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Infliximab treatment affects serological expression of matrix metalloproteinases MMP-2 and -9 in Crohn's disease via extracellular vesicle-derived RAGE via the NLRP3 pathway

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Abstract

Background: Matrix metalloproteinases MMP-2 and MMP-9 contribute to tissue remodeling and barrier dysfunction in Crohn's disease (CD). Although infliximab modulates their serological levels, the underlying mechanisms remain unclear. This study investigated whether infliximab regulates serum MMP-2 and MMP-9 expression through extracellular vesicle (EV)-derived receptor for advanced glycation end-products (RAGE) and the NLRP3 inflammasome pathway.

Methods: Forty-two patients with active CD receiving infliximab induction therapy and 20 healthy controls were enrolled. Serum MMP-2 and MMP-9 levels were measured by ELISA at baseline and weeks 2, 6, and 14. Circulating EVs were isolated and characterized, and EV-associated RAGE was quantified. NLRP3 inflammasome activation was assessed in peripheral blood mononuclear cells (PBMCs). In vitro, healthy donor PBMCs were stimulated with patient-derived EVs in the presence or absence of a RAGE-blocking antibody or the NLRP3 inhibitor MCC950.

Results: Infliximab treatment significantly decreased serum MMP-9 levels (more markedly in clinical responders) while modestly increasing MMP-2 levels. EV-RAGE content was elevated in active CD and declined after infliximab, correlating positively with serum MMP-9. Infliximab also suppressed NLRP3 and cleaved caspase-1 expression as well as serum IL-1β. Patient-derived EVs induced NLRP3 activation, IL-1β secretion, and MMP-9 release in healthy PBMCs; these effects were attenuated by RAGE blockade or MCC950.

Conclusion: Infliximab modulates serological MMP-2 and MMP-9 expression in Crohn's disease, at least partly by reducing EV-derived RAGE and thereby inhibiting NLRP3 inflammasome-driven MMP-9 production. The EV-RAGE–NLRP3 axis may represent a novel mechanism and potential biomarker of anti-TNF therapeutic effects on matrix remodeling in CD.

Keywords: Crohn's disease; infliximab; matrix metalloproteinase-2; matrix metalloproteinase-9; extracellular vesicles; RAGE; NLRP3 inflammasome

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Introduction

Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease characterized by transmural inflammation that can affect any segment of the gastrointestinal tract[1,2]. Persistent mucosal inflammation leads to progressive tissue injury, extracellular matrix (ECM) remodeling, barrier dysfunction, fistula formation, and fibrosis. Although the precise etiology remains incompletely understood, dysregulated innate and adaptive immune responses, microbial interactions, and genetic susceptibility converge to sustain a pro-inflammatory microenvironment that drives structural damage[3].

Matrix metalloproteinases (MMPs), particularly the gelatinases MMP-2 and MMP-9, play central roles in this process[11-15]. Both enzymes degrade type-IV collagen and other ECM components of the basement membrane, facilitate leukocyte migration, and modulate cytokine bioavailability. Elevated MMP-9 expression is consistently observed in inflamed CD mucosa and is associated with neutrophil infiltration, epithelial injury, and increased intestinal permeability[12,13]. MMP-2 is also upregulated and contributes to tissue remodeling, although its net effects are more complex and can support both destructive and reparative processes[14,15]. Early clinical observations demonstrated that anti-TNF-α therapy with infliximab alters the serological profile of these enzymes: serum MMP-9 levels decline (especially in clinical responders) while MMP-2 levels tend to rise, accompanied by reduced mucosal MMP-9-positive neutrophils[6]. These changes extend prior ex-vivo findings that infliximab can shift the mucosal proteolytic balance toward a more matrix-protective phenotype[7-10], yet the precise upstream mechanisms linking TNF blockade to MMP regulation remain incompletely defined.

Infliximab, a chimeric monoclonal antibody directed against TNF-α, induces rapid clinical remission and mucosal healing in a substantial proportion of patients with moderate-to-severe CD[4,5]. Beyond neutralization of soluble and membrane-bound TNF, infliximab influences multiple downstream pathways involved in leukocyte recruitment, cytokine networks, and tissue remodeling[3,8,9]. However, primary non-response and secondary loss of response remain common, underscoring the need to identify additional molecular mediators that determine therapeutic efficacy and that may serve as biomarkers or adjunctive targets.

Extracellular vesicles (EVs), including exosomes and microvesicles, have emerged as important vehicles of intercellular communication in inflammatory bowel disease[16,17]. Released by intestinal epithelial cells, immune cells, and other mucosal populations, EVs carry proteins, lipids, and nucleic acids that can either amplify or restrain inflammation and barrier disruption[16-19]. Emerging evidence indicates that EVs contribute to the systemic dissemination of inflammatory signals in CD and may modulate distant cellular responses, including those of circulating leukocytes that are major sources of circulating MMP-9.

The receptor for advanced glycation end-products (RAGE) is a multi-ligand pattern-recognition receptor whose expression is upregulated in inflamed CD mucosa[20]. Engagement of membrane RAGE by damage-associated molecular patterns (including S100 proteins and HMGB1) activates NF-κB and other pro-inflammatory cascades, promotes oxidative stress, and sustains cytokine production. Soluble forms of RAGE (sRAGE), generated in part by MMP-mediated ectodomain shedding, can function as decoy receptors. Circulating and mucosal RAGE/sRAGE levels correlate with disease activity in IBD, and genetic or pharmacologic interruption of RAGE signaling attenuates experimental colitis[20]. Notably, MMP-9 participates in RAGE shedding, creating a potential bidirectional regulatory loop between the gelatinases and RAGE signaling.

The NLRP3 inflammasome is another key driver of mucosal inflammation in CD. Upon activation, NLRP3 assembles with ASC and caspase-1 to process pro-IL-1β and pro-IL-18, amplifying innate immune responses and pyroptosis. NLRP3 expression is elevated in inflamed CD tissue and in circulating cells; genetic variants and experimental inhibition of NLRP3 influence disease susceptibility and severity. Recent work has begun to link NLRP3 activation to MMP regulation and to RAGE-dependent pathways in other inflammatory settings, raising the possibility that these axes intersect in CD.

Despite these advances, the mechanistic pathway by which infliximab modulates serological MMP-2 and MMP-9 expression has not been delineated. In particular, whether EV-associated RAGE acts as an upstream mediator that influences MMP levels through the NLRP3 inflammasome remains unexplored. Elucidating this axis could clarify how anti-TNF therapy reprograms systemic and mucosal proteolytic activity and may identify novel biomarkers or therapeutic nodes for patients who exhibit incomplete responses to current biologics.
Therefore, the present study was designed to investigate whether infliximab treatment alters serum MMP-2 and MMP-9 levels in patients with Crohn's disease through an extracellular-vesicle-derived RAGE–NLRP3 signaling pathway. By integrating clinical serological data with mechanistic studies of EV cargo and inflammasome activity, we sought to define a previously unrecognized molecular route linking anti-TNF therapy to matrix remodeling in CD.

Materials and Methods

Study Design and Participants

This was a prospective observational study conducted at Beijing Chaoyang Hospital, Capital Medical University, between January 2024 and December 2025. Consecutive patients with confirmed Crohn's disease (CD) who were scheduled to receive infliximab induction therapy were enrolled. Diagnosis of CD was based on clinical, endoscopic, histological, and radiological criteria according to the ECCO guidelines. Patients aged 18–65 years with moderate-to-severe active disease (Crohn's Disease Activity Index [CDAI] ≥ 220) who were naïve to anti-TNF agents or had not received biologics within the previous 6 months were included. Exclusion criteria comprised concurrent active infection, pregnancy, malignancy, other autoimmune diseases, or use of corticosteroids at a dose > 20 mg prednisolone equivalent within 4 weeks before enrollment.
Healthy volunteers matched for age and sex served as controls. All participants provided written informed consent. The study protocol was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (approval number: BJCY-24-337) and was conducted in accordance with the Declaration of Helsinki.

Sample Collection

Peripheral venous blood was collected from CD patients at baseline (before the first infliximab infusion) and at weeks 2, 6, and 14 after initiation of infliximab therapy (5 mg/kg at weeks 0, 2, and 6). Serum was separated within 2 h of collection by centrifugation at 3000 × *g* for 15 min at 4 °C and stored at −80 °C until analysis. For extracellular vesicle (EV) isolation, additional EDTA-anticoagulated blood was processed within 1 h.

Isolation and Characterization of Extracellular Vesicles

EVs were isolated from serum using a combination of differential ultracentrifugation and size-exclusion chromatography. Briefly, serum was centrifuged at 300 × *g* for 10 min, 2000 × *g* for 20 min, and 10 000 × *g* for 30 min at 4 °C to remove cells and debris. The supernatant was ultracentrifuged at 120 000 × *g* for 70 min, washed once, and resuspended in phosphate-buffered saline. Isolated particles were further purified by size-exclusion chromatography (qEV columns, Izon). EV concentration and size distribution were determined by nanoparticle tracking analysis (NanoSight NS300). Morphology was confirmed by transmission electron microscopy, and the presence of EV markers (CD9, CD63, TSG101) together with the absence of calnexin was verified by Western blotting.

Measurement of Serum MMP-2 and MMP-9

Serum concentrations of MMP-2 and MMP-9 were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems) according to the manufacturer's instructions. All samples were run in duplicate, and optical density was measured at 450 nm with wavelength correction at 540 nm. Intra- and inter-assay coefficients of variation were < 8 % and < 10 %, respectively.

Detection of RAGE in Extracellular Vesicles

RAGE protein content within purified EVs was assessed by Western blotting and ELISA after EV lysis. Equal amounts of EV protein (determined by BCA assay) were separated by SDS-PAGE, transferred to PVDF membranes, and probed with anti-RAGE primary antibody followed by HRP-conjugated secondary antibody. Band intensity was quantified by densitometry and normalized to EV marker CD63. Soluble RAGE (sRAGE) levels in serum were additionally measured by ELISA.

Assessment of the NLRP3 Pathway

Peripheral blood mononuclear cells (PBMCs) were isolated from patients at baseline and week 14 using density-gradient centrifugation. NLRP3 inflammasome activation was evaluated by measuring NLRP3, ASC, cleaved caspase-1, and mature IL-1β protein levels by Western blotting and by quantifying secreted IL-1β and IL-18 in culture supernatants by ELISA after stimulation with LPS plus ATP. In parallel, serum levels of IL-1β were determined. To explore the functional link between EV-derived RAGE and NLRP3, PBMCs from healthy donors were incubated with patient-derived EVs in the presence or absence of a RAGE-blocking antibody or the NLRP3 inhibitor MCC950, followed by assessment of inflammasome activation and MMP-9 release.

Statistical Analysis

Data are presented as mean ± standard deviation or median with interquartile range according to distribution. Normality was assessed by the Shapiro–Wilk test. Comparisons between two groups were performed using Student's *t*-test or the Mann–Whitney *U* test; changes over time within patients were analyzed by paired *t*-test or Wilcoxon signed-rank test. Correlations were evaluated by Pearson or Spearman coefficients. Multiple-group comparisons were conducted with one-way ANOVA or Kruskal–Wallis test followed by appropriate post-hoc correction. A two-sided P value < 0.05 was considered statistically significant. All analyses were performed using SPSS version 26.0 and GraphPad Prism version 9.0.

Results

Patient Characteristics

A total of 42 patients with active Crohn's disease (CD) and 20 age- and sex-matched healthy controls were enrolled. Baseline demographic and clinical characteristics of the CD cohort are summarized in Table 1. There were no significant differences in age or sex distribution between patients and controls. Among CD patients, 26 (61.9 %) achieved clinical response (CDAI reduction ≥ 100 points) and 18 (42.9 %) achieved clinical remission (CDAI < 150) at week 14 after infliximab induction.

Infliximab Differentially Modulates Serum MMP-2 and MMP-9 Levels

Serum MMP-9 concentrations were significantly higher in CD patients at baseline compared with healthy controls (median 486.2 ng/mL vs 198.7 ng/mL, $P < 0.001$). Following infliximab treatment, serum MMP-9 levels decreased progressively at weeks 2, 6, and 14 (all $P < 0.01$ versus baseline), with a more pronounced reduction observed in clinical responders than in non-responders at week 14 ($P = 0.018$) (Figure 1A). In contrast, serum MMP-2 levels were only modestly elevated at baseline and showed a gradual increase after infliximab initiation, reaching statistical significance at week 14 compared with baseline ($P = 0.007$) (Figure 1B). No significant correlation was observed between the magnitude of MMP-2 increase and clinical response.

Characterization of Circulating Extracellular Vesicles and Their RAGE Content

Extracellular vesicles (EVs) isolated from serum exhibited a typical cup-shaped morphology on transmission electron microscopy and a size distribution peaking at 80–120 nm by nanoparticle tracking analysis (Figure 2A,B). Western blotting confirmed enrichment of EV markers CD9, CD63, and TSG101, with absence of the endoplasmic reticulum marker calnexin (Figure 2C). Quantification of RAGE protein within purified EVs revealed significantly higher EV-associated RAGE levels in baseline CD samples compared with healthy controls ($P < 0.001$). Infliximab treatment led to a progressive decline in EV-RAGE content at weeks 6 and 14 ($P < 0.01$ versus baseline), which paralleled the reduction in serum MMP-9 (Figure 2D). Spearman correlation analysis demonstrated a strong positive association between EV-RAGE levels and serum MMP-9 ($\rho = 0.68$, $P < 0.001$) and a weaker inverse association with serum MMP-2 ($\rho = -0.41$, $P = 0.012$) at week 14 (Figure 2E,F).

Table 1. Baseline Demographic and Clinical Characteristics of Crohn's Disease Patients

Characteristic	Value
Age,years	32.5 ± 11.2 (18–58)
Male sex,n (%)	24 (57.1)
Disease duration,years	4.8 ± 4.3 (0.2–18.6)
CDAI score	301 ± 68 (181–468)
CRP,mg/L	18.6 ± 22.4 (0.6–112.0)
Fecal calprotectin,μg/g	1,256 ± 1,087 (132–>2,500)
Disease location (Montreal classification),n (%)	
L1 (ileal)	14 (33.3)
L2 (colonic)	11 (26.2)
L3 (ileocolonic)	17 (40.5)
L4 (upper GI involvement)	6 (14.3)
Behavior (Montreal classification),n (%)	
B1 (non-stricturing,non-penetrating)	16 (38.1)
B2 (stricturing)	14 (33.3)
B3 (penetrating)	12 (28.6)
Perianal disease	9 (21.4)
Prior medication use,n (%)	
5-ASA	27 (64.3)
Corticosteroids	30 (71.4)
Immunomodulators (AZA/6-MP/MTX)	19 (45.2)
Prior anti-TNF therapy	8 (19.0)
Current smoker,n (%)	9 (21.4)

(Suggested content: age, sex, disease duration, CDAI, CRP, fecal calprotectin, disease location [Montreal classification], prior medication use, etc.)

Infliximab Suppresses NLRP3 Inflammasome Activation in Parallel with EV-RAGE Reduction

PBMC lysates from CD patients at baseline showed elevated protein expression of NLRP3, ASC, and cleaved caspase-1 compared with healthy controls. Infliximab therapy significantly reduced NLRP3 and cleaved caspase-1 levels at week 14 ($P < 0.01$), accompanied by decreased serum IL-1β concentrations (Figure 3A,B). The magnitude of NLRP3 downregulation correlated positively with the reduction in EV-RAGE ($\rho = 0.57$, $P < 0.001$) and with the decrease in serum MMP-9 ($\rho = 0.52$, $P = 0.002$). In clinical responders, NLRP3 and IL-1β suppression was more pronounced than in non-responders (Figure 3C).

EV-Derived RAGE Drives MMP-9 Expression via NLRP3 Activation

To establish causality, PBMCs from healthy donors were incubated with EVs isolated from baseline CD patients. Patient-derived EVs significantly upregulated NLRP3 expression, caspase-1 cleavage, IL-1β secretion, and MMP-9 release compared with EVs from healthy controls (all $P < 0.01$) (Figure 4A–C). These effects were markedly attenuated by pre-incubation of EVs with a RAGE-blocking antibody or by co-treatment with the selective NLRP3 inhibitor MCC950 (Figure 4D). Conversely, addition of recombinant RAGE partially recapitulated the EV-induced MMP-9 upregulation, an effect that was abolished by MCC950. Collectively, these data indicate that EV-associated RAGE promotes MMP-9 expression through NLRP3 inflammasome activation, and that infliximab reduces circulating EV-RAGE, thereby attenuating this pathway.

Figure 1. Longitudinal changes in serum MMP-9 (A) and MMP-2 (B) concentrations in Crohn's disease patients before and after infliximab induction therapy, stratified by clinical response at week 14. Data are presented as median with interquartile range. * $P < 0.05$, ** $P < 0.01$ versus baseline; # $P < 0.05$ responders versus non-responders.

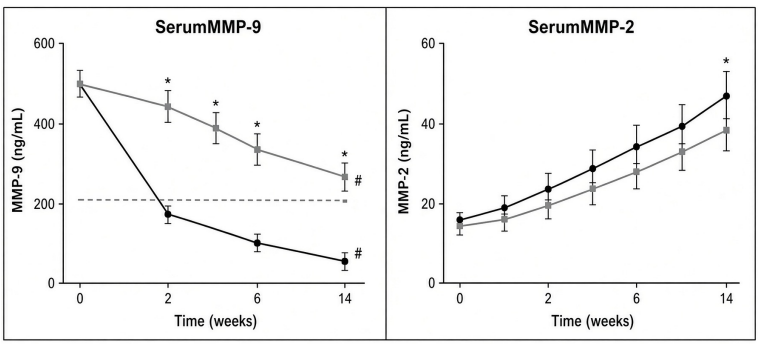


Figure 2. Characterization of serum extracellular vesicles and EV-associated RAGE. (A) Representative transmission electron microscopy image. (B) Nanoparticle tracking analysis size distribution. (C) Western blot of EV markers. (D) Quantification of EV-RAGE levels over time. (E,F) Correlation plots of EV-RAGE with serum MMP-9 and MMP-2 at week 14.

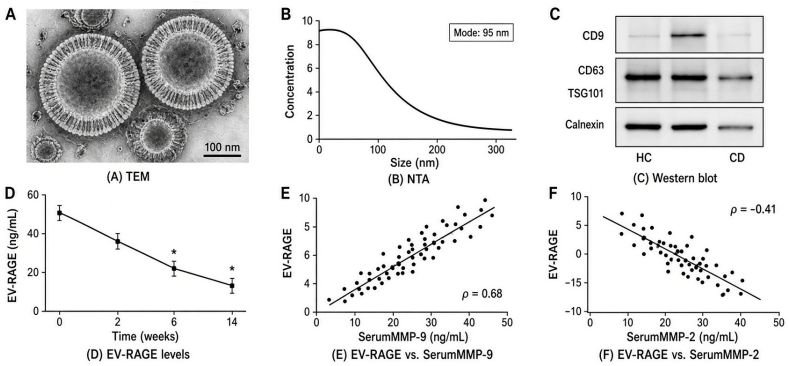


Figure 3. Infliximab suppresses NLRP3 inflammasome components and IL-1β. (A) Representative Western blots of NLRP3, ASC, and cleaved caspase-1 in PBMCs. (B) Serum IL-1β levels. (C) Comparison between responders and non-responders at week 14.

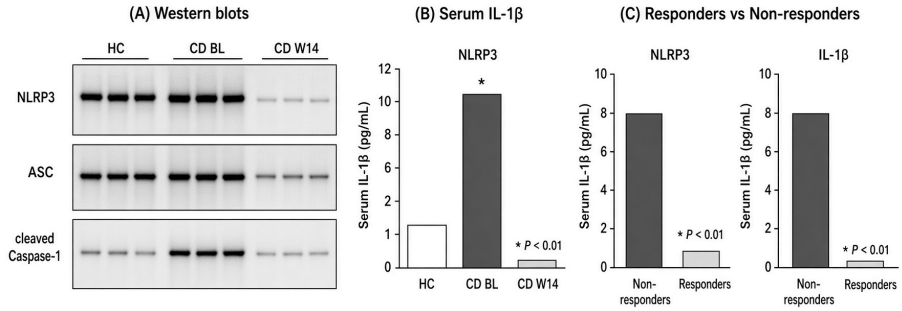
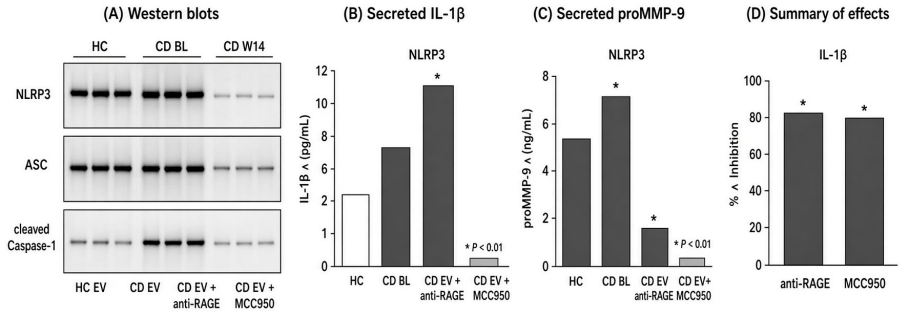


Figure 4. Mechanistic validation that EV-derived RAGE regulates MMP-9 via the NLRP3 pathway. Healthy donor PBMCs were treated with patient or control EVs in the presence or absence of RAGE-blocking antibody or MCC950. (A) NLRP3 and cleaved caspase-1 protein levels. (B) Secreted IL-1β. (C) MMP-9 release. (D) Summary of inhibitory effects.



Discussion

In the present study, we demonstrate that infliximab treatment differentially regulates the serological expression of MMP-2 and MMP-9 in patients with Crohn's disease, and provide evidence that this effect is mediated, at least in part, through reduction of extracellular vesicle (EV)-associated RAGE and subsequent suppression of the NLRP3 inflammasome pathway. These findings extend earlier observations that anti-TNF therapy alters circulating gelatinase levels and offer a previously unrecognized molecular mechanism linking EV cargo, innate immune signaling, and matrix remodeling[37-39].

Consistent with previous reports, we observed a progressive decline in serum MMP-9 after infliximab induction, which was more pronounced in clinical responders, together with a modest increase in serum MMP-2. The reduction in MMP-9 is biologically plausible, given that MMP-9 is predominantly produced by neutrophils and macrophages under TNF-driven inflammatory conditions and contributes to basement-membrane degradation and epithelial barrier disruption in CD. The concurrent rise in MMP-2 may reflect a shift toward a reparative proteolytic phenotype, as MMP-2 has been implicated in both tissue injury and controlled ECM remodeling. Importantly, our data indicate that these serological changes are not merely epiphenomena of reduced systemic inflammation but are closely associated with alterations in circulating EV composition[38,39].

We found that EV-associated RAGE was markedly elevated in active CD and declined in parallel with MMP-9 after infliximab therapy. RAGE is known to be upregulated in inflamed intestinal mucosa and to amplify NF-κB–dependent cytokine production; its soluble and EV-bound forms can further disseminate inflammatory signals[21-25,34]. Because MMP-9 itself participates in RAGE ectodomain shedding, a feed-forward loop

between gelatinase activity and RAGE bioavailability may exist in untreated disease[35]. Infliximab appears to interrupt this loop by lowering both EV-RAGE content and MMP-9 production. The strong positive correlation between EV-RAGE and serum MMP-9, together with the in-vitro demonstration that patient-derived EVs stimulate MMP-9 release in a RAGE-dependent manner, supports a causal relationship[21,24,25].

Mechanistically, we show that EV-RAGE promotes MMP-9 expression through NLRP3 inflammasome activation[26-32]. Baseline PBMCs from CD patients exhibited heightened NLRP3 and cleaved caspase-1 levels that decreased after infliximab, and these changes correlated with both EV-RAGE reduction and MMP-9 decline. In functional assays, blockade of RAGE or pharmacological inhibition of NLRP3 (MCC950) abolished the ability of CD-derived EVs to induce IL-1β secretion and MMP-9 release[33]. These results align with emerging evidence that NLRP3 can regulate MMP activity in other inflammatory settings and that RAGE ligands can trigger inflammasome assembly[26,27,29,31,32]. Thus, the EV-RAGE–NLRP3 axis represents a plausible pathway by which infliximab reprograms systemic proteolytic activity beyond simple TNF neutralization.

Clinically, the more robust suppression of EV-RAGE, NLRP3, and MMP-9 in responders suggests that this pathway may contribute to therapeutic efficacy and could serve as a biomarker for monitoring or predicting response[40,41]. Whether early changes in EV-RAGE or NLRP3 activity can identify primary non-responders warrants prospective validation. In addition, the data raise the possibility that adjunctive targeting of RAGE or NLRP3 might enhance or restore responsiveness in patients with incomplete anti-TNF responses, although this hypothesis requires formal testing. Current treatment paradigms emphasize treat-to-target strategies and the use of additional biologics such as vedolizumab or ustekinumab in anti-TNF failures[41-44].

Several limitations should be acknowledged. First, the sample size is modest and derived from a single center, limiting generalizability. Second, the study focused on circulating EVs and PBMCs; mucosal EV populations and tissue-level NLRP3/MMP interactions were not examined. Third, while the in-vitro experiments establish a functional link, the precise molecular intermediates between NLRP3 activation and MMP-9 transcription or secretion remain to be fully elucidated. Finally, the observational design cannot exclude the contribution of concurrent medications or disease-related factors independent of infliximab.

In summary, infliximab reduces serum MMP-9 and modestly elevates MMP-2 in Crohn's disease, at least partly by diminishing EV-derived RAGE and thereby attenuating NLRP3 inflammasome-driven MMP-9 production. These findings provide a novel mechanistic framework for understanding anti-TNF effects on matrix remodeling and highlight the EV-RAGE–NLRP3 axis as a potential biomarker and therapeutic target in IBD[26-28,33].

Conclusion

Infliximab treatment modulates serological MMP-2 and MMP-9 expression in Crohn's disease through an extracellular vesicle-derived RAGE–NLRP3 pathway. Reduction of EV-associated RAGE suppresses NLRP3 inflammasome activation, leading to decreased MMP-9 production. This mechanism offers new insight into the tissue-remodeling effects of anti-TNF therapy and identifies a potential target for optimizing treatment strategies in Crohn's disease.

Author contributions Conceptualization: D.L. and J.S.; Methodology: FB.T.; Validation: Y.H.; Formal analysis: D.L.; Investigation: FB.T; Data curation: D.L. Supervision: J.S.; Project administration: SL.Y. All authors read and approved the final manuscript. Funding This research received no external funding.

Data availability The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate This retrospective study was approved by Beijing Chao-yang Hospital Human Research Ethics Committee (Approval No. BJCY2025-331). The requirement for informed consent was waived by the Ethics Committee because of the retrospective nature of the study and the use of anonymous data. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki.

Consent for publication Not Applicable.

Competing interests The authors declare no competing interests.

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