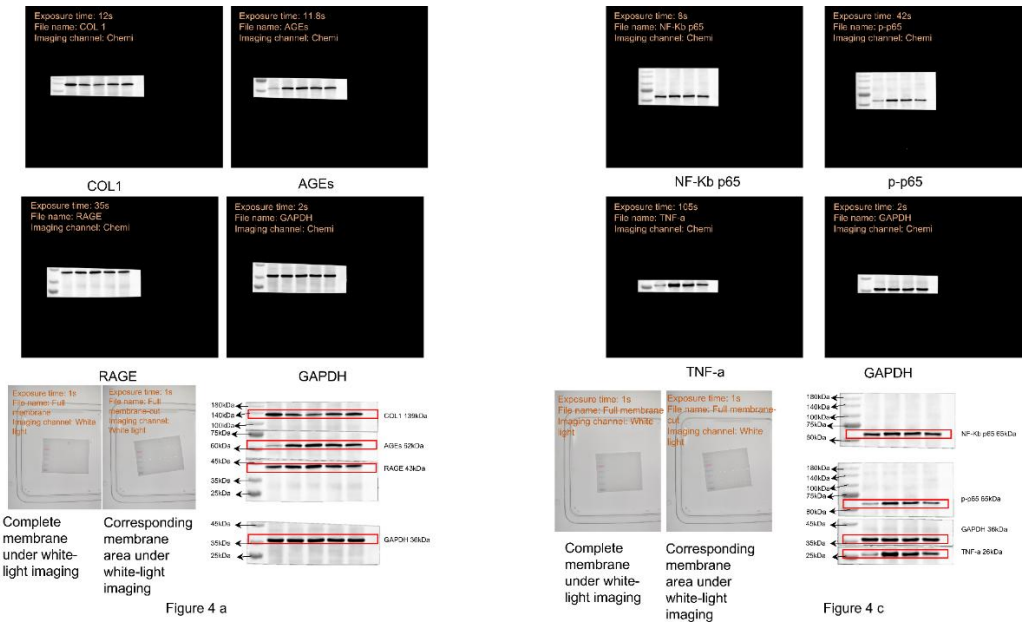


Figure 4 a

Figure 4 c

Supplementary Figure 1 Raw data of Figure 4A-C.

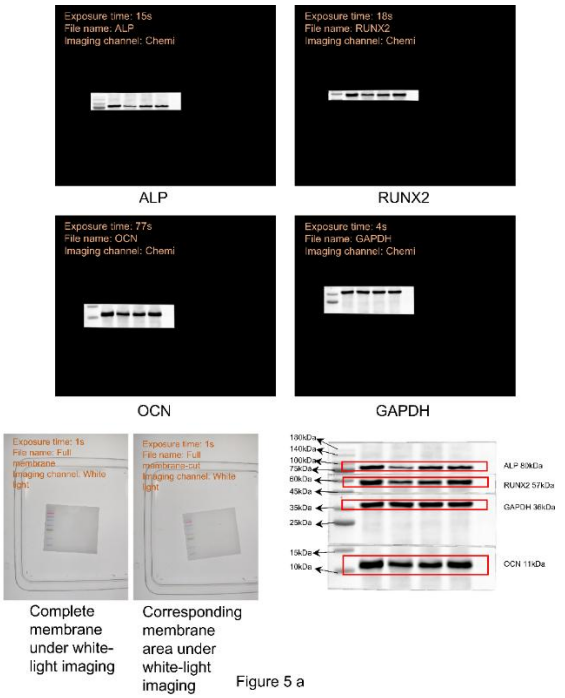


Figure 5 a

Supplementary Figure 2 Raw data of Figure 5A.

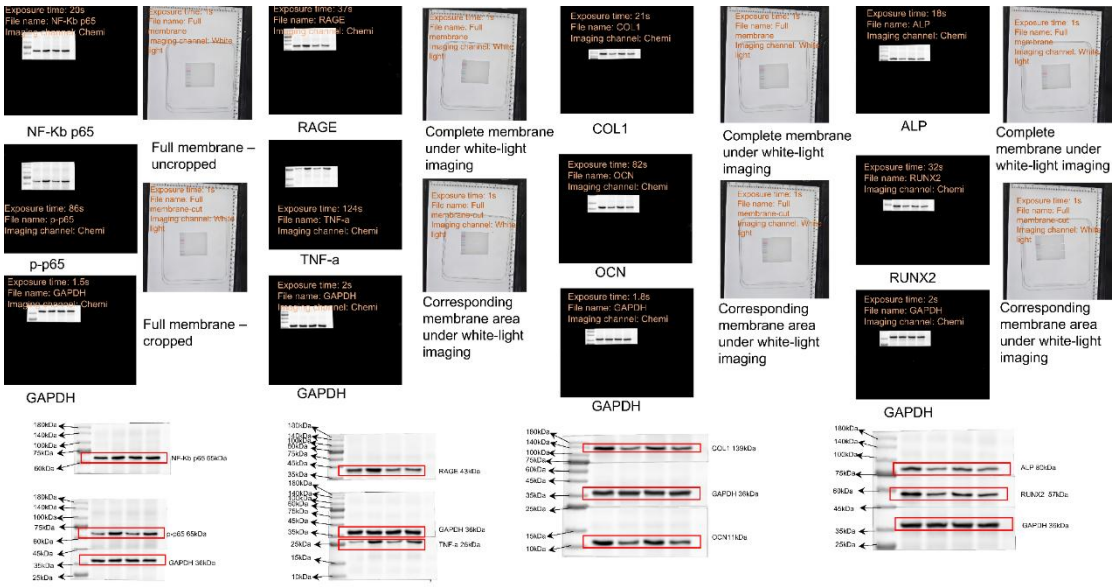


Figure 6 a Figure 6 c Figure 6 e Figure 6 g

Supplementary Figure 3 Raw data-Figure 6A, C, E, and G.

Supplementary Table 1 Primary antibodies and horseradish peroxidase-conjugated secondary antibodies were obtained from Proteintech or Bioss

English name	Abbreviation	Specification / Size	Catalog No.	Brand / supplier (city)	Country
advanced glycation end products	AGEs	100ul	bs-1158P	Bioss (Beijing Biosynthesis Biotechnology Co., Ltd., Beijing)	China
canagliflozin	Cana	10 mg	M2002	AbMole (Abmole Bioscience Inc., Houston, TX)	USA
methylglyoxal	MGO	50 g	M109035	Aladdin (Shanghai Aladdin Biochemical Technology Co., Ltd., Shanghai)	China
Aminoguanidine Hydrochloride		≥98%，25 g	A151036-25g	Aladdin (Shanghai Aladdin Biochemical Technology Co., Ltd., Shanghai)	China
collagen I	COL1	2 mL	40125ES10	Yeasen Biotechnology (Shanghai) Co., Ltd., Shanghai	China
Phorbol 12-myristate 13-acetate	PMA	10 mg	HY-18739	MedChemExpress LLC, Monmouth Junction, NJ	USA

Supplementary Table 2 Antibody catalogue numbers, host species, working dilutions, and manufacturer-stated molecular weights

English name	Abbreviation/Target	Size/Specification	Catalog No.	Brand / supplier (city)	Country	Host/Isotype	Antibody type	Working dilution	Molecular weight
Collagen Type I Monoclonal antibody	COL1 / COL1A1	20 μL	67288-1-Ig	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Mouse / IgG1	Monoclonal	WB 1:5000–1:50000	139 kDa
Anti-AGE / AGE-modified protein antibody	AGE-modified proteins	50 μL	bs-1158R	Bioss (Beijing Biosynthesis Biotechnology Co., Ltd., Beijing)	China	Rabbit / IgG	Polyclonal	WB 1:1000	62kDa
AGER/RAGE Polyclonal antibody	RAGE / AGER	50 μL	16346-1-AP	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Rabbit / IgG	Polyclonal	WB 1:3000	43 kDa

NF-κB p65 Polyclonal antibody	p65 / RELA	50 μL	10745-1-AP	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Rabbit / IgG	Polyclonal	WB 1:2000	65 kDa
Phospho-NF-κB p65 (Ser536) Recombinant antibody	p-p65 / p-RELA	50 μL	80379-2-RR	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Rabbit / IgG	Recombinant monoclonal	WB 1:5000	65 kDa
TNF-alpha Polyclonal antibody	TNF-α / TNF	50 μL	17590-1-AP	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Rabbit / IgG	Polyclonal	WB 1:4000	26 kDa
ALPL Polyclonal antibody	ALP / ALPL	50 μL	11187-1-AP	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Rabbit / IgG	Polyclonal	WB 1:2000	80 kDa
RUNX2 Recombinant antibody	RUNX2	50 μL	82636-2-RR	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Rabbit / IgG	Recombinant monoclonal	WB 1:5000; IF 1:500	57 kDa

Osteocalcin/OCN Polyclonal antibody	OCN / BGLAP	50 μL	16157-1-AP	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Rabbit / IgG	Polyclonal	WB 1:2000	11 kDa
GAPDH Monoclonal antibody	GAPDH	100 μL	60004-1-Ig	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Mouse / IgG	Monoclonal	WB 1:20000	36 kDa
Multi-rAb HRP-Goat Anti-Mouse Recombinant Secondary Antibody (H+L)	Anti-Mouse IgG	50 μL	RGAM001	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Goat anti-Mouse	Recombinant secondary antibody	1:20000	N/A
Multi-rAb HRP-Goat Anti-Rabbit Recombinant Secondary Antibody (H+L)	Anti-Rabbit IgG	50 μL	RGAR001	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	Goat anti-Rabbit	Recombinant secondary antibody	1:20000	N/A
WB antibody diluent	—	50 mL	PR20039	Proteintech (Wuhan Sanying Biotechnology Co., Ltd., Wuhan)	China	N/A	N/A	N/A	N/A

Supplementary Table 3 Primer sequences

Name	Sequence (5'->3')
COLLAGEN	
Forward primer	ACCTCCGGCTCCTGCTCCTCTTAG
Reverse primer	GCGCCGGGGCAGTTCTTGGTCT
RAGE (Ager)	
Forward primer	CCTGGATGGGAAACCCAACT
Reverse primer	CAGGTCACAGGTGGCCTATT
P65(Rela)	
Forward primer	GCTCCTAAGGTGCTGACA
Reverse primer	ACCTCCGAAAGCGAGATA
TNF(Tnf)	
Forward primer	CCAGACCCTCACACTCAGATCA
Reverse primer	GGAGGCTGACTTTCTCCTGGTA

ALP(Alpl)	
Forward primer	TCCGTGGGTCGGATTCCT
Reverse primer	GCCGGCCCAAGAGAGAA
RUNX（RUNX2）	
Forward primer	CACAAGTGCGGTGCAAACTT
Reverse primer	TGCTTGCAGCCTTAAATGACT
OCN(Bglap)	
Forward primer	CTGACCTCACAGATGCCAAG
Reverse primer	AAGGTAGTGAACAGACTCCG
GAPDH	
Forward primer	GTGCTGAGTATGTCGTGGAGT
Reverse primer	TGTCTTCTGAGTGGCAGTGAT

Supplementary Table 4 The siRNA sequences and working concentration of 50 nM

Name	Target Gene	Species	Gene ID / RefSeq	Target Sequence, 5′–3′	Sense Strand, 5′–3′	Antisense Strand, 5′–3′	Modification	Supplier / Vendor	Transfection Reagent	Final siRNA Concentration	Transfection Duration	Subsequent Treatment	Validation Marker / Validation Index
siNC	Non-targeting control	Mouse	N/A	N/A	UUCUCCGAACGUGUCACGUdTdT	ACGUGACACGUUCGGAGAAdTdT	3′ dTdT overhang	Shanghai GenePharma Co., Ltd., Shanghai, China	Lipofectamine™ RNAiMAX Transfection Reagent (cat. no. 13778150; Invitrogen, Thermo Fisher Scientific, Carlsbad, CA, USA)	50 nM	24–48 h	NGF 或 AGEs 200 μg/mL	Negative control; does not target any known mouse gene

si Ager-1	Ager / RAGE	Mouse	Gene ID: 11596; NM_007425.3	TGC AGT TTC AGC CTG GGC C	UGC AGU UUC AGC CUG GGC CdTdT	GGC CCA GGC UGA AAC UGC AdTdT	3′ dT dT overhang	Shanghai GenePharma Co., Ltd., Shanghai, China	Lipofectamine™ RNAiMAX Transfection Reagent (cat. no. 13778150; Invitrogen, Thermo Fisher Scientific, Carlsbad, CA, USA)	50 nM	24–48 h	AGEs 200 μg/mL	Ager detection by qPCR; RAGE detection by Western blot
si Ager-2	Ager / RAGE	Mouse	Gene ID: 11596; NM_007425.3	CTG TCA GCA TCA GGG TCA C	CUG UCA GCA UCA GGG UCA CdTdT	GUG ACCC UGA UGC UGA CAGdTdT	3′ dT dT overhang	Shanghai GenePharma Co., Ltd., Shanghai, China	Lipofectamine™ RNAiMAX Transfection Reagent (cat. no. 13778150; Invitrogen, Thermo Fisher Scientific, Carlsbad, CA, USA)	50 nM	24–48 h	AGEs 200 μg/mL	Ager detection by qPCR; RAGE detection by Western blot

siAger-3	Ager / RAGE	Mouse	Gene ID: 115966; NM_007425.3	GGAGGGACGTGCAGCT G	GGAGGGACGUGCAGCU GdTdT	CAGCUCUGCACGUUUCCdTdT	3′ dTdTover hang	Shanghai GenePharma Co., Ltd., Shanghai, China	Lipofectamine™ RNAiMAX Transfection Reagent (cat. no. 13778150; Invitrogen, Thermo Fisher Scientific, Carlsbad, CA, USA)	50 nM	24–48 h	AGEs 200 μg/mL	Ager detection by qPCR; RAGE detection by Western blot
NF-κB activator	NF-κB pathway reactivation	Mouse cells	N/A	N/A	N/A	N/A	N/A	MedChemExpress LLC, Monmouth Junction, NJ, USA	N/A	PMA 100 nM	Treated simultaneously with AGEs or treated before sample collection	AGEs + siRAGE + PMA	p-p65/p65 detection by Western blot; Rela and Tnf detection by qPCR

Note: siNC, negative control siRNA; siAger, siRNA targeting mouse Ager/RAGE; PMA, phorbol 12-myristate 13-acetate. MC3T3-E1 cells were transfected with siRNA at a final concentration of 50 nM for 24–48 h, followed by treatment with AGEs 200 μg/mL with or without PMA. Knockdown efficiency was confirmed by qPCR and Western blotting. NF-κB reactivation was verified by increased p-p65/p65 ratio and downstream Tnf expression.