Biochemical and Biophysical Research Communications 444 (2014) 461–466

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Participation of the extracellular domain in (pro)renin receptor dimerization

Chiharu Suzuki-Nakagawa [a], Misa Nishimura [b], Tomoko Tsukamoto [b], Sho Aoyama [b], Akio Ebihara [a,b], Fumiaki Suzuki [a,b], Tsutomu Nakagawa [a,b,*]

[a] The United Graduate School of Agricultural Sciences, Gifu University, Gifu, Japan
[b] Department of Applied Life Science, Faculty of Applied Biological Sciences, Gifu University, Gifu, Japan

ARTICLE INFO

Article history:
Received 10 January 2014
Available online 25 January 2014

Keywords:
(Pro)renin receptor
ATP6AP2
Dimerization
Extracellular domain
Retention

ABSTRACT

The (pro)renin receptor [(P)RR] induces the catalytic activation of prorenin, as well as the activation of the mitogen-activated protein kinase (MAPK) signaling pathway; as such, it plays an important regulatory role in the renin–angiotensin system. (P)RR is known to form a homodimer, but the region participating in its dimerization is unknown. Using glutathione S-transferase (GST) as a carrier protein and a GST pull-down assay, we investigated the interaction of several (P)RR constructs with full-length (FL) (P)RR in mammalian cells. GST fusion proteins with FL (P)RR (GST-FL), the C-terminal M8-9 fragment (GST-M8-9), the extracellular domain (ECD) of (P)RR (GST-ECD), and the (P)RR ECD with a deletion of 32 amino acids encoded by exon 4 (GST-ECDd4) were retained intracellularly, whereas GST alone was efficiently secreted into the culture medium when transiently expressed in COS-7 cells. Immunofluorescence microscopy showed prominent localization of GST-ECD to the endoplasmic reticulum. The GST pull-down analysis revealed that GST-FL, GST-ECD, and GST-ECDd4 bound FLAG-tagged FL (P)RR, whereas GST-M8-9 showed little or no binding when transiently co-expressed in HEK293T cells. Furthermore, pull-down analysis using His-tag affinity resin showed co-precipitation of soluble (P)RR with FL (P)RR from a stable CHO cell line expressing FL h(P)RR with a C-terminal decahistidine tag. These results indicate that the (P)RR ECD participates in dimerization.

1. Introduction

The (pro)renin receptor [(P)RR] is a newly identified regulator of the renin–angiotensin system that is essential for blood pressure control and electrolyte balance [1]. Human (P)RR [h(P)RR] is a 350-amino acid receptor comprised of a signal peptide, a large extracellular domain (ECD), a single transmembrane domain, and a short cytoplasmic domain from the N-terminus to the C-terminus. (P)RR binds renin (EC 3.4.23.15) and its inactive proenzyme prorenin, which triggers the phosphorylation of extracellular signal-related protein kinase (ERK) 1/2 [1]. On the other hand, (P)RR increases the catalytic activity of renin and activates prorenin non-proteolytically to generate angiotensin I [1,2]. (P)RR is related to the organ damage associated with hypertension and diabetes (reviewed in [3,4]).

In addition to its roles as the cell surface receptor of renin and prorenin, other roles in Wnt/β-catenin signaling [5] and intracellular vacuolar H^+-ATPase function [6,7] have recently been reported for (P)RR. Accordingly, many reports have shown that endogenous and exogenously expressed (P)RR is predominantly localized intracellularly [8–13].

To date, three molecular forms of (P)RR have been identified: the full-length (FL) form [1], a truncated transmembrane form with the C-terminal region (M8-9 fragment) [14], and the most recently identified form, a truncated soluble form with the N-terminal region [soluble (P)RR; s(P)RR] [11]. s(P)RR is generated intracellularly through proteolytic cleavage of FL (P)RR by furin [11] or ADAM19 [12] at the Golgi apparatus. s(P)RR has been detected in the plasma [11,15] and urine [16]. It binds renin [11] and also binds and activates prorenin *in vitro* [12,16,17], indicating its potential as a biomarker for certain diseases [4,15].

Many biochemical studies have shown that FL (P)RR forms a homodimer [1,9]. A mutant (P)RR with a deletion of 32 amino acids encoded by exon 4 of the (P)RR gene that is observed in patients with X-linked mental retardation and epilepsy [18] has been demonstrated to bind to FL (P)RR and to exert a dominant negative

Abbreviations: ECD, extracellular domain; ER, endoplasmic reticulum; FL, full-length; (P)RR, (pro)renin receptor; s(P)RR, soluble (pro)renin receptor.

* Corresponding author at: Department of Applied Life Science, Faculty of Applied Biological Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan. Fax: +81 58 293 2910.
E-mail address: nakagawa@gifu-u.ac.jp (T. Nakagawa).

http://dx.doi.org/10.1016/j.bbrc.2014.01.073
0006-291X/

effect [19]. However, the specific region responsible for its dimerization remains unknown. In this study, the region important for dimerization was elucidated by expressing several (P)RR constructs in mammalian cells. Moreover, we investigated the intracellular localization of (P)RR.

2. Materials and methods

2.1. Antibodies

Anti-(P)RR antibody (GTX114169) was purchased from GeneTex (Irvine, CA, USA), and its binding epitope has been mapped to amino acid (aa) residues 146–281 of h(P)RR as described in the Supplementary data section. Other antibodies used were anti-GST (Santa Cruz Biotechnology; Dallas, TX, USA), anti-6His 9F2 (Wako Pure Chemical Industries; Osaka, Japan), anti-actin and anti-FLAG M2 (Sigma–Aldrich; St. Louis, MO, USA), anti-KDEL and anti-GM130 (MBL; Nagoya, Japan), and Cy2-conjugated anti-rabbit immunoglobulin G and Rhodamine Red X-conjugated anti-mouse immunoglobulin G (Jackson ImmunoResearch Laboratories; West Grove, PA, USA).

2.2. Plasmid constructions

The h(P)RR cDNA was obtained by polymerase chain reaction (PCR) from a human kidney cDNA library (Clontech Laboratories; Mountain View, CA, USA). pcDNA3-h(P)RR-10His, which encodes h(P)RR with a foreign signal peptide at the N-terminus and a decahistidine tag at the C-terminus, was constructed by inserting the DNA fragment corresponding to aa 17–350 of h(P)RR into pcDNA3-10His [20], which contains a substitution of an ILVPRGS sequence for the IVPRGS sequence (thrombin cleavage site) encoded by the original plasmid. To construct pEBMulti-FLAG-h(P)RR, a DNA fragment encoding FL h(P)RR with a FLAG epitope (DYKDDDDK) between the signal peptide (aa 1–16) and the ECD was amplified by PCR and subcloned into the mammalian expression plasmid pEBMulti-Hyg (Wako Pure Chemical Industries). The h(P)RR constructs [aa 17–350 (FL), aa 17–304 (ECD), the ECD with deletion of aa 101–132 (ECDd4), and aa 282–350 (M8-9)] and the endoplasmic reticulum (ER) retention sequence of human calreticulin (QAKDEL) fused to *Schistosoma japonicum* glutathione S-transferase (GST) that was preceded by a 24-amino acid signal peptide from the sheep angiotensinogen sequence at the N-terminus, as shown in Fig. 1, were generated in the mammalian expression plasmid pcDNA3 (Invitrogen; Carlsbad, CA, USA). The sequence integrity of all inserts was confirmed by DNA sequencing.

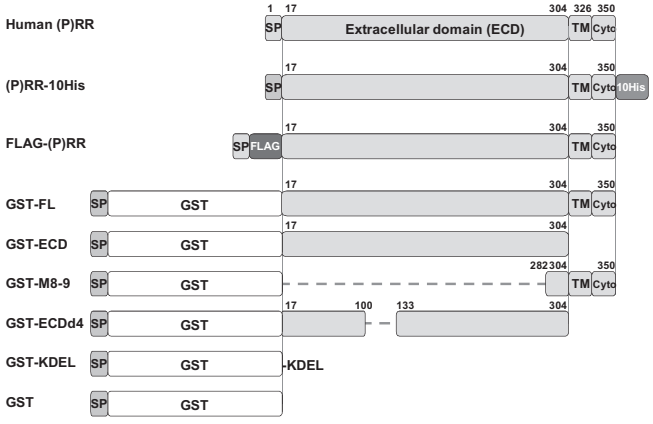

Fig. 1. Schematic representation of human (P)RR and constructs used in this study. (P)RR-10His, full-length (FL) h(P)RR with a C-terminal decahistidine tag (10His); FLAG-(P)RR, FL h(P)RR with an N-terminal FLAG tag (FLAG); GST-FL, FL h(P)RR fused to GST; GST-ECD, the extracellular domain (ECD) of h(P)RR fused to GST; GST-M8-9, M8-9 fragment of h(P)RR fused to GST; GST-ECDd4, the h(P)RR ECD carrying a deletion fused to GST; GST-KDEL, GST fused with the KDEL ER-retention sequence; GST, GST alone. Numbers indicate amino acid positions in the h(P)RR sequence. Dashed lines indicate the deleted regions. SP, signal peptide; TM, transmembrane domain; Cyto, cytoplasmic domain.

2.3. Cell culture, transfection, and establishment of stable cell lines

COS-7 (RCB0539) and HEK293T (RCB2202) cells were provided by the RIKEN BRC through the National Bio-Resource Project of MEXT, Japan, and maintained in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin at 37 °C in 5% CO_2.

Cells cultured for 24 h were transiently transfected with the expression plasmid(s) based on the polyethyleneimine-mediated method [21]. Briefly, for COS-7 cells grown in a 6-well plate, plasmid DNA (2 μg) was mixed with 6 μg of polyethyleneimine (Polysciences; Warrington, PA, USA) in 0.2 ml of 150 mM NaCl and incubated for 20 min at room temperature. The culture medium was replaced by fresh medium (1.5 ml/well), and the DNA–polyethyleneimine mixture was plated to the cells. The cells were cultured for a further 48 h.

A Chinese hamster ovary (CHO) cell line expressing h(P)RR-10His was established by employing our previously described method [20]. Briefly, pcDNA3-h(P)RR-10His and pmDHFR, encoding mouse dihydrofolate reductase, were transfected into dihydrofolate reductase-deficient CHO cells using the polyethyleneimine-mediated method. A clonal cell line with high production of the recombinant protein, CHO/h(P)RR-10His, was used in this study.

2.4. Cell lysate and culture supernatant

COS-7 cells in serum-free medium were transfected for 48 h with plasmids as described above. Culture supernatants were collected and concentrated using Amicon Ultra-0.5 10K (Millipore; Billerica, MA, USA). The cells were washed with phosphate-buffered saline (PBS), pH 7.4, and lysed in ice-cold PBS containing 1% Triton X-100 and centrifuged to remove debris. CHO cells at 90–100% confluence were cultured for 48 h in a 60-mm diameter dish. Culture supernatants were collected. Cells were washed with PBS, lysed in ice-cold PBS containing 0.5% Triton X-100, and centrifuged to remove debris.

2.5. Immunofluorescence microscopy

COS-7 and CHO cells were grown on a gelatin-coated cover glass placed in a 6-well plate. COS-7 cells were transiently transfected with the desired plasmids as described above and cultured for 48 h. The cells were fixed in 3.7% formaldehyde in PBS on ice for 30 min, permeabilized in PBS containing 0.1% Triton X-100 and 0.1% Tween 20 at room temperature for 30 min, and then incubated for 30 min in blocking solution (PBS containing 2% fetal bovine serum and 0.1% Tween 20). The cells were then incubated at 4 °C overnight with either anti-(P)RR or anti-GST antibodies together with either anti-KDEL or anti-GM130 antibodies diluted in the blocking solution. After washing with 0.1% Tween 20 in PBS, cells were incubated at room temperature for 1 h with Cy2-conjugated anti-rabbit immunoglobulin G antibody to detect either (P)RR or GST and Rhodamine Red X-conjugated anti-mouse immunoglobulin G antibody to detect either KDEL or GM130 in blocking solution. The nuclei were stained with H33342 (Nacalai Tesque; Kyoto, Japan). Fluorescence images were obtained using an LSM 710 confocal microscope (Carl Zeiss; Germany).

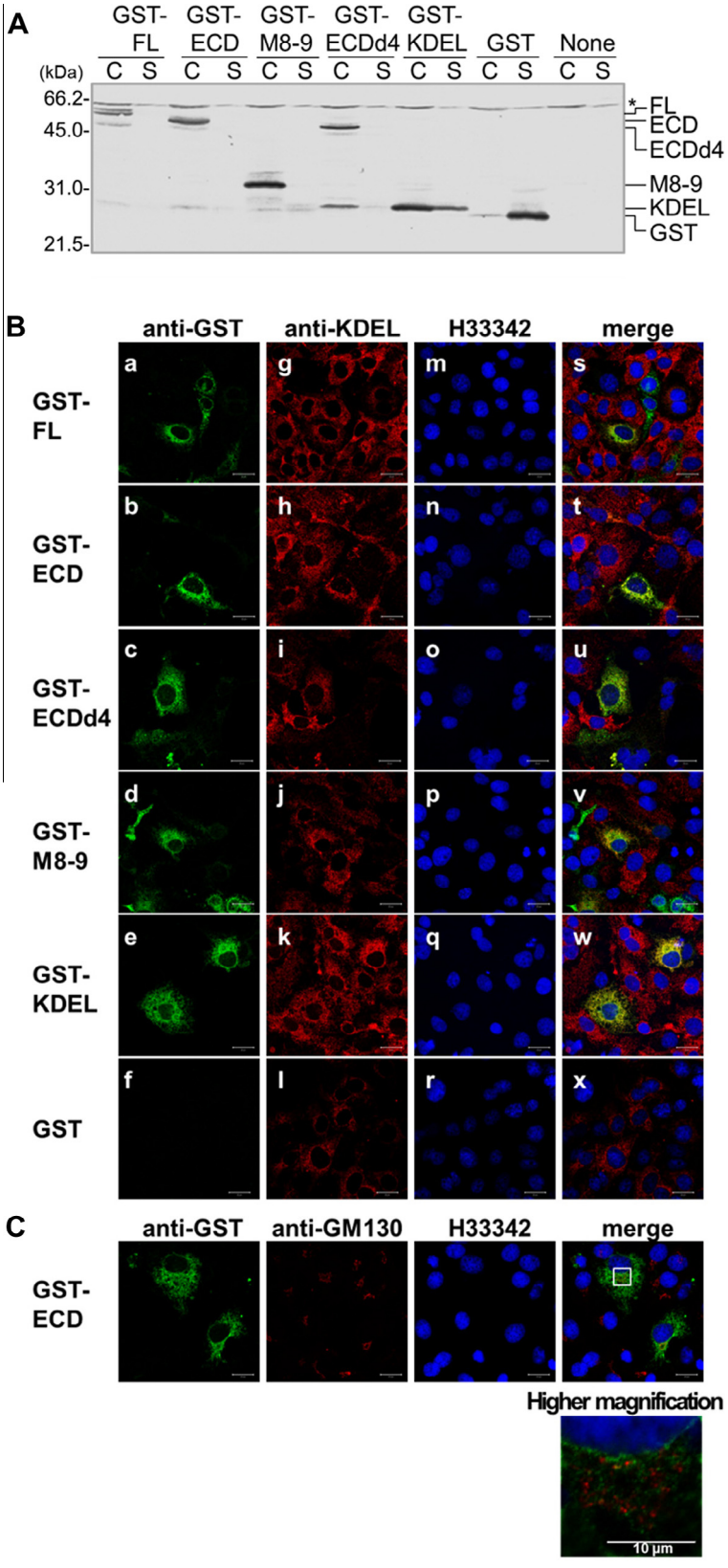

Fig. 2. Localization of the GST-fusion (P)RR constructs expressed in COS-7 cells. (A) COS-7 cells were transiently transfected with either an expression plasmid encoding the indicated GST-fusion construct or an empty vector (None) under serum-free conditions, and cultured for 48 h. The cell lysates (C; 8% of the collected amount) and culture supernatants (S; 40%) were analyzed by SDS-PAGE followed by immunoblotting using anti-GST antibody. Asterisks indicate non-specific bands. The immunoblot shown is representative of at least three independent experiments. (B, C) COS-7 cells after transfection were subjected to double-immunofluorescence labeling using anti-GST antibody (green) together with either anti-KDEL antibody as an ER marker (B; red) or anti-GM130 antibody as a Golgi marker (C; red), and analyzed by confocal microscopy. The scale bar represents 20 μm. The framed area in C is also shown at higher magnification. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.6. GST pull-down assay

The plasmids encoding each GST-fusion protein and pEBMulti-FLAG-h(P)RR were co-transfected into HEK293T cells using polyethyleneimine and cultured for 48 h. The cells were washed with PBS and lysed in ice-cold buffer A (0.5% Triton X-100 in PBS) containing a protease inhibitor cocktail (Sigma–Aldrich) and centrifuged to remove debris. The cell lysates were incubated with glutathione Sepharose 4B (GE Healthcare; Buckinghamshire, UK) at 4 °C for 1 h with slow rotation. Glutathione Sepharose was then pelleted by centrifugation, and the supernatant was discarded. The pellet was washed three times with ice-cold buffer A and was then incubated in sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) sample buffer diluted with PBS at 95 °C for 10 min. After centrifugation, the supernatant was analyzed by SDS-PAGE followed by immunoblotting with anti-GST or anti-FLAG M2 antibodies.

2.7. His-tagged protein pull-down assay

The CHO/h(P)RR-10His cells were washed with PBS and lysed in ice-cold buffer B (50 mM Tris–HCl, pH 7.4, 140 mM NaCl, and 1% Nonidet P-40) containing a protease inhibitor cocktail (Nacalai Tesque) and centrifuged to remove debris. The cell lysates were incubated with Dynabeads His-Tag Isolation and Pulldown (Invitrogen), which are magnetic beads coated in a cobalt-based immobilized metal affinity chromatography chemistry, at 4 °C for 10 min with slow rotation. The beads were then collected with a magnetic separator, and the supernatant was discarded. The beads were washed four times with ice-cold buffer B and were then eluted with 300 mM imidazole in 50 mM sodium phosphate buffer (pH 8.0) containing 300 mM NaCl and 0.01% Tween 20 on ice for 10 min. The beads were separated and the supernatant was analyzed by SDS-PAGE followed by immunoblotting with anti-(P)RR or anti-actin antibodies.

3. Results

3.1. Localization of GST-fusion h(P)RR constructs expressed in COS-7 cells

In our search for a region responsible for the dimerization of (P)RR in cells, we produced several (P)RR constructs using GST as a carrier protein (Fig. 1). The GST-fusion proteins were transiently expressed in COS-7 cells. Cell lysates and culture supernatants were analyzed by immunoblotting (Fig. 2A). GST alone was predominantly detected in the culture supernatant, indicating that the carrier protein (GST moiety) itself was efficiently secreted into the medium. As expected, GST-KDEL, containing a well-known ER-retention sequence, was detected mainly in the cell lysate. Not only GST-FL and GST-M8-9, which contain the transmembrane domain, but also GST-ECD and GST-ECDd4, which lack both the transmembrane and cytoplasmic domains, were detected in the cell lysates. These (P)RR constructs were not detected in the culture supernatants under the experimental conditions.

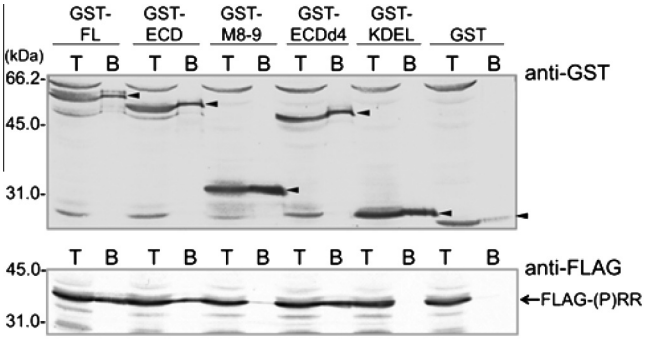

Fig. 3. Interaction of the GST-fusion h(P)RR constructs with FL h(P)RR. Each indicated GST-fusion h(P)RR construct and FLAG-h(P)RR were co-expressed in HEK293T cells. Cleared cell lysates were prepared and used for a GST pull-down assay with glutathione Sepharose beads. The total cleared cell lysates (T) and bound proteins (B) were analyzed by SDS-PAGE followed by immunoblotting using anti-GST (upper panel) or anti-FLAG antibodies (lower panel). The immunoblots shown are representative of at least two independent experiments. Arrowheads indicate the predicted bands for each GST-fusion construct.

Double-immunofluorescence labeling of the transfected COS-7 cells showed that the subcellular distributions of GST-FL, GST-ECD, GST-ECDd4, GST-M8-9, and GST-KDEL coincided with the ER marker (Fig. 2B, s-w). In addition, the localization of GST-ECD was distinct from that of the GM130-labeled Golgi (Fig. 2C). Consistent with the immunoblotting results, GST alone showed little or no intracellular staining (Fig. 2B, f).

3.2. Interaction of the (P)RR ECD with FL (P)RR

To elucidate the region responsible for (P)RR dimerization, we examined the possible interaction of each GST-fusion (P)RR construct with FLAG-tagged FL (P)RR [FLAG-(P)RR] (see Fig. 1) by conducting a GST pull-down assay. FLAG-(P)RR was clearly detected in the bound fractions of GST-FL, GST-ECD, and GST-ECDd4, but not in those of the negative controls, GST alone and GST-KDEL (Fig. 3, lower panel). GST-M8-9 produced a weak or no FLAG-(P)RR band in the bound fraction. These results indicate that the (P)RR ECD is able to form a complex with FL (P)RR.

3.3. Molecular forms and subcellular distribution of h(P)RR expressed in CHO cells

In previous studies, in addition to FL (P)RR, a considerable amount of s(P)RR was detected in some cell types, especially CHO cells [11,12]. To investigate the possibility that s(P)RR binds to the FL receptor, a CHO cell line stably expressing h(P)RR with a C-terminal decahistidine tag [h(P)RR-10His] was established and used to characterize the molecular properties of h(P)RR in cells. In immunoblotting, anti-(P)RR antibody showed two bands at approximately 42 kDa and 30 kDa in the cell lysate, respectively, whereas only the 30-kDa band was detected in the culture supernatant (Fig. 4A, left panel). An approximately 13-kDa band in addition to the 42-kDa band was detected in the cell lysate with anti-6His antibody, whereas the 30-kDa band was not detected in either the cell lysate or the culture supernatant (Fig. 4A, right panel). These results indicate that the 42-, 30-, and 13-kDa bands corresponded to FL h(P)RR-10His, s(P)RR, and the M8-9 fragment with a decahistidine tag, respectively.

In order to determine the localization of each form of h(P)RR-10His, double-immunofluorescence labeling with anti-(P)RR and anti-organelle marker antibodies was performed. As shown in Fig. 4B, merged images indicated that the staining pattern with anti-(P)RR antibody exhibited a perinuclear distribution that was similar to the pattern observed for the KDEL-labeled ER. By contrast, the staining pattern did not coincide with that observed for GM130-labeled Golgi. As shown by immunoblotting with anti-(P)RR antibody (Fig. 4A), the band intensities of FL (P)RR and s(P)RR were almost the same in the cell lysate of CHO/h(P)RR-10His, and the anti-(P)RR antibody used in this study did not recognize the M8-9 fragment (Figs. S1 and S2), indicating that both s(P)RR and FL (P)RR were predominantly localized to the ER.

To examine the possible interaction of s(P)RR with FL (P)RR in the CHO/h(P)RR-10His cells, His-tagged protein affinity pull-down assays were performed. In addition to FL h(P)RR-10His, s(P)RR was detected in the bound fraction, whereas actin, a negative control,

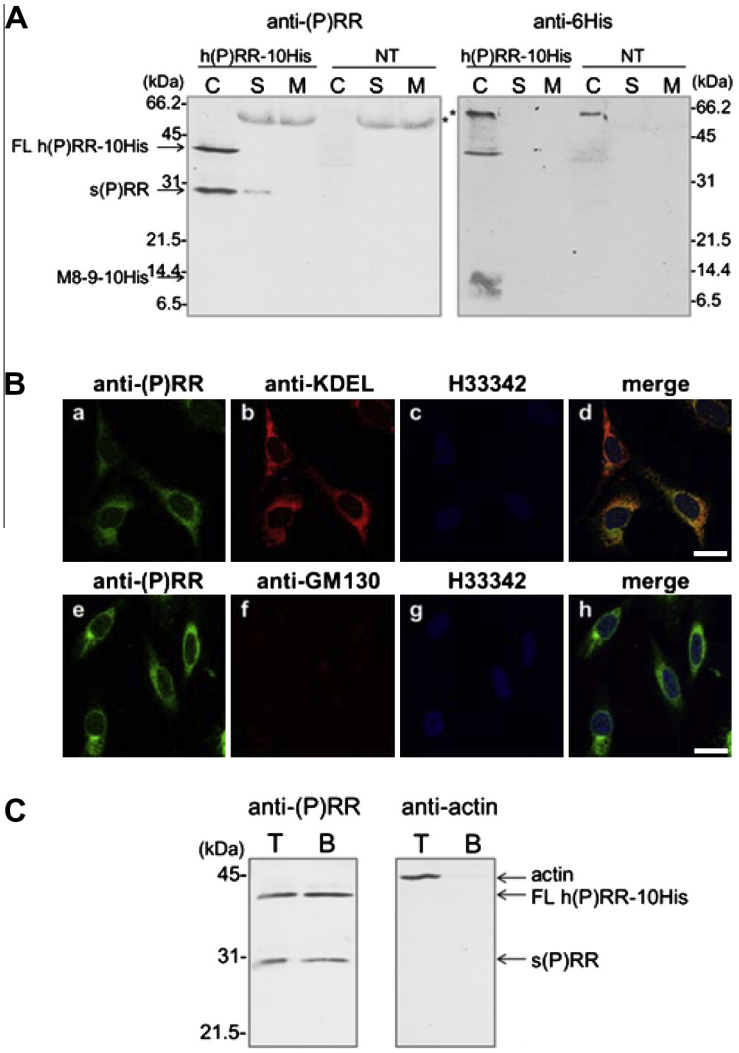

Fig. 4. Molecular forms and localization of h(P)RR stably expressed in CHO cells. (A) CHO/h(P)RR-10His cells and non-transfected CHO cells (NT) were cultured in a fresh medium for 48 h. Cell lysates (C; 10% of the collected amount) and culture supernatants (S; 1%), as well as the fresh medium (M; equal volume to S), were analyzed by SDS-PAGE followed by immunoblotting using anti-(P)RR (left panel) or anti-6His antibodies (right panel). Asterisks indicate non-specific protein bands. The immunoblots shown are representative of at least three independent experiments. (B) CHO/h(P)RR-10His cells were subjected to double-immunofluorescence labeling using anti-(P)RR antibody (a and e; green) together with either anti-KDEL antibody as an ER marker (b; red) or anti-GM130 antibody as a Golgi marker (f; red), and analyzed by confocal microscopy. c and g, H33342; d and h, merged images; scale bars, 20 μm. (C) Cleared cell lysate was prepared from CHO/h(P)RR-10His cells and used for His-tag pull down with His-tag affinity beads. Equal portions of the total cleared cell lysate (T) and bound proteins (B) were analyzed by SDS-PAGE followed by immunoblotting using either anti-(P)RR (left panel) or anti-actin antibodies (right panel). The immunoblots shown are representative of at least two independent experiments. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was not (Fig. 4C), indicating that s(P)RR formed a complex with FL (P)RR.

4. Discussion

The present study provides evidence that the (P)RR ECD participates in dimerization. The h(P)RR ECD mutant lacking the region encoded by exon 4 (aa 101–132) was able to form a complex with FL (P)RR, indicating that the region responsible for dimerization lies within aa 17–100 and/or 133–281 of h(P)RR. These results support previous findings showing that the mutant (P)RR lacking the region encoded by exon 4 was able to form heterodimers with FL (P)RR and exerted a dominant negative effect [19].

Using maltose-binding protein as a carrier protein in a crystallographic study, Zhang et al. [22] reported that the residues in the cytoplasmic domain of (P)RR may play a role in (P)RR dimerization, although the driving force was relatively weak. In addition, the transmembrane domain of single transmembrane receptors contributes to the stability of receptor dimers (reviewed in [23]). In the present study, FL (P)RR was weakly detected in the complex containing the M8-9 fragment fused with GST (Fig. 3), which suggests that the transmembrane and cytoplasmic domains of (P)RR might play a role in dimer stabilization.

Localization of (P)RR in the plasma membrane was observed in human mesangial cells [1]. In contrast to the renin/prorenin-binding function of the cell surface (P)RR, many reports have shown that endogenous and exogenously expressed (P)RR is predominantly localized intracellularly [8–13]. The present results in CHO and COS-7 cells support the perinuclear localization of (P)RR reported by other groups [9,10,12,13].

Although s(P)RR is released into the extracellular space, a considerable amount of s(P)RR is observed intracellularly in some cell types [11,12]. This intracellular localization of s(P)RR has not received substantial attention to date. Yoshikawa et al. [12] reported that (P)RR was localized in both the ER and Golgi apparatus in vascular smooth muscle cells, using an anti-(P)RR antibody that could detect both FL (P)RR and s(P)RR. This ER localization

of s(P)RR corresponds with our present results in CHO and COS-7 cells, although co-localization of (P)RR and the Golgi marker protein was not detected in our experiments.

The ER-retention motif KXXXX at the C-terminus of FL (P)RR has been reported previously [9]. GST-ECD transiently expressed in COS-7 cells was detected predominantly in the ER despite the absence of this ER-retention motif (Fig. 2B and C). Under our experimental conditions, both FL (P)RR and s(P)RR that was generated by the endogenous protease were detected predominantly in the ER in CHO cells expressing h(P)RR-10His (Fig. 4B). We suggest that s(P)RR, at least in part, is retained intracellularly by its association with FL (P)RR containing the ER-retention motif. s(P)RR has been reported to be generated in the *trans*-Golgi network [11]. Therefore, generated s(P)RR might, in part, be retrieved back to the ER via retrograde transport while remaining associated with the uncleaved FL (P)RR or via an as yet unknown mechanism. Because our experiment did not reveal the stoichiometry of the interaction of s(P)RR with FL (P)RR, the presence of a (P)RR oligomer rather than a dimer might explain the efficient retention of (P)RR ECD constructs and s(P)RR observed in COS-7 and CHO cells.

Secreted s(P)RR has been shown to activate the prorenin *in vitro* [16,17], leading to the prediction that the secreted s(P)RR contributes to angiotensin I generation by activating extracellular prorenin *in vivo*. The results of the present study suggest that FL (P)RR at the plasma membrane could anchor the secreted s(P)RR on the cell surface. The mutant FL (P)RR lacking the region encoded by exon 4 was previously shown to exhibit normal renin binding but impaired ERK1/2 activation, and co-expression of the mutant (P)RR with intact FL (P)RR resulted in decreased ERK1/2 activation [19]. If the homodimerization of intact FL receptors is necessary for intracellular signaling, our findings support the idea that s(P)RR functions as a natural antagonist of FL (P)RR at the plasma membrane [11]. Further study is needed to confirm this hypothesis.

In conclusion, we demonstrated that the ECD of (P)RR participates in dimerization, and that s(P)RR, in part, is retained inside the cell through forming a complex with FL (P)RR. These findings provide novel insight into the regulatory mechanism of s(P)RR secretion, which might play a role in the biology and physiology of (P)RR.

Acknowledgments

We thank Kazuki Arakawa and Chihiro Tomatsu for assistance in plasmid construction. We also thank Professor Tadashi Inagami for his encouragement. This work was supported in part by the JSPS KAKENHI (Grant No. 22580102) and by a grant from Gifu University (KASSEIKA KEIHI) to T.N.

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.2014.01.073.

References

[1] G. Nguyen, F. Delarue, C. Burcklé, L. Bouzhir, T. Giller, J.D. Sraer, Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin, J. Clin. Invest. 109 (2002) 1417–1427.
[2] A.H. Nabi, K.B. Biswas, T. Nakagawa, A. Ichihara, T. Inagami, F. Suzuki, Prorenin has high affinity multiple binding sites for (pro)renin receptor, Biochim. Biophys. Acta 1794 (2009) 1838–1847.
[3] A. Ichihara, M. Sakoda, A. Kurauchi-Mito, T. Narita, K. Kinouchi, K. Murohashi-Bokuda, H. Itoh, Possible roles of human (pro)renin receptor suggested by recent clinical and experimental findings, Hypertens. Res. 33 (2010) 177–180.
[4] G. Nguyen, Renin, (pro)renin and receptor: an update, Clin. Sci. (Lond) 120 (2011) 169–178.
[5] C.M. Cruciat, B. Ohkawara, S.P. Acebron, E. Karaulanov, C. Reinhard, D. Ingelfinger, M. Boutros, C. Niehrs, Requirement of prorenin receptor and vacuolar H^+-ATPase-mediated acidification for Wnt signaling, Science 327 (2010) 459–463.
[6] K. Kinouchi, A. Ichihara, M. Sano, G.H. Sun-Wada, Y. Wada, A. Kurauchi-Mito, K. Bokuda, T. Narita, Y. Oshima, M. Sakoda, Y. Tamai, H. Sato, K. Fukuda, H. Itoh, The (pro)renin receptor/ATP6AP2 is essential for vacuolar H^+-ATPase assembly in murine cardiomyocytes, Circ. Res. 107 (2010) 30–34.
[7] F. Riediger, I. Quack, F. Qadri, B. Hartleben, J.K. Park, S.A. Potthoff, D. Sohn, G. Sihn, A. Rousselle, V. Fokuhl, U. Maschke, B. Purfürst, W. Schneider, L.C. Rump, F.C. Luft, R. Dechend, M. Bader, T.B. Huber, G. Nguyen, D.N. Muller, Prorenin receptor is essential for podocyte autophagy and survival, J. Am. Soc. Nephrol. 22 (2011) 2193–2202.
[8] J.J. Saris, P.A.C. 't Hoen, I.M. Garrelds, D.H.W. Dekkers, J.T. den Dunnen, J.M.J. Lamers, A.H. Jan Danser, Prorenin induces intracellular signaling in cardiomyocytes independently of angiotensin II, Hypertension 48 (2006) 564–571.
[9] J.H. Schefe, M. Menk, J. Reinemund, K. Effertz, R.M. Hobbs, P.P. Pandolfi, P. Ruiz, T. Unger, H. Funke-Kaiser, A novel signal transduction cascade involving direct physical interaction of the renin/prorenin receptor with the transcription factor promyelocytic zinc finger protein, Circ. Res. 99 (2006) 1355–1366.
[10] M. Sakoda, A. Ichihara, Y. Kaneshiro, T. Takemitsu, Y. Nakazato, A.H. Nabi, T. Nakagawa, F. Suzuki, T. Inagami, H. Itoh, (Pro)renin receptor-mediated activation of mitogen-activated protein kinases in human vascular smooth muscle cells, Hypertens. Res. 30 (2007) 1139–1146.
[11] C. Cousin, D. Bracquart, A. Contrepas, P. Corvol, L. Muller, G. Nguyen, Soluble form of the (pro)renin receptor generated by intracellular cleavage by furin is secreted in plasma, Hypertension 53 (2009) 1077–1082.
[12] A. Yoshikawa, Y. Aizaki, K. Kusano, F. Kishi, T. Susumu, S. Iida, S. Ishiura, S. Nishimura, M. Shichiri, T. Senbonmatsu, The (pro)renin receptor is cleaved by ADAM19 in the Golgi leading to its secretion into extracellular space, Hypertens. Res. 34 (2011) 599–605.
[13] G. Sihn, C. Burckle, A. Rousselle, T. Reimer, M. Bader, (Pro)renin receptor: subcellular localizations and functions, Front. Biosci. (Elite Ed.) 5 (2013) 500–508.
[14] J. Ludwig, S. Kerscher, U. Brandt, K. Pfeiffer, F. Getlawi, D.K. Apps, H. Schägger, Identification and characterization of a novel 9.2-kDa membrane sector-associated protein of vacuolar proton-ATPase from chromaffin granules, J. Biol. Chem. 273 (1998) 10939–10947.
[15] N. Watanabe, K. Bokuda, T. Fujiwara, T. Suzuki, A. Mito, S. Morimoto, S.C. Jwa, M. Egawa, Y. Arai, F. Suzuki, H. Sago, A. Ichihara, Soluble (pro)renin receptor and blood pressure during pregnancy: a prospective cohort study, Hypertension 60 (2012) 1250–1256.
[16] A.A. Gonzalez, L.S. Lara, C. Luffman, D.M. Seth, M.C. Prieto, Soluble form of the (pro)renin receptor is augmented in the collecting duct and urine of chronic angiotensin II-dependent hypertensive rats, Hypertension 57 (2011) 859–864.
[17] K.B. Biswas, A.N. Nabi, Y. Arai, T. Nakagawa, A. Ebihara, A. Ichihara, T. Inagami, F. Suzuki, Qualitative and quantitative analyses of (pro)renin receptor in the medium of cultured human umbilical vein endothelial cells, Hypertens. Res. 34 (2011) 735–739.
[18] J. Ramser, F.E. Abidi, C.A. Burckle, C. Lenski, H. Toriello, G. Wen, H.A. Lubs, S. Engert, R.E. Stevenson, A. Meindl, C.E. Schwartz, G. Nguyen, A unique exonic splice enhancer mutation in a family with X-linked mental retardation and epilepsy points to a novel role of the renin receptor, Hum. Mol. Genet. 14 (2005) 1019–1027.
[19] A. Contrepas, J. Walker, A. Koulakoff, K.J. Franek, F. Qadri, C. Giaume, P. Corvol, C.E. Schwartz, G. Nguyen, A role of the (pro)renin receptor in neuronal cell differentiation, Am. J. Physiol. Regul. Integr. Comp. Physiol. 297 (2009) R250–R257.
[20] T. Nakagawa, K. Nishiuchi, J. Akaki, H. Iwata, R. Satou, F. Suzuki, Y. Nakamura, Efficient production of recombinant human (pro)renin utilizing a decahistidine tag attached at the C-terminus, Biosci. Biotechnol. Biochem. 71 (2007) 256–260.
[21] O. Boussif, F. Lezoualc'h, M.A. Zanta, M.D. Mergny, D. Scherman, B. Demeneix, J.P. Behr, A versatile vector for gene and oligonucleotide transfer into cells in culture and in vivo: polyethylenimine, Proc. Natl. Acad. Sci. USA 92 (1995) 7297–7301.
[22] Y. Zhang, X. Gao, R.M. Garavito, Structural analysis of the intracellular domain of (pro)renin receptor fused to maltose-binding protein, Biochem. Biophys. Res. Commun. 407 (2011) 674–679.
[23] E. Li, K. Hristova, Receptor tyrosine kinase transmembrane domains: function, dimer structure and dimerization energetics, Cell Adh. Migr. 4 (2010) 249–254.