Podocyte Migration during Nephrotic Syndrome Requires a Coordinated Interplay between Cathepsin L and α3 Integrin*

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Jochen Reiser,a,b Jun Oh,a,c,d Isao Shirato,a,* Katsuhiko Asanuma,a,c,e Andreas Hug,f
Thomas M. Mundel,f Karen Honey,f Kazumi Ishidoh,f Eiki Kominami,j Jordan A. Kreidberg,f
Yasuhiko Tomino,e and Peter Mundela,b,h

From the aDepartments of Medicine, bAnatomy and Structural Biology, Albert Einstein College of Medicine, Bronx, New York 10461, the Departments of cMedicine and dBiochemistry, Juntendo University, Tokyo 113-8421, Japan, the eDepartment of Neurology, University of Heidelberg, 69120 Heidelberg, Germany, the fDepartment of Surgery, University of Muenster, 48149 Muenster, Germany, the gDepartment of Immunology, University of Washington, Seattle, Washington 98195, and the hDepartment of Medicine, Children’s Hospital, Boston, Massachusetts 02115

Podocyte foot process effacement and disruption of the slit diaphragm are typically associated with glomerular proteinuria and can be induced in rats by the injection of puromycin aminonucleoside. Here, we show that the induction of puromycin aminonucleoside nephrosis involves podocyte migration conducted by a coordinated interplay between the cysteine protease cathepsin L and α3 integrin. Puromycin aminonucleoside treatment up-regulates cathepsin L expression in podocytes in vivo as well as expression and enzymatic activity of cathepsin L in podocytes in vitro. Isolated podocytes from mice lacking cathepsin L are protected from cell pyrocytin aminonucleoside-induced cell detachment. The functional significance of cathepsin L expression was underscored by the observation that puromycin aminonucleoside-induced cell migration was slowed down in cathepsin L-deficient podocytes and by the preservation of cell-cell contacts and expression of vital slit diaphragm protein CD2AP. Cathepsin L expression and activity were induced in podocytes lacking α3 integrin. Similarly, acute functional inhibition of α3 integrin in wild type podocytes with a blocking antibody increased the expression of cathepsin L activity. Down-regulation of α3 integrin protected against puromycin aminonucleoside-induced podocyte detachment. In summary, these data establish that podocyte foot process effacement is a migratory event involving a novel interplay between cathepsin L and α3 integrin.

Glomerular podocytes serve as a final barrier to urinary protein loss by the formation and maintenance of podocyte foot processes and the interposed slit diaphragm (SD). All forms of nephrotic syndrome are characterized by podocyte foot process (FP) effacement and/or molecular reorganization of the slit diaphragm (1). FP effacement requires a precise interplay of multiple cellular functions including structural alterations of the cytoskeleton, movement of FP over the basement membrane, and reconstruction of the slit diaphragm (1). The discovery of several novel podocyte proteins and their mutation analysis including nephrin (2), CD2AP (3), α-actinin-4 (4), podocin (5), nephrin (6), and FAT (7) have shed light on the pathogenesis of FP effacement and proteinuria and emphasized the critical role of podocyte FP and the SD in maintaining the function of the glomerular filtration barrier.

Cathepsin L is a lysosomal protease that plays an important role in the intracellular protein degradation, activation of enzyme precursors, and tumor invasion (8, 9). Normally located in lysosomes of mammalian cells, it can be secreted from the cell under certain conditions. At present, the cathepsin family contains the serine proteases (cathepsins A and G) and the asparagine proteases (cathepsins D and E). Some cathepsins also belong to cysteine proteinases, e.g. cathepsin L. All these enzymes exist in their processed form as disulfide-linked heavy and light chain subunits with molecular masses ranging from 20 to 35 kDa. Cathepsin C is the noted exception, existing as an oligomeric enzyme with a molecular mass of ~200 kDa. Secreted forms of cathepsins are critical for degradation of the extracellular matrix during an inflammatory or adaptive response to process the environment for the new condition (10). Under normal conditions, podocytes express low levels of cathepsin L in their lysosomes (11).

Podocyte FPs form a scaffolding around the capillary loops that are anchored to the glomerular basement membrane (GBM) via α3β1 integrin (12) and α/β-dystroglycans (13, 14). α3β1 integrin represents a receptor for certain isoforms of laminin, including laminin-5 in the epidermal basement membrane and laminin-10/11 in the GBM (15). In podocytes, α3β1 integrin is expressed at the basal side of FP. Podocytes of α3 integrin-deficient (α3−/−) mice bear a strong morphological resemblance to podocytes in congenital nephrotic syndrome and other pathologic conditions with FP effacement (15, 16). The α3 integrin deletion therefore represents a genetic model system that allows the analysis of the molecular basis of FP assembly and dynamics.

Similar to the inactivation of the α3 integrin gene, a single injection of puromycin aminonucleoside (PAN) induces reversible nephritic syndrome with podocyte FP effacement and proteinuria in rats (17) and mice (18). In vitro, puromycin leads to the reorganization of the actin cytoskeleton, focal contacts, and...
EXPERIMENTAL PROCEDURES

**Differential Display PCR of Puromycin Aminonucleoside Nephrosis—** Male adult Sprague-Dawley rats (body weight, 200 g) were treated with a single intraperitoneal injection of PAN (15 mg/100 g of body weight, Sigma) (21). Proteinuria reached the maximum on day 8 and declined gradually thereafter as described before (22). Kidneys were harvested 8 (maximum of proteinuria) and 28 days (return of proteinuria to baseline levels) after the injection of PAN and 8 days after the injection of PBS. 10 rats were used in each group. Total RNA was prepared from homogenized glomeruli, and differential display PCR was performed exactly as described before (23).

**Northern Blot Analysis—** Total RNA was prepared from isolated glomeruli with the RNaseasy kit (Qiagen) according to the manufacturer's instructions. Poly(A)+ mRNA was purified with the Oligotex mRNA purification kit (Qiagen), separated on a 1.2% denaturing formaldehyde gel, and transferred onto GeneScreen Plus membranes (PerkinElmer Life Sciences). Northern blot analyses were done with a 32P-labeled probe (23). Protein expression and function were due to the absence of \(\alpha_3\) integrin.

**Cell Culture—** Wild type podocytes were cultured as described (25). \(\alpha_3\) integrin-deficient (\(\alpha_3^{-/-}\)) conditionally immortalized podocyte cell lines were generated by intercrossing the Immortomouse carrying a temperature-sensitive T-antigen as a control. The banding pattern of anchored primer A and B was used to confirm the identity of the samples. Each experiment was carried out in three independent sets of experiments and visualized using enhanced chemiluminescence (ECL) immunoblot detection kits (Amersham Biosciences) (24). The rabbit polyclonal anti-mouse synaptopodin antibody was used as described before (24). Anti-\(\alpha_2\) tubulin was purchased from Sigma. Mouse monoclonal anti-human \(\alpha_3\) integrin (P1B5) was obtained from Chemicon (Temecula, CA). The functional activity of P1B5 to block ligand interaction in living cells was visualizing with cresyl violet as a substrate (36).

**Integrin Inhibition Assay—** Reversible functional blocking of \(\alpha_3\) integrin was done as described by Wei et al. (31). In brief, \(\alpha_3\) integrin deficient podocyte rescued by human \(\alpha_3\) integrin expression, and differentiated wild type podocytes were incubated with P1B5 monoclonal antibody (5 \(\mu\)g/ml) for 1 h at 37 °C. Then, the activity of cathepsin L was analyzed in living cells using fluorophore cresyl violet as a substrate (36). In control experiments, mouse monoclonal anti-synaptopodin was used.

**RESULTS**

**Reversible Up-regulation of Cathepsin L mRNA during PAN Nephrosis—** To explore changes in glomerular gene expression during PAN nephrosis, differential display-PCR was performed using RNA from isolated rat glomeruli harvested 8 (peak of FP effacement and proteinuria) and 28 days (return to baseline) after the injection of PAN. RNA from PBS-treated rats served as a control. The banding pattern of anchored primer A and random primer 23 revealed a PCR product that was absent in the control group, up-regulated in the 8-day PAN group, and decreased in the 28-day PAN group (Fig. 1a, left panels). Since we were interested in genes associated with the onset and regression of FP effacement and proteinuria, this PCR product was further characterized. The 468-bp PCR product was identical with the 3′ end of rat cathepsin L mRNA. The differential expression of cathepsin L in PAN nephrosis was confirmed by Northern blot (Fig. 1a, right panels). When compared with PBS controls, cathepsin L was strongly up-regulated at day 8 after PAN treatment and decreased to baseline expression levels at day 28 (Fig. 1a, right panels).

**Cathepsin L Protein Expression Is Up-regulated in Glomerular Podocytes following PAN Injection in Vivo—** To test whether the induction of cathepsin L mRNA expression was accompanied by an increased protein expression and to determine the intraglomerular distribution of cathepsin L, double labeling immunohistochemistry with the podocyte marker synaptopodin (24) was performed. Cathepsin L was only weakly expressed in glomeruli of PBS-treated rats (Fig. 1b). On day 4 after PAN injection, cathepsin L expression was significantly increased in podocytes as shown by co-localization with synaptopodin (Fig. 1c). Podocyte cathepsin L staining was strongest on day 8 after PAN exposure (Fig. 1d) and decreased thereafter to near baseline expression levels at day 28 (Fig. 1e).

**PAN Increases Cathepsin L Expression and Activity in Cultured Podocytes—** To explore the functional significance of
podocyte cathepsin L expression, we analyzed the expression and activity of cathepsin L in cultured podocytes. By Western blot, a single 22-kDa band was observed in non-treated podocytes (Fig. 2a) that corresponds to the intralysosomal processed form of cathepsin L (37). After treatment with PAN for 72 h, we found a strong up-regulation of cathepsin L and the induction of the 45-kDa non-processed pro-enzyme procathepsin L (38). Equal protein load was confirmed by reprobing the membrane with anti-α-tubulin (Fig. 2a). In controls, cathepsin L was weakly expressed in perinuclear vesicles (Fig. 2b, left panel). PAN-treated podocytes showed a strong cathepsin L staining throughout the entire cytoplasm (Fig. 2b, right panel). To test whether the up-regulation of cathepsin L protein expression was accompanied by an increased enzyme activity, we measured total cellular cathepsin L activity (35). Cathepsin L activity in PAN-treated podocytes was significantly increased at 30 min (control, 7478 activity units; PAN, 9615 activity units; increase 28.3%, p < 0.05) and 45 min (control, 9404 activity units; PAN, 12071 activity units; increase 28.5%, p < 0.05) (Fig. 2c). Next, to visualize the subcellular sites of cathepsin L activity, we used a fluorogenic substrate CV-(FR)2, which emits fluorescence light upon cleavage by cathepsin L (36). In non-treated podocytes, we found a low baseline activity in lysosomes (Fig. 2d, left panel). In PAN-treated podocytes, we observed increased activity extending far into podocyte processes (Fig. 2d, right panel).

**The Lack of Cathepsin L Ameliorates PAN-induced Podocyte Detachment and Slows Down Cell Migration**—The substantial changes in cathepsin L expression and activity after treatment of podocytes with PAN prompted us to explore how cathepsin L deficiency modulates the effects of PAN on podocytes. Therefore, we compared cell adhesion in primary podocyte cultures from wild type and cat L−/− mice (28). Although there was no significant difference between PAN-treated wild type and cat L−/− podocytes at 24 h after PAN treatment, we noted a significant difference in cell adhesion after 48 h (Fig. 3a). At this time, 95% of cat L−/− podocytes were still attached when compared with 89% of wild type podocytes (p < 0.01). This difference became even more obvious at 72 h (cat L−/−, 74%, wild type, 54%; p < 0.0001). These data suggest an anti-adhesive effect of cathepsin L. Since detachment of cells requires cell movement and migration (39), we next analyzed the migratory response of podocytes before and after treatment with PAN. No significant differences were found in basic migration between wild type and cat L−/− podocytes (Fig. 3b), suggesting that cathepsin L is critical for the regulation of podocyte migration under normal conditions. However, after exposure to PAN for 48 h, the number of migratory wild type podocytes increased by 132% (p < 0.001) (Fig. 3b). In contrast, the migration of cat L−/− podocytes was significantly slowed down by 72% (p < 0.001) (Fig. 3b).
Cat L\(^{-/-}\) Podocytes Are Protected against PAN-induced Disassembly of Cell-Cell Junctions—Since cat L\(^{-/-}\) podocytes are protected against PAN-mediated injury, we tested whether the lack of this enzyme would affect slit diaphragm protein distribution. Therefore, we analyzed cell-cell contacts of primary podocyte cultures by light microscopy and immunocytochemistry for CD2AP, a vital SD protein (3). Wild type and cat L\(^{-/-}\) podocytes showed well developed interdigitating cell-cell contacts with morphologic features similar to the adherens junction as described before (34). 72 h after PAN treatment, wild type podocytes revealed a loss of interdigitating cell-cell contacts and reorganization into tight junctions (Fig. 4c). In contrast, interdigitating adherens junction contacts of cat L\(^{-/-}\) podocytes were preserved after PAN treatment (Fig. 4e). In untreated wild type and cat L\(^{-/-}\) podocytes, CD2AP was found at interdigitating cell-cell contacts (Fig. 4e, f and g). After PAN treatment, CD2AP labeling was strongly reduced in wild type podocyte (Fig. 4g). In contrast, the expression and localization of CD2AP were preserved in cat L\(^{-/-}\) podocytes (Fig. 4h).

Regulation of Cathepsin L Activity by \(\alpha_3\) Integrin—Podocytes of \(\alpha_3^{-/-}\) mice are unable to maintain normal podocyte structure, including the elaboration of mature foot processes along the GBM (16). Therefore, \(\alpha_3^{-/-}\) mice provide a genetic model to study podocyte FP effacement. To test whether changes in the expression of cathepsin L in podocytes are restricted to the PAN model or whether cathepsin L is induced in other models of FP effacement, we analyzed cathepsin L in podocytes derived from \(\alpha_3^{-/-}\) mice. In \(\alpha_3^{-/-}\) podocytes, cathepsin L protein expression was strongly induced (Fig. 5a, left panel). Similarly to PAN-treated wild type podocytes (Fig. 2a), an additional 45-kDa band corresponding to procathepsin L was observed in \(\alpha_3^{-/-}\) podocytes (Fig. 5a, left panel). In \(\alpha_3^{-/-}\) cells rescued by stable transfection of human \(\alpha_3\) integrin, the expression of procathepsin L and cathepsin L was normalized, and only a faint 21-kDa band representing the intralysosomal form of cathepsin L could be detected (Fig. 5a, right panel). Immunofluorescence labeling of cathepsin L in \(\alpha_3^{-/-}\) podocytes revealed a strong staining throughout the entire cytoplasm (Fig. 5b, left panel). In contrast, cathepsin L was restricted to perinuclear lysosomes in podocytes rescued with \(\alpha_3\) integrin (Fig. 5b, right panel), a pattern similar to that observed in untreated wild type cells (Fig. 2b, left panel). Furthermore, cathepsin L activity was increased and extended far into the periphery of cell processes (Fig. 5c, left panel). In rescued podocytes, the activity of cathepsin L was localized in perinuclear lysosomes (Fig. 5c, right panel), similar to untreated wild type podocytes (Fig. 2d, left panel). These results suggest that the expression, activity, and subcellular localization of cathepsin L in podocytes are
negatively regulated by α3 integrin. To further explore the functional relationship between cathepsin L and α3 integrin, we inhibited the extracellular domain of α3 integrin with an α3 integrin-specific blocking antibody (31) for 1 h and examined the effect of this inhibition on cathepsin L activity. Blockade of α3 integrin shifted cathepsin L activity from its perinuclear localization into podocyte processes (Fig. 5f). As a positive control for the functional blockade of α3 integrin, we administered PIBS antibody to cultured podocytes rescued with human α3 integrin. Similar to the blocking experiments for cultured wild type podocytes, cathepsin L activity was redistributed into the processes of the rescued cells within 1 h (data not shown).

Thus, in addition to human α3 integrin, the PB15 can also block the activity of murine α3 integrin. A negative control antibody did not alter the perinuclear localization of cathepsin L activity (Fig. 5g). These data suggest that regulation of cell adhesion via α3 integrin is functionally linked to cathepsin L, which in turn is necessary for PAN-induced cell migration.

**Down-regulation of α3 Integrin Protects against PAN-induced Podocyte Detachment**—Podocytes derived from α3<sup>−/−</sup> mice express high levels of (pro-)cathepsin L and cathepsin L, similar to wild type podocytes after PAN treatment, and the acute functional inhibition of α3 integrin results in the shift of cathepsin L activity. Therefore, we tested whether the PAN-induced increase of cathepsin L in wild type podocytes is followed by changes in the expression of α3 integrin. The Western blot analysis of PAN-treated wild type podocytes showed a marked down-regulation of α3 integrin expression when compared with non-treated control cells 48 h after PAN treatment (Fig. 6a). To explore the functional consequences of down-regulated α3 integrin in the course of PAN treatment, we used the rescued α3<sup>−/−</sup> podocyte cells that constitutively express human α3 integrin at their focal contacts (Fig. 6b, middle) in amounts comparable with wild type cells (Fig. 6b, left panel). In the rescued cells, the expression of α3 integrin is under the control of a cytomegalovirus promoter and not altered by PAN treatment (Fig. 6b, right panel). Therefore, this constitutively active system of α3 integrin expression is well suited to study the effects of PAN treatment on podocyte attachment with or without the ability to down-regulate α3 integrin. Rescued podocytes constitutively expressing α3 integrin underwent severe detachment as early as 24 h after the initiation of PAN treatment when compared with 98% of wild type and α3<sup>−/−</sup> cells (Fig. 6d). 48 h after PAN treatment, 50% of rescued cells remained attached when compared with 95% of wild type (p < 0.001) and 88% of α3<sup>−/−</sup> podocytes (p < 0.001). 72 h after PAN exposure, 50% of wild type and α3<sup>−/−</sup> cells remained attached, whereas more than 90% of the constitutively α3 integrin-expressing cells were detached (p < 0.001). These results demonstrate that down-regulation of α3 integrin is a protective response to podocyte injury.

**DISCUSSION**

This study describes that the induction of nephrotic syndrome involves podocyte migration orchestrated by a coordinated interplay between cathepsin L and α3 integrin. In particular, we established that (i) the increased expression and activity of cathepsin L are associated with the onset of proteinuria; (ii) the increased migration of podocytes after PAN treatment is abrogated in cat L<sup>−/−</sup> podocytes, and cat L<sup>−/−</sup> podocytes are protected against PAN-induced disassembly of cell-cell junctions; (iii) the subcellular localization of cathepsin L activity is regulated by α3 integrin expression and function; and (iv) the down-regulation of α3 integrin expression protects against PAN-induced podocyte detachment.

The identification of cathepsin L as a mediator of podocyte migration is interesting in two aspects. First, it provides a novel concept that FP effacement of podocytes is a migratory event and second, it shows that cell motility in a non-malignant cell may depend on a matrix-modifying enzyme. Cathepsin L was not necessary to maintain a basic migration in podocytes under normal conditions since no differences in migration were observed between wild type and cathepsin L<sup>−/−</sup> podocytes. However, cathepsin L was necessary for an augmented migratory response to PAN treatment. Clearly, future studies will be necessary to test whether the changes in migratory behavior are solely due to the lack of cathepsin L or whether the deletion of cathepsin L also affects the function of other proteins. Cathepsin L may not only alter size- and charge-selective properties of the filtration barrier but may modify extracellular moieties to engage a subset of integrins or dystroglycans on podocyte FP to allow FP to spread on the GBM, thereby establishing FP effacement. These movements require disassembly of podocyte cell-cell contacts, an event that by itself may cause or augment proteinuria. Our results in podocytes establish similarities with tumor metastasis in which cathepsin L is involved in tissue invasion and disease progression (40). The functional significance of cathepsin L in podocyte pathobiology is underscored by the finding that cat L<sup>−/−</sup> podocytes are protected from cell detachment and cell-cell junction disassembly. These data also provide a molecular explanation for the previous observation that a specific cathepsin L inhibitor significantly reduces anti-GBM antibody-induced proteinuria (41).

Another major finding of the present study is the observation that the subcellular distribution of cathepsin L depends on the expression and activity of α3 integrin. The functional blockade of α3 integrin resulted in an immediate, reversible redistribution of cathepsin L activity into the periphery of podocyte processes. This shift may initiate the response of podocytes to alter the extracellular matrix composition by enzymatic cleavage of extracellular components to change cell adhesion and motility. Another explanation would be that cathepsin L cleaves or degrades intracellular α3 integrin, thereby leading to the elimination of α3 integrin in focal contacts. In fact, infra-
Upon an insult, stationary podocytes transform into migratory podocytes. This migratory response leads to the up-regulation of cathepsin L expression and activity as well as SD remodeling, FP effacement, and proteinuria. Down-regulation of α3 integrin causes an increased attachment of podocytes to the GBM. Thereafter, podocytes can either recover with restoration of the normal filtration barrier or, if the insult persists, detach and promote progression of glomerular disease.

Cellular cleaving activity of cathepsins has been described before (42), and more experiments are necessary to test whether this is the case for α3 integrin as well. Cultured podocytes secrete cathepsin L in response to various growth factors (11) and cytokines (43), which are also found in various human glomerular diseases with FP effacement and proteinuria (44). Cultured podocytes transform into migratory podocytes. This migratory response against podocyte detachment. Our data suggest that cathepsin L expression and activity in podocytes of mice.

In summary, our results suggest a molecular interplay of 3 integrin results in prolonged adhesion and protects 3 integrin to 3 integrin in the pathogenesis of podocyte FP effacement and proteinuria. Based on these results, we propose 575–582.

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Fig. 7. Working model integrating the roles of Lα3 α3 integrin and in podocyte FP effacement. Upon an insult, stationary podocytes transform into migratory podocytes. This migratory response leads to up-regulation of cathepsin L expression and activity as well as SD remodeling, FP effacement, and proteinuria. Down-regulation of α3 integrin causes an increased attachment of podocytes to the GBM. Thereafter, podocytes can either recover with restoration of the normal filtration barrier, or, if the insult persists, detach and promote progression of glomerular disease.
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