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Recipient T Cells Mediate Reperfusion Injury after Lung Transplantation in the Rat

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Leukocytes have been implicated in ischemia-reperfusion (IR) injury of the lung, but the individual role of T cells has not been explored. Recent evidence in mice suggests that T cells may play a role in IR injury. Using a syngeneic (Lewis to Lewis) rat lung transplant model, we observed that recipient CD4+ T cells infiltrated lung grafts within 1 h of reperfusion and up-regulated the expression of CD25 over the ensuing 12 h. Nude rats (rnu/rnu) and heterozygous rats (rnu/+) were used to determine the role of T cells in IR injury. No significant difference in lung function was observed between nude and heterozygous recipient rats after 2 h of reperfusion. However, after 12 h of reperfusion, recipient nude rats had significantly higher oxygenation and lower peak airway pressure than recipient heterozygous rats. This was associated with significantly lower levels of IFN-γ in transplanted lung tissue of recipient nude rats. Reconstitution of recipient nude rats with T cells from heterozygous rats restored IR injury after 12 h of reperfusion. The effect of T cells was independent of neutrophil recruitment and activation in the transplanted lung. These results demonstrate that recipient T cells are activated and mediate IR injury during lung transplantation in rats. The Journal of Immunology, 2003, 171: 4995–5002.

Lung transplantation has enjoyed increasing success in the last decade. It has evolved from an experimental endeavor to the mainstream of therapy for many end-stage lung diseases. The Registry of the International Society for Heart and Lung Transplantation reported in 2002 that almost 15,000 lung transplants have been performed worldwide and that >1,500 lung transplants are performed annually (1). Despite the success of lung transplantation, rejection, infection, and poor immediate graft function present persistent problems and contribute to a mortality rate of 20–30% at 1 year (2). Most recipients develop some degree of reperfusion injury, and ~10% of them end up with severe lung injury, requiring extended support with positive pressure ventilation, pharmacological therapy, and occasionally extracorporeal membrane oxygenation (3). In addition to a high mortality rate, severe reperfusion injury can also be associated with an increased risk of acute rejection that may lead to graft dysfunction in the long term (4–6).

Ischemia-reperfusion (IR) injury occurs in a biphasic pattern (7). The early phase of reperfusion depends primarily on donor characteristics, but these lose importance during the ensuing 24 h, and recipients characteristics then become predominant (8). Donor/passenger macrophages have been shown to be activated during ischemia and to mediate the early phase of reperfusion injury, whereas neutrophils are primarily involved in the late phase of reperfusion injury (9, 10). The recruitment of neutrophils into the lung results from the release of mediators before and after reperfusion. IL-8, one of the main chemoattractants for neutrophil, is released in lung tissue after reperfusion, and its level 2 h after reperfusion correlates with lung function and patient status during the ensuing 24 h in the intensive care unit (11).

Although most of the work on leukocytes in IR injury has focused on the role of neutrophils and macrophages, recent studies suggest that lymphocytes may also be involved in reperfusion injury. Richter et al. (12) demonstrated that human lung donor parenchyma contains a large number of passenger macrophages and activated lymphocytes, among which T cells and NK cells predominated. Similar findings have been observed in liver transplantation with many activated CD8+ T cells, γδ T cells, and NK cells being transmitted with the liver graft to the recipient (13–16). In addition, recent studies in nontransplant models of warm ischemia of the liver and kidney have demonstrated that nude mice, CD4+CD8+ knockout mice, and CD4+−depleted mice experienced significantly less severe reperfusion injury than nonimmunodeficient mice (17–19). Le Moine et al. (20) also observed that donor nude mice had less severe reperfusion injury after 2 h of reperfusion than control immunodeficient mice in an ex vivo model of liver reperfusion. Hence, T cells seem to play a major role in reperfusion injury, but no study has yet been performed in a transplantation model to determine whether T cells were activated despite the absence of alloantigen stimuli and whether the donor and/or the recipient T cells mediated reperfusion injury. The objectives of this study were then to determine: 1) whether T cells infiltrated the lung graft after reperfusion; 2) whether donor and/or recipient T cells mediated reperfusion injury; and 3) whether donor and/or recipient T cells were activated after reperfusion in a rat lung transplant model. We found that recipient T cells infiltrated the transplanted lung rapidly after reperfusion and that they mediated reperfusion injury after 12 h of reperfusion and up-regulated the expression of CD25 on their surface.

Materials and Methods

Animals

Experiments were performed using 10- to 12-wk-old male inbred Lewis rats (Charles River, Montreal, Quebec, Canada), athymic nude rats (rnu/H9253/H9254) and nude/H11022/H11011 BALB/c mice.
rnu), and heterozygous rats (rnu+/+) (Harlan Breeder, Indianapolis, IN). Five animals were used in each group for all experiments. All animals received care in compliance with the Principles of Laboratory Animal Care (21) and the Guide to the Care and Use of Experimental Animals (22). The experimental protocol was approved by the Animal Care Committee of the Toronto General Hospital Research Institute.

Lung transplantation model

The rat single lung transplant model used in this study has been described in greater detail by us elsewhere (23). Briefly, donor rats were anesthetized by an i.p. injection of 1 ml of sodium pentobarbital (Somnotol; MTC Pharmaceuticals, Cambridge, Ontario, Canada) and intubated through a tracheostomy with a 14-gauge i.v. catheter. The tracheostomy tube was then connected to a volume-controlled ventilator (Harvard Rodent Ventilator Model 683; Harvard Apparatus, South Natick, MA), and the animals were ventilated at a rate of 80 breaths/min, a tidal volume (VT) of 10 ml/kg, an inspired fraction of oxygen of 1.0, and a positive end-expiratory pressure (PEEP) of 2 cm H2O. Lungs were flushed in situ with 20 ml of low-potassium-dextran-glucose preservation solution (Perfadex; Vitrolife, Göteborg, Sweden). The left pulmonary artery was then placed into 40 ml of low-potassium-dextran-glucose solution at 4°C for 12 h.

Recipient animals were anesthetized in a halothane chamber and intubated with a 14-gauge i.v. catheter. All recipient animals were ventilated with 100% O2 mixed with 1.5% halothane at a rate of 80 breaths/min, a PEEP of 2 cm H2O, and a VT of 10 ml/kg. The left pulmonary artery, main bronchus, and pulmonary vein were anastomosed with the corresponding recipient structures using the cuff technique. If the transplanted lung was reperfused for 2 h, we used a modification of our model to measure the airway pressure from the transplanted lung throughout the reperfusion period. This model has been described in details elsewhere (24). Briefly, the left main bronchus of the transplanted lung was connected to an extra-corporeal ventilator and ventilated with 100% O2 mixed with 1.5% halothane at a rate of 80 breaths/min, a PEEP of 2 cm H2O, and a VT of 4.5 ml/kg for 5 min before any functional measurement was performed. If the transplanted lung was reperfused for 2 h, we used a modification of our model to measure the airway pressure from the transplanted lung throughout the reperfusion period.

Assessment of lung graft function

The peak airway pressures (PAwp) and arterial pressure of oxygen (PaO2) of the transplanted lung have been shown to be reliable markers of lung function in a rat left single lung transplant model (23, 25). PAwpPs from the transplanted lung were measured with a three-way tap inserted between the endotracheal tube of the transplanted lung and the ventilator and connected to a pressure transducer. PAwpPs were measured continuously during the 2-h reperfusion period or at the end of the 12 h reperfusion during 5 min to achieve a steady state. At the end of the reperfusion period after the last PAwp measurement was performed, a blood gas sample was drawn from the left pulmonary vein of the transplanted lung or from the carotid artery if the right hilum was clamped.

Immunohistochemistry

Frozen sections (7 μm) where prepared on sialinated treated glass slides. Sections where air dried and fixed in acetone for 10 min at room temperature. Immunohistochemical procedure on frozen sections for mouse anti-CD3 (BD PharMingen, San Diego, CA), at a dilution of 1/50, was performed on the NEXES autoimmuno stainer (Ventana Medical Systems, Tucson, AZ). CD3 is a marker for T cells and CD11b is a marker of activated neutrophils and macrophages that is absent on lymphocytes. To avoid cross-reactivity between similar species, detection was conducted using a modification of the M.O.M ABC system (Vector Laboratories, Burlingame, CA). Brieﬂy, anti-CD3 or anti-CD11b (BD PharMingen, San Diego, CA) were incubated with the tissue sections for 30 min at room temperature. The sections were then washed and incubated with biotinylated goat anti-mouse polyclonal IgG at 1/50 dilution (BD PharMingen). Negative control slides were performed with the primary Ab omitted and replaced with nonimmunized control goat serum. The counterstain of preference was hematoxylin for nuclear detail. After the entire lung section was viewed, immunoreactive cells were counted in 10 random high-powered (×400) fields, and total numbers of cells were quantified in a blinded manner.

Cytokine measurements

At the end of the reperfusion period, lung tissue samples were immediately snap frozen in liquid nitrogen and stored at −80°C. Tissues were subsequently homogenized and incubated at 4°C in cell lysis buffer containing 10 mM HEPES (pH 7.9), 10 mM KCl, 0.1 mM EDTA, 0.1 mM EGTA, 1 mM DTT, 0.5 mM PMSF, and 0.6% octylphenoxypolyethoxyethanol (Nonidet P-40) (26). Homogenates were then sonicated and centrifuged at 12,000 rpm for 10 min at 4°C. Supernatants and plasma samples were assayed in duplicate using specific ELISA kits for rat IFN-γ and rat macrophage inflammatory protein-2 (MIP-2), according to the manufacturer’s instruction. Specific Cytoscreen Immunoassay Kits (BioSource International, Camarillo, CA) were used for all cytokines. The OD of each well was read at 450 nm with an NM-600 microplate reader (Dynatech Laboratories, Chantilly, VA). The final concentration was calculated by converting the OD readings against a standard curve. The protein content was determined by the Bradford method (27). Data are presented as units of cytokine per mg protein.

T cell adoptive transfer

Spleens were collected from immune competent heterozygous rnu/+ rats. Freshly isolated spleens were placed into RPMI (HEPES) medium containing 10% FCS and cells were separated by filtration through a 200-μm mesh screen. Splenic cells were collected by centrifugation and RBC were removed by lysis in NH4Cl at room temperature for 5 min in the dark. Mononuclear cells were harvested by centrifugation and washed three times with 10% FCS-containing medium. T cell enrichment was performed using nylon wool column chromatography. Briefly, sterile nylon wool-packed columns were equilibrated in RPMI with 10% FCS, and cells were incubated on the column for 1 h at 37°C in 5% CO2. Nonadherent cells (predominantly T cells) were then eluted in 30 ml of RPMI and collected by centrifugation. The percentage of CD4+ and CD8+ T cells was assessed in nylon wool T cell-enriched fraction by flow cytometry. Enriched T cells were then washed three times with PBS to remove serum from the preparation. Enriched T cells (25 106) were injected i.v. via the tail vein of each rnu/rnu rat. The rats were then kept in sterile condition for 6 days before being used as donor or recipient animals. The 6-day time point was based on preliminary experiments showing that longer time points of up to 3 wk did not enhance the efficiency of T cells reconstitution.

FACS

The left lung was crushed in 5 ml of HBSS, and cell aggregates were separated by filtration through a 200-μm pore size nylon screen. Cells were collected by centrifugation for 5 min at 1500 rpm. They were resuspended in NH4Cl for 5 min at room temperature to remove RBC. Cells were then washed three times in PBS to remove serum from the preparation. Enriched T cells (25 106) were injected i.v. via the tail vein of each rnu/rnu rat. The rats were then kept in sterile condition for 6 days before being used as donor or recipient animals. The 6-day time point was based on preliminary experiments showing that longer time points of up to 3 wk did not enhance the efficiency of T cells reconstitution.

Statistical analysis

All data are expressed as mean ± SD. A one-way ANOVA was used to determine statistical significance. For differences in PAwp, the Friedman repeated measures ANOVA was performed, p < 0.05 was considered statistically significant. The Graphpad software package (Graphpad Software, San Diego, CA) was used for all statistical analyses.

Results

Kinetics of T cell infiltration in the lung during ischemia and after reperfusion

The large majority of studies analyzing the infiltration of leukocytes in IR of the lung have focused their attention on neutrophils. T cells have generally not been sought or rigorously identified with definitive techniques, and very early times after reperfusion have not been examined. Using Lewis rats as donors and recipients, we quantified the number of lymphocytes and CD3+ T cells and determined the proportion of CD3+, CD4+, and CD8+ T cells in the left lung before the retrieval procedure (normal lung), at the end of
the cold ischemic time, and after reperfusion of the transplanted left lung. The reperfusion period was divided into five time points: 10, 30, and 60 min, followed by 3 and 12 h of reperfusion. Donor lungs contained ~250,000 lymphocytes that remained unchanged during the cold ischemic time. The number of lymphocytes in the transplanted lung tissue began to rise within 10 min of reperfusion and increased up to 2 million after 1 h of reperfusion (Fig. 1). During the ensuing 12 h of reperfusion, the number of lymphocytes progressively decreased. Using immunostaining, we observed that the number of CD3+ T cells significantly increased after 1 h of reperfusion and that they were principally located in the lung parenchyma (Fig. 1). T cells infiltrating lung tissue were predominantly CD4+ T cells, which increased from 22% in donor lungs to 41% after 1 h of reperfusion (Fig. 1). In the recipient blood, the number of lymphocytes and the proportion of CD3+, CD4+, and CD8+ T cells did not significantly change during the first 12 h of reperfusion (data not shown). These findings suggest that lymphocytes and predominantly CD4+ T cells infiltrate the transplanted lung rapidly after reperfusion and may thus play an active role in mediating IR injury.

Early reperfusion injury is dependent of donor but not recipient T cells

Because T cell infiltration peaked in the transplanted lung after 1 h of reperfusion, we wanted to determine the role of donor and recipient T cells in the early phase of reperfusion injury. We therefore compared four groups during a 2-h reperfusion period. The first group included heterozygous rats as donor and recipient (H-H), the second group included nude rats as donor and heterozygous rats as recipient (N-H), the third group included heterozygous rats as donor and nude rats as recipient (H-N), and the fourth group included nude rats as donor and recipient (N-N). After completion of the 2-h reperfusion period, we observed that transplantation with lungs from donor nude rats was associated with more severe reperfusion injury. Indeed, the groups N-H and N-N had lower PaO2 and higher PAwP after 2 h of reperfusion than the groups H-H and H-N (Fig. 2). No significant difference in lung function, however, was observed according to whether the recipient was nude rats (group H-N) or heterozygous rats (group H-H). Hence, these data indicate that although recipient T cells infiltrate the transplanted lung rapidly after reperfusion, they do not contribute to reperfusion injury after 2 h of reperfusion. Donor parameters appeared to have more influence on the degree of injury during this early phase of reperfusion.

Late reperfusion injury is dependent of recipient T cells

Previous studies have suggested that IR injury can be differentiated into two phases: the early phase of reperfusion injury, which corresponds to the first few hours of reperfusion during which function of the transplanted lung is mainly dependent of donor characteristics; and the late phase of reperfusion, which occurs thereafter and is principally dependent of recipient factors (7, 8).
We therefore analyzed lung function in two groups after 12 h of reperfusion. Heterozygous rats were used as donors in both groups, and recipients were divided into nude rats in one group and heterozygous rats in the other. After 12 h of reperfusion, the group that included nude rats as recipient presented with significantly better lung function characterized by lower PAwP and higher PaO\textsubscript{2} than the group that included heterozygous rats as recipient (Fig. 3).

Nude rats are genetically mutant animals lacking T cells. However, they may develop compensatory mechanism to palliate the T cell deficiency. Hence, to confirm that T cells had a role in the late phase of reperfusion injury, we reconstituted nude rats with T cells. T cell population was enriched from the spleen of heterozygous rats using nylon wool chromatography (Fig. 3).

T cell-reconstituted nude rats were then used as recipients. After 12 h of reperfusion, when T cell reconstituted nude rats were used as recipients, they demonstrated a return of the reperfusion injury as determined by PaO\textsubscript{2} and PAwP of the transplanted lung (Fig. 3). These data indicate that despite a rapid infiltration of lymphocytes in lung tissue after reperfusion, recipient T cells mediate reperfusion injury in the late phase of reperfusion only.

Recipient CD4\textsuperscript{+} T cells expressed CD25 after 12 h of reperfusion

We have demonstrated that recipient T cells infiltrate lung graft and mediate reperfusion injury after 12 h of reperfusion. Hence, to confirm that reperfusion injury may activate T cells despite the absence of alloantigen stimuli, we determined the level of CD25\textsuperscript{+} T cells in lung graft tissue before and after 12 h of reperfusion using Lewis rats as donors and recipients. We demonstrated that ~4% of CD4\textsuperscript{+} T cells expressed CD25 in the normal lung and that no significant change was observed after 2 h of reperfusion. However, after 12 h of reperfusion, up to 23% of CD4\textsuperscript{+} T cells expressed the marker CD25 in the transplanted lung tissue (Fig. 4). In the blood, in contrast, the proportion of CD4\textsuperscript{+} CD25\textsuperscript{+} T cells remained unchanged during the 12-h reperfusion period (Fig. 4).

Using nude rats and heterozygous rats alternatively as donors and recipients, we determined that the activated CD4\textsuperscript{+} T cells originated from the recipient rats. Indeed, transplantation of lungs from heterozygous rats to nude recipient was associated with only 3% of CD4\textsuperscript{+} CD25\textsuperscript{+} T cells after 12 h of reperfusion. In contrast, transplantation of lungs from nude rats into heterozygous recipients was associated with a large increase in CD4\textsuperscript{+} CD25\textsuperscript{+} T cells in the graft after 12 h of reperfusion (Fig. 4).

Recipient T cells release IFN-\gamma in lung tissue after 12 h of reperfusion

The cytokine IFN-\gamma is characteristically released by activated T cells. We therefore determined the level of IFN-\gamma in the transplanted lung tissue from recipient nude rats and from recipient
heterozygous rats after 12 h of reperfusion. We observed that better lung function in recipient nude rats was associated with significantly lower levels of IFN-γ in lung tissue than in recipient heterozygous rats (Fig. 5). The level of IFN-γ, however, was not significantly different between recipient heterozygous rats and recipient nude rats enriched with T cells transfer (A and B). These data indicate that reperfusion injury may be mediated by the release of IFN-γ from activated T cells after 12 h of reperfusion.

T cell-induced reperfusion injury is not mediated by neutrophil activation

Neutrophils mediate reperfusion injury during the late phase of reperfusion, and flow cytometry of the transplanted lung tissue in our model of Lewis to Lewis rat lung transplant showed that T cell infiltration in lung graft occurred before the neutrophil recruitment (Fig. 6). We therefore questioned whether the effect of T cells on reperfusion injury after 12 h of reperfusion could have been mediated by the recruitment and activation of neutrophils in the transplanted lung. We used heterozygous rats as donor and recipient in one group and heterozygous rats as donor and nude rats as recipient in the other group. MIP-2 (rodent analog of IL-8), an important chemokine for neutrophil attraction and activation in lung transplantation, was measured in lung graft tissue after 2 and 12 h of reperfusion, but no significant difference was observed between the two groups at these time points (Fig. 6). In addition, the number of activated neutrophils determined by CD11b staining in the transplanted lung after 12 h of reperfusion was not significantly different between the two groups (Fig. 6). These data suggest that T cell-mediated reperfusion injury is independent of neutrophil recruitment and activation.

Discussion

This study demonstrates that recipient T cells infiltrate the transplanted lung after a period of cold ischemia and mediate lung injury during the late phase of reperfusion. These findings are consistent with previous studies in T cell-deficient mice, suggesting that CD4+ T cells were involved in the mechanism of IR injury of the liver, kidney, and intestine (17, 19, 28). Our results for the first time provide direct evidence that recipient (but not donor) CD4+ T cells are activated during reperfusion injury despite the absence of alloantigen stimuli and the short period of reperfusion.

Classically, T cells are thought to require several days after transplantation to be exposed to foreign Ags by APCs and to be
activated (29). Although this holds true for naive T cells, other types of T cells may be involved in IR injury. Effector T cells and possibly some memory T cells can maintain the expression of specific cytokine receptor on their cell surface and proliferate in vivo in the absence of Ag stimulation (30). This Ag-independent proliferation of T cells is known as bystander activation. Recent studies have also shown that polarized memory Th1 cells can be re-activated and up-regulate the expression of CD25 after a few hours of stimulation and that they home directly into inflamed tissue instead of lymph nodes (31–33).

Some regulatory T cells are characterized by the coexpression of CD4+ and CD25+ markers on their cell surface (34). However, these regulatory T cells usually coexpress both markers at all times. The up-regulation of CD25+ on previously CD25−CD4+ T cells is considered to be a marker of activation and may be associated with the release of IFN-γ in vitro (31, 32).

The burst of oxygen free radicals as well as complement activation and cytokine release could potentially contribute to T cell activation during the transplantation process (11, 35). However, the mechanism by which T cell mediates reperfusion injury remains unknown. We have hypothesized that their action could be mediated by the recruitment and activation of neutrophils because T cell preceded neutrophil infiltration in the transplanted lung tissue in our model. However, the level of MIP-2 was not significantly different between recipient nude and heterozygous rats, and the quantification of activated neutrophils in lung graft was similar between the two groups as well. Another potential mechanism of action could be mediated by the release of IFN-γ from activated CD4+ T cells. We observed that nude recipients had significantly lower levels of IFN-γ in lung tissue than heterozygous recipients, and the level significantly increased when recipient nude rats were transferred with T cells from heterozygous rats before transplantation. Similar findings have been observed by Burne et al. (19), who also reported that IR injury was not restored if nude mice received transfers of T cells from IFN-γ-deficient mice.

Our results have important clinical implications in the prevention and treatment of IR injury. Humanized mAbs against IL-2Rα (CD25) are currently used in clinical transplantation as induction therapy to prevent rejection (36). However, their role in IR injury has not been analyzed systematically. In one randomized study.

**FIGURE 4.** Detection of CD4+ T cell activation by up-regulation of CD25. A, Normal lung tissue contains ~4% of CD4+CD25+ T cells. B, After 2 h of reperfusion with Lewis to Lewis rat lung transplantation (Tx), the proportion remains the same with ~4% of CD4+CD25+ T cells in lung tissue. C, After 12 h of reperfusion with Lewis to Lewis rat lung transplantation, the level of CD4+CD25+ T cells increased up to 23% in lung tissue. D, In contrast to lung tissue, there is no change in the proportion of CD4+CD25+ T cells in the blood from recipient Lewis rats after 12 h of reperfusion; the proportion of CD4+CD25+ T cells in normal blood is similar to that in the lung and is ~4% (data not shown). E, When heterozygous rats were used as donor and nude rats as recipient, the levels of CD4+CD25+ T cells remained low in lung tissue after 12 h of reperfusion. F, In contrast, when nude rats were used as donor and heterozygous rats as recipient, lung tissue contained ~16% of CD4+CD25+ T cells after 12 h of reperfusion, demonstrating that recipient CD4+ T cells are activated after reperfusion. QR, Quantum red.
involving kidney transplantation, the authors have observed that the group of patients treated with anti-IL-2R Ab before reperfusion resumed urine output earlier and had less renal dysfunction at 1 month than the control group treated with placebo (37). Future experimental studies should help to determine whether the administration of anti-CD25 Abs to the recipient before reperfusion protects the graft from IR injury.

This study presents some limitations due to the use of athymic nude rats. Hence, some of the changes that we observed may have been due to uncontrolled abnormalities in nude rats. T cell depletion in wild-type rats would have been optimal to confirm our results, but CD3 or CD4 T cell depletion in rats was not feasible despite our attempts with various doses of Abs. The reconstitution of IR injury by T cells transfer to recipient nude rats and the activation of recipient CD4 T cells during the same time frame, however, strongly supports our results on the role of T cells in IR injury.

An interesting finding from our study was the enhanced IR injury when nude rats were used as donors. This suggests that T cells may have a suppressive and protective role during cold ischemia or that lungs from nude rats contain other immunological characteristics that render them more susceptible to cold ischemia (38, 39). Nude rats have a more developed innate...
immune system and contain more NK cells and γδ T cells in lung tissue than immunocompetent rats (39). Future studies should determine whether NK cells and γδ T cells are involved in IR injury.

In conclusion, this study demonstrates that recipient CD4+ T cells rapidly infiltrate lung graft tissue and up-regulate CD25, a marker of T cells activation, after 12 h of reperfusion. Recipient T cells did not appear to be involved in the early phase of reperfusion injury. However, after 12 h of reperfusion, recipient T cells mediated reperfusion injury and were associated with significant release of IFN-γ in lung tissue. These findings may have important implication for the prevention and treatment of IR injury. Future studies should determine more precisely the type of T cells and their mechanism of activation.

References


