Effect of sCD74/MIF in donor vs. recipient group	Ctrl vs. MIF	2.08
		Ctrl vs. sCD74	0.87
		Ctrl vs. sCD74/MIF	2.25
Suppl. Figure 8A	Oasl2 mRNA	Ctrl vs. MIF	0.69
		Ctrl vs. sCD74	1.22
		Ctrl vs. sCD74/MIF	1.32
		MIF vs. sCD74/MIF	0.93
		sCD74 vs. sCD74/MIF	0.44
Suppl. Figure 8B	Tgtp2 mRNA	Ctrl vs. MIF	1.03
		Ctrl vs. sCD74	1.02
		Ctrl vs. sCD74/MIF	1.10
		MIF vs. sCD74/MIF	0.31
		sCD74 vs. sCD74/MIF	0.14
Suppl. Figure 8C	Ccl2 mRNA	Ctrl vs. MIF	1.07
		Ctrl vs. sCD74	0.56
		Ctrl vs. sCD74/MIF	1.83
		MIF vs. sCD74/MIF	0.41
		sCD74 vs. sCD74/MIF	1.46
Suppl. Figure 8D	Ccl7 mRNA	Ctrl vs. MIF	1.41
		Ctrl vs. sCD74	1.36
		Ctrl vs. sCD74/MIF	3.65
		MIF vs. sCD74/MIF	1.18
		sCD74 vs. sCD74/MIF	2.82
Suppl. Figure 15A	WT: CD74 surface expression at 0.5h	Ctrl vs. MIF	0.11
		Ctrl vs. sCD74	0.13
		Ctrl vs. sCD74/MIF	0.48
		MIF vs. sCD74/MIF	0.38
		sCD74 vs. sCD74/MIF	0.41
Suppl. Figure 15B	WT: CXCR2 surface expression at 0.5h	Ctrl vs. MIF	0.49
		Ctrl vs. sCD74	0.12
		Ctrl vs. sCD74/MIF	0.84
		MIF vs. sCD74/MIF	0.35
		sCD74 vs. sCD74/MIF	0.81
	Cd74-/-: CXCR2 surface expression at 0.5h	Ctrl vs. MIF	0.21
		Ctrl vs. sCD74	0.78
		Ctrl vs. sCD74/MIF	0.32
		MIF vs. sCD74/MIF	0.13
		sCD74 vs. sCD74/MIF	1.07
Suppl. Figure 15C	WT: CXCR4 surface expression at 0.5h	Ctrl vs. MIF	0.80
		Ctrl vs. sCD74	0.12
		Ctrl vs. sCD74/MIF	0.75
		MIF vs. sCD74/MIF	0.16
		sCD74 vs. sCD74/MIF	0.82
		Ctrl vs. MIF	0.02

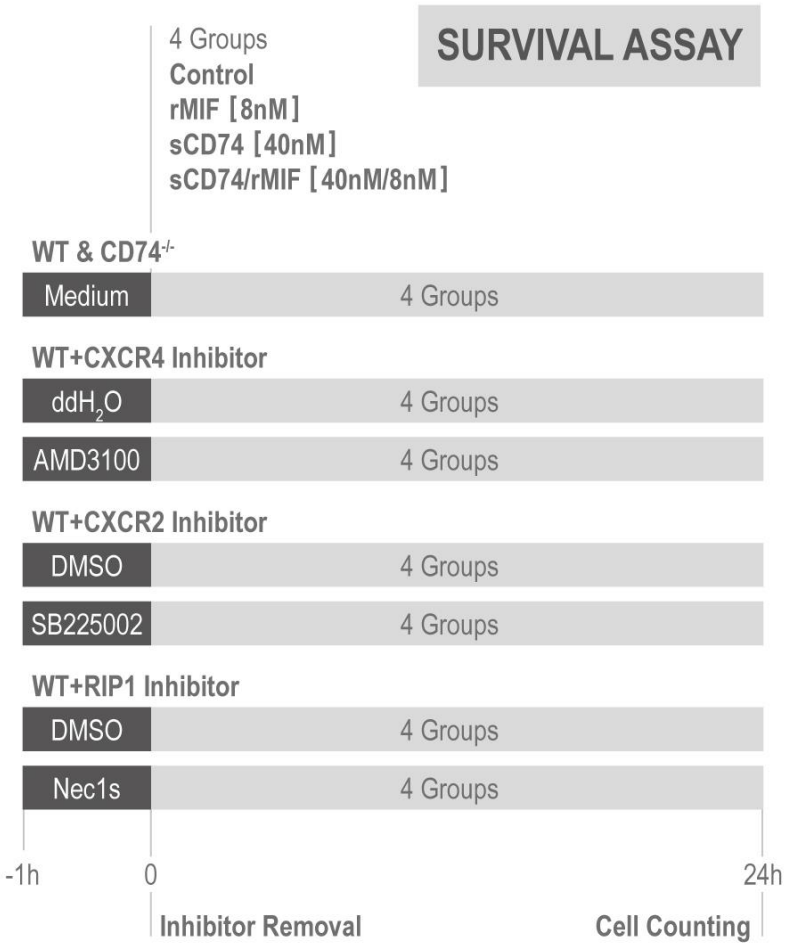
	Cd74-/-: CXCR4 surface expression at 0.5h	Ctrl vs. sCD74	0.25
		Ctrl vs. sCD74/MIF	0.03
		MIF vs. sCD74/MIF	0.02
		sCD74 vs. sCD74/MIF	0.25
Suppl. Figure 15D	WT: CD74 surface expression at 4h	Ctrl vs. MIF	1.71
		Ctrl vs. sCD74	0.01
		Ctrl vs. sCD74/MIF	0.02
		MIF vs. sCD74/MIF	2.10
		sCD74 vs. sCD74/MIF	0.03
Suppl. Figure 15E	WT: CXCR2 surface expression at 4h	Ctrl vs. MIF	0.33
		Ctrl vs. sCD74	0.11
		Ctrl vs. sCD74/MIF	1.59
		MIF vs. sCD74/MIF	1.20
		sCD74 vs. sCD74/MIF	2.00
	Cd74-/-: CXCR2 surface expression at 4h	Ctrl vs. MIF	2.17
		Ctrl vs. sCD74	0.98
		Ctrl vs. sCD74/MIF	1.91
		MIF vs. sCD74/MIF	0.18
		sCD74 vs. sCD74/MIF	2.67
Suppl. Figure 15F	WT: CXCR4 surface expression at 4h	Ctrl vs. MIF	4.11
		Ctrl vs. sCD74	2.82
		Ctrl vs. sCD74/MIF	5.20
		MIF vs. sCD74/MIF	2.49
		sCD74 vs. sCD74/MIF	3.60
	Cd74-/-: CXCR4 surface expression at 4h	Ctrl vs. MIF	0.21
		Ctrl vs. sCD74	0.15
		Ctrl vs. sCD74/MIF	0.41
		MIF vs. sCD74/MIF	0.23
		sCD74 vs. sCD74/MIF	0.23
Suppl. Figure 15G	WT: CD74 surface expression at 8h	Ctrl vs. MIF	1.07
		Ctrl vs. sCD74	0.27
		Ctrl vs. sCD74/MIF	5.62
		MIF vs. sCD74/MIF	5.14
		sCD74 vs. sCD74/MIF	2.26
Suppl. Figure 15H	WT: CXCR2 surface expression at 8h	Ctrl vs. MIF	0.01
		Ctrl vs. sCD74	0.37
		Ctrl vs. sCD74/MIF	2.66
		MIF vs. sCD74/MIF	1.68
		sCD74 vs. sCD74/MIF	2.76
	Cd74-/-: CXCR2 surface expression at 8h	Ctrl vs. MIF	1.18
		Ctrl vs. sCD74	0.53
		Ctrl vs. sCD74/MIF	1.15
		MIF vs. sCD74/MIF	0.04
		sCD74 vs. sCD74/MIF	1.47
Suppl. Figure 15I	WT: CXCR4 surface expression at 8h	Ctrl vs. MIF	3.42
		Ctrl vs. sCD74	2.39
		Ctrl vs. sCD74/MIF	3.00

		MIF vs. sCD74/MIF	0.36
		sCD74 vs. sCD74/MIF	1.47
	Cd74-/-: CXCR4 surface expression at 8h	Ctrl vs. MIF	0.21
		Ctrl vs. sCD74	0.13
		Ctrl vs. sCD74/MIF	0.59
		MIF vs. sCD74/MIF	0.41
		sCD74 vs. sCD74/MIF	0.49
Suppl. Figure 16A	WT: CD74 surface expression at 5min	Ctrl vs. MIF	1.67
		Ctrl vs. sCD74	2.08
		Ctrl vs. sCD74/MIF	2.65
		MIF vs. sCD74/MIF	0.37
		sCD74 vs. sCD74/MIF	0.32
Suppl. Figure 16B	WT: TLR2 surface expression at 0.5h	Ctrl vs. MIF	0.28
		Ctrl vs. sCD74	0.35
		Ctrl vs. sCD74/MIF	0.63
		MIF vs. sCD74/MIF	0.43
		sCD74 vs. sCD74/MIF	0.39
	Cd74-/-: TLR2 surface expression at 0.5h	Ctrl vs. MIF	0.63
		Ctrl vs. sCD74	0.01
		Ctrl vs. sCD74/MIF	0.68
		MIF vs. sCD74/MIF	0.14
		sCD74 vs. sCD74/MIF	0.65
Suppl. Figure 16C	WT: TLR4 surface expression at 0.5h	Ctrl vs. MIF	0.07
		Ctrl vs. sCD74	0.13
		Ctrl vs. sCD74/MIF	0.21
		MIF vs. sCD74/MIF	0.29
		sCD74 vs. sCD74/MIF	0.35
	Cd74-/-: TLR4 surface expression at 0.5h	Ctrl vs. MIF	0.14
		Ctrl vs. sCD74	0.67
		Ctrl vs. sCD74/MIF	3.62
		MIF vs. sCD74/MIF	1.19
		sCD74 vs. sCD74/MIF	0.50
Suppl. Figure 16D	WT: TNFRI surface expression at 0.5h	Ctrl vs. MIF	0.17
		Ctrl vs. sCD74	0.14
		Ctrl vs. sCD74/MIF	0.09
		MIF vs. sCD74/MIF	0.08
		sCD74 vs. sCD74/MIF	0.23
	Cd74-/-: TNFRI surface expression at 0.5h	Ctrl vs. MIF	1.81
		Ctrl vs. sCD74	3.98
		Ctrl vs. sCD74/MIF	2.91
		MIF vs. sCD74/MIF	0.28
		sCD74 vs. sCD74/MIF	0.00
Suppl. Figure 16E	WT: TLR2 surface expression at 4h	Ctrl vs. MIF	1.23
		Ctrl vs. sCD74	0.72
		Ctrl vs. sCD74/MIF	1.25
		MIF vs. sCD74/MIF	0.61
		sCD74 vs. sCD74/MIF	0.88

	Cd74-/-: TLR2 surface expression at 4h	Ctrl vs. MIF	0.80
		Ctrl vs. sCD74	0.17
		Ctrl vs. sCD74/MIF	0.98
		MIF vs. sCD74/MIF	0.53
		sCD74 vs. sCD74/MIF	1.00
Suppl. Figure 16F	WT: TLR4 surface expression at 4h	Ctrl vs. MIF	0.70
		Ctrl vs. sCD74	0.23
		Ctrl vs. sCD74/MIF	0.46
		MIF vs. sCD74/MIF	0.33
		sCD74 vs. sCD74/MIF	0.26
	Cd74-/-: TLR4 surface expression at 4h	Ctrl vs. MIF	0.67
		Ctrl vs. sCD74	2.06
		Ctrl vs. sCD74/MIF	0.19
		MIF vs. sCD74/MIF	0.36
		sCD74 vs. sCD74/MIF	1.28
Suppl. Figure 16G	WT: TNFRI surface expression at 4h	Ctrl vs. MIF	0.32
		Ctrl vs. sCD74	0.43
		Ctrl vs. sCD74/MIF	0.78
		MIF vs. sCD74/MIF	0.23
		sCD74 vs. sCD74/MIF	0.29
	Cd74-/-: TNFRI surface expression at 4h	Ctrl vs. MIF	0.03
		Ctrl vs. sCD74	0.40
		Ctrl vs. sCD74/MIF	0.70
		MIF vs. sCD74/MIF	0.64
		sCD74 vs. sCD74/MIF	0.51
Suppl. Figure 16H	WT: TLR2 surface expression at 8h	Ctrl vs. MIF	1.51
		Ctrl vs. sCD74	0.00
		Ctrl vs. sCD74/MIF	1.77
		MIF vs. sCD74/MIF	0.50
		sCD74 vs. sCD74/MIF	1.79
	Cd74-/-: TLR2 surface expression at 8h	Ctrl vs. MIF	0.73
		Ctrl vs. sCD74	0.11
		Ctrl vs. sCD74/MIF	0.84
		MIF vs. sCD74/MIF	0.45
		sCD74 vs. sCD74/MIF	0.77
Suppl. Figure 16I	WT: TLR4 surface expression at 8h	Ctrl vs. MIF	0.74
		Ctrl vs. sCD74	0.84
		Ctrl vs. sCD74/MIF	0.89
		MIF vs. sCD74/MIF	0.18
		sCD74 vs. sCD74/MIF	0.20
	Cd74-/-: TLR4 surface expression at 8h	Ctrl vs. MIF	0.99
		Ctrl vs. sCD74	1.18
		Ctrl vs. sCD74/MIF	1.45
		MIF vs. sCD74/MIF	1.00
		sCD74 vs. sCD74/MIF	1.89
Suppl. Figure 16J	WT: TNFRI surface expression at 8h	Ctrl vs. MIF	0.04
		Ctrl vs. sCD74	0.51

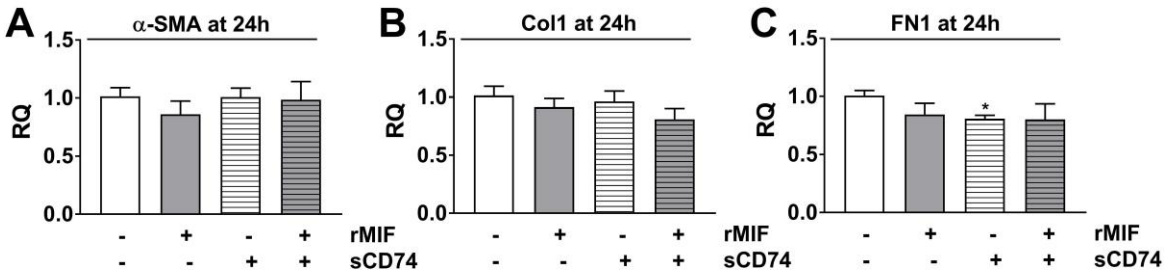
		Ctrl vs. sCD74/MIF	0.19
		MIF vs. sCD74/MIF	0.22
		sCD74 vs. sCD74/MIF	0.62
	Cd74-/-: TNFRI surface expression at 8h	Ctrl vs. MIF	0.86
		Ctrl vs. sCD74	2.23
		Ctrl vs. sCD74/MIF	0.53
		MIF vs. sCD74/MIF	0.09
		sCD74 vs. sCD74/MIF	0.19

Figure S1. Experimental Setup.



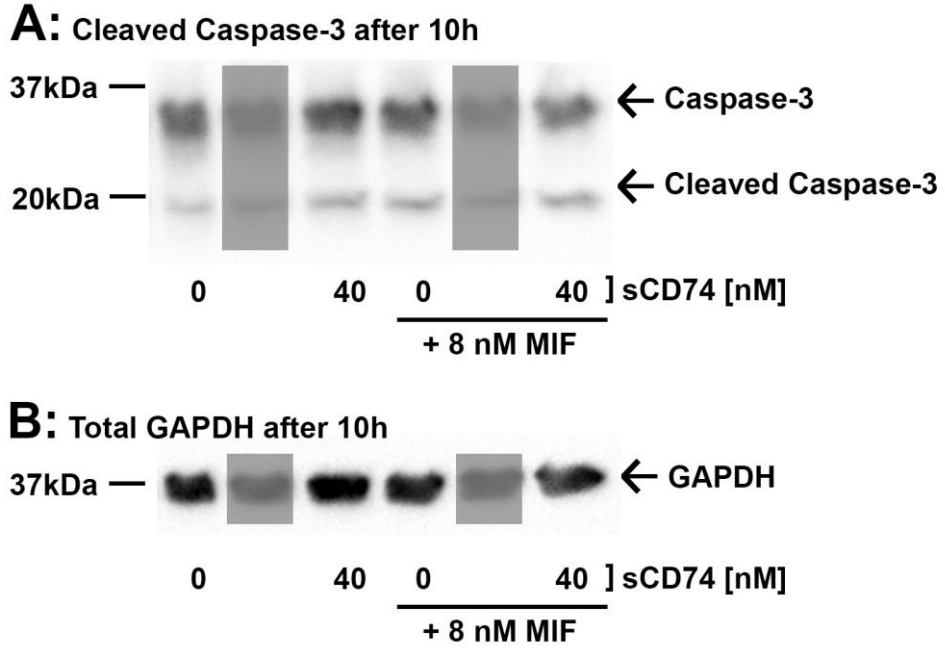
Cardiac myofibroblasts were randomized into four groups, which were incubated either with medium (group1: control), 8 nmol/L rMIF (group2: rMIF), 40 nmol/L sCD74 (group3: sCD74) or five-fold molar excess of sCD74 to rMIF (group4: sCD74/rMIF) for 24 h. For inhibition studies in WT myofibroblasts, cells were treated with either the inhibitor compound (AMD3100, SB225002, Nec1s) or the appropriate solvent as control (ddH_2O or DMSO). Following 1 h of incubation, both solvent and inhibitor-pretreated cells were stimulated either with medium, rMIF, sCD74 or sCD74/rMIF and maintained for further 20-24 h.

Figure S2. Treatment with sCD74/MIF did not induce de-differentiation of myofibroblasts to a quiescent fibroblast.



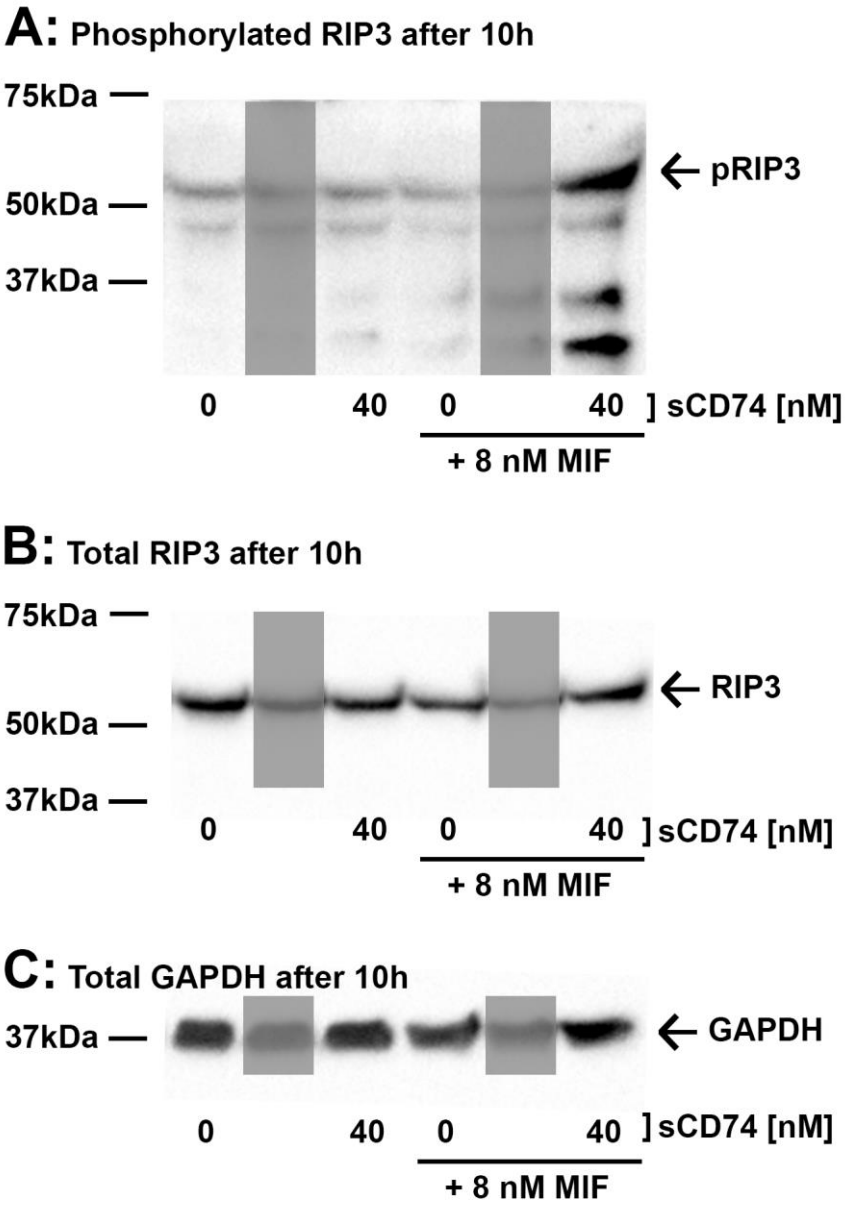
Following treatment of cardiac myofibroblasts with vehicle, sCD74, rMIF or sCD74/rMIF for 24 h, mRNA expression of **(A)** α-smooth muscle actin (α-SMA), **(B)** collagen 1α1 (Col1α1) and **(C)** fibronectin 1 (FN1) were assessed via RT-qPCR method. Data represent mean±SEM of six independent experiments and were analyzed with a two-tailed, unpaired t-test corrected for multiple comparison (n=5). *p<0.05 vs. control.

Figure S3. Representative blots of cleaved caspase-3 and GAPDH 10 h after treatment with increasing concentrations of sCD74 either with or without MIF.



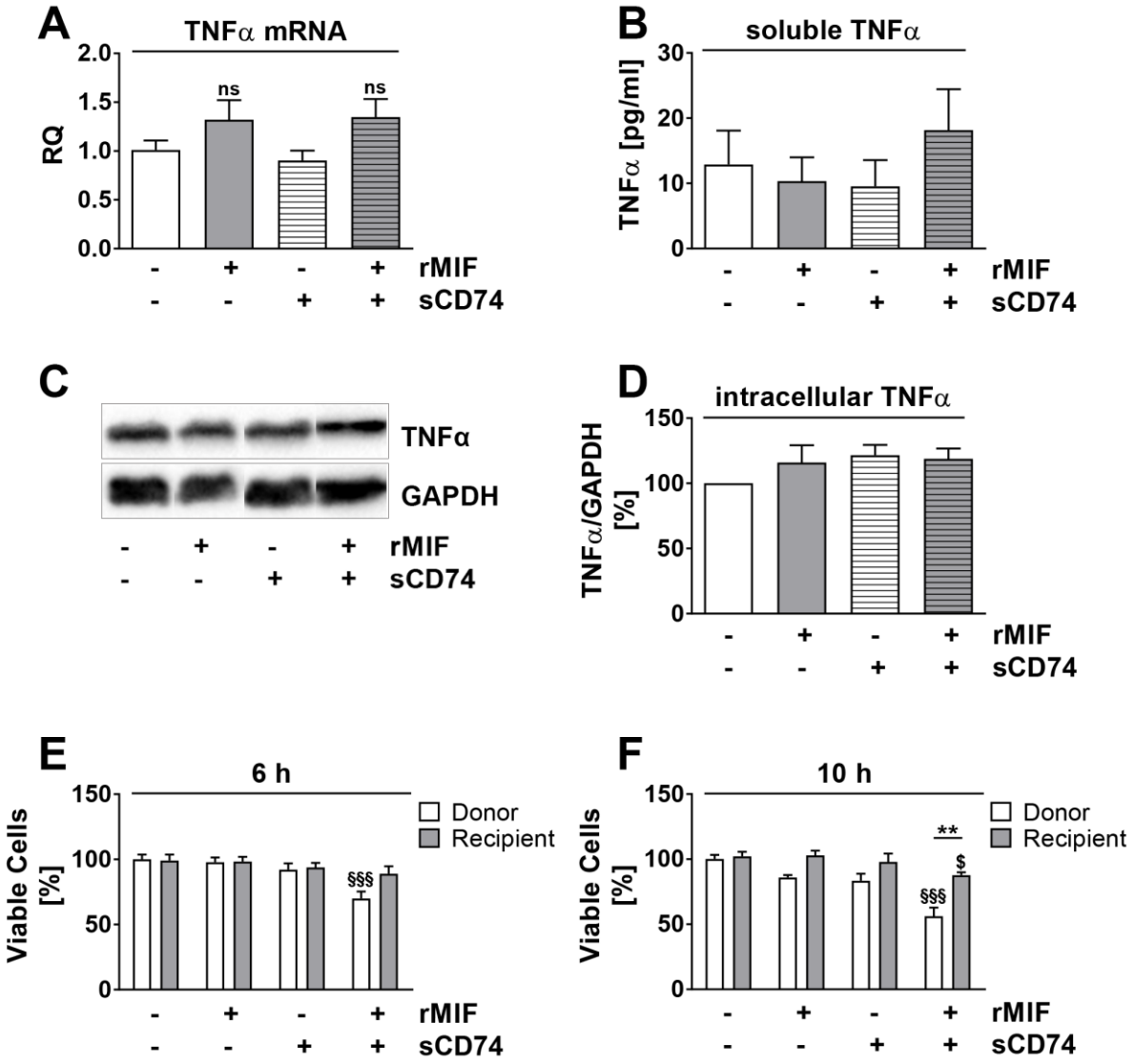
WT myofibroblasts were stimulated with medium and 40 nmol/L sCD74 either in the absence or presence of 8 nmol/L rMIF. **(A)** Full-length and cleaved caspase-3 and **(B)** GAPDH were assessed 10 h after stimulation by Western blotting.

Figure S4. Representative blots of pRIP3, RIP3 and GAPDH 10 h after treatment with increasing concentrations of sCD74 either with or without MIF.



WT myofibroblasts were stimulated with medium and 40 nmol/L sCD74 either in the absence or presence of 8 nmol/L rMIF. **(A)** Phosphorylation of RIP3, **(B)** total RIP3 and **(C)** GAPDH were assessed 10 h after stimulation by Western blotting.

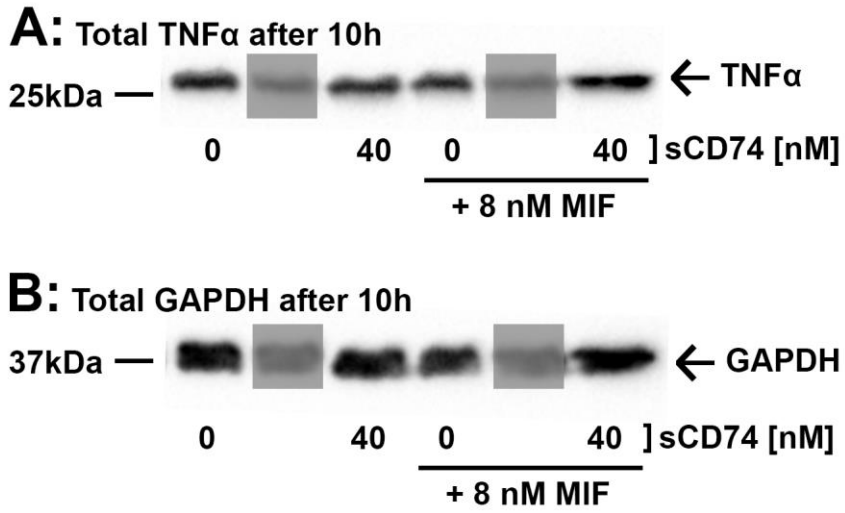
Figure S5. TNFα could not be identified as mediator of sCD74/MIF-induced necroptosis.



WT fibroblasts were stimulated solitarily or simultaneously with 40 nmol/L sCD74 and 8 nmol/L rMIF. **(A)** mRNA levels (via RT-PCR) as well as **(B)** extracellular (via ELISA) and **(C-D)** intracellular protein levels of TNFα (via Western blotting) were determined. Instead of showing the whole blot, relevant bands were cut out and arranged in the respective order. The uncut blots are shown in Figure S6). **(E-F)** For the supernatant transfer experiments, WT myofibroblasts were stimulated solitarily or simultaneously with sCD74 and rMIF (donor). After supernatant was transferred to untreated WT cells (recipient). Both donor and recipient cells

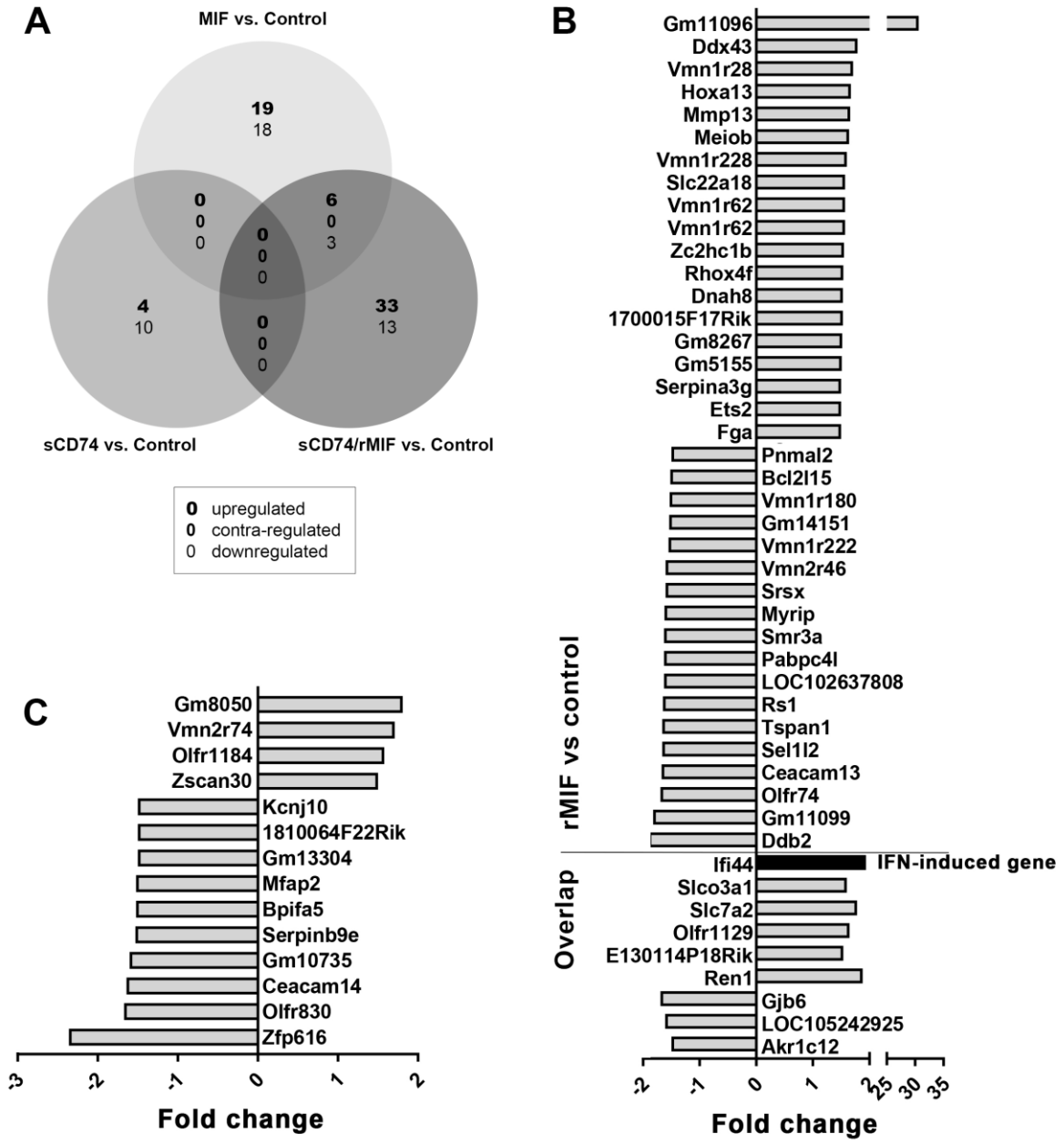
were maintained for further 20-24 h followed by Trypan blue staining and automated counting. Data represent mean±SEM of at least (A) eight, (B) six, (D) eight, (E) ten and (F) eight independent experiments. Data were analyzed with a two-tailed, unpaired t-test and corrected for multiple comparison (A-D: n=5; E-F: n=7) using Bonferroni posttest. $^{§§§}p<0.001$ vs. control of donor cells; $^{\$}p<0.05$ vs. control of recipient cells; **p<0.01 donor vs. recipient.

Figure S6. Representative blots of TNFα and GAPDH 10 h after treatment with increasing concentrations of sCD74 either with or without MIF.



WT myofibroblasts were stimulated with medium and 40 nmol/L sCD74 either in the absence or presence of 8 nmol/L rMIF. **(A)** TNFα and **(B)** GAPDH were assessed 10 h after stimulation by Western blotting.

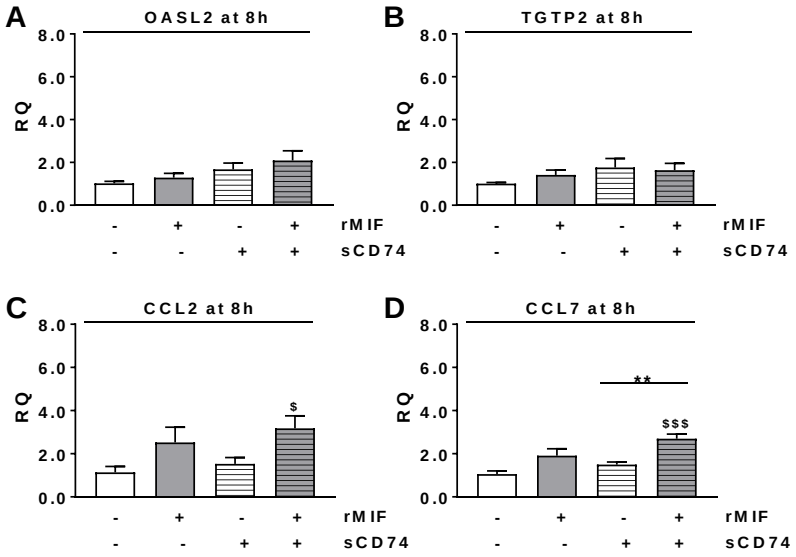
Figure S7. sCD74/MIF-dependent gene expression differs largely from those induced by MIF or sCD74.



(A) Venn diagram of overlapping and unique effects of sCD74, rMIF and sCD74/rMIF on gene expression. A total of 115 genes with a fold change ≥1.5 among the differentially expressed genes are represented. Venn diagram was generated using Vennplex**. (B)**The genes with at least 1.5-fold change following rMIF treatment compared to control were depicted. The marginal overlap between rMIF and sCD74/rMIF stimulation were marked. **(C)** The genes with at least 1.5-fold change following

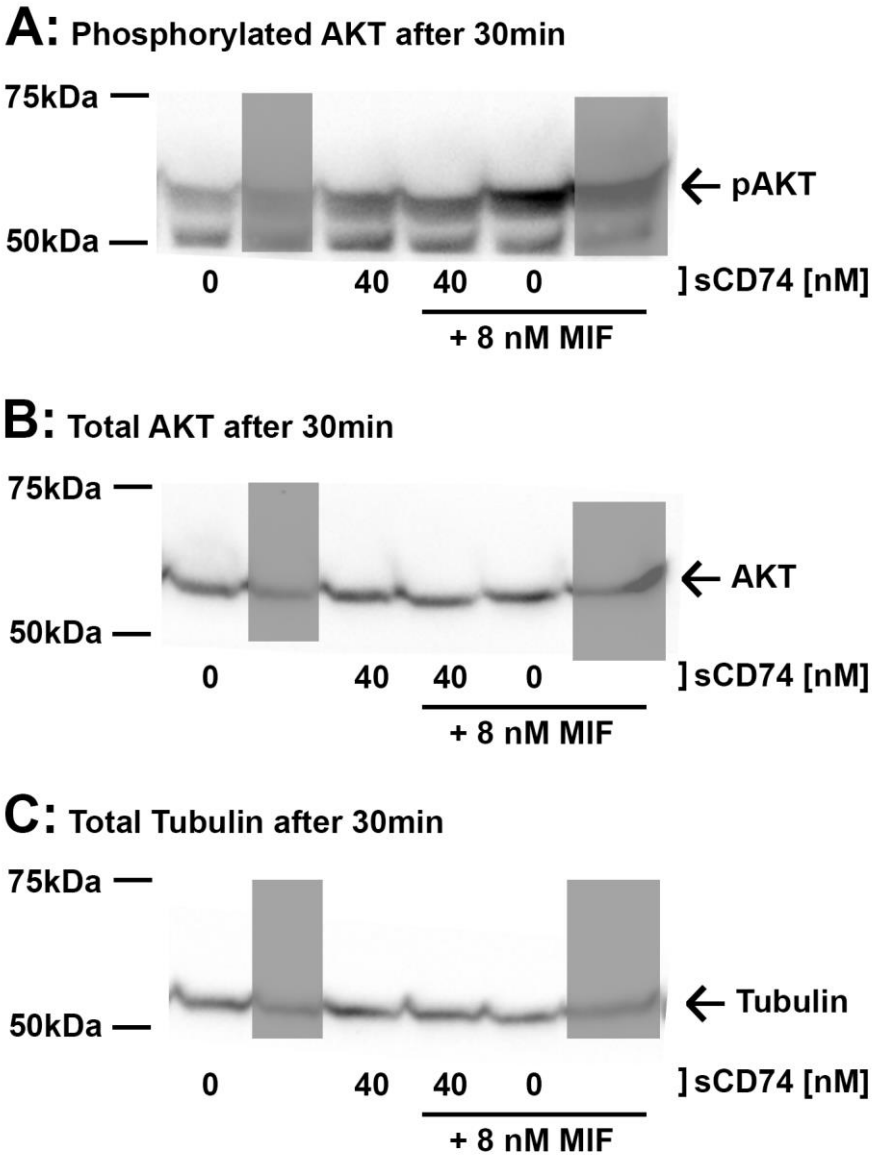
sCD74 treatment compared to control were depicted. Type I IFN-induced genes are labeled as black bars. Genes labeled as grey bars seem not to contribute to specialized function and pathways. Independent triplicates were performed. The corresponding p-values are listed in Table S1.

Figure S8. Treatment with sCD74/MIF significantly upregulates gene expression of cytokines.



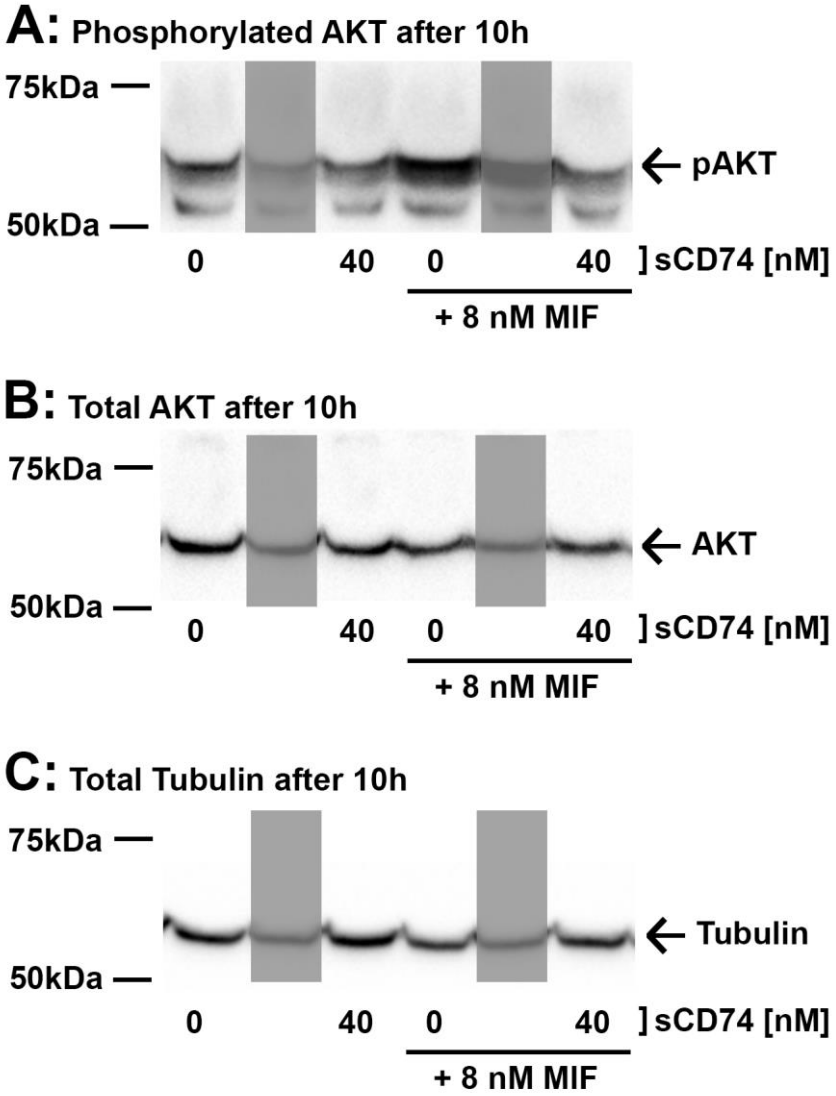
RT-qPCR was performed with the cDNA and Taqman probes. Data represent mean±SEM of at least four independent experiments and were analyzed with a two-tailed, unpaired t-test with multiple correction (n=5). $^{\$}p<0.05$; $^{\$\$\$}p<0.001$ vs. control respectively; $^{**}p<0.01$ vs. sCD74.

Figure S9. Representative blots of pAKT, AKT and Tubulin 30 min after treatment with increasing concentrations of sCD74 either with or without MIF.



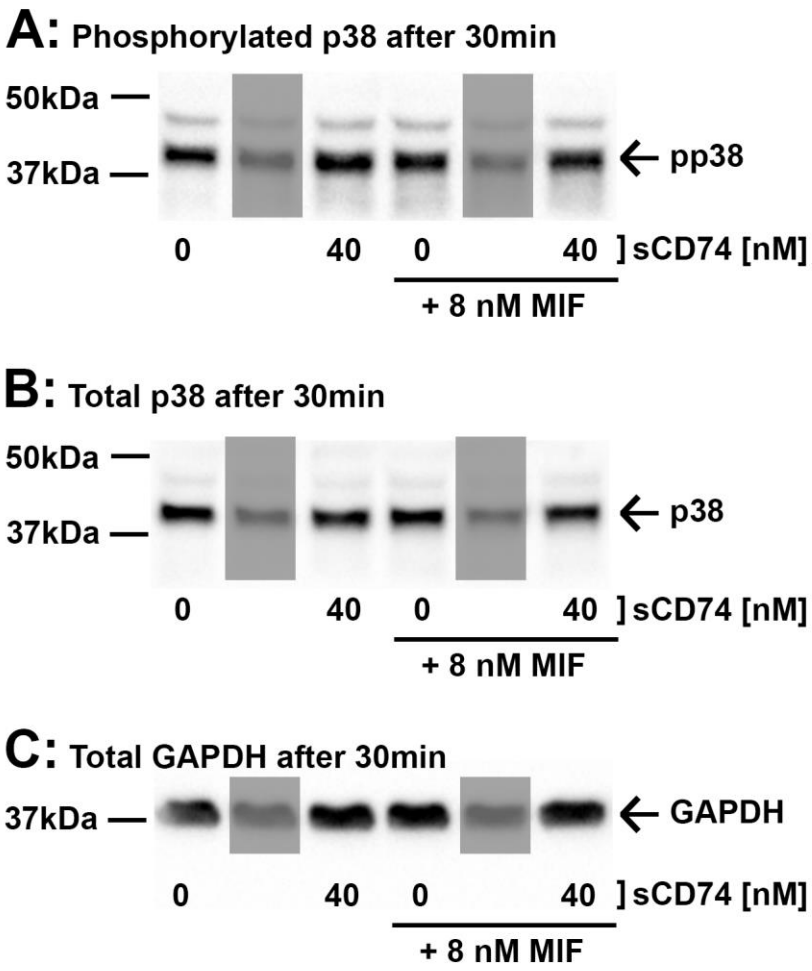
WT myofibroblasts were stimulated with medium and 40 nmol/L sCD74 either in the absence or presence of 8 nmol/L rMIF. **(A)** Phosphorylation of AKT, **(B)** total AKT and **(C)** Tubulin were assessed 30 min after stimulation by Western blotting.

Figure S10. Representative blots of pAKT, AKT and Tubulin 10 h after treatment with increasing concentrations of sCD74 either with or without MIF.



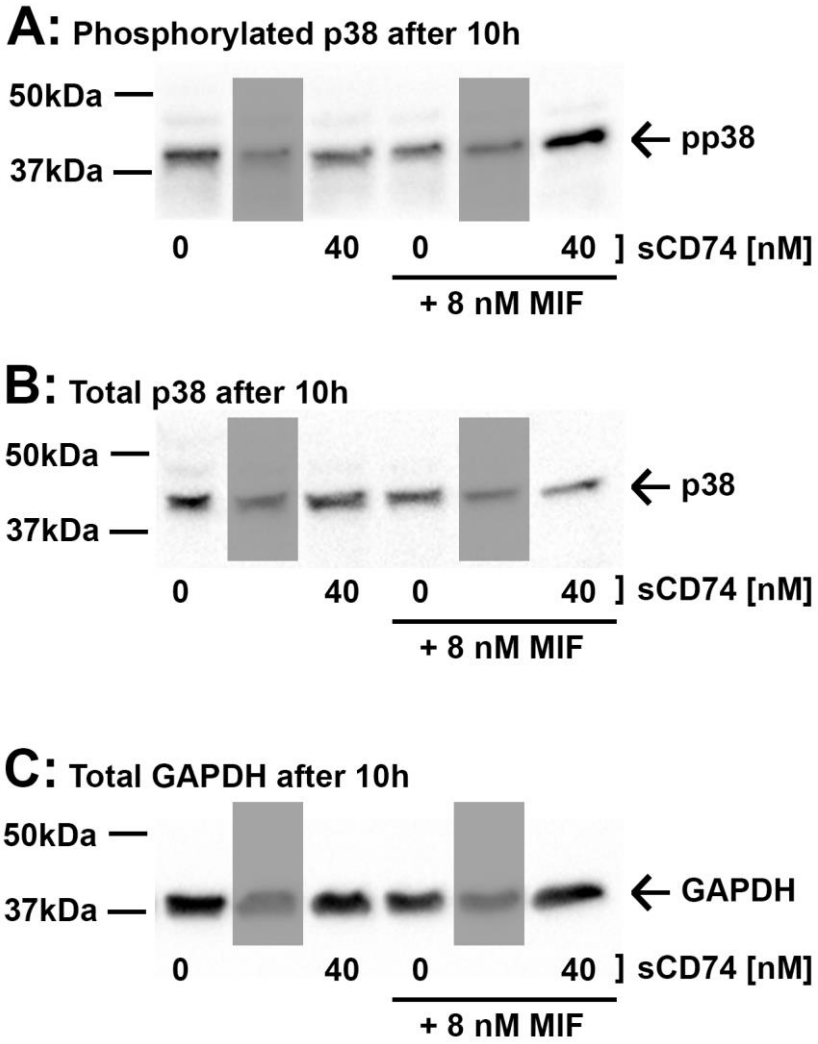
WT myofibroblasts were stimulated with medium and 40 nmol/L sCD74 either in the absence or presence of 8 nmol/L rMIF. **(A)** Phosphorylation of AKT, **(B)** total AKT and **(C)** Tubulin were assessed 10 h after stimulation by Western blotting.

Figure S11. Representative blots of pp38, p38 and GAPDH 30 min after treatment with increasing concentrations of sCD74 either with or without MIF.



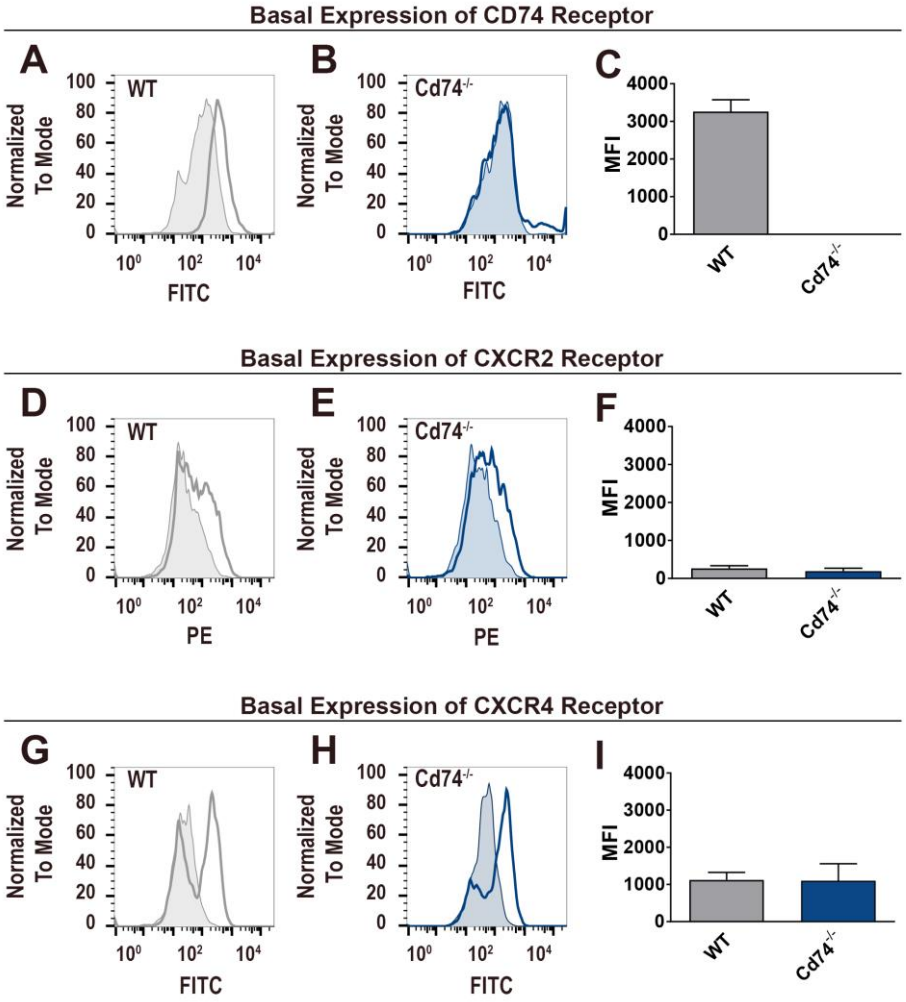
WT myofibroblasts were stimulated with medium and 40 nmol/L sCD74 either in the absence or presence of 8 nmol/L rMIF. **(A)** Phosphorylation of p38, **(B)** total p38 and **(C)** GAPDH were assessed 30 min after stimulation by Western blotting.

Figure S12. Representative blots of pp38, p38 and GAPDH 10 h after treatment with increasing concentrations of sCD74 either with or without MIF.



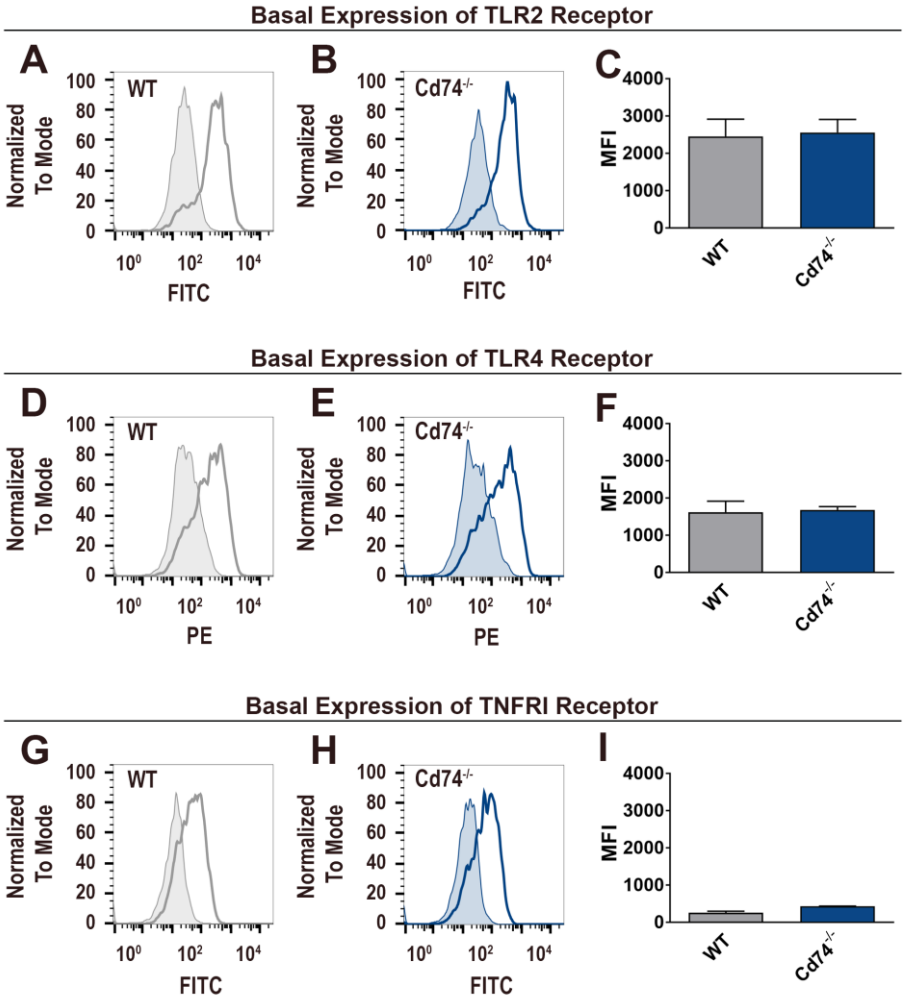
WT myofibroblasts were stimulated with medium and 40 nmol/L sCD74 either in the absence or presence of 8 nmol/L rMIF. **(A)** Phosphorylation of p38, **(B)** total p38 and **(C)** GAPDH were assessed 10 h after stimulation by Western blotting.

Figure S13. Basal surface expression levels of MIF receptors CD74, CXCR2 and CXCR4 in WT and *Cd74*$^{-/-}$ myofibroblasts.



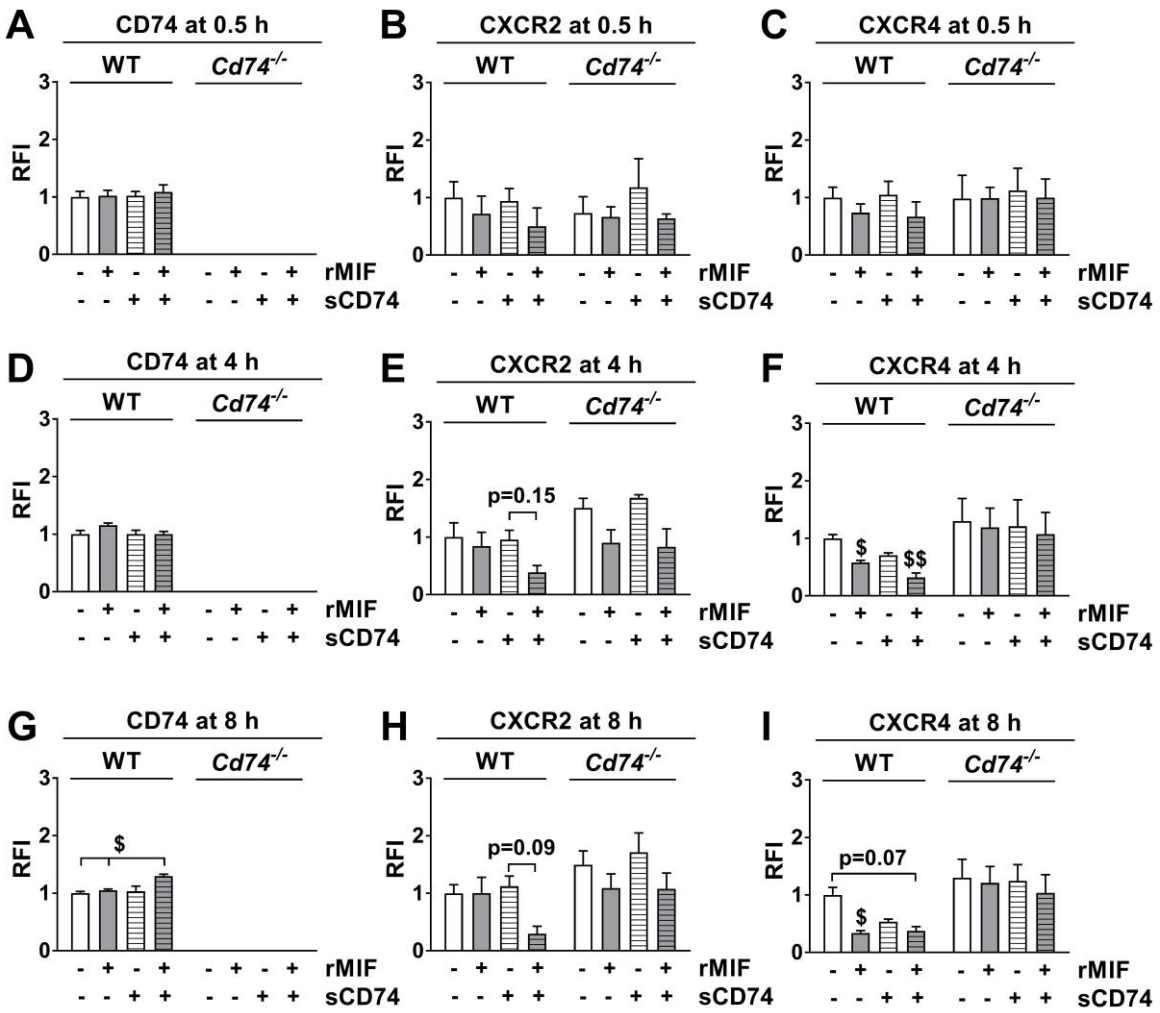
WT and *Cd74*$^{-/-}$ myofibroblasts were detached by scraping and cell surface expression of **(A-C)** CD74, **(D-F)** CXCR2 and **(G-I)** CXCR4 receptor were analyzed by flow cytometry. The median fluorescence intensity (MFI) of isotype control was subtracted from MFI of its appropriate antibody preparation. Data represent mean±SEM of at least three independent experiments.

Figure S14. Basal surface expression of TLR2, TLR4 and TNFRI in WT and *Cd74*$^{-/-}$ myofibroblasts.



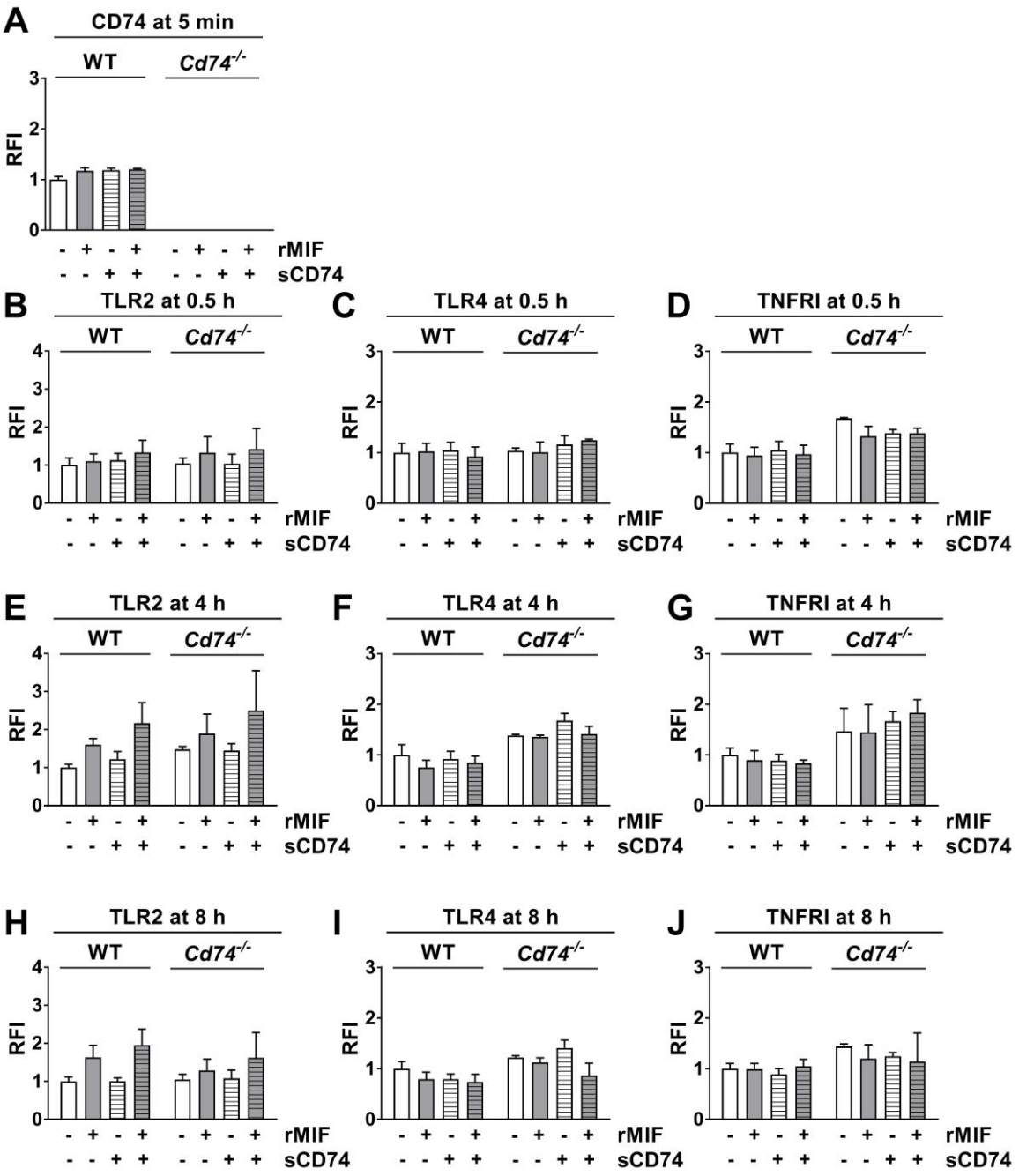
WT and *Cd74*$^{-/-}$ myofibroblasts were detached by scraping and cell surface expression of **(A-C)** TLR2, **(D-F)** TLR4 and **(G-I)** TNFRI receptor were analyzed by flow cytometry. The median fluorescence intensity (MFI) of isotype control was subtracted from MFI of its appropriate antibody preparation. Data represent mean±SEM of at least three independent experiments.

Figure S15. sCD74/rMIF induces rapid and prolonged chemokine receptor internalization.



WT and *Cd74*$^{-/-}$ myofibroblasts were stimulated with sCD74 either alone or with MIF for **(A-C)** 0.5 h, **(D-F)** 4 h and **(G-I)** 8 h. Subsequently, cells were detached by scraping and cell surface expression of **(A, D, G)** CD74, **(B,E,H)** CXCR2 and **(C,F,I)** CXCR4 receptor were analyzed by flow cytometry. The relative fluorescence intensity (RFI) of isotype control was subtracted from MFI of its appropriate antibody preparation. Data represent mean±SEM of at least three independent experiments. $^{\$}p<0.05$, $^{\$\$}p<0.01$ vs. control respectively.

Figure S16. Increased TLR2 expression following sCD74/rMIF stimulation.



WT and *Cd74*$^{-/-}$ myofibroblasts were stimulated with sCD74 either alone or with MIF for **(A)** 5 min **(B-D)** 0.5 h, **(E-G)** 4 h and **(H-J)** 8 h. Subsequently, cells were detached by scraping and cell surface expression of **(A)** CD74, **(B, E, H)** TLR2, **(C,F,I)** TLR4 and **(D,G,J)** TNFRI receptor were analyzed by flow cytometry. The relative fluorescence intensity (RFI) of isotype control was subtracted from MFI of its appropriate antibody preparation. Data represent mean±SEM of at least three independent experiments.