

Endogenous Inhibitors of Kidney Inflammation

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Received: June 4, 2015 Revised: July 12, 2015

Accepted: July 16, 2015

Published online: October 26, 2015

ABSTRACT

Although inflammation is the physiological response to pathogen invasion and tissue damage, it can also be responsible for significant tissue damage. Therefore, the inflammatory response must be carefully regulated to prevent critical inflammatory damage to vital organs. Typically, local endogenous regulatory mechanisms adjust the magnitude of the response such that the injurious condition is resolved and homeostasis is maintained. Humoral mechanisms that restrain or inhibit inflammation include glucocorticoid hormones, anti-inflammatory cytokines such as IL-10 and transforming growth factor- β (TGF- β), and soluble cytokine receptors; other mediators facilitate tissue healing, like lipoxins and resolvins. There is growing evidence that inflammation plays a critical role in the development and progression of heart disease, cancer, stroke, diabetes, kidney diseases, sepsis, and several fibroproliferative disorders. Consequently, understanding the mechanisms that regulate inflammation may offer therapeutic targets for inhibiting the progression of several diseases. In this article, we review the significance of several novel endogenous anti-inflammatory mediators in the protection from kidney injury and the potential of these regulatory molecules as therapeutic targets for treatment of kidney inflammatory diseases.

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Key words: Inflammation; fibrosis; adenosine; inflammatory reflex; Slit

Trostel J, Garcia GE. Endogenous Inhibitors of Kidney Inflammation. *Journal of Nephrology Research* 2015; 1(2): 61-68 Available from: URL: <http://www.ghrnet.org/index.php/jnr/article/view/1237>

INTRODUCTION

Inflammation is an essential immune response that enables survival during infection or injury and maintains tissue homeostasis under several conditions. The inflammatory response consists of four components: Inflammatory inducers, the sensors that detect the inducers, the inflammatory mediators induced by the sensors, and the target tissues^[1]. In many cases, inflammation is self-limiting because of intrinsic mechanisms designed to control the inflammatory process. Resolution of inflammation is an active and highly regulated process that involves cells and soluble factors.

Cells contributing to resolution of inflammation

During inflammation, apoptotic cells are ingested typically by macrophages; and ingestion of apoptotic cells triggers macrophages to release anti-inflammatory cytokines such as TGF- β and IL-10. Apoptosis is not the only mechanism by which macrophages switch from being pro-inflammatory at the outset of an inflammatory response to anti-inflammatory later in the process. Tissue damage induced by inflammation promotes production of glucocorticoid hormones that can convert monocytes/macrophages from pro-inflammatory to an anti-inflammatory state.

Other cells that contribute to resolution of inflammation are T regulatory cells. These T cells which are characterized by the secretion of TGF- β and IL-10, also can suppress inflammation. T regulatory cells have been found to suppress various immune cells such as CD8+ T cells, dendritic cells (DCs), monocytes/macrophages,

B cells, natural killer cells, and natural killer T cells. T regulatory cells are essential to maintain a non-inflammatory environment in the gut, to suppress allergic immune responses to environmental food antigens, and to decrease chronic inflammation^[2,3].

Soluble factors contributing to resolution of inflammation

Soluble products that contribute to resolution of inflammation include the inflammation-resolving cytokines IL-10 and TGF- β . Other secreted proteins driving resolution include secretory leukocyte protease inhibitor (SLPI) that suppresses the ability of TNF- α to activate neutrophils.

Other secreted proteins besides cytokines play controlling roles in the resolution of inflammation including adenosine and acetylcholine. Adenosine signaling through the A2A adenosine receptor (A2AR) on immune cells is essential to suppress inflammation. In A2AR deficient mice the intensity and duration of inflammatory responses are increased.

Acetylcholine release after vagus nerve stimulation inhibits production of TNF- α , IL-1 β , IL-6, and IL-18 by macrophages via activation of the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR).

In sum, multiple mechanisms normally ensure resolution of inflammation. However, nonresolving inflammation can be caused if the inflammatory trigger is not eliminated, it is prolonged, or it is excessive^[1,3].

In the kidney, the concept of “glomerular self-defense” was introduced by Kitamura and Fine in 1999. They clearly demonstrated that during inflammatory injury, glomerulus acquires the potential for protecting itself from further damage^[4]. The authors identified intracellular signaling molecules that impose checks and balances on

pro-inflammatory pathways during kidney inflammation, such as heat shock proteins, antioxidant enzymes, kinase-inhibiting proteins, and cyclin kinase inhibitor. In addition, the role of secreted/extracellular formation of soluble products driving resolution of inflammation was described, including: inhibitors of cytokines and growth factors, proteinase inhibitors, complement regulatory proteins, oxygen radical scavengers, and inhibitors of adenine nucleotides^[4].

Evidence supports that inflammation has an important role in the development and progression of most chronic kidney diseases. It involves a complex inflammatory process in which following tissue injury, epithelial/endothelial cells release cytokines/chemokines to recruit and activate inflammatory cells. Activated inflammatory cells secrete profibrotic cytokines and cytokines/chemokines to attract more inflammatory cells and amplify the inflammatory reaction. Mesangial cells and fibroblasts are activated, tubular epithelial to mesenchymal is triggered, and excessive extracellular matrix deposition is observed (Figure 1)^[5,6]. Therefore, advances in our understanding of kidney inflammation would be of great therapeutic benefit for inhibiting progressive kidney fibrosis.

In this review we highlight novel endogenous mechanisms underlying resolution of kidney inflammation and discuss how these mechanisms can be targeted to protect from kidney injury in inflammatory diseases.

ADENOSINE AND ITS RECEPTORS

Adenosine is an endogenous purine nucleoside present in the extracellular space at low concentrations; however, elevation in extracellular adenosine is found in conditions of ischemia,

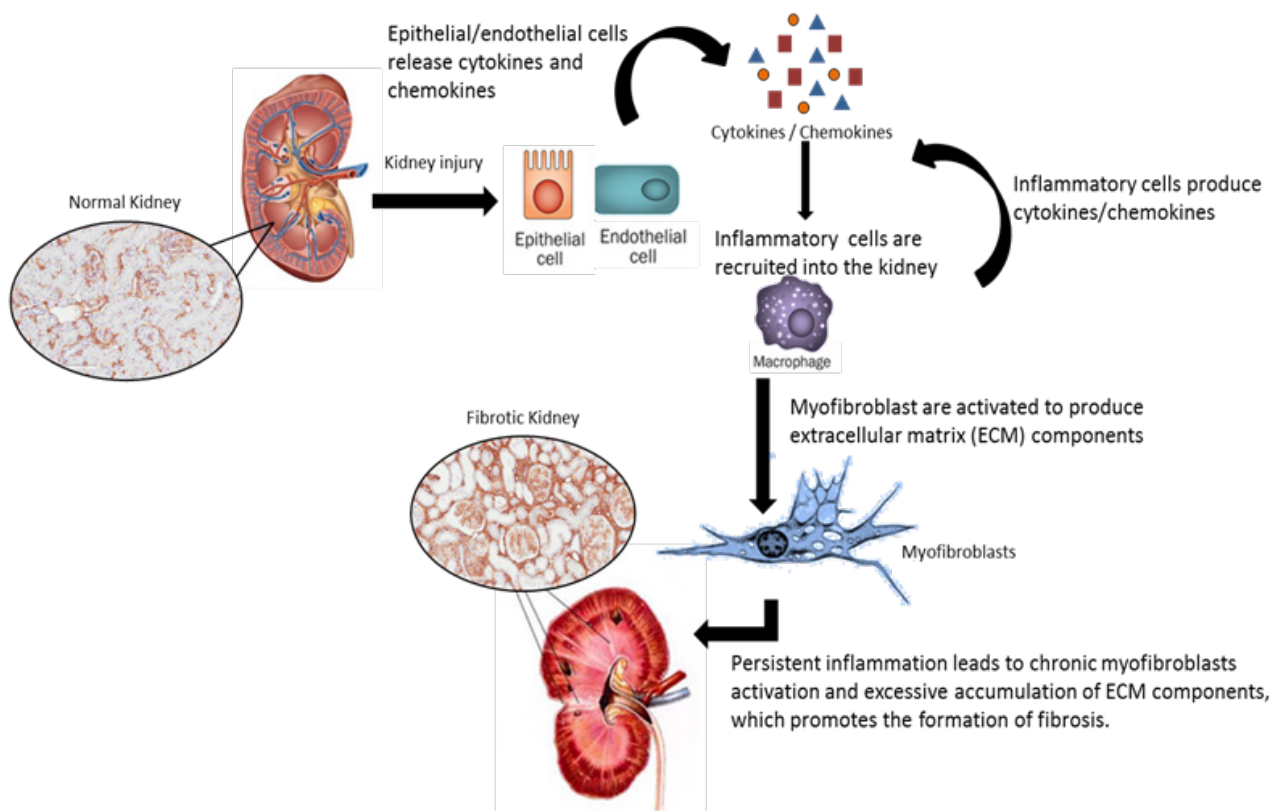


Figure 1 Development of fibrosis in chronic inflammatory reaction: Inflammation will damage the kidney, following tissue injury; kidney cells release inflammatory mediators (cytokines/chemokines) to attract inflammatory cells, these inflammatory cells release cytokines/chemokines to attract more inflammatory cells to amplify the inflammatory response. Infiltrates secrete cytokines and growth factors; coordinated action of cytokines, growth factors such as TGF- β , and extracellular matrix components, promote differentiation of fibroblast to myfibroblasts. Myofibroblasts produce extracellular matrix (ECM) components. Persistent inflammation leads to chronic myofibroblast activation, and excessive accumulation of ECM which promotes the formation of a permanent fibrotic scar.

hypoxia, inflammation, and trauma^[7,8]. Adenosine following its release binds specific cell-surface adenosine receptors. There are four distinct receptor subtypes for adenosine, that is A₁, A_{2A}, A_{2B} and A₃ adenosine receptors. Adenosine receptors are G-protein coupled receptors and particularly Gs-protein-coupled A_{2A} and A_{2B} adenosine receptors can increase intracellular cAMP levels by activating adenylate cyclase. Adenosine A_{2A} receptors (A_{2A}Rs) are generally regarded as the receptor subtype most relevant for the anti-inflammatory effect of adenosine. Activation of A_{2A}R on macrophages can inhibit the production of interleukin (IL) -12, TNF- α , and NO, and enhance the secretion of IL-10 in response to lipopolysaccharide^[9].

Critical role of A_{2A}R in the control of inflammation

A_{2A}Rs are found ubiquitously in the body; their expression is highest in the immune system and the striatopallidal system in the brain. Adenosine triggers A_{2A}R on activated immune cells and leads to an increase in intracellular cAMP. cAMP, an intracellular off signal, inhibits intracellular signal pathways, leading to the interruption of proinflammatory processes in immune cells. The essential role of A_{2A}Rs in downregulation of inflammation and protection from tissue injury was demonstrated by markedly enhanced liver damage and sepsis in A_{2A}R-deficient mice using sub-threshold doses of inflammatory stimuli^[10].

Kidney protection from ischemia-reperfusion by A_{2A}Rs

Pharmacological activation of A_{2A}Rs attenuates ischemia-reperfusion injury in mice and rats. Pretreatment with a selective agonist of A_{2A}Rs (5 hours before ischemia) improves kidney function, reduces tubular injury, and ischemic necrosis. Importantly, delayed administration of the A_{2A}R agonist until the reperfusion period is able to reduce plasma creatinine levels and kidney injury^[11-13]. This protection is mediated by reduction in the expression of adhesion molecules (ICAM-1 and P-selectin) in endothelial layers of peritubular capillaries and interlobular arteries^[12]. Tissue protection of A_{2A}R agonists in ischemia-reperfusion requires activation of receptors expressed on bone marrow-derived cells. Using chimeric mice in which bone marrow was ablated by lethal radiation and reconstituted with donor bone marrow cells derived from WT or A_{2A}R-KO mice, it was observed that A_{2A}R activation reduced the induction of pro-inflammatory cytokines in WT mice receiving WT bone-marrow cells (WT \rightarrow WT mice) but not in WT mice receiving bone-marrow cells lacking the A_{2A}R gene (A_{2A}R KO \rightarrow WT mice)^[14]. The signaling intermediate of A_{2A}R-mediated kidney protection is cAMP, since in vivo treatment with cAMP mimics the effect of A_{2A}R agonists and in vitro studies, A_{2A}R agonists increase cAMP accumulation and decrease activated neutrophils adherence^[11,15].

Role of A_{2A}R activation in diabetic nephropathy

Activation of A_{2A}R before or after the induction of diabetes protects kidneys from injury. Macrophages infiltration and the levels of cytokines in the urine (CCL2/MCP-1, TNF- α , and IFN- γ) were significantly reduced in rats treated with a A_{2A}R-agonist (ATL-146e, delivered through osmotic minipump). As a consequence of the reduction of kidney inflammation the renal function was better preserved in rats treated with ATL-146e. In addition, interstitial fibrosis, mesangium expansion, and thickness of the tubular basement membrane were significantly attenuated in the ATL 146e-treated groups^[16]. Interestingly, pharmacological activation of A_{2A}R before or after induction of diabetes restored the mRNA expression of podocin and nephrin^[16].

Activation of podocytes A_{2A}R preserves its function and structure

Although A_{2A}Rs are found predominantly in immune cells, it was demonstrated that immortalized mouse podocytes express A_{2A}Rs. Activation of A_{2A}Rs in puromycin aminonucleoside nephropathy, a model characterized by proteinuria and effacement of podocytes foot processes, attenuated these effects^[17].

A_{2A}Rs activation protects form kidney injury in the acute and progressive phases of glomerulonephritis

Crescentic glomerulonephritis (GN) is a life-threatening disease in which glomerular inflammation progresses rapidly into chronic kidney disease. Using a model of anti-glomerular basement membrane (GBM) antibody-associated glomerulonephritis (GN), that is analogous to human crescentic GN, we found that macrophages infiltrating nephritic kidney express A_{2A}R^[18]. Pharmacological activation of A_{2A}Rs in the acute phase of the disease (8 hours after the induction of the disease) or in the progressive phase of the disease (at day 6 after the injection of the antibody) was able to protect from the acute and established injury by decreasing macrophages and CD8⁺ cells infiltration and suppressing the expression of chemokines^[18,19]. Notably, when pharmacological activation of A_{2A}R was delayed until extracellular matrix deposition was established (day 14 after the induction of the disease), glomerular macrophages infiltration was reduced by 83%. There was also a marked improvement in glomerular lesion histology, as well as decreased proteinuria. A_{2A}R activation significantly reduced type I, III, and IV collagen deposition, and E-cadherin expression was restored in association with a reduction of α -smooth muscle actin-positive myofibroblasts in the interstitium, suggesting that activation of A_{2A}Rs arrest kidney disease progression^[19].

A_{2A}R attenuates kidney interstitial fibrosis in unilateral ureteral obstruction model (UUO)

Using the unilateral ureteral obstruction model it was demonstrated that pharmacological activation of A_{2A}R starting at day one after UUO, significantly decreased collagen deposition at day 3 after UUO. At day 7 after induction of UUO, collagen deposition, alpha-smooth muscle actin expression and TGF- β expression were reduced and E-cadherin expression was restored. In contrast, in A_{2A}R deficient mice, kidney interstitial fibrosis was exacerbated^[20]. The protective effect of A_{2A}R activation, however, was lost at day 14 post-UUO. These studies suggest that pharmacological activation of A_{2A}R protects from early progressive interstitial fibrosis in UUO.

A_{2B} adenosine receptors

Stimulation of A_{2B}R upregulates IL-6 and plays a pro-inflammatory role in the exacerbation of allergic asthma and colitis. However, studies using gene-deficient mice have shown an anti-inflammatory role of A_{2B}, since A_{2B}R deficient mice have spontaneous vascular inflammation and exacerbated lung injury. Because A_{2B}R are expressed on both immune (macrophages, lymphocytes, dendritic cells, and neutrophils) and non-immune cells (smooth muscle cells, endothelial cells, and epithelial cells), these controversial results may be caused by difference in cell type specific responses to adenosine via A_{2B}R during inflammation^[8,21-23].

A_{2B}R protects kidney from ischemia during ischemia preconditioning (IP)

IP protects from kidney injury and this effect was associated with increased expression of A_{2B}R within the reno-vasculature. Moreover,

mice lacking this receptor were not protected from ischemia and the anti-inflammatory effects of kidney IP were abolished^[24]. Using A2BR bone marrow chimeric mice it was demonstrated that A2BR^{-/-} → A2BR^{+/+} chimeric mice showed similar degree of kidney protection by IP as A2BR^{+/+}, suggesting that reno-vascular A2BR (but not bone-marrow cells A2BR) is responsible for increased kidney resistance to ischemia and attenuates ischemia reperfusion injury^[24].

A2BR attenuates diabetic nephropathy

In a model of diabetic nephropathy the expression of A2BR was induced in the kidney vasculature. Treatment with an A2BR agonist attenuated histological changes in the kidney, reduced albuminuria, VEGF expression, and urinary MCP-1 excretion, and restored the expression of nephrin. In contrast, in A2BR deficient mice diabetic nephropathy was more severe, indicating that A2BR could be a therapeutic target for diabetic nephropathy^[25].

A2BR-mediated induction of IL-6 contributes to kidney fibrosis

Recently, it was reported the development of kidney fibrosis in ADA deficient mice (that have increased levels of adenosine because the catabolism of adenosine is prevented due to the lack of adenosine deaminase) and in angiotensin II-infused mice. Treatment with an A2BR antagonist or genetic deletion of A2BR attenuated fibrotic changes, suggesting that adenosine/A2BR signaling was responsible for kidney fibrosis. The authors also found that unilateral ureteral obstruction-induced fibrosis was attenuated in A2BR deficient mice. Interestingly, using kidney explants was demonstrated that adenosine increased IL-6 and pro-collagen mRNA levels, effects that were abolished using explants from A2BR deficient mice or an A2BR antagonist^[26]. These studies suggest that adenosine/A2BR signaling induces IL-6 production to contribute to kidney fibrosis.

INFLAMMATORY REFLEX/CHOLINERGIC ANTI-INFLAMMATORY PATHWAY

There is increasing evidence for a bidirectional communication between the immune and neuroendocrine systems. Cytokines, peptide hormones, and neurotransmitters, as well as their receptors, are present in the brain and in the endocrine and immune systems. Several immunoregulatory cytokines, including IL-1, IL-2, IL-6, IFN- γ , and TNF are produced not only in the immune system but in the neuroendocrine system as well. On the other hand, the synthesizing enzyme choline acetyltransferase, the signaling molecule acetylcholine, and the respective receptors (nicotinic and muscarinic) are expressed in non-neuronal cells. As an example, acetylcholine, the principle vagal neurotransmitter, is produced by epithelial cells, T lymphocytes, and endothelial cells. Recently, it has been identified that stimulation of the vagus nerve activates adrenergic splenic neurons to release norepinephrine that stimulates acetylcholine synthesis in splenic memory T cells. Acetylcholine released by these splenic T cells binds to $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) expressed on macrophages in the red pulp and marginal zone to suppress the synthesis and release of cytokines^[27-29]. Vagal nerve stimulation (VNS) protects against systemic inflammation in experimental ischemia and reperfusion, hemorrhage and resuscitation, pancreatitis, colitis, endotoxemia, septic shock, and severe sepsis^[27,30]. In addition, stimulation of the $\alpha 7$ nAChR attenuates experimental arthritis and pancreatitis^[31,32]. In contrast, in $\alpha 7$ nAChR-deficient mice, inflammation is markedly increased in endotoxemia and adjuvant arthritis^[29,33].

Inflammatory reflex attenuates kidney ischemia-reperfusion injury

Pre-ischemic treatment with cholinergic agonists, nicotine or GTS-21 (a selective $\alpha 7$ nAChR agonist), reduced neutrophil infiltration and TNF production, and as a consequence of the decreased kidney inflammation, the acute tubular damage and kidney dysfunction were attenuated. Interestingly, in vagotomized animals, pretreatment with nicotine significantly attenuated kidney injury after ischemia-reperfusion, suggesting that activation of $\alpha 7$ nAChR localized in the kidney mediates the protective effect of the cholinergic agonists^[34]. Unfortunately, delayed treatment with $\alpha 7$ nAChR agonists after the onset of reperfusion, did not protect kidneys from injury.

More recently it was demonstrated that in mice exposed to ultrasound (US) 24 hours before ischemia-reperfusion, the renal function was preserved and the kidney injury was attenuated by activating the cholinergic anti-inflammatory pathway. Splenectomy, lack of CD4⁺T cells, and absence of $\alpha 7$ nAChR removed the protection elicited by US, supporting the key role of the inflammatory reflex in US-prevention of ischemia-reperfusion injury^[35].

Although these studies suggest that vagus nerve, spleen, T, cells and the $\alpha 7$ nAChR are required for kidney protection in ischemia-reperfusion, the possibility that localized renal $\alpha 7$ nAChR protects from kidney damage during ischemia-reperfusion cannot be excluded^[34,36].

Interestingly, in a recent study, adoptive transfer of splenocytes from mice previously exposed to ultrasound protected recipient mice from kidney ischemia-reperfusion injury, suggesting that ultrasound alone affects splenocyte function^[36].

Nicotinic acetylcholine receptor agonists protects septic acute kidney injury

In a model of acute kidney injury induced by lipopolysaccharide (LPS) in mice, administration of nicotine or GTS-21 (a selective $\alpha 7$ nAChR agonist), previous to lipopolysaccharide administration, reduced kidney damage, leukocyte infiltration, serum TNF- α , and kidney concentration of cytokines/chemokines. In addition, $\alpha 7$ nAChR agonists attenuated kidney NF κ B activation, an effect that was associated with decreased proteasome activity in renal tissue *in vivo*. These studies indicate that nicotinic agonists attenuates LPS-induced kidney injury by suppression of inflammation and proteasome activity^[37].

Consequences of impairment of cholinergic anti-inflammatory pathway

It has been reported that in the coarctation-induced hypertension model in rats and in spontaneously hypertensive rats (SHRs), the vagal tone, the expression of the vesicular acetylcholine transporter (VACHT) (that takes acetylcholine into secretory organelles where the transmitter is stored until release), and the $\alpha 7$ nAChR were significantly reduced. In addition, proinflammatory cytokines were increased in the kidney, heart and aorta in SHRs. Evidence of hypertension induced-end-organ damage was also found in SHRs. These effects were prevented when SHRs were treated chronically with PNU-282987, an $\alpha 7$ nAChR agonist. Importantly, in $\alpha 7$ nAChR deficient mice subjected to hypertension by clipping 1 kidney artery, the levels of proinflammatory cytokines and hypertension induced-end-organ damage were greater than in WT controls^[38]. These studies suggest that diminished $\alpha 7$ nAChR signaling is a major mechanism in the pathogenesis of cardiovascular inflammation and end organ damage in hypertension.

Recently, we found that the absence of $\alpha 7$ nAChR in glomerulonephritis amplifies inflammation and accelerates onset of fibrosis, indicating that the endogenous nicotinic acetylcholine receptor $\alpha 7$ subunit is essential to inhibit inflammation and progressive kidney injury in glomerulonephritis^[39].

SLIT PROTEINS

Slit are secret proteins known for their role of repulsion in axon guidance and neuronal migration^[40]. Slit proteins and their Robo receptors have been also shown to play a crucial role in development of non-CNS organ systems including the kidney, heart, and lung. Both neuronal and leukocyte cell migration share similar characteristics and, interestingly, Slit has been found to inhibit leukocyte migration^[41].

There are three Slit genes and each gene has a distinct expression pattern: Slit 1 is specific to the brain, Slit 2 and Slit 3 are expressed in the brain as well as other tissues. The expression of Slit 2 in the kidney and lung is comparable to that in the brain. Expression of Slit3 is the highest in the lung and also detectable in the kidney, brain, heart, spleen, and lymph nodes^[41].

Slits modulate inflammation in experimental crescentic glomerulonephritis

In glomerulonephritis, endogenous glomerular Slit2 expression was downregulated. Treatment with recombinant Slit2 in the acute phase of the disease (treatment commenced 6 hours after the induction of the disease) resulted in improved kidney function, less kidney damage, and reduced macrophage infiltration. These studies suggest that Slit2, given early, is able to inhibit leukocyte recruitment during the initiation period and thus attenuate the disease process. However, treatment delayed on day 7 after the induction of the disease did not improve kidney function although kidney damage was to some extent improved. These results indicate that late treatment with recombinant Slit2 was unable to resolve inflammation that was already present but may have been able to inhibit further leukocyte recruitment^[42].

Slit 2 attenuates kidney ischemia-reperfusion injury and dysfunction

Slit2 protein is detected in the glomeruli and tubulointerstitium of normal kidneys. However, endogenous levels of Slit2 were significant downregulated after ischemia-reperfusion. Administration of exogenous Slit2 1 hour before the induction of the ischemia-reperfusion injury, prevented acute tubular injury and markedly reduced infiltration of neutrophils and monocytes/macrophages into the post-ischemic kidney^[43,44]. In *in vitro* studies, it was found that Slit2 reduced neutrophil capture, neutrophil adhesion to activated endothelial cells, and chemoattractant-induced neutrophil transendothelial migration^[44]. These studies indicate that Slit2 potently inhibits multiple steps involved in recruitment of circulating neutrophils and that Slit2 represents a potential strategy for the prevention and treatment of acute kidney injury.

STANNIOCALCIN

Stanniocalcin is a naturally occurring and ubiquitously expressed calcium-regulating peptide. The mammalian stanniocalcin-1 (STC-1) gene is widely expressed and its mRNA levels are highest in the ovary, followed by kidney, adrenal, prostate, and heart. Within the kidneys, STC-1 is involved in transport-related processes, organogenesis, and mitochondrial function^[45]. From

an inflammatory perspective, STC-1 attenuates chemokinesis and decreases the chemotactic response to chemokines by blunting the rise in intracellular calcium, following chemokine stimulation in macrophages. In addition, STC-1 suppresses superoxide generation in macrophages^[46,47].

Stanniocalcin attenuates inflammation and kidney injury in anti-glomerular basement membrane (GBM) glomerulonephritis (GN)

In WT mice, anti-GBM GN led to a glomerular accumulation of macrophages, crescent formation, sclerotic glomeruli, and tubulointerstitial injury. Macrophage infiltration was significantly attenuated in STC-1 transgenic (Tg) mice and consequently, the crescentic formation, sclerotic glomeruli, and tubulointerstitial injury were markedly reduced. In addition, kidney function was preserved in STC-1 Tg mice. Interestingly, infiltration of T cells in the interstitium were similar in WT and STC-1 Tg mice, suggesting that STC-1 has no significant effect on T-cell infiltration. In addition, there was no difference in the expression of cytokines characteristic of TH1- or TH2-mediated T-cell responses, suggesting that STC-1 does not affect T-cell activation^[48].

Stanniocalcin protect from ischemia-reperfusion injury

Using mouse ischemia-reperfusion kidney injury model in wild-type (WT) and STC-1 transgene (Tg) mice, that display in the kidney preferential expression of STC-1 Tg in endothelial cells and macrophages, it was observed that transgenic overexpression of STC-1 confers resistance to ischemia-reperfusion. In WT mice kidney function was decreased and cellular vacuolization, tubular dilatation, and cast formation were observed following ischemia-reperfusion. Kidney injury was associated with increased macrophages and T cells infiltration. In contrast, in STC-1 Tg mice the kidney function was preserved and kidney injury prevented. Protection from kidney injury in STC-1 Tg mice was mediated through suppression of oxidant stress. In WT kidneys marked elevation in superoxide and hydrogen peroxide was observed but not in STC-1 Tg kidneys. However, pre-treatment of STC-1 Tg mice with paraquat (a generator of reactive oxygen species) at a low dose, which does not produce kidney injury, reproduced the results observed in WT mice after ischemia-reperfusion.

The protective role of stanniocalcin in ischemia-reperfusion was further supported by the finding that stanniocalcin deficient mice displayed high susceptibility to ischemia-reperfusion damage^[49,50].

PERSPECTIVE

One of the most challenging aspects of studying inflammation is the diversity and complexity of the inflammatory mediators and their effects on target tissues, making the development of anti-inflammatory therapy singularly difficult.

Anti-inflammatory agents should be active drugs that reduce production or activities of proinflammatory mediators. In addition, therapies need to have minimal risks of organ toxicity while ensuring that host immune defense is not impaired. Therapeutic strategies should involve combined interventions and each intervention should target at least one pathway, not just a molecule.

Although new agents are in rapid stage of development, the reinforcement of endogenous defense mechanisms by pharmacological manipulations (for example, using agonists) may provide novel avenues to the treatment of inflammatory diseases. Notably, targeting natural regulators of inflammation should be associated with less secondary effects.

Table 1 Potential therapeutic applications of natural inhibitors of inflammation in kidney diseases.

Preventive treatment	A _{2A} R	A _{2B} R	Slit2	α7nAChR/VNS	Stanniocalcin
Perioperative acute kidney injury	✓	✓	✓	✓	✓
Early phase	✓		✓	✓	✓
Glomerulonephritis	✓		✓	✓	✓
Ischemia/reperfusion	✓	✓	✓	✓	
Diabetic nephropathy					
Late phase	✓				
Glomerulonephritis	✓				
Ischemia/reperfusion	✓				
Diabetic nephropathy					

Endogenous mechanisms of downregulation of inflammation could be used as follow: A_{2A}R agonists, A_{2B}R agonists, Slit2, VNS/α7nAChR agonists, and stanniocalcin could be used to prevent ischemia-reperfusion injury. In the early phase of kidney diseases A_{2A}R could inhibit the production of pro-inflammatory mediators from inflammatory cells, induce the production of the anti-inflammatory IL-10, and protect podocytes. Slit2 and stanniocalcin may prevent infiltration of inflammatory cells and avert amplification of the inflammation; activation of α7nAChR may inhibit the production of pro-inflammatory mediators by macrophages and avoid activation of inflammatory cells. Treatment with A_{2A}R agonists once the disease is established may arrest the progression of kidney diseases. In table 1 we summarize the potential therapeutic applications of natural inhibitors of inflammation in kidney diseases, and include the table.

ACKNOWLEDGMENT

This work was supported in part by Norman S. Coplion Grant (G.E.G.) and National Institutes of Health DK082509 (G.E.G.).

This manuscript is a tribute to and in memory of Lili Feng, a model scientist that always demonstrated equal creativity and talent as an investigator. Lili Feng was recognized as a superb mentor to young scientists, many of whom have gone on to distinguished careers in the biomedical sciences.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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