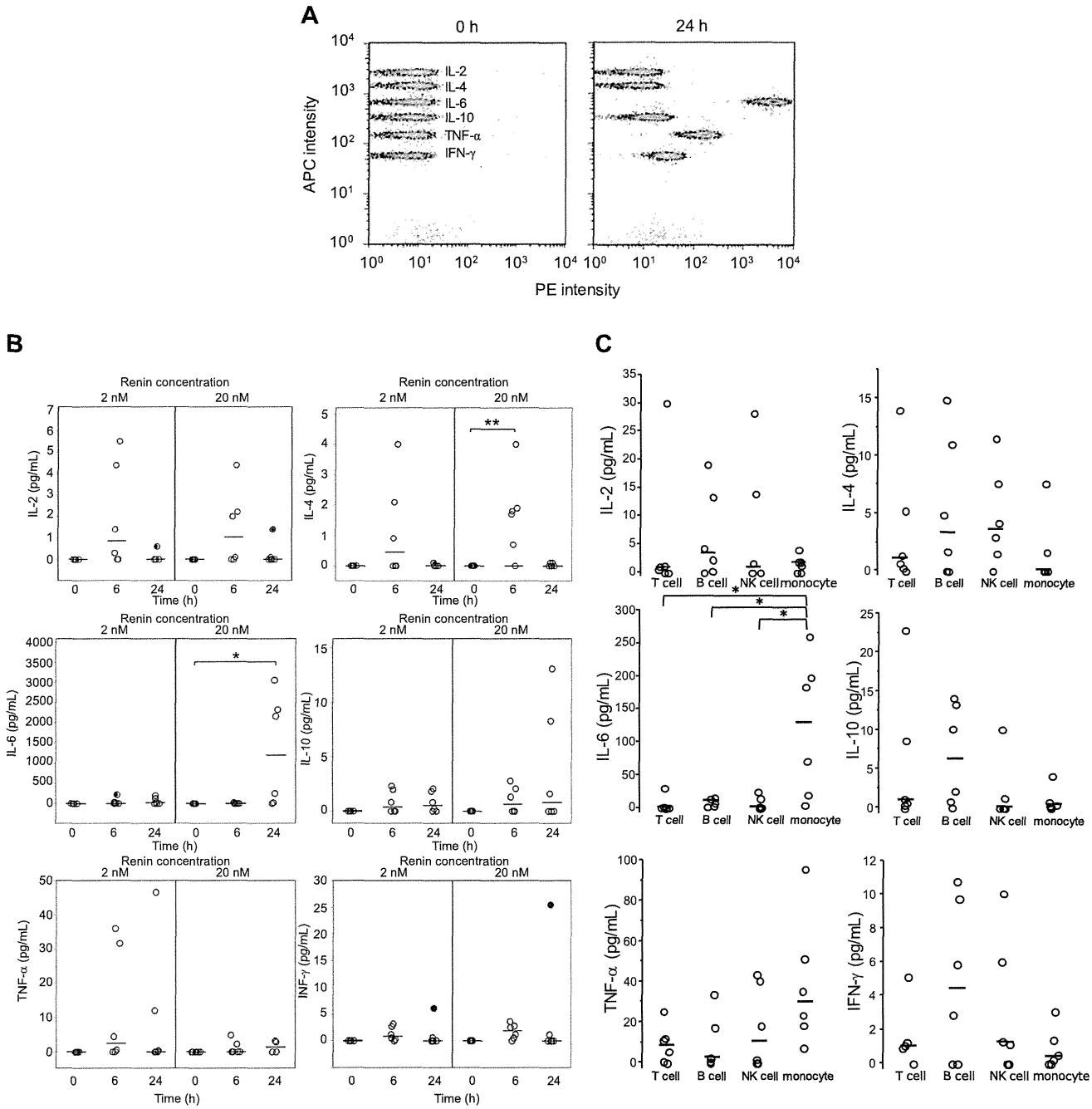

Fig. 5. Cytokine levels evaluated by cytometric bead array. *A*: representative dot plots show cytokine (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ) levels of prestimulated (0 h) and poststimulated PBMCs incubated with 20 nmol/l renin for 24 h. *B*: cytokine levels at 0, 6, or 24 h after renin stimulation (2 or 20 nmol/l) as evaluated by cytometric bead array ($n = 6$). Filled circle and bold line represent outlier and median, respectively. *C*: dot plots of cytokine release from isolated cells from PBMCs stimulated by renin using flow cytometry ($n = 6$). IL-6 was released by mainly monocytes. Bold lines represents mean. $^*P < 0.05$ compared with monocytes.

under ERK1/2 inhibitor U0126 using PBMCs from four healthy subjects. The expression of *COX-2* was significantly increased by renin stimulation, and this expression was inhibited in the presence of U0126 (Fig. 7).

(P)RR knockdown and ERK1/2 phosphorylation. To examine the response of ERK1/2 phosphorylation to renin via (P)RR, we knocked down (P)RR expression using siRNA in a human monocyte cell line (U937) because (P)RR expression was highest in monocytes and was expressed in macrophages infiltrating ANCA-associated GN. Human recombinant renin induction of ERK1/2 phosphorylation was renin concentration and time dependent in U937 cells (Fig. 8, *A* and *B*). The greatest reduction of (P)RR expression (50%) was observed 48 h after (P)RR siRNA treatment (Fig. 8*C*). The knockdown of (P)RR in U937 cells did not

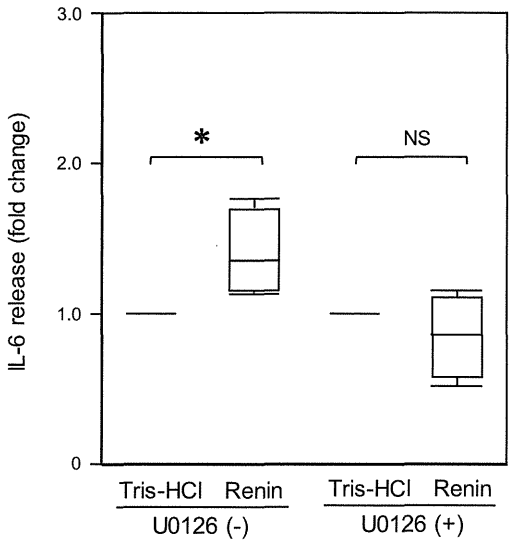

Fig. 6. Cytokine levels in human PBMCs (n = 4) evaluated by cytometric beads array in the presence of ERK1/2 inhibitor (U0126). Values are presented as the median (central line), interquartile range (box), and range (whiskers). U0126 (+), in the presence of U0126; U0126 (−), in the absence of U0126. NS, not significant. *$P < 0.05$.

affect cell growth or viability (Fig. 8*D*). ERK1/2 phosphorylation was significantly decreased by (P)RR siRNA treatment in U937 cells compared with control siRNA (Fig. 8*E*).

(P)RR expression in human crescentic GN. To test whether (P)RR is expressed by inflammatory cells responsible for GN, renal tissues from three cases of ANCA-associated GN were stained (Fig. 9). High numbers of macrophages (Fig. 9*J*) infiltrated around glomeruli. There were few infiltrating T cells (Fig. 9*A*), B cells (Fig. 9*D*), and NK cells (Fig. 9*G*). Infiltrating T cells (Fig. 9*B*), B cells (Fig. 9*E*), NK cells (Fig. 9*H*), and macrophages (Fig. 9*K*) around glomeruli with crescent formation and in the tubulointerstitium (Fig. 10*A*) were stained with (P)RR. By contrast, lymphocytes and macrophages did not infiltrate around glomeruli or the mesangium and tubulointerstitial area in the tissues of a control model, MCNS (Fig. 10*B*).

DISCUSSION

The present study revealed the expression and functional role of (P)RR in human lymphocytes and monocytes, and (P)RR expression in tissue-infiltrating T cells and macrophages, that have a major role in the pathophysiology of ANCA-associated GN (40, 48). (P)RR was present in the cellular cytosolic region. Both full-length and soluble forms of (P)RR were expressed in primary isolated PBMCs (Fig. 1*C*). However, there is no visible band for THE soluble form of (P)RR (Fig. 1*D*). This discrepancy might be due to the kinetics of soluble (P)RR. Generally, protein secretion has two distinct pathways: the regulated secretory pathway and the constitutive pathway (22). Soluble (P)RR is considered to be secreted through the latter pathway and to be cleaved in the intracellular compartments of cells and secreted into the extracellular space over a short period of time without storage in post-Golgi vesicles (49). The expression level of (P)RR was not affected by renin stimulation (data not shown). ERK1/2 phosphorylation, inflammatory cytokine secretion, and *COX-2* expression were observed after renin stimulation. Thus (P)RR expressed by inflammatory cells is functionally active. In addition, (P)RR expression in infiltrating macrophages from the glomeruli and interstitium was observed in renal biopsy tissues from human crescentic GN. Feldt et al. showed ERK1/2 activation via (P)RR using various blockers, but not siRNA, in U937 cells. However, we used (P)RR siRNA and evaluated ERK1/2 phosphorylation in the same cell line.

To the best of our knowledge, this is the first study to demonstrate that functional (P)RR are expressed in a human monocyte cell line (13), primary isolated monocytes and lymphocytes, and infiltrating T cells and macrophages of ANCA-associated GN. Moreover, renin stimulation induced secretion of inflammatory cytokines and expression of *COX-2*, an important enzyme for the inflammatory reaction, independently of angiotensin receptors.

Previous studies showed a relationship between the RAS and immunoreactions. The RAS exerts a deleterious effect through the induction of inflammatory responses. Inflammatory cells such as macrophages and T cells were significant sources of tissue ACE and contributed to increased local ANG II in atherosclerotic plaques of human coronary arteries (11). Broad immunosuppression during ANG II-induced renal damage reduced albuminuria, inflammatory cell infiltration of the kidney, and renal structural damage through a blood pressure-independent mechanism (34). Furthermore, AT_1R is involved in the pathogenesis of glomerular injury in active immune complex-mediated GN. ACE inhibitors and ANG II receptor blocker could have renoprotective benefits such as the reduction of proteinuria, glomerular extracellular matrix deposition, mesan-

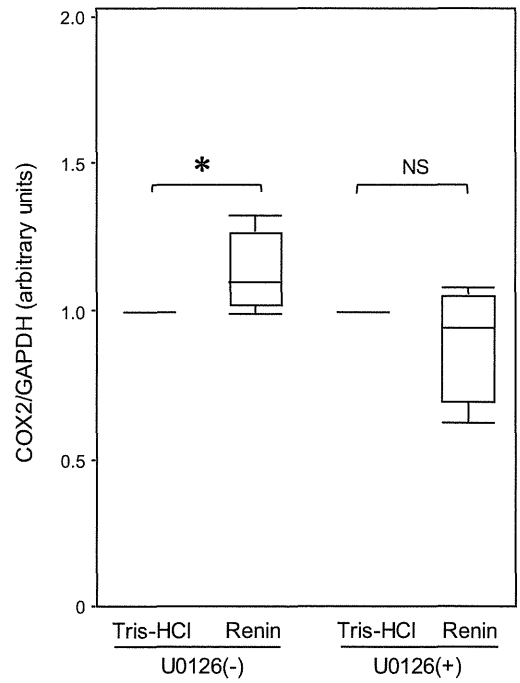

Fig. 7. Expression level of *cyclooxygenase-2* (*COX-2*) in human PBMCs. *COX-2* expression in PBMCs in 4 healthy subjects after renin stimulation is shown. *GAPDH* was used as an internal control. The expression of *COX-2* was significantly increased by renin stimulation, and this increase was inhibited in the presence of U0126, a specific ERK1/2 inhibitor. *$P < 0.05$.

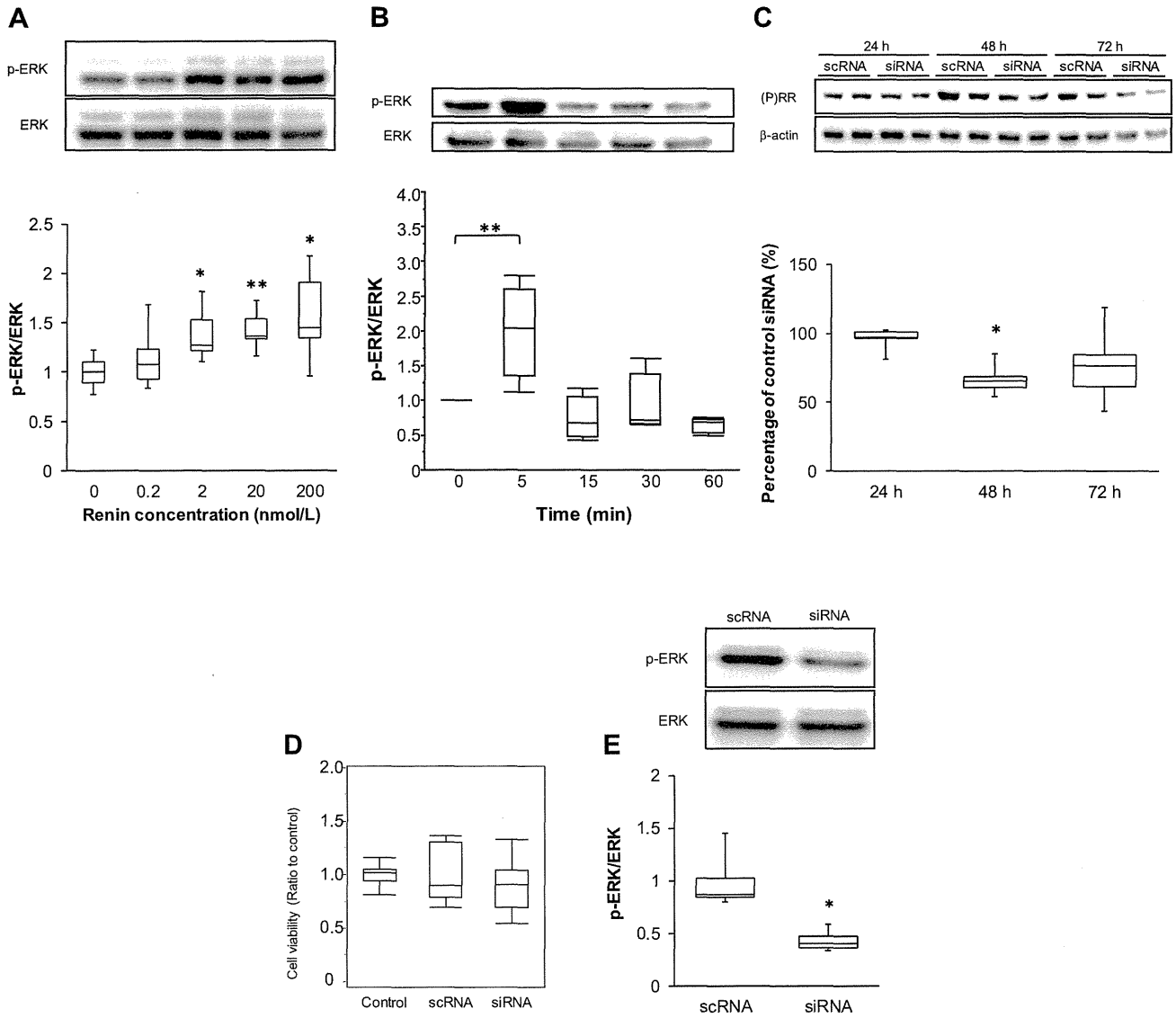

Fig. 8. ERK1/2 phosphorylation of U937 cells. *A*: U937 cells were incubated for 5 min in the presence of various concentrations of renin, and Western blotting was performed. Graphs show the ratio of p-ERK and total ERK in the presence of various concentrations of renin. Values are presented as the median (central line), interquartile range (box), and range (whiskers). $^{**}P < 0.01$ vs. 0 nmol/l. $^{*}P < 0.05$ vs. 0 nmol/l. *B*: U937 cells were incubated in the presence or absence of 20 nmol/l renin for the indicated times, and Western blotting was performed. Graphs show the ratio of p-ERK and total ERK in the presence of 20 nmol/l for the indicated times. Values are presented as the median (central line), interquartile range (box), and range (whiskers). $^{**}P < 0.01$ vs. 0 min. *C*: expression of (P)RR in U937 cells transfected with (P)RR small interfering RNA (siRNA) or nontargeting siRNA (scRNA). Values are presented as the median (central line), interquartile range (box), and range (whiskers). The levels of proteins were quantified by densitometric analysis. $^{*}P < 0.05$ compared with scRNA. *D*: cell viability in U937 cells with knocked down (P)RR by (4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide (MTT) assay. *E*: ERK1/2 phosphorylation by renin stimulation was decreased in (P)RR siRNA-transfected U937 cells. Values are presented as the median (central line), interquartile range (box), and range (whiskers). $^{*}P < 0.05$ compared with scRNA.

gial cell activation, and renal plasminogen activator inhibitor-1 (PAI-1) independently of blood pressure control (17). Moreover, ANG II induces various responses in human inflammatory cells, including NF-κB activation (24), chemotaxis in monocytes (23), and modulation of intracellular redox status in neutrophils (12) as well as upregulating tissue RAS levels that activate T cells (9). These results indicated the RAS is responsible for active GN and the immune responses derived from AT_1R signaling. In this study, immune responses such as ERK1/2 phosphorylation, cytokine release, and *COX-2* expression by renin stimulation in the presence of AT_1R and AT_2R blockers were observed in human inflammatory cells. We observed that induction of ERK1/2 phosphorylation was renin concentration dependent in the nanomolar range (Fig. 4*A*), as previously reported (13). However, plasma concentrations of prorenin and renin are in the picomolar range, and thus the interaction between renin/prorenin and (P)RR seems impossible except for renin/prorenin-synthesizing organs (25). (P)RR may contribute to the activation of the ERK1/2 pathway directly and induces cytokines release independently of the

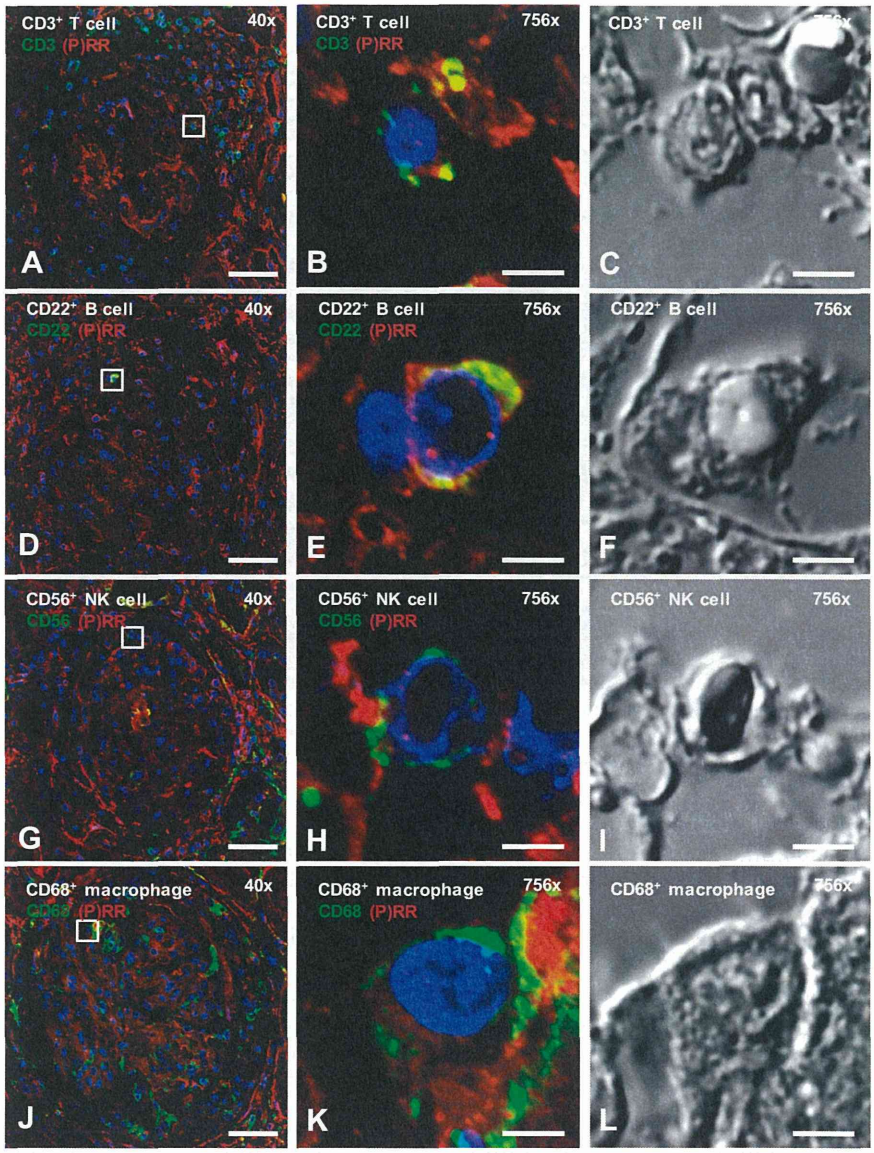

Fig. 9. Immunohistochemical study of (P)RR in human anti-neutrophil cytoplasmic antibody-associated crescentic glomerulonephritis. Low-power field (*left*) and high-power field (*middle*) show lymphocytes or macrophages stained with the indicated specific antibodies (green). *A* and *B*: $CD3^+$ T cells. *D* and *E*: $CD22^+$ B cells. *G* and *H*: $CD56^+$ NK cells. *J* and *K*: $CD68^+$ macrophages, (P)RR antibody (red), and 4,5-diamidino-2-phenylindole (DAPI; blue). *Right*: differential interference contrast of the same cross section with high-power field panels. (P)RR colocalized with $CD3^+$ T cells and $CD68^+$ monocytes. Scale bars = 50 μm (*A*, *D*, *G*, and *J*) and 5 μm (*B*, *C*, *E*, *F*, *H*, *I*, *K*, *L*).

ANG II generation pathway in PBMCs after infiltration of the kidney.

(P)RR is a 350-amino acid protein with a single transmembrane domain (36). When prorenin binds to (P)RR, it generates ANG I in the absence of cleavage of the prosegment (36), and directly activates MAPK ERK1/2 signaling in several cell types, including mesangial cells (21, 36), collecting duct cells (2), vascular smooth muscle cells (3, 14), monocytes(13), and neurons (8). A previous study suggested that direct renin/prorenin-induced ERK1/2 activation resulted in increased profibrotic gene expression, including TGF-β1 and PAI-1, and thereby increased cell proliferation (51). However, the activated ERK1/2 pathway in lymphocytes and monocytes induces secretion of cytokines including IL-6 and TNF-β in T cells (29) and IL-6 (27) and TNF-α (26) in monocytes. Moreover, ERK1/2 activation occurred in a rat Thy-1 model of mesangioproliferative nephritis, and blocking the ERK1/2 pathway resulted in a significant reduction of mesangial cell proliferation (5). In addition, ERK1/2 activation in human renal injury is associated with cell proliferation, histological deterioration, and renal dysfunction (31). In our study, all experiments were performed in the presence of an AT_1R blocker and AT_2R blocker. These blockers did not have any effect on ERK1/2 phosphorylation and completely blocked ERK1/2 phosphorylation via the renin/ANG II pathway (data not shown). These findings with our study showing that renin stimulation of PBMCs induces ERK1/2 phosphorylation, cytokine release and *COX-2* expression indicates (P)RR contributes to the pathophysiology of GN and renal injury via renin/prorenin-induced ERK1/2 activation.

The (P)RR expression level in monocytes was high in our study. Monocytes/macrophages have inflammatory roles in renal disease and are implicated in the induction of injury and fibrosis. Many human biopsy studies have shown glomerular or interstitial macrophages correlate with poor outcomes, including progression of disease, severity of histopathological pre-

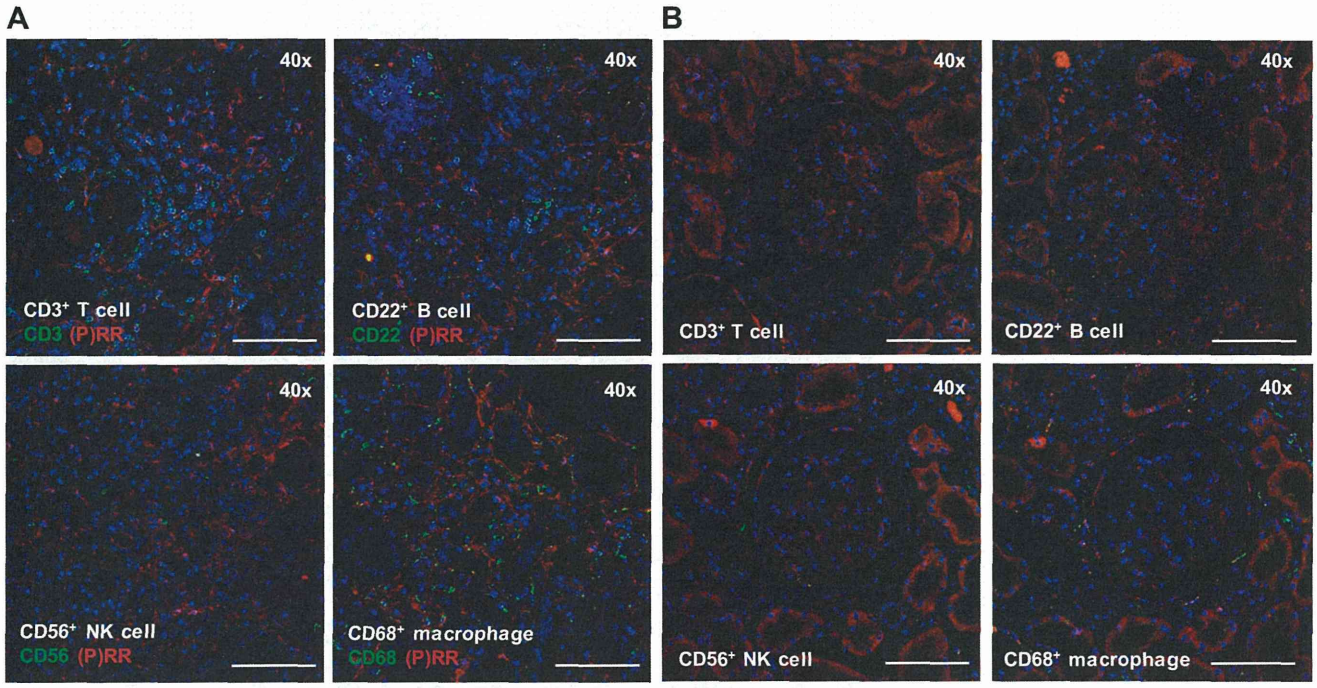

Fig. 10. Immunofluorescence of (P)RR in the tubulointerstitial area of human anti-neutrophil cytoplasmic antibody-associated crescentic glomerulonephritis (*A*) and human minimal-change nephrotic syndrome (*B*). Lymphocytes and monocytes were stained with specific antibodies for $CD3^+$ T cells, $CD22^+$ B cells, $CD56^+$ NK cells, and $CD68^+$ macrophages. (P)RR stained with (P)RR-specific antibody (red), and nuclei stained with DAPI (blue). Scale bars = 100 μm.

sentation, likelihood of future fibrosis, or tubular atrophy (4, 15). Through intracellular signaling pathways including MAPK, macrophages release several proinflammatory cytokines such as TNF-α and IL-6 and proinflammatory chemokines such as monocyte chemotactic protein (MCP), which is involved in the pathogenesis of crescentic GN (46). Ozawa et al. (38) demonstrated chronic ANG II infusion in rats activated MCP-1 and TGF-β1, which induced macrophage infiltration in renal tissues. Furthermore, TGF-β1 is also associated with crescent formation in GN (41), and MCP-1 and TGF-β1 release is mediated by the RAS. Further studies are required to determine whether MCP-1 and TGF-β1 are released by (P)RR stimulation.

In this study, we demonstrated that IL-6 was secreted from PBMCs stimulated by renin under AT_1R and AT_2R blockers. Actually, IL-6 was produced by a variety of cells including T cells and monocytes/macrophages (1, 45), and IL-6 could contribute to the pathogenesis or progression of the renal diseases (16). Moreover, the ERK1/2 pathway is considered to be important for the regulation of the production of IL-6 in the human kidney (28). Therefore, (P)RR expressed in lymphocytes and monocytes may be involved in immune inflammatory responses mediated by proinflammatory cytokines such as IL-6 via the ERK1/2 pathway. Moreover, we demonstrated that *COX-2*, an important enzyme for the inflammatory reaction, was increased by renin and suppressed under an ERK inhibitor in human PBMCs. These experiments were performed in the presence of AT_1R and AT_2R blockers. Thus these immunoreactions including cytokine release and *COX-2* expression were induced via (P)RR-mediated direct activation of the ERK1/2 pathway independently of ANG II in human primary PBMCs.

Finally, our flow cytometric data demonstrated that expression patterns of (P)RR in PBMCs differed among participants. Interestingly, some subjects had a higher percentage of (P)RR-positive cells than others (Fig. 3*C*). We did not identify specific characteristics, such as sex, age, habit, past history, shape of the body, or biomarkers that may have accounted for this difference. Therefore, the cause of different (P)RR expression levels is unclear and should be studied further. We also examined the relationship between T cell subpopulations and (P)RR expression because T cells have an important role in GN. However, we did not identify a significant correlation between T cell subpopulations and (P)RR expression.

Several limitations should be acknowledged. It was very difficult to transfect siRNA into human lymphocytes and monocytes and maintain cell viability. Our results also revealed that (P)RR expression in monocytes was high and that (P)RR was expressed by ANCA-associated GN-infiltrating macrophages. Therefore, we used a human leukemic monocyte lymphoma cell line, U937 cells, to overcome these issues. Moreover, we showed that (P)RR was expressed in lymphocytes and macrophages infiltrating in GN. However, the number of samples was insufficient, and the pathophysiological functions of (P)RR in GN are still unclear. We examined the expression of (P)RR in PBMCs from healthy subjects, and future studies should investigate (P)RR expression in GN patients. Although the role of soluble (P)RR in inflammation is unclear, there is no currently available antibody that fully discriminates the soluble and full-length forms of (P)RR. In addition, further investigations using larger human sample sizes and various disease conditions, and animal models of GN such as ANCA-treated or transgenic mice models, are required

to clarify the association of lymphocyte (P)RR expression and the immune system.

In conclusion, the present study demonstrated for the first time that functional (P)RR is expressed by human immune cells, especially monocytes and NK cells, and is expressed in infiltrating lymphocytes and macrophages during active GN such as ANCA-associated GN. These findings indicate that (P)RR contributes to inflammation as a RAS component during active GN, independently of the AT_1R pathway.

ACKNOWLEDGMENTS

The authors are grateful to the Biomedical Research Unit of Tohoku University Hospital and Center of Research Instruments of Institute of Development, Aging and Cancer of Tohoku University for use of their equipment. We thank Dr. Tomokazu Souma, Chika Takahashi, Prof. Hironobu Sasano, and the staff members of the Department of Pathology, Tohoku University Graduate School of Medicine for technical assistance.

GRANTS

This study was supported in part by Grants for Scientific Research (21390259, 22659164, 23300243, 23790242, 25461205, and 25860156) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in Japan; Network Medicine Global-COE Program from the MEXT in Japan; the Japan Society for the Promotion of Science (JSPS), and the Institut National de la Santé et de la Recherche Médicale (INSERM) under the Japan-France Research Cooperative Program; and a Banyu Foundation Research Grant.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: K.N., T.H., E.S., and T.M. provided conception and design of research; K.N., T.H., E.S., K.K., M.I., and K.T. performed experiments; K.N., T.H., and E.S. analyzed data; K.N., T.H., E.S., and T.I. interpreted results of experiments; K.N., T.H., and E.S. prepared figures; K.N., T.H., and E.S. drafted manuscript; K.N., T.H., E.S., T.M., A.I., G.N., H.S., and S.I. edited and revised manuscript; K.N., T.H., and E.S. approved final version of manuscript.

REFERENCES

1. **Aarden LA, De Groot ER, Schaap OL, Lansdorp PM.** Production of hybridoma growth factor by human monocytes. *Eur J Immunol* 17: 1411–1416, 1987.
2. **Advani A, Kelly DJ, Cox AJ, White KE, Advani SL, Thai K, Connelly KA, Yuen D, Trogadis J, Herzenberg AM, Kuliszewski MA, Leong-Poi H, Gilbert RE.** The (Pro)renin receptor: site-specific and functional linkage to the vacuolar H+-ATPase in the kidney. *Hypertension* 54: 261–269, 2009.
3. **Batenburg WW, Lu X, Leijten F, Maschke U, Muller DN, Danser AH.** Renin- and prorenin-induced effects in rat vascular smooth muscle cells overexpressing the human (pro)renin receptor: does (pro)renin-(pro)renin receptor interaction actually occur? *Hypertension* 58: 1111–1119, 2011.
4. **Bohle A, Wehrmann M, Bogenschutz O, Batz C, Vogl W, Schmitt H, Muller CA, Muller GA.** The long-term prognosis of the primary glomerulonephritides. A morphological and clinical analysis of 1747 cases. *Pathol Res Pract* 188: 908–924, 1992.
5. **Bokemeyer D, Panek D, Kramer HJ, Lindemann M, Kitahara M, Boor P, Kerjaschki D, Trzaskos JM, Floege J, Ostendorf T.** In vivo identification of the mitogen-activated protein kinase cascade as a central pathogenic pathway in experimental mesangioproliferative glomerulonephritis. *J Am Soc Nephrol* 13: 1473–1480, 2002.
6. **Boyum A.** Isolation of leucocytes from human blood. A two-phase system for removal of red cells with methylcellulose as erythrocyte-aggregating agent. *Scand J Clin Lab Invest Suppl* 97: 9–29, 1968.
7. **Brasier AR, Recinos A, 3rd, Eledrisi MS.** Vascular inflammation and the renin-angiotensin system. *Arterioscler Thromb Vasc Biol* 22: 1257–1266, 2002.
8. **Contrepas A, Walker J, Koulakoff A, Franek KJ, Qadri F, Giaume C, Corvol P, Schwartz CE, Nguyen G.** A role of the (pro)renin receptor in neuronal cell differentiation. *Am J Physiol Regul Integr Comp Physiol* 297: R250–R257, 2009.
9. **Coppo M, Boddi M, Bandinelli M, Degl'innocenti D, Ramazzotti M, Marra F, Galastri S, Abbate R, Gensini GF, Poggesi L.** Angiotensin II upregulates renin-angiotensin system in human isolated T lymphocytes. *Regul Pept* 151: 1–6, 2008.
10. **Cousin C, Bracquart D, Contrepas A, Corvol P, Muller L, Nguyen G.** Soluble form of the (pro)renin receptor generated by intracellular cleavage by furin is secreted in plasma. *Hypertension* 53: 1077–1082, 2009.
11. **Diet F, Pratt RE, Berry GJ, Momose N, Gibbons GH, Dzau VJ.** Increased accumulation of tissue ACE in human atherosclerotic coronary artery disease. *Circulation* 94: 2756–2767, 1996.
12. **El Bekay R, Alvarez M, Monteseirin J, Alba G, Chacon P, Vega A, Martin-Nieto J, Jimenez J, Pintado E, Bedoya FJ, Sobrino F.** Oxidative stress is a critical mediator of the angiotensin II signal in human neutrophils: involvement of mitogen-activated protein kinase, calcineurin, and the transcription factor NF-kappaB. *Blood* 102: 662–671, 2003.
13. **Feldt S, Batenburg WW, Mazak I, Maschke U, Wellner M, Kvakan H, Dechend R, Fiebeler A, Burckle C, Contrepas A, Jan Danser AH, Bader M, Nguyen G, Luft FC, Muller DN.** Prorenin and renin-induced extracellular signal-regulated kinase 1/2 activation in monocytes is not blocked by aliskiren or the handle-region peptide. *Hypertension* 51: 682–688, 2008.
14. **Feldt S, Maschke U, Dechend R, Luft FC, Muller DN.** The putative (pro)renin receptor blocker HRP fails to prevent (pro)renin signaling. *J Am Soc Nephrol* 19: 743–748, 2008.
15. **Ferrario F, Castiglione A, Colasanti G, Barbiano di Belgioioso G, Bertoli S, D'Amico G.** The detection of monocytes in human glomerulonephritis. *Kidney Int* 28: 513–519, 1985.
16. **Fukatsu A, Matsuo S, Tamai H, Sakamoto N, Matsuda T, Hirano T.** Distribution of interleukin-6 in normal and diseased human kidney. *Lab Invest* 65: 61–66, 1991.
17. **Guo S, Kowalewska J, Wietecha TA, Iyoda M, Wang L, Yi K, Spencer M, Banas M, Alexandrescu S, Hudkins KL, Alpers CE.** Renin-angiotensin system blockade is renoprotective in immune complex-mediated glomerulonephritis. *J Am Soc Nephrol* 19: 1168–1176, 2008.
18. **Herlitz H, Tarkowski A, Svalander C, Volkmann R, Westberg G.** Beneficial effect of captopril on systemic lupus erythematosus-like disease in MRL lpr/lpr mice. *Int Arch Allergy Appl Immunol* 85: 272–277, 1988.
19. **Hirose T, Hashimoto M, Totsune K, Metoki H, Asayama K, Kikuya M, Sugimoto K, Katsuya T, Ohkubo T, Hashimoto J, Rakugi H, Takahashi K, Imai Y.** Association of (pro)renin receptor gene polymorphism with blood pressure in Japanese men: the Ohasama study. *Am J Hypertens* 22: 294–299, 2009.
20. **Hirose T, Hashimoto M, Totsune K, Metoki H, Hara A, Satoh M, Kikuya M, Ohkubo T, Asayama K, Kondo T, Kamide K, Katsuya T, Ogihara T, Izumi S, Rakugi H, Takahashi K, Imai Y.** Association of (pro)renin receptor gene polymorphisms with lacunar infarction and left ventricular hypertrophy in Japanese women: the Ohasama study. *Hypertens Res* 34: 530–535, 2011.
21. **Huang Y, Wongamorntham S, Kasting J, McQuillan D, Owens RT, Yu L, Noble NA, Border W.** Renin increases mesangial cell transforming growth factor-beta1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. *Kidney Int* 69: 105–113, 2006.
22. **Kelly RB.** Pathways of protein secretion in eukaryotes. *Science* 230: 25–32, 1985.
23. **Kintscher U, Wakino S, Kim S, Fleck E, Hsueh WA, Law RE.** Angiotensin II induces migration and Pyk2/paxillin phosphorylation of human monocytes. *Hypertension* 37: 587–593, 2001.
24. **Kranzhofer R, Browatzki M, Schmidt J, Kubler W.** Angiotensin II activates the proinflammatory transcription factor nuclear factor-kappaB in human monocytes. *Biochem Biophys Res Commun* 257: 826–828, 1999.
25. **Krop M, Lu X, Danser AH, Meima ME.** The (pro)renin receptor. A decade of research: what have we learned? *Pflügers Arch* 465: 87–97, 2013.
26. **Kurihara Y, Nakahara T, Furue M.** alphaVbeta3-integrin expression through ERK activation mediates cell attachment and is necessary for production of tumor necrosis factor alpha in monocytic THP-1 cells stimulated by phorbol myristate acetate. *Cell Immunol* 270: 25–31, 2011.
27. **Lee CL, Lam EY, Lam KK, Koistinen H, Seppala M, Ng EH, Yeung WS, Chiu PC.** Glycodelin-A stimulates interleukin-6 secretion by human

monocytes and macrophages through L-selectin and the extracellular signal-regulated kinase pathway. *J Biol Chem* 287: 36999–37009, 2012.
28. **Leonard M, Ryan MP, Watson AJ, Schramek H, Healy E.** Role of MAP kinase pathways in mediating IL-6 production in human primary mesangial and proximal tubular cells. *Kidney Int* 56: 1366–1377, 1999.
29. **Li T, Sun M, Yin X, Wu C, Wu Q, Feng S, Li H, Luan Y, Wen J, Yan L, Zhao B, Xu C, Sun Y.** Expression of the calcium sensing receptor in human peripheral blood T lymphocyte and its contribution to cytokine secretion through MAPKs or NF-kappaB pathways. *Mol Immunol* 53: 414–420, 2013.
30. **Martinez FO, Helming L, Gordon S.** Alternative activation of macrophages: an immunologic functional perspective. *Annu Rev Immunol* 27: 451–483, 2009.
31. **Masaki T, Stambe C, Hill PA, Dowling J, Atkins RC, Nikolic-Paterson DJ.** Activation of the extracellular-signal regulated protein kinase pathway in human glomerulopathies. *J Am Soc Nephrol* 15: 1835–1843, 2004.
32. **Mehta PK, Griendling KK.** Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. *Am J Physiol Cell Physiol* 292: C82–C97, 2007.
33. **Mosser DM, Edwards JP.** Exploring the full spectrum of macrophage activation. *Nat Rev Immunol* 8: 958–969, 2008.
34. **Muller DN, Shagdarsuren E, Park JK, Dechend R, Mervaala E, Hampich F, Fiebeler A, Ju X, Finckenberg P, Theuer J, Viedt C, Kreuzer J, Heidecke H, Haller H, Zenke M, Luft FC.** Immunosuppressive treatment protects against angiotensin II-induced renal damage. *Am J Pathol* 161: 1679–1693, 2002.
35. **Nguyen G.** Renin and prorenin receptor in hypertension: what's new? *Curr Hypertens Rep* 13: 79–85, 2011.
36. **Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD.** Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 109: 1417–1427, 2002.
37. **Ootaka T, Saito T, Soma J, Yoshinaga K.** Analysis of leukocyte surface antigens on ethanol-fixed paraffin-embedded tissue material. *J Immunol Methods* 131: 183–193, 1990.
38. **Ozawa Y, Kobori H, Suzaki Y, Navar LG.** Sustained renal interstitial macrophage infiltration following chronic angiotensin II infusions. *Am J Physiol Renal Physiol* 292: F330–F339, 2007.
39. **Rasini E, Cosentino M, Marino F, Legnaro M, Ferrari M, Guasti L, Venco A, Lecchini S.** Angiotensin II type 1 receptor expression on human leukocyte subsets: a flow cytometric and RT-PCR study. *Regul Pept* 134: 69–74, 2006.
40. **Rastaldi MP, Ferrario F, Tunesi S, Yang L, D'Amico G.** Intraglomerular and interstitial leukocyte infiltration, adhesion molecules, and interleukin-1 alpha expression in 15 cases of antineutrophil cytoplasmic autoantibody-associated renal vasculitis. *Am J Kidney Dis* 27: 48–57, 1996.
41. **Shimizu M, Kondo S, Urushihara M, Takamatsu M, Kanemoto K, Nagata M, Kagami S.** Role of integrin-linked kinase in epithelial-mesenchymal transition in crescent formation of experimental glomerulonephritis. *Nephrol Dial Transplant* 21: 2380–2390, 2006.
42. **Takahashi K, Hiraishi K, Hirose T, Kato I, Yamamoto H, Shoji I, Shibasaki A, Kaneko K, Satoh F, Totsune K.** Expression of (pro)renin receptor in the human brain and pituitary, and co-localisation with arginine vasopressin and oxytocin in the hypothalamus. *J Neuroendocrinol* 22: 453–459, 2010.
43. **Takahashi K, Kikuchi K, Maruyama Y, Urabe T, Nakajima K, Sasano H, Imai Y, Murakami O, Totsune K.** Immunocytochemical localization of adrenomedullin 2/intermedin-like immunoreactivity in human hypothalamus, heart and kidney. *Peptides* 27: 1383–1389, 2006.
44. **Takahashi K, Totsune K, Murakami O, Saruta M, Nakabayashi M, Suzuki T, Sasano H, Shibahara S.** Expression of urocortin III/stresscopin in human heart and kidney. *J Clin Endocrinol Metab* 89: 1897–1903, 2004.
45. **Van Snick J, Cayphas S, Vink A, Uyttenhove C, Coulie PG, Rubira MR, Simpson RJ.** Purification and NH2-terminal amino acid sequence of a T-cell-derived lymphokine with growth factor activity for B-cell hybridomas. *Proc Natl Acad Sci USA* 83: 9679–9683, 1986.
46. **Wada T, Furuichi K, Sakai N, Iwata Y, Yoshimoto K, Shimizu M, Kobayashi K, Mukaida N, Matsushima K, Yokoyama H.** A new anti-inflammatory compound, FR167653, ameliorates crescentic glomerulonephritis in Wistar-Kyoto rats. *J Am Soc Nephrol* 11: 1534–1541, 2000.
47. **Weiss D, Kools JJ, Taylor WR.** Angiotensin II-induced hypertension accelerates the development of atherosclerosis in apoE-deficient mice. *Circulation* 103: 448–454, 2001.
48. **Wilde B, Thewissen M, Damoiseaux J, van Paassen P, Witzke O, Tervaert JW.** T cells in ANCA-associated vasculitis: what can we learn from lesional versus circulating T cells? *Arthritis Res Ther* 12: 204, 2010.
49. **Yoshikawa A, Aizaki Y, Kusano K, Kishi F, Susumu T, Iida S, Ishiura S, Nishimura S, Shichiri M, Senbonmatsu T.** The (pro)renin receptor is cleaved by ADAM19 in the Golgi leading to its secretion into extracellular space. *Hypertens Res* 34: 599–605, 2011.
50. **Zhang J, Noble NA, Border WA, Owens RT, Huang Y.** Receptor-dependent prorenin activation and induction of PAI-1 expression in vascular smooth muscle cells. *Am J Physiol Endocrinol Metab* 295: E810–E819, 2008.
51. **Zhang J, Wu J, Gu C, Noble NA, Border WA, Huang Y.** Receptor-mediated nonproteolytic activation of prorenin and induction of TGF-beta1 and PAI-1 expression in renal mesangial cells. *Am J Physiol Renal Physiol* 303: F11–F20, 2012.

厚生労働科学研究費補助金　難治性疾患等政策研究事業（難治性疾患政策研究事業）

資　料

市民公開講座

「腎臓病・糖尿病に負けない生き方」

～腎臓病・糖尿病とともに生きる～

腎臓病の症状は悪くなってもあまり自覚症状がなく見過ごされるケースが多くあります。
腎臓病の早期発見と治療を呼びかける専門医による講演会を開催します。
日常の注意点から治療方法まで、役立つ情報が満載です。

とき 9/20(日)
12:00開場　13:00開演
［15:20終了予定］

ところ 朝日ホール
名古屋市中区栄1-3-3 朝日会館15階
＊地下鉄東山線・鶴舞線「伏見」駅下車
7番出口を西へ徒歩3分
＊JR「名古屋」駅下車徒歩15分


坪井 直毅先生


和田 隆志先生


丸山 彰一先生


武藤　智先生


小関 裕二先生


田中 文彦先生

プログラム

●開会挨拶　名古屋大学 総長 松尾 清一先生

講演1「気にしていますか、あなたの腎臓」(15分)
名古屋大学 腎臓内科 講師 坪井 直毅先生

講演2「糖尿病からあなたの腎臓を守りましょう!」(20分)
金沢大学大学院 血液情報統御学 教授 和田 隆志先生

講演3「腎炎・ネフローゼと言われたら」(20分)
名古屋大学 腎臓内科 准教授 丸山 彰一先生

～ 休　憩 (20分) ～

講演4「多発性嚢胞腎(のうほうじん)ってどんな病気?」(20分)
帝京大学 准教授 武藤　智先生

講演5「体験! あなたにもできる簡単エクササイズ」(20分)
増子記念病院 リハビリテーション科 課長 小関 裕二先生

講演6「これだけは知っておきたい! 腎臓にやさしい食事」(20分)
名古屋大学 栄養管理部 田中 文彦先生

※プログラム及び講師につきましては変更する場合もありますので、あらかじめご了承ください。

応募方法

郵便番号、住所、氏名、年齢、電話番号、参加希望人数(5名様まで)を明記の上、往復はがき、FAX、e-mailのいずれかで下記のあて先までお送りください。
※往復はがきで応募の方は、返信用はがきにもあなたの郵便番号、住所、氏名を記入。

あて先

◎往復はがき 〒466-8550
名古屋市昭和区鶴舞 65 番地
名古屋大学医学部附属病院 腎臓内科
「腎臓病・糖尿病セミナー」係

◎FAX 052-744-2209

◎e-mail
jin-shogai@med.nagoya-u.ac.jp

※応募締め切り／9月11日(金)必着

応募多数の場合は抽選とします。
当選者の発表は招待状の発送をもってかえさせていただきます。
※お送りいただきました個人情報は、名古屋大学でとりまとめ、案内状の発送および個人を特定しないデータとして利用させていただきます。

300名様無料ご招待!
この機会にぜひご参加ください!

お問い合わせ先

名古屋大学医学部附属病院 腎臓内科
TEL(052)741-2111(代表)
◎9:00～17:00(土・日・祝を除く)

◎主催　厚生労働科学研究費補助金難治性疾患等政策研究事業(難治性疾患政策研究事業)「難治性腎疾患に関する調査研究」班／日本医療研究開発機構研究費(難治性疾患等実用化研究事業(腎疾患実用化研究事業))「糖尿病性腎症の進展予防にむけた病期分類―病理―バイオマーカーを統合した診断法の開発」班／日本慢性腎臓病対策協議会(J-CKDI)
◎後援　朝日新聞社広告局

http://jin-shogai.jp/mt/public/hp/

厚生労働科学研究費補助金難治性疾患政策研究事業

難治性腎疾患に関する調査研究

お問い合わせフォーム

文字サイズを変更 | 小 | 中 | 大 |

【IgA腎症・急速進行性糸球体腎炎・ネフローゼ症候群・多発性嚢胞腎】症例数が少なく、原因が不明で、治療法が確立されていない疾患で、長期間生活に支障を及ぼすものについて、研究班を設置し、原因の究明・治療法の確立に取り組む、厚生労働省の事業。

HOME　　前のページへ戻る

検索

メインメニュー

- 01-研究班のご紹介(2)
- 02-研究班班長のご挨拶(1)
- 03-研究協力者一覧(13)
- 04-活動予定・報告(2)
- 05-診断の治療指針(医療従事者向け)(4)
- 06-研究班の業績(1)
- 07-患者様向けQ&A(4)
- 08-リンク(1)
- 09-臨床研究(1)
- 10-研究成果報告(1)
- 11-お知らせ

最近のブログ記事

- 小児慢性腎臓病患者における 移行医療についての提言(8 /27)
- エビデンスに基づく診療ガイドライン2014 英語版(8 /25)
- ◆研究管理推進委員会(8 /25)

【病気の解説】

- IgA腎症 IgA nephropathy
- 急速進行性糸球体腎炎 Rapidly progressive glomerulonephritis; RPGN
- ネフローゼ症候群 Nephrotic syndrome
- 多発性嚢胞腎 Polycystic kidney disease

症例数が少なく、原因が不明で、治療法が確立されていない疾患で、長期間生活に支障を及ぼすものについて、研究班を設置し、原因の究明・治療法の確立に取り組む、厚生労働省の事業。 → 詳細を見る

小児慢性腎臓病患者における 移行医療についての提言

■小児慢性腎臓病患者における移行医療についての提言
－思春期・若年成人に適切な医療を提供するために－
→こちらをご覧下さい(PDFファイル)

2015年8月27日

エビデンスに基づく診療ガイドライン2014 英語版

■IgA 腎症
Evidence-Based Clinical Practice Guidelines for IgA Nephropathy 2014
→こちらをご覧下さい(PDFファイル)

■急速進行性糸球体腎炎
Evidence-Based Clinical Practice Guidelines for Rapidly Progressive Glomerulonephritis 2014
→こちらをご覧下さい(PDFファイル)

難治性腎疾患に関する調査研究班 班長 丸山彰一

国民の皆さんや腎臓病と闘っておられる患者さんに貢献できるよう、活動しています。

→ 研究班班長のご挨拶

月別アーカイブ

- 2015年8月(3)
- 2014年12月(12)
- 2013年7月(1)
- 2013年2月(2)
- 2012年11月(1)
- 2012年9月(1)
- 2012年3月(6)
- 2012年2月(4)
- 2012年1月(1)

患者様向けQ&A

診断の治療指針(医療従事者向け)