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Anti-arthritis effect of a novel quinazoline derivative through inhibiting production of TNF-α mediated by TNF-α converting enzyme in murine collagen-induced arthritis model

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ABSTRACT

TNF-α is a dominant inflammatory mediator in the pathogenesis of inflammatory diseases including rheumatoid arthritis. In our research, we discovered 2-chloro-N-(4-(2-morpholinoethoxy)phenyl)quinazolin-4-amine (**9c**) exhibited an outstanding anti-inflammatory activity on inhibiting TNF-α production with an IC_{50} of 8.86 μM in RAW264.7 cells. Interestingly, **9c** had no effect on mRNA level of TNF-α but up-regulated the precursor of TNF-α (pro-TNF-α). Then, we studied TNF-α converting enzyme (TACE), which is the most important proteases responsible for the release of TNF-α from pro-TNF-α to soluble TNF-α. The results showed **9c** reduced TACE both on the levels of mRNA and protein in a dose-dependent manner. In vivo study, collagen-induced arthritis (CIA) mice were treated by **9c** orally. **9c** exhibited significant anti-arthritis effect by ameliorating arthritic score, reducing inflammatory cell infiltration, protecting joints from destruction and decreasing the production of systemic TNF-α, IL-6, IL-1β. The underlying mechanism of **9c** on CIA was coincided with the in vitro, which was mediated by TACE. In conclusion, we discovered a novel quinazoline derivative which ameliorates arthritis through inhibiting production of TNF-α mediated by TACE for the first time.

1. Introduction

Rheumatoid arthritis (RA) is characterized by infiltration of immune cells, joint inflammation, pannus formation and joint destruction as a chronic inflammatory diseases [1]. TNF-α is a crucial inflammatory cytokine in the pathogenesis of inflammatory diseases including rheumatoid arthritis [2–4]. TNF-α is abundantly expressed in the RA synovium, predominantly by macrophages, and is easily detected in the synovial fluid [5]. TNF-α is now targeted in the standard treatment of patients with RA [6]. TNF-α is synthesized as a 26 kDa transmembrane precursor (pro-TNF-α), which is converted to a 17 kDa soluble mature protein by TNF-α converting enzyme (TACE) through proteolytic process [7]. TACE, also known as a disintegrin and metalloproteinase 17 (ADAM17), cleaves cell surface proteins, such as cytokines (e.g. TNF-α), cytokine receptors (e.g. IL-6R and TNF-R), ligands of ErbB (e.g. TGFα and amphiregulin) and adhesion proteins (e.g. L selectin and ICAM-1). TACE modulates inflammation by activation of TNFR- and IL-6R-mediated signal transduction. Therefore, TACE activation is considered a pro-inflammatory event [8]. TACE is the primary enzyme in cleaving TNF-α from membrane-bound pro-TNF-α to soluble form. So, TACE is considered an effective therapeutic target in TNF-α mediated disorders including RA [9].

Quinazolines, represented an interesting group of N-containing heterocycles, are well known for their wide range of pharmacological activities including anti-inflammatory activity [10]. In general, quinazolines are known to possess remarkable anti-inflammatory activity by inhibiting TNF-α [11], NF-κB [12], NOS-II

Abbreviations: pro-TNF-α, precursor of TNF-α; TACE, TNF-α converting enzyme; CIA, collagen-induced arthritis; **9c**, 2-chloro-N-(4-(2-morpholinoethoxy)phenyl) quinazolin-4-amine; MTX, methotrexate.

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[13]. But until now, no quinazoline derivative was used in the treatment of RA by inhibiting TACE. In the present study, twelve quinazoline derivatives were synthesized and evaluated. Among them, **9c** exhibited an outstanding anti-inflammatory activity on inhibiting TNF-α production in LPS-stimulated RAW264.7 cells. We investigated the underlying mechanism of the inhibition of **9c** on TNF-α production and demonstrated the therapeutic potential of **9c** treatment in CIA.

2. Materials and methods

2.1. Materials and reagent

Bovine Type II Collagen (CII), Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA) were obtained from Chondrex (Redmond, WA). LPS (Escherichia coli serotype 0111:B4), MTT and other analytical grade chemicals were purchased from Sigma–Aldrich (St. Louis, MO, USA). Antibodies against TACE, GAPDH and TNF-α were purchased from Boster Biotechnology (Wuhan, CN), Cell Signaling Technology (Danvers, MA, USA) and Abcam (Cambridge, MA, USA) separately. Primers were synthetized by Sangon Biotech (Shanghai, CN).

2.2. Animals

DBA1/J male mice (8–10weeks old) were obtained from Beijing HFK Bioscience Co., Ltd, and maintained in specific pathogen free air at a temperature of 22 ± 2 °C on a 12-h light/dark cycle with food and water ad libitum and relative humidity of 50%. Standard laboratory chow and water ad libitum were ensured. Animal environments were carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the Sichuan University in China (IACUC number: 20100318).

2.3. Synthesis of compounds

Compounds of **9a**–**9l** (Supplemental Table 1) has been synthesized (Supplemental scheme 1**)** and identified by high-performance liquid chromatography, mass spectrometry and nuclear magnetic resonance as supplementary information, and dissolved in DMSO or sodium carboxymethyl cellulose containing with 0.5% (v/v) Tween-80.

2.4. RAW264.7 cell culture and stimulate

RAW264.7 cells (American Type Culture Collection, Rockville, MD,USA) were cultured in RPMI 1640 supplemented with 10% fetal bovine serum, penicillin (100 U/ml) and streptomycin (100 μg/ml) in 5% CO_2 incubator at 37 °C. In experiments, RAW264.7 cells were seeded into a 96-well or 6-well culture plate at a density of 1×10^5 cells/ml and incubated for 24 h, and then stimulated by LPS (1 μg/mL) and treated by compounds for 24 h.

2.5. Cell viability

Cells were treated with compounds **9a**–**9l** (20 μM) or different concentrations of **9c** combination with LPS for 24 h. Then cells were incubated in 5 mg/mL MTT reagent for 4 h. The culture medium was removed and the formazan product was dissolved in DMSO. The optical density was measured using a microplate reader at 570 nm.

2.6. Induction of collagen-induced arthritis

40 male DBA/1J mice were divided into 4 groups randomly (n = 10). 2 mg/ml of bovine CII dissolved in 0.05 M acetic acid was emulsified in equal volumes of CFA (containing 1 mg/mL of inactivated *Mycobacterium tuberculosis*) and DBA/1J mice were injected with 150 μl emulsion into the base of tail intradermal. On day 21, Mice were suffered a booster injection with an emulsion of 75 μl emulsion of CII and IFA. Thereafter, all mice were monitored daily for signs of arthritis: redness and swelling of a fore or hind paw. After the onset of CIA, DBA/1J mice were treated orally daily for 30 days with **9c** at a dose of 5 mg/kg or 20 mg/kg, Methotrexate (MTX) at a dose of 0.5 mg/kg, or vehicle (the group of Model). MTX was chosen as a positive control.

2.7. ELISA of TNF-α, IL-6 and IL-1β in RAW264.7 cells and serum

Cells treated with LPS containing with Compounds of **9a**–**9l** (20 μM) or a series concentration of **9c** for 24 h. The cell supernatant or CIA mice serum was measured by ELISA kits (R&D, Minneapolis, MN) according to the manufacturer's protocol.

2.8. RT-PCR of TNF-α and TACE in RAW264.7 cells

Cells stimulated with LPS and concomitantly treated with or without different concentrations of **9c** for 24 h. Total RNA was extracted by Trizol (Ambion, Austin, TX). The final RNA pellet was dissolved in diethylpyrocarbonate-treated water and its concentration was measured spectrophotometric ally. And cDNAs were reverse transcribed in Premix Ex Taq (TaKaRa, Shiga, Japan) by PCR instrument under the following conditions: denaturation at 94 °C for 5 s, primer annealing at 60 °C for 30 s, and primer extension at 72 °C for 30 s. PCR products were run on a 1% agarose gel. Primer sequences for the PCR were as follows: GADPH (forward: 5′-CCATGTTCGTCATGGGTGTGAACCA-3′,reverse:5′-GCCAGTAGAGGCAGGGATGTTC-3),TNF-α(forward:5′-ATCCGCGACGTGGAACTG-3′,reverse:5′-ACCGCCTGGAGTTCTGGAA-3′), and TACE(forward:5′-CTTGCCAAGATCCA GCA-3′, reverse:5′-AGCAATAAAGTTTGTGGGAA-3′).

2.9. Western blot of pro-TNF-α and TACE in RAW264.7 cells and ankle joints

Cells stimulated by LPS were incubated with and **9c** for 24 h. Ankle joints of CIA mice were removed after sacrificed and ground by a mortar in liquid nitrogen. Cells and abrasive products lysed in RIPA buffer containing with protease inhibitor cocktail, PMSF. Protein concentrations in clarified lysates were determined and samples were standardized to equal concentrations. Protein samples were then subjected to 10% sodium dodecylsulfate–polyacrylamide gel electrophoresis and transferred onto the polyvinylidene difluoride membrane. The membrane was blocked in 5% non-fat milk and then incubated with primary antibody and subsequently with appropriate horseradish peroxidase-conjugated secondary antibody. Proteins were visualized with enhanced chemiluminescence [14].

2.10. Assessment of the arthritic score

The arthritic score was initiated from treatment and the animals were inspected every three days. For the development of CIA and inflammation of the four paws was graded from 0 to 4: grade 0, paws with no swelling and focal redness; grade 1, paws with swelling of finger joints; grade 2, paws with mild swelling of ankle or wrist joints; grade 3, paws with severe inflammation of the

entire paw; and grade 4, paws with deformities or ankyloses. Each paw was graded and the four scores were totaled so that the possible maximum score per mouse was 16 [15].

2.11. Histological examination

DBA1/J mice were sacrificed 30 days after treatment and ankle joints were removed and fixed with 4% paraformaldehyde more than 48 h. The joints were decalcified in EDTA buffer for 21 days and then embedded in paraffin blocks. Joint sections were stained with H&E or safranin O-fast green. The histological changes were examined under microscope.

2.12. Statistical analysis

All results were expressed as means ± SD. Differences between groups were evaluated using an independent-samples T test. The results were considered significantly different at $p < 0.05$.

3. Results

3.1. A series of novel quinazoline derivatives inhibited production of TNF-α in RAW264.7 cells

Twelve synthesized compounds were performed by the preliminary screening of TNF-α level on RAW264.7 cells at 20 μM. As shown in Fig. 1, all of these analogs reduced TNF-α level remarkably. Among these compounds, **9c**, **9d** and **9e** effectively suppressed TNF-α production than others at 20 μM (the inhibitory rates were more than 65%), and **9c** showed the most potent inhibitory effect and its inhibitory rate reached 81.47% without an evident cell toxicity at 20 μM (Fig. 1A and B). Compound **9c** was picked out because of superior activity on TNF-α lowering effect than other derivatives. And then we determined a series of concentrations of **9c** on inhibition TNF-α production, **9c** attenuated TNF-α production with an IC_{50} of 8.86 μM (Fig. 2B) and had a low cell toxicity ($IC_{50} > 80$ μM) (Fig. 2C).

3.2. *9c* reduced mRNA of TNF-α and up-regulated protein of pro-TNF-α in RAW264.7

Since compound **9c** significantly suppressed secretion of TNF-α, cells were collected for the detection of TNF-α mRNA level by RT-PCR analysis. As shown in Fig. 2D, **9c** had no clear effects on the transcription of TNF-α at 5 μM, 10 μM or 20 μM, but the precursor of TNF-α was up-regulated significantly in a dose-dependent manner after treating by **9c** (Fig. 2E).

3.3. *9c* reduced TACE both on levels of mRNA and protein in RAW264.7

Since TACE is the primary enzyme in cleaving TNF-α from membrane-bound pro-TNF-α to soluble form, we investigated whether **9c** influenced the expression of TACE. It was gratifying that the mRNA and protein levels of TACE were both down-regulated by **9c** in a dose-dependent manner (Fig. 3A and B), suggesting **9c** may an inhibitor of TACE.

3.4. *9c* inhibited production of IL-6 and IL-1β in RAW264.7 cells

Overexpression of TNF-α increase the production of IL-6 and IL-1β, and TACE modulates IL-6R-mediated signal transduction. Hence, we evaluated the levels of IL-6 IL-1β in RAW264.7 cells after being treated by **9c**. As shown in Fig. 3C, **9c** decreased the production of IL-6 at 10 μM ($p < 0.05$) and 20 μM ($p < 0.001$) significantly. At the same time, IL-1β was reduced in a dose-dependent manner by treatment with **9c**. The concentration of IL-1β was decreased from 857 pg/ml to 556 pg/ml by treating with **9c** at 5 μM, and it was 205 pg/ml at 20 μM (Fig. 3D).

3.5. *9c* ameliorated arthritis in CIA model

To investigate the effect of **9c** on arthritis, mice were treated orally with **9c** at a dose of 5 mg/kg or 20 mg/kg, and methotrexate, as a positive control, was also treated with a dose of 0.5 mg/kg daily. Every three days the arthritic score and body weight were recorded. As shown in Fig. 4A, **9c** attenuated the arthritis severity in a dose-dependent manner in the therapeutic process. The change of arthritic score in high dose (**9c**, 20 mg/kg) was from 8.5 to 3.2. In contrast, it was 4.6 in MTX, suggesting **9c (**20 mg/kg) had a better activity on slowing the progression of the disease than MTX (0.5 mg/kg). The body weights of arthritic model and MTX treatment mice were slightly reduced, while the body weights **9c** (5 mg/kg and 20 mg/kg) treatments were slightly increased (Fig. 4B), indicating a low toxicity of **9c** in vivo.

For the H&E staining, joints from the arthritic model mice showed severe inflammation of the synovium with thickening of the lining layer, infiltration by inflammatory cells, and bone erosions of cartilage and subchondral. While treatment with **9c**, especially the dose of 20 mg/kg, was observed with less signs of inflammatory, cartilage and bone erosions (Fig. 4C). Cartilage destruction was further demonstrated by the depletion of matrix proteoglycan, as evidenced by safranin O staining. As shown in Fig. 4C, little safranin O staining was observed in the ankle joints of CIA model or MTX treatment mice, while massive matrix proteoglycan was dyed with safranin O in high dose of **9c** (20 mg/kg), indicating **9c** treatment protected cartilage from destruction

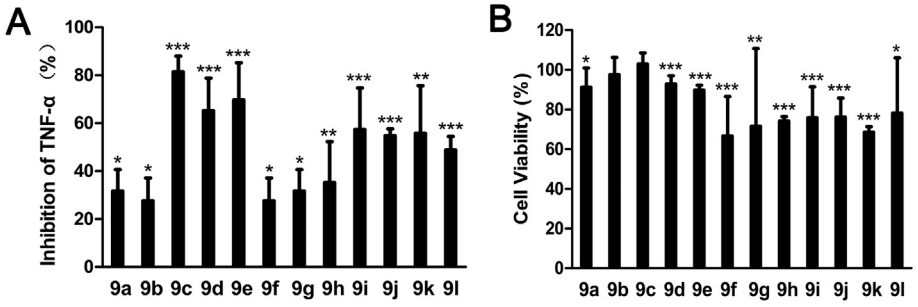

Fig. 1. Effects of Compounds on TNF-α production in LPS-stimulated RAW264.7 cells. (A) The inhibition of Compounds **9a**–**9l** at 20 μM on TNF-α production was determined by ELISA. (B) The cell viability was analyzed by MTT. Values (means ± SD) were from three independent experiments (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs LPS).

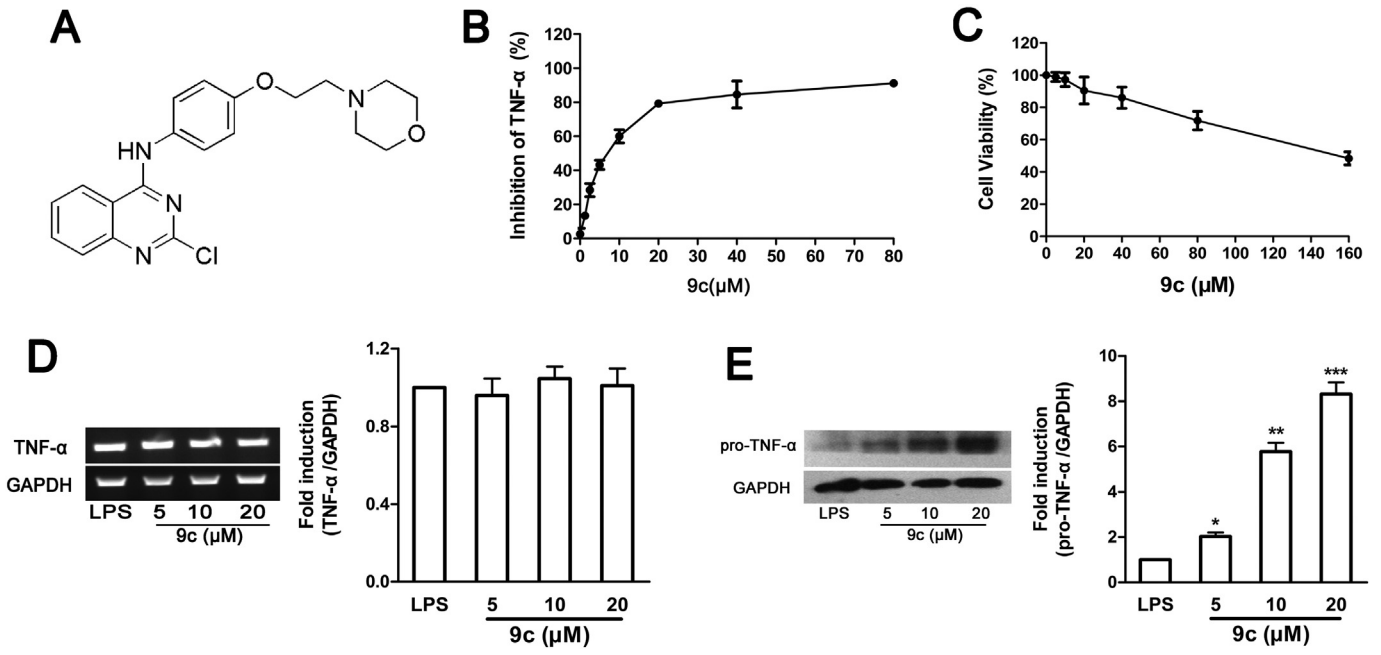

Fig. 2. Structure of **9c** and the effect of **9c** on TNF-α in LPS-stimulated RAW264.7 cells. (A) Structure of **9c**. (B)A series concentration of **9c** inhibited TNF-α production. (C)The cell viability of RAW264.7 cells treatment with **9c**. The levels of TNF-α mRNA (D) and pro-TNF-α (E) in LPS-stimulated RAW264.7 cells. Values (means ± SD) were from three independent experiments (*P < 0.05, **P < 0.01, ***P < 0.001 vs LPS).

significantly compared with the model group. **9c** exhibited a better treatment capability than MTX on arthritis by relieving pathological proceeding.

To explore whether **9c** supported the mechanism of in vitro, we detected the production of TNF-α in systemic level by ELISA and the protein levels of TACE and the precursor of TNF-α in ankle joint by Western blot. As in vitro, **9c** treatment increased pro-TNF-α, but reduced TACE and serum TNF-α in a dose-dependent manner significantly (Fig. 4D and E).

Furthermore, serum IL-6 and IL-1β levels were also detected by ELISA. **9c** reduced serum IL-6 significantly from 147 pg/ml to 105 pg/ml and 37 pg/ml at dose of 5 mg/kg and 20 mg/kg respectively (Fig. 4F). At the same time, serum IL-1β was reduced significantly from 344 pg/ml to 200 pg/ml and 162 pg/ml at dose of 5 mg/kg and 20 mg/kg respectively (Fig. 4G). The results suggested **9c** exhibited an anti-arthritis effect through inhibiting production of TNF-α mediated by TNF-α converting enzyme.

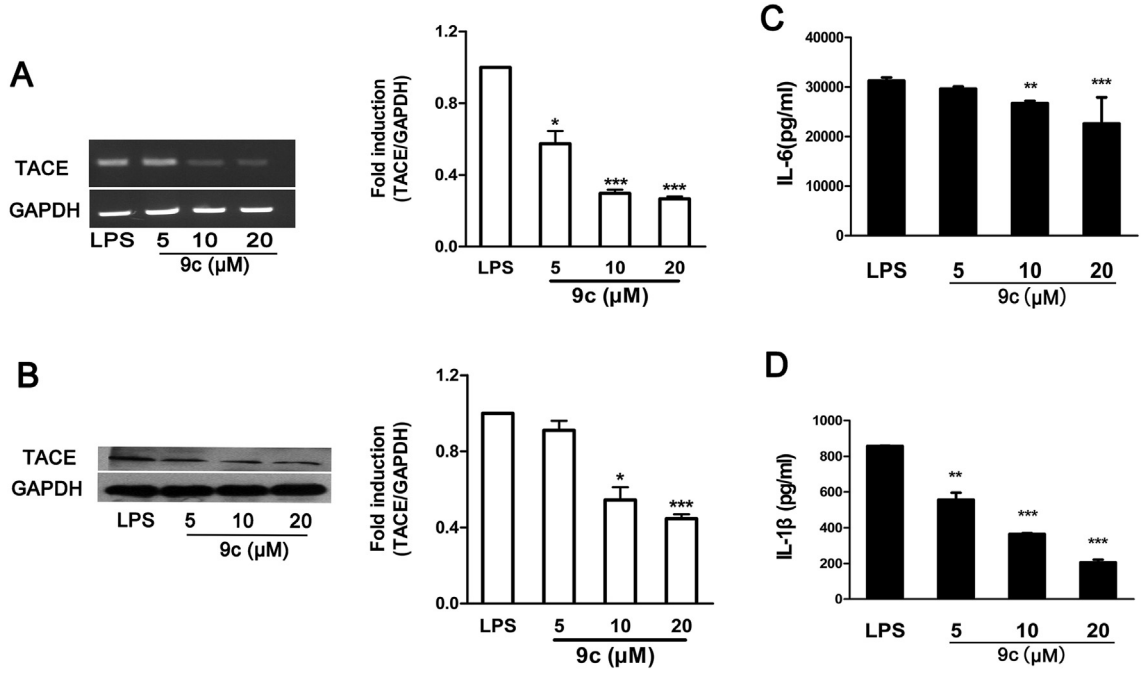

Fig. 3. Inhibition of **9c** on TACE, IL-6 and IL-1β in LPS-stimulated RAW264.7 cells. Effect of **9c** on TACE mRNA (A), TACE protein (B), IL-6 (C) and IL-1β (D) in LPS-stimulated RAW264.7 cells at 5 μM, 10 μM and 20 μM. Values (means ± SD) were from three independent experiments (*P < 0.05, **P < 0.01, ***P < 0.001, vs LPS).

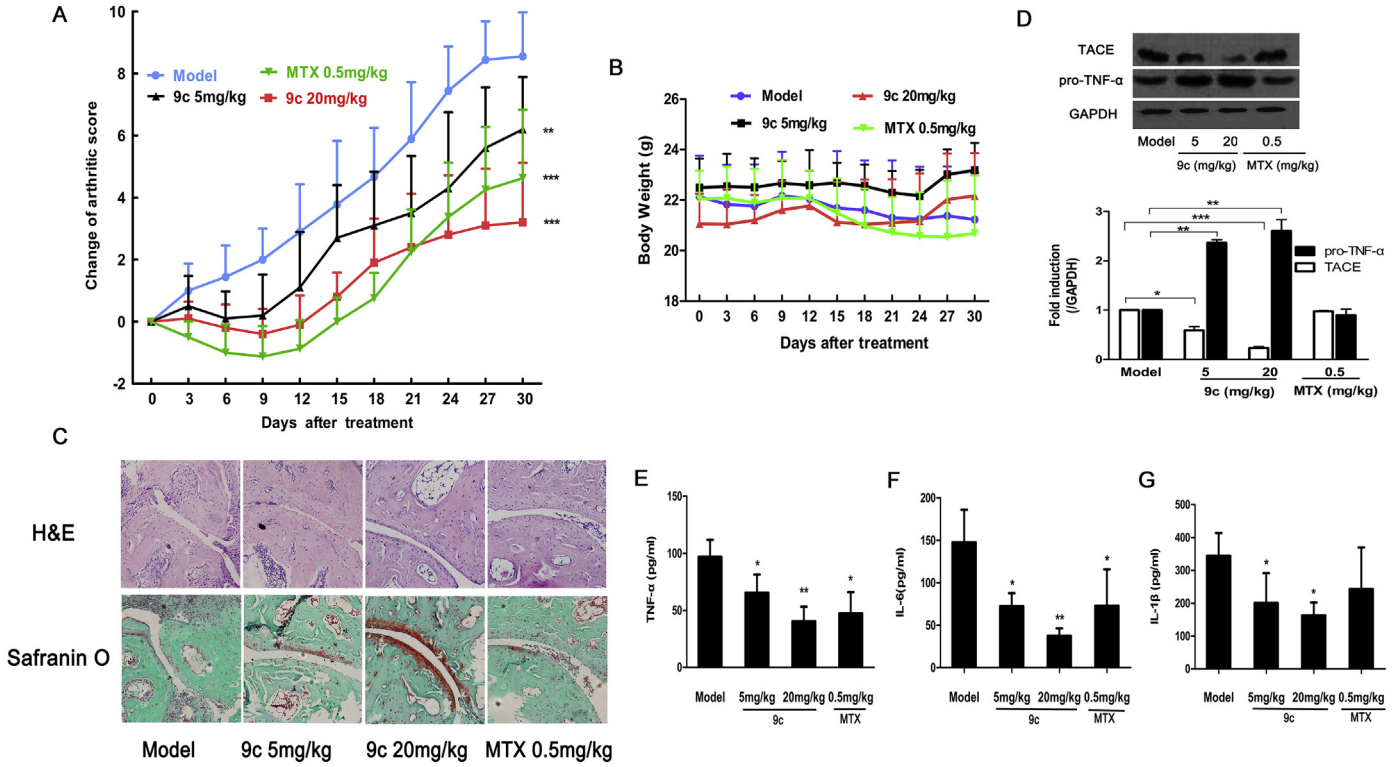

Fig. 4. Anti-arthritic effect of **9c** on CIA model. **9c** was dosed at 5 mg/kg or 20 mg/kg and MTX was dosed at 0.5 mg/kg, po, bid in the vehicle of sodium carboxymethyl cellulose containing with 0.5% (v/v) Tween-80. The arthritic score (A) and body weight (B) in CIA mice was changed after treatment with **9c**. (C) The stains of H&E and safranin O-fast green of CIA mice, Magnification, ×200. The protein levels of pro-TNF-α and TACE (D) and the levels of serum TNF-α (E), IL-6 (F), IL-β(G) in CIA mice. Values are expressed as the mean ± SD (n = 10, *P < 0.05; **P < 0.01; ***P < 0.001, vs model).

4. Discussion

It has been reported that some quinazoline derivatives possess potent anti-inflammatory activity as inhibitor of TNF-α [11,16], this is the first study to demonstrate that a quinazoline derivative (**9c**) inhibited production of TNF-α mediated by TACE. As a pro-inflammatory cytokine, TNF-α is a critical factor in condition of inflammation, and TNF-α inhibitor has a fundamental effect in the control of the chronic inflammatory diseases such as RA [2]. In our present research, a series of quinazoline derivatives were synthesized and evaluated. Among them, **9c** had the outstanding anti-inflammatory activity through inhibiting TNF-α production in LPS-stimulated RAW264.7 cells and systemic TNF-α in CIA significantly.

In further research we investigated the underlying mechanisms of **9c** on TNF-α production. It had no obvious effect on the levels of TNF-α mRNA, but the levels of pro-TNF-α were increased. We inferred the release of pro-TNF-α to soluble TNF-α had been inhibited, and the most important enzyme of the process, TACE was studied. TACE is one of ADAMs family cleaved membrane-bound proteins and/or degrade the extracellular matrix [17], and TACE is a ubiquitously expressed protease implied in the ectodomain shedding of a wide variety of trans-membrane proteins, such as growth factor ligands, cytokines, and receptors [18]. TACE was reduced indeed after treating with **9c** in vivo and vitro. **9c** might be an inhibitor of TACE. Active TACE was found in cartilage tissue [19], chondrocytes of patients with osteoarthritis [20] and synovial tissue of rheumatoid arthritis patients [21]. TACE is closely related to inflammatory diseases including RA. Human RA cartilage displays overexpressed TACE that is involved in monocyte migration, indicating that the metalloproteinase is responsible, at least in part, for the increase of the TNF-α shedding. The low oxygen condition observed in RA seems to up-regulate the transcription of TACE, through a modulation of the HIF-1 factor, in synovial cells and a positive correlation between TACE and HIF-1 protein levels in RA synovium exists confirming the importance of this positive feedback loop in the pathology of RA [22–24]. Additionally, TACE is related to IL-15 receptor α, which is involved in the collagen-induced arthritis [25,26]. Hence, we evaluated the therapeutic potential of **9c** in CIA. **9c** exhibited good treatment capability on arthritis by slowing the progression of the disease and relieving pathological proceeding. **9c** at a dose of 20 mg/kg ameliorated the disease more effectively than the positive control, MTX (0.5 mg/kg). TACE activates TNFR- and IL-6R-mediated signal transduction, overexpression of TNF-α increases the production of other cytokines [8], Hence, we detected the production of IL-6 and IL-1β in macrophages and CIA mice. **9c** presented an ability of decreasing cytokines significantly. Since TNF-α is a target of anti-inflammatory therapies, it was speculated that inhibition of TACE might be a therapeutic strategy in the treatment of inflammation or inflammation associated autoimmunity.

Overall, we discovered a novel quinazoline derivative which ameliorates arthritis through inhibiting production of TNF-α mediated by TACE for the first time. Our data strongly indicate that **9c** could provide an additional therapeutic strategy for RA. Because TNF-α involves multiple diseases, **9c** may be also a potential drug candidate in other TNF-α mediated inflammatory disorders.

Conflict of interest

The authors have no conflict of interest.

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Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.04.111.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2015.04.111.

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