Induction of B7-1 in podocytes is associated with nephrotic syndrome

Jochen Reiser,1 Gero von Gersdorff,1 Martin Loos,1 Jun Oh,1 Katsuhiko Asanuma,1 Laura Giardino,1 Maria Pia Rastaldi,2 Novella Calvaresi,2 Haruko Watanabe,3 Karin Schwarz,1 Christian Faul,1,4 Matthias Kretzler,5 Anne Davidson,1,6 Hikaru Sugimoto,7 Raghu Kalluri,7 Arlene H. Sharpe,8 Jordan A. Kreidberg,9 and Peter Mundel1,4

1Department of Medicine, Albert Einstein College of Medicine, New York, New York, USA. 2Renal Research Association, Renal Immunopathology Center, San Carlo Borromeo Hospital, Milan, Italy. 3Department of Pediatrics, Tokyo Metropolitan Toshima Hospital, Tokyo, Japan. 4Department of Anatomy and Structural Biology, Albert Einstein College of Medicine, New York, New York, USA. 5Department of Medicine, Ludwig-Maximilians-Universität, Munich, Germany. 6Department of Microbiology and Immunology, Albert Einstein College of Medicine, New York, New York, USA. 7Center for Matrix Biology, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA. 8Department of Pathology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, USA. 9Department of Medicine, Children’s Hospital, and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA.

Kidney podocytes and their slit diaphragms form the final barrier to urinary protein loss. This explains why podocyte injury is typically associated with nephrotic syndrome. The present study uncovered an unanticipated novel role for costimulatory molecule B7-1 in podocytes as an inducible modifier of glomerular permselectivity. B7-1 in podocytes was found in genetic, drug-induced, immune-mediated, and bacterial toxin–induced experimental kidney diseases with nephrotic syndrome. The clinical significance of our results is underscored by the observation that podocyte expression of B7-1 correlated with the severity of human lupus nephritis. In vivo, exposure to low-dose LPS rapidly upregulates B7-1 in podocytes of WT and SCID mice, leading to nephrotic-range proteinuria. Mice lacking B7-1 are protected from LPS-induced nephrotic syndrome, suggesting a link between podocyte B7-1 expression and proteinuria. LPS signaling through toll-like receptor-4 reorganized the podocyte actin cytoskeleton in vitro, and activation of B7-1 in cultured podocytes led to reorganization of vital slit diaphragm proteins. In summary, upregulation of B7-1 in podocytes may contribute to the pathogenesis of proteinuria by disrupting the glomerular filter and provides a novel molecular target to tackle proteinuric kidney diseases. Our findings suggest a novel function for B7-1 in danger signaling by nonimmune cells.

Introduction

The kidney glomerulus is a highly specialized structure that ensures selective ultrafiltration of plasma so that essential proteins are retained in the blood. The common denominator in a variety of kidney diseases, such as diabetes mellitus, focal segmental glomerulosclerosis, and systemic lupus erythematosus, is glomerular dysfunction (nephrotic syndrome), involving a massive loss of protein in the urine (proteinuria) (1). Kidney or systemic diseases that result in nephrotic syndrome are important causes of morbidity and mortality affecting both adults and children. Glomerular podocytes serve as the final barrier to urinary protein loss by the formation and maintenance of podocyte foot processes (FPs) and the interposed slit diaphragm (SD) (1). All forms of nephrotic syndrome are characterized by abnormalities in podocytes, including retraction (effacement) of podocyte FPs and/or molecular reorganization of the SD. FP effacement is a dynamic process that correlates closely with the development of proteinuria both in human disease and in experimental models. FP effacement requires a precise interplay of multiple cellular functions, including structural alterations of the cytoskeleton, movement of FPs over the basement membrane, and reconstruction of the SD (1). From a clinical perspective, it is important to recognize that early structural changes in podocytes such as substructural alterations in SD composition or FP effacement have to be reversed within a certain period of time to prevent development of severe and progressive glomerular damage (2). Recent years have been extremely fruitful in providing an extensive amount of information on the molecular composition of the SD and its anchoring structures, which form multiple interactions and provide signaling platforms. The discovery of several novel podocyte proteins and their mutation analysis, including nephrin (3), CD2AP (4), α-actinin-4 (5), podocin (6), and nephi1 (7), have shed light on the pathogenesis of proteinuria and emphasized the critical role of the podocyte and the SD in maintaining the function of the glomerular filtration barrier.

Podocyte FPs form a scaffolding around the capillary loops that are anchored to the glomerular basement membrane (GBM) via α3β1 integrin (8) and α-/β-dystroglycans (9, 10). 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 (11). In podocytes, α3β1 integrin is expressed at the basal side of FPs. Podocytes of α3 integrin–deficient (α3–/–) mice bear a strong morphological resemblance to podocytes in congenital nephrotic syndrome and other pathological conditions with FP effacement (11, 12). The α3 integrin deletion therefore represents a genetic model for B7-1 in podocytes.
system that allows the analysis of the molecular basis of FP assembly and dynamics.

B7-1, also termed CD80, is a transmembrane protein normally expressed on the surface of B cells and other APCs (13–15). On APCs, B7-1 acts as a costimulatory molecule through binding to its cognate receptors CD28 and CTLA-4 on T cells (13–15). Little is known about B7-1 expression by non–bone marrow–derived cells. In human keratinocytes, B7-1 gene expression is upregulated by allergens and irritants (16). In P815 mastocytoma tumor cells, B7-1 gene expression is induced by oxidative stress (17), which is reminiscent of the induction of B7-1 in podocytes by puromycin, described below. In the kidney, B7-1 can be induced in glomerular endothelial cells by warm ischemia/reperfusion injury in rats (18).

The innate immune system senses pathogen-associated molecular motifs through toll-like receptors (TLRs), thereby initiating an immunological response (19). In APCs, LPS is the strongest endogenous inducer of B7-1 expression through TLR-4 signaling (20). Here we show that danger signaling occurs also in non–bone marrow–derived glomerular podocytes and underlies a dramatic physiological response. Podocytes sense LPS by TLR-4, which triggers the reorganization of the kidney–filtration apparatus, leading to podocyte FP effacement and proteinuria. This response requires the induction of costimulatory molecule B7-1, since proteinuria was abrogated in B7-1–/– mice. We discuss a novel function for B7-1 in the danger signaling of nonimmune cells.

Methods

Cell culture. WT podocytes were cultured as described before (21). We generated conditionally immortalized α3β1–/– podocyte cell lines by intercrossing α3 integrin heterozygous mice (12) with the ImmortoMouse (Charles River Laboratories Inc., Wilmington, Massachusetts, USA), which carries a temperature-sensitive T antigen as transgene (22). Glomeruli were isolated from kidneys of E18 homozygous embryos, and eight α3β1–/– clonal podocyte cell lines were obtained by limiting dilution. To show that observed changes in podocyte gene expression and function were due to the absence of α3 integrin, three α3β1–/– clones were stably transfected with human α3 integrin cDNA as described before for α3β1–/– collecting duct epithelial cells (23).

Differential display PCR. Total RNA was isolated from differentiated WT and α3β1–/– podocytes that had been grown under nonpermissive conditions for 14 days using the RNaseasy kit (QIAGEN Inc., Valencia, California, USA). After DNase treatment, reverse transcription was carried out with three different anchored synthetic oligonucleotide primers from the RNAimage kit (GenHunter, Nashville, Tennessee, USA). Differential display PCR reactions were performed in duplicate using 96 different primer combinations as described before (24). Differentially expressed PCR products were cloned into the pCR2 vector using the TA cloning kit (Invitrogen, Carlsbad, California, USA) and sequenced. Sequence analyses and database searches were done with the software program package HUSAR (Heidelberg Unix Sequence Analysis Resources; German Cancer Research Center, Heidelberg, Germany). The following primers specific for B7-1, yielding a 172-bp product, were used: sense, 5′-TGTATGCCAGGAAACAGGT-3′; antisense, 5′-AGCCCGATCACCAC-TGATTA-3′.

Antibodies. The following protein-specific primary antibodies were used: anti–B7-1 (16-10A1; Pharmingen, San Diego, California, USA), and mouse monoclonal anti-synaptopodin (25). Rabbit was a gift from L. Holzman (University of Michigan, Ann Arbor, Michigan, USA); rabbit polyclonal anti-nephrin (22). Glomeruli were isolated from kidneys of E18 homozygous embryos, and eight α3β1–/– clonal podocyte cell lines were obtained by limiting dilution. To show that observed changes in podocyte gene expression and function were due to the absence of α3 integrin, three α3β1–/– clones were stably transfected with human α3 integrin cDNA as described before for α3β1–/– collecting duct epithelial cells (23).

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Results

B7-1 is induced in podocytes in genetic and drug-induced models of FP effacement. Podocytes in kidneys of α3−/− mice are unable to maintain normal podocyte structure, including the elaboration of mature FPs along the GBM (12). Therefore α3−/− mice provide an excellent genetic model to study podocyte FP effacement. α3−/− mice die during the perinatal period with severe kidney and lung defects, precluding extensive study of the role of this cell matrix receptor in podocytes in vivo. To delineate the molecular mechanisms underlying FP effacement in α3−/− mice, we took advantage of our previously established cell culture system for WT podocytes (21) and generated α3−/− podocytes. In an effort to identify molecular mechanisms underlying FP effacement in this cell matrix receptor in podocytes in vivo. To delineate the

Figure 1

B7-1 expression in podocytes. (A) Differential display PCR of WT (+/+ ) and α3−/− (−/−) podocytes. The arrow indicates the position of B7-1. (B) Induction of B7-1 mRNA expression in α3−/− podocytes. RT-PCR from three independent samples (a–c) on serial dilution (1:5 to 1:25) of cDNA standardized for β-actin. Con, H2O control. (C) Rescue (Res) of α3−/− podocytes by stable transfection with human α3 integrin restored B7-1 expression to WT levels. RT-PCR for GAPDH shows equal RNA concentrations. (D) Dose-dependent increase of B7-1 mRNA in WT podocytes in response to puromycin (0.1, 1, 5, 10, and 50 μg/ml). (E) Time course of B7-1 and α3 integrin mRNA expression in puromycin aminonucleoside–treated (PAN-treated) WT podocytes. As early as 6 and 24 hours, B7-1 is induced by PAN, whereas α3 integrin levels remain unchanged. (F) B7-1 is not expressed in E18 WT kidneys (left panel) but is expressed in podocytes of α3−/− kidneys as shown by double labeling with synaptopodin (right panels).
Mice, an established New Zealand black/white (NZB/W) F1 female and urinary protein loss, we analyzed B7-1 expression in 30-week-old 4+ proteinuric lupus mice (Figure 2B) but not in age-matched animals that showed only trace proteinuria (Figure 2C). To determine the significance of glomerular B7-1 expression in human glomerulonephritis, we analyzed B7-1 expression in human kidney biopsies from different stages of lupus nephritis. Glomerular B7-1 expression correlated with the disease stage in that it increased from WHO class II to V and was strongest in WHO class V kidney biopsies (Figure 2, D and E). As in the murine condition (Figure 2C), glomerular B7-1 colocalized with the podocyte marker synaptopodin (25) (Figure 2E). Taken together, these data underscore the clinical relevance of B7-1 expression in podocytes. They suggest that B7-1 in podocytes contributes to the pathogenesis of proteinuria.

**Induction of B7-1 in podocytes of nephrin−/− mice.** The nephrin gene NPHS1 is the target gene of congenital nephrotic syndrome of Finnish type, an autosomal-recessive disorder, characterized by massive proteinuria in utero and nephrosis at birth (3). Inactivation of NPHS1 in mice results in massive proteinuria, edema, and perinatal lethality (27, 38). To test whether the induction of B7-1 in podocytes under nephrotic conditions is specific for lupus nephritis, we analyzed the expression of B7-1 in nephrin−/− mice (27). B7-1 colocalized with synaptopodin in podocytes of nephrin−/− mice (Figure 3A). In contrast, no podocyte B7-1 expression was found in WT littermates (Figure 3B). These data imply that podocyte B7-1 expression is not specific for lupus nephritis but is also found in noninflammatory conditions with proteinuria and is not dependent on immune complexes.

**B7-1 expression in podocytes in vitro is induced by LPS through TLR-4 signaling and leads to the reorganization of the actin cytoskeleton.** B7-1 expression in APCs can be induced by LPS through TLR-4/CD14-mediated signaling (20). Interestingly, podocytes constitutively express TLR-4 and its coreceptor CD14 and hence respond to LPS (Figure 4A). Therefore, we explored the effects on podocytes. Exposure to LPS specifically upregulated B7-1 (Figure 4B) and induced the disruption of stress fibers (Figure 4C), creating a cortical ring of F-actin and a submembranous space lacking actin fibers (Figure 4D). This cytopathic effect is reminiscent of the actin changes that are observed in FP effacement in vivo (1) and suggests that LPS may contribute to the pathogenesis of FP effacement and proteinuria through the reorganization of the podocyte actin cytoskeleton.

**LPS upregulates B7-1 in podocytes in vivo and leads to nephrotic syndrome in WT but not in B7-1−/− mice.** To test this hypothesis further, we injected a single low dose of LPS intraperitoneally into adult female WT BALB/c mice and analyzed the effects on kidney histology, podocyte B7-1 expression, and urinary protein excretion. Histologically, kidneys of LPS-injected mice were

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**Figure 2**

B7-1 expression in podocytes in murine and human lupus nephritis correlates with the severity of proteinuria. (A) B7-1 is not expressed in normal mouse kidney (left). In the lupus kidney, strong glomerular (G) B7-1 expression is observed (middle). In addition, infiltrating interstitial B cells stain positive (arrows). At higher magnification (right), B7-1 expression is found in podocytes (arrows) in the glomerulus. (B) Double labeling with synaptopodin confirmed that intraglomerular B7-1 expression is restricted to podocytes in 4+ proteinuric (4+ prot) nephritis. (C) B7-1 is absent in an age-matched lupus mouse with trace proteinuria (trace prot). (D and E) In human lupus nephritis, glomerular B7-1 expression increases from WHO class II to V and colocalizes with synaptopodin in podocytes (E).
not distinguishable from PBS-injected controls (Figure 5A). In particular, no signs of inflammation were found. LPS induced upregulation of B7-1 in podocytes (Figure 5B) and FP effacement within 24 hours (Figure 5D, left panel). In contrast, PBS injection did not induce podocyte B7-1 expression (Figure 5C) or FP effacement (Figure 5D, right panel). Most significantly, LPS injection caused severe proteinuria ($n = 13$; base line, $0.8 \pm 0.4$, vs. LPS, $2.7 \pm 0.9$; $P < 0.001$, two-sided $t$ test) within 24 hours (Figure 5G). In contrast, no proteinuria was found in PBS-injected controls (data not shown). We next established that LPS-induced nephrotic syndrome is independent of the mouse strain, since we found it also in WT 129 ($n = 9$; base line, $0.7 \pm 0.5$, vs. LPS, $2.1 \pm 0.78$; $P < 0.001$, $t$ test) and C57BL/6 mice ($n = 23$; base line, $0.5 \pm 0.29$, vs. LPS, $1.9 \pm 0.56$; $P < 0.0001$, $t$ test) (Figure 5G). The LPS-induced proteinuria was transient and returned to base-line levels after 72 hours (data not shown). To establish a causal relationship between podocyte B7-1 upregulation and development of proteinuria, the experiments were repeated with B7-1–/– mice (28). No proteinuria was observed in LPS-injected B7-1–/– mice ($n = 5$; base line, $1.0 \pm 0$, vs. LPS, $0.6 \pm 0.55$, $P$ not significant, $t$ test) (Figure 5G). The differences in proteinuria between WT and B7-1–/– mice were statistically significant ($P < 0.001$, $t$ test). These data suggest that B7-1 induction in podocytes is necessary for the development of LPS-induced proteinuria.

**LPS-induced nephrotic syndrome is independent of T or B cells.** To rule out that the LPS-induced proteinuria resulted from the activation of T or B cells rather than from a direct action on podocytes, SCID mice, which are devoid of T and B cells (29) were treated with LPS. As in WT mice, LPS injection in SCID mice caused podocyte B7-1 expression (Figure 5E) and severe proteinuria ($n = 6$; base line, $1.2 \pm 0.4$, vs. LPS, $3.2 \pm 0.9$; $P < 0.001$, $t$ test) within 24 hours (Figure 5G). In contrast, B7-1 staining was absent from PBS-treated SCID mice (Figure 5F). Hence, the induction of B7-1 expression by podocytes in response to LPS is independent of T or B cells. Taken together, these data indicate a causal link between podocyte B7-1 expression and urinary protein loss that is independent of lymphocyte infiltration or activation.

Figure 3
Induction of B7-1 in podocytes of nephrin–/– mice. (A) B7-1 is induced in podocytes of nephrin–/– mice as shown by double labeling with synaptopodin. (B) B7-1 is absent from podocytes of WT littermate controls. These data establish that the expression of B7-1 in podocytes in vivo can occur independently of immune complexes or inflammatory cells.

**B7-1 modifies the glomerular filter by sequestration of SD proteins.** How does B7-1 upregulation in podocytes contribute to the pathogenesis of proteinuria? To test whether the ligation of B7-1 transduces intracellular signals in podocytes, thereby modulating the composition of the SD, we used a microbead approach to cross-link B7-1. With this approach, three key proteins of the SD, nephrin (3), CD2AP (4), and ZO-1 (39), were analyzed in α3+/– podocytes by immunocytochemistry after binding of microbeads coated with CTLA-4-Ig or anti–B7-1 antibody (Figure 6). The detailed microscopic analysis revealed that nephrin was redistributed from cell-cell contacts (Figure 6A) and accumulated around CTLA-4-Ig–coated (Figure 6B) or anti–B7-1–coated microbeads (Figure 6C). The association of SD proteins with anti–B7-1–coated microbeads was confirmed by confocal microscopy, which showed a ring of nephrin lining the microbeads (Figure 6D).

Similar results were obtained for CD2AP, which was redistributed from the cell membrane and the actin filaments (Figure 6E) to microbeads (Figure 6F–H). ZO-1 relocated from cell-cell contacts (Figure 6I) to the microbeads (Figure 6, J–L). To show that the redistribution of SD proteins was specifically mediated by B7-1, several control experiments were performed. First, microbeads were coated with a mutated variant of murine CTLA-4-Ig that can no longer bind to Fc receptor. Second, microbeads were coated with an irrelevant antibody with an intact Fc fragment. The microbeads coated with the irrelevant antibody (dendrin) could to some extent adhere to podocytes but did not cause the rearrangement of ZO-1 (Figure 6M). Third, uncoated microbeads were used. No binding was observed with uncoated microbeads or beads coated with the irrelevant antibody (data not shown). Moreover, B7-1 clustering beads had no effect on cultured WT podocytes, which do not express B7-1 (data not shown). In summary, the results of the bead experiments are specific and conclusive. They suggest that B7-1 may contribute to the pathogenesis of proteinuria by disrupting the SD complex.

**Discussion**
This study is the first to demonstrate that B7-1 is expressed in podocytes under a variety of stress conditions. Moreover, the results of this study establish the clinical significance of application of the new method.
podocyte B7-1 expression and elucidate its role in the pathogenesis of nephrotic syndrome. We specifically demonstrate that podocyte B7-1 reorganizes the actin cytoskeleton of podocytes and modulates SD organization. The effects are independent of T cells and B cells and represent a novel unique function of B7-1. This study also is the first to show that LPS injection in mice induces B7-1-dependent nephrotic syndrome with FP effacement and urinary protein loss.

So far, B7-1 had been assumed to be predominantly expressed on B cells and other professional APCs. The traditional role of B7-1 is T cell costimulation (13–15). Along with the interaction of the T cell receptor with antigen-MHC complexes, the interaction of B7 with its receptors CD28 and CTLA-4 on T cells plays a pivotal role in T cell–mediated immunity (13–15). In T cells, binding of B7-1 to its receptors on the T cell surface triggers migration of protein kinases, actin-binding proteins, and other accessory molecules to the T cell–APC interface (40, 41). This formation of the immunological synapse causes a rearrangement of the T cell actin cytoskeleton (40, 42–44), activates protein tyrosine kinases that couple to PI3K, and controls the activity of Ras- and Rho-family GTPases in T cells (45).

The role of B7-1 in T cell costimulation is well established and defines a dialogue between a B7-1–expressing APC and a T cell to which the costimulatory signal is conveyed (13–15). In contrast, B7-1–mediated outside-in signaling in B7-1–expressing APCs is still obscure. With respect to outside-in signaling through B7-1 on B7-1–expressing cells, two studies have been published. One study showed that cross-linking of B7-1 on B lymphoma Raji cells induces tyrosine phosphorylation of intracellular proteins, indicating a role of B7-1 in outside-in signaling (46). Further support for a role of B7-1 in outside-in signaling comes from a recent report showing that CTLA-4Ig–mediated ligation of B7-1 regulates tryptophan catabolism in dendritic cells (47). These changes are reminiscent of the changes seen in SD protein redistribution after ligation/activation of B7-1 in podocytes (Figure 6).

In human keratinocytes, B7-1 gene expression is induced by allergens and irritants (16). In P815 mastocytoma tumor cells, B7-1 gene expression is induced by oxidative stress (17). In APCs, MyD88-independent LPS/TLR-4 signaling is the strongest activator of B7-1 expression (20, 48). Similarly, B7-1 induction in podocytes appears to be downstream of various signaling pathways, including TLR signaling (Figure 5). Generally, somatic cells grown in culture are, for the most part, quite indifferent to LPS (20), and earlier studies had shown that macrophages are the primary target cells of LPS in septic shock (20). Here we demonstrate that podocytes constitutively express the LPS receptor TLR-4 and its coreceptor CD14 and respond to LPS exposure with upregulation of B7-1. This is another unanticipated finding of the present study.

The LPS experiments (Figures 4 and 5) allowed us to explore several important questions. First, they established that the induction of podocyte B7-1 in conditions with FP effacement and proteinuria was causative and not the consequence of the nephrotic condition, since B7-1–/– mice were protected from LPS-induced proteinuria. Second, one might argue that the effects of LPS are predominantly mediated through the action of T cells. Our data refute this hypothesis, because (a) SCID mice lacking T and B cells showed the same degree of FP effacement and proteinuria as WT mice; (b) exposure of cultured podocytes in the absence of any other cells was sufficient to upregulate B7-1 and reorganize the podocyte actin cytoskeleton; and (c) the cell-free microbead-mediated cross-linking of B7-1 on α3− podocytes was...
sufficient to redistribute vital SD proteins. Collectively, these data suggest that B7-1 expression by podocytes represents a pathogenic mechanism for disruption of the glomerular filtration apparatus that is independent of T cell activation.

An intriguing question remains, why do podocytes upregulate B7-1? In the grass shrimp, *Palaemonetes pugio*, podocytes are involved in the ultrafiltration of hemolymph where micro- and macromolecular substances are cleared (49). In the pre-molt stage of this shrimp, podocyte assemblages extend into the efferent hemolymph channels and are in direct contact with immune cells, and they may serve as a component of the LPS-sensing (20) innate immune response. The upregulation of podocyte B7-1 by LPS may be a phylogenetically preserved mechanism, which can be reactivated under pathological conditions, e.g., in patients with Gram-negative sepsis. Consistent with this idea, the development of transient proteinuria has been found during the course of Gram-negative sepsis (50). Moreover, a prospective study showed that in postoperative septic patients microalbuminuria is an early indicator of increased glomerular permeability, but not in nonseptic patients (51). The resulting, transient, proteinuria may be a physiological response aimed at clearing the circulation from pathogen-associated molecules. In human minimal-change disease, the onset of nephrotic syndrome is often preceded by an infection or allergic reaction (52). This raises the intriguing possibility that nephrotic syndrome in minimal-change disease represents the persistence of a normally beneficial response caused by genetic defects in the B7-1 pathway or by other unphysiological activators. The sustained B7-1 activation in podocytes, in turn, results in continuing nephrotic syndrome.

In summary, we have demonstrated a novel function for B7-1 in the pathogenesis of proteinuria that is distinct from its role in costimulation (Figure 7). Our findings suggest a novel function for B7-1 in danger signaling by podocytes. The B7-1 knockout by itself is not conclusive since it is not podocyte specific. While the SCID mice control for T or B cell–mediated effects, it is still possible that dendritic cells or other APCs might contribute to the observed effects. Future studies with a podocyte-specific B7-1 knockout should allow us to address this question.

We propose that transient B7-1–induced nephrotic syndrome may be a physiological response. Clearly, future studies will be required to explore this hypothesis in detail, but it could potentially explain how a normally beneficial danger-sensing mechanism can have deleterious effects in certain genetic backgrounds. Understanding the role of B7-1 in podocytes should allow new avenues toward the development of novel, selective podocyte-protective therapies that modulate danger signaling in podocytes and tackle proteinuria. It will be interesting to see whether B7-1–dependent pathways are also operative in chronic kidney disease.

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Figure 6

Redistribution of SD proteins to sites of B7-1 engagement. (A) In untreated α3–/– podocytes, nephrin is expressed at cell-cell contacts. (B and C) Incubation of podocytes with microbeads coated with CTLA-Ig (B) or anti–B7-1 antibody (C) redistributes nephrin around microbeads (arrows). (D) The association of nephrin with microbeads was confirmed by confocal microscopy. (E–L) Similar redistribution patterns were seen for CD2AP (E–H) and ZO-1 (I–L). Arrows in F and J: accumulation of CD2AP (F) and ZO-1 (J) around microbeads. Asterisk in K: microbead. (M) In contrast, microbeads coated with an irrelevant antibody could to some extent adhere to podocytes (arrowhead) but did not affect the localization of ZO-1 at cell-cell contacts (arrows).

Figure 7

Pathways leading to B7-1–mediated proteinuria. Various stimuli may lead to podocyte B7-1 induction. These include genetic stimuli (e.g., deletion of α3 integrin or nephrin), toxic stimuli (PAN-induced reactive oxygen species [ROS]), or direct stimulation of the TLR-4/CD14 receptor on the podocyte. B7-1 then induces FP effacement and disruption of the SD complex, thereby modifying glomerular permselectivity.
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Address correspondence to: Peter Mundel, Division of Nephrology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, New York, New York 10461, USA. Phone: (718) 430-3219; Fax: (718) 430-8963; E-mail: mundel@aecom.yu.edu.

Jochen Reiser’s present address is: Renal Unit, Massachusetts General Hospital, and Harvard Medical School, Charlestown, Massachusetts, USA.