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Ischemia-reperfusion and immediate T cell responses

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Ischemia reperfusion injury (IRI) is an increasingly important problem in clinical transplantation and is also implicated in a variety of non-transplant conditions, including myocardial ischemia, shock and stroke. Clinical and experimental data have established that IRI has both immediate and long-term effects on the allograft, contributing both to acute rejection and chronic allograft dysfunction [1]. However, at present there is no specific therapy available for prevention or for treatment of IRI.

The pathogenesis of IRI represents a complex interplay between biochemical, cellular, vascular endothelial and tissue specific factors, with inflammation being a common feature. There is considerable data implicating an important role for the innate immune response in IRI. According to the classic model, acute ischemia leads to production of oxygen free radicals, secretion of inflammatory cytokines/chemokines and activity of adherent molecules that are important initiators of the innate immune response which lead to tissue damage and endothelial cell activation [2–8]. Polymorphonuclear cells (PMNs) are the major leukocytes observed in tissue necrosis following ischemia. The neutrophil accumulation had been thought to be the prime cellular mediator of microvascular plugging and local tissue destruction in IRI. Monocyte/macrophage infiltration occurs later during IRI and likely contributes to extension of early injury as well as repair [9]. In addition, the role of the complement system in IRI has been firmly established, with activation demonstrated partially through the alternative pathway [10]. Both T and B cells constitute the primary arms of the adaptive immune response and were not felt to play a role in the acute phase of IRI. However, recent data have challenged this assumption and demonstrate an important modulatory role of T cells in IRI.

Evidence supporting a role of T cells as mediators in IRI

Numerous studies have identified T cells in both renal and non-renal organs after IRI. Initially considered as “innocent bystanders” in sites of inflammation, both indirect and direct evidence from several different animal models now support T cells may mediate in IRI. Indirect evidence in IRI came from studies of therapeutic agents targeting T cells. The calcineurin inhibitor, FK506, was found to attenuate experimental hepatic and mesenteric IRI in rats partially by reducing leukocyte adhesion [11,12]. FK506 was also reported to reduce infarct size in rats after focal cerebral ischemia [13]. Neither rapamycin (which inhibits T cell activation), nor cyclosporine A (CsA) (a calcineurin inhibitor), was protective in the same experiment; both improved bowel IRI [14]. Mycophenolate mofetil (MMF), an anti-proliferative immunosuppressive agent, was demonstrated to be protective in IRI of cardiac transplantation, accompanied by decreased leukocyte infiltration [15]. Whereas some studies reported a protective effect of MMF in the kidney after experimental IRI [16,17], one study found that MMF retarded repair due to toxic injury [18]. In more recent studies, a new

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immunosuppressant, FTY720 that modulates lymphocyte migration was found to attenuate renal and liver IRI in rodents [19–23]. FTY720 pretreatment resulted in improved renal function in association with reduced T cell infiltration in both cold and warm IRI models.

Reduced intragraft neutrophil infiltration was also observed with no change in expression of adhesion molecules. In the warm liver IRI model, the protection of FTY720 was partially attributed to the reduction of T lymphocyte infiltration and inhibition of MAPK (Raf-MEK-Erk) pathway [23]. However, FTY720 may have effects on endothelial cells that are independent of T cell function [24]. The activation of hepatocyte survival Akt signaling was also found in FTY720- treated normal and cirrhotic livers after IRI and may contribute to the improved liver function [21]. However, side effects of FTY720 have limited general use in the transplant population.

The protective effect of T cell costimulatory molecule blockade provides further indirect evidence for the role of T cells in the pathogenesis of IRI. Blockade of the T cell CD28-B7 costimulatory pathway with CTLA4Ig significantly attenuated renal dysfunction after cold IRI [25]. Anti-B7-1 antibody but not anti-B7-2, markedly reduced leukocyte accumulation in the kidney and improved renal function in rats after warm IRI, suggesting a predominant role of the B7-1 pathway in the protection of renal IRI through inhibition of T cell adherence and activation [26]. B7-1 expression was also identified on endothelial cells of the ascending vasa recta in postischemic human kidney (within 1 hour), suggesting a potential role of T cell co-stimulation in human renal IRI [8]. Recently, it has been reported that the CD154-CD40 T cell costimulatory pathway is active in the pathogenesis of hepatic and cerebral IRI [27,28]. Gene therapy-mediated prolonged local CD154 blockade (Ad-CD40 Ig), antibody-induced systemic CD154 blockade (MR1 mAb), and genetically targeted CD154 absence (CD154 KO mice) all ameliorated liver injury after warm ischemia. This protection was accompanied by diminished intrahepatic T cell accumulation, decreased VEGF expression, reduced TNF type 1 cytokine production and inhibition of hepatocyte apoptosis.

It has been well established that leukocyte adhesion molecules, including CD11/CD18, ICAM-1, integrins and selectins play an important role in the initiation of IRI [3]. Studies have shown that blockade of CD11/CD18 and ICAM-1 protected experimental rodents from renal IRI, which was initially considered due to reduced infiltration of neutrophils [29,30]. However, other groups subsequently demonstrated that induction of neutropenia did not lead to protection from IRI, suggesting that the interaction of T cells with these molecules may be operative [31]. P-selectin targeted treatment has been effective in liver and kidney models of IRI. A recent study demonstrated that P-selectin signaling had an important role in murine intestinal IRI in that either the blockade of or the genetic deficiency of P-selectin was protective. The protection was accompanied by a reduction of both T cell and PMN infiltration, and the induction of a Th2 dominant cytokine environment, implicating T cells as modulators in this inflammatory process [32].

T cells directly mediate IRI in liver (Table 1). The T cell deficient athymic *nu/nu* mice did not manifest warm hepatic IRI, but did so after adoptive transfer of wild type T cells[33]. Other researchers confirmed these results in *nu/nu* mice using a cold liver IRI model and found that donor pretreatment with IL-10 attenuated the liver injury induced by T cell reconstitution [34].

Similar results were observed in severe combined immunodeficiency (SCID) mice. SCID mice were relatively resistant to liver IRI, while T cell adoptive transfer, particularly $CD4^+$ T cells, restored the injury [35,36]. T cells also directly mediate kidney IRI. Mice deficient in both $CD4^+$ and $CD8^+$ T cells had reduced functional and structural abnormalities after IRI [37]. Athymic *nu/nu* mice were also protected from renal IRI, and adoptive transfer of wild type T

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cells abolished these effects both in clamp and whole body IRI models [38,39]. Interestingly, neither neutrophil nor macrophage infiltration was changed in this model, suggesting a neutrophil/macrophage-independent effect of T cells in IRI.

Different roles of T cell subsets in IRI

Differential roles of $CD4^+$ and $CD8^+$ T cell subsets have been elucidated in various IRI models. In *nu/nu* mice, adoptive transfer of $CD4^+$ but not $CD8^+$ T cells restored injury in renal IRI [40]. To determine the effect of an intervention in wild type mice, T cell depleting antibodies to CD4 (GK1.5) and CD8 (2.43) were administered to mice prior to IRI. This combination depleted T cells but did not protect renal function after ischemia. However, the addition of a third antibody (30.H12) that targets Th1.2 antigen decreased T cells further, in particular the $CD4^+$ subset, and led to renal protection [39]. In the late phase (6 weeks) of severe renal IRI, there was a marked infiltration of $CD4^+$ T cells throughout the injured kidney, which may promote the development of chronic renal disease [41]. The predominant role of $CD4^+$ T cells in IRI was observed in other organs. Depletion of $CD4^+$ T cells but not $CD8^+$ T cells reduced subacute injury and inflammation in mice after hepatic IRI [33]. Kinetic analysis of T cell infiltration in the liver in IRI mice demonstrated a marked accumulation of $CD4^+$ T cells in the early phase of reperfusion (within 1 hour) with no change in the number of $CD8^+$ T cells [33]. In a warm hepatic IRI rodent model, an accumulation and transendothelial migration of $CD4^+$ but not $CD8^+$ T cells 30% of which were colocalized with platelets was found during early reperfusion. CD62P and CD4 deficiency, as well as CD40-CD40L and CD28-B7 disruption, attenuated postischemic platelet adherence, suggesting a CD62P-mediated, costimulatory pathway-dependent effect of T cells on IRI [42]. In a syngeneic rat lung transplant model, recipient $CD4^+$ T cell infiltration in the lung graft was observed within 1 hour of reperfusion followed by up-regulation of the T cell activation marker, CD25, over the ensuing 12 hours [43]. *In vivo* depletion of $CD4^+$ but not $CD8^+$ T cells significantly reduced infarct size in a heart IRI model [44]. Activation of the adenosine A_{2A} receptor (A2AR) by CGS-21680 or ATL146e reduced IRI in liver, kidney and heart models [44–46]. Accumulation of $CD4^+$ T cells in the heart after myocardial infarction was markedly reduced by ATL146e treatment. ATL146e administration also reduced injury after renal and heart ischemia in RAG1 KO mice reconstituted with wild type but not A2AR KO $CD4^+$ T cells, implicating $CD4^+$ T cells as the primary targets of A2AR agonists [44,45]. $CXCR3^+CD4^+$ T cells were also demonstrated to play a critical role in the innate immune response in cold liver IRI model [47].

Recently, NKT cells were also reported to play an important role in liver IRI. NKT cells were found to be the major expander cell in the liver after IRI, and CD1d KO mice were protected from IRI [48]. The protective effect of A2AR activation in liver IRI was also associated with reduced activity of NKT cells [46].

IFN-γ-producing Th1 cells may be important in the pathogenesis of IRI. Increased serum or tissue IFN-γ level was observed in IRI animal models [45,46,49,50], as well as in patients undergoing hepatic resection following intermittent portal clamping [51]. Flow cytometric analysis of infiltrated lymphocytes in ischemic kidney revealed increased IFN-γ and TNF-α producing T cells 24 hours after renal IRI [52]. Increased IFN-γ production was not only found in ischemic organs, but also in splenic T cells in the late phase of severe renal IRI without any change in $CD4^+$ and $CD8^+$ T cells numbers [41]. Adoptive transfer of splenic lymphocytes from mice with severe renal IRI induced albuminuria in naïve mice accompanied by migration of donor lymphocytes to recipient kidney and increase of activated and memory T cells in recipient spleen [53]. $CD4^+$ T cells deficient in CD28 or IFN-γ did not restore ischemic injury in *nu/nu* mice, CD4 KO mice or RAG1 KO mice [40]. Furthermore, activation of A2AR on $CD4^+$ T cells reduced IFN-γ production by 98%, while this inhibitory effect was blocked by

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100% in $CD4^+$ T cells from A2AR KO mice [54]. ATL146e significantly reduced plasma IFN-γ levels in mice with myocardial reperfusion injury (44). These data suggest that the protection of A2AR agonist in IRI may reflect suppression of IFN-γ production. STAT signaling is essential for the differentiation of Th1 (STAT4)/Th2 (STAT6) cells and their cytokine production. STAT6 deficient mice developed more severe renal injury after ischemia, while STAT4 deficient mice had mildly improved function, suggesting the Th2 cells protect against renal IRI [55]. STAT6 may also protect against liver IRI [56]. Recent data showed that IL-4 but not IL-12 deficient mice developed more severe renal injury after ischemia, also suggesting a protective effect of Th2 cells in IRI [57]. However, the significance of the Th1 and Th2 cytokine environment remains controversial, since both protective and deleterious effects of the Th2-type cytokine IL-10 has been reported in various IRI models [58,59].

The role of the T cell receptor (TCR) in renal IRI was recently demonstrated. TCRαβ deficient mice had significantly improved renal function with reduced TNF-α and IL-6 production after IRI, while TCRγδ deficient mice only presented slight amelioration [60]. While initially another group failed to observe a role of TCR in renal IRI [61], the importance of TCR in kidney IRI was confirmed by careful knockout and antibody depletion studies [62].

Several recent studies have demonstrated a more complex role of T cells in IRI in that T cells appear to exhibit protective effects (Table 2). To explore the functional role of kidney-infiltrating lymphocytes after IRI, these cells were transferred into T cell deficient *nu/nu* mice at 24 hours after ischemia [52]. Unexpectedly, transfer of these cells led to attenuated renal dysfunction after IRI in the recipient mice, suggesting a protective effect of ischemic kidney infiltrating lymphocytes in IRI. Kinetic analysis of lymphocyte infiltration revealed a marked increase in T cell accumulation in post-ischemic kidney both in sham-operated and IRI mice 3 hours after renal IRI, that may represent the effects of laparotomy and anesthesia alone, but also a marked reduction 24 hours after surgery. T cell numbers in the kidney 24 hours after surgery were significantly lower in renal IRI mice compared with sham. These data suggest infiltrating T cells have a complex role in the different phases of IRI. The protective role of splenic lymphocytes 5 days after renal IRI was also demonstrated when transferred to wild type mice with IRI [63]. However, the particular cell type responsible for the aforementioned protective effects has not been identified yet.

$CD4^+$ T cells have divergent functions in liver IRI [64]. CD4 KO mice had significantly greater liver injury but far less neutrophil infiltration. Adoptive transfer of $CD4^+$ T cells restored the wild type response. The increased activation of liver infiltrating neutrophils was observed in CD4 KO mice, suggesting $CD4^+$ T cells might suppress activation of neutrophils. Interestingly, RAG-1 KO mice with deficiency of both B and T cells were not protected from IRI, and in fact, appeared to have worse injury than wild type mice [65,66]. However, adoptive transfer of either B or T cells into RAG-1 KO mice significantly improved the function of ischemic kidney without any change in neutrophil infiltration. The RAG-1 KO, although lacking mature T and B cells, can have an increase in other immune mediators such as NK cells, complement and macrophages that may promote early injury responses after IRI. Although numerous data have demonstrated a critical role of regulatory T cells in autoimmune disease, little is known so far as to whether these cells play a role in IRI. One preliminary study reported that depletion of $CD4^+CD25^+$ regulatory T cells by PC61 (anti-CD25) had little impact on the early phase of IRI, but led to higher necrosis indices 3d after IRI, compared with IgG-treated control mice. Thus, $CD4^+CD25^+$ cells may facilitate recovery from IRI [67].

Mechanisms of T cell activation in IRI

T cell activation involves antigen-dependent and -independent pathways (Figure 1) [2–8]. Antigen-independent T cells activation probably plays a pivotal role in IRI. Oxygen free

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radicals, regulated upon activation: normal T cell expressed/secreted (RANTES), and cytokines, including TNF-α, IFN-γ, IL-2 and IL-6 have all been demonstrated to activate T cells directly. Chemokines such as growth-related oncogene (GRO/CXCL1), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein (MIP-1), and interferon-inducible protein 10 (IP-10) have also been implicated in the early inflammatory responses in transplanted organs.

Recently, toll-like receptor (TLR)-mediated pathways have been demonstrated to be activated by non-infectious stimuli in IRI. TLRs are primarily expressed in antigen presenting cells (APCs) and are also present on endothelial and stromal cells [68–70]. TLR4 deficient mice were protected from IRI of lung, liver, heart and brain, implicating the role of TLR4 in the initiation of IRI [71–75]. In the kidney, both TLR2 and TLR4 expression were increased after IRI [76], and TLR2 KO mice exhibited attenuated renal injury after IRI [77]. Heat shock proteins, as well as other molecules induced by IRI, including matrix components and inducible defensins, are putative agonists of TLRs [6,68]. Activation of TLRs induces dendritic cell maturation leading to the proliferation and differentiation of T cells.

It is well known that the complement system plays an important role in IRI as a manifestation of innate immunity. Complement also regulates adaptive immune responses. C3a and C5a played opposing roles for T cells polarization in allergic asthma where CD3a promoted Th2 polarization while CD5a prevented a Th2 response [78]. In addition, CD46, a member of the complement regulatory receptor family, widely expressed on human cells [79], induced regulatory T cell function (IL-10 production) when cross-linking with CD3 on human $CD4^+$ T cells. More recently, decay-accelerating factor (Daf, or CD55) was reported to regulate T cells responses through C3/C5 dependent pathway [80].

Dendritic cells and B cells in IRI

Dendritic cells (DCs) are the major professional antigen-presenting cells of the immune system, with the unique capacity to trigger na ve T cell responses. Recent studies have provided novel insights into the potential role of DCs in mediating immune responses in IRI. Increased numbers of DCs expressing a more mature phenotype were identified in ischemic kidney in the early phase (within 24 hours) after IRI, while these activated DCs with a strong capacity to induce T cell proliferation migrated from the kidney into the renal lymph node 1 day after IRI [81]. Accumulation of DCs in liver and kidney was observed within 1 hour and peaked at 24 hours after IRI [82]. Transplantation of a syngeneic renal graft also increased DC accumulation in the kidney [83]. DCs freshly isolated from liver after IRI exhibited a mature phenotype with an inhibitory profile of increased IL-10 and reduced IL-12 production [84].

Endothelial cell activation might be involved in DC trafficking, partially by production of chemokines and NOS, suggesting that endothelial dysfunction may accelerate DC-mediated immune activation [85]. Endothelial cells also express costimulatory molecules and can serve as APCs for T cell activation [86]. The important role of DCs in mediating immune responses in hepatic IRI was also reported in part by enhanced TLR4 reactivity [87]. TLRs are expressed abundantly on DCs and play a pivotal role in DC activation [68], which suggests a potential involvement of DC in the immune responses in IRI.

B cells may also participate in IRI. B cell deficient mice were relatively protected from renal IRI [88]. Transfer of serum from wild type mice restored the injury, suggesting a role of a soluble mediator such as antibody. However, not all B cell deficient mice are protected from IRI. As mentioned above, RAG-1 KO mice deficient in both B and T cells were not protected from IRI [65], and adoptive transfer of either B or T cells attenuated kidney injury. Only small numbers of B cells (4%~10% reconstitution) were sufficient to yield major changes in kidney injury. B cells might also be involved in tissue repair after acute injury [89]. These data suggest

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that immune cells mediate a contribution to the pathogenesis of IRI. How exactly immune cells do so warrants further investigation.

Conclusion

T cells contribute to the pathogenesis of IRI. Thus, the function of T cells extends beyond the conventional dogma. T cells function in IRI of kidney, liver, lung, brain and intestinal in both alloantigen-dependent and -independent tissue injury but also possibly in putative repair mechanisms. These discoveries open up the exciting possibility of harnessing immunotherapeutic agents previously developed for more classic immune diseases to test their efficacy in the prevention and treatment of IRI.

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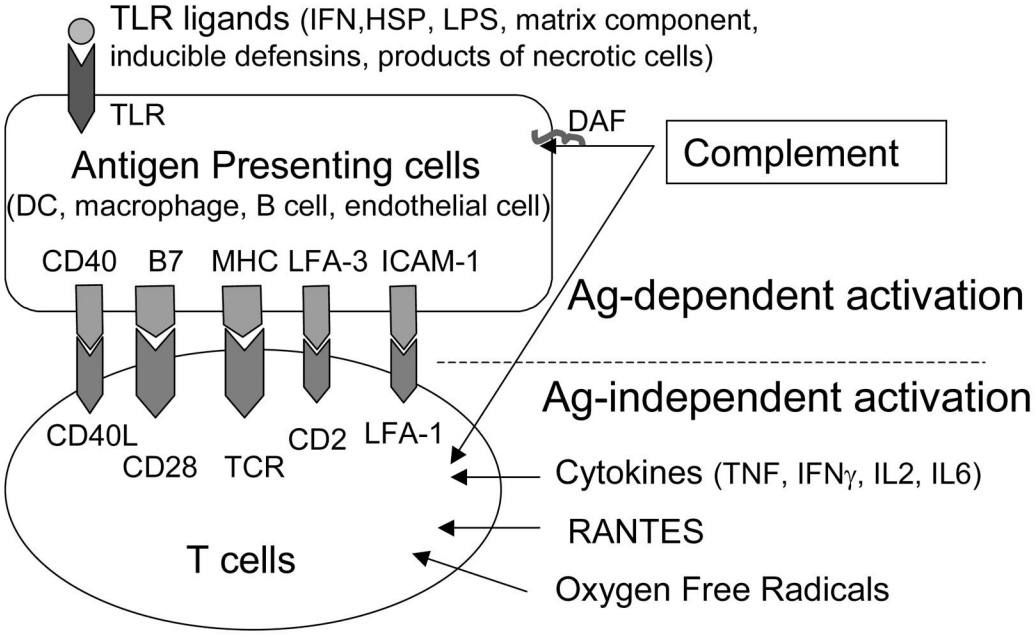

Figure 1. Antigen-dependent and -independent T cell activation

Two signals are provided by APCs to activate T cells, including antigen-specific signal received as a result of binding of the T cell receptor to peptide presented by MHC molecule, and the second signal provided by costimulatory molecules such as B7-1 (CD80), B7-2 (CD86) and CD40. T cells can also be directly activated through Ag-independent pathways by cytokines, RANTES and oxygen free radicals. Complement system serves both during innate immunity, as well as a mediator of adaptive immunity by directly activating APCs and T cells. In IRI, Ag-independent pathways play an important role in T cell activation. Moreover, several proteins induced by IRI, including HSP, matrix component, inducible defensins, products of necrotic cells, as well as cytokines can activate APCs through TLR contributing to the T cells proliferation. Dendritic cells, macrophages, B cells and endothelial cells are involved in Ag presentation to T cells.

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Table 1

Direct evidence for a role of T cells in rodent IRI models

Organ	Model	Finding	Ref.
Liver	IRI	Nu/nu mice & CD4 depleted mice protected; T cell transfer restores injury; $CD4^+$ but not $CD8^+$ T cell infiltration.	33
Liver	Cold IRI	Nu/nu mice protected; INF-γ and TNF-γ associated; IL-10 pre-treatment benefits.	34
Blood vessel	TNF-α treated	Reduced endothelial cell adhesion molecule expression in SCID & Rag KO mice, $CD4^+$ but not $CD8^+$ T cell transfer restores injury.	35
Gut, liver	IRI	SCID mice protected; T cell transfer restores injury, but not CD4-depleted T cells, or T cells from INF-γ KO mice.	36
Kidney	IRI	CD4/CD8 KO mice protected.	37
Kidney	IRI	Nu/nu mice protected from whole body IRI.	38
Kidney	IRI	T cell depletion (especially $CD4^+$) protective.	39
Kidney	IRI	Nu/nu mice protected; $CD4^+$ but not $CD8^+$ T cell depletion protective; $CD4^+$ T cell transfer restores injury, but not cells from IFN-γ or CD28 KO mice.	40
Kidney	IRI	$CD4^+$ T cell infiltration in the late phase of IRI.	41
Liver	IRI	$CD4^+$ T cell infiltration with binding of platelets; CD62P& CD4 deficiency, CD40/CD40L & B7/CD28 blockage protective.	42
Lung	Cold IRI	Nu/nu mice protected from syngeneic lung transplant; T cell transfer restores injury	43
Heart	IRI	RAG1 KO mice protected; $CD4^+$ T cell transfer restores injury; A2AR activation protective by reducing $CD4^+$ T cell infiltration.	44
Kidney	IRI	RAG1 KO mice protected; $CD4^+$ T cell transfer restores injury; IFN-γ associated; A2AR activation protective.	45
Kidney	IRI	RAG1 KO mice protected; NKT cell transfer restores injury; IFN-γ associated; A2AR activation protective.	46
Liver	IRI	CD1d KO mice & nu/nu mice protected.	48
Kidney	IRI	TCR KO mice protected.	60

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Table 2

Divergent role of lymphocytes in warm IRI models

Organ	Finding	Ref.
Kidney	Transfer of ischemic kidney infiltrated lymphocytes into nu/nu mice protective.	52
Kidney	CD4 depletion or TCRα KO not protected.	61
Kidney	Transfer of splenic lymphocytes from IRI protective.	63
Liver	CD4 KO mice with greater IRI but less neutrophil infiltration.	64
Kidney	RAG1 KO mice not protected; Transfer of T or B cells protective.	65
Kidney	RAG1 KO mice not protected.	66