Biochemical and Biophysical Research Communications 409 (2011) 58–63

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Analysis of apolipoprotein A-I as a substrate for matrix metalloproteinase-14

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ARTICLE INFO

Article history:
Received 16 April 2011
Available online 28 April 2011

Keywords:
Apolipoprotein A-I
Cleavage site
Lipid metabolism
Matrix metalloproteinase
Substrate

ABSTRACT

Substrates for matrix metalloproteinase (MMP)-14 were previously identified in human plasma using proteomic techniques. One putative MMP-14 substrate was apolipoprotein A-I (apoA-I), a major component of high-density lipoprotein (HDL). *In vitro* cleavage assays showed that lipid-free apoA-I is a more accessible substrate for MMP-14 compared to lipid-bound apoA-I, and that MMP-14 is more prone to digest apoA-I than MMP-3. The 28-kDa apoA-I was cleaved into smaller fragments of 27, 26, 25, 22, and 14-kDa by MMP-14. ApoA-I sites cleaved by MMP-14 were determined by isotope labeling of C-termini derived from the cleavage and analysis of the labeled peptides by mass spectrometry, along with N-terminal sequencing of the fragments. Cleavage of apoA-I by MMP-14 resulted in a loss of ability to form HDL. Our results suggest that cleavage of lipid-free apoA-I by MMP-14 may contribute to reduced HDL formation, and this may be occurring during the development of various vascular diseases as lipid metabolism is disrupted.

1. Introduction

Matrix metalloproteinases (MMPs) are a family of structurally and functionally related zinc-containing endopeptidases [1]. MMP proteolytic activity is inhibited by specific tissue inhibitors of metalloproteinases (TIMPs) and non-specific inhibitors that include α_2-macroglobulin and α_1-antiprotease [2]. Disruption of the finely tuned balance of MMPs and their inhibitors has been observed in a number of pathological conditions such as cardiovascular disease and metastasis [3].

Increasing numbers of MMP substrates continue to be identified that range from extracellular matrix components (ECM) to non-ECM components such as cellular receptors, growth factors, and other soluble proteins [4–8]. In an attempt to identify novel MMP substrates, we developed a method for screening potential MMP substrates using proteomic approach [4]. As a result, apolipoprotein A-I (apoA-I) was identified as one of substrates of MMP-14 in human plasma.

Mature human apoA-I is a 28-kDa polypeptide that is 243 amino acids long, and is synthesized in the liver and small intestine [9]. ApoA-I is well known as a major component of high-density lipoprotein (HDL) that promotes efflux of cholesterol from cells [10]. ApoA-I is a cofactor for lecithin:cholesterol acyltransferase (LCAT), which is responsible for the formation of most cholesteryl esters in plasma. Here, we examined if apoA-I can be directly cleaved by MMPs and sought to determine the MMP-14 cleavage sites in the apoA-I sequence. Moreover, we examined effect of MMP-14 cleavage on incorporation of apoA-I into liposomes.

2. Materials and methods

2.1. Preparation of human apoA-I and HDL3

Human apoA-I [11,12] and HDL3 [13] were prepared from plasma as described previously.

2.2. Preparation of MMP catalytic domains and proMMPs, and activation of proMMPs

The catalytic and hinge domains of human MMP-14 (cMMP-14; Y^{112}-I^{318}), the catalytic domain of human MMP-3 (cMMP-3; F^{100}-P^{273}), the pro, catalytic, and hinge domains of human MMP-1 (pchMMP-1; F^{20}-A^{277}), and human MMP-7 (A^{93}-K^{267}) were expressed as inclusion bodies in *Escherichia coli*, and purified by previously reported refolding methods [14]. Recombinant proMMP-2 and proMMP-9 were expressed and purified as described [15]. Pro-MMPs were activated in reaction buffer (20 mM Tris–HCl, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2$, 0.5 mM $ZnCl_2$, 0.001% Brij-35) in the presence of 1 mM 4-aminolphenyl mercuric acetate (APMA) prior to use. The optimal activated condition for each proMMP was for 40 min at 200 nM pchMMP-1, for 20 min at 200 nM proMMP-2, and for 2 h at 200 nM proMMP-9, at 37 °C.

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doi:10.1016/j.bbrc.2011.04.105

2.3. Detection of apoA-I in plasma proteins incubated with MMP-14

Human plasma proteins (6 μg) were incubated with 240 ng of cMMP-14 in 15 μl of MMP reaction buffer at 37 °C for 0–180 min. Reaction products were subjected to Western blot analysis using an anti-apoA-I polyclonal antibody (Rockland Immunochemicals, Inc., Gilbertsville, PA, USA).

2.4. Cleavage of apoA-I by MMPs

ApoA-I was digested with catalytically active MMPs in specified reaction conditions. Reactions were stopped by the addition of sodium dodecyl sulfate (SDS) sample buffer. Each sample was subjected to 15% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS–PAGE) and stained with Coomassie Brilliant Blue (CBB) R-250.

2.5. N-terminal sequencing of the MMP-14-cleaved fragments of apoA-I

ApoA-I digested by cMMP-14 was electroblotted to PVDF membrane and each fragment on the blot was analyzed by Edman degradation at the Tufts Core Facility (Tufts University, Medford, MA, USA) as described previously [16].

2.6. C-terminal end-O^{18} labeling of cMMP-14-cleaved apoA-I fragments

ApoA-I (1 μg) was cleaved by cMMP-14 in 16 μl of MMP reaction buffer containing H_2O^{16}/H_2O^{18} (1:1) in 1:20 enzyme/substrate molar ratio for 4 h at 37 °C. The reaction was stopped by the addition of ethylenediaminetetraacetic acid (EDTA) to a final concentration of 10 mM. The C-terminal O^{18}-labeled fragments of apoA-I were directly analyzed by matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS) as described previously [8] or were separated by SDS–PAGE followed by in-gel digestion and MALDI-TOF MS.

2.7. In-gel digestion, MALDI-TOF MS, and peptide fingerprinting

Gel slices containing MMP-14-digested apoA-I fragments were subjected to in-gel digestion with trypsin, Asp-N, or Glu-C (Roche Molecular Biochemicals, Indianapolis, IN, USA) and analyzed by MALDI-TOF MS as described previously [4]. Mass spectra were analyzed using ProFound searches (http://www.prowl.rockefeller.edu) for peptide fingerprinting.

2.8. Reconstitution of HDL using apoA-I digested by MMP-14

Purified apoA-I (100 μg) was digested with cMMP-14 at a 1:20 enzyme/substrate molar ratio for the indicated time intervals at 37 °C in 1.6 ml of MMP reaction. Samples taken at the specified time points were treated with EDTA to a final concentration of 10 mM to halt the digest reaction, then dialyzed against 10 mM ammonium bicarbonate buffer (pH 8.0) containing 0.5 mM EDTA, lyophilized, and resuspended with 100 μl resuspending buffer (10 mM Tris–HCl, pH 8.0, 140 mM NaCl, 1 mM EDTA). Reconstituted HDL (rHDL) containing apoA-I samples were prepared by dialysis in the initial molar ratios of palmitoyloleoyl phosphatidylcholine/cholesterol/apoA-I/sodium cholate of 95:5:1:150, as described [17]. Formation of rHDL was analyzed by 8–25% native

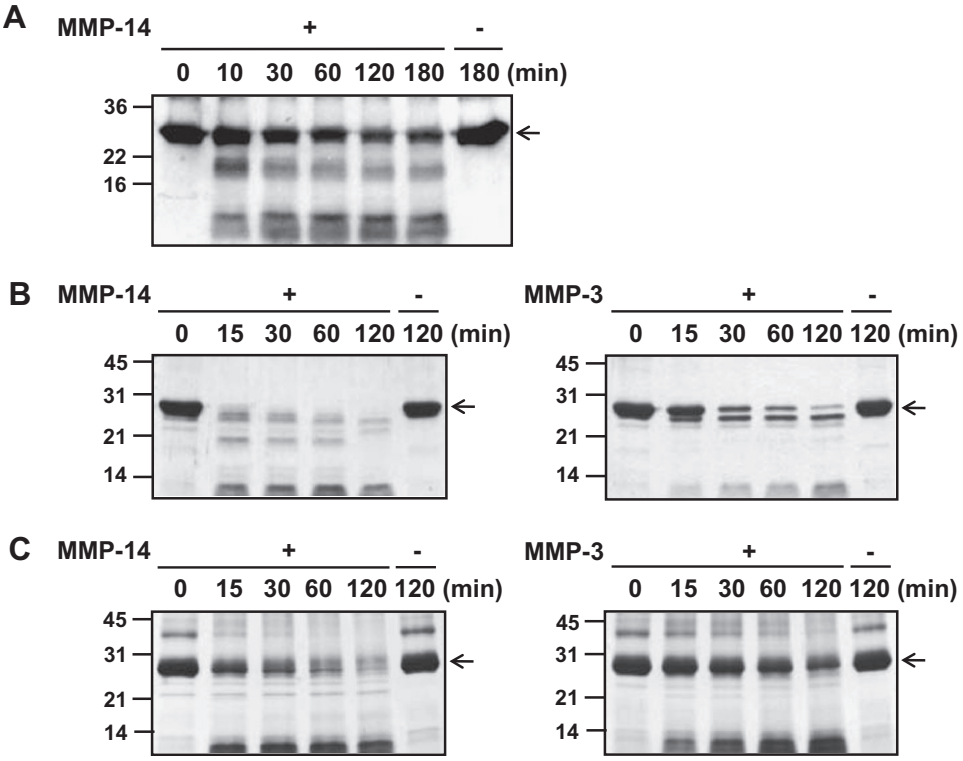

Fig. 1. Digestion of purified apoA-I, apoA-I within plasma proteins, or apoA-I as part of HDL3 by MMP-14 or MMP-3. (A) Detection of apoA-I cleavage in plasma proteins incubated with MMP-14. Plasma proteins (6 μg) were incubated with 240 ng of cMMP-14 for 180 min at 37 °C. The samples were subjected to Western blot analysis using an anti-apoA-I polyclonal antibody. (B) Cleavage of purified apoA-I by MMP-14 and MMP-3. The purified apoA-I (3 μg) was incubated with cMMP-14 (left) or cMMP-3 (right) in a 1:50 enzyme/substrate molar ratio for the indicated time intervals at 37 °C in 2 μl of MMP reaction buffer. The samples were subjected to 15% SDS–PAGE, and then stained with CBB R-250. (C) Cleavage of apoA-I within HDL3 by MMP-14 and MMP-3. HDL3 was incubated with cMMP-14 (left) or cMMP-3 (right), at the condition used in the above (B) section. Numbers on the left side of the SDS-gel denote molecular weights of protein markers (Bio-Rad Laboratories, Hercules, CA, USA) shown as kDa.

polyacrylamide gradient gel electrophoresis (GE Healthcare Bio-Science, Piscataway, NJ, USA) as described previously [18].

3. Results

3.1. Cleavage of apoA-I by MMP-14 in the plasma proteins

To ensure cleavage of apoA-I by MMP-14, plasma proteins incubated with cMMP-14 for various time intervals were examined by Western blot analysis using an anti-apoA-I polyclonal antibody. While apoA-I in plasma was not degraded by incubation for 180 min in the absence of cMMP-14, the digested fragments gradually appeared in the presence of cMMP-14 over time (Fig. 1A).

3.2. Digestion of apoA-I in lipid-free state or within HDL3 by MMP-3 or MMP-14

Given that apoA-I in plasma can be cleaved by MMP-14 (Fig. 1A), we proceeded to analyze whether a specific form of apoA-I, either lipid-free or the form imbedded within HDL3, is cleaved by MMP-14, under previously described conditions [19]. The efficiency of apoA-I cleavage by cMMP-14 or cMMP-3 was also compared. Lipid-free apoA-I (Fig. 1B) was cleaved more efficiently by both MMPs than apoA-I within HDL3 (Fig. 1C). The intact 28-kDa band of apoA-I disappeared much more rapidly when digested with cMMP-14 in comparison with cMMP-3 (Fig. 1B and C), indicating that apoA-I is much more susceptible to cleavage by MMP-14 than MMP-3.

3.3. Cleavage of purified apoA-I by various MMPs

To determine if MMPs other than MMP-14 and MMP-3 can also cleave apoA-I, purified apoA-I was incubated with various MMPs. ApoA-I cleavage efficiency appeared to differ between MMPs, with MMP-14 being the most efficient cutter followed by MMP-7, MMP-3, and MMP-2 in order (Fig. 2A). To resolve the process of degrading apoA-I by MMP-14, purified apoA-I was incubated with cMMP-14 in a 1:20 enzyme/substrate molar ratio and cleavage was examined in a time-dependent manner. The intact 28-kDa form of apoA-I was digested into fragments with molecular masses of 27, 26, 25, 22, and 14-kDa (labeled a–e, respectively) at early time points, and the intact form gradually disappeared by 180 min of MMP-14 digestion (Fig. 2B).

3.4. Determination of the cleavage sites of apoA-I by MMP-14

To determine the MMP-14-mediated cleavage sites on apoA-I, N-terminal sequencing of fragments "a–e" was performed. N-termini of fragments "a–e" started at the N-terminal Asp (D^1) of the intact apoA-I (Fig. 3B). Each fragment was then subjected to in-gel digestion with trypsin or GluC, MALDI-TOF MS, and peptide fingerprinting (Supplementary Table 1 and 2). Although C-terminal peptides of the fragments were not identified by this approach, it was found that the fragments "a–e" include residues D^1-K^{226}, D^1-R^{215}, D^1-E^{198}, D^1-R^{171}, and D^1-R^{116}, respectively (Fig. 3B).

To determine C-termini of apoA-I fragments, apoA-I was digested by cMMP-14 in the presence of 50% H_2O^{18}, and the digested apoA-I was examined by SDS–PAGE. Each fragment labeled with O^{18} at the C-terminus was further digested in-gel with trypsin, AspN, or GluC, in normal water, and the extracted peptides were analyzed by MALDI-TOF MS in reflector mode. Doublet spectra as a consequence of having both O^{16} and O^{18} at their C-termini (discrepancy of 2.01 Da) were detected from the AspN-digested peptides of fragment "a" and from GluC-based cleavage products of fragment "e". Specific fragments included *m/z* 1948.07 and 1950.08 from 14-a-AspN fragment "a", and *m/z* 1032.50 and 1034.51 from 14-e-GluC fragment "e". These masses were assigned to D^{213}-F^{229} and L^{114}-P^{121} of apoA-I, respectively (Supplementary Fig. 1A–C). From the C-terminal identification of these fragments, two cleavage sites, $P^{121}\downarrow L^{122}$ and $F^{229}\downarrow L^{230}$ were pinpointed (Fig. 3C and Supplementary Fig. 1D).

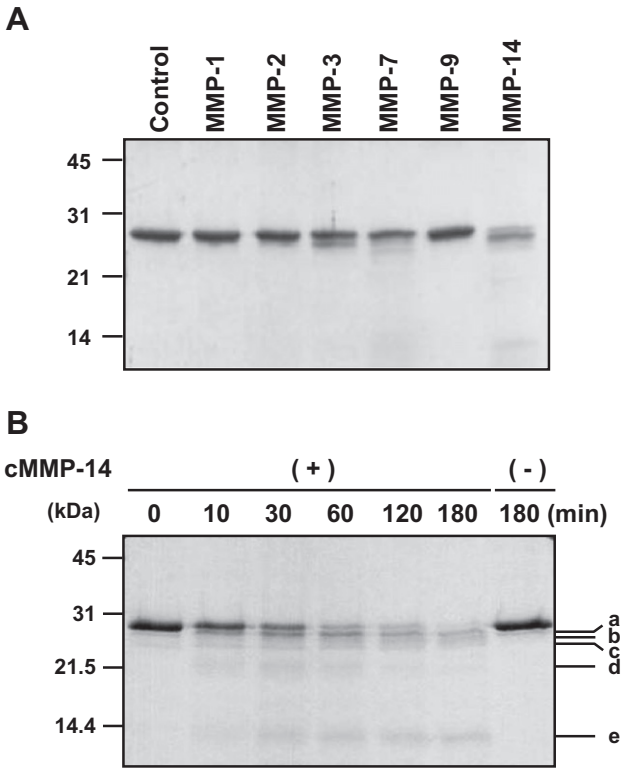

Fig. 2. Cleavage of purified apoA-I by various MMPs. (A) ApoA-I (1 μg) was digested by various MMPs (MMP-1, 2, 3, 7, 9, and 14) in a 1:20 enzyme/substrate molar ratio at 37 °C for 60 min in 16 μl of MMP reaction buffer. (B) ApoA-I (1 μg) was digested by cMMP-14 in a 1:20 enzyme/substrate molar ratio at 37 °C, as a function of incubation time in 16 μl of MMP reaction buffer. Samples were subjected to 15% SDS–PAGE, and then stained with CBB R-250.

Compared to fragments "a" and "e," fragments "b–d" were less abundant during degradation process of apoA-I by MMP-14. These fragments could be transient intermediate forms that are further cleaved into smaller fragments. To identify the C-termini of smaller fragments of apoA-I, C-termini of MMP-14-cleaved apoA-I fragments were labeled in the presence of 50% H_2O^{18}. Then, O^{18}-labeled fragments less than 5000 Da were examined by MALDI-TOF MS in reflector mode. By this method, three doublet spectra were detected; *m/z* 1137.68 and 1139.69 (14-1 fragment), *m/z* 1833.03 and 1835.04 (14-2 fragment), and *m/z* 2579.33 and 2581.34 (14-3 fragment). These masses were assigned to L^{214}-E^{223}, L^{214}-F^{229}, and L^{159}-A^{180} of apoA-I, respectively (Supplementary Fig. 2A and B). From the N- and C-termini of these fragments, five cleavage sites, $A^{158}\downarrow L^{159}$, $A^{180}\downarrow L^{181}$, $D^{213}\downarrow L^{214}$, $E^{223}\downarrow S^{224}$, and $F^{229}\downarrow L^{230}$ were identified (Fig. 3D and Supplementary Fig. 2C). Based on cleavage sites, apparent molecular weights, N-terminal sequencing data, and potential sequence ranges, it appears that fragments "b", "c", and "d" span D^1-E^{223}, D^1-D^{213}, D^1-A^{180}, respectively (Fig. 3).

3.5. Analysis of rHDL formed with apoA-I cleaved by MMP-14

It has been known that apoA-I interacts with lipids from hepatocytes and peripheral cells by activation of ATP-binding cassette transporter A1 (ABCA1) to generate lipid-poor pre-β- or discoidal

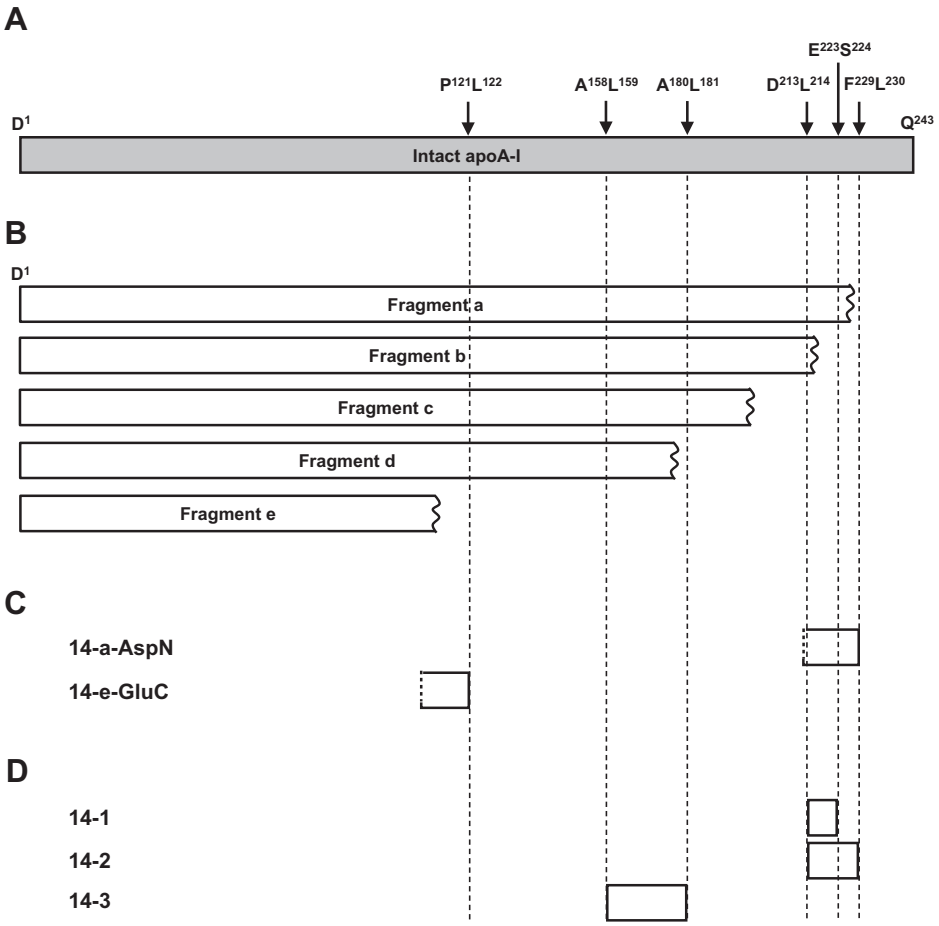

Fig. 3. Determination of MMP-14 cleavage sites on apoA-I. (A) Schematic diagram of apoA-I and MMP-14 cleavage sites. MMP-14 cleavage sites on apoA-I are represented as arrows. (B) The N-terminal sequence and approximate C-terminal region of apoA-I fragments. N-termini of fragments "a–e" were all determined to start at the N-terminal Asp (D^1) of apoA-I. Each fragment separated by SDS–PAGE was subjected to in-gel trypsin or Glu-C digestion, MALDI-TOF MS, and peptide fingerprinting. From these coverage results along with N-terminal sequencing data, it was shown that fragments "a–e" at least span D^1-K^{226}, D^1-R^{215}, D^1-E^{198}, D^1-R^{171}, and D^1-R^{116}, respectively. (C) Determination of the C-termini of major apoA-I fragments. ApoA-I was digested by cMMP-14 in the presence of 50% H_2O^{18}. Each fragment was labeled with O^{18} at the C-terminus and subjected to in-gel digestion, MALDI-TOF MS, and peptide fingerprinting. Doublet spectra as a consequence of the same fragment differing by O^{16} or O^{18} at the C-terminus, which were detected from the AspN-digested peptides of fragment "a" and the GluC-digested peptides of fragment "e", are shown. (D) Detection of MMP-14 cleavage sites from small apoA-I fragments. C-termini of apoA-I fragments generated by MMP-14 cleavage were labeled with O^{18} as described above. Three small fragments showing doublet spectra detected by MALDI-TOF MS are shown.

HDL [20,21]. Then, esterification of cholesterol by LCAT in blood allows pre-β-HDL to enlarge into spherical HDL structures [22,23]. *In vitro,* rHDL can be formed with apoA-I and lipids. To examine if initial products of apoA-I cleavage by MMP-14 are able to be incorporated into HDL, apoA-I was incubated with MMP-14 for various time intervals and this mixture was reconstituted with phospholipid and cholesterol into rHDL proteoliposomes. While intact apoA-I efficiently formed rHDL by association with lipids, MMP-14-digested apoA-I rapidly lost the ability to form rHDL (Fig. 4). rHDL was poorly formed by 5 min even though most of the intact apoA-I remained. It is possible that cleaved products of apoA-I may inhibit the formation of rHDL, or that digest reagents may interfere with rHDL formation.

4. Discussion

We show that MMP-14 is the most efficient enzyme for cleavage of apoA-I among the tested MMPs, including MMP-3. As predicted from the embedded structure of apoA-I in HDL particles [22,23], we found that lipid-free apoA-I was more susceptible to cleavage by MMP-14 or MMP-3 than apoA-I within HDL3. In a similar context, it was shown that apoA-I in pre-β-HDL is more susceptible to MMP-3 cleavage than apoA-I in HDL3 [19]. ApoA-I seems to be resistant to MMPs when protected by lipids, less in pre-β-HDL and more in HDL3.

To identify MMP-14 cleavage sites on apoA-I, we have determined the N-terminal sequence and the C-terminal sequence of the major fragments through Edman degradation and proteomics techniques, respectively. For C-terminal sequence determination, major fragments were labeled with O^{18} at their C-termini by cleavage of apoA-I with MMP-14 in the presence of isotopic water (H_2O^{16}:H_2O^{18} = 1:1). Then, each isotope-labeled fragment was subjected to in-gel digestion and mass analysis to detect the O^{18}-labeled C-terminal peptide, as previously described [8]. By this approach, the C-termini of fragments "a" and "e" were determined, but C-termini of other fragments were not, probably due to the limited quantity of these fragments. For identification of C-termini, apoA-I was digested with MMP-14 in the presence of isotopic water (H_2O^{16}:H_2O^{18} = 1:1) for extended times to generate smaller fragments labeled with O^{18} at their C-termini. Then, O^{18}-labeled small fragments were assigned to apoA-I by mass analysis and peptide fingerprinting. As a result, cleavage sites of apoA-I digested with MMP-14 were determined to be: $P^{121}\downarrow L^{122}$, $A^{158}\downarrow L^{159}$,

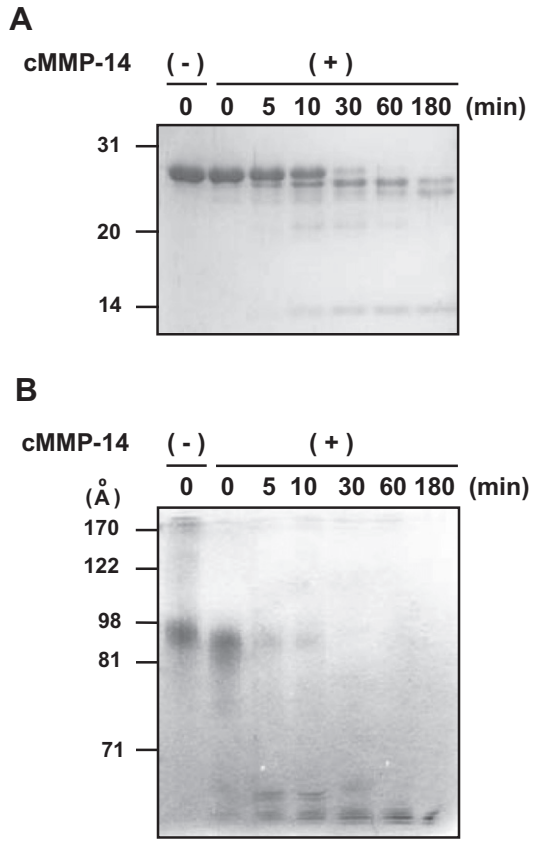

Fig. 4. Analysis of rHDL formation with purified apoA-I digested by MMP-14. (A) Purified apoA-I was digested by cMMP-14 in a 1:20 enzyme/substrate molar ratio for the indicated time intervals at 37 °C. And the reaction was stopped by the addition of EDTA to a final concentration of 10 mM. The digested apoA-I samples (1.2 μg) were concentrated, dialyzed, and then subjected to 15% SDS–PAGE. (B) ApoA-I-containing rHDL was prepared by sodium cholate dialysis. rHDL samples containing 350 ng apoA-I were subjected to 8–25% native polyacrylamide gradient gel electrophoresis (GE Healthcare Bio-Science, Piscataway, NJ, USA). Particle sizes of molecular markers (HMW Native, GE Healthcare BioScience) are shown as Å in the left side of the gel.

$A^{180}\downarrow L^{181}$, $D^{213}\downarrow L^{214}$, $E^{223}\downarrow S^{224}$, and $F^{229}\downarrow L^{230}$. Along with the sequence coverage data for each band, fragments "a–e" were assigned to positions D^1-F^{229}, D^1-E^{223}, D^1-D^{213}, D^1-A^{180}, and D^1-P^{121}, respectively (Fig. 3).

ApoA-I is a major component of HDL and plays an important role in the initiation of reverse cholesterol transport through cellular cholesterol efflux, lipid binding, the activation of LCAT, and the recognition of receptors and lipid transfer proteins [10,24]. ApoA-I has an N-terminal domain (residues D^1-A^{187}) and a C-terminal domain (residues R^{188}-Q^{243}) [23]. The N-terminal domain is composed of four amphipathic α-helices and it appears to be responsible for stabilizing the lipid-free conformation in addition to facilitating lipid association. The C-terminal domain, composed of two amphipathic α-helices, was predicted to show high lipid affinity, lipid-sensitive triggering, and self-association [23,25]. It appears that the hydrophobic portions of all helices are involved in lipid binding. Residues L^{44}-G^{65} include the N-terminal half of the first helix and residues A^{210}-N^{241} include the sixth helix. These regions are recognized to be important for the initial association with lipids. Residues Y^{100}-P^{121} include the N-terminal half of the third helix, and are required for strong association with lipids. Residues L^{122}-P^{143} include the C-terminal half of the third helix, and are essential for binding to lipids and formation of mature HDL. Residues L^{144}-G^{186} correspond to the fourth helix and were assigned to the LCAT activation domain. Residues R^{149}-Q^{243} span the fourth to sixth helices, which play a role in HDL receptor binding [10,25,26]. Among the cleavage sites on apoA-I that are recognized by MMP-14, three sites ($D^{213}\downarrow L^{214}$, $E^{223}\downarrow S^{224}$, and $F^{229}\downarrow L^{230}$) are present in the initial lipid association region. The $P^{121}\downarrow L^{122}$ site is present within the lipid-binding region, and the two other sites ($A^{158}\downarrow L^{159}$ and $A^{180}\downarrow L^{181}$) are located in the LCAT activation domain. In addition, most cleavage sites ($A^{158}\downarrow L^{159}$, $A^{180}\downarrow L^{181}$, $D^{213}\downarrow L^{214}$, $E^{223}\downarrow S^{224}$, and $F^{229}\downarrow L^{230}$) are present in the HDL receptor binding domain. A previous study that analyzed cleavage of apoA-I in HDL3 by MMP-3 showed that degradation products lacking the C-terminal 2∼6-kDa region reduce HDL-induced cholesterol efflux [19]. We found that MMP-14 gradually shortened apoA-I from the C-terminus. Therefore, we assumed that cleavage of apoA-I by MMP-14 could abrogate its functions to interact with lipids or receptors for lipid metabolism and reverse cholesterol transport.

ApoA-I is responsible for the structural integrity of HDL particles and regulates HDL formation, maturation, and assembly [27,28]. When we tested the formation of rHDL with lipid-free apoA-I with or without MMP-14 cleavage, we found that apoA-I rapidly lost its capacity to make rHDL upon MMP-14 cleavage. Thereby, we assume that digestion of lipid-free apoA-I by MMP-14 would greatly impact HDL formation and lipid metabolism involving HDL.

MMP-14 is known to be expressed at high levels on the cell surface of endothelial cells, vascular smooth muscle cells, and macrophages, present at the inflammation sites or atherosclerotic plaques [29–31]. It is likely that MMP-14 concentrations can be reached within local lesions high enough to degrade apoA-I. ApoA-I not only involves in reverse cholesterol transport as a major protein of HDLs but it also functions as an anti-inflammatory reagent [32] and an anti-oxidant reagent [33]. These roles of apoA-I are important for protection from various vascular diseases such as atherosclerosis. We thus think that increased understanding of apoA-I as a substrate of MMP-14 would provide useful information for the development of new therapeutics for vascular diseases.

Acknowledgments

This work was supported by Grants from the Korea Science and Engineering Foundation through the project for Studies on Ubiquitome Functions (2005-2001143 to S.-T.L.) and the Mid-Career Researcher Program (2010-0026103 to S.-T.L.), and from the 2011 Yonsei University Research Fund. Jun Hyoung Park was a pre-doctoral trainee of the Brain Korea 21 program (Ministry of Education, Science, and Technology, Republic of Korea).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2011.04.105.

References

[1] K. Kessenbrock, V. Plaks, Z. Werb, Matrix metalloproteinases: regulators of the tumor microenvironment, Cell 141 (2010) 52–67.
[2] K. Brew, H. Nagase, The tissue inhibitors of metalloproteinases (TIMPs): an ancient family with structural and functional diversity, Biochim. Biophys. Acta 1803 (2010) 55–71.
[3] A.R. Nelson, B. Fingleton, M.L. Rothenberg, L.M. Matrisian, Matrix metalloproteinases: biologic activity and clinical implications, J. Clin. Oncol. 18 (2000) 1135–1149.
[4] I.K. Hwang, S.-M. Park, S.Y. Kim, S.-T. Lee, A proteomic approach to identify substrates of matrix metalloproteinase-14 in human plasma, Biochim. Biophys. Acta 1702 (2004) 79–87.
[5] J.Y. Sung, S.-M. Park, C.H. Lee, J.W. Um, H.J. Lee, J. Kim, Y.J. Oh, S.-T. Lee, S.R. Paik, K.C. Chung, Proteolytic cleavage of extracellular secreted α-synuclein via matrix metalloproteinases, J. Biol. Chem. 280 (2005) 25216–25224.
[6] S.Y. Kim, S.-M. Park, S.-T. Lee, Apolipoprotein C-II is a novel substrate for matrix metalloproteinases, Biochem. Biophys. Res. Commun. 339 (2006) 47–54.

[7] S.-M. Park, I.K. Hwang, S.Y. Kim, S.J. Lee, K.S. Park, S.-T. Lee, Characterization of plasma gelsolin as a substrate for matrix metalloproteinases, Proteomics 6 (2006) 1192–1199.
[8] J.H. Park, S.-M. Park, S.H. Park, K.-H. Cho, S.-T. Lee, Cleavage and functional loss of human apolipoprotein E by digestion of matrix metalloproteinase-14, Proteomics 8 (2008) 2926–2935.
[9] S.K. Karathanasis, V.I. Zannis, J.L. Breslow, Isolation and characterization of the human apolipoprotein A-I gene, Proc. Natl. Acad. Sci. USA 80 (1983) 6147–6151.
[10] P.G. Frank, Y.L. Marcel, Apolipoprotein A-I: structure–function relationships, J. Lipid. Res. 41 (2000) 853–872.
[11] H.B. Brewer, Jr., R. Ronan, M. Meng, C. Bishop, Isolation and characterization of apolipoproteins A-I, A-II, and A-IV, Methods Enzymol. 128 (1986) 223–246.
[12] K.H. Park, W. Jang, K.Y. Kim, J.R. Kim, K.-H. Cho, Fructated apolipoprotein A-I showed severe structural modification and loss of beneficial functions in lipid-free and lipid-bound state with acceleration of atherosclerosis and senescence, Biochem. Biophys. Res. Commun. 392 (2010) 295–300.
[13] K.H. Park, D.G. Shin, J.R. Kim, K.-H. Cho, Senescence-related truncation and multimerization of apolipoprotein A-I in high-density lipoprotein with an elevated level of advanced glycated end products and cholesteryl ester transfer activity, J. Gerontol. A Biol. Sci. Med. Sci. 65 (2010) 600–610.
[14] H.M. Koo, J.-H. Kim, I.K. Hwang, S.-J. Lee, T.-H. Kim, K.-H. Rhee, S.-T. Lee, Refolding of the catalytic and hinge domains of human MT1-MMP expressed in *Escherichia coli* and its characterization, Mol. Cells 13 (2002) 114–120.
[15] S.-J. Lee, H.J. Yoo, Y.S. Bae, H.-J. Kim, S.-T. Lee, TIMP-1 inhibits apoptosis in breast carcinoma cells via a pathway involving pertussis toxin-sensitive G protein and c-Src, Biochem. Biophys. Res. Commun. 312 (2003) 1196–1201.
[16] P. Matsudaira, Sequence from picomole quantities of proteins electroblotted onto polyvinylidene difluoride membranes, J. Biol. Chem. 262 (1987) 10035–10038.
[17] C.E. Matz, A. Jonas, Micellar complexes of human apolipoprotein A-I with phosphatidylcholines and cholesterol prepared from cholate-lipid dispersions, J. Biol. Chem. 257 (1982) 4535–4540.
[18] K.-H. Cho, D.M. Durbin, A. Jonas, Role of individual amino acids of apolipoprotein A-I in the activation of lecithin:cholesterol acyltransferase and in HDL rearrangements, J. Lipid. Res. 42 (2001) 379–389.
[19] L. Lindstedt, J. Saarinen, N. Kalkkinen, H. Welgus, P.T. Kovanen, Matrix metalloproteinases-3, -7, and -12, but not -9, reduce high density lipoprotein-induced cholesterol efflux from human macrophage foam cells by truncation of the carboxyl terminus of apolipoprotein A-I. Parallel losses of pre-beta particles and the high affinity component of efflux, J. Biol. Chem. 274 (1999) 22627–22634.
[20] A. Brooks-Wilson, M. Marcil, S.M. Clee, L.H. Zhang, K. Roomp, M. van Dam, L. Yu, C. Brewer, J.A. Collins, H.O. Molhuizen, O. Loubser, B.F. Ouelette, K. Fichter, K.J. Ashbourne-Excoffon, C.W. Sensen, S. Scherer, S. Mott, M. Denis, D. Martindale, J. Frohlich, K. Morgan, B. Koop, S. Pimstone, J.J. Kastelein, J. Genest, Jr., M.R. Hayden, Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency, Nat. Genet. 22 (1999) 336–345.
[21] J.Y. Lee, J.S. Parks, ATP-binding cassette transporter AI and its role in HDL formation, Curr. Opin. Lipidol. 16 (2005) 19–25.
[22] W.S. Davidson, T.B. Thompson, The structure of apolipoprotein A-I in high density lipoproteins, J. Biol. Chem. 282 (2007) 22249–22253.
[23] M.J. Thomas, S. Bhat, M.G. Sorci-Thomas, Three-dimensional models of HDL apoA-I: implications for its assembly and function, J. Lipid. Res. 49 (2008) 1875–1883.
[24] K.-H. Cho, Biomedicinal implications of high-density lipoprotein: its composition, structure, functions, and clinical applications, BMB Rep. 42 (2009) 393–400.
[25] A.A. Ajees, G.M. Anantharamaiah, V.K. Mishra, M.M. Hussain, H.M. Murthy, Crystal structure of human apolipoprotein A-I: insights into its protective effect against cardiovascular diseases, Proc. Natl. Acad. Sci. USA 103 (2006) 2126–2131.
[26] C.M. Allan, N.H. Fidge, J.R. Morrison, J. Kanellos, Monoclonal antibodies to human apolipoprotein AI: probing the putative receptor binding domain of apolipoprotein AI, Biochem. J. 290 (Pt 2) (1993) 449–455.
[27] J.P. Segrest, L. Li, G.M. Anantharamaiah, S.C. Harvey, K.N. Liadaki, V. Zannis, Structure and function of apolipoprotein A-I and high-density lipoprotein, Curr. Opin. Lipidol. 11 (2000) 105–115.
[28] Y.L. Marcel, R.S. Kiss, Structure–function relationships of apolipoprotein A-I: a flexible protein with dynamic lipid associations, Curr. Opin. Lipidol. 14 (2003) 151–157.
[29] T.B. Rajavashisth, J.K. Liao, Z.S. Galis, S. Tripathi, U. Laufs, J. Tripathi, N.N. Chai, X.P. Xu, S. Jovinge, P.K. Shah, P. Libby, Inflammatory cytokines and oxidized low density lipoproteins increase endothelial cell expression of membrane type 1-matrix metalloproteinase, J. Biol. Chem. 274 (1999) 11924–11929.
[30] T.B. Rajavashisth, X.P. Xu, S. Jovinge, S. Meisel, X.O. Xu, N.N. Chai, M.C. Fishbein, S. Kaul, B. Cercek, B. Sharifi, P.K. Shah, Membrane type 1 matrix metalloproteinase expression in human atherosclerotic plaques: evidence for activation by proinflammatory mediators, Circulation 99 (1999) 3103–3109.
[31] B.K. Ray, A. Shakya, J.R. Turk, S.S. Apte, A. Ray, Induction of the MMP-14 gene in macrophages of the atherosclerotic plaque: role of SAF-1 in the induction process, Circ. Res. 95 (2004) 1082–1090.
[32] D.M. Levine, T.S. Parker, T.M. Donnelly, A. Walsh, A.L. Rubin, In vivo protection against endotoxin by plasma high density lipoprotein, Proc. Natl. Acad. Sci. USA 90 (1993) 12040–12044.
[33] M.I. Mackness, C. Abbott, S. Arrol, P.N. Durrington, The role of high-density lipoprotein and lipid-soluble antioxidant vitamins in inhibiting low-density lipoprotein oxidation, Biochem. J. 294 (1993) 829–834.