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Review

Exploiting the Nephrotoxic Effects of Venom from the Sea Anemone, *Phyllodiscus semoni*, to Create a Hemolytic Uremic Syndrome Model in the Rat

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Abstract: In the natural world, there are many creatures with venoms that have interesting and varied activities. Although the sea anemone, a member of the phylum *Coelenterata*, has venom that it uses to capture and immobilise small fishes and shrimp and for protection from predators, most sea anemones are harmless to man. However, a few species are highly toxic; some have venoms containing neurotoxins, recently suggested as potential immune-modulators for therapeutic application in immune diseases. *Phyllodiscus semoni* is a highly toxic sea anemone; the venom has multiple effects, including lethality, hemolysis and renal injuries. We previously reported that venom extracted from *Phyllodiscus semoni* induced acute glomerular endothelial injuries in rats resembling hemolytic uremic syndrome (HUS), accompanied with complement dysregulation in glomeruli and suggested that the model might be useful for analyses of pathology and development of therapeutic approaches in HUS. In this mini-review, we describe in detail the venom-induced acute renal injuries in rat and summarize how the venom of *Phyllodiscus semoni* could have potential as a tool for analyses of complement activation and therapeutic interventions in HUS.

Keywords: sea anemone; hemolytic uremic syndrome; complement; complement regulators; marine envenomation; renal failure

1. Introduction

Diverse types of land animals produce natural toxins that are harmful to humans; these include venoms from snakes [1–3], spiders [4–6], scorpions [7], caterpillars [8] and platypus [9]. In marine/aquatic environments [10], various situations in which envenomation by aquatic animals has injured people have been reported. Culprits include cnidarians such as fire coral (*Millepora alcicornis*) [11,12]. Portuguese man-of-war and other jellyfishes such as box jellyfishes (*Chironex fleckeri*) [13], sea wasp (*Chiropsalmus quadrigatus*, called Habu-kurage in Japan) [14] and irukandiji (*Carukia barnesi*) [15,16], sea anemones [15,17,18], seaworms, echinoderms, molluscs such as the cone shell and the blue-ringed octopus, fishes such as scorpion fishes and sea snakes, all of which have toxic bites or stings for feedings and protection from enemies (Table 1). Other marine organisms cause food poisoning, such as ciguatera poisoning caused by consuming the flesh of *Lutjanids*, *Serranids*, *Epinephelids*, *Lethrinids* and so on [15], shellfish poisoning cause by Brevetoxins and domoic acid [19], and neurotoxin (Tetrodotoxin) poisoning of puffer fishes or globefishes [19]. Components of some venoms are highly toxic for humans and can rarely cause multiple organ failure and lethal shock.

Table 1. Marine envenomations that cause severe injuries in humans.

Classification		Type of envenomation	References
Phylum	**Genus, Species**		
Cnidaria			
	Jellyfishes		
	Portuguese man-of-war (*Physalia physalis*)	sting	[15]
	Irukandji jellyfish (*Carukia barnesi*, *Malo kingi*)	sting	[15,16]
	Mauve stinger (*Pelagia noctiluca*)	sting	[15]
	Box jellyfish (*Chironex fleckeri*)	sting	[13]
	Chesapeake Bay sea nettle (*Chrysaora quinquecirrha*)	sting	[15]
	Sea wasp (*Chiropsalmus quadrigatus*)	sting	[14]
	Fire coral (*Millepora alcicornis*)	sting	[11,12]
	Sea anemones		
	The Hell's Fire sea anemone (*Actinodendron plumosum*)	sting	[10,20]
	Night sea anemone (*Phyllodiscus semoni*)	sting	[18,21]
	Haddon's carpet anemone (*Stichodactyla haddoni*)	sting	[22]
	Snakelock's anemone (*Anemonia sulcata* (=*Anemonia viridis*))	sting	[23]
	Condylactis sp.	sting	[24]
Echinodermata			
	Sea urchins		
	Flower sea urchin (*Toxopneustes pileolus*)	sting	[25]
	Purple sea urchin (*Paracentrotus lividus*)	sting	[26]
	Sea star		
	Crown-of-Thorns starfish (*Acanthaster planci* (*Linnaeus*))	sting	[27,28]

Table 1. *Cont.*

Mollusca			
	Cone shells (*Conidae*)	sting	[29,30]
	Blue-ringed octopus (*Hapalochlaena*)	bite	[31,32]
	Shellfish poisoning by brevetoxins and domoic acid	food	[19]
Chordata			
	Stone fish, lion fish, scorpionfish (*Scorpaernidae*)	sting	[20,33–35]
	Stingray (*Dasyatidae*)	sting	[36]
	Weeverfish (*Trachinus*)	sting	[37]
	Striped eel catfish (*Plotosus lineatus*, *Plotosus japonicus*)	sting	[38]
	Globe fishes (*Tetraodontidae*)	food	[19]
Hydrophiidae			
	Hydorophis, *Laticauda*, *Pelamis*	bite	[39,40]

On the other hand, some toxins have found use as experimental agents and some have been investigated as therapeutics. For example, it was reported that NN-32 purified from the venom of the cobra *Naja naja* might have anti-cancer effects in animal models [41]. A number of venoms have been shown to have complement (C) activating components that directly or indirectly contribute to tissue damage [3,5,7,42]. One of these, the C3-like protein cobra venom factor (CVF) purified from venom of the Egyptian or Thai cobra, is widely used as an experimental tool to induce excessive activation and consumption of C in animal models [43–47]. A humanized CVF has been tested as a therapeutic approach in man [48,49]. The C activating component of brown recluse spider (*Loxosceles* genus) venom has also been proposed as a tool for biological purposes [50].

Research on the venoms of marine animals has also yielded interesting and clinically relevant data. For example, dideoxpetrasynol A, a protein toxin from the sponge *Petrosia* sp., caused apoptosis in human melanoma cells [51], *Chiropsalmus quadrigatus* toxins (CqTX) induced apoptosis in glioma cell lines [52], extracts from *Acanthaster planci* (Crown-of-Thorns) starfish also induced apoptosis in human breast cancer cell lines [53]. The pore-forming proteins Bc2 and equinatoxin (EqTx-II) from sea anemones were cytotoxic for glioblastoma cell lines [54], and another pore-forming toxin, membrane-attack complex/perforin (MACPF) domain lethal toxin from the nematocyst venom of the Okinawan sea anemone *Actineria villosa* [55] has been proposed as a cytotoxic agent to target some cancers. Several other toxin-derived agents have been shown to have antitumor activities and proposed as therapeutics [56–59]. As examples of toxins with other targets, the toxin APETx2 of the sea anemone *Anthropleura elegantissima* has been used as a pharmacological tool to inhibit $Na_v1.8$ in rat dorsal root ganglion neurons [60] in order to prevent and treat inflammatory and postoperative pain [61–63], a sea anemone polypeptide, ATX II, has been used in the long QT syndrome model [64] and was shown to have an antiarrthythmic action [65], and the ShK toxin from the sea anemone *Stichodactyla helianthus* is a potent blocker of the Kv1.3 potassium channel, inhibits T lymphocyte proliferation [66] and has been proposed as a therapeutics for autoimmune diseases such as multiple sclerosis [67]. Of note, ziconide is a derivative of conotoxin derive from a coneshell, *Conus magus*, and successfully used as a non-opioid intrathecal therapy [68,69]. Therefore, research on new toxins from marine animals might have potential to develop therapeutic agents (Table 2) and experimental materials.

Table 2. Agents extracted from venom of marine organisms and derivatives.

Organisms	Agents	Targets	References
	(A) Extracted agents		
Jellyfish			
Chiropsalmus quadrigatus	CqTX	glioma cells	[52]
Chrysaora quinquecirrha	Sea nettle nematocyst venom (SNV)	cancer cells	[70]
Starfish			
Crown-of-Thorns starfish	extracts	breast cancer cells	[53]
Sponge			
Callyspongia truncate	callystatin A	cancer cells	[71]
Discodermia dissoluta	(+)-Discodermolide	cancer cells	[57]
Dysidea arenaria	arenastatin A	cancer cells	[71]
Hyrtios altum	altohyrtin A	cancer cells	[71]
Petrosia sp.	dideoxpetrasynol A	melanoma cells	[51]
S*pirastrella spinispirulifera*, *Hyrtios erecta*	Spongistatin 1	cancer cells, leukemia	[72]
Sea anemone			
Actineria villosa	MACPF	cancer cells	[55]
Actinia equina	EqTX-II	glioblastoma cells	[54]
Anemonia viridis	ATX-II	antiarrthymia	[65]
Anthropleura elegantissima	APETx2	inflammation, postoperative pain	[60–63]
Bunodosoma caissarum	Bc2	glioblastoma cells	[54]
Radianthus macrodactylus	PTX-A	cancer cells	[59]
Stichodactyla helianthus	sticholysin I (StI)	cancer cells	[56]
Stichodactyla helianthus	ShK	T lymphocyte proliferation, Autoimmune diseases	[66,67]
	(B) Derivatives of extracted agents		
Sponge			
Discodermia dissolute	(+)-Discodermolide-paclitaxel hybrids	cancer cells	[73]
Dysidea arenaria	analogoue of arenastatin A	cancer cells	[58]
Sea anemone			
Stichodactyla helianthus	StI W111C	cancer cells	[74]
Stichodactyla helianthus	ShK analogues	autoimmune diseases	[75]
Cone shell			
Conus magus	Ziconotide (a derivative of conotoxin)	non-opioid intrathecal therapy	[68,69]

This minireview focuses on the sea anemone, a coelenterate of the phylum *Cnidaria*. Sea anemones have sting venoms to catch and immobilize small fishes and shrimps for feeding and protection. Most are not harmful for humans or only cause mild dermatitis. A few species possess highly toxic venoms and are hazardous for humans. The Hell's Fire sea anemone (*Actinodendron plumosum*) is named for the severe skin ulceration caused by its sting [10,20]. Envenomation by the sea anemone *Stichodactyla haddoni* caused shock and organ failure, including fulminant hepatitis [22,24]. *Phyllodiscus semoni* (*P. semoni*) is another sea anemone dangerous to humans. The sting usually induces severe dermatitis with ulceration and profound swelling in the regions of contact [18,21]. More serious sequelae of

envenomation by *P. semoni* include the development of acute renal failure without evidence of dysfunction of other organs [18].

We recently reported that the venom, termed PsTX-T, extracted from nematocysts of *P. semoni* had nephrotoxin activity and induced acute renal injuries in rodents [76]. This nephrotoxin acutely induced glomerular endothelial injuries, with a similar pathology to atypical hemolytic uremic syndrome (aHUS). This animal model might be attractive to analyze pathological mechanisms and to develop new agents for therapeutic use in aHUS. In the present mini review, we summarize the nature and time-course of the natural venom-induced acute renal injuries and explore the mechanisms of nephrotoxicity of *P. semoni* venom nephrotoxin in a rodent system.

2. Acute Kidney Injuries Induced by Natural Venoms

Natural venoms represent a rare cause of acute kidney injuries. These can be broadly divided into three categories; food poisons, biting poisons and sting poisons (envenomation), as indicated in Table 3. Renal injury has been reported following envenomation by snakes, spiders, caterpillars and scorpions [1,2,4,8,77–79]. Acute kidney injuries (AKI) induced by natural venoms included acute tubular necrosis caused by impairment of renal hemodynamics, intravascular hemolysis, rhabdomyolysis, disseminated intravascular coagulation (DIC) and direct toxin-mediated effects, including thrombotic microangiopathy similar to that observed in HUS. There are many reports of renal injuries caused by snake bites [78,80], usually accompanied by systemic organ failures and/or shock. For instance, snake envenomation often induced hemolysis, rhabdomyolysis and DIC, and sometimes was accompanied by acute renal failure with thrombotic microangiopathy, particularly following bites of taipan (*Oxyuranus scutellatus*) [81], tiger snake (*Notechis scutatus*) [82], or the "Fer-de-Lance" pit viper (*Botherops lanceolatus*) [83]. In Japan, envenomation by habu-snakes induced systemic reactions with hemolysis, DIC and AKI [84]. The habu-snake venom was also reported to directly induce acute endothelial injuries in glomeruli [85]. In addition to snake bites, stings of bees and wasps, envenomation by scorpions and spiders and other causative creatures have been reported as causes of AKI (Table 3).

Renal injuries caused by marine animal toxins can also divided into these three categories. Marine envenomation can cause dermal injuries, neurotoxicity, hemolysis, and systemic shock reactions, including anaphylactic shock; some victims developed acute renal failure (Table 3). The causes of renal injuries include systemic shock, hemolysis, rhabdomyolysis, and direct nephrotoxic effects. For instance, acute renal failure with hemolysis was caused by a Portuguese man-of-war sting [86,87]; minimal change nephritis was described in association with fire coral (*Millepora* species) exposure [12]; tetrodotoxin of puffer fish is orally active and induces AKI as well as other organ failures [88]; envenomation by sea anemone and sea snakes was also reported to cause acute renal failure [18,39,89,90].

Table 3. Natural toxins that induce acute kidney injuries in humans and animal experimental models.

Organisms		Type of renal injuries/pathology	Human or animal models (References)
1. Land envenomation			
(1) Biting			
Snakes: viper (*Viperidea*) and cobra (*Elapidae*)			
	Habu snakes (*Trimeresurus*)	Mesangial proliferative glomerulonephritis, mesangial injuries	[84,85,91,92]
	Mamushi snake (*Gloydius blomhoffii*)	ATN * with hemolysis	[92]
	Tiger snake (*Notechis scutatus*)	TMA **, ATN with rhabdomyolysis	[82,93]
	"Fer-de-Lance" pit viper (*Botherops lanceolatus*)	TMA	[83]
	Bothrops (*B.*) *jararaca*, *B. jarararacussu*, *B.moojeni*	Renal cortical necrosis	[1,94,95]
	Brazilian rattlesnake (*Crotalus durissus*)	Rhabdomyolysis and hemolysis related renal injuries	[96–98]
	Russell's viper (*Vipera russellii*)	Cortical necrosis, ATN with rhabdomyolysis, mesangiolysis	[2,99]
	Lansberg's pit viper (*Porthidium lansbergii*)	ATN, glomerular and tubular changes	[100,101]
	Taipan (*Oxyuranus scutellatus*)	HUS ***	[81]
Spider			
	Brown recluse spider (*Loxosceles intermedia*)	Hemolysis and rhabdomyolysis related renal injuries, glomerulonephritis	[4,102]
(2) Sting			
Honey Bee (*Apis mellifera*)		ATN with hemolysis and rhabdomyolysis, renal ischemia	[103]
Hornet (*Vespa crabro*)		ATN with hemolysis and rhabdomyolysis	[104]
Wasp (*Vespa magnifica*)		ATN with hemolysis and rhabdomyolysis, or by direct toxic effects	[105,106]
Iranian scorpion (*Hemiscorpius lepturus*)		HUS	[107,108]
Lonomia caterpillars (*Lonomia obliqua*)		Hemodynamic changes and disseminated intravascular coagulation related renal injuries	[8,109]

Table 3. *Cont.*

(3) Food poison				
	Mushroom			
		Cortinarius sp.	Chronic interstitial nephritis	[110,111]
		Amanita (*A.*) *phylloides*, *A. proxima*, *A. smithiana*, *A. pseudoporphyria*, *A. boudierim*, *A. gracilior*, *A. echinocephala*	ATN, acute interstitial nephritis	[112–116]
		Lepiota sp.	Acute renal failure (no detail pathology)	[117]
	Squirting cucumber (*Ecbalium Elaterium*)		Renal failure (no detail pathology)	[118]
	Herb			
	Chinese herb (*Aristolochia* sp.)		Chinese harb nephropathy, ATN, tubulointerstitial nephritis	[119,120]
		2. Marine envenomation		
(1) Biting				
	Sea snakes (*Hydrophis cyanocinctus*, *Laticauda semifasciata*)		ATN, renal ischemia	[39,89,90,121]
(2) Sting				
	Lionfish (genus *Pterois*)		ATN	[122]
	Jelly fishes			
		Portuguese man-of-war (*Physalia physalis*)	ATN with hemolysis	[86,123]
		Box-jellyfish (*Chirodropids*)	ATN	[124]
	Fire coral (*Millepora species*)		Minimal change nephrotic syndrome	[12]
	Sea anemone (*Phyllodiscus semoni*, *Condylactis* sp.)		ATN, TMA, renal ischemia	[18,24,76]
(3) Food poisons				
	Puffer (Globe) fish (*Lagocephalus*, *Lactoria*)		ATN with rhabdomyolysis, renal ischemia	[88,125,126]

* Acute tubular necrosis; ** Thrombotic microangiopathy; *** Hemolytic uremic syndrome.

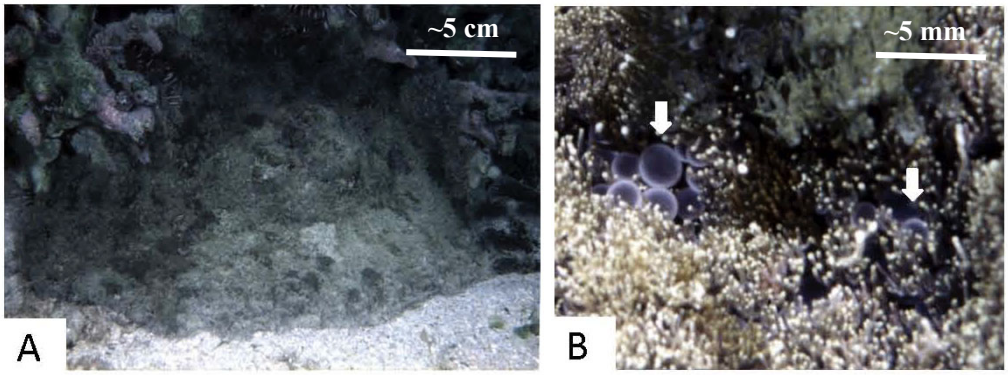
3. Envenomation by Sea Anemones including *P. semoni* and the Acute Kidney Injuries

The sea anemone, categorized in phylum coelenterate (*Cnidaria*), class *Anthozoa*, is armed with venom-secreting nematocysts to aid in the capture of prey and to protect from predators. Most sea anemones are harmless for man or at worst cause dermatitis by contact irritants/toxins. However, venom of some sea anemones is extremely harmful for man; *Actinodendron plumosum* (Hell's Fire sea

anemone), *Actineria villosa* (Okinawan sea anemone, called fusa-unbachi in Japan) and *P. semoni* all cause severe injury including dermatitis [15,127], hepatitis [24], renal failure [18] and anaphylactic shock [22]. The sea anemones *Anemonia sulcata* and *Anemonia equine*, were reported to cause severe dermatitis with hyper- and parakeratosis with many infiltrative cells in the skin [128], while toxins from other sea anemones, including *Actinia equina*, *Anemonia sulcata*, *Anthopleura xanthgrammica*, *Bunodosoma granulifera*, *Bunodosoma caissarum* and *Stichodactyla helianthus*, were cytolytic, haemolytic, neurotoxic and cardiotoxic [129–135].

P. semoni is categorized in *Aliciidae*, a family of sea anemones, commonly called "night sea anemone", distributed in the Western Pacific ocean; it is also called in Japanese "unbachi-isoginchaku" which means "sea-wasp anemone" in Okinawa (South Japan). The shape of the animal changes with its circumstances (Figure 1A). The sting induces severe dermatitis with local ulceration and swelling that often takes months to resolve. We recently reported a more serious sequela of envenomation by *P. semoni*; the victim developed unexplained acute renal failure without evidence of dysfunction of other organs [18,76]. The venom, PsTX-T, which was extracted from the nematocysts and a 115 kDa protein extracted from venom which we called PsTX-115, also induced nephrotoxic effects in rodents [76]. From the venom, haemolytic protein toxins were also identified, a 20 kDa protein, PsTX-20A, and 60 kDa proteins, PsTX-60A and -60B [136,137].

Figure 1. Photographs of *Phyllodiscus semoni* (Unbachi-isogintyaku) and nematocysts. (**A**) The intact organism as found in the seas off Okinawa Island; (**B**) Close-up view of the globular vesicles (white arrows) with nematocysts. Scales bar is in the upper right corner of frame B. The underwater photos were taken by M. Mizuno.



4. Thrombotic Microangiopathy, Renal Pathology and Renal Function after Exposure of Rats to Venom of *P. semoni*, PsTX-T

We reported that acute renal injuries were induced by intravenous injection of 0.03 mg/body of crude venom of *P. semoni*, PsTX-T, in rats [76]. Although the nephrotoxin was purified as the ~115 kDa protein extracted from venom (PsTX-115), PsTX-T was more convenient to obtain the enough amount and was useful to investigate the pathology and the further experiments. Therefore, we used PsTX-T to investigate the detail pathology. The venom had specific acute nephrotoxic effects because the toxin directly bound in glomeruli. Renal damage included endothelial injuries in glomeruli and, later, extended into glomerular epithelial cells. Electron microscopy showed endothelial injuries as early as

10 min after PsTX-T administration; after 24 h, the renal pathology was mainly thrombotic microangiopathy with subendothelial widening of the glomerular capillary, mesangiolysis and deposition of fibrin-like material (Figure 2A-1 to -5). Up to day 5, fibrin exudation from glomerular capillaries was observed, accompanied with severe tubular necrosis (Figure 2). Crescent formation was observed in focal and segmental glomeruli in some rats on day 10 after injection of PsTX-T (Figure 2D-1 to -5). After 14 days, focal glomerular sclerosis remained in renal cortex, but most glomeruli were restored (Figure 2E-1 and -2). At that time, most of the renal tubular necrosis was also recovered (Figure 2E-3 to -5). Semi-quantitative microscopy findings are summarised in Figure 3A. When we analyzed accumulation of total inflammatory cells in glomeruli, the number of inflammatory cells peaked between day 3 and day 5 (Figure 3D). The glomerular neutrophil infiltration, likely a major feature of the pathology, peaked between 24 h and day 3.

Figure 2. Time course of renal pathology after injection of PsTX-T. A-1, B-1, C-1, D-1, E-1 and F-1 are glomeruli in cortex under 200× magnifications. A-2, B-2, C-2, D-2, E-2 and F-2 are glomeruli under 400× magnifications. A-3, B-3, C-3, D-3, E-3 and F-3 are tubuli in cortex under 200× magnifications. A-4, B-4, C-4, D-4, E-4 and F-4 are outer medulla under 200× magnifications. A-5, B-5, C-5, D-5, E-5 and F-5 are inner medulla under 200× magnifications. For light microscopic (LM) analyses, tissues were fixed in methacarn overnight and embedded in paraffin. Two-micrometer sections were stained with periodic acid-Schiff. Time course is noted across the top of the plates. Arrows indicate deposition of fibrin-like materials. Arrowheads indicate cellular proliferation. Scale bars are in the upper left corner of frames A-1 to A-5. Adapted from [76], Copyright © 2007, with permission from Elsevier.

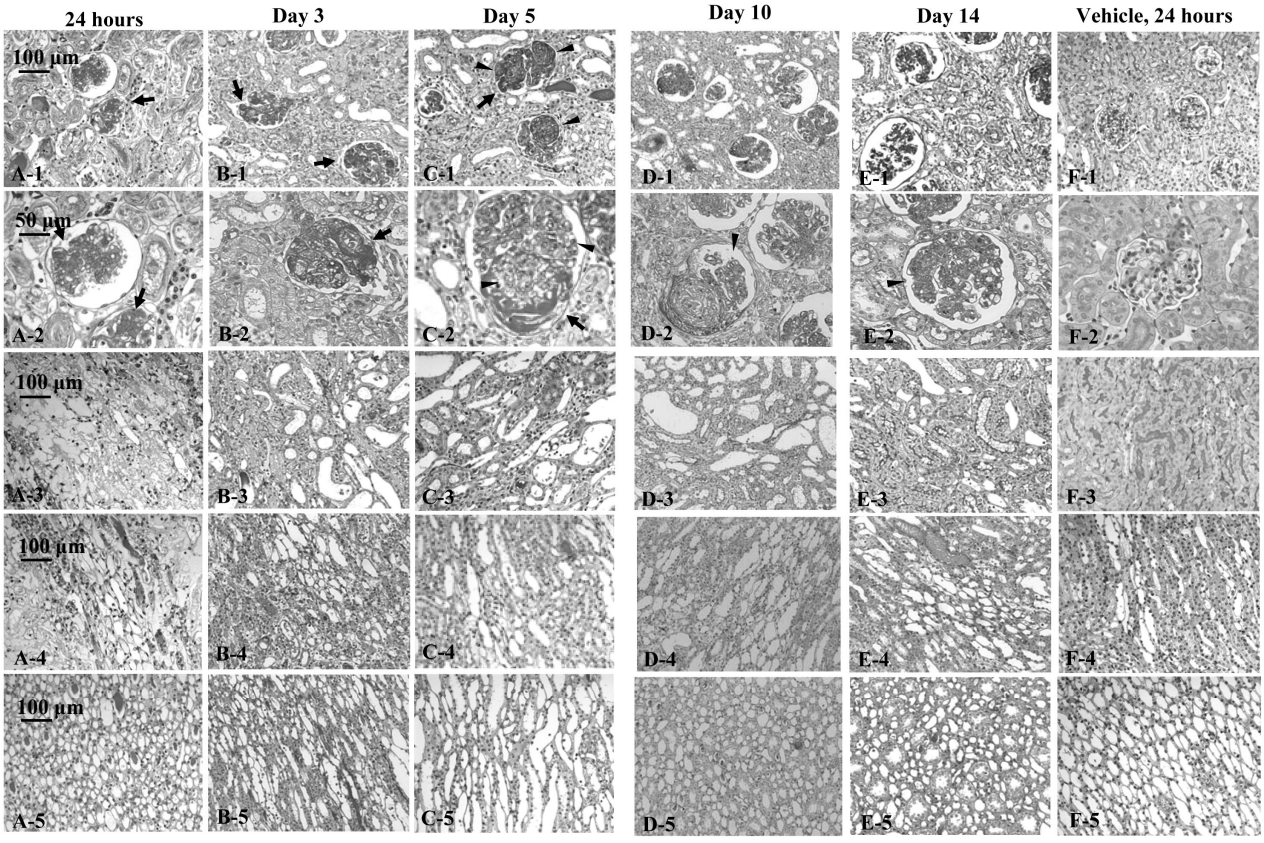
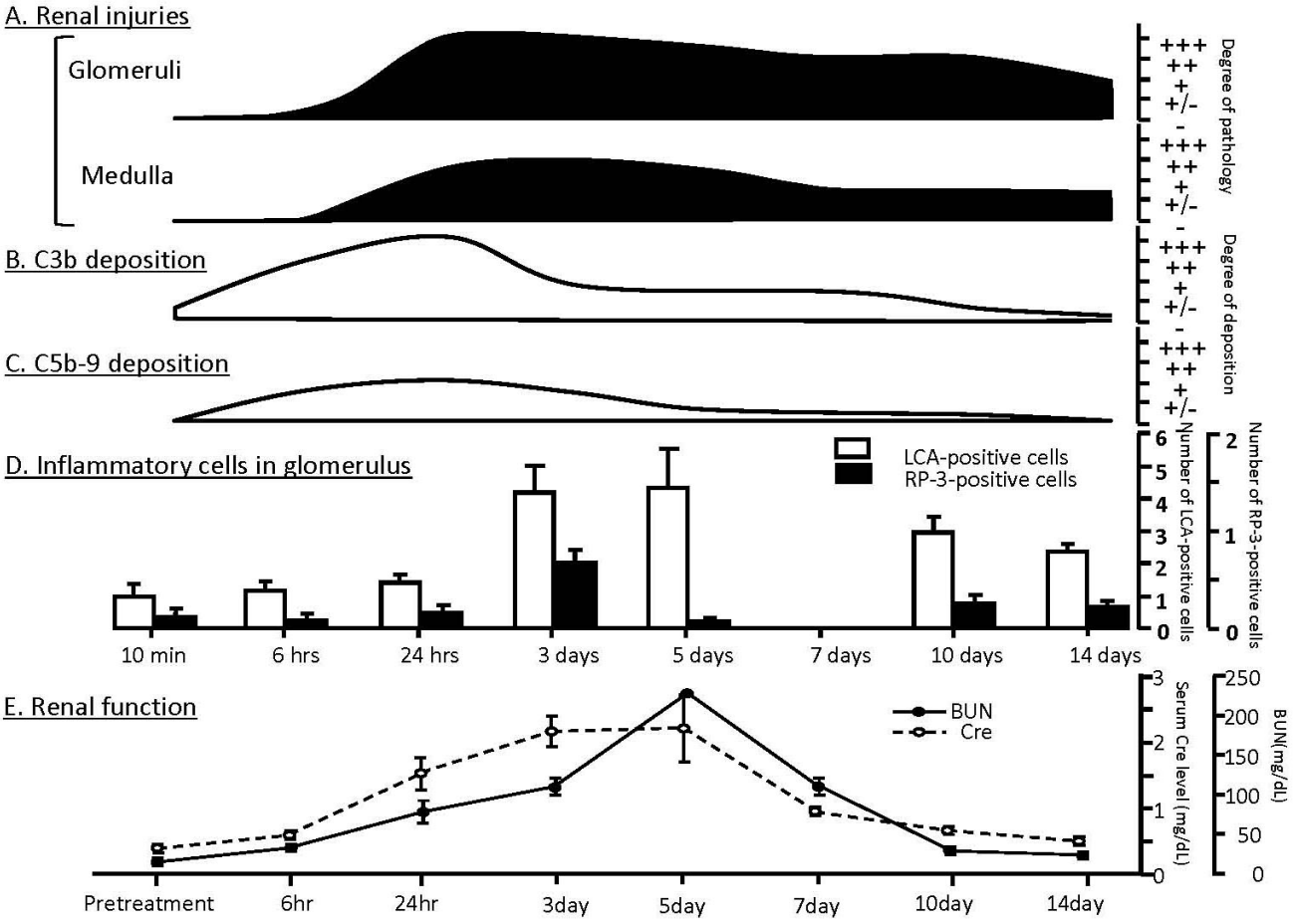


Figure 3. Summary of time course of renal injuries, C3b/C5b-9 deposition and infiltration of inflammatory cells in glomeruli after intravenous injection of PsTX-T. Panel A summarises severity of renal injuries assessed under light microscopy and scored as -, no change, through +++ injury, scaled according to the number of affected glomeruli and area of tubular injuries: -, no change; +/-, minimal change; +, less than 25%; ++, between 25% and 75%; +++, widespread injury with severe damage involving over 75%. Panels B and C summarise degrees of C3 deposition and membrane attack complex (MAC; C5b-9) deposition in glomeruli of the kidney after PsTX-T administration; the degree of deposition of C3b or C5b-9 was scored as −, negative, through +++ according to the positive staining area: −, negative staining; +/−, minimal staining; +, positive staining less than 25%; ++, between 25% and 50%; +++, more than 50%. Panel D shows total number of infiltrating inflammatory cell recognized as leukocyte common antigen (LCA)-positive cells and RP-3 positive neutrophils in glomeruli. Panel E shows time course of impaired renal function. Cre: creatinine, BUN: blood urea nitrogen. Each value is shown as mean ± SE.



The time course of renal dysfunction is summarized in Figure 3E. Briefly, serum creatinine and blood UN levels were elevated at 6 h after administration of PsTX-T although ultra-microscopic changes had already been observed at 10 min after i.v. injection of PsTX-T. Levels of serum creatinine and blood UN peaked between day 3 and 5 after PsTX-T injection (Table 4). Decreases of blood hemoglobin and hematocrit levels were observed on day 7.

Table 4. Causes of renal thrombotic microangiopathy including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS).

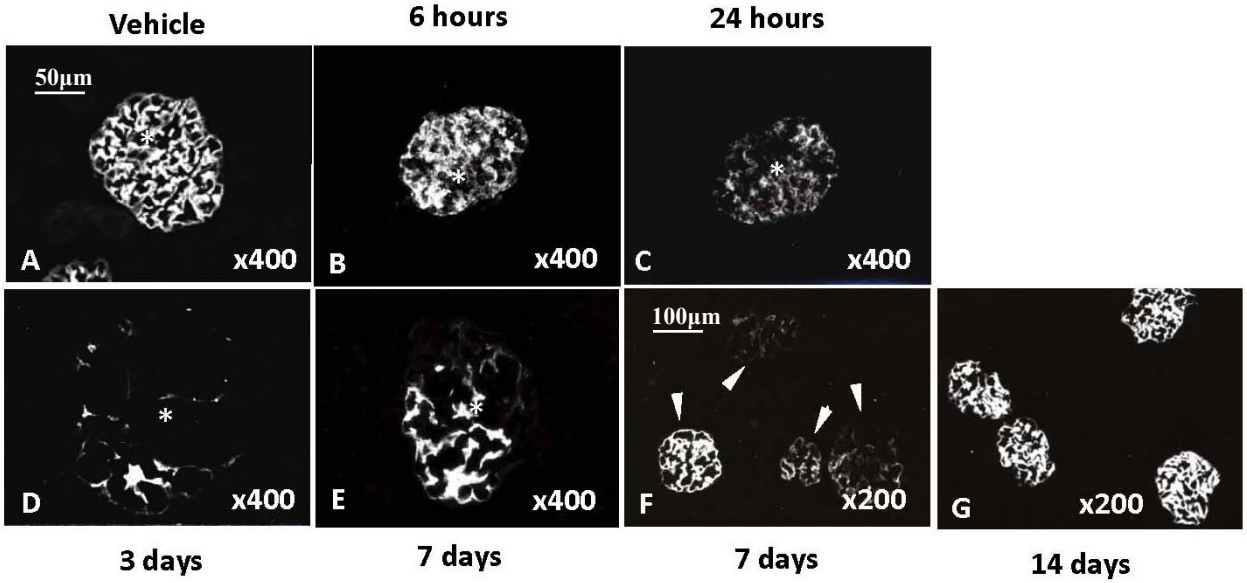
1. Infection-related		
	Bacteria	
		Escherichia coli (O157:H7, O104:H4, *etc.*), *Shigella dysenteriae* type 1, *Salmonella typhi*, *Salmonella pneumonia*, *Campylobacter jejuni*, *Yersinia pseudotuberculosis*, *Pseudomonas* sp., *Bacteroides* sp., *Mycobacterium tuberculosis*
	Virus	
		Rubella, Coxsackievirus, Echoviruses, Influenza virus, Epstein-Barr virus, Rotaviruses, Cytomegalovirus, Human immunodeficiency virus
2. Drug-related		
	Immunosuppressant and chemotherapy	
		Cyclosporine, Tacrolimus, OKT3, Dopidogrel, Valacyclovir, Cyclosporine, Mitomycin C, Cisplatin, Daunorubicin, Cytosine arabinoside, Methyl CCNU, Chlorozotocin, Zinostatin, Deoxycoformycin, Gemcitabine
	Other drugs	
		Oral contraceptives, Quinine, Penicillin, Penicillamine, Metronidazole, Ticlopidine, Clopidogrel
3. Toxins		
		Carbon monoxide, Bee sting, Arsenic poisoning, Snake bites, Iodine, *etc.*
4. ADAMTS 13 * related TTP		
		Deficiency of ADAMTS 13 activity, Inhibitor of ADAMS 13 (antibody to ADAMS 13)
5. Abnormalities of complement components and complement regulators (aHUS)		
		Mutations in complement regulators/components (factor H, factor I, factor B, C3, CD46) Anti-factor H autoantibodies, *etc.*
6. Secondary		
	Malignant neoplasm	
	Transplantation	(conditioning for hematopoietic stem cell transplantation, GVHD **, chronic transplant rejection)
	Autoimmune disease	
		Systemic lupus erythematosus, Scleroderma renal crisis, Antiphospholipid antibody syndrome, Polyarteritis nodosa, Primary glomerulopathies (MPGN ***, *etc.*), malignant nephrosclerosis with malignant hypertension
7. Other reasons		
	Pregnancy or postpartum	
	Radiation	

This table is modified from the following references [138–142]. * A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ** Graft versus host diseases; *** Membranoproliferative glomerulonephritis.

5. Impairment of Complement Regulator Expression and Enhanced Complement Deposition in Kidney after Exposure of PsTX-T in Rat

Deposition of complement activation products C3b and C5b-9 was observed as early as 1 h after injection of PsTX-T and peaked at 24 h (Figure 3B,C). Complement deposition appeared to precede morphological changes as assessed by IF analysis. Decreased expression of the complement regulators (CRegs) CD55 (decay accelerating factor; DAF) and CD59 accompanied the severe morphologic changes of renal injury [76]. As disease resolved at later timepoints, glomerular CRegs expression such as CD55 was restored in parallel with recovery of renal integrity (Figure 4).

Figure 4. Distribution of CD55 in glomeruli after PsTX-T injection. After administration of PsTX-T, binding of anti-CD55 was decreased at 6 h (**B**) and lowest between 24 h and 3 days (**C** and **D**). Expression of CD55 was restored in most of the glomeruli by 14 days after injection of PsTX-T (**G**). For immunohistological analysis, kidney was embedded in OCT compound (Sakura Finetechnical Co., Tokyo, Japan), snapfrozen in liquid nitrogen, cryostat-sectioned at 2 μm, and fixed with acetone for 10 min at room temperature. To investigate the expression of CD55, sections were incubated with anti-rat CD55 (clone; RD-III7) followed by fluorescenin isothiocyanate-labeled anti-rat CD55 as our previous report [76]. Original magnifications are shown in right bottom of each frame. Scale bars are in the upper right corner of frames A and F.



6. Thrombotic Microangiopathy in Kidney, HUS, aHUS and Impairment of Complement Regulation

Thrombotic microangiopathy is induced under various situations (Table 4). Typical HUS is a thrombotic microangiopathy with hemolytic anemia, thrombocytopenia and acute renal failure that is epidemic, diarrhea related and caused by Verotoxin (Shiga toxin)-producing *Escherichia coli* (O157:H7, O104:H4). Atypical HUS (aHUS) is non-diarrhea related and familial. At least half of aHUS cases are caused by impairment of C regulation. Mutations in factor H, CD46 (membrane

cofactor protein; MCP), factor I factor B, and C3, or autoantibodies against factor H have all been described as causes of aHUS [138,143,144].

Plasma exchange therapy and plasma infusion were the conventional management for aHUS [145]. Renal replacement therapy was performed in patients with renal failure. A complement-targeted therapy, eculizmab which is an anti-C5 antibody developed to prevent C-activation related anemia in patients with PNH and improve survival [146], has recently been used to treat aHUS associated with C dysregulation [147]. Although recurrence of aHUS and graft loss is common post-renal transplantation [148,149], long-term remission and graft survival was reported in post-transplant aHUS patients treated with eculizmab [150,151]. Eculizmab has thus become attractive as a therapeutic choice for aHUS associated with C dysfunction. For aHUS, and perhaps also for typical HUS, there is potential to develop new and presumably more effective anti-complement therapies; development of better animal models of aHUS with thrombotic microangiopathy for testing new agents.

The PsTX-T-induced renal injuries observed in the rat model were accompanied by impaired local C regulation and C activation, and the pathology closely resembled that seen in the acute phase of HUS, later progressing to focal and segmental glomerular sclerosis. In this model, we also showed that an anti-complement agent, sCR1, improved the renal injuries [76]. Until now, many anti-C agents have been developed to try to control pathologic conditions and were reported to be useful in various animal modes [152–154]. In the present, replacement therapy of C1-inhibitor is also another established treatment for hereditary angioedema in addition to anti-C5 antibodies for C-dependent hemolytic anemia in patients with paroxysmal nocturnal hemoglobinuria, respectively [155,156]. Like these, development of anti-C agents is an important category and development of new animal models may have large potential to test the newly developed agents. These findings suggest that PsTX-T induced renal injury provides an animal model that will be useful in testing anti-C therapies for aHUS and typical HUS.

7. Conclusion and Future

The nematocyst-extracted venom, PsTX-T, acutely caused thrombotic microangiopathy with C activation and decreased membrane CReg expression in rat glomeruli, confirming that PsTX-T was a direct nephrotoxin. The nature and time course of glomerular injuries after administration of PsTX-T closely resembled the course and pathology seen in HUS, including local C activation and loss of C regulators in the kidney. Suppression of C activation until expression of CReg recovers inhibits the renal injuries induced by PsTX-T. This model might be useful to search for pathologic mechanisms and to develop therapeutic approach for HUS, especially to develop anti-complement therapy.

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