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Effects of macrophage colony-stimulating factor (M-CSF) on protease production from monocyte, macrophage and foam cell in vitro: a possible mechanism for anti-atherosclerotic effect of M-CSF

Naoko Tojo, Eiji Asakura *, Mamoru Koyama, Toshizumi Tanabe, Norifumi Nakamura

Drug Discovery Pharmaceutical Research Division, Yoshitomi Pharmaceutical Industries, Ltd., 2-25-1, Shodai-Ohtani, Hirakata, Osaka 573, Japan

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Abstract

M-CSF is a growth factor that stimulates proliferation and differentiation of monocyte/macrophage-lineage cells. In our previous studies, M-CSF regresses atherosclerotic lesions preformed in aorta of high cholesterol-fed rabbit. Immunohistochemical analysis indicated that extracellular matrix (ECM), such as collagen, was especially eliminated in the intima of atherosclerotic lesion. To define the collagen-lowering potential of M-CSF, we have studied the effects of M-CSF on production of collagen-degrading proteases, such as MMP-1, -9 and urokinase in vitro. Monocytes freshly isolated from human peripheral blood produced MMP-9, but not urokinase, and M-CSF enhanced MMP-9 production. Macrophages were prepared by culturing monocytes for 10 days in the presence or absence of M-CSF, and protease production was assayed. M-CSF augmented production of MMP-9 and urokinase in a dose-dependent manner. M-CSF also enhanced MMP-1 production of macrophages, but not significantly. Foam cells were prepared by culturing macrophages in the presence of acetyl LDL, and protease production from these cells were also elevated by M-CSF. These results suggest that M-CSF exogenously administered in atherosclerotic rabbits might regress the thickened intima by activating macrophages to degrade collagen accumulated in the lesion.

Keywords: Macrophage colony-stimulating factor; MMP; Urokinase; Macrophage; Foam cell; Atherosclerosis

1. Introduction

M-CSF is produced by variety of cell types including macrophage, endothelial cell, fibroblast and lymphocyte [1–4]. In recent studies, local production of M-CSF and its gene expression have been detected during atherogenesis [7,8], suggesting that M-CSF may play an important role in the atherosclerotic lesions. Serum cholesterol-lowering activity of M-CSF was at first found in a clinical trial concerning chronic neuropenia boys [9], and has been also experimentally demonstrated using rabbits and non-human primates [10–12]. Additional studies have shown that M-CSF enhances the clearance of lipoproteins and modified lipoproteins through LDL receptor and scavenger receptor [10,13], and that M-CSF enhances cholesterol metabolism by upregulation of activities of neutral cholesteryl ester hydrolase (CEH) and acidic CEH and acyl CoA cholesterol acyltransferase

* Corresponding author. Fax: +81-720-57-5020; E-mail: ac43320@yoshtomi.co.jp

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[14]. M-CSF also stimulates secretion of apo E and retroendocytosis of cholesterol ester by HDL-dependent processes [15]. Anti-atherosclerotic effects of M-CSF were demonstrated by repeated injection of M-CSF into Watanabe heritable hyperlipidemic (WHHL) rabbits, resulting in prevention of atherosclerosis progression [10,16].

In our early study, administration of M-CSF led to the regression of atherosclerotic lesion which was preformed in high cholesterol diet rabbits [17]. In this paper, we performed immunohistochemical analyses on the intima of atherosclerotic lesion of these rabbits. Furthermore, we investigated in vitro effects of M-CSF on protease production from monocyte, macrophage and foam cell which might degrade ECM accumulated in atherosclerotic lesion. We assayed type I collagenase (MMP-1), gelatinase (MMP-9) and urokinase that degrades ECM and activates MMPs through activation of plasmin [18,19], and found that M-CSF augments protease production from monocyte, macrophage and foam cell.

2. Materials and methods

2.1. M-CSF

Recombinant human M-CSF (Genetics Institute, Cambridge, MA) was purified from culture supernatants of Chinese hamster ovary (CHO) cells transfected with cDNA of human M-CSF. This preparation showed a specific activity of 4×10^8 U/mg protein by colony formation assay with mouse bone marrow cells, and had endotoxin of less than 10 pg/10^5 U/ml by Limlus assay (Seikagakukogyo, Tokyo).

2.2. In vivo studies

Twelve-week-old male New Zealand white rabbits (2.4–3.0 kg, Kitayama, Kyoto) were fed with 2.0% cholesterol for 8 weeks. Then the rabbits were taken normal diet, and 80 μg/kg of M-CSF or human serum albumin (HSA), as a control, was intramuscularly administered once a day for another 12 weeks. Animals were sacrificed under anesthesia with thiopentalsodium. The aorta from arch to abdominal region was excised and cut to open lengthwise.

2.3. Immunohistochemistry

The aortic strip was fixed in PBS containing 1% formalin for more than 12 h at 4°C. Then the specimens were embedded in paraffin, and immunostained with anti-collagen I–V polyclonal antibody (Sanbio, Netherlands) using streptoavidin-biotin method (Histofine SAB-PO (R) kit, Nichirei, Tokyo). Collagen was identified as light-brown color by immunohistochemical staining. The immunostained specimens were projected onto a microcomputer imaging device (Luzex IID, Nireco, Tokyo) to measure collagen-positive area.

2.4. Cells

Human peripheral blood was obtained from healthy volunteers who gave informed consent. Using Percoll density gradient centrifugation, monocytes were prepared from mononuclear cells that were prepared from blood by Ficoll-Paque density gradient centrifugation [20].

2.5. Cell culture

Monocytes were suspended in 1:1 (v/v) mixture of Ham's F-12/Dulbecco's modified eagle's medium (Nissui, Tokyo) supplemented with 10% human serum (Type AB, Sigma, St. Louis, MO), and cultured for 2 days in the presence or absence of M-CSF. Culture supernatants were harvested, and stored at −80°C until assays. Macrophages were prepared by cultivation for 10 days in the media described above,

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Fig. 1. Collagens decrease in aorta of atherogenic rabbits by treatment with M-CSF. Rabbits were fed with 2.0% cholesterol diet for 8 weeks, and followed by treatment with 80 μg/kg of M-CSF (a) or HSA (b) by intramuscularly administration once a day for another 12 weeks. Collagens accumulated in atherogenic aorta were stained with anti-collagen I–V polyclonal antibody (×39). Treatment with M-CSF diminished the thickened intima (upper half of the specimens), and decreased collagen content. Similar results were obtained from ten (M-CSF) and seven (HSA) rabbits.


(a)
(b)

which were changed every 3–4 days, and cultured for an additional 2 days in medium without M-CSF and serum. Foam cells were prepared by culturing macrophages with 100 μg/ml of acetyl LDL for 2 days in medium without serum. Each culture supernatant was collected, and stored at −80°C.

2.6. Assays

Cellular DNA was measured by the method of Labarca et al. [21]. MMP-1 was measured by degradation of FITC-labeled type I collagen after activation by trypsin (Yagai, Yamagata, Japan). MMP-9 was assayed by gelatin zymography as described previously [22]. Sample of each lane was adjusted the volume to same quantity of cellular DNA. Urokinase was assayed by ELISA (Biopool, Sweden).

2.7. Oil red O stain

Foam cells were fixed in 10% formalin for 5 min, and washed in water. Cells were treated with 60% isopropanol for 1 min, and then stained for 15 min at 37°C with 0.18% oil red O in 60% isopropanol. After washing in 60% isopropanol and water, cells were counter-stained with Hematoxylin for 5 min.

2.8. Statistics

Paired *t*-test was used to determine the significance of differences. A *P*-value of < 0.05 was considered as statistically significant, but most of the significant values were at least $P < 0.01$.

3. Results

3.1. Effect of M-CSF on atherosclerotic lesions in aorta of cholesterol-fed rabbits

From our previous studies, M-CSF reduced atherosclerotic lesion in cholesterol-fed rabbits by activation of reverse cholesterol transport. Furthermore, we analyzed atherogenic aorta of these rabbits by immunohistochemical staining. Collagen was accumulated in the intimal lesion of control rabbits, and 45% of thickened intima was collagen positive (Fig. 1b, $n = 7$). In contrast, the collagen-positive area in the intima decreased to 29% by M-CSF-treatment (Fig. 1a, $n = 10$). Because intimal thickness of M-CSF-treated rabbits was half as much as that of control rabbits, M-CSF reduced 63% of collagen in the aorta of atherosclerotic lesion. Thus, the effect of M-CSF on atherosclerotic lesion is not only simple regression of the thickness of intima of aorta, but also reduction of collagen positive ratio. From these results, we presumed that M-CSF accelerates degradation of collagens, and studied effects of M-CSF on protease production from monocyte, macrophage and foam cell.

3.2. Effect of M-CSF on protease production of monocytes

Peripheral blood monocytes from six different donors were cultured in 10% human serum containing medium with or without 10^4 U/ml of M-CSF for 2 days, and proteases in the supernatants were measured. Sample of each lane was adjusted the volume to same quantity of cellular DNA. Monocytes isolated from all tested donors produced MMP-9, which was identified as clear bands at molecular weight of 92 kDa in zymograms, and M-CSF enhanced MMP-9 production of monocytes (Fig. 2). Activated form of MMP-9 with molecular weight of 83 kDa [23] was detected as a minor band, but MMP-2, another gelatinase with molecular weight of 72 kDa [24,25] was not detected in the zymograms. Urokinase was not detected (< 4.3 pg/μg DNA). MMP-1 activity could not be detected probably because of inhibitor(s) included in human serum [26,27].

3.3. Effect of M-CSF on protease production of macrophages

Macrophages were prepared by culturing monocytes for 10 days in the presence or absence of 10^4 U/ml of M-CSF. Media were replaced by those of serum free, and cells were cultured for additional 2 days. MMP-1, MMP-9 and urokinase produced in the supernatants were measured. Since M-CSF supported cellular survival during cultivation in vitro (Fig. 3), cell numbers were estimated as DNA amounts, and protease productivity was normalized. Macrophage produced these enzymes, and production of MMP-9 and urokinase was elevated during

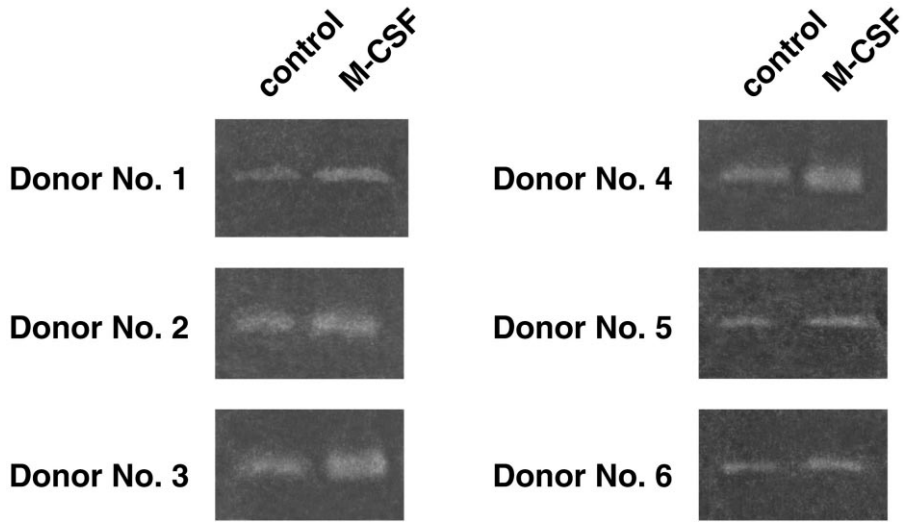

Fig. 2. M-CSF enhances MMP-9 production of monocytes. Monocytes of six donors were cultured with or without 10^4 U/ml of M-CSF. After 2 days, activity of MMP-9 in the culture supernatants was measured by gelatin zymography. Sample of each lane was adjusted the volume to same quantity of cellular DNA.

cellular differentiation from monocyte to macrophage in vitro (Figs. 2 and 4). M-CSF-treated macrophages obtained from five donors produced higher amounts of these proteases than control cells (Fig. 4), although the effect of M-CSF on MMP-1 production was not significant ($P > 0.05$). The production of active form MMP-9 (83 kDa) was elevated by M-CSF in parallel with that of inactive form (92 kDa). The active form of MMP-1, which was identified as collagenolytic activity without activation by trypsin, was not detected in the culture supernatants whichever M-CSF was added or not (data not shown).

3.4. *Effect of M-CSF on protease production of foam cells*

Foam cells were prepared by culturing macrophages in serum-free medium containing 100 μg/ml of acetyl LDL for 2 days. These cells looked granulous, and clearly stained with oil red O, indicating that these cells were foam cells. The pattern and intensity of oil red O staining were not different between M-CSF-treated and control foam cells (data not shown). Proteases in the culture supernatants were assayed (Fig. 4). The productivity of these proteases was not different between macrophages and foam cells (Fig. 4), and M-CSF enhanced protease production from foam cells as well as from macrophages.

3.5. *Dose effect of M-CSF on survival and protease production of macrophages*

Monocytes were cultured for 10 days with M-CSF at concentrations of 0, 10^2, 10^3, 10^4 and 10^5 U/ml, and further cultured in serum-free media for 2 days. M-CSF at more than 10^3 U/ml supported cellular

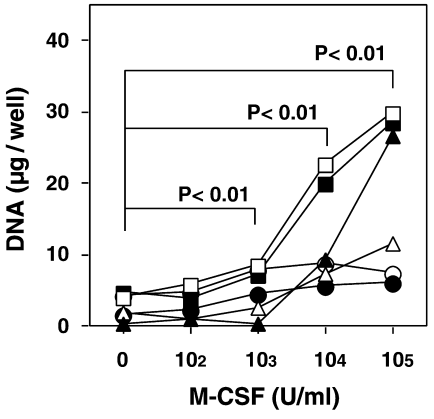

Fig. 3. M-CSF supports survival and proliferation of monocytes. Monocytes of six donors were cultured in the presence of M-CSF at concentrations of 0, 10^2, 10^3, 10^4, 10^5 U/ml. After 10 days, DNA contents were measured. $P < 0.01$; compared with M-CSF-untreated control.

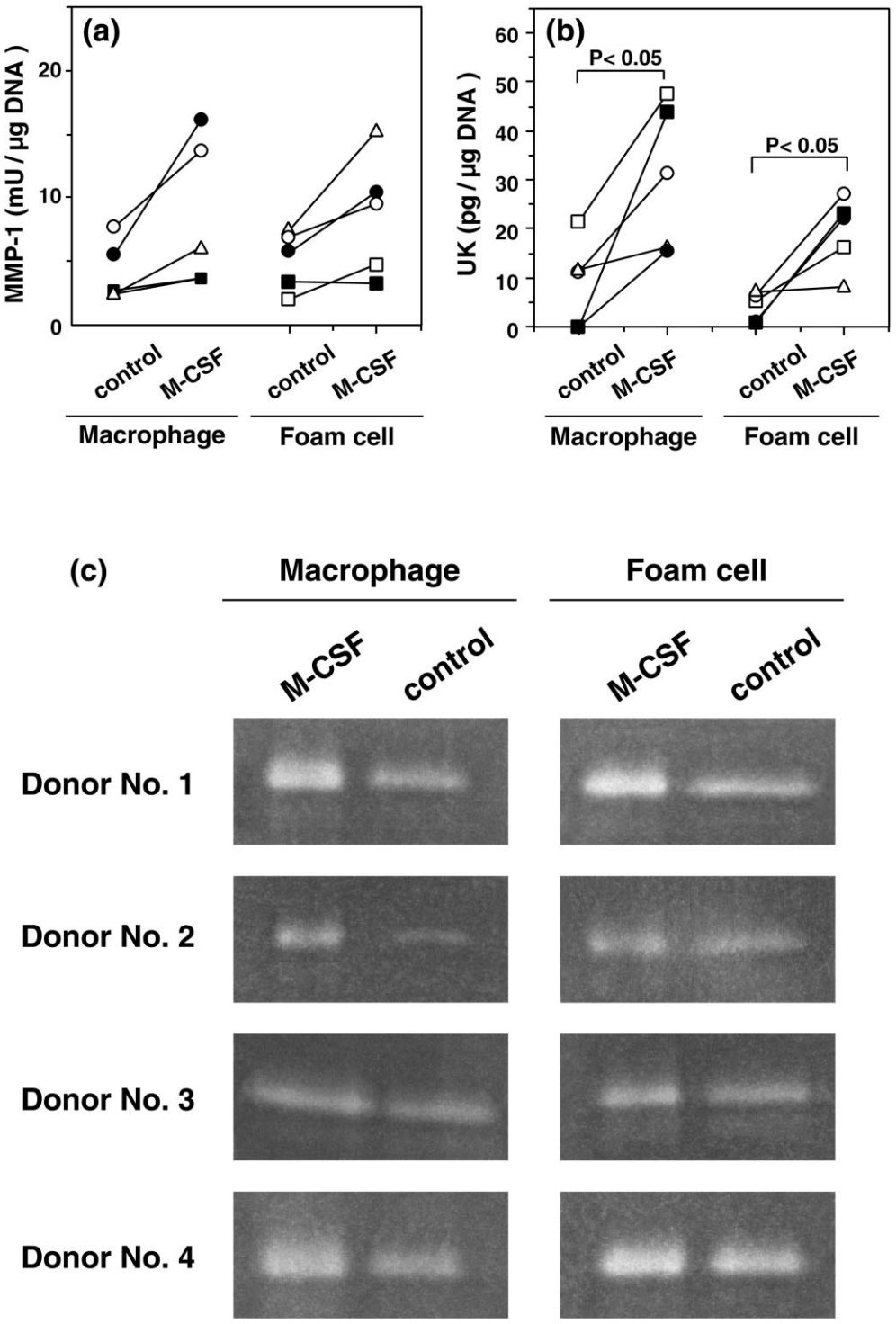

Fig. 4. Effect of M-CSF on protease production of macrophage and foam cell. Macrophages were obtained by culture of monocytes for 10 days with or without 10^4 U/ml of M-CSF, and cultured for another 2 days in serum free medium with or without 100 μg/ml of acetyl-LDL. MMP-1 (a), UK (b) and MMP-9 (c) in the supernatants were assayed. $P < 0.05$; compared with M-CSF-untreated control.

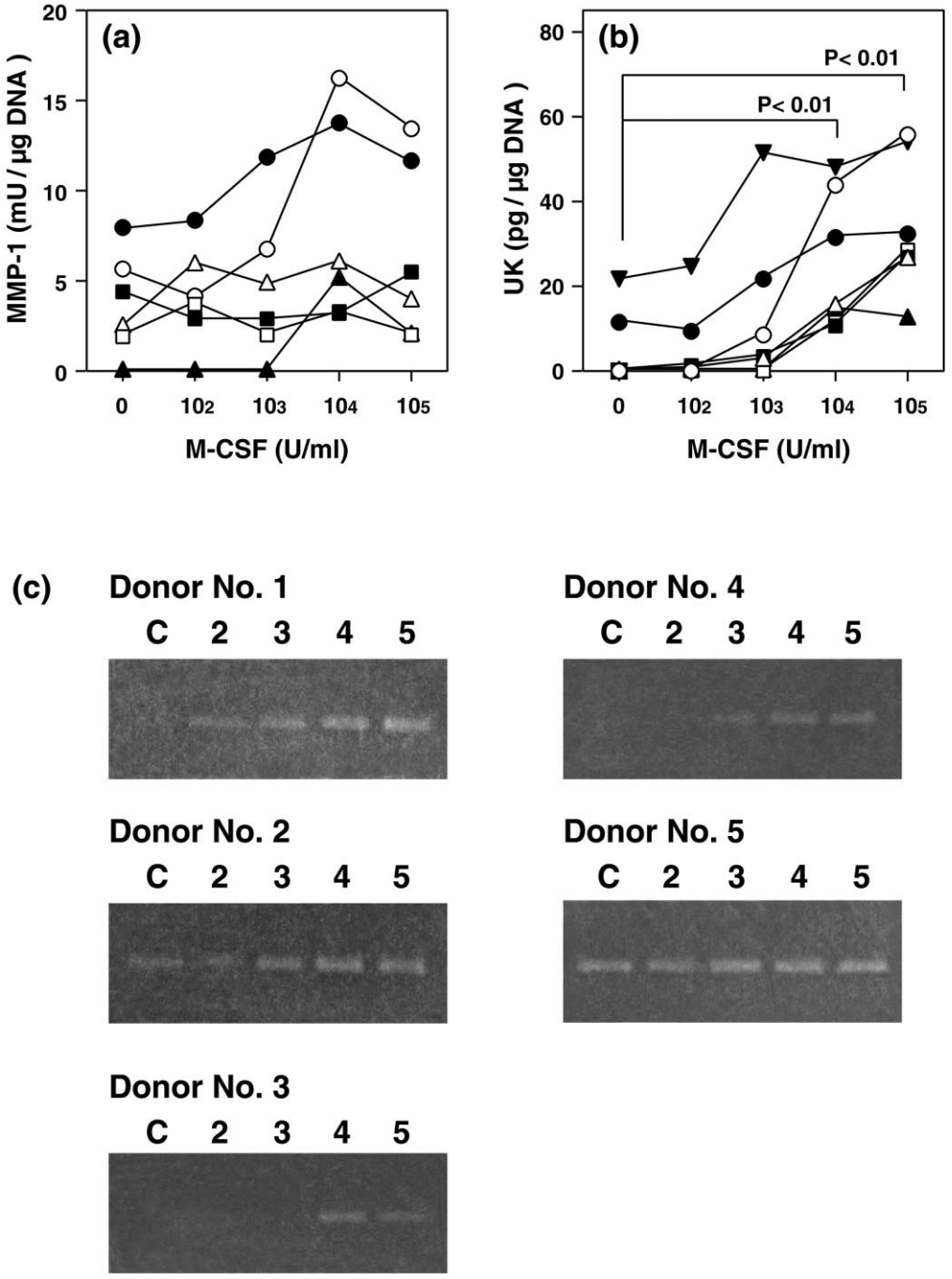

Fig. 5. Dose–response of M-CSF on protease production of macrophage. Macrophages were obtained by culture of monocytes for 10 days with 0–10^5 U/ml of M-CSF, and cultured for another 2 days. MMP-1 (a) and UK (b) in the supernatants were assayed. MMP-9 (c) produced from cells of equal DNA amounts were analyzed by gelatin zymography. Culture supernatants of macrophage treated with M-CSF at the concentrations of 0 (lane c), 10^2 (lane 2), 10^3 (lane 3), 10^4 (lane 4), 10^5 (lane 5) U/ml of M-CSF were examined. $P < 0.01$; compared with M-CSF-untreated control.

survival significantly (Fig. 3). M-CSF at more than 10^3 U/ml also enhanced MMP-9 and urokinase production from macrophages (Fig. 5b,c). MMP-1 production of macrophages prepared from several donors was elevated by M-CSF, although effect of M-CSF on MMP-1 production was not significant (Fig. 5a). These results indicated that M-CSF supports monocyte/macrophage survival, and enhances protease production in a dose-dependent manner, which might degrade collagens and other ECMs accumulated in atherosclerotic lesion.

4. Discussion

M-CSF is known as a glycoprotein which stimulates the proliferation and the differentiation of monocytes/macrophages [5,6]. Recent studies suggested that M-CSF might play an important role in atherosclerosis [7–16]. Macrophage is one of the major cell types in atherosclerotic lesion [7,8,28]. Administration of M-CSF led to the reduction in plasma cholesterol [8–13] and the prevention of atherosclerosis progression in WHHL rabbits [16]. These effects of M-CSF have been explained due to the regulation of cholesterol metabolism by increasing the number of LDL receptor and scavenger receptor [10,13] and by up-regulation of neutral and acidic CEH [14]. In our previous study, we demonstrated that M-CSF promotes the regression of atherosclerosis which has been made in rabbits by high cholesterol diet (2%) for 8 weeks [17]. Intramuscular administration of M-CSF at 80 μg/kg/day for 12 weeks halved the mean intimal thickness of aortic arch, when compared with that of HSA-injected (0.34 vs. 0.60 mm, respectively). Immunohistochemical analysis revealed that one of the most remarkable effect of M-CSF on the atherosclerotic lesion is the reduction of the area positively stained for collagen type I–V (Fig. 1). Since cells of monocyte/macrophage-lineage produce proteases that degrade collagens [29–39], we investigated effects of M-CSF on protease production from monocyte, macrophage and foam cell. Rouis et al. reported that acetyl LDL induces proteases from macrophages [40], and that M-CSF enhances scavenger receptor expression and uptake of modified LDL [10,13]. Thus, we at first speculated that M-CSF may enhance the protease production induced by acetyl LDL. However, our data suggests that M-CSF enhances protease production by itself, and that MMP-1, MMP-9 and urokinase production from macrophage is not affected by acetyl LDL. A elastinolytic metalloprotease induced by acetyl LDL, which is reported by Rouis et al. [39], is not MMP-9, but might be other protease like MMP-3, which shows less elastinolytic activity than MMP-9 [24,25]. Our results that foam cells produced similar amounts of urokinase as macrophages did might conflict with those of others who reported that acetyl LDL induces urokinase production from murine macrophages [41,42]. The discrepancy is not understood, but M-CSF is also a potent inducer of urokinase from macrophages [43–45] as we observed in this paper, and M-CSF is produced during cultivation in vitro [46–48]. Thus, it may be possible that urokinase was induced by endogenous M-CSF, which overcame the urokinase induction by acetyl LDL. It is also thought that the discrepancy may be due to the difference between murine and human macrophage.

In this paper, we studied the effect of M-CSF on atherosclerosis in terms of protease production of monocyte, macrophage and foam cell. Macrophage has been found to produce various MMPs, such as interstitial collagenase (MMP-1), 92-kDa gelatinize (MMP-9) and stromelysin (MMP-3). These MMPs are produced as inactive precursors that are activated by plasmin and or by MMPs. [18,19]. MMP-3 can activate MMP-1 and MMP-9, and plasmin is also able to activate these pro-enzymes in atherosclerotic lesion. Because plasminogen exists in the lesion [49], urokinase produced by macrophage is thought to be able to activate MMP precursors indirectly.

From our results, a possible mechanism of M-CSF anti-atherosclerotic effect is thought as follows. Production of MMP-9 is increased during differentiation from monocytes to macrophages, and enhanced by M-CSF. As MMP-9 is known as protease which is active in tissue invasion [50,51], MMP-9 might play an important role in atherosclerosis trans-endothelial migration of monocyte to atherosclerotic lesions. In intimal lesion, macrophage and foam cell produce MMP-1, MMP-9 as well as urokinase that can activates MMP precursors. M-CSF enhances this protease production, and might activate degradation of collagens accumulated there. Moreover, M-CSF sup-

ports macrophage survival [52,53] and may rescue foam cell from apoptotic cell death. In conclusion, it might be possible that the effects of M-CSF on atherosclerosis are due not only to enhancement of cholesterol metabolism, but also to enhancement of protease production.

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