Published in final edited form as:
Curr Opin Organ Transplant. 2014 April ; 19(2): 115–120. doi:10.1097/MOT.0000000000000064.

T cells in Organ Ischemia Reperfusion Injury

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Abstract

Purpose of review—Ischemia and reperfusion injuries occur in multiple clinical settings and contribute to organ dysfunction/failures. Despite the innate inflammatory immune nature, T cells are critically involved in the pathogenesis of IRI, which includes not only $CD4^+$ T cells, but also $CD8^+$ and γδ T cells. This review focuses on questions of how putative Ag-specific T cells are involved, which include whether they function in Ag-dependent manner; how they function, cytokine- or costimulatory molecule-mediated mechanisms; and whether different T cell subsets, Th1, Th17, Treg, are all involved and play distinctive roles?

Recent findings—Specific T cell populations, such as effector memory CD4 T cells, promote inflammatory immune activation by IR independent of their adaptive properties, i.e., Ag-independent. They function by secreting cytokines and expressing costimulatory molecules to either promote or inhibit innate immune activation or facilitate tissue repair/homeostasis, as exemplified by Th1, Th17 or Th2, Treg cells respectively.

Summary—T cell targeted therapies need to be refined with strategies to maximally eliminate the pro-inflammatory but spare the anti-inflammatory/immune regulatory properties of T cells, for future clinical application to ameliorate IRI.

Keywords

Ischemia reperfusion injury; Innate immune activation; T cells; Th1; Th17; Treg; IL-17

T cells are critical in IRI of multiple organ types

Our understanding of T cells as important mediators of organ IRI comes from three lines of observations. Immune suppressive agents, such as FK506, Mycophenolate mofetil and FTY720, which were developed initially to target T cells to prolong allograft survival, were effective to protect organs from IRI in syngeneic transplant models or non-transplant models of both cold and/or warm IRI. Second, the costimulation blockade, which again targets T

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Conflicts of interest: There are no conflicts of interest.

cells to inhibit their activation, has been shown to attenuate IRI of multiple organs. Direct evidence of T cell functions in IRI was presented in studies of T cell deficient animals using either gene KO animals or T-cell specific depleting mAbs, in combination with adaptive transfer of purified T cell subsets. The role of T cells in tissue IRI was not limited to certain organs. Initially identified in livers and kidneys, direct documentations of T cell function are now presentated in heart, brain and limb models with variations in kinetics (hours to days post reperfusion) and cell types (CD4 vs. CD8) [1-6]. Thus, T cells, particularly the CD4 subset, are unequivocally key mediators in the pathogenesis of IRI.

T cells are putatively Ag-specific adaptive immune cells and their activation requires at least two signaling: T cell receptors and co-stimulation molecules, such as CD28 or CD154. Meanwhile, tissue immune response against IR is an innate immune dominated inflammatory response which occurs immediately after reperfusion in the range of hours. Thus, *de novo* T cell activation from its naïve status is unlikely to complete within such short period of time. Furthermore, IR-triggered tissue inflammation can proceed in the absence of exogenous Ags, i.e., sterile inflammation, such as those in partial warm ischemia of livers and kidney or myocardial infarction. Thus, the first challenging question for us to understand T cell biology in IRI is how T cells are activated and exert their function in an immediate innate inflammatory setting without obvious “cognate” Ags.

Activated CD4 T cells exhibit various immune functions with distinctive phenotypes. Cytokine secretions, as the primary effector mechanism of these T cells are used to differentiate CD4 T cell subsets. IFN-g from Th1 cells and IL-17 from Th17 cells have been shown to promote inflammatory pathology, while IL-4/IL-13 from Th2 and IL-10 from Treg are capable of inhibiting/ resolving inflammation. Therefore, the second question pertinent to T cell biology in IRI is whether these different CD4 T cells are involved and what roles they play in the pathogenesis of IRI. In the following sections, we will update and discuss recent findings on these two issues in various organ IR models.

Mechanism of T cell activation and function in IRI

To gain mechanistic insight of T cell functions in IRI, genetic modified mice carrying different transgenes or gene KO relevant to T cell functions have been utilized in IR experiments. In a focal cerebral ischemia model with both infarct size and neurological functional score as endpoints [7], the importance of conventional T cells (αβ) in the brain IRI was confirmed, which is in agreement with previous studies [5,8]. It was also shown that CD1d (representing NKT/NK) and γδT cells were less relevant in the disease pathogenesis. Interestingly, both CD4 and CD8 T cells were able to recreate IRI in RAG deficient mice regardless of T cell Ag-specificities. Thus, clonal T cells from a single TCR transgenic mice, either CD4 (2D2) or CD8 (OT I) function equally well as polyclonal T cells from WT mice. Furthermore, the brain IRI could develop independent of CD28, B7-1, and PD1. These results suggest that T cells function in IRI independent of their adaptive immune properties, a conclusion that is against our current concept of T cell biology. In particular, the role of CD28/B7-1 costimulatory pathway in the pathogenesis of IRI was the initially identified link of T cells in IRI in a rat kidney model [9]. Roles of γδT cells in organ IRI seem to vary in different ischemic organs and reperfusion stages. They have been shown to contribute to the

late stage brain infarction by producing IL-17, following the initial macrophage activation and IL-23 production [8]. In renal models, these unconventional T cells seem to infiltrate into ischemia organ first and facilitate the subsequent recruitment of αβ T cells [10]. Thus, the development of renal IRI was delayed in γδT cell deficient mice. Although liver IRI was not significantly reduced in TCRγ deficient mice, a reduction in liver neutrophil accumulation, measured by lower tissue MPO activities, was noticed [11]. Thus, the involvement of T cells in IRI now include all types of T cells: CD4/CD8/γδT, which differ in organ- and disease stage-specific manners.

The issue of T cell Ag-specificity in IRI has puzzled us for decade. It has been addressed in kidney, liver and brain models with quite different conclusions. Opposite to what described above in the brain, the development of liver IRI was reduced in single TCR transgenic, OT II, mice [11]; and kidney IRI in nude mice reconstituted with DO11.10 T cells was also reduced, as compared to those with WT polyclonal T cells [12]. We have been trying to resolve this Ag-specificity issue by using RAG deficient OT II CD4 TCR Tg system. We have hypothesized that previously activated CD4 T cells (effector memory subset) are the ones involved in liver inflammatory immune response against IR and they function in livers independent of their Ag-specificities. This is based on our finding that effector memory CD4 T cells are selectively enriched in livers with the $CD62L^{low}CXCR3^{+}$ phenotype [13]. We have also found that allogeneic skin graft recipients had significantly increased IRI in their own livers and nude mice reconstituted with CD4 T cells from these allograft recipients developed more severe liver IRI than those with CD4 T cells from isograft recipients [14]. Although liver IRI was lower in both OT II mice and nude mice reconstituted with naïve OT II cells, *in vitro* activated OT II T cells by their cognate OVA peptides became quite effective in recreating liver IRI in nude mice, comparable to WT CD4 T cells (ZY, data not published). It turned out that WT polyclonal CD4 from naïve animals had a significant proportion of effector memory cells, which were activated previously during their development in vivo possibly due to their cross-reactivities with endogenous tissue Ags or environmental Ags, while RAG deficient OT II cells which lack any reactivities to these Ags were purely naïve. This may explain why naïve OT II cells were not as competent as WT polyclonal T cells to recreate IRI in nude mice. Thus, it was the activated CD4 T cell subet which was able to promote tissue inflammatory immune response against IR independent of Ag-specificities.

Activated CD4 T cells function through two major mechanisms, cytokine secretion and cell surface costimulatory molecule expression. IFN-g has been proposed as the key T cell-derived effector molecule to promote inflammatory immune activation by IR. Although large amounts of correlative data exist in literature that links IFN-γ levels with severities of IRI, questions on CD4 as its cellular sources and its precise functions remain controversial. In a renal ischemia model, RAG deficient mice received IFN-g KO CD4 T cells suffered significant less injuries than those received WT cells [15]. A follow-up study by FACS phenotype analysis of infiltrating cells showed that neutrophils and NKT cells became the predominant IFN-g producing cells later on (few hours after kidney reperfusion) and NKT activations were responsible for the neutrophil infiltration and IFN-g production [16]. A more recent study added another twist to the cellular/cytokine cascade of IFN-g induction

that neutrophil-derived IL-17 was responsible for activating NKT cell, and probably neutrophil as well, to produce IFN-g [17]. Thus, a two-way feed-back loop between NKT and neutrophils drives the ultimate IFN-g output in ischemic kidneys. Both CD4 and IFN-g have been associated with stoke. However, CD4 T cells were not the major source of IFN-g that splenocytes from IFN-g KO mice remained capable of restoring brain IRI in RAG deficient hosts [5]. In liver IR models, we failed to detect drastic effects of NK/NKT cell depletion in the disease pathogenesis [11,13]. Roles of IFN-g were also negligible, as severities of liver IRI were the same in IFN-g receptor KO mice [18] and in WT mice treated with anti-IFN-g mAbs [13]. We showed that it was the type I interferon, which was activated downstream of TLR4, played a key role in liver inflammatory immune response against IR [18,19]. We have hypothesized that activated CD4 T cells promote liver innate immune activation by reverse-signaling through CD154-CD40, which traditionally is the helper function of CD4 T cells. Thus, livers are largely protected against IRI following CD154 blockade in WT mice or in nude mice reconstituted with CD154-deficient CD4 T cells [20]. Moreover, agonist anti-CD40 mAbs were able to restore liver injury in CD4 KO mice [13]. CD40 signaling has been shown to synergize with various TLR ligands to facilitate full “pro-inflammatory” activation phenotype in DC and macrophages, in particular, the elaboration of functional IL-12p70 complex [21] [22]. T cell–macrophage/DC interactions may involve multiple costimulatory signaling pathways with potentially both positive and negative outcomes. The engagement of PD-1 and PD-L1 has been shown to promote liver cytoprotection [23]. Blockade of T-cell immunoglobulin and mucin domain 1 (TIM-1)-TIM4 inteaction resulted in reduction, while anti-TIM3 exacerbated liver IRI [24-26]. It remains to be determined how these different costimulatory molecules are functioning to regulate innate immune responses: whether different types of T cells express distinctive subsets of these molecules or same T cells express these different molecules at different stages of the disease.

Th17 and Treg cells in IRI

Although roles of Th1/Th2 cells in the pathogenesis of organ IRI has been addressed, results have not been clear cut. Stat 4 deficient mice, which are defective in Th1 cell differentiation, were shown to have similar degree of liver IRI in one report [27], while the other one showed liver protection and that cells from these KO mice failed to recreated liver IRI in nude mice [28]. In a renal IRI model, although Stat4 KO mice were not protected, Stat6 and IL-4 deficient mice suffered increased tissue injuries [29]. Since $CD4^+$T cells are now characterized not only by Th1, Th2, but also Th17 cells, regulatory T cells (Treg) and T follicular helper cells (Tfh), with both pro- and anti-inflammatory functions, questions of whether and how these newer T helper cells are involved become integral parts of the whole issue about CD4 T cell effector functions in IRI.

Ample examples of IL-17 in IRI are currently present in literatures. However, majorities, if not all, have been associated with unconventional T cells or innate immune cells as the cellular source of IL-17. IL-17A was a key regulator in initiating neutrophil-induced inflammatory responses and hepatic injury in the subacute phase (20h) after reperfusion [30]. More specifically, RORγt+IL-17+ neutrophils and IL-17A-producing NK cells were shown to play critical roles in a modified model of liver IRI which occurred in RAG

deficient hosts [31,32]. Although we have shown that acute liver IRI was diminished in IRF3 deficient hosts by the disruption of type I IFN induction downstream of TLR4, a recent study revealed a novel liver protection mechanism mediated by IRF3 that functioned late (48h) during IR [33]. It turned out that IRF3 deficient resulted in a significant increase of IL-23 induction in KCs, leading to the activation of liver iNKT cells and γδT cells. These cells mediated a delayed neutrophil-associated inflammatory liver damages by producing IL-17A. Unconventional CD3+ cells, including γδ T cells and double-negative T cells, were identified in another study, as the major cellular sources of IL-17A, mediating a late phase of acute liver IRI (24h post reperfusion) [34]. Interestingly, in a model of liver IR-induced intestinal and kidney injuries, Paneth cell-derived IL-17A play a key role in not only extrahepatic organ dysfunction but also liver IRI [35].

In murine cerebral IRI models, cellular interactions resulting in the activation of IL-17 pathway have been elaborated. It was shown that macrophage-derived IL-23 was increased early and activated γδ, but not $CD4^+$, T cells to produce IL-17, which played pivotal roles in the delayed phase of apoptotic neuronal death [8]. In fact, both conventional $CD4^+$ T cells and γδT cells contributed to the development of infarct and neurological deficit after IR. $CD4^+$ T cells produced IFN-γ which induced TNF-α production in macrophages, whereas γδT cells secreted IL-17A which recruited neutrophil [36]. Adding to the complexity of inflammatory cellular interactions leading to IRI, neutrophil production of IL-17A was found upstream of IL-12/IFN-γ in an acute kidney IRI model [17]. The DC-initiated NKT cell activation via the IL-12-IFN-γ pathway was insufficient to drive the development of kidney injuries by itself, as both tissue injury and IFN-γ production were diminished in IL-17A and IL-17R KO mice. Furthermore, IFN-γ administration reversed the kidney protection in IL-17A KO mice from IR, whereas IL-17A failed to do the same in IFN-γ KO mice. Thus, although neutrophils are generally activated and recruited by IL-17 and function as effectors, they can also produce IL-17 and feed-back the inflammatory immune activation cascade. indeed, neutrophil were found to be able to produce IFN-γ in response to IL-17, which was dependent on COX-2-mediated PGE2 and inhibited by netrin-1[37]. The activation of IL-17 pathway by IR was also found in myocardial and lung models. The coronary artery ligation and reperfusion resulted in γδT cells, not CD4+ T cells, to produce IL-17, responsible for cardiomyocyte apoptosis and neutrophil infiltration [38]. In lungs, iNKT, but not CD4+ T cells were found to be the key player by producing IL-17A [39]. RAGE activation by HMGB1 in iNKT cells triggered the IL-17 production [40]. One unique feature of CD4+ Th17 was discovered in a murine hindlimb ischemia model that these cells actually contributed to neovascularization 14-21 days post reperfusion [41].

The resolution of tissue inflammation is an essential homeostatic mechanism. In addition to the intrinsic regulatory mechanism of innate immune responses, mediated by innate immune activation products, such as SOCS, IL-10, IL-1RA, the question of whether regulatory T cells (Tregs) play roles in organ IRI is of high significance. In a murine model of ischemic acute kidney injury, a significant trafficking of $CD4^+Fox3P^+$Tregs into kidneys was observed on day 3-10 post reperfusion [42]. Experiments using anti-CD25 to deplete Treg or RAG deficient mice reconstituted with Treg proficient or deficient lymphocytes showed that Tregs were able to protect kidneys from IRI by suppressing either T cells [42] and/or innate immune cells via an IL-10-dependent mechanism [43]. Controversial findings were reported

in brain ischemia models. While anti-CD25 Ab treatment profoundly increased delayed brain damage and deteriorated functional outcome by augmenting postischemic activation of resident and invading inflammatory cells including microglia and T cells [44]; depletion of Tregs in the DEREG mouse model dramatically reduced infarct size and improved neurologic function 24 hours after stroke [45]. Interestingly, both protective and deteriorating effects of CD25+Treg in ischemic stroke could be recapitulated in adaptive transfer models. Mechanistically, it was the IL-10 that mediated the protective effect of Treg, while their interactions with the ischemic brain endothelium and platelets increased microvascular thrombus formation and disrupted cerebral reperfusion. It was postulated that these distinctive effects might actually exert at different stages of brain IRI and be likely model-specific (e.g., reversible vs. irreversible IRI): Treg promotes stroke pathogenesis in the acute phase, while it inhibits inflammation and facilitates tissue repair at relatively late phase of infarct development. In a murine hindlimb ischemia model, Treg deficiency in CD28 or B7 KO mice or by anti-CD25 mediated depletion resulted in enhanced postischemic inflammatory response and neovascularization at day 21 post reperfusion [46]. The adenosine 2A receptor [A(2A)R] was found to be important for the anti-inflammatory functions of Treg cells that cells from its gene KO or CD73 (encodes the enzyme to generate extracellular adenosine) KO mice failed to confer kidney protection from IRI [47]. It was further shown that the A2AR activation induced PD-1 expressions on Treg, which was critical for its protective effect. Heat-shock protein 70 was also shown to mediate Treg expansion in heat pre-conditioned mice which were protected from kidney IRI [48]. We have shown in a liver partial warm ischemia model that ex vivo induced Treg cells were able to protect livers from IRI by inhibiting KC activations [49]. Thus, Treg cells play a protective role in their abilities to resolve inflammation and promote tissue repair.

Conclusion

Roles of T cells in the pathogenesis of organ IRI have been firmly established in various organ models. Their functional variations may reflect their differences in tissue-specific T cell/innate immune cell compositions, in T cell infiltration kinetics relative to disease developmental stages, and in disease mechanistic details. Although the question how these putative Ag-specific cells are activated by IR remains open, we can now better appreciate their functions in terms of cytokine productions, cell surface molecule expressions and their interactions with innate immune cells. Thus, refined T cell targeted therapies, which maximally eliminates the pro-inflammatory but spare the anti-inflammatory/immune regulatory properties of these cells, are warranted for their future clinical application.

Acknowledgments

The authors would like to acknowledge the funding support from NIH Grants RO1 DK083408 (YZ), The Dumont Research Foundations; and grants from National Nature Science Foundation of China 81100270, 1310108001, 81210108017 (LL).

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Key points

Different T cell subsets, including CD4, γδ T cells and Treg, are involved in the pathogenesis of IRI.

Th1 and Th17/IL-17 producing-γδ T cells promote inflammatory immune activation.

Treg cells contribute to the resolution of tissue inflammatory and tissue repair.

T cells may function as innate immune cells without Ag-specific activation.