Semaphorins and Plexins in Kidney Disease

Jingjing Xia^a Thomas Worzfeld^{b, c}

^aDepartment of Dermatology, Center for Molecular Medicine Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, ^bInstitute of Pharmacology, Biochemical-Pharmacological Center (BPC), University of Marburg, Marburg, and ^cMax-Planck-Institute for Heart and Lung Research, Department of Pharmacology, Bad Nauheim, Germany

Key Words

Semaphorin · Plexin · Diabetic nephropathy · Glomerulosclerosis · Glomerulonephritis · Injury · Repair · Systemic lupus erythematosus · Lupus nephritis · Hypertension · Podocyte · Tubule · Immune · Inflammation · Fibrosis · Mitotic spindle · Cell division

Abstract

Semaphorins are soluble or membrane-bound cues, which control multiple aspects of cell-cell communication, differentiation, morphology and function. Most of their effects are mediated by a family of transmembrane receptors called plexins. Semaphorins and plexins have emerged as central regulators of diverse physiological and pathophysiological processes in various organs. This review summarizes the role of semaphorins and plexins in renal pathophysiology and their potential use as biomarkers of kidney disease.

© 2016 S. Karger AG, Basel

Introduction

Semaphorins comprise a family of membrane-bound or diffusible factors that were initially discovered for their role as axon guidance cues in the developing

nervous system. They are now recognized as key regulators of multiple cellular functions in the renal, immune, nervous, bone and cardiovascular systems, both during development as well as in the adult organism [1, 2]. In mammals, 20 semaphorins have been identified, which are grouped into 5 classes, 3–7, based on structural characteristics (fig. 1). Plexins, a family of single-pass transmembrane proteins, represent the main semaphorin receptors and are classified into 4 subfamilies, A–D (fig. 1). The structural hallmark of semaphorins and plexins is the Sema domain, a ~500-amino-acid seven-blade β -propeller fold, which mediates the semaphorin–plexin interaction. In some cases, the binding of semaphorins to plexins is stabilized by plexin co-receptors, the neuropilins [1] (fig. 1). Multiple semaphorins and plexins are expressed during kidney organogenesis and have been shown to control diverse developmental processes like branching of the ureteric bud, establishment of the glomerular filtration barrier and patterning of the renal vasculature [3, 4]. In the adult, semaphorin–plexin signaling is crucially involved in multiple aspects of renal pathophysiology. This review focuses on the biological roles of semaphorins and plexins and their potential as biomarkers in kidney disease.

Fig. 1. The mammalian semaphorin-plexin system. In mammals, 20 semaphorins (grouped in 5 classes, 3–7) and 9 plexins (classified in 4 subfamilies, A–D) have been identified so far, all of which share the Sema domain as their common feature. While class-3-semaphorins are secreted, semaphorins of other classes are membrane bound. Some class-4-semaphorins can be released from the cell membrane by proteolytic cleavage. The intracellular portion of all plexins comprises a GAP domain, which is separated into 2 parts by a RBD. In some cases, the semaphorin-plexin interaction requires stabilization by neuropilin-1 or -2. PSI = Plexin-semaphorin-integrin; Ig = immunoglobulin; PDZ = post synaptic density 95/discs large/zonula occludens-1; GPI = glycosylphosphatidylinositol; IPT = immunoglobulin-plexin-transcription factor; RBD = Rho GTPase-binding domain; SEA motif = consists of the amino acids serine, glutamic acid and alanine; MAM = meprin-A-5 protein-receptor protein tyrosine phosphatase mu.

Semaphorins and Plexins in Glomerular Diseases

Semaphorin 3A in Diabetic Nephropathy

Diabetes mellitus is the leading cause of chronic kidney disease and affects primarily the renal corpuscle. The clinical manifestations of diabetic nephropathy, proteinuria and a progressive loss of glomerular function, correlate with histological changes that are characterized by thickening of the glomerular basement membrane and

glomerular sclerosis. Semaphorin 3A, a soluble, secreted semaphorin (fig. 1), has been found to be expressed in immortalized murine podocytes in vitro as well as in podocytes of adult humans, mice and rats in vivo [5–8] (table 1). In a mouse model of diabetes, and in diabetic patients, Semaphorin 3A expression levels in podocytes are elevated [8, 9]. Evidence for a functional significance of Semaphorin 3A in kidney physiology and diabetic nephropathy comes from gain-of-function and loss-of-function studies in mice us-

Table 1. Expression of semaphorins and plexins in the adult kidney

Expression in normal kidney		Species	Expression changes in disease	References
<i>Semaphorins</i>				
Sema3A	Podocytes	Human	↑ in diabetic nephropathy	[8]
		Mouse	↑ in STZ-induced diabetes	[5–7, 9]
		Rat	n.a.	[7]
	TECs of distal tubules and collecting ducts	Human	↔ in diabetic nephropathy	[8]
		Mouse	↑ and additional expression in TECs of proximal tubules in ischemia/ reperfusion injury ↑ in cisplatin-induced acute kidney injury ↑ in STZ-induced diabetes	[7, 9, 17, 18]
		Rat	n.a.	[7]
Sema3B	Podocytes (immortalized)	Mouse	n.a.	[5]
Sema3C	Podocytes (immortalized)	Mouse	n.a.	[5]
Sema3D	Podocytes (immortalized)	Mouse	n.a.	[5]
Sema3E	Podocytes (immortalized)	Mouse	n.a.	[5]
Sema3F	Podocytes	Mouse, rat	n.a.	[5, 7]
	TECs of distal tubules and collecting ducts	Mouse, rat	n.a.	[7]
Sema4A	TECs of proximal tubules	Mouse	↑ in ischemia/reperfusion injury	[13]
Sema4B	TECs of all tubular segments	Mouse	↑ in ischemia/reperfusion injury	[13]
Sema4C	Glomeruli	Mouse	↔ in ischemia/reperfusion injury	[13, 21]
	Interstitial cells	Mouse	↑ in ischemia/reperfusion injury	[13, 21]
Sema4D	TECs of proximal tubules	Mouse	↑ in ischemia/reperfusion injury	[12–14]
Sema4F	Whole kidney (localization unclear); expressed at low levels	Mouse	↔ in ischemia/reperfusion injury	[13]
Sema4G	Whole kidney (localization unclear); expressed at high levels	Mouse	↑ or ↓ in ischemia/reperfusion injury (depending on time point after injury)	[13]
<i>Plexins</i>				
Plexin-A1	Podocytes (immortalized)	Mouse	n.a.	[5, 6]
	Whole kidney (localization unclear)	Mouse	↔ in STZ-induced diabetes ↑ in ischemia/reperfusion injury	[6, 9, 18]
Plexin-A2	Podocytes (immortalized)	Mouse	n.a.	[5]
	Whole kidney (localization unclear)	Mouse	↑ in STZ-induced diabetes ↔ in ischemia/reperfusion injury	[9, 18]
Plexin-A3	Podocytes (immortalized)	Mouse	n.a.	[5]
	Whole kidney (localization unclear)	Mouse	↔ in STZ-induced diabetes ↓ in ischemia/reperfusion injury	[9, 18]
Plexin-B1	Glomeruli	Mouse	n.a.	[12, 21]
	TECs of distal tubules and collecting ducts	Mouse	n.a.	[14]
Plexin-B2	Podocytes (immortalized)	Mouse	n.a.	[5]
	Glomeruli	Mouse	n.a.	[21]
	TECs of all tubular segments	Mouse	↑ in ischemia/reperfusion injury	[13, 21]
Plexin-D1	Podocytes (immortalized)	Mouse	n.a.	[5]
STZ = Streptozotocin; TEC = tubular epithelial cell; n.a. = not assessed.

Fig. 2. Semaphorins and plexins in glomerular diseases. **a** Sema3A is expressed by podocytes (dashed arrow) and binds to its receptor Plexin-A1 on podocytes, which interacts with nephrin (left). In diabetic nephropathy, Sema3A expression in podocytes is upregulated, and excess Sema3A disrupts the nephrin/podocin/CD2AP complex (right). **b** In glomerulonephritis, Sema4D expressed on

T-cells interacts with CD72 on dendritic cells to promote T-cell activation, and with CD72 on B-cells to enhance B-cell activation and antibody production (these interactions typically occur in lymphoid organs). An interaction between Sema4D on T-cells and Plexin-B1 on glomerular cells might also be pathophysiologically relevant.

ing both pharmacological as well as genetic approaches (fig. 2a). Systemic administration of exogenous recombinant Sema3A into mice or doxycycline-inducible, podocyte-specific overexpression of Sema3A in transgenic mice induce marked morphological abnormalities in the renal corpuscle including podocyte damage and glomerular endothelial swelling, which are accompanied by proteinuria [6, 10]. Consistent with these effects of Sema3A in normal mice, podocyte-specific overexpression of Sema3A in diabetic mice worsens glomerulosclerosis and kidney function [8]. Conversely, diabetic mice expressing mutant Sema3A, and diabetic mice injected with a peptide that blocks Sema3A-induced effects in neurons [11]

show less albuminuria, attenuated glomerulosclerosis and interstitial fibrosis, and a decrease in macrophage infiltration and in the renal expression of pro-inflammatory and pro-fibrotic genes, while kidney function is improved [9]. Interestingly, treatment of diabetic mice with a Sema3A-inhibitory peptide is effective after the onset of proteinuria, suggesting that approaches targeting Sema3A might hold therapeutic potential [9]. Mechanistically, excessive Sema3A impacts on the integrity of the slit diaphragm by interfering with the nephrin-podocin-CD2-associated protein (CD2AP) junctional complex [5, 6, 10] (fig. 2a). Nephrin is a transmembrane adhesion molecule that forms homophilic interactions between neighboring

podocyte foot processes. It interacts with podocin, a membrane-associated intracellular scaffold, which controls actin dynamics through several proteins, including the multidomain scaffolding protein CD2AP, thereby maintaining podocyte intercellular junctions and podocyte morphology. In mice with podocyte-specific overexpression of *Sema3A*, or after administration of exogenous *Sema3A*, nephrin expression is downregulated [6, 10]. Moreover, in immortalized murine podocytes and in isolated glomeruli, *Sema3A* treatment interferes with the interaction between nephrin and podocin as well as between podocin and CD2AP [5]. *Sema3A* is known to bind to receptor complexes composed of an A-family plexin and neuropilin-1 [1]. Studies analyzing the expression of these *Sema3A* receptors have detected Plexin-A1, Plexin-A2 and Plexin-A3 as well as neuropilin-1 in kidney lysates and immortalized cultured podocytes [5, 9] (table 1). Biochemical experiments indicate that Plexin-A1 directly interacts with the cytoplasmic domain of nephrin [6], suggesting that Plexin-A1 could mediate *Sema3A* effects on the nephrin-podocin-CD2AP complex. In addition, Plexin-A1 interacts with the actin disassembly factor MICAL-1 in immortalized cultured podocytes, and knockdown of MICAL-1 renders podocytes insensitive to a *Sema3A*-induced contraction [6, 8]. In diabetic mice overexpressing *Sema3A* in podocytes, podocyte-specific genetic deletion of Plexin-A1 ameliorates diabetic nephropathy, strongly suggesting that Plexin-A1 on podocytes mediates adverse *Sema3A*-induced effects [8].

Semaphorin 4D in Glomerulonephritis

Glomerulonephritis, an inflammation of the renal corpuscle, is one of the most common causes of kidney disease and often leads to chronic renal failure. Different forms of glomerulonephritis can be classified according to their pathogenesis, their histological features and their clinical course. *Sema4D* is expressed by T-cells as well as in kidney tubules [12–14] (table 1), and global inactivation of the *Sema4D* gene has beneficial effects in different mouse models of glomerulonephritis including attenuated glomerular injury and less deposition of immunoglobulins in the glomeruli [12, 15] (fig. 2b). On a systemic level, these mice show reduced formation of antigen-specific antibodies, lower proliferation of antigen-specific lymphocytes and decreased T cell responses [12, 15]. It has been suggested that the adverse effects of leukocyte-derived *Sema4D* in glomerulonephritis are mediated by its receptor, Plexin-B1, expressed in glomeruli [12]. However, functional evidence for this has not been reported so far. It is likely that the role of *Sema4D*

in glomerulonephritis relies, at least to a significant extent, on its function in the immune system, where it mediates communication between T-cells and dendritic cells as well as between T-cells and B-cells through its alternative receptor CD72 [1, 15] (fig. 2b). A humanized anti-*Sema4D* monoclonal antibody that interferes with the binding of *Sema4D* to Plexin-B1 and CD72 is currently in clinical trials for several indications [1] and might have beneficial effects in glomerulonephritis.

Semaphorins and Plexins in Acute Kidney Injury

Acute kidney injury is a very frequent and challenging clinical problem associated with high morbidity and mortality, particularly in intensive care unit patients [16]. As a consequence of injury, tubular epithelial cells (TECs) die from necrosis or apoptosis, which triggers dedifferentiation and proliferation of surviving TECs to eventually restore tubular integrity and function. This repair process is critically influenced by an inflammatory response in the interstitium surrounding the tubules [16]. Several semaphorins have been shown to be crucially involved both in inflammatory processes promoting tubular injury as well as in epithelial repair processes that are required for restoration of kidney function.

Sema3A in Acute Kidney Injury

In normal mouse kidneys, *Sema3A* is expressed in distal and collecting tubules as well as in podocytes [17, 18] (table 1). Following acute kidney injury induced by transient ischemia or by cisplatin, *Sema3A* protein expression is upregulated in distal and collecting tubules [17, 18]. Under these pathophysiological conditions, infiltrating immune cells are likely to serve as an additional source of *Sema3A* in the kidney [18, 19]. The functional role of *Sema3A* in ischemia/reperfusion injury in vivo has been assessed by both pharmacological as well as genetic approaches employing mice, which carry a loss-of-function mutation in the *Sema3A* gene. These mice, while having normal tubular morphology and function under physiological conditions, show less tubular injury, decreased apoptosis of TECs and lower serum creatinine levels 1 day after ischemia/reperfusion injury [18] (fig. 3). This is accompanied by a decrease in the renal mRNA expression of pro-inflammatory and pro-apoptotic mediators and less neutrophil infiltration in the kidney [18]. In line with this, prophylactic treatment of mice before ischemia/reperfusion injury with an inhibitor of lipoxygenase or with a recombinant peptide, both of which block *Sema3A*-in-

Fig. 3. Semaphorins and plexins in acute kidney injury. Following acute kidney injury induced by ischemia/reperfusion, some epithelial cells die, and an inflammatory response is induced. Early after injury, Sema3A appears in the urine, where it could serve as a biomarker. Surviving TECs divide in parallel to the epithelial plane to restore epithelial architecture. In the absence of functional Sema3A, tubular injury and apoptosis are decreased, and injury-

induced inflammation in the kidney is attenuated. In the absence of Plexin-B2 or its ligands Sema4B, 4D and 4G, surviving epithelial cells fail to align their divisions with the epithelial plane, resulting in tubular obstruction. Box on lower left: an epithelial cell-cell contact is magnified, showing the interaction between Plexin-B2 and Sema4B, 4D and 4G. KO = Knockout.

duced effects in neurons [11, 20], inhibits apoptosis of TECs and lowers serum creatinine [18]. While the relative significance of the different cell types as sources for Sema3A remains to be dissected, these data establish Sema3A to promote ischemia-induced renal inflammation and tubular injury. The cellular and molecular mechanisms through which Sema3A exerts these effects are not yet entirely clear. Of particular interest is the question on the relevant cell types that are responsive to Sema3A and the identity of the Sema3A receptors expressed by them. Several lines of evidence suggest that dendritic cells and macrophages are a main target of Sema3A in acute kidney injury. Infusion of primary murine dendritic cells, that had been treated with Sema3A for 2 days, prior to ischemia/reperfusion injury increases tubular injury and the mRNA expression of pro-inflammatory mediators in the kidney [18]. Furthermore, Sema3A increases LPS-induced expression of cytokines and chemokines in a macrophage cell line and in primary murine dendritic cells in vitro, suggesting a role of Sema3A in TLR4 signaling in

these cells [18]. This would be in accordance with in vivo findings showing that administration of Sema3A aggravates the release of cytokines caused by TLR agonists or bacterial sepsis [19]. In addition to immune cells, Sema3A might directly impact on TECs, as it increases LPS-induced expression of cytokines and chemokines and also aggravates cisplatin-induced apoptosis in these cells in vitro [18]. Which receptors mediate the injury-promoting effects of Sema3A in the kidney is not known to date.

Semaphorin 4B/4D/4G-Plexin-B2 Signaling in Acute Kidney Injury

In addition to class-3-semaphorins, the adult kidney expresses several class-4-semaphorins [13, 14, 21] (table 1). While Sema4A, 4B and 4D are found on renal TECs, Sema4C is expressed in the interstitium, and the localization of Sema4G is not known. One of the receptors of these semaphorins, Plexin-B2, is strongly expressed on renal TECs [13, 21] (table 1). In mice under normal physiological conditions, genetic inactivation of

any of these semaphorins alone, of Sema4B, 4D and 4G together, or of Plexin-B2 specifically in renal TECs, has no impact on kidney morphology and function [13]. After ischemia/reperfusion injury however, Sema4B/4D/4G-triple-deficient and Plexin-B2-deficient mice display striking abnormalities in kidney repair [13]. Following the ischemic insult, surviving TECs of these mice do not show a clear preference for cell divisions parallel to the basement membrane, and cells divide perpendicular instead of parallel to the epithelial plane (fig. 3). This eventually leads to multi-layering of the tubular epithelium and to complete tubular occlusion with loss of renal function [13] (fig. 3). Experiments employing a series of transgenic mice carrying subtle mutations in the Plexin-B2 gene that interfere with particular Plexin-B2-mediated signaling pathways, and of mice with an inducible, TEC-specific inactivation of the small GTPase Cdc42 combined with in vitro experiments indicate that Plexin-B2 controls cell division orientation through its GTPase-activating protein (GAP) domain and regulation of Cdc42 activity [13]. The precise molecular mechanisms that link Sema4B/4D/4G-Plexin-B2 signaling to the spindle orientation machinery to correctly align cell divisions during kidney repair remain to be determined.

Semaphorins and Plexins as Biomarkers in Kidney Diseases

For decades, the diagnosis of acute kidney injury has been based on glomerular filtration failure that leads to the rise of the filtration markers creatinine and urea in the blood. However, these markers typically do not accumulate in the blood until hours or even days after injury. This imposes the need for new, sensitive and specific biomarkers that allow for earlier diagnosis and therapeutic intervention. While Sema3A is absent from the urine of normal mice, it becomes detectable after ischemia/reperfusion- or cisplatin-induced injury many hours before creatinine levels elevate in the serum [17]. Studies in humans have shown that these preclinical findings in mice also hold true in pediatric patients undergoing cardiopulmonary bypass surgery, where Sema3A levels in the urine rise as early as 2 h after surgery, while serum creatinine increases significantly only after 48 h [17]. Similar results were obtained in adult patients in various other clinical settings of acute kidney injury [22, 23]. Also in chronic diseases affecting the kidney, urine Sema3A has been shown to serve as an indicator of disease severity. This has been demonstrated for

diabetic nephropathy in several drug-induced and genetic mouse models of diabetes and in diabetic patients [9], as well as in hypertensive patients with chronic kidney disease [24]. Of note, in patients suffering from systemic lupus erythematosus, serum Sema3A levels have been reported to inversely correlate with disease activity and the presence of lupus nephritis [25]. The potential use of Sema3A as a biomarker is currently investigated in 2 observational clinical trials: UMIN000013422, enrolling patients with renal diseases, and NCT02406716, enrolling patients with heart failure.

Concluding Remarks

Work of the last decade has delineated crucial functions of the semaphorin–plexin system in various mouse models of kidney diseases. It has become clear that semaphorin–plexin signaling plays diverse roles in renal pathophysiology with particular semaphorins and plexins exerting beneficial and others having adverse effects. The data obtained in preclinical mouse models suggest that the semaphorin–plexin system represents a novel and promising pharmacological target in kidney diseases, and future work will have to clarify whether these findings can be translated to humans. Moreover, preclinical and clinical data show that Sema3A has the potential to serve as a biomarker in renal diseases, particularly as an early indicator of acute kidney injury. Given the versatile roles of its numerous members in diverse cell types, additional functions of the semaphorin–plexin system in renal pathophysiology are likely to emerge in the future.

Disclosure Statement

T.W. holds a patent on B-type plexin antagonists and uses thereof.

References

- 1 Worzfeld T, Offermanns S: Semaphorins and plexins as therapeutic targets. *Nat Rev Drug Discov* 2014;13:603–621.
- 2 Jongbloets BC, Pasterkamp RJ: Semaphorin signalling during development. *Development* 2014;141:3292–3297.
- 3 Peralá N, Sariola H, Immonen T: More than nervous: the emerging roles of plexins. *Differentiation* 2012;83:77–91.
- 4 Reidy K, Tufro A: Semaphorins in kidney development and disease: modulators of ureteric bud branching, vascular morphogenesis, and podocyte-endothelial crosstalk. *Pediatr Nephrol* 2011;26:1407–1412.

- 5 Guan F, Villegas G, Teichman J, Mundel P, Tufro A: Autocrine class 3 semaphorin system regulates slit diaphragm proteins and podocyte survival. *Kidney Int* 2006;69:1564–1569.
- 6 Reidy KJ, Aggarwal PK, Jimenez JJ, Thomas DB, Veron D, Tufro A: Excess podocyte semaphorin-3A leads to glomerular disease involving plexinA1-nephrin interaction. *Am J Pathol* 2013;183:1156–1168.
- 7 Villegas G, Tufro A: Ontogeny of semaphorins 3A and 3F and their receptors neuropilins 1 and 2 in the kidney. *Mech Dev* 2002;119(suppl 1):S149–S153.
- 8 Aggarwal PK, Veron D, Thomas DB, Siegel D, Moeckel G, Kashgarian M, Tufro A: Semaphorin3A promotes advanced diabetic nephropathy. *Diabetes* 2015;64:1743–1759.
- 9 Mohamed R, Ranganathan P, Jayakumar C, Nauta FL, Gansevoort RT, Weintraub NL, Brands M, Ramesh G: Urinary semaphorin 3A correlates with diabetic proteinuria and mediates diabetic nephropathy and associated inflammation in mice. *J Mol Med (Berl)* 2014;92:1245–1256.
- 10 Tapia R, Guan F, Gershin I, Teichman J, Villegas G, Tufro A: Semaphorin3A disrupts podocyte foot processes causing acute proteinuria. *Kidney Int* 2008;73:733–740.
- 11 Williams G, Eickholt BJ, Maison P, Prinjha R, Walsh FS, Doherty P: A complementary peptide approach applied to the design of novel semaphorin/neuropilin antagonists. *J Neurochem* 2005;92:1180–1190.
- 12 Li M, O'Sullivan KM, Jones LK, Lo C, Semple T, Kumanogoh A, Kikutani H, Holdsworth SR, Kitching R: Endogenous CD100 promotes glomerular injury and macrophage recruitment in experimental crescentic glomerulonephritis. *Immunology* 2009;128:114–122.
- 13 Xia J, Swiercz JM, Banon-Rodriguez I, Matkovic I, Federico G, Sun T, Franz T, Brakebusch CH, Kumanogoh A, Friedel RH, Martin-Belmonte F, Grone HJ, Offermanns S, Worzfeld T: Semaphorin-plexin signaling controls mitotic spindle orientation during epithelial morphogenesis and repair. *Dev Cell* 2015;33:299–313.
- 14 Fazzari P, Penachioni J, Gianola S, Rossi F, Eickholt BJ, Maina F, Alexopoulou L, Sottile A, Comoglio PM, Flavell RA, Tamagnone L: Plexin-B1 plays a redundant role during mouse development and in tumour angiogenesis. *BMC Dev Biol* 2007;7:55.
- 15 Li M, O'Sullivan KM, Jones LK, Semple T, Kumanogoh A, Kikutani H, Holdsworth SR, Kitching AR: CD100 enhances dendritic cell and CD4+ cell activation leading to pathogenic humoral responses and immune complex glomerulonephritis. *J Immunol* 2006;177:3406–3412.
- 16 Bonventre JV, Yang L: Cellular pathophysiology of ischemic acute kidney injury. *J Clin Invest* 2011;121:4210–4221.
- 17 Jayakumar C, Ranganathan P, Devarajan P, Krawczeski CD, Looney S, Ramesh G: Semaphorin 3A is a new early diagnostic biomarker of experimental and pediatric acute kidney injury. *PLoS One* 2013;8:e58446.
- 18 Ranganathan P, Jayakumar C, Mohamed R, Weintraub NL, Ramesh G: Semaphorin 3A inactivation suppresses ischemia-reperfusion-induced inflammation and acute kidney injury. *Am J Physiol Renal Physiol* 2014;307:F183–F194.
- 19 Wen H, Lei Y, Eun SY, Ting JP: Plexin-A4-semaphorin 3A signaling is required for toll-like receptor- and sepsis-induced cytokine storm. *J Exp Med* 2010;207:2943–2957.
- 20 Mikule K, Gatlin JC, de la Houssaye BA, Pfenniger KH: Growth cone collapse induced by semaphorin 3A requires 12/15-lipoxygenase. *J Neurosci* 2002;22:4932–4941.
- 21 Zielonka M, Xia J, Friedel RH, Offermanns S, Worzfeld T: A systematic expression analysis implicates Plexin-B2 and its ligand Sema4C in the regulation of the vascular and endocrine system. *Exp Cell Res* 2010;316:2477–2486.
- 22 Doi K, Noiri E, Nangaku M, Yahagi N, Jayakumar C, Ramesh G: Repulsive guidance cue semaphorin 3A in urine predicts the progression of acute kidney injury in adult patients from a mixed intensive care unit. *Nephrol Dial Transplant* 2014;29:73–80.
- 23 Lewandowska L, Matuszkiewicz-Rowinska J, Jayakumar C, Oldakowska-Jedynak U, Looney S, Galas M, Dutkiewicz M, Krawczyk M, Ramesh G: Netrin-1 and semaphorin 3A predict the development of acute kidney injury in liver transplant patients. *PLoS One* 2014;9:e107898.
- 24 Viazzi F, Ramesh G, Jayakumar C, Leoncini G, Garneri D, Pontremoli R: Increased urine semaphorin-3A is associated with renal damage in hypertensive patients with chronic kidney disease: a nested case-control study. *J Nephrol* 2015;28:315–320.
- 25 Vadasz Z, Haj T, Halasz K, Rosner I, Slobodin G, Attias D, Kessel A, Kessler O, Neufeld G, Toubi E: Semaphorin 3A is a marker for disease activity and a potential immunoregulator in systemic lupus erythematosus. *Arthritis Res Ther* 2012;14:R146.