Biochemical and Biophysical Research Communications 443 (2014) 847–851

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Laminin receptor mediates anti-inflammatory and anti-thrombogenic effects of pigment epithelium-derived factor in myeloma cells

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ARTICLE INFO

Article history:
Received 27 November 2013
Available online 14 December 2013

Keywords:
Laminin receptor
PEDF
Inflammation
Myeloma cells
Thrombogenesis

ABSTRACT

Pigment epithelium-derived factor (PEDF) has anti-inflammatory and anti-thrombogenic properties both in cell culture and animal models. Although adipose triglyceride lipase (ATGL) and laminin receptor (LR) are two putative receptors for PEDF, which receptor mainly mediates the beneficial effects of PEDF is largely unknown. In this study, we addressed the issue. siRNA raised against LR (siLR) and siATGL transfection dramatically decreased LR and ATGL levels in human cultured myeloma cells, respectively. Ten nM PEDF significantly reduced vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), intercellular cell adhesion molecule-1 (ICAM-1) and plasminogen activator inhibitor-1 (PAI-1) mRNA levels in siCon- or siATGL-transfected myeloma cells, whereas PEDF increased *rather than* decreased these gene expressions in siLR-transfected cells. Neutralizing antibody directed against LR (LR-Ab) or LR antagonist actually bound to LR and reduced mRNA levels of VEGF, MCP-1, ICAM-1 and PAI-1 in myeloma cells. Further, pre-treatment of LR-Ab or LR antagonist suppressed the binding of PEDF to LR and resultantly blocked the effects of PEDF in myeloma cells. In addition, high concentration of LR agonist mimicked the actions of PEDF on these gene expressions in myeloma cells. This study indicates that PEDF causes anti-angiogenic, anti-inflammatory and anti-thrombogenic reactions in myeloma cells through the interaction with LR. Target domain of LR agonist and antagonist might be involved in the PEDF-signaling to gene suppression in myeloma cells.

1. Introduction

Pigment epithelium-derived factor (PEDF), a glycoprotein that belongs to the superfamily of serine protease inhibitors, was first purified from the conditioned media of human retinal pigment epithelial cells as a factor which possesses potent neuronal differentiating activity [1]. PEDF is produced from a variety of tissues, including adipocytes, vascular and inflammatory cells [2], and has been shown to be an endogenous inhibitor of angiogenesis both in cell culture and animal models [3,4]. Moreover, we, along with others, have recently found that PEDF not only blocks advanced glycation end product– cytokine– or growth factor-induced endothelial cell damage, platelet aggregation, macrophage and T cell activation, but also inhibits hyperpermeability, inflammation, thrombus formation, and cardiovascular remodeling through its anti-oxidative and anti-inflammatory properties [5–15]. These observations suggest that PEDF could exert beneficial effects on vascular damage as well as tumor expansion and might be a novel therapeutic target for cardiovascular disease and cancers.

Adipose triglyceride lipase (ATGL) and laminin receptor (LR) are two putative receptors for PEDF [16,17]. The former receptor is required for the PEDF-induced lipolysis and triglycerides degradation in liver and adipocytes [18,19], whereas the latter mediates the anti-angiogenic activity of PEDF in endothelial cells [17]. However, which receptor is mainly involved in anti-inflammatory and anti-thrombogenic effects of PEDF is largely unknown. We have very recently found that PEDF could block vascular endothelial growth factor (VEGF)-induced proliferation and survival of human multiple myeloma cells through its anti-oxidative properties [20]. The findings suggest that cultured myeloma cells are one of the suitable cells for examining the PEDF actions *in vitro*. So, we examined here which putative PEDF receptors could mediate its anti-inflammatory and anti-thrombogenic properties in cultured myeloma cells.

2. Materials and methods

2.1. Materials

LR agonist, Lam.B1$_{925–933}$ and LR antagonist, murine epidermal growth factor fragment acetyl-(Cys(Acm)$_{33–42}$-amide (mEGF$_{33–42}$) were purchased from American Peptide Company, Sunnyvale, CA, USA and Bachem Americans, Inc. Torrance, CA, USA, respectively.

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http://dx.doi.org/10.1016/j.bbrc.2013.12.060

Neutralizing antibodies (Abs) directed against LR (LR-Ab) from Abcam, Tokyo, Japan. Normal mouse IgG from Santa Cruz Biotechnology Inc. Dallas, TX, USA.

2.2. Preparation of PEDF proteins

PEDF proteins were purified as described previously [21]. SDS–PAGE analysis of purified PEDF proteins revealed a single band with a molecular mass of about 50 kDa, which showed positive reactivity with monoclonal Abs raised against human PEDF (Transgenic, Kumamoto, Japan).

2.3. Binding affinity of Lam.B1$_{925–933}$, mEGF$_{33–42}$, LR-Ab, and PEDF to LR

The binding affinity of Lam.B1$_{925–933}$, mEGF$_{33–42}$, LR-Ab, and PEDF to LR was measured using sensitive 27-MHz Quarts crystal microbalance (QCM) (Affinix Q; Initium, Tokyo, Japan) according to the method of Okahata et al. [22]. In brief, recombinant LR (Abnova, Taipei, Taiwan) was immobilized on a QCM surface through self-assembled monolayer of 16-mercaptohexadecanoic acid as described previously [23]. mEGF$_{33–42}$ (100 nM), or LR-Ab (13 nM) were added to the reaction vessel in the absence or presence of PEDF (100 nM), and the time course of the frequency decrease on the QCM was monitored. The binding amount of PEDF to LR was calculated from Sauebrey's equation [24]. According to this equation, 1 Hz frequency change corresponds to 0.62 ng/cm^2 of binding amount on the surface.

2.4. Cells

Human multiple myeloma cells, RPMI8226 (Human Science, Osaka, Japan) were cultured in RPMI1640 medium with 2 mM GultaMAX (Life Technologies Corporation, Carlsbad, CA, USA), supplemented with 10% heat-inactivated fetal bovine serum (FBS) containing 100 U/ml penicillin, and 100 g/ml streptomycin (Mediatech Inc., AK, USA). Experiments were carried out in a medium containing 1% FBS.

2.5. Construction and transfection of small interfering RNAs (siRNAs)

Sense and antisense human LR and ATGL siRNAs (siLR and siATGL) used in the experiments were chemically synthesized (Sigma Aldrich Japan K.K. Tokyo, Japan); sense and antisense of siLR were 5′-AACCUUCACUAACCAGAUCCAtt-3′ and 5′-UGGAUCUGGUUAGUGAAGGUUtt-3, respectively, and those of siATGL 5′-GAAUGUCAUUAUAUCCCACUUtt-3′ and 5′-AAGUGGGAUAUAAUGACAUUCtt-3′. Control non-silencing siRNAs (siCon) were obtained from Life Technologies Japan Ltd. (Silencer Negative Control #1 siRNA). Then the siRNA duplexes were transfected to myeloma cells using Lipofectamine RNAiMAX (Ilife Technologies Japan Ltd. Tokyo, Japan) as described previously [25]. After 4 days of transfection, LR, ATGL and α-tubulin protein levels were analyzed with Western blots.

2.6. Western blotting analysis

Proteins were extracted from siCon-, siLR and siATGL-transfected myeloma cells with lysis buffer as described previously [26]. Then the samples were separated by SDS–PAGE and transferred to nitrocellulose membranes. Membranes were probed with Abs against LR (Santa Cruz), ATGL (Abcam) or α-tubulin (Sigma, St. Louis, MO, USA), and then immune complexes were visualized with an enhanced chemiluminescence detection system (Amersham Bioscience, Buckinghamshire, UK).

2.7. Real-time reverse transcription-PCR (RT-PCR)

siCon-, siLR, siATGL-transfected or non-transfected myeloma cells were treated with or without the indicated concentrations of PEDF in the presence or absence of 0–500 nM Lam.B1$_{925–933}$, 10 nM mEGF$_{33–42}$, or 10 mg/ml neutralizing LR-Ab for 4 h. Then total RNA was extracted with RNAqueous-4PCR kit (Ambion Inc., Austin, TX, USA) according to the manufacturer's instructions. Quantitative real-time RT-PCR was performed using Assay-on-Demand and TaqMan 5 fluorogenic nuclease chemistry (Applied Biosystems) according to the supplier's recommendation. IDs of primers for human VEGF, monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), plasminogen activator inhibitor-1 (PAI-1), and 18S gene were Hs00900055_m1, Hs00234140_m1, Hs00164932_m1, Hs01126604_m1, and Hs03003631_g1, respectively.

2.8. Statistical analysis

All values were presented as mean ± standard error. Student's *t*-test or one-way analysis of variance followed Tukey's test was performed for statistical comparisons; $p < 0.05$ was considered significant.

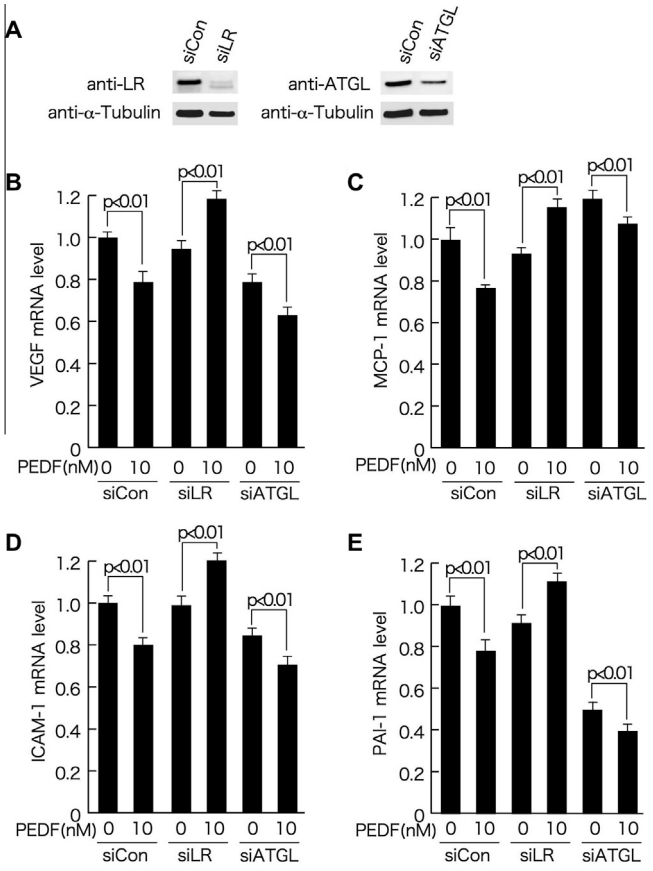

Fig. 1. Effects of siLR and siATGL on PEDF-exposed myeloma cells. siCon, siLR or siATGL were transfected to myeloma cells using Lipofectamine RNAiMAX. (A) After 4 days of transfection, LR, ATGL and α-tubulin protein levels were analyzed with Western blots. (B)–(E) siCon-, siLR, or siATGL-transfected myeloma cells were treated with or without 10 nM PEDF for 4 h. Then total RNAs were transcribed and amplified by real-time PCR. Data were normalized by the intensity of 18S mRNA-derived signals and then related to the value obtained with siCon treatment alone. $N = 3$ per group.

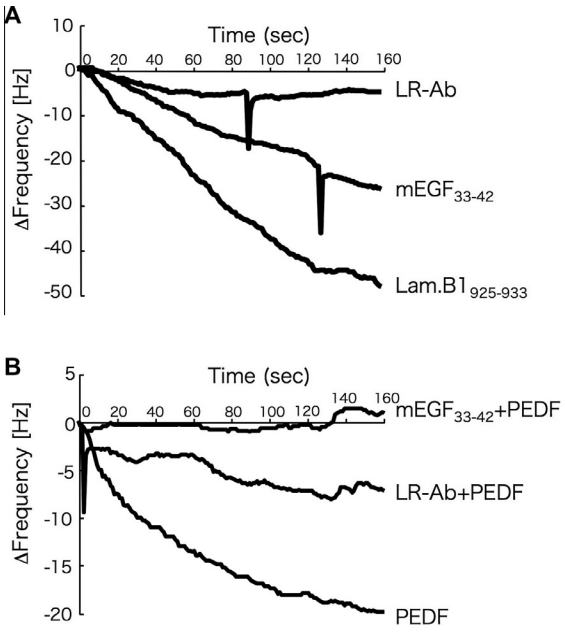

Fig. 2. Binding affinity of Lam.B1$_{925-933}$, mEGF$_{33-42}$, LR-Ab, and PEDF to LR. Representative frequency response profiles of the QCM. (A) *In vitro*-binding assay of Lam.B1$_{925-933}$, mEGF$_{33-42}$, or LR-Ab to LR in QCM. (B) In the presence or absence of Lam.B1$_{925-933}$, mEGF$_{33-42}$, or LR-Ab, binding affinity of PEDF to LR was assayed by monitoring the time course of the frequency decrease on the QCM. Three independent experiments were performed and obtained the same results.

3. Results

We examined whether siLR or siATGL transfection could affect the effects of PEDF on myeloma cells. As shown in Fig. 1A, siLR and siATGL transfection dramatically suppressed protein expression levels of LR and ATGL in myeloma cells, respectively. Ten nM PEDF significantly decreased VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in siCon- or siATGL-transfected myeloma cells (Fig. 1B–E). However, in siLR-transfected myeloma cells, anti-angiogenic, anti-inflammatory and anti-thrombogenic effects of PEDF were lost; 10 nM PEDF increased *rather than* decreased the mRNA levels of VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in myeloma cells (Fig. 1B–E). These findings suggest the involvement of LR in anti-angiogenic, anti-inflammatory and anti-thrombogenic signaling of PEDF in myeloma cells.

So, we next investigated the effects of LR agonist, LR antagonist and neutralizing LR-Ab on PEDF-exposed myeloma cells. For this, we first studied the binding affinity of LR agonist, LR antagonist and LR-Ab to LR and examined whether they could affect the binding affinity of PEDF to LR. When LR agonist, Lam.B1$_{925-933}$, LR antagonist, mEGF$_{33-42}$, LR-Ab, PEDF were added to the reaction vessel, the frequency on the QCM was decreased in a time-dependent manner to about −50, −25, −8, or −20 Hz, respectively (Fig. 2A and B), thus indicating that these agents actually bound to LR. Among them, LR agonist, Lam.B1$_{925-933}$ had the strongest binding affinity to LR, and amount of PEDF bound to LR was estimated to be 12.4 ng/cm^2. Moreover, as shown in Fig. 2B, pre-treatment with Lam.B1$_{925-933}$, mEGF$_{33-42}$, or LR-Ab significantly blocked the

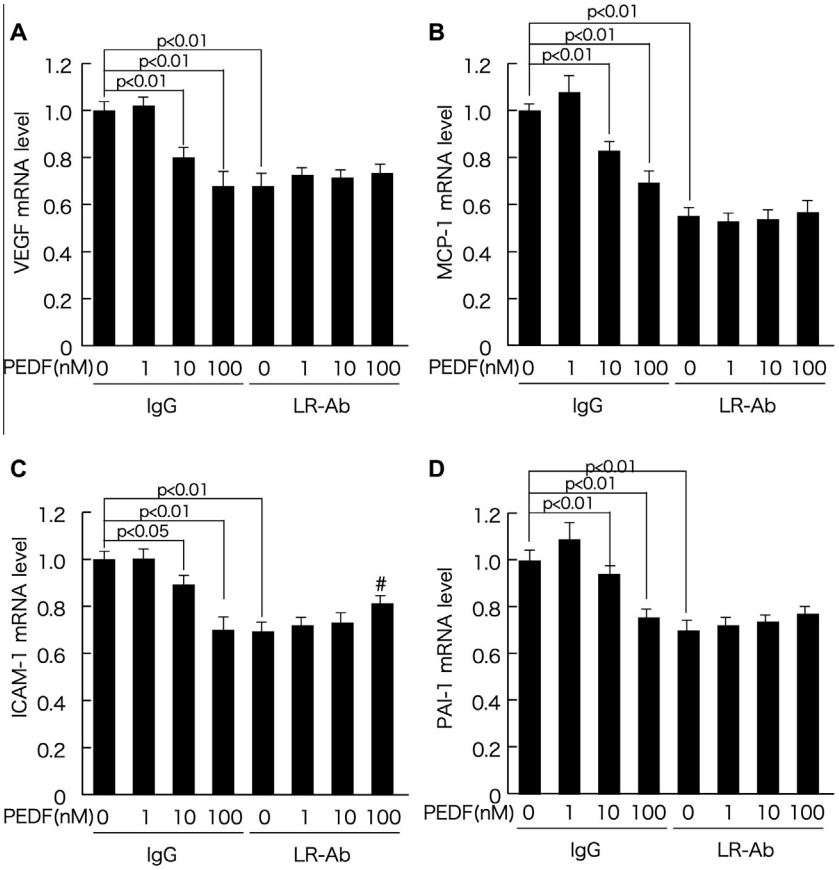

Fig. 3. Effects of LR-Ab on VEGF (A), MCP-1 (B), ICAM-1 (C) and PAI-1 (D) mRNA levels in PEDF-exposed myeloma cells. Myeloma cells were treated with or without the indicated concentrations of PEDF in the presence or absence of 10 μg/ml LR-Ab or IgG for 4 h. Then total RNAs were transcribed and amplified by real-time PCR. Data were normalized by the intensity of 18S mRNA-derived signals and then related to the value obtained with IgG treatment alone. $N = 3$ per group. #, $p < 0.05$ compared with the value with LR-Ab alone.

binding of PEDF to LR; LR antagonist, $mEGF_{33-42}$ completely inhibited the binding of PEDF to immobilized LR.

We further examined the effects of $Lam.B1_{925-933}$, $mEGF_{33-42}$, or LR-Ab on anti-angiogenic, anti-inflammatory and anti-thrombogenic properties of PEDF. As shown in Figs. 3 and 4, PEDF dose-dependently decreased VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in non-treated or IgG-treated myeloma cells. Although LR-Ab or 10 nM $mEGF_{33-42}$ treatment alone significantly reduced VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels, PEDF effects on VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels were completely abolished in LR-Ab or $mEGF_{33-42}$-exposed myeloma cells. Moreover, high concentration of LR agonist mimicked the effects of PEDF; 500 nM $Lam.B1_{925-933}$ significantly decreased VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in myeloma cells (Fig. S1).

4. Discussion

There are two putative functional receptors for PEDF, LR and ATGL [16,17]. Since we have recently found that PEDF acts directly on myeloma cells and inhibits the VEGF-induced growth proliferation *in vitro* [20]. This is a reason why we chose cultured myeloma cells for investigating which types of receptor could mediate the biological actions of PEDF. In this study, we found for the first time that cultured RPMI8226 myeloma cells had both types of receptor for PEDF and that 10 nM PEDF significantly reduced VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in siCon-transfected cells. Moreover, suppression of ATGL levels by siATGL transfection did not affect the actions of PEDF on myeloma cells, whereas inhibitory effects of PEDF on mRNA levels in myeloma cells were abolished by siLR treatment. These observations suggest that PEDF could have anti-angiogenic, anti-inflammatory and anti-thrombogenic properties in cultured myeloma cells through the interaction with LR, but not ATGL. We did not know an exact reason why VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels were increased *rather than* decreased in siLR-transfected cells. However, in this study, the magnitude of PEDF-induced decrease in VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in siATGL-transfected cells was similar to that in siCon-transfected cells (Fig. 1B–E). If ATGL is involved in PEDF-induced up-regulation of VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels, inhibitory effects of PEDF on these mRNA levels should be enhanced in siATGL-transfected cells. So, it is unlikely that PEDF increased VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in siLR-transfected cells via the enhanced interaction with ATGL. Other receptor than ATGL might play a role in the up-regulation of VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in PEDF-exposed and siLR-transfected myeloma cells.

To further examine the functional involvement of LR, we next investigated the effects of LR-Ab, LR antagonist, $mEGF_{33-42}$ and LR agonist, $Lam.B1_{925-933}$ on the PEDF actions in myeloma cells. In this study, we found that PEDF dose-dependently decreased VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in non-treated or IgG-treated myeloma cells. Furthermore, LR-Ab or LR antagonist, $mEGF_{33-42}$ suppressed the binding of PEDF to LR and resultantly blocked the biological effects on myeloma cells (Figs. 2–4); inhibitory effects of PEDF on these mRNA levels were completely lost in LR-Ab or LR antagonist-treated cells. These findings further support the concept that PEDF could exert the anti-angiogenic,

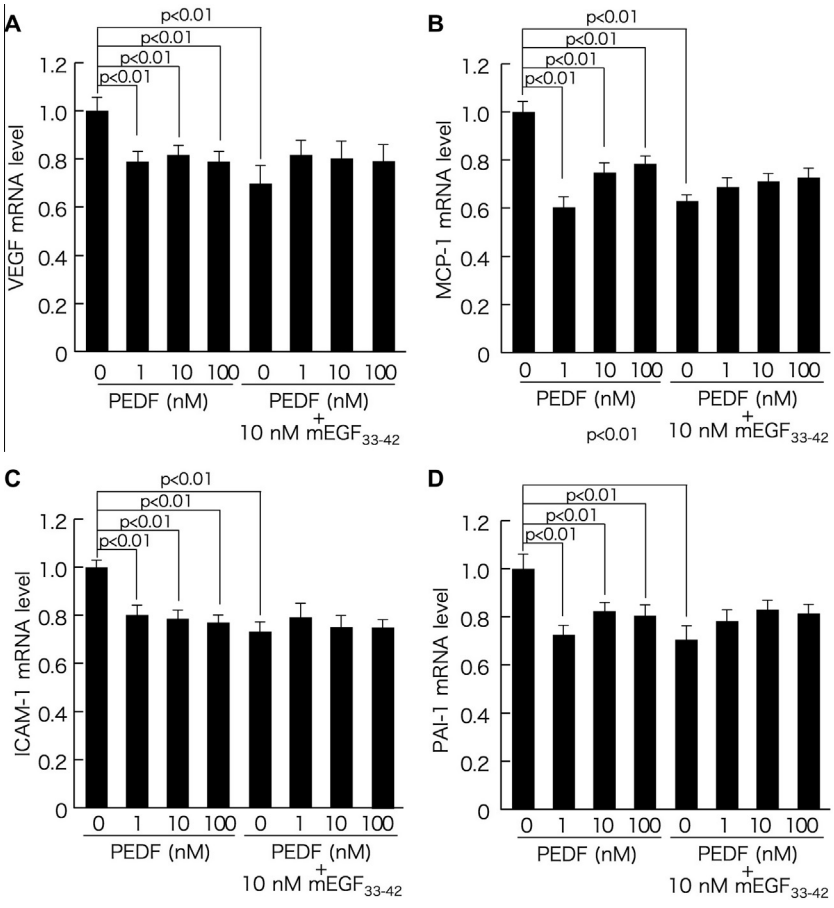

Fig. 4. Effects of LR antagonist, $mEGF_{33-42}$ on VEGF (A), MCP-1 (B), ICAM-1 (C) and PAI-1 (D) mRNA levels in PEDF-exposed myeloma cells. Myeloma cells were treated with or without the indicated concentrations of PEDF in the presence or absence of 10 nM LR antagonist, $mEGF_{33-42}$ for 4 h. Then total RNAs were transcribed and amplified by real-time PCR. Data were normalized by the intensity of 18S mRNA-derived signals and then related to the value obtained with no treatment. $N = 3$ per group.

anti-inflammatory and anti-thrombogenic actions in myeloma cells through LR. In the present study, LR-Ab or LR antagonist, $mEGF_{33-42}$ alone significantly reduced VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in myeloma cells. Therefore, engagement of LR with LR-Ab or LR antagonist (Fig. 2A) might be involved in the actions. In other words, LR-Ab or LR antagonist alone could mimic the effects of PEDF in myeloma cells partly through the interaction of LR.

In this study, we also found that higher concentrations of LR agonist, $Lam.B1_{925-933}$ (100–500 nM) actually bound to LR and significantly reduced VEGF, MCP-1, ICAM-1 and PAI-1 mRNA levels in myeloma cells (Fig. S1). Laminin has been shown to bind to the residues 205–229 of LR, which is also a target domain for both LR antagonist, $mEGF_{33-42}$ and LR agonist, $Lam.B1_{925-933}$ [27]. These observations suggest that PEDF might exert anti-angiogenic, anti-inflammatory and anti-thrombogenic effects in myeloma cells through the interaction with the residues 205–229 of LR. Bernard et al. reported [17] that domain of residues 205–229 of LR could be involved in anti-angiogenic actions of PEDF in endothelial cells, thus further supporting the functional importance of the domain in various biological actions of PEDF.

Acknowledgments

This work was supported in part by Grants of MEXT-Supported Program for the Strategic Research Foundation at Private vUniversities, the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan (S.Y.).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.12.060.

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