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ORIGINAL ARTICLE

Chemokine (C–X–C motif) receptor 2 blockade by SB265610 inhibited angiotensin II-induced abdominal aortic aneurysm in Apo $E^{-/-}$ mice

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Abstract

Inflammation plays a critical role in the development of abdominal aortic aneurysm (AAA). Chemokine receptor CXCR2 mediates inflammatory cell chemotaxis in several diseases. However, the role of CXCR2 in AAA and the underlying mechanisms remain unknown. In this study, we found that the CXCR2 expressions in AAA tissues from human and angiotensin II (Ang II)-infused apolipoprotein E knockout (Apo $E^{-/-}$) mice were significantly increased. The pharmacological inhibition of CXCR2 (SB265610) markedly reduced Ang II-induced AAA formation. Furthermore, SB265610 treatment significantly reduced collagen deposition, elastin degradation, the metal matrix metalloprotease expression and accumulation of macrophage cells. In conclusion, these results showed CXCR2 plays a pathogenic role in AAA formation. Inhibition of CXCR2 pathway may represent a novel therapeutic approach to treat AAA.

Keywords Chemoreceptor · CXCR2 · AAA · Inflammation · Macrophage

Abbreviations

CXCR2	Chemokine (C–X–C motif) receptor 2
AAA	Abdominal aortic aneurysms
Ang II	Angiotensin II
MMPs	Metalloproteinases
DCs	Dendritic cells
TNF-α	Tumor necrosis factor-α
IFN-γ	Interferon-γ

Hao Nie and Hong-Xia Wang contributed equally to the present work.

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Introduction

Abdominal aortic aneurysm (AAA) is permanent dilation of the abdominal aorta common in people aged > 65 years, which can lead to fatal aortic rupture, if left untreated. Histological features of AAA involve smooth muscle cell apoptosis, elastin fragmentation and inflammatory cell infiltration in adventitial and medial layers of vessel [1–3]. The pathogenesis of AAA is a highly complex process, including genetic abnormalities, biomechanical wall stress, apoptosis, and proteolytic degradation of the aortic wall, an as yet uncertainty [4]. However, recent studies demonstrated that chemokine-directed chronic transmural inflammatory cell infiltration is one of the main features of AAA. The cellular components of the inflammatory cells include lymphocytes and mononuclear phagocytes, and these cells can release proinflammatory mediators and matrix-degrading enzymes including matrix metalloproteinases (MMPs), then generate elastin degradation peptides that induce immune response [2, 3, 5]. However, the specific chemokine initiating these cells' migration to AAA is not known.

CXCR2 is a G protein-coupled receptor that is activated by CXC chemokines, including murine CXCL1, CXCL2, and CXCL5. CXCR2 is expressed by multiple cell types including lymphocytes, monocytes, dendritic cells (DCs), and endothelial cells. Interactions between CXCR2 and its ligands play an essential role in mediating these immune cells' migration to sites of inflammation [6]. Recent studies suggest that CXCR2 plays a critical role in the development of inflammatory responses in response to a wide range of insults [7–10]. Especially, Anzai et al. demonstrated that neutralizing antibodies to CXCR2 suppressed expansion and rupture of dissected aorta via reduced neutrophil accumulation [11]. However, little is known as to whether CXCR2 can influence the immune cells to the AAA.

In this study, we sought to investigate the aortic expression of CXCR2 in human samples and during AAA formation in ApoE$^{-/-}$ mice induced by chronic subcutaneous infusion of angiotensin II (Ang II). We further evaluated the functional role of CXCR2 in the recruitment of inflammatory cells within the aortic wall and the potential therapeutic utility of SB265610 in AAA in vivo. We found treatment of mice with SB265610 markedly decreased AAA formation and inflammatory cell infiltration such as macrophages. Thus, these results suggest that CXCR2 plays a critical role in the development of AAA via prompting inflammatory cell infiltration. The CXCR2 inhibitor SB265610 may be a novel therapeutic drug for the treatment of AAA disease.

Materials and methods

Study patients

Five participants with diagnosed AAA were recruited to this study, and the patients were hospitalized in the Department of Vascular Surgery in Peking Union Medical College Hospital (Beijing, China) from January 2015 to October 2015. 5 control subjects without AAA were obtained from heart transplant donors who have similar clinical characteristics with AAA. Patients with acute coronary syndrome and clear infectious disease were excluded. The study protocol was approved by the Ethical Committee of Peking Union Medical College Hospital, and informed consent was obtained.

Mice and study protocol

Male apoE$^{-/-}$ mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. All mice were maintained in a barrier facility, and ambient temperature ranged from 20 to 24 °C. Mice were fed diet and water ad libitum. Mice at 8–12 weeks of age were used in an angiotensin II-induced AAA model by subcutaneous infusion of angiotensin II (Sigma-Aldrich, St. Louis, MO) at a dose of 1000 ng/kg/min or saline using osmotic minipumps (Alzet MODEL 1007D; DURECT, Cupertino, CA) for 28 days as described previously. The selective CXCR2 antagonist SB265610 (Axon, Groningen, The Netherlands) was administered intraperitoneally (2 mg/kg/days) beginning 1 day before angiotensin II infusion and continued during angiotensin II treatment. Blood pressure was measured noninvasively using the Softron BP-98A Blood Pressure Analysis System (Softron Systems, Tokyo, Japan) as described previously [10, 12]. All procedures were approved by the Animal Care and Use Committee of Peking Union Medical College Hospital. The investigation conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Analysis and quantification of AAA

To quantify the incidence and size of AAA ($n = 21$ per group), abdominal aortic diameter was measured with a Vevo 770 ultrasound system (VisualSonics Inc.) and MNI, respectively, as described [13]. The outer diameter of the suprarenal aorta was also measured with a caliper. For quantifying aneurysm incidence, an aneurysm was defined as a 50% or greater increase in the external width of the suprarenal aorta compared to aortas from saline-infused mice as described previously. Aneurysm severity was rated from Type I to Type IV according to the method of Daugherty et al. [14].

Histopathology and immunohistochemistry

Mice were anesthetized with tribromoethanol (0.25 mg/g intraperitoneally), and artery tissues were perfused with normal saline and fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned (5 μm) ($n = 8$ per group). Aortic sections were stained with hematoxylin and eosin (H&E), Masson trichrome and Verhoeff–Van Gieson (VVG) as described previously [13, 15]. Immunohistochemical staining was performed with primary antibody against CXCR2 (1:500; Abcam Technology), Mac-2 and MMP2/9 (1:200, Santa Cruz Biotechnology, Santa Cruz, CA). Digital photographs were taken at 10× or 20× magnification of over ten random fields from each aorta. The images were evaluated in a blinded fashion by a pathologist, and were captured using a Nikon Labophot 2 microscope (Nikon, Tokyo, Japan).

Quantitative real-time RT-PCR

Total RNA was extracted from fresh mouse aortas using TRIzol method (Invitrogen) ($n = 5$ per group). RNA samples (1 μg) were reverse transcribed to generate first-strand cDNA. Quantitative RT-PCR (qPCR) analysis was as

described previously. The primers of IL-1β, TNF-α, IL-6, and GAPDH were designed as described previously [16].

Western blotting

Aortas were lysed in extraction buffer containing in mmol/L: Tris/HCl 50 (pH 7.4), KCl 154, glucose 5, EDTA 0.5, PMSF 1, DTT 2, and 1% Triton X-100 (n = 3 per group). Samples were loaded onto 10% SDS-PAGE and transferred to polyvinylidene fluoride membrane, immunoblotted with primary antibodies CXCR2 (1:1000; Abcam Technology) and GAPDH (1:5000; Cell Signaling Technology) followed by secondary antibodies conjugated with HRP. Bands were detected by use of an enzyme-linked chemiluminesence detection kit (Merck Millipore). The density was quantified with luminescent image analyzer (Fujifilm) and normalized to GAPDH [17].

MMP activity assay

The activities of MMP2 and MMP9 in aortas from mice were evaluated according to the protocols as described [12, 13]. Five micrograms of protein from homogenates of aortic tissues was electrophoresed in SDS-PAGE gels containing 1 mg/ml gelatin (n = 3 per group). Then the gel was washed in 2.5% Triton X-100 and incubated in zymography developing buffer. Finally, the gel was stained with Coomassie brilliant blue.

Flow cytometry

Flow cytometry was performed as described previously ($n = 5$ per group) [10, 12]. The whole vessel was perfused with phosphate buffer solution (PBS) to exclude blood cells and was dissected, minced with fine scissors, and then enzymatically digested with a cocktail of 0.125% trypsin, 0.1% collagenase type I, 0.1% collagenase type II and 0.1% collagenase type IV in PBS at 37 °C for 1 h. The cell suspension was centrifuged at 300×*g* for 5 min at 4 °C, and then the supernatant was passed through a 70-μm cell strainer (the cell final concentration of each tube is 10^7/ml). The isolated cells were further stained with CD3 FITC and CD45 Percp (T lymphocytes), CD11b FITC and Gr-1 APC-H7 (neutrophil marker), CD45 Percp, CD11b FITC and F4/80 BV421 (macrophage marker) antibodies, and their homologous isotype-matched negative controls and were sorted using a FACS Fortessa flow cytometer.

Statistical analysis

Data are presented as mean ± SEM. Statistical differences between groups were analyzed by the parametric test, one-way analysis of variance (ANOVA), followed by the Tukey–Kramer test for group differences.

Results

CXCR2 expression is upregulated in AAA tissues from human and Apo $E^{-/-}$ mice

To investigate whether CXCR2 is involved in AAA, the abdominal aorta tissue from human AAA and age-matched control was first analyzed for the expression of CXCR2. As shown in Fig. 1a, CXCR2 expression was markedly increased in AAA tissue compared with age-matched control (Fig. 1a).

To determine whether CXCR2 expression was altered during AAA formation and progression, abdominal aortas in Apo $E^{-/-}$ mice were collected on the 7th (1w-Ang II) and 14th (2w-Ang II) day after saline or Ang II infusion, and then the expression of CXCR2 was detected. As shown in Fig. 1b, CXCR2 expression in the Ang II-infused mice was significantly higher than the control group on the 7th or 14th days.

Pharmacological inhibition of CXCR2 by SB265610 reduces Ang II-induced AAA formation in Apo $E^{-/-}$ mice

To elucidate the potential role of CXCR2 in AAA formation, mice were administrated with CXCR2 inhibitors (SB265610) intraperitoneally under infusion of Ang II by osmotic pump. Similar to the previous study [10], the results showed that infusion of Ang II induced a significant increase in blood pressure and this Ang II effect was markedly attenuated in Ang II + SB265610 group (Fig. 2a). Furthermore, SB265610 treatment also decreased mortality, aneurysm formation and development (none, Type I, Type II, Type III, and Type IV) induced by Ang II (Fig. 2b, c). Treatment with SB265610 alone did not affect the aortic diameter. These results were further confirmed by high-frequency ultrasound (Fig. 2d). Together, these results indicate that SB265610 treatment can markedly attenuate Ang II-induced aneurysm incidence and severity.

SB265610 inhibits Ang II-induced aortic wall remodeling in Apo $E^{-/-}$ mice

It is reported that artery wall remodeling is a hallmark of AAA formation and progression. Therefore, the effect of CXCR2 on suprarenal artery remodeling was determined in Apo $E^{-/-}$ mice using H&E, Masson, VVG staining and MMP2/9 expression. As shown in Fig. 3a–g, SB265610 significantly suppressed the abdominal aortic wall thickening,

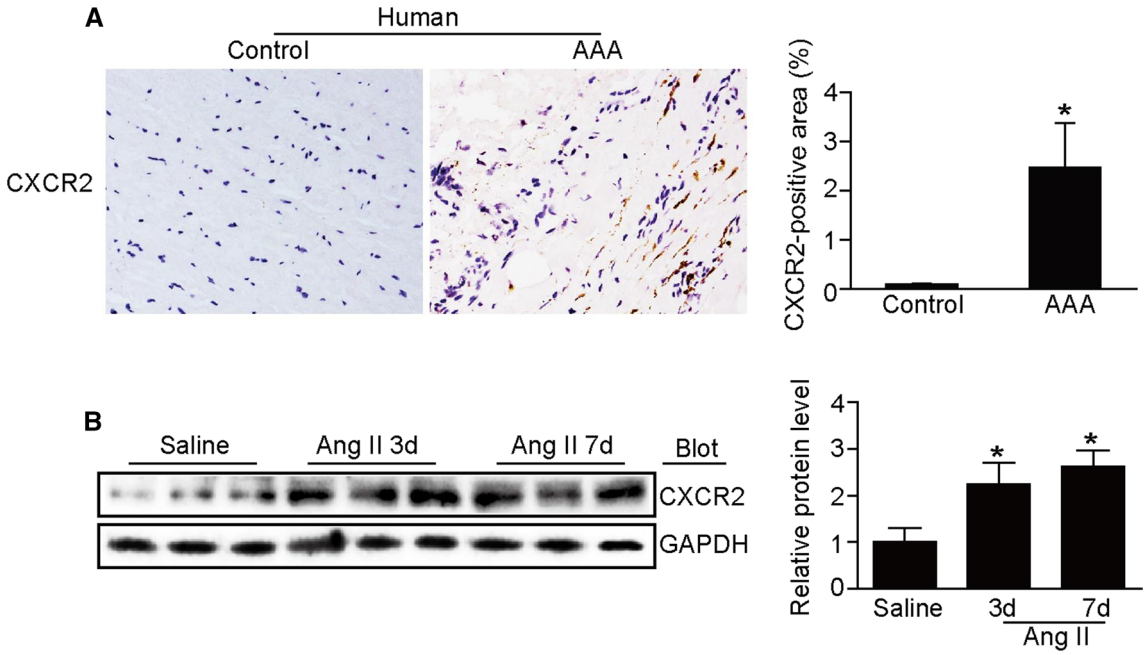

Fig. 1 CXCR2 expression was increased in the arterial tissue of human AAA tissue or Ang II-infused Apo $E^{-/-}$ mice. **a** The expression of CXCR2 was examined by immunohistochemical staining in aorta sections of human AAA. **b** The expression of CXCR2 was detected by western blotting in aortic sections of mice infused with Ang II for 3 and 7 days. Data expressed as mean ± SEM ($n = 4$ per group). *$p < 0.05$ vs control or saline

media disruption with thrombus formation, collagen deposition, elastic fiber breakage and local expression and activation of MMPs with elastinolytic activity-induced by Ang II infusion. There was no significant difference in the aortic wall remodeling alterations between saline and SB265610 groups (Fig. 3a–g).

SB265610 inhibits Ang II-induced inflammatory response in Apo $E^{-/-}$ mice

Chronic transmural inflammation is one of the main features of AAAs. The cellular components of the inflammatory process include mononuclear phagocytes, lymphocytes and blood plasma cells. In addition, CXCR2 is expressed on macrophages and neutrophils and on nonmyeloid cells such as fibroblasts, smooth muscle cells, and endothelial cells. To determine whether inhibiting CXCR2 in vivo was efficient in decreasing immune cell infiltration into the aorta, we measured the number of neutrophils, T lymphocytes and macrophages in harvested aorta by flow cytometry (Fig. 4a–c). SB265610 injection significantly decreased angiotensin II-induced infiltration of CD45 + myelomonocytes, especially F4/80 + macrophages in the aorta. SB265610 did not change the number of neutrophils and T cells (Fig. 4a–c), and the change of macrophages was further determined by Mac-2 expression by IHC (Fig. 4d). Furthermore, SB265610 injection significantly decreased the inflammatory factors' expression including IL-1β, IL-6 and TNFα induced by Ang II administration (Fig. 4e).

Discussion

In this study, we demonstrated that the expressions of CXCR2 was significantly upregulated in AAA tissue from Ang II-infused Apo $E^{-/-}$ mice. Inhibition of chemokine receptor CXCR2 activity by pharmacologic CXCR2 inhibitor attenuated Ang II-induced AAA formation. Further, CXCR2 inhibitor treatment markedly reduced Ang II-induced inflammation, fibrosis, elastin degradation and inhibited MMP activities. Thus, these data provide the novel in vivo evidence for the critical role of CXCR2 + leukocytes in promoting AAA formation in Apo$E^{-/-}$ mice after Ang II infusion. Inhibition of CXCR2 activation may, therefore, be a promising approach for treatment of AAA.

The transmural inflammation seen in AAA involves a variety of inflammatory cell types, where macrophages and lymphocytes are the most prominent with mast cells and neutrophils migrating to a lesser extent [2, 3]. However, it is unknown how AAA stimuli such as angiotensin II promote the infiltration of these cells into the vascular wall in the early stages of AAA; one plausible mechanism involves the action of chemoattractant cytokines, which regulate leukocyte trafficking [6]. Emerging evidence indicates that several

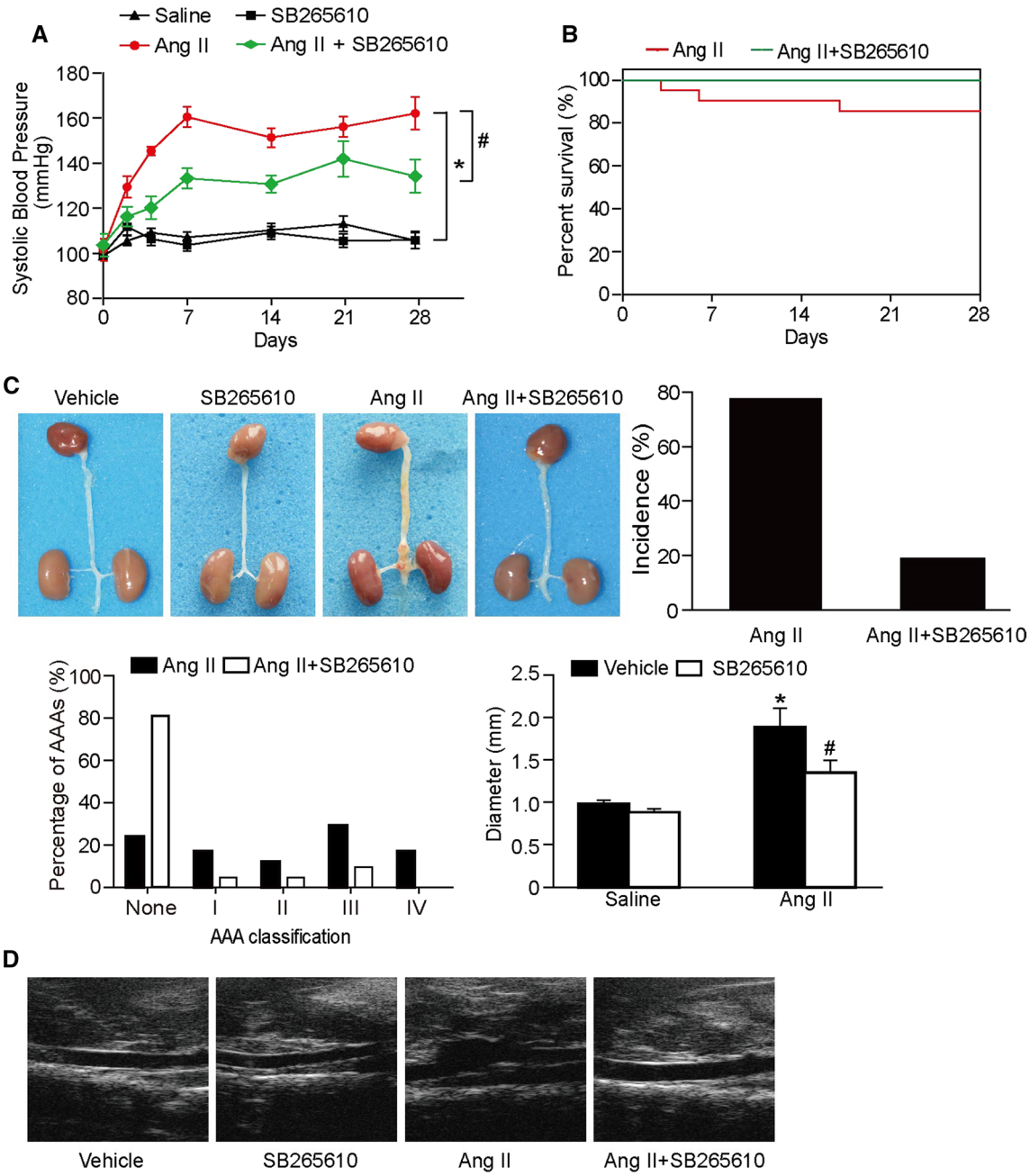

Fig. 2 Pharmacological inhibition of CXCR2 reduced angiotensin II-induced hypertension, the incidence and severity of abdominal aortic aneurysms in ApoE$^{-/-}$ mice. The ApoE$^{-/-}$ mice were injected with SB265610 1 day before angiotensin II infusion and continued during angiotensin II treatment. **a** Systolic blood pressure was measured by the noninvasive tail-cuff method. **b** The mortality of the Ang II or Ang II + SB265610-treated mice. **c** Representative aortas of each group, incidence and classification of aortic aneurysm, and mean maximal diameter of the aorta in each group. **d** Representative images by high-frequency ultrasound of abdominal aortas. Data expressed as mean ± SEM ($n = 21$ per group). $^{*}p < 0.05$ vs saline; $^{\#}p < 0.05$ vs Ang II

chemokines (MCP-1, CCL5, and CCL12) and their receptors (CCR2, CCR1/3/5, and CCR4) play an important role in the development of AAA [18–20]. In mouse model of acute aortic dissection, blockade of CXCR2 can attenuate transmural inflammation via inhibition of neutrophil recruitment and hence suppresses aortic rupture [11]. Chemokine receptor pathways strongly influence the migration of monocytes/macrophages, production of reactive oxygen species, smooth muscle cell apoptosis and elastin fragmentation. Chemokine receptor CXCR2 is expressed on multiple immune cell types and is essential for recruitment of neutrophils at inflammation sites. In the present study, our data revealed that

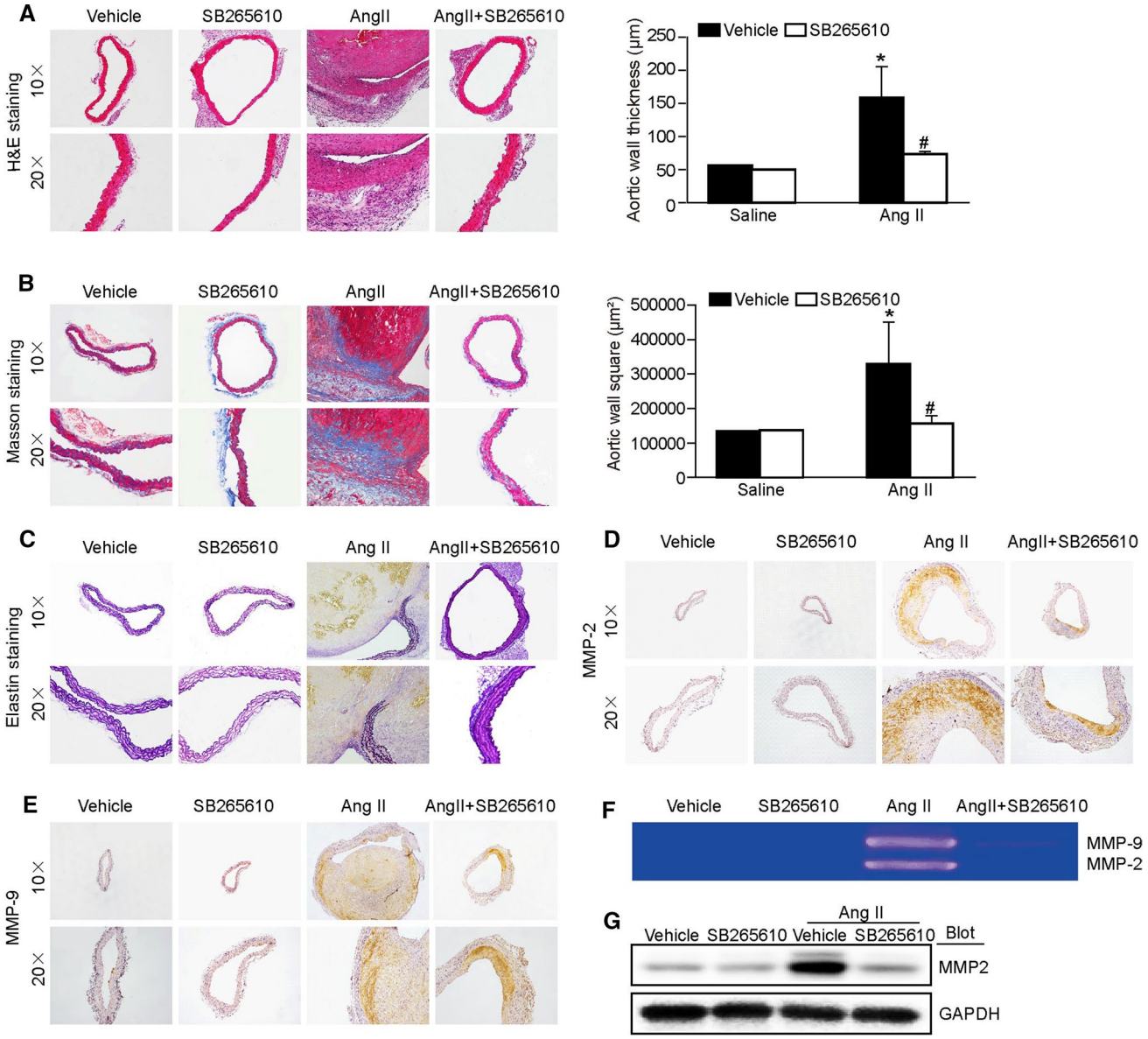

Fig. 3 SB265610 inhibits aortic wall remodeling and MMP activity the in Ang II-infused mice. **a** H&E staining of the aorta and mean aortic wall thickness in each group ($n=8$ per group). **b** Masson staining of the aorta and mean aortic wall square. **c** The representation of elastin staining in abdominal aorta. **d**–**e** The representation of immunohistochemical staining for MMP-2 and MMP-9 in abdominal aorta. **f** The representation of MMP zymography gel ($n=3$ per group). **g** Western blot analysis for the protein levels of MMP-2 in abdominal aorta. Data expressed as mean ± SEM $^{*}p<0.05$ vs saline; $^{\#}p<0.05$ vs Ang II

inhibition of CXCR2 activity decreased the extent of vascular medial hypertrophy, collagen deposition, elastin fracture and matrix metalloproteinase activity which demonstrated a critical role for CXCR2 in AAA.

Macrophages have also been shown to play a key role in AAA progression [2, 21, 22]. Macrophages are key components of the inflammatory process. Tumor necrosis factor (TNF)-α, IL-6, IL-1β, and interferon (IFN)-γ are proinflammatory macrophage-associated cytokines studied as biomarkers of AAA progression. In this study, our flow cytometry measurements showed that inhibition of CXCR2 effectively reduced AAA formation and infiltration of F4/80 + macrophages in aorta in response to angiotensin II (Figs. 2, 4). These findings demonstrate that macrophages mainly mediated by CXCR2 involve angiotensin II-induced AAA formation.

Our study demonstrated for the first time that CXCR2 was induced in AAA walls in mice, and inhibitor of CXCR2 decreases AAA formation and prevents aortic wall destruction in mice by decreasing inflammation, fibrosis and elastin

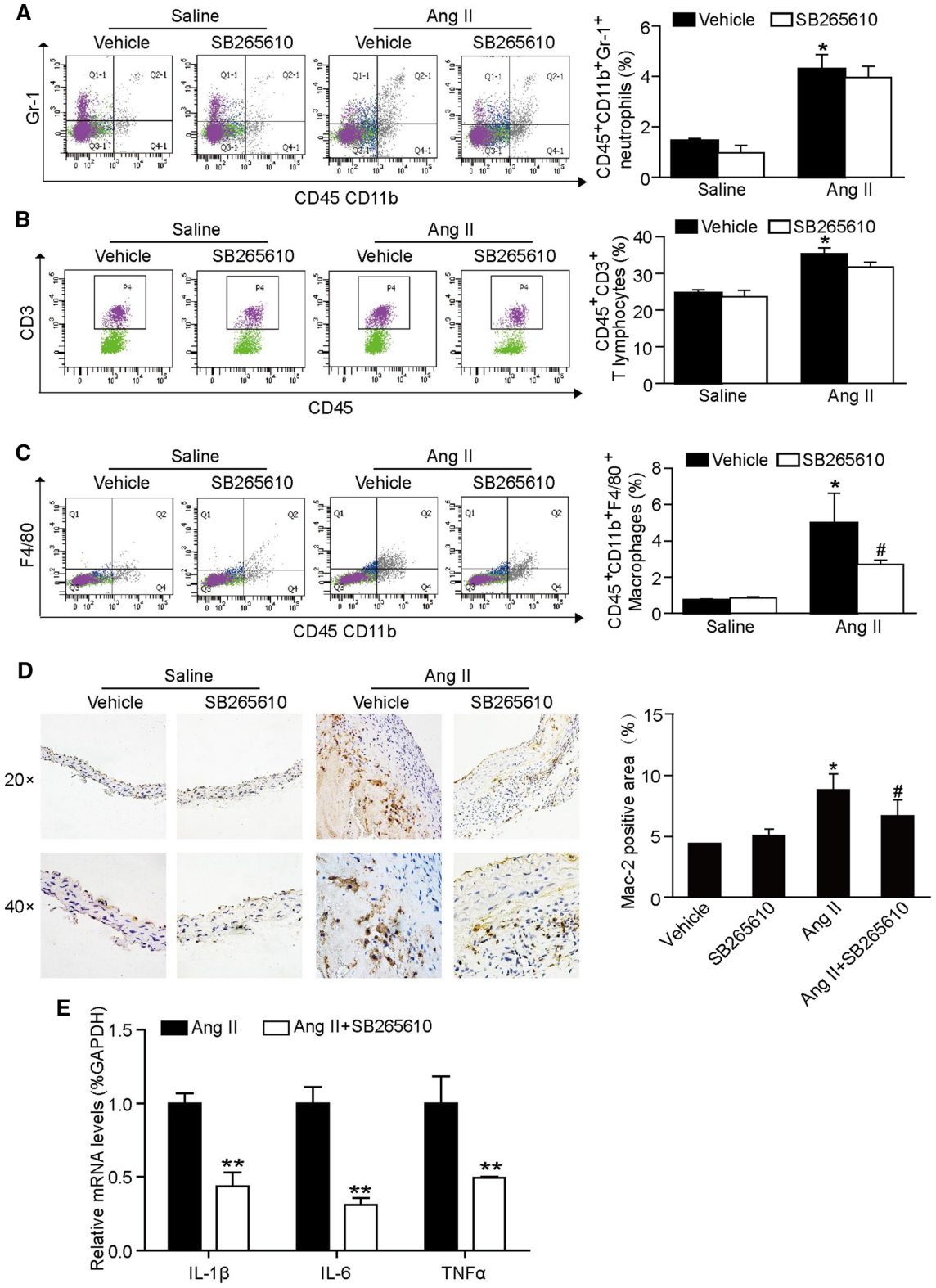

Fig. 4 CXCR2 antagonist SB265610 inhibits the accumulation of macrophages and the expression of inflammatory cytokines in the AAAs. **a–c** The representation of flow cytometry analysis for quantifying the number of $CD45^+CD11b^+Gr\text{-}1^+$ neutrophils, $CD45^+CD3^+$ T lymphocytes and $CD45^+CD11b^+F4/80^+$ macrophages in abdominal aorta ($n=5$ per group). **d** The representation of immunohistochemical staining for Mac-2 in abdominal aorta (left). Bar graph shows the quantification of the percentage of Mac-2-positive area (right). **e** qPCR analysis for the mRNA expression of IL-1β, IL-6 and TNF-α in abdominal aorta from Ang II and Ang II + SB265610 group ($n=5$ per group). Data expressed as mean ± S.E.M $^*p<0.05$ vs saline; $^{\#}p<0.05$ vs Ang II. $^{**}p<0.05$ vs Ang II

fraction. The therapeutic effect of CXCR2 on AAA progression is achieved at least in part through inhibition of CXCR2 effect, which subsequently diminishes infiltration of macrophages and production of inflammatory cytokines. Thus, CXCR2 inhibitor may offer an effective therapeutic strategy to slow AAA progression.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no competing or financial interests associated with the manuscript.

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