Mini Review

Possible roles of adiponectin in inflammatory process of rheumatoid arthritis

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Adipokines are cytokines secreted from adipocytes. They play an essential role in both metabolic diseases and inflammatory diseases such as rheumatoid arthritis (RA). In RA patients, concentrations of typical adipokines in the synovial fluid or serum tend to be higher than in control subjects; therefore, the role of adipokines in inflammation has been under intense investigation. Adiponectin (Ad) in particular plays a role in many biological processes, however, its influence on inflammation is controversial. From our investigations into how Ad may act in inflammation we concluded that infiltrating macrophages and neutrophils at sites of local inflammation, such as in the synovial tissues of RA patients, are activated by inflammatory cytokines and secrete elastase resulting in the production of globular Ad (gAd), and that that gAd augments the inflammatory response.

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Introduction

Rheumatoid arthritis (RA) is a chronic progressive autoimmune inflammatory disease of unknown etiology that particularly affects the joints of the hands and feet. The synovial tissue of affected joints is infiltrated by inflammatory cells, such as macrophages and lymphocytes, leading to hyperplasia with neovascularization, which causes joint swelling, stiffness, and pain. This ultimately leads to cartilage destruction and bone resorption in the joints, with some patients suffering permanent disability. The overproduction of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) plays an important role in the development of RA, and the introduction of anti-TNF-α or anti-IL-6 receptor (IL-6R) therapy dramatically improves symptoms in patients with severe RA and prevents the progression of joint destruction. In more recent years, CCR6-positive cells, particularly T$_h$17 cells, were emphasized. T$_h$17 cell is a novel subset of CD4+ helper T cells that characteristically produce IL-17, IL-21, and IL-22. Many studies have demonstrated that T$_h$17 plays an essential role in the onset of arthritis in mouse models[1, 2]. In RA patients, IL-17-producing CD4 T cells are increased in synovial tissue and peripheral blood[3], suggesting an important role in RA pathogenesis.

Table 1 Characteristics of key adipokines

| Adipokine	Primary source	Receptor	Main function
Adiponectin	Adipocytes	Adiponectin receptor-1 and -2	Improvement of insulin sensitivity
Leptin	Adipocytes	Leptin receptor	Regulation of appetite and metabolism
Resistin	Adipocytes (rodent) Peripheral blood mononuclear cells (PBMC) (human)	Unknown	Promotion of insulin resistance
Visfatin	Adipocytes	Insulin receptors	Improvement of insulin sensitivity
MCP-1	Adipocytes, stromal cells	CCR2	Recruitment of monocytes
TNF	Adipocytes, stromal cells	TNF receptor-1 and -2	Development of inflammation
IL-6	Adipocytes, stromal cells, muscle cells, hepatocytes	IL-6 receptor	Development of inflammation
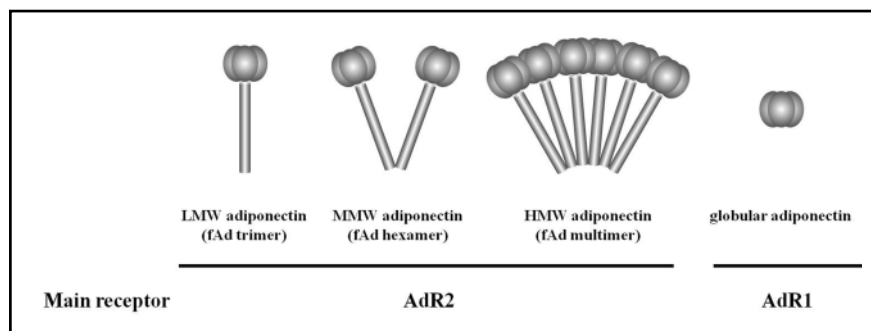
Fig.1 Adiponectin isoforms

Adipokines secreted from adipocytes have come to be considered to represent a new family of compounds that act as key players in the complex network of soluble mediators involved in the pathophysiology of RA. The levels of typical adipokines such as adiponectin (Ad), leptin, resistin, and visfatin in the synovial fluid and serum of RA patients tend to be higher than in healthy subjects[4-10]. Although it has been reported that the levels of some adipokines correlate with levels of inflammatory markers in RA patients[8, 9, 11], the role of adipokines in inflammation is still unclear.

Characteristics of key adipokines

Adipokines are intimately involved in metabolic diseases such as diabetes and arteriosclerosis. Table 1 provides an overview of the characteristics of key adipokines. In these metabolic diseases, Ad, leptin, and visfatin are known as "good adipokines", and in contrast, resistin, monocyte chemoattractant protein-1 (MCP-1), TNF-α, and IL-6 are known as "bad adipokines". However, these adipokines have different effects on inflammation. For example, resistin promotes the expression of inflammatory cytokines such as TNF-α and IL-6 in human mononuclear cells[12], leptin increases the production of TNF-α and IL-6 from monocytes[13], and visfatin induces IL-1, TNF-α, and IL-6[14]. Under conditions of inflammation, leptin and visfatin are therefore "bad adipokines" like resistin. In this article, we focus on the biological activity of Ad in inflammatory process of RA because Ad is the most abundant adipokine in the blood[15].

Ad isoforms and signaling

Ad exists in plasma in three main forms of full-length adiponectin (fAd)—a low-molecular-weight (LMW) trimer, a medium-molecular-weight hexamer, and a high-molecular-weight (HMW) multimer—and one form of globular Ad (gAd) (Fig.1). Adiponectin receptor-1 and -2 (AdR1 and AdR2) serve as receptors for fAd and gAd. Whereas AdR1 has a high affinity for gAd and a low affinity for fAd, AdR2 has a moderate affinity for both isoforms. AdR1 is abundantly

Table 2 Effect of adiponectin on inflammation

Effect of adiponectin on inflammation	
Anti-inflammatory effect	Inhibition of pro-inflammatory cytokine production[12, 13]
	Inhibition of MMP production[14]
	Inhibition of ROS production[15]
	Inhibition of the severity of CIA mice[16, 17]
Pro-inflammatory effect	Induction of pro-inflammatory cytokines[22, 23]
	Induction of VEGF[21]
	Induction of MMPs[21]
	Induction of COX-2 and PGE$_2$[24]

expressed in skeletal muscle, whereas AdR2 is predominantly expressed in the liver. Ad increases AMPK and PPARα ligand activities through both receptors, inducing anti-diabetic and anti-atherogenic effects[16, 17]. AdR1 deficiency induces a reduction in Ad-induced AMPK activation, resulting in the increase of glucose production and insulin resistance, whereas AdR2 deficiency induces a decrease in activity of PPARα signaling, resulting in insulin resistance. The loss of both receptors affects the binding and functions of Ad, leading to acceleration of glucose intolerance. Additionally, the activities of Ad vary from isoform to isoform; for example, HMW Ad has the strongest effect on AMPK activation and is thought to be the most active form in terms of glucose homeostasis[18, 19]. Therefore, the HMW complex may be the most biologically active form and may have more pathophysiological relevance in humans. Serum HMW Ad shows a strong linear correlation with serum total Ad, and the ratio of HMW to total Ad is more closely associated with coronary artery disease in Type II diabetes than either HMW or total Ad[20].

Ad and RA

After the initial evidence that Ad might be involved in the pathogenesis of RA, the pathogenic and physiological roles of Ad in RA and other rheumatic diseases began to be actively investigated. Although the role of Ad is far from being completely defined, both anti- and pro-inflammatory properties have been reported (Table 2).

With respect to its anti-inflammatory properties, Ad inhibits the expression of various pro-inflammatory cytokines[21, 22] and matrix metalloproteinases (MMPs)[23]; Ad blocks the production of reactive oxygen species (ROS) that leads to oxidative damage[24]; and Ad mitigates the severity of collagen-induced arthritis (CIA) in mice[25, 26]. On the other hand, it is reported that Ad levels in patients with RA are high and correlated with disease severity[27]. More-

over, it is reported that there is an association between serum Ad levels and radiographic damage in patients with RA[28]. It has been shown that Ad induces production of IL-6, IL-8, vascular endothelial growth factor (VEGF), MMP-1, MMP-13, cyclo-oxygenase 2 (COX-2), and prostaglandin E$_2$ (PGE$_2$) in RA synovial fibroblasts[29-33]. As discussed above, some of the apparent discrepancies in the diverse functions of Ad are linked to the level of oligomerization of the protein: HMW isoforms have been reported to have actions opposite to those of LMW isoforms.

Effect of Ad in macrophages

As stated in the introduction, not only synovial cells but macrophages and lymphocytes, such as T$_h$17 cells also play important roles in RA. Particularly, many reports have been published on the effect of Ad in macrophages and both anti- and pro-inflammatory properties have been also suggested[34-36]. Interestingly, most researches on the anti-inflammatory effect of Ad are supported by data from Ad-pretreatment before leading to inflammation. The paper by Tsatsansis et al. indicated that pre-exposure of Ad unmasked its pro-inflammatory properties[34]. However, they also have showed that Ad induces pro-inflammatory cytokines. To develop a better understanding about pro-inflammatory property of Ad by simultaneous addition, we examined the effect of Ad on CCL20/MIP-3α expression in THP-1 macrophages. CCL20/MIP-3α belongs to the CC chemokine family, is known as a chemokine for T$_h$17 cells. In patients with RA, CCL20/MIP-3α concentration in blood and synovial fluid is elevated[37] and is one of the parameters of inflammation. THP-1 macrophages, which are derived from THP-1 monocytes stimulated with phorbol myristate acetate (PMA), were cultured with fAd (10 μg/mL), IL-6 (10 ng/mL), or TNF-α (10 ng/mL) for 24 h. The expression of CCL20/MIP-3α was slightly increased by addition of fAd alone but was synergistically increased by fAd
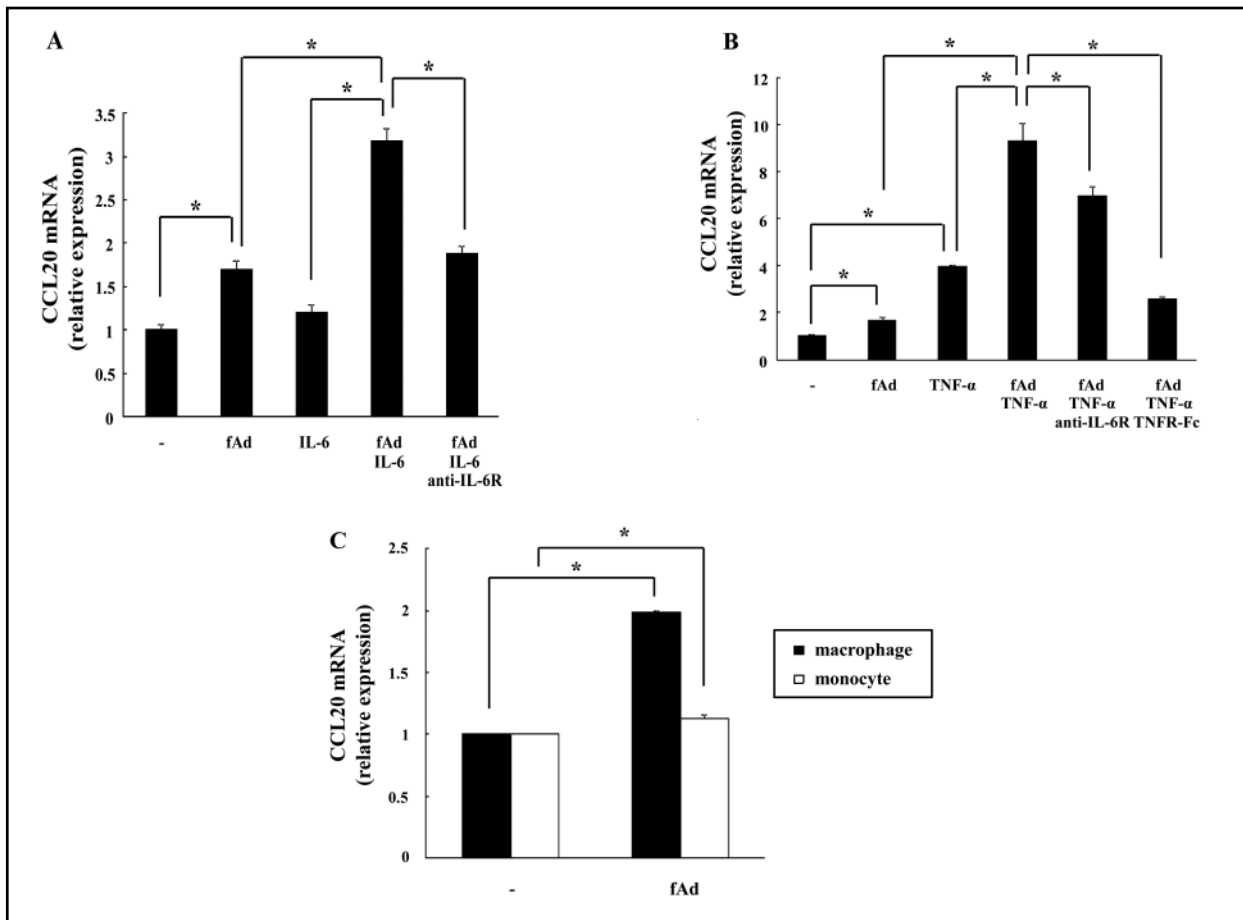
Fig.2 CCL20 expression in THP-1 macrophages and THP-1 monocytes treated with fAd, IL-6, and TNF-α

(A)THP-1 macrophages were cultured for 24 h with fAd (10 μg/mL), IL-6 (10 ng/mL), fAd (10 μg/mL) +IL-6 (10 ng/mL), or fAd (10 μg/mL)+IL-6 (10 ng/mL)+anti-IL-6R (100 μg/mL). After culturing, cell lysate was collected and the mRNA expression for CCL20 was measured by real-time PCR. Statistical significances were analyzed by t-test (* $p<0.05$)

(B)THP-1 macrophages were cultured for 24 h with fAd (10 μg/mL), TNF-α (10 ng/mL), fAd (10 μg/mL) + TNF-α (10 ng/mL), fAd (10 μg/mL) +TNF-α (10 ng/mL) + anti-IL-6R (100 μg/mL), or fAd (10 μg/mL) +TNF-α (10 ng/mL) +TNFR-Fc (1 mg/mL). After culturing, cell lysate was collected and the mRNA expression for CCL20 was measured by real-time PCR. Statistical significances were analyzed by t-test (* $p<0.05$)

(C)THP-1 macrophages and THP-1 monocytes were cultured for 24 h with fAd (10 μg/mL). After culturing, cell lysate was collected and the expression of CCL20 mRNA was measured by real-time PCR. Statistical significances were analyzed by t-test (* $p<0.05$)

plus the co-addition of IL-6 or TNF-α (Fig.2A, B). Furthermore, the synergistic effect of fAd plus TNF-α was partially blocked by anti-IL-6R antibody. This indicates that IL-6 induced by TNF-α partially participates in TNF-α-induced CCL20/MIP-3α expression. In contrast, we confirmed that TNFR-Fc did not reduce CCL20 expression by fAd + IL-6, suggesting that fAd and IL-6 would directly induce CCL20, not through TNF-α, in THP-1 macrophages (data not shown). As we expected, these results indicate that Ad acts as a pro-inflammatory factor in macrophages.

Cleavage of globular adiponectin from full-length adiponectin

As already mentioned in Ad isoforms and signaling, Ad exists as fAd or as gAd. Many studies have been reported on three isoforms of fAd, such as the importance of HMW isoform. However, little research on gAd has been reported even though there might be many differences of effects between fAd and gAd because fAd and gAd are different in affinities for their receptors. In recent years, since it was shown that leukocyte elastase from macrophages and neutrophils may generate gAd[38, 39], it has been thought that
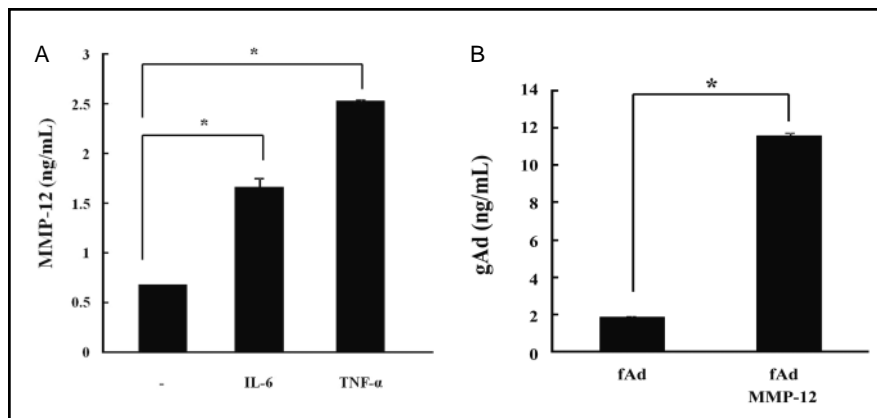
Fig.3 MMP-12 production in THP-1 macrophages and THP-1 monocytes and gAd production by MMP-12

(A) THP-1 macrophages and THP-1 monocytes were cultured for 24 h with IL-6 (10 ng/mL) or TNF-α (10 ng/mL). After culturing, cell supernatant was collected and the concentration of MMP-12 was measured by ELISA. The production of MMP-12 was not detected (<1.2 pg/mL) in THP-1 monocytes. Statistical significances were analyzed by t-test ($*p<0.05$)

(B) fAd (100 μg/mL) was incubated with MMP-12 (100 ng/mL) for 24 h at 37 ℃. The concentration of gAd was then measured by ELISA. Statistical significances were analyzed by t-test ($*p<0.05$)

gAd plays a key role on inflammation. In particular, Waki et al. have reported on elastase secreted by PMA-stimulated THP-1 cells. Therefore, we considered the involvement of gAd as the mechanism underlying the synergistic effect of fAd plus cytokines. In our study, fAd slightly induced CCL20/MIP-3α expression in THP-1 monocytes, but in THP-1 macrophages prominently (Fig.2C). Next, when we measured the concentration of MMP-12 in cell supernatants, we found that MMP-12 was produced in THP-1 macrophages and that this was significantly increased by IL-6 and by TNF-α; however, the production of MMP-12 was not detected (<1.2 pg/mL) in THP-1 monocytes (Fig. 3A). MMP-12, which is a protease, is also called macrophage elastase. Furthermore, as we expected, fAd was cleaved into gAd by MMP-12 (Fig.3B), and gAd production was induced in THP-1 macrophages by the co-incubation of fAd with IL-6 or TNF-α (Fig.4A).

Difference of pro-inflammatory properties between fAd and gAd

Difference of activities between fAd and gAd is still controversially discussed. However, as with activities of fAd vary with the levels of oligomerization, moreover, it can be easily imagined that there are differences in activities between fAd and gAd. In fact, it has been also reported on the difference of activities between fAd and gAd[17, 38]. We also compared the effect of fAd and gAd on the expression of CCL20/MIP-3α in THP-1 macrophages and found that gAd more potently induced the expression of CCL20/MIP-3α mRNA than did fAd (Fig.4C). Furthermore, we investigated the influence of UK370106 (a highly selective MMP-3 and MMP-12 inhibitor) on the increased production of gAd and CCL20/MIP-3α [40, manufacturer's website (www.scbt.com/datasheet-204375-uk-370106.html)]. UK370106 inhibited the cytokine-induced gAd production (Fig.4A). In addition, UK370106 significantly inhibited fAd-induced CCL20/MIP-3α mRNA expression, and also inhibited the increased expression of CCL20/MIP-3α by IL-6 and TNF-α (Fig.4B). Although UK370106 is also a potent inhibitor of MMP-3, the expression of MMP-3 was not increased by IL-6 or TNF-α in THP-1 macrophages (data not shown). Therefore, it would appear that the effect of UK370106 is mainly the inhibition of MMP-12. These findings strongly suggest that gAd plays an important role in the inflammatory response. The synergistic effect of fAd plus cytokines was induced by the following steps: 1)IL-6 or TNF-α augmented MMP-12 production in macrophages, 2)MMP-12 cleaved fAd into gAd, and 3)gAd induced CCL20/MIP-3α production in THP-1 macrophages.

Conclusion
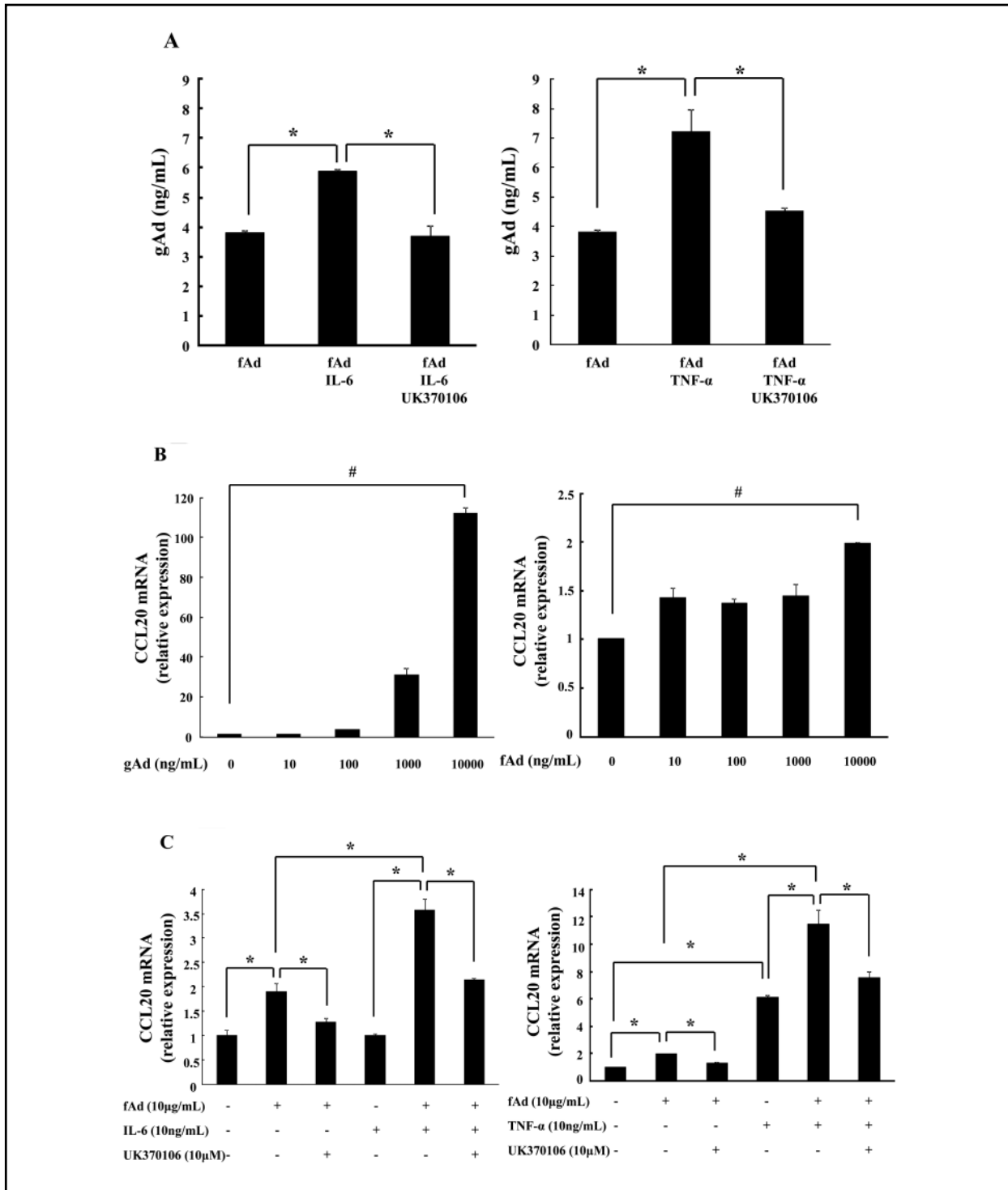
In RA, many macrophages and lymphocytes, such as

Fig.4   Effect of MMP inhibitor on gAd production and CCL20 expression and effect of gAd and fAd on CCL20 expression in THP-1 macrophages

(A)THP-1 macrophages were cultured for 24 h with fAd (10 μg/mL) and fAd (10 μg/mL) +IL-6 (10 ng/mL) or fAd (10 μg/mL) + TNF-α (10 ng/mL) in the presence or absence of UK370106 (10 μM). After culturing, cell supernatant was collected and the concentration of gAd was measured. Statistical significances were analyzed by t-test (*$p<0.05$)

(B)THP-1 macrophages were cultured for 24 h with fAd or gAd. After culturing, cell lysate was collected and the expression of mRNA for CCL20 was measured by rel-time PCR. Statistical significances were analyzed by Dunnett's multiple comparison test (#$p<0.05$)

(C)THP-1 macrophages were cultured for 24 h with fAd +IL-6 or fAd + TNF-α in the presence or absence of UK370106. Cell lysate was collected and the expression of CCL20 mRNA was measured by real-time PCR. Statistical significances were analyzed by t-test (*$p<0.05$)
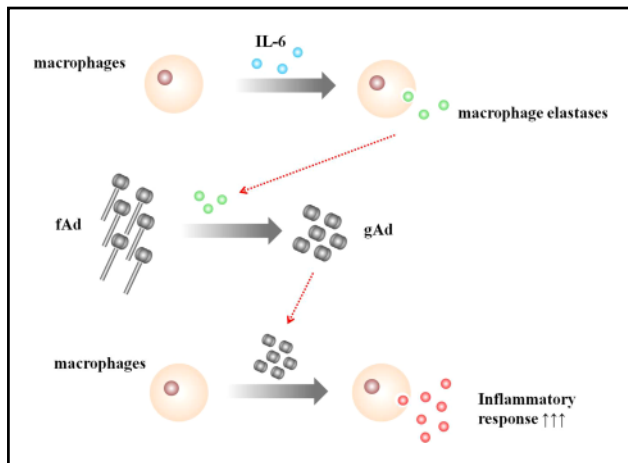
Fig.5 Effect of adiponectin at the site of inflammation

Many inflammatory cells such as macrophages infiltrate into synovial tissue in RA. The infiltrating macrophages are stimulated by inflammatory cytokines to secrete elastase, resulting in the cleavage of fAd into gAd. Production of gAd augments the inflammatory response such as CCL20 production of macrophages at the site of inflammation.

Th17 cells infiltrate into affected synovial tissue. Therefore, it is very likely that the infiltrating macrophages are induced by inflammatory cytokines to secrete elastase, resulting in the production of gAd. Production of gAd augments the inflammatory response at the site of inflammation (Fig.5). Further studies are necessary to clarify the role of gAd in RA patients.

Source of funding

None

Conflict of interests

None

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