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Soluble CD93 Induces Differentiation of Monocytes and Enhances TLR Responses

Jae-Won Jeon,*† Joon-Goo Jung,‡ Eui-Cheol Shin,§ Hye In Choi,† Ho Youn Kim,¶ Mi-La Cho,‖ Sun-Wha Kim,‡ Young-Soon Jang,† Myung-Ho Sohn,‡ Ji-Hyun Moon,† Young-Hun Cho,‡ Kwang-Lae Hoe,‡ Yeon-Soo Seo,* and Young Woo Park†

The cell surface protein CD93 is known to be involved in the regulation of phagocytosis and cell adhesion. Although typically membrane-bound, a soluble form of CD93 (sCD93) has recently been identified. Currently, however, the role of sCD93 in monocyte function is unknown. In the current study, we analyzed the functional effects of sCD93 on THP-1 monocytic cells and human primary monocytes. Various forms of recombinant human sCD93 were used to investigate the effects of this molecule on both human primary monocytes and a monocytic cell line, THP-1. We found that sCD93 induced differentiation of monocytes to macrophage-like cells, as evidenced by activated cell adhesion and increased phagocytic activities. In addition, this differentiation resulted in an enhanced response to TLR stimulation in terms of differentiation marker expression and proinflammatory cytokine production. Furthermore, sCD93 enhanced LPS-stimulated TNF-α production even prior to monocyte differentiation. To investigate a possible role for sCD93 in the pathogenesis of chronic inflammatory diseases, we assessed the concentration of sCD93 in synovial fluid from patients with rheumatoid arthritis and found it to be significantly increased compared with synovial fluid from patients with osteoarthritis. Together, these data revealed a function for sCD93 that may have implications in inflammation and inflammatory diseases including rheumatoid arthritis.

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The type 1 transmembrane glycoprotein CD93 (C1qRP) is encoded by the CD93 gene found on chromosome 20, position p11.21 in humans (1–3). CD93 consists of a signal peptide, a C-type carbohydrate-recognition domain (CRD), five epidermal growth factor (EGF)-like domains, a mucin domain, a single transmembrane domain, and an intracellular domain with a potential tyrosine kinase phosphorylation site (2, 4–8). CD93 homologs in mouse and rat are known as AA4 and are 67–87% identical (rat versus mouse: 87%; human versus mouse: 67%; human versus rat: 77%) to the human isoform (9–12). Expression of CD93 occurs in various cell types including myeloid cells, hematopoietic stem cells, NKL cells, platelets, microglia, and endothelial cells, but not in tissue macrophages (2, 12–16).

CD93 was originally shown to play a role in the regulation of C1q-mediated phagocytosis in an inhibition assay through use of anti-CD93 mAbs (8). In further studies, these mAbs were also shown to inhibit phagocytosis mediated by mannose-binding lectin and pulmonary surfactant protein, indicating a critical role for CD93 in the regulation of phagocytosis. Indeed, CD93-null mice displayed impaired clearance of apoptotic cells, which is mediated by phagocytic myeloid cells. Furthermore, immobilized anti-CD93 IgM mAb triggered phagocytosis in vitro (5, 17). However, the mechanism by which CD93 regulates phagocytosis remains unclear.

In addition to its role in phagocytosis, CD93 is known to be involved in the regulation of cell adhesion. Ligation of CD93 with an anti-CD93 mAb induced homotypic aggregation of LPS-stimulated U937 cells and triggered rapid spreading of HUVEC cells in vitro (18, 19). This suggests that the expression of CD93 on endothelial cells and myeloid cells might play a role in the regulation of cell adhesion and in the homing of inflammatory cells (6, 15, 20).

Recently, two separate studies reported the identification of a soluble form of CD93 (sCD93) (7, 21). Initially, it was demonstrated that hypoglycosylation of CD93 caused an increase in the levels of sCD93 in culture medium. This suggested that sCD93 was proteolytically cleaved from the surface-bound form (7). Further studies showed that CD93 was rapidly shed from the surface of human myeloid cells, and sCD93 was detected in human plasma (21, 22). Additionally, Greenlee et al. (23) demonstrated production of sCD93 in vivo under inflammatory conditions. However, the function of sCD93 remains to be defined.

In the current study, we synthesized various forms of recombinant human sCD93 to elucidate the functional effects of sCD93. Specifically, we analyzed the effects of sCD93 on differentiation of monocytes and on TLR responses by using human primary monocytes and a monocytic cell line.
Materials and Methods

**Reagents and culture media**

LPS, THP-1 Blue cells (human monocytic leukemia line with an NF-eB–inducible reporter), TLR agonists, and QUANTI-Blue detection medium were purchased from InvivoGen (San Diego, CA). PMA was purchased from Sigma-Aldrich (St. Louis, MO). Normal human IgG control protein was purchased from Jackson ImmunoResearch Laboratories (West Grove, PA). Recombinant human sCD93 mAb and sCD93-his protein (R&D Systems, Minneapolis, MN), FITC-conjugated Abs against CD1a, CD11b, and control IgG were purchased from BD Biosciences (San Jose, CA). FITC-conjugated anti-His Ab was purchased from Invitrogen (Carlsbad, CA). Human monocytic leukemia THP-1 cells were purchased from American Type Culture Collection (Manassas, VA). The THP-1 cells and human primary monocytes were maintained in RPMI 1640 medium supplemented with 10% heat-inactivated FBS, penicillin G (100 IU/ml), streptomycin (100 μg/ml), 1-glutamine (2 mM), HEPEs (10 mM), and sodium pyruvate (1.0 mM).

**Preparation of human primary monocytes**

PBMCS were isolated from venous blood of normal donors by Ficoll density gradient, and primary monocytes were subsequently isolated by 14% magnetic beads (Miltenyi Biotec, Auburn, CA). The purity of the isolated human primary monocytes was verified with anti-CD14-FITC Ab (BD Biosciences) by flow cytometry (Beckman Coulter, Fullerton, CA), and it was 90–94%.

**Production of recombinant human sCD93**

Four different forms of recombinant human sCD93 were constructed into pcDNA3.1 vector as follows (Supplemental Fig. 1): 1) human IgG1 Fc (named Fc only); 2) CRD and EGF domains of human CD93 (aa 24–470) (named Fc only); 2) CRD and EGF domains of human CD93 (aa 24–470) (human IgG1 Fc region (primer set: 5'-ACAGATGCTCAGCGAGCAGACGACGAG-TG3', 5'-CGCCTCCGTGTCAGCGAGCAGACGACGAG-TG3'); and 3) CRD and EGF domains of human CD93 (aa 24–470) (human IgG1 Fc region (primer set: 5'-ACAGATGCTCACCTCGGACAAACCTCA-CACA-3', 5'-CCGCTCGAGCTATTACCAGCGACGACGACGAG-TG3')).

**Assessment of cytokine production**

THP-1 cells were incubated with hsCD93-Fc or controls for 48 h and further incubated with or without LPS for 24 h. The culture supernatants were collected and cytokine levels were examined with the Quantikine assay kit (R&D Systems) according to the manufacturer’s instructions. Cytokine production was also assessed in primary human monocyte cultures. Human primary monocytes were rested for 24 h, incubated with hsCD93-Fc, hsCD93-His, or controls for 48 h, and further incubated with or without LPS for 24 h. The culture supernatants were collected, and cytokine levels were examined with the Quantikine assay kit (R&D Systems).

**Secreted embryonic alkaline phosphatase reporter assay**

THP-1 blue cells express the whole set of TLRs, from TLR1–TLR10, and they contain a reporter plasmid that expresses a secreted embryonic alkaline phosphatase (SEAP) under the control of NF-κB and AP-1 transcription factors. THP-1 blue cells were incubated with hsCD93-Fc or controls for 48 h and further incubated with or without a TLR agonist for 24 h. The following TLR agonists were used: Pam3CSK4 (0.1 μg/ml) for TLR1/2, HKLM (10^5 cell) for TLR2, LPS E coli K12 (1.0 μg/ml) for TLR4, flagellin (1.0 μg/ml) for TLR5, FSL-1 (0.2 μg/ml) for TLR6/2, and ssRNA40 (5.0 μg/ml) for TLR8. To quantify secreted SEAP, the culture supernatant was incubated with the QUANTI-Blue colorimetric assay reagent (Invivogen) for 24 h at 37°C. The OD at 655 nm was measured with a VERSAmax tunable microplate reader (Molecular Devices, Toronto, Ontario, Canada). All assays were run in triplicate.

**Real-time quantitative PCR**

The CFX96 system (Bio-Rad, Hercules, CA) was used for real-time PCR analysis. Thermal cycling was performed as follows: initial denaturation at 95°C for 3 min followed by 40–45 cycles of 95°C for 15 s and 60°C for 1 min. For each sample, 2 μl cDNA was added to 23 μl IQ SYBR Supermix (Bio-Rad) containing a primer pair, and each reaction was performed in duplicate. The standard comparative cycle threshold method was used to determine the relative gene expression levels, and the cycle threshold value of each sample was normalized to GAPDH. The corresponding primer pairs of TLR2, TLR4, MYD88, and GAPDH were purchased from Bioneer (Daejeon, Republic of Korea).

**Sandwich ELISA for sCD93**

A 96-well micro assay plate (BD Biosciences) was coated with mouse anti-human CD93 MAb (2 μg/ml) and then blocked with 3% skim milk. Human synovial fluid was added and incubated for 2 h. After washing, the plate was incubated with goat anti-human CD93 Ab (10 μg/ml) for 1 h. Subsequently, the plate was incubated with anti-goat IgG-HRP for 1 h. After washing, the plate was colorimetrically developed with o-phenylenediamine dihydrochloride substrate (Sigma-Aldrich), and absorbances were read with the VERSAmax tunable microplate reader (Molecular Devices).

**Results**

sCD93 induces differentiation of monocytes to macrophage-like cells

To study the functional role of sCD93 on monocytes, we prepared recombinant forms of human sCD93. As the domain structure of naturally shed sCD93 is not clear, we constructed four versions of recombinant sCD93: Fc only, hsCD93-Fc, hsCD93-Mucin-Fc, and hsCD93-His (Fig. 1A, 1B). Using a functional assay, we evaluated the role of the mucin domain by comparing hsCD93-Fc and
hsCD93-Mucin-Fc (Supplemental Fig. 2) and found similar effects on cytokine production, indicating that the mucin domain is dispensable for function of sCD93. In the current study, therefore, we used hsCD93-Fc and hsCD93-His for all functional assays.

We began our studies by determining whether sCD93 could bind to human monocytes, as the receptor expression patterns for CD93 are unclear. We found that hsCD93-Fc was able to bind to the cell surface of THP-1 cells (Fig. 1C) and human primary monocytes (Fig. 1D), thus indicating that monocytes express a putative receptor for sCD93. Moreover, this binding was partially blocked by anti-CD93 Ab (Fig. 1E). In addition, hsCD93-His was also able to bind to the cell surface of human primary monocytes, indicating that the His tag did not interfere with hsCD93–receptor interactions (Fig. 1E).

Next, we tested the effect of hsCD93-Fc on cell adherence, a functional indicator of macrophage differentiation (24). We found that hsCD93-Fc could induce THP-1 cell adhesion within 1 h in a dose-dependent manner (Fig. 2A, Supplemental Fig. 3). In addition, monomeric sCD93 without the Fc region (hsCD93-His) was also able to induce cell adherence, although the effect was less potent than that of hsCD93-Fc. After 3 d of culture in the presence of hsCD93-Fc, THP-1 cells exhibited a flattened morphology with extensive pseudopodia (Fig. 2B). This macrophage-like morphological change was also observed with PMA treatment. A similar morphology was observed in freshly isolated human monocytes after a shorter period (24 h) (Supplemental Fig. 4).

As morphological changes are indicative of monocyte differentiation, we next determined whether hsCD93-Fc could enhance phagocytic activity, a functional property of mature macrophages. Phagocytosis was evaluated by coculturing human primary monocytes with monomeric RFP-expressing E. coli. Subsequently, fluorescent microscopy and flow cytometry were performed to detect the RFP signals from phagocytosed E. coli (Fig. 2C, Supplemental Fig. 5). To differentiate true phagocytosis from bacterial adherence to the cell surface, we performed a Z-stack analysis of confocal microscopy images and confirmed that ingested bacteria were located in the cytoplasm of monocytes (Supplemental Fig. 6). Human primary monocytes treated with hsCD93-Fc for 3 d exhibited enhanced phagocytic activity (Fig. 2C). Moreover, anti-CD93 Ab partially abrogated the effect of hsCD93-Fc on the phagocytic activity, illustrating the specificity of the response. In addition, heat-denatured hsCD93-Fc did not enhance the phagocytic activity of monocytes. Although the effect was less than that observed for the Fc form, hsCD93-His was also shown to enhance phagocytic activity (Fig. 2D). Taken together, these data suggest that sCD93 induces the differentiation of monocytes to macrophage-like cells, as evidenced by enhanced cell adhesion and increased phagocytic activities.

**Differentiation of cells by sCD93 increases their sensitivity to TLR stimulation**

We studied the biological function of sCD93 by assessing its effects on monocyte differentiation and cytokine production. For this purpose, THP-1 cells were cultured with or without hsCD93-Fc for 48 h and subsequently stimulated with LPS for an additional 24 h. These time points were determined in a set of preliminary experiments in which we evaluated the effects of sCD93 at various times and found the most pronounced cellular responses at 48 h (Supplemental Fig. 7).
Expression of the differentiation markers CD1a and CD11b was marginally increased by hsCD93-Fc alone and moderately increased by LPS alone (Fig. 3A). Intriguingly, pretreatment with hsCD93-Fc greatly enhanced the LPS-induced increases in CD1a and CD11b expression (18.2-fold and 5.06-fold, respectively). A similar phenomenon was observed for cytokine production. When evaluating the proinflammatory cytokines TNF-α, IL-1β, and IL-6 (Fig. 3B), we found that pretreatment with hsCD93-Fc enhanced their LPS-stimulated production. Similar results were observed when monomeric recombinant sCD93 (hsCD93-His) was used (Fig. 3C). In particular, hsCD93-His alone slightly induced TNF-α production. In addition, anti-CD93 Ab completely abrogated hsCD93-Fc–induced TNF-α production (Fig. 3D). These results were confirmed in human primary monocytes (Fig. 3E). Taken together, these results indicate that hsCD93-Fc increased the sensitivity of monocytes to LPS in terms of both differentiation and cytokine production.

Next, we explored the effect of hsCD93-Fc on the response to TLR agonists other than LPS through use of a reporter system. THP-1 Blue cells secrete the protein SEAP into the culture medium upon TLR agonist-induced NF-κB activation. We found that pretreatment with hsCD93-Fc greatly enhanced the LPS-induced increases in CD1a and CD11b expression (18.2-fold and 5.06-fold, respectively). A similar phenomenon was observed for cytokine production. When evaluating the proinflammatory cytokines TNF-α, IL-1β, and IL-6 (Fig. 3B), we found that pretreatment with hsCD93-Fc enhanced their LPS-stimulated production. Similar results were observed when monomeric recombinant sCD93 (hsCD93-His) was used (Fig. 3C). In particular, hsCD93-His alone slightly induced TNF-α production. In addition, anti-CD93 Ab completely abrogated hsCD93-Fc–induced TNF-α production (Fig. 3D). These results were confirmed in human primary monocytes (Fig. 3E). Taken together, these results indicate that hsCD93-Fc increased the sensitivity of monocytes to LPS in terms of both differentiation and cytokine production.

Next, we explored the effect of hsCD93-Fc on the response to TLR agonists other than LPS through use of a reporter system. THP-1 Blue cells secrete the protein SEAP into the culture medium upon TLR agonist-induced NF-κB activation. We found that hsCD93-Fc increased the sensitivity of THP-1 Blue cells to several TLR agonists including those specific for TLR2, TLR4, TLR5, TLR6, and TLR8, but not the agonist for TLR1 (Fig. 4). To probe the mechanism underlying this effect, we investigated whether hsCD93-Fc might affect the expression of the TLRs or downstream molecule MyD88 by conducting a real-time PCR study. However, we found no evidence of either (data not shown).

Therefore, this suggests that another mechanism is responsible for the enhanced sensitivity to TLR stimulation.

**Effect of sCD93 on undifferentiated monocytes**

By a series of experiments, we showed that sCD93 induces differentiation of monocytes and that the differentiation results in increased sensitivity to TLR stimulation. Next, we studied if sCD93 enhances TLR responses of monocytes even without induction of differentiation. To clarify this issue, we examined LPS-stimulated TNF-α production from THP-1 monocytes with or without sCD93 cotreatment (Fig. 5). Both hsCD93-Fc and hsCD93-His significantly enhanced LPS-stimulated TNF-α production when coadministered with LPS. Thus, soluble CD93 synergizes with LPS, increasing TNF-α production even without monocyte differentiation.

**sCD93 was increased in synovial fluid of patients with rheumatoid arthritis**

To elucidate possible clinical implications of sCD93 production, we studied synovial fluid from patients with rheumatoid arthritis (RA) and compared it to that from patients with osteoarthritis (OA), a noninflammatory disease control. sCD93 was more abundant in the synovial fluid of patients with RA than in synovial fluid from patients with OA (Fig. 6A). However, in plasma, there was no significant difference observed, although the mean value was higher in the plasma of patients with RA (Fig. 6B). These data indicate that CD93 might play a role in the pathogenesis of inflammatory diseases. Moreover, sCD93 might be considered as a biomarker for chronic inflammatory diseases, such as RA.
Discussion

The existence of a sCD93 was only recently discovered, and its biological functions have not yet been elucidated. In this study, we analyzed various forms of recombinant human sCD93 to evaluate the effects of this molecule on monocyte differentiation and function (Fig. 1). We determined that sCD93 induced both monocyte adherence and morphological changes and enhanced phagocytosis (Fig. 2), suggesting that sCD93 is able to induce monocyte differentiation.

Increased monocyte phagocytosis following incubation with sCD93 is consistent with the previous observation that CD93-null mice exhibit a defect in the clearance of apoptotic cells (5, 25), as the scavenging of apoptotic cells is known to be achieved through phagocytosis (26, 27). Thus, defective clearance of apoptotic cells in CD93-null mice might actually be caused by the lack of sCD93. Very recently, Greenlee et al.'s (23) recent study using the cerebral ischemia model showed increased leukocyte infiltration and CCL21 expression in CD93 knockout (K/O) mice compared with wild-type mice, suggesting that CD93 acts to downmodulate inflammatory responses. The discrepancy between their study and our current study may be explained by the difference in pathological conditions. Specifically, cerebral ischemia induces inflammatory responses by causing tissue damage, and this may produce qualitatively different results than inflammatory responses generated via introduction of microbiological substances such as LPS. Thus, it is possible that CD93 might play different roles in microbiological inflammation versus sterile inflammation. Another possible explanation is that in a K/O model system, the absence of CD93 during development may change the physiology of the K/O animal by inducing overexpression of compensatory molecules such as CCL21. To clarify this issue, the use of conditional CD93 K/O mice would be warranted.

Our data also support a role for sCD93 as a promoter of inflammatory responses, because we observed increased cytokine production in response to LPS stimulation in monocytes that had been pretreated with sCD93 (Figs. 3, 4). However, Harhausen et al.'s (28) recent study using the cerebral ischemia model showed increased leukocyte infiltration and CCL21 expression in CD93 knockout (K/O) mice compared with wild-type mice, suggesting that CD93 acts to downmodulate inflammatory responses. The discrepancy between their study and our current study may be explained by the difference in pathological conditions. Specifically, cerebral ischemia induces inflammatory responses by causing tissue damage, and this may produce qualitatively different results than inflammatory responses generated via introduction of microbiological substances such as LPS. Thus, it is possible that CD93 might play different roles in microbiological inflammation versus sterile inflammation. Another possible explanation is that in a K/O model system, the absence of CD93 during development may change the physiology of the K/O animal by inducing overexpression of compensatory molecules such as CCL21. To clarify this issue, the use of conditional CD93 K/O mice would be warranted.

FIGURE 3. hsCD93-Fc pretreatment increased the sensitivity of monocytes to LPS. A, THP-1 cells were cultured with hsCD93-Fc (5 μg/ml) or hIgG control (5 μg/ml) for 48 h. Subsequently, cells were incubated with or without 1 μg/ml of LPS for an additional 24 h. Cells were collected and labeled with anti–CD1a-FITC or anti–CD11b-FITC. Flow cytometry data indicate the expression of the differentiation markers CD1a and CD11b. Mean fluorescence intensity was indicated in each histogram. B, THP-1 cells were cultured with hsCD93-Fc (5 μg/ml) or controls (5 μg/ml) for 48 h. Subsequently, cells were incubated with or without 1 μg/ml of LPS for an additional 24 h. Culture supernatants from THP-1 cells were collected and the concentration of TNF-α, IL-1β, and IL-6 were determined with a Quantikine assay kit. Data represent the mean ± SEM. Similar results were obtained from three independent experiments. C, In the same setting, THP-1 cells were treated with Fc only (5 μg/ml), hsCD93-Fc (5 μg/ml), or hsCD93-His (1 μg/ml), and the concentration of TNF-α was determined. Data represent the mean ± SEM. Similar results were obtained from three independent experiments. D, In the same setting, THP-1 cells were treated with Fc only (1 μg/ml), hsCD93-Fc (1 μg/ml), or hsCD93-Fc (1 μg/ml) in combination with goat anti-hCD93 polyclonal Ab (2 μg/ml), and the concentration of TNF-α was determined with a Quantikine assay kit. Data represent the mean ± SEM. Similar results were obtained from two independent experiments. E, Primary human CD14+ monocytes were isolated and cultured with hsCD93-Fc or Fc control at indicated various concentrations for 48 h. Subsequently, cells were incubated with or without 1 μg/ml LPS for an additional 24 h. Culture supernatants were collected, and the concentrations of TNF-α, IL-1β, and IL-6 were determined. Data represent the mean ± SEM. Similar results were obtained from three independent experiments. *p < 0.05; **p < 0.01.
As mentioned above, we also determined that sCD93 increased monocyte sensitivity to LPS and other TLR agonists, as demonstrated by increases in differentiation marker expression, cytokine production, and NF-κB reporter activity (Figs. 3–5). To explore a potential mechanism for these observations, we investigated the expression of TLRs and MyD88 after hsCD93-Fc treatment and found them to remain stable (data not shown). Hence, the mechanism by which sCD93 exerts this function remains unknown. Future studies will be directed at identification of the cellular receptor for sCD93 and the downstream signaling pathways. In initial attempts to identify the cellular receptor for sCD93, we have isolated sCD93-binding proteins by immunoprecipitation and identified the binding proteins using MALDI-TOF. This process yielded the sequences of several putative receptor proteins (Y.-S. Jang and J.-W. Jeon, unpublished observations), and we are currently attempting to identify which protein serves as a receptor for sCD93. We have also examined cell signaling pathways affected by hsCD93-Fc treatment. Interestingly, the phosphorylation of ERK and p38 was specifically induced by hsCD93-Fc treatment.

FIGURE 4. hsCD93-Fc pretreatment increased the sensitivity of monocytes to other TLR agonists. Poststimulation of THP-1 Blue cells with hsCD93-Fc (5 μg/ml) or controls (5 μg/ml) for 48 h, the cells were treated with the indicated TLR agonists for an additional day. Culture supernatants were assessed for SEAP reporter activity with the QUANTI-blue reagent (Invivogen) to evaluate the degree of NF-κB activation by TLR agonists.

FIGURE 5. Human sCD93 cotreatment with LPS increased the secretion of TNF-α. THP-1 cells were cultured with Fc only (5 μg/ml), hsCD93-Fc (5 μg/ml) with or without LPS (1 μg/ml), hsCD93-His (1 μg/ml) with or without LPS (1 μg/ml), or LPS only (1.0 μg/ml) for 48 h. Culture supernatants from THP-1 cells were collected at the indicated times and the concentration of TNF-α was determined. The one result was presented in two separate columns, A (Fc form) and B (His form), to easily distinguish each line. Data represent the mean ± SEM. Similar results were obtained from two independent experiments.

FIGURE 6. sCD93 was overexpressed in RA synovial fluid. The concentrations of sCD93 in synovial fluid (A) and plasma (B) from patients with RA and OA were determined by sandwich ELISA. Statistical analysis was performed using a two-tailed paired Student t test. *p < 0.01.
In the current study, we demonstrated that synovial fluid from patients with RA contained higher levels of sCD93 than that from patients with OA (Fig. 6). Although it is unknown whether the overexpression of CD93 or sCD93 plays a role in the development of RA, these results suggest a potential clinical application for CD93. First, sCD93 could be a potential biomarker for RA. However, further study will be required to determine if there is a correlation between the concentrations of sCD93 in the synovial fluid and the severity of RA. Second, sCD93 could be a potential target for developing new RA treatments. Future studies to determine whether sCD93 is involved in the pathogenesis of RA are certainly warranted.

In summary, we identified a functional role for sCD93 and revealed the presence of sCD93 in the chronic inflammatory diseases RA. In the future, detailed studies will be warranted to specifically investigate the mechanism of action of sCD93 and the role of sCD93 in the pathophysiology of chronic inflammatory diseases.

Disclosures

The authors have no financial conflicts of interest.

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