Ischemic Acute Renal Failure

An inflammatory response against injured & dying renal cells

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Epitaph of a kidney cell:

"Do not go gentle into that good night.
Rage, rage against the dying of the light."

- Dylan Thomas

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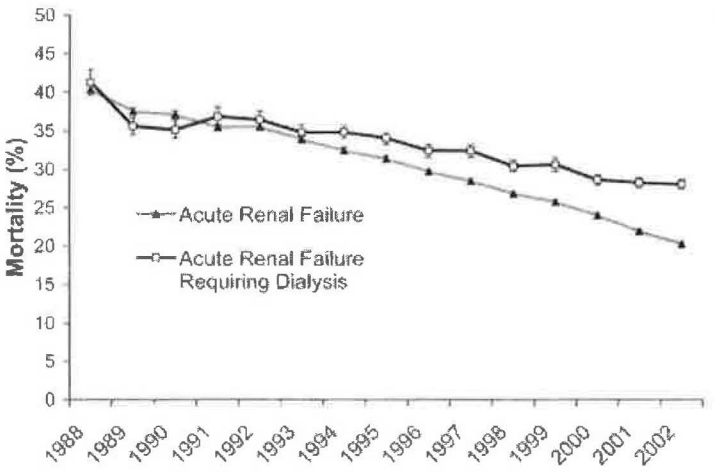
Research Interests:

Management of renal/ pancreas transplant recipients
Pathophysiology of acute renal failure,
Transplant rejection and tolerance

Parts of this grand rounds will be published in the chapter, "The Inflammatory response to ischemic acute renal injury" by CY Lu & M Senitko, in next edition of Seldin and Giebisch "The Kidney".

The clinical problem: the mortality of acute renal failure remains high.

Acute renal failure (ARF)[a] is a syndrome characterized by a decline in renal function over the course of hours to weeks, and is associated with renal parenchymal injury, primarily to the renal tubules. It occurs in approximately 5% of inpatients and 30% of patients in intensive care units [1]. A recent meta-analysis indicates that the mortality of patients with ARF remains 50% despite modern medical technology [2]. Two other studies using insurance records suggest that the mortality has decreased over recent years [3;4]. The difference between the meta-analysis and the retrospective insurance studies is not clear. But, the latter may have included more patients with less severe ARF. In any case, even the most optimistic studies show a recent mortality of approximately 40% [5]. We need to do better.



High mortality after acute renal failure
(Waikar SS J Am Soc Nephrol 2006. 17:1143-1150).

The highest mortality occurs in patients who require dialysis. However, even small decreases in renal function are associated with increased mortality. For example, after cardiothoracic surgery in over 4000 patients, an increase in serum creatinine of 0.1 to 0.5 mg/dl increased mortality by 90% at 30 days after surgery [6].

The continued high mortality of ARF contrasts with the improved survival after myocardial infarction, which has dropped from 50% to 6% over the last 25-30 years [7]. Initially promising therapies for ARF have not only failed in clinical trials, but in some cases, harm rather than help. These now defunct therapies include loop and osmotic diuretics, renal dose dopamine, atrial natriuretic peptide, insulin-like growth factor and endothelin-receptor antagonists [8].

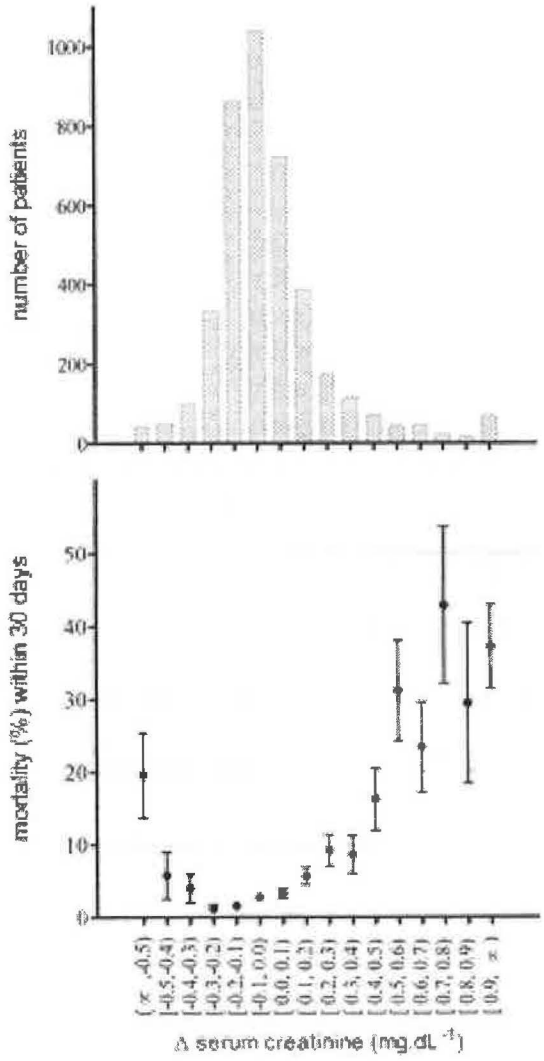
Why is this mortality so high? Answering this question is a major challenge in modern nephrology. This grand rounds will discuss some emerging concepts about how the inflammatory response to ischemic renal injury exacerbates, and may ameliorates that injury.

[a] The nomenclature for acute renal failure has been changed over the years. Previously, this syndrome was called "acute tubular necrosis" or ATN; more recently, some prefer the term "acute kidney injury" or AKI.

Problems in making the diagnosis of ARF.

ARF is one major cause of acute renal dysfunction.

One major difficulty in treating ARF is making the diagnosis in time to make a difference in the course of the disease. The problem is differentiating ARF from the other etiologies of acute renal dysfunction. These etiologies have been divided into three broad categories, and have been discussed in many excellent standard textbooks and review articles (for example [1]). We summarize them briefly.



Small increases in serum creatinine are associated with increased mortality. Lassnigg A. J. Am Soc Nephro 15:1597-1605. 2004.

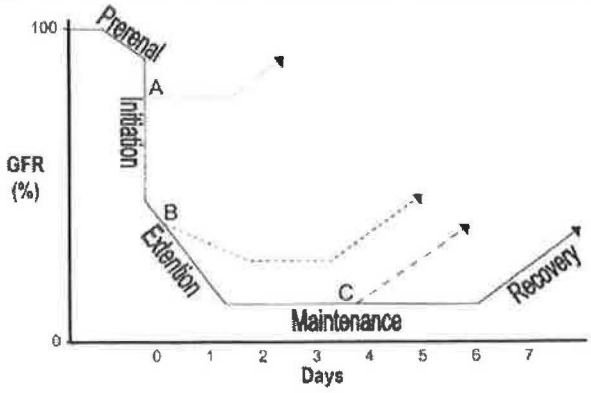
1) Pre-renal causes occur in 55-60% of patients. In these situations, the renal parenchyma is intact, and the decrease renal function is due to decreased perfusion of the kidneys. These include decreased intravascular volume, for example after hemorrhage; decreased cardiac output, for example after excessive doses of antihypertensives; renal vasoconstriction, for example after excessive cyclosporine doses; and administration of drugs that impair autoregulation of renal blood flow, for example angiotensin-converting enzyme inhibitors or inhibitors of prostaglandin synthesis inhibitors.

2) Post renal causes occur in less than 5% of patients but should not be missed because many of these causes may be treated. Again, the renal parenchyma is intact, and the decreased renal function is caused by obstruction of urine flow. Obstruction may occur in the ureters, bladder neck, or urethra.

3) Intra-renal causes occur in the remainder of patients. Unlike pre-renal and post-renal causes of renal dysfunction the initial pathophysiology lies within the kidney and is accompanied by early structural lesions in the parenchyma. Intra-renal causes include diseases of the large renal vessels; glomeruli and renal microvasculature; and tubulointerstitial nephritis , for example associated with allergic responses to drugs.

ARF, the focus of this grand rounds, is a major intra-renal cause of renal dysfunction. In the clinical setting, multiple etiologies are often present at the same time. These include decreased renal perfusion (ischemia), injury of non-renal organs, infection, and toxins (either exogenous such as radiocontrast and other drugs, or endogenous such as myoglobin). Indeed a difficulty in treating ARF may be the multiple etiologies, each of which may have a different pathophysiology.

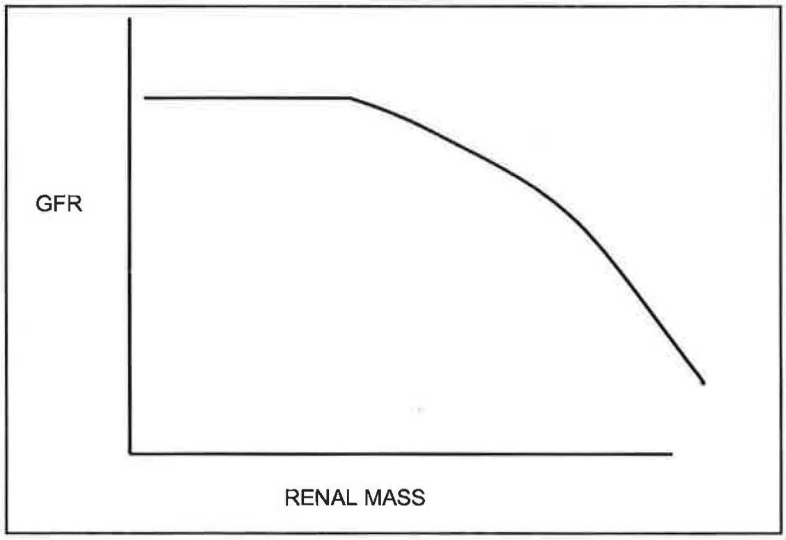
This grand rounds will focus on ischemic ARF, which contributes to many cases of ARF.



Molitoris. J Am Soc Nephrol 14: 265-267 2003.

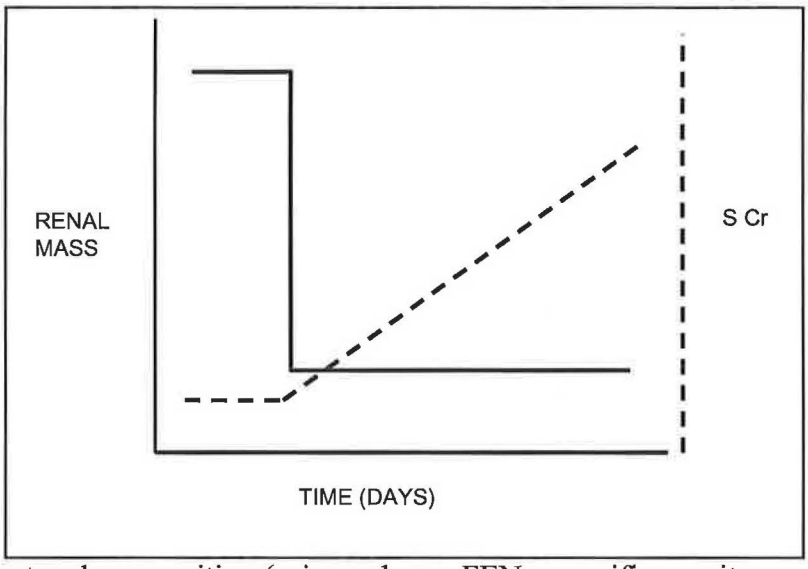
<u>Difficulty in making the diagnosis of ARF early enough to initiate therapy</u>.

Although making the diagnosis of renal dysfunction is conceptually simple, and easy at late stages in the disease when few therapeutic options are available. The problem is making the diagnosis early enough for meanful treatment. Ischemic ARF may be divided into 5 major phases: prerenal, initiation, extension, maintenance, and recovery [9;10]. Unfortunately, our patients are usually well into the maintenance phase before we make the diagnosis.



Because we do not know how to easily and directly measure renal injury, our current diagnosis relies on assaying two major renal functions and assuming that decreased functions are directly correlated with injury. Unfortunately, this may not be true, particularly early after injury [8;11]. One function is the glomerular filtration rate (GFR). Even if we were able to easily and reliably measure the GFR, this would be a poor indicator of injury because, in many patients, the renal mass must be markedly reduced before the GFR decreases. An excellent example is the preserved GFR of normal people who lose half their renal mass. These normal people are living kidney donors who give one of their two kidneys to a loved one with endstage renal disease. Furthermore, we have problems measuring the GFR. We rely on the serum creatinine as

surrogate. Unfortunately, it takes time (in many cases, days) for the serum creatinine to rise after renal injury, the same increment in serum creatinine may have different clinical implications depending the baseline creatine, and, in addition, the serum creatinine depends on the patient's diet, muscle mass, and metabolic state. These issues of measuring the GFR and interpreting the serum creatinine were ably discussed by Dr. Henry Quinones in a recent Grand Rounds.



The other major renal function used to diagnose renal injury is the urine output and composition (urine volume, FENa, specific gravity, etc). However, the normal kidney may put out 0.5 to almost 50 liters of urine in a day. The normal urine may be concentrated and contain almost no sodium, or be dilute and rich in sodium depending upon the subject's physiologic state. Interpreting what urine the kidney should be producing in a given patient at a given time may be a formidable challenge, and requires a detailed history and excellent serial physical exams. For example, a high FENa and low urine osmolality may be found in a hypotensive, oliguric patient with ARF, or in a normal person who has just ingested a big MAC combo, super-sized, at MacDonald's.

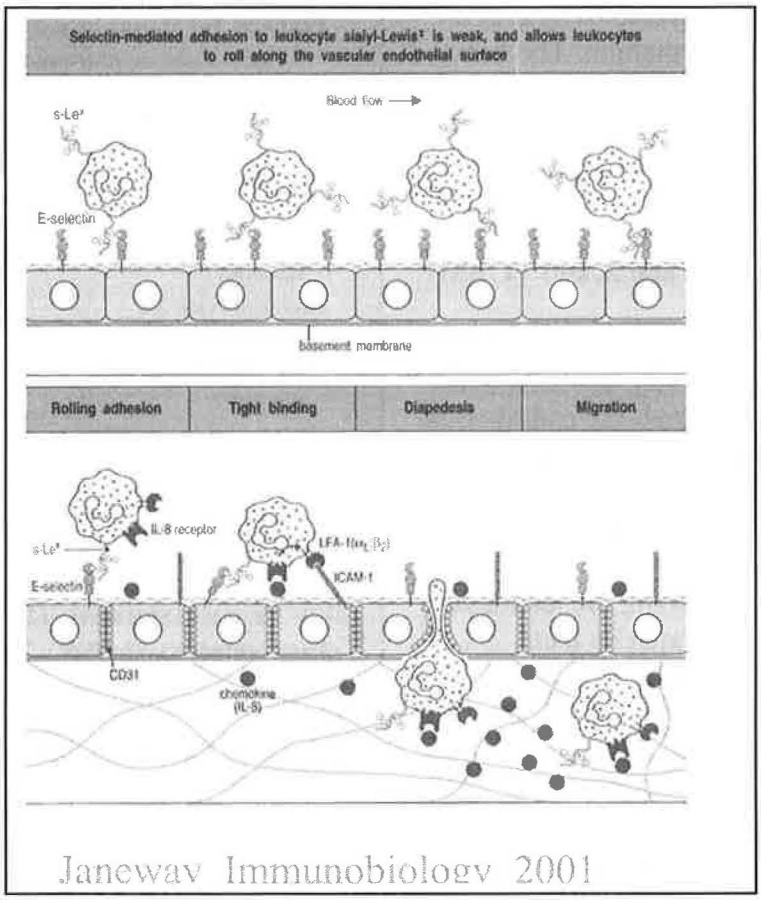
An important and easily available test is the urine analysis. If "renal failure casts" are present, the likelihood of ARF is very high [12]. Unfortunately, many patients with ARF will not have "renal failure casts", and the urine may not be examined by experienced observers. The urine analysis is an underutilized test.

Despite these limitations, the serum creatinine and urine output are what are available now. Definitions for ARF based on these measurements are used in recent multicenter studies: PICARD (Program to Improve Care in Acute Renal Disease) [13], and the RIFLE criteria ("risk of renal dysfunction: injury to the kidney") of the Acute Dialysis quality Initiative (ADQI) [14-17]. Those wishing to read excellent discussions of the current clinical state of treating ARF, complete with unanswered questions, may wish to read these important articles.

We need an "instantaneous" marker of renal injury analogous to the cardiac troponin. New markers of renal injury are being investigated that may fulfill that need. The most promising are molecules produced by injured renal tubules. These include interleukin 18, KIM 1 [18], and NGAL [19-21]. The latter was reviewed by Dr. John Hartono at a recent resident update conference.

Inflammation exacerbates ischemic ARF during the "extension" and "maintenance" phase.

We define inflammation as mediators ordinarily considered necessary for eliminating infectious pathogens. These include leukocytes, the molecules produced by these cells, and the molecules that regulate leukocyte functions. These also include molecules such as interleukin 18 and complement that kill pathogens but may be produced by cells other than leukocytes. The relatively "new" idea is that ischemic injury elicits inflammation, and this inflammation exacerbates and regulates the injury.



Before discussing the relationship between ischemic injury and inflammation, we will discuss the regulation of the inflammatory response. Understanding these basics is important for understanding how experimental inhibition of inflammation ameliorates ischemic renal injury.

A number of experimental therapies prevent the infiltrate and thus ameliorates renal injury after ischemia . To understand how these work, we must review the five major steps that occur during the translocation of leukocytes from the blood, across the endothelium, and into the interstitium. See reviews ([22]).

First, injured renal tubule cells release pro-inflammatory molecules, discussed later in this grand rounds.

Second, in response to these mediators, endothelial cells express adhesion molecules.

Third, leukocytes in the blood adhere by weak, reversible interactions to P and E selectins, vascular cell adhesion molecule-1 (VCAM-1), and hyaluronate on the activated endothelium.

Fourth, during this weak adherence, the leukocytes receive activation signals, including chemokines such as interleukin 8 and MCP-1 produced by injured renal tubules, which change the conformation of their cell-surface beta 2 integrins so that these bind theircounterligands on the endothelium. The beta 2 integrins on leukocyte cell surfaces are LFA-1, mac-1, and VLA 4, which bind to counterligands on the endothelium; these include ICAM 1 and 2, and VCAM 1.

Fifth, the leukocytes move across the endothelium (diapedesis), and migrate to the sites of injury in response to chemotactic molecules.

TABLE 2. Incidence of delayed graft function, rejection, CMV disease, and posttransplant length of stay

	Intraoperatively (n=27) (%)	Postoperatively (n=31) (%)
Delayed graft function	4 (14.8)[a]	11 (35.5)
Rejection episodes	1 (3.7)	5 (16)
Cellular rejection episodes	1 (3.7)	2 (6.5)
Humoral rejection episodes (%)	0	9.7
CMV disease rate at 6 mo (%)	3.7	6.5
Posttransplant length of stay (days)	7.5[b]	11

[a] $P<0.05$.
[b] $P=0.02$.

Intra- vs post operative Thymoglobulin. Goggins. Transplantation 76:798. 2003.

Sixth, the leukocytes are activated by their interactions with inflammatory molecules embedded in the extracellular matrix, molecules on the cell surfaces of the renal tubule cells, and cytokines.

Seventh, the activated leukocytes produce molecules such as reactive oxygen species (ROS) and nitric oxide that damage renal cells.

Inflammation has been observed after experimental rodent ischemic injury not only in the kidney [23-25], but also the heart [26;27], brain [28-30]. Inhibiting the inflammation by preventing one or more of the seven steps above, ameliorates ischemic injury in most studies.

But our goal is not to treat ischemic ARF in rodents but in our patients. Does this hypothesis apply to humans. A number of investigators have noted the potential difficulties in extrapolating rodent studies to human ARF [31-33].

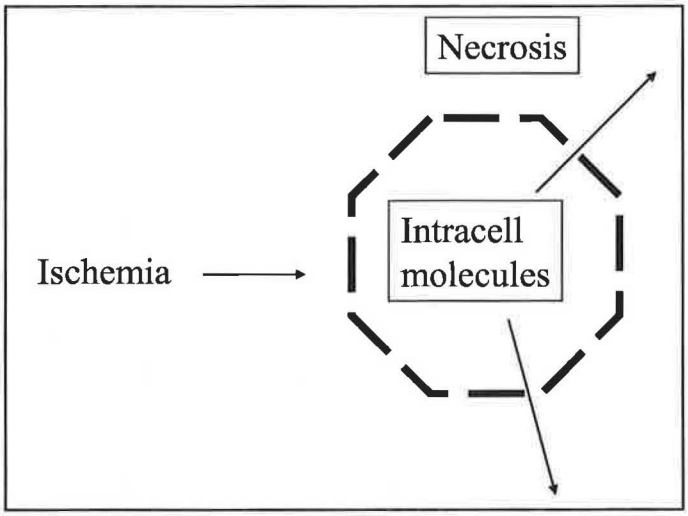
Inflammation does occur during human ischemic acute renal failure, leukocytes are present [34]. The importance of pro- and anti- inflammatory genes is supported by increased susceptibility of patients correlates with polymorphisms of these genes [35]. Post-anastomosis biopsies of renal allografts show inflammation, particularly in deceased, compared to living, donors [36-40]. Furthermore, intraoperative biopsies have also indicated expression of pro-inflammatory genes [41-44]. Such inflammation may be a response to ischemic injury to the allograft due to the hypotension associated with the trauma that caused brain death, due to the cold storage, and due to the warm ischemia

during creation of the vascular anastomoses. In addition, inflammation in the cadaver kidneys was also caused by neurohormonal effects of brain death [45]. Inflammation during these intraoperative biopsies are not due to rejection because there is no time for immune recognition of the transplant. Furthermore, biopsies of kidneys between identical twins, where there is no allo-recognition, also shows inflammation that must be due to ischemic injury occurring during the transplant process [46].

Some of the most convincing studies of the maladaptive effects of the inflammatory response to ischemic injury involve polyclonal anti-thymocyte antibodies. These preparations contain antibodies to endothelial adhesion molecules and ameliorate ischemic injury to renal [47], or hepatic [48] transplants, and muscle [48-50].

The right stuff in the wrong place: the proinflammatory effects of intracellular molecules released into the extracellular space by necrotic cells.

Although the inflammatory response to ischemia may an important determinant of the extent of injury and repair, how ischemic injury is translated into inflammation is a major outstanding question. Recent data indicate that molecules, normally residing within cells, elicit inflammation when they are released into the extracellular space by necrotic cells.



<u>TLR4 detects molecules released by injured cells, and mediates the inflammatory response to ischemia.</u>

A major discovery was the insight that receptors, such as TLR4, not only recognizes endotoxin, but also recognizes molecules released by injured cells [51-59]. These molecules are called "endogenous" because they are produced by mammalian cells and to differentiate them from endotoxin, the "exogenous" TLR4 ligand that is produced by gram negative bacteria.

Striking confirmation for the importance of TLR4 in ischemic disease were experiments comparing inflammation and injury in wildtype mice versus TLR4 deficient mutant mice after ischemia to the heart [60;61], liver [62-64], lung [65], and kidney [66]. In all of these studies, mutant mice with non-functional TLR4 are protected from ischemic injury.

The ligands for TLR4 include heat shock protein 70 [51;52]. Other ligands may be fragments of the extracellular matrix that result from its degradation after tissue injury. Two of these fragments, heparan sulfate and hyaluronan, activate TLR4 [58;59;67-69], and may participate in ischemic ARF. Low molecular weight heparan sulfates are released

when neutrophil elastase degrades heparan sulfate proteoglycans in the extracellular matrix (see review [70]). Inhibition of neutrophil elastase ameliorated ischemic acute renal failure in rodents, possibily by inhibiting the production of heparan sulfate fragments [71]. Hyaluronan increases in the ischemic kidney [72]. Low molecular weight hyaluronans are released when hyaluronidases from tubules and leukocyes degrade the extracellular matrix. Small hyaluronans stimulate renal tubular cells to produce MCP-1 (a macrophage chemokines), and TNFα (a proinflammatory cytokine) in vitro [73]. Biglycan is another extracellular matrix component that may stimulate TLR4 after tissue injury [74].

Other endogenous molecules also interact with TLR4, but they are less well studied than the hsp's and extracellular matrix components discussed above. Fibronectin IIIA is a variant fibronectin that is produced by stressed cells [75], and is increased during ischemic ARF [76]. β-defensin is found in kidneys stressed by infection [77], but β-defensin production during ischemic ARF has not previously been examined. Hsp60 is not known to increase after renal ischemia, but might still be released during ischemic ARF and stimulate TLR4 [57]. Tamm Horsfall protein may also be a TLR4 ligand [78].

Multi-ligand receptors for multi-receptor ligands may detect ischemic injury?

The previous sections indicates that there are many endogenous TLR4-ligands in addition to endotoxin, the exogenous TLR4 ligand. How does TLR4 act as a "receptor" for these diverse molecules? That one receptor may interact with multiple ligands has become a recurring theme in immunology. TLR4 is just one example of a growing family of "multiligand receptors". Other such receptors include RAGE (for example references [79;80]), and CD91 (also known as LRP [for example references [81;82]]). One explanation of how TLR4 is activated by different ligands is that all the ligands have, in common, large hydrophobic regions that interact with the leucine rich region of TLR4. See review [83].

In the same manner, endogenous TLR4 ligands may have more than one receptor. For example, hsp proteins are intracellular chaperones, designed to bind to many denatured proteins by virtue of their exposed hydrophobic regions. It should therefore not be surprising that that hsp should bind to many cell surface receptors by virtue of their hydrophobic regions. Thus, a number of receptors [52;84-86], in addition to TLR4 have been proposed for the endogenous TLR4 ligands. These include CD91 [87;88], TLR2, and RAGE. These are discussed in greater detail below.

These interactions between the hydrophobic regions of cell surface receptors such as TLR4 and the hydrophobic regions of ligands such as hsp may reflect the two functions of these receptor-ligand systems [83]. On the one hand, as discussed above, these receptor-ligand systems allow the immune system to detect injury. This may include the detection of denatured intracellular proteins via the CATERPILLAR family of molecules [89-91]. This family of proteins may regulate the "inflammatory caspases" (caspase 1 and 11) that process interleukin 1β and interleukin 18 into their active form. Interleukin 18 has a maladaptive role in ischemic acute renal injury [92;93]. On the otherhand, these receptor-

ligand systems allow these receptors to recognize many molecules produced by pathogens, such as endotoxin, that are also hydrophobic.

Why there should be so many ways to detect molecules released by injured cells is not clear. Do all injured cells release the same molecules, are different molecules released after different types of death and injury, do different molecules and receptors elicit different inflammatory responses? In very broad strokes, we will discuss the different modes of programmed cell death and the different inflammation elicited by different types of death later in the chapter. However, a profound understanding of these questions remain to be elucidated by future research.

Other receptors that detect molecules released by injured cells and thus trigger inflammation: TLR2, RAGE, and CD91.

TLR2: TLR2 is related to TLR4 and may also recognize hsp's [94-96]. Mice with non-functional TLR2 are protected from ischemic renal failure [97]. Renal tubules express both TLR2 and TLR4 after severe ischemic injury [98;99]. TLR2 may also be important in ischemic injury to the liver [100] and heart [101].

In some experimental systems, uric acid is released by necrotic cells and mediates an inflammatory response [102;103]. Some data suggests that TLR2 on leukocytes detects this extracellular uric acid [104;105].

RAGE: Although RAGE is best known as the receptor for advanced glycation endproducts and for its contribution to the secondary complications of diabetes mellitus, including diabetic nephropathy [106-109], RAGE also detects molecules released by injured cells, and triggers an inflammatory response.

Of the RAGE injury ligands, the best understood is HMGB1 [110;111]. HMGB1 is expressed by all eukaryotic cells and is highly conserved through evolution. It was originally described as nuclear protein that enables interactions between DNA and nuclear proteins that regulate transcription. However, in the late 1990's a search for mediators of shock revealed that HMGB1 elicited lethal inflammation [112]. Antibodies against HMGB1 prevented shock. Subsequent experiments showed that HMGB1 was released by necrotic cells, and actively secreted by leukocytes of the innate immune response. The little inflammation seen after apoptosis, as opposed to necrosis, may result from sequestration of HMGB1 within the nucleus of apoptotic cells.

HMGB1 consists of three domains. The A and B boxes bind to DNA, and the C box is negatively charged. The proinflammatory effect of HMGB1 may be reproduced by recombinant B box. Recombinant A box peptide is a specific antagonist of the proinflammatory effects. Thus, there is therapeutic potential in using these genetically engineered peptides to either increase or decrease inflammation.

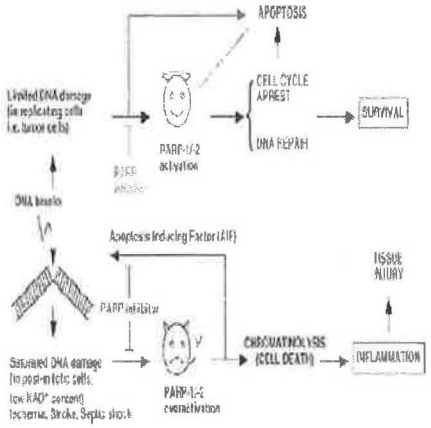
The major receptor for HMGB1 is RAGE [110;111]. However, the inhibition of RAGE with specific agents does not entirely inhibit the effects of HMGB1. Therefore other ligands have also been proposed. These include heat shock proteins and members of the intracellular S100 family of proteins [80;113-115]. Release of RAGE-ligands is important not only during ischemia and shock, but also may play a role in autoimmune disease [116] where ongoing injury may perpetuate the maladaptive inflammation.

Although the role of RAGE-HMGB1 in renal ischemia is not known, inhibition of RAGE with a soluble blocking receptor does ameliorate hepatic ischemia [117].

CD91: This is also a receptor for heat shock proteins [81;86;118] released by injured cells. It has been targeted as a means of increasing immunity against tumors. In addition to binding heat shock proteins, CD91 also binds α2-macroglobulin [119;120], collectin and calreticulin [121], and is known as LDL receptor related protein [122].

When death is no accident: necrosis as a programmed event.

The above section shows that molecules released from necrotic cells elicit an inflammatory response. Necrosis is often considered accidental death. However, a growing body of data indicates that necrosis may also be a programmed event [123-128]. This suggests that when inflammation is desirable, a cell may be programmed to die a necrotic death, and thus release the pro-inflammatory molecules discussed above.



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Poly (ADP-ribose) polymerase [PARP] and programmed necrosis.

The PARP's are a family of 18 genes. PARP-1 regulates necrosis [129-131]. That an enzyme regulates necrosis indicates that death is no accident, but is programmed. Pharmacologic inhibition of PARP ameliorates ischemic acute renal injury in rodents [132;133]. Transgenic knockout of PARP-1 also decreases injury after acute renal ischemia [134;135]. Inhibition of PARP-1 also ameliorates ischemic injury of the brain and liver.

The best known function of PARP-1 is to repair DNA damage, such as occurs in response to oxidative stress during ischemic acute renal failure. Renal PARP-1 levels increase during ischemic acute renal failure [132;136].

It is not intuitively obvious why such a repair enzyme should be required for necrosis. One possibility is that, it the face of massive DNA damage, PARP depletes intracellular NAD+ and thus ATP stores. This leads to necrosis, especially in the setting of mitochondrial damage as discussed later in this section [137-139]. However, necrosis is not necessarily correlated with intracellular energy stores in all model systems. Another possibility is that PARP-1 enhances the activity of NFκB and other pro-inflammatory transcription factors. PARP may also increase mitochondrial release of AIF.

Some suggest that caspases degrade PARP and thus direct cell death down an apoptotic pathway [140]. However, there is decreased ischemic acute renal injury in mice expressing a genetically engineered PRAP-1 that cannot be degraded by caspases [141]

Cyclophilin D, mitochondria, and programmed necrosis.

Another argument that necrosis is regulated comes from studies of mice with transgenic knockout of cyclophilin D. Such mice have decreased necrosis during ischemic acute renal failure [142-144]. Cerebral ischemia was similarly ameliorated in these knockout animals [145]. These results extend data that cyclosporine, by inhibiting cyclophilin D, ameliorates ischemic injury in some tissues [146;147]

Cyclophilin D regulates the mitochondrial permeability transition, and the subsequent release of mitochondrial molecules that regulate cell death. The above data suggest an important role for mitochondria in regulating necrosis [146;148-150]. Whether opening this pore results in necrosis or apoptosis may depend upon several factors. One is the length of time that the pore is open – transient opening might result in apoptosis; longer opening, necrosis [151]. In addition the availability of ATP may switch the mitochondrial signal from necrosis to apoptosis [149]. This is in line with data showing that lower, more prolonged decreases in ATP are associate with necrosis, while shorter and lesser ATP depletion result in necrosis in renal cells [152], and that lesser oxidant injury also leads to apoptosis instead of necrosis [153;154]. Finally, intracellular pH also regulates. The return of the pH from acidic to more alkaline with reperfusion makes necrosis more likely [149].

Additional examples of programmed necrosis in vivo.

We will now review three additional striking examples of the importance of programmed necrosis in vitro.

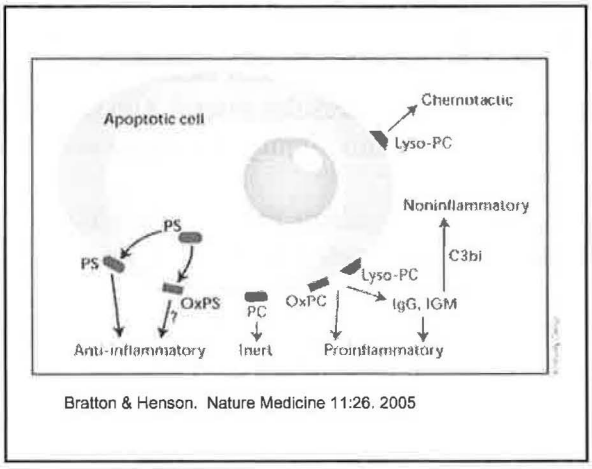
One example is the host defense against murine vaccinia virus. This virus protects itself by preventing apoptotic programs within infected host cells. In mice with wildtype TNFR2, infected cells die by programmed TNFα-mediated necrosis, and elicit a protective inflammatory response. Mice with TNFR2 knockout have a reduced programmed necrosis and thus reduced anti-viral inflammatory response and decreased viral clearance [155].

The second example is the difference between cerulean pancreatitis in rats versus mice. The worse outcome in the latter is due to greater programmed necrosis. Rats have high apoptosis and low necrosis and thus a better clinical outcome. Mice have low apoptosis and high necrosis and thus a worse outcome with more inflammation. This difference was due to different function of the X-linked inhibitor of caspases (XIAP) in these two species. There was less inhibition of caspases, and thus less inhibition of apoptosis, in the rat by XIAP [156].

The third example is the exacerbation of shock when apoptosis is inhibited in mice given TNFα. In this case, switched programmed cell death from apoptosis to necrosis had fatal consequences [157].

After suicide, disposal of the corpse: regulation of inflammation by macrophages after they phagocytose apoptotic cells.

Apoptosis occurs during ischemic acute renal failure [158-164]. The goal of this discussion is not the regulation of this apoptosis but rather the effect of apoptosis on inflammation. In other words, we discuss phagocytic clearance of the apoptotic cells before their loss of membrane integrity and leakage of the proinflammatory molecules discussed in the previous section. Such clearance is regulated by "eat me", "don't eat me", "come get me" signals.



Bratton & Henson. Nature Medicine 11:26. 2005

The surface of the apoptotic cell has "eat me" signals that trigger phagocytosis by macrophages. A major signal is phosphatidylserine that has somehow "flipped" from the intracellular leaflet to the extracellular leaflet of the plasma membrane where it is recognized by macrophage receptors including the phosphatidylserine receptor after bridging by Annexin I. Other less well understood interactions between apoptotic cell and macrophage also contribute to the "eat me" signal. These include sites also capable of binding collectins such as mannose binding protein, C1q, C3b/bi, oxidized LDL, and thrombospondin 1. In addition, the apoptotic cell surface has decreased "don't eat me" signals such as CD31. Furthermore, phosphatidylcholine on apoptotic cell surfaces is cleaved by phospholipase A2 to form lysophosphatidyl choline which is the best understood chemoattractant "come get me" signal issued by apoptotic cells to macrophages. [See review [165]].

Under many circumstances, macrophages, which have engulfed apoptotic cells, release anti-inflammatory molecules that prevent further inflammation. (for example [166;167]). The phosphatidylserine receptor on macrophages may trigger the release of inhibitory

cytokines, but this begs the question of why this receptor is not triggered when macrophage phagocytose necrotic debris, including phosphatidylserine on the intracellular side of cell membrane fragments [168]. In the absence of a receptor for phosphatidylserine, macrophages cannot ingest apoptotic cells, and the lungs of such mice fill with cellular debris and inflammation [169;170]. This may reflect the consequences of overwhelming the phagocytotic system with too many apoptotic corpses as perhaps occurs during ischemic acute renal failure [161]. This situation may reflect "post-apoptotic necrosis" and the release of proinflammatory mediators.

However, there are a number of experimental circumstances where phagocytosis of apoptotic cells results in the release of pro-inflammatory molecules by macrophages, and where ingestion of necrotic debris results in the release of anti-inflammatory molecules. This may reflect the influence of cytokines in the microenvironment [171], or the redox potential of the microenvironment that can oxidize phospholipids and turn them into macrophage activating signals [172;173].

Conclusion.

Acute renal ischemia elicits an inflammatory response. We have focused a large part of this review on the nature of the inflammation and its possible consequences. Among the factors that elicit and regulate the inflammatory response to injury, including complement [174;175], and gene activation by hypoxia/ reactive oxygen species [176-178], we have focused this review on how the mode of cell death and products of injured and dying cell regulate inflammation because of the recent major developments in these areas.

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