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Mechanisms of T Lymphocytes in the Damage and Repair Long Term after Renal Ischemia Reperfusion Injury

Dolores Ascon and Miguel Ascon
Cell Therapy Unit. Brijen Biotech, LLC. The BioInnovation Center, University of Maryland BioPark, Baltimore, MD 21201, U.S.A.

1. Introduction

Acute kidney injury (AKI) is a frequent event associated with decreased allograft survival in patients with transplanted kidneys and high mortality in patients with native kidneys (1,2). AKI is a common complication in hospitalized patients, and its incidence has risen substantially over the past 15 years (1-3). As a conservative estimate, roughly 17 million admissions annually in the United States are complicated by AKI, resulting in over $10 billion in costs to the health care system (4). Kidney transplants from living unrelated donors (not well HLA matched) with minimal ischemic injury have improved allograft survival, compared with grafts from well matched cadaveric donors with significant ischemia (5, 6). This implies that renal ischemia reperfusion injury (IRI) can have important consequences on long-term graft survival and native kidneys.

IRI is a highly complex cascade of events that includes interactions between vascular endothelium, interstitial compartments, circulating cells, and numerous mediator molecules (7). Renal ischemic injury has been found to permanently damage peritubular capillaries causing hypoxia, which may be involved in the progression of chronic renal disease after AKI (7, 8). Tubulointerstitial influx of inflammatory cells is found in many forms of chronic renal diseases, including ‘nonimmune’ diseases such as diabetes and hypertension (9). T-lymphocyte infiltration has also been observed early after moderate ischemia injury (10,11) however, the dynamics of infiltrating lymphocyte populations long term after moderate or severe ischemic injury is not very clear.

It has been demonstrated that T and B lymphocytes are important mediators in the pathogenesis of renal IRI (10, 12) however, the mechanisms by which these cells induce kidney injury is largely unknown. The trafficking of pathogenic lymphocytes into kidneys after moderate and severe ischemic injury has been postulated to contribute to kidney damage (11, 13, 14) however the physiologic state and the dynamics of trafficking of these populations long term after ischemia have not been rigorously studied. Furthermore, the activation and expression of the effector-memory phenotype by infiltrated lymphocytes suggests the possibility that these lymphocytes are responding to an injury-associated antigen (15, 16). In addition, these lymphocytes are responsible to produce inflammatory mediators not only causing local kidney structure damage, but also the severe effects
on the other long distance organs, including lung, heart, intestine, brain, liver, bone medulla. Here we describe the trafficking of T lymphocytes into the mice (male C57BL/6J) kidneys both, in normal mice, earlier (3 to 24 h), and long term (1 to 11 weeks) after the renal injury was performed as previously described (17, 18, 19). The different T cell phenotypes and cytokine/chemokines raised at different times are compared with the baseline level cells maintained in normal kidneys (17). In the long term studies, to make our observations clinically relevant for both allograft and native kidneys, we have studied these phenomena in both a moderate bilateral ischemia (akin to ischemia in native kidneys) and a severe unilateral ischemia (akin to IRI in an allograft). The different kidney infiltrating T cell phenotypes and its effector molecules raised at different times after ischemia injury are presented and discussed.

2. Overview of experimental acute kidney injury

The mechanisms involved in renal ischemia-reperfusion injury (IRI) are complex (20, 21), involving both innate and adaptive immunity (22, 23). Following IR, the cascade of events leading to endothelial cell dysfunction, tubular epithelial cell injury and activation of tissue-resident and infiltrating leukocytes consists of the coordinated action of cytokines/chemokines, reactive oxygen intermediates and adhesion molecules (21, 23). The early phase of innate immune response to IR begins within minutes of reperfusion, whereas the late phase adaptive response requires days to manifest. For our experiments, a well-established model of renal IRI in mice was used (17, 18, and 19).

3. Early trafficking of T lymphocytes into kidneys after IRI

**Trafficking of CD4+ and CD8+ T lymphocytes**

We have examined the trafficking of CD4+ and CD8+ T cell subsets into kidneys after ischemic injury (18). After 3 h of renal IRI, the percentages of CD4+ and CD4+NK1.1+ cells increased similarly in both sham-operated and IRI mice as compared with normal mice. However, 24 h after renal IRI, while the percentage of CD4+ T cells in the IRI mice was similar to that of control groups, the percentage of CD4+NK1.1+ cells increased (3.2%) when compared with normal (1.2%) and sham-operated (1.6%) mice. The percentage of CD8+ T cells was similar in all groups 3 and 24 h after renal IRI and no expression of NK1.1 Ag was observed on these cells. However, the increased percentage of the CD4+ NK1.1+ cells in the IRI group 24 h after renal IRI could be related to renal ischemic injury because at this time point serum creatinine was increasing and visible kidney structure damage was observed. Table 1 shows summarized results.

**Expression of CD69 on CD4+ and CD8+ T lymphocytes**

We have investigated the activation state of the intrarenal CD4+ and CD8+ T cell subsets analyzing the expression of activation markers CD69 and CD25 (18). After 3 h of renal IRI, we observed increased expression of CD69 on CD4+ T cells in sham-operated (14.7%) and IRI (14.2%) compared with normal mice (7.1%). CD69 expression on CD8+ T cells tended to increase at 3 h, but was not statistically significant. After 24 h of renal IRI, the expression of CD69 on CD4+ and CD8+ T cells declined to lower levels than normal mice. Moreover, no increased expression of CD25 Ag on CD4+ and CD8+ T cells in any of the studied groups.
was found. Results demonstrated that CD4+ and CD8+ T lymphocytes infiltrating kidneys of sham-operated and IRI mice display some features of activated T lymphocytes. We hypothesized that T cells might be activated after renal IRI; however, we found a similarly increased expression of CD69 on the CD4+ and CD8+ T cells in both sham-operated and IRI mice 3 h after renal IRI. Results are summarized in Table 1.

**Kidney assessment and histology changes earlier after ischemia injury**

We evaluated the ischemic kidneys following the serum creatinine levels 3 and 24 h after renal IRI (18). After 3 h of renal IRI, a significant increase in serum creatinine of IRI mice (n = 8, 1.18 mg/dl) when compared with normal (n = 8, 0.50 mg/dl) and sham-operated (n = 8, 0.70 mg/dl) mice was observed. After 24 h of renal IRI, serum creatinine significantly increased in the IRI mice (n = 8, 2.83 mg/dl) as compared with control groups. In the sham-operated mice, serum creatinine was slightly increased compared with normal mice 3 h after surgery (Fig. 1). The kidney structural injury in the cortex and the medulla of IRI mice was evaluated. Compared with kidneys of normal mice (Fig. 1A) and sham-operated mice, 3 (Fig. 1B) and 24 h (Fig. 1C) after surgery, IRI mice show slightly tubular epithelial necrosis 3 h after renal IRI (Fig. 1D) and significant tubular injury with loss of tubular structure 24 h after renal IRI (Fig. 1E).

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**Fig. 1.** Kidney injury after 30-min bilateral ischemia. Serum creatinine of IRI mice (•) compared with normal (▴) and sham-operated (○) mice 3 and 24 h after renal IRI. A, Normal mouse kidney (no IRI). B and C, Sham-operated mice kidneys showing normal histology 3 and 24 h after surgery, respectively. D, IRI mouse kidney showing same proteinaceous casts in tubules 3 h after renal IRI. E, IRI kidney showing severe damage 24 h after renal IRI. (Pictures used with permission and courtesy of the original authors [18]).
Kidney Transplantation – New Perspectives

4. Lymphocyte Phenotypes

<table>
<thead>
<tr>
<th>Lymphocyte Phenotypes</th>
<th>Normal mice</th>
<th>Early trafficking</th>
<th>Long term trafficking</th>
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<tr>
<td></td>
<td>0h 3h 24h</td>
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</tr>
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</tr>
<tr>
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<td>1.8c</td>
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</table>

Table 1. T lymphocytes phenotypic trafficking into mouse kidney after IRI, expressed as cells percentages.

4. Trafficking of T lymphocytes into kidneys long term after IRI

Trafficing of CD4⁺ and CD8⁺ T cells

Analysis of infiltrating lymphocytes long term after renal IRI (19, 24) revealed increased percentages of CD4⁺ (29%) and CD8⁺ (16%) T lymphocytes in IRI kidneys compared with kidneys of sham mice (CD4⁺: 11% and CD8⁺: 6%) after 2 weeks of bilateral renal IRI. However, similar percentage of CD4⁺ and CD8⁺ T cells was observed in sham and IRI kidneys 6 weeks after bilateral renal IRI. 6 weeks after unilateral renal IRI, we observed a significantly increased percentage of CD4⁺ (48%) and CD8⁺ (21%) T lymphocytes compared with kidneys from sham mice (CD4⁺: 16% and CD8⁺: 7%) and contralateral kidneys (CD4⁺: 11% and CD8⁺: 5%). No changes in CD4⁺ and CD8⁺ T-cell populations were observed in any of the groups 11 weeks after unilateral renal IRI. Results are summarized in Table 1. The higher levels of CD4⁺ and CD8⁺ T cells 6 and 11 weeks after ischemia as well as the return to normal levels of some populations as CD69⁺ and CD44⁺ markers after 6 weeks, demonstrate the possible limit and suppression of the immune response after long-term renal IRI. Potential modulators of this immunosuppression could be the regulatory T cells CD4⁺CD25⁺ or CD4⁺CD25⁺FoxP3 (25, 26) as increased populations of these regulatory T cells have been observed in long-term allogenic transplants (27).

Infiltrating of CD4⁺ and CD8⁺ T lymphocytes expressing CD69

After 2 weeks of bilateral renal IRI (19), we observed an increased expression of CD69 on CD4⁺ (17%) and CD8⁺ (9%) T cells in IRI mice when compared with sham mice (CD4⁺: 6% and CD8⁺: 2%). Similarly, increased expression of CD69 on CD4⁺ (22%) and CD8⁺ (18%) T cells in IRI mice compared with sham mice (CD4⁺: 15% and CD8⁺: 11%) was observed after 6
Mechanisms of T Lymphocytes in the Damage and Repair Long Term after Renal Ischemia Reperfusion Injury

weeks of bilateral renal IRI. Six weeks after unilateral ischemia, we observed a significantly increased expression of CD69 on CD4+ (29%) and CD8+ (15%) T cells compared with kidneys from sham mice (CD4+: 7% and CD8+: 2%) and contralateral kidneys (CD4+: 4% and CD8+: 2%). However, 11 weeks after renal IRI, only CD4+ T cells from IRI kidneys showed increased expression of CD69 (28%) when compared with sham (13%) and contralateral (12%) kidneys. Results are summarized in Table 1. The increased infiltration of the activated CD69+ marker T lymphocytes in both unilateral and bilateral IRI kidneys, is consistent with upregulation of the early activation marker CD69 antigen observed in allograft rejections and some autoimmune diseases (28–31). Activated cells produce inflammatory factors which can participate in tissue damage including fibrosis, as observed in patients with systemic sclerosis and pulmonary fibrosis (32, 33).

Infiltrating of CD4+ and CD8+ T cells displaying effector-memory phenotype

Two weeks after bilateral renal IRI (19), significantly increased percentage of effector-memory CD4+CD44hiCD62L- T cells in IRI kidneys (77%) was observed when compared with kidneys from sham mice (54%). Six weeks after bilateral renal IRI, a significantly increased percentage of CD8+CD44hiCD62L- T cells in IRI kidneys (90%) compared with sham mice (79%) was observed. Similarly, 6 weeks after unilateral renal IRI, the IRI kidneys showed significantly increased percentage of CD4+CD44hiCD62L- T cells (96%) when compared with kidneys from sham mice (71%) and contralateral kidneys (65%). A significant increase in percentage of CD4+CD44hiCD62L- T cells was observed in IRI kidneys (93%) when compared with sham (80%) and contralateral kidneys (75%) 11 weeks after renal IRI. Results are summarized in Table 1. The high levels of effector-memory CD4+CD44hiCD62L- T cells, the ‘footprints’ of an immune response to antigens, in both unilateral and bilateral IRI kidneys, are consistent with the response to self-antigens involved in the pathogenesis of skeletal and intestinal ischemia induced by hypoxic stress (34), indicating that immune response to renal IRI could be also initiated by specific antigens.

Decreasing of NKT lymphocytes

Similar percentage of NKT cells (CD4+NK1.1+) was observed after 2 weeks of bilateral renal IRI (19). However, 6 weeks after bilateral renal IRI, we found a significantly decreased percentage of NKT cells in IRI kidneys (2%) when compared with kidneys of sham mice (4%). Eleven weeks after unilateral renal IRI, decreased percentage of NKT cells was observed in IRI kidneys (0.4%) when compared to sham (1.91%) and contralateral kidneys (3.1%; Figure 4a). However, no changes were observed in mice that underwent bilateral renal IRI with reduced ischemia times. In Table 1 are summarized the results. The decreased number of NKT cells 6 and 11 weeks after bilateral and unilateral renal IRI, respectively, are similar to that in liver injury (35) and rheumatoid arthritis (36).

Effect of CD4+ and CD8+ T-cell depletion on kidney-cell infiltration

To determine the pathophysiological role of infiltrating CD4+ and CD8+ T cells long term after ischemia, we depleted these cells before and after unilateral ischemia during the 6-week experiments (19). Depletion started 24 h preischemia and 3 days posts ischemia and cell analysis by flow cytometry was performed weekly in blood and after 6 weeks in kidney samples. Blood was 98% depleted of CD4+ and CD8+ T cells during the 6 weeks after renal IRI. In kidneys, the CD4+CD69+, CD8+CD69+, CD4+CD44hiCD62L, and CD4+NK1.1+ cells were also depleted by approximately 98%, in relationship with the cell profiles of nondepleted control mice (data are not showed).
Histology of structural damage after long term ischemia

To observe the degree of structural damage of ischemic kidneys after 6 weeks of renal IRI in depleted mice, the kidney histology of depleted and control mice were compared. The damage in the cortex (Figure 2a) was similar in control and both depleted mice, however, medullary damage (Figure 2b) was more extensive in control and post-ischemia depleted mice (Figure 2c) than in preischemia depleted mice. Therefore, the reduced damage observed in the kidney medulla of preischemia depleted mice when compared to control mice could be related to the low expression of IFN-γ (Table 2). The IFN-γ produced by CD4+ and CD8+ T lymphocytes is involved early after renal ischemia (37, 38), and has been detected in acute and chronic kidney rejections (39). However, the increased expression of IL-1β in postischemia depleted mice could be related to the increased structural damage of kidney observed and could have distant organ affects (40).

Fig. 2. Kidney tissue from IRI mice after 2 weeks of 25 min of bilateral ischemia (a, upper panel) shows some proteinaceous casts in tubules compared with normal histology of normal and sham mouse kidneys. Kidney structure 6 weeks after unilateral renal IRI (b, lower panel) shows normal histology of sham and contralateral kidneys compared with severe kidney damage, loss of structure, and cyst formation in IRI kidneys. (Pictures used with permission and courtesy of the original authors [19]).

Regulatory T (Treg) cells involved in damage inhibition and reparative phase

Treg cells are lymphocytes with immunosuppressive properties. One important subset of Treg cells express CD4 and CD25 on the cell surface and the transcription factor, FoxP3 (41). The mechanisms of suppression by Treg cells are diverse and include: production of antiinflammatory cytokines such as IL-10 or TGF-β, direct cell-cell contact or CTLA-4 mediated inhibition and production of extracellular adenosine (42). Recently, Treg cells have been identified in normal mouse kidneys (17, 43). In WT mice, treatment with an anti-CD25
monoclonal antibody (PC61) selectively decreased kidney, spleen and blood CD4+ FoxP3+ Treg cell numbers by approximately 50%, five days after PC61 treatment (44). At that time point, Treg cell deficiency potentiated kidney IRI, measured by plasma creatinine, acute tubular necrosis (ATN), neutrophil and macrophage accumulation and pro-inflammatory cytokine transcription in the kidney after 24 hr of reperfusion (43). In lymphocyte-deficient Rag-1 KO mice, adoptive transfer of WT, but not IL-10 KO, Treg cells blocked IR-induced inflammation and kidney injury (43). These findings demonstrate that Treg cells can directly suppress the early innate inflammation, induced by IR, in an IL-10 dependent manner. In a different study, PC61 was administered 1 day prior to IRI, and while BUN levels and ATN scores were no different than control antibody-treated mice at 24 hr of reperfusion, the necrosis failed to resolve by 72 hr in the PC61-treated mice (45). In other study, using a murine model of ischemic acute kidney injury it was found that the percentage of the CD25+ Foxp3+ Treg subset in the total kidney-infiltrating TCRβ+CD4+ T lymphocyte compartment was increased from 1.8 to 2.6% in IR kidneys at 3 and 10 days (46). This infiltration was accompanied of an enhanced pro-inflammatory cytokine production. These results strongly support an important role of regulatory T cells during IRI and in kidney repair after IRI.

<table>
<thead>
<tr>
<th>Cytokines chemokines</th>
<th>Normal mice</th>
<th>Early trafficking</th>
<th>Long term trafficking</th>
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</thead>
<tbody>
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<td>3h&lt;sup&gt;b&lt;/sup&gt;</td>
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</table>

<sup>a</sup>IFN-γ and TNF-α at 0 and 24h were determined by flow cytometry as internal cell cytokines.
<sup>b</sup>MIP-2, MCP-1, KC, and IP-10 at 3 and 24 h were determined using qPCR.
<sup>c</sup>All cytokines and chemokines during the long term trafficking (at 1 and 6 weeks) were determined using qPCR.
<sup>d</sup>Protein levels of CCL5 (RANTES) were detected by ELISA values in pg/mg.

Table 2. Cytokines and chemokines expressed after IRI in kidney.
5. Upregulation of cytokines and chemokines long term after IRI

Expression of cytokines

Cytokine and chemokines are known to modulate lymphocyte and kidney cell interactions to mediate kidney injury and fibrosis. We found (19) an increased intracellular cytokine production of TNF-α and IFN-γ by CD3T⁺ cells infiltrating kidneys after 24 hours of IRI in mice. This observation suggests that lymphocytes infiltrating into the postischemic kidneys could have a major downstream effect on later inflammation and organ dysfunction. Thus, not only the trafficking of T cells postischemia is a potential mechanism, but what those infiltrating cells are doing at the site of injury could be crucial for pathogenesis. Given that infiltrating T cells are activated and selectively expanded in kidney long term after IRI, we hypothesized that there would be a different upregulation of these molecules postischemia in depleted and nondepleted mice. Using real-time RT-PCR, a significant upregulation of IL-1β, IL-6, tumor necrosis factor (TNF)-α, IFN-γ, MIP-2, and RANTES was seen 6 weeks after 60 min of unilateral renal IRI in normal (nondepleted T cells), compared to sham and contralateral kidneys. Depletion of CD4 and CD8 T cells starting preischemia led to significant decrease in kidney IFN-γ levels. In contrast, depletion starting 3 days after ischemia led to significant increase in IL-1β. However, the IRI kidneys of both depleted and nondepleted groups had prominent expression levels of TNF-α and RANTES. As demonstrated in both depleted and nondepleted mice 6 weeks after unilateral ischemia, the cytokines and chemokines including IL-1β, IL-6, TNF-α, MIP-2, and RANTES were significantly upregulated. The results are summarized in the Table 2. It has been reported that in moderate ischemia a modest upregulation of TNF-α and RANTES and strong upregulation of IL-1β, IL-6, IFN-γ, and MIP-2 exist (47), whereas after severe ischemia strong upregulation of TNF-α and RANTES and to a lesser extent IL-1β, IL-6, IFN-γ, and MIP-2 occur (48, 49). Similarly, in patients with acute rejection and chronic allograft nephropathy significant expression of TNF-α and RANTES were reported (49).

Expression of CXC and CC chemokines

Chemokines are mainly known for their ability to attract inflammatory cells to sites of injury. Recently, the highest levels of chemokine expression at the stage of active repair (i.e. 7 days after ischemic injury) was observed, and temporal chemokines expression pattern in more detail was examined (50). The expression of the CC and CXC chemokines at additional reperfusion periods after ischemic injury was evaluated to determine if there is a biphasic expression coinciding with the inflammatory and reparative response after ischemic injury. Some chemokine results are summarized in the Table 2. The four CC chemokines were expressed in a monophasic fashion with a clear peak 7 days after ischemic injury. In contrast, the CXC chemokines had a biphasic expression after ischemic injury with the first peak in the early (i.e. inflammatory) phase and the second peak during the reparative phase. The CXC chemokines Cxcl1/KC, Cxcl2/MIP-2a and Cxcl10/IP-10 had the highest expression during the inflammatory phase.

6. Effect of renal ischemic injury on distant organs

Acute kidney injury (AKI) in native kidneys is a major clinical problem with high mortality and morbidity in the intensive care unit. This problem remains unchanged for the past 50 years in part because AKI is associated with extra-renal complications (51, 52, 53). Much of
the increased risk of death associated with AKI is usually related to multi-organ dysfunction including brain, heart, lungs, liver and small intestine. After kidney IRI, inflammatory cytokines and chemokines in plasma IL-1β, IL-6, KC (IL-8), TNF-α, TNF-β, INF-γ, IL-17A, C5a, and MCP-1 increased significantly which eventually could lead to develop multi-organ failure. (54, 55, 56). In particular, AKI caused by IRI increased pulmonary vascular permeability with capillary leak (57) and change of fluid absorption in alveolar epithelial cells (58). Inflammation and apoptosis could be important mechanisms connecting the effect of AKI on lung and distant organs as show in changes of inflammatory transcriptome identified in lung after kidney IRI (59). Studies using gene microarrays analysis found marked changes in immune, inflammatory, and apoptotic processes (60). Caspase-dependent pulmonary apoptosis concurrent with activated T cell trafficking was also demonstrated in kidney after IRI (61). Altered gene expression associated with inflammation, apoptosis, and cytoskeletal structure in pulmonary endothelial cells after kidney IRI suggested possible mechanisms underlying the increased pulmonary microvascular permeability (62). Increase of IL-1β, IL-6, TNFα, MCP-1, KC (IL-8) and ICAM-1 may act as mediators in the crosstalk between kidney and lung (55, 60, 63). AKI following

Fig. 3. AKI induce distant organ effects. AKI leads to changes in distant organs, including brain, lungs, heart, liver, and small intestine, involving multiple inflammatory pathways, including increased expression of soluble pro-inflammatory mediators, innate and adaptive immunity, cellular apoptosis, microvascular inflammation and dysregulation of transport activity, oxidative stress, transcriptional responses, etc.

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IRI has been reported to increase apoptosis and production of IL-1, TNF-α, and ICAM-1 in cardiac tissue (56). Changes in the microvasculature after kidney IRI were also demonstrated in brain and conferred susceptibility to stroke (64). In brain has been found increased expression of KC (IL-8), granulocyte colony-stimulating factor (G-CSF), and glial fibrillary acidic protein, an inflammatory marker (65). More recently, hepatic and small intestine dysfunction has been observed in patients suffering from AKI. Liver injury after ischemic shows peri-portal hepatocyte vacuolization, necrosis and apoptosis with inflammatory changes. Small intestinal injury after ischemic was characterized by villous lacteal capillary endothelial apoptosis, epithelial necrosis and increased leukocyte (neutrophils, macrophages and lymphocytes) infiltration. Vascular permeability was severely impaired in both liver and small intestine. After ischemic insult TNF-α, IL-17A and IL-6 levels in plasma, liver and small intestine increased significantly. Furthermore, up-regulation of KC (IL-8), MCP-1, MIP-2, ICAM-1 has been found in liver and small intestine (54). The Figure 3, shows a summarized picture of the cross talking between AKI and several long distance organs.

7. References

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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and that’s why conscious educational efforts are still needed for kidney transplantation, for many people being the only chance for an active lifestyle and improved quality of life, to win common social acceptance and stop triggering negative connotations. Apart from transplantation controversies piling up over years transplantologists also have to face many other medical difficulties. The chapters selected for this book are of high level of content, and the fact that their authors come from many different countries, and sometimes even cultures, has facilitated a comprehensive and interesting approach to the problem of kidney transplantation. The authors cover a wide spectrum of transplant-related topics.

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