1. Introduction

Transforming growth factor (TGF)-beta consists of three isoforms (TGF-beta 1, TGF-beta 2 and TGF-beta 3) and is synthesized and secreted in nearly every cell type (Massague, 1990), including in the kidneys and kidney transplants (Horvath et al., 1996; Ando et al., 1998). A variety of biological activities of TGF-beta have been demonstrated in different experimental systems, including stimulation of cellular proliferation and cellular differentiation, or oppositely induction of cell apoptosis and anti-proliferation (Siegel and Massague, 2003), suggesting that TGF-beta, particularly TGF-beta 1, is a key regulatory factor for tissue homeostasis. In cultured renal cells, these three TGF-beta isoforms have similar activities (Yu et al., 2003; Qi et al., 2006), but the activities of TGF-beta 2 and TGF-beta 3 may be partially mediated by TGF-beta 1 (Yu et al., 2003).

Kidney transplantation is the best therapy for individuals who unfortunately have end-stage kidney disease; individuals with kidney transplants live longer with a better quality of life compared to those on dialysis (Port et al., 1993; Laupacis et al., 1996; Schnuelle et al., 1998). However, the progressive loss of kidney transplants remains an elusive objective in clinical care of these patients as indicated by 2009 OPTN/SRTR annual report; the unadjusted kidney graft survival for deceased donors was decreased to 95.3% after 3 months, 91.0% after 1 year, 69.3% after 5 years and 43.3% after 10 years, whereas the similar trend was seen for living donors. It has been shown in numerous studies that ischemia-reperfusion injury, acute rejection episodes, chronic rejection and/or nephrotoxicity of immunosuppressive drugs are the risk factors for this problem (Li and Yang, 2009; de Fijter, 2010), and evidence in literature suggests that there is a possible association of up-regulation of TGF-beta expression and its signaling with poor outcomes in kidney transplantation (Pribylova-Hribova et al., 2006; Einecke et al., 2010). In this chapter, the role of TGF-beta in each of these factors in the progression of kidney transplant dysfunction is discussed.

2. The beneficial effects of TGF-beta on kidney transplant survival

2.1 TGF-beta, a growth and survival factor for renal regeneration after ischemia-reperfusion injury

Graft ischemia-reperfusion injury in kidney transplants is an inevitable event that occurs following the disruption of blood supply to a donor kidney when harvested, and reperfusion with recipient’s blood after transplanted. Ischemia-reperfusion injury to kidney grafts is associated with delay graft function that has a negative impact on graft survival...
and worsens both acute and chronic rejection episodes (Peeters et al., 2004; Chapman et al., 2005). The loss of functioning tubular epithelial cells in renal ischemia-reperfusion injury is caused by both apoptosis and necrosis (Savill, 1994; Gobe et al., 1999a). Thus, its severity may depend on the resistance of renal cells to cell death during the injury, and recovery on cellular regeneration after the damage.

A significant up-regulation of TGF-beta 1 expression has been detected in regenerating renal tubules following ischemic injury in the kidneys (Basile et al., 1996), as well as in renal biopsies of kidney transplants from cold ischemic donors or at five days post-transplantation (Lario et al., 2003). However, the role of TGF-beta in cellular process of ischemia-reperfusion injury or its repair is still contradicted. In cultured renal epithelial cells, addition of TGF-beta 1 directly induces cell apoptosis (Bhaskaran et al., 2003) or promotes angiotensin II- or staurosporine-mediated cell death (Bhaskaran et al., 2003; Dai et al., 2003), while in contrast renal protection of TGF-beta 1 has been reported by several recent studies; TGF-beta 1 is required for renal protection of volatile anesthetics in the protection from H2O2-induced apoptosis in cultured human proximal tubular epithelial cells (Lee et al., 2007), and reduces cellular necrosis and inflammation in renal ischemia-reperfusion injury (Lee et al., 2004). Our recent study demonstrates that a deficiency in TGF-beta 1 expression worsens the severity of renal ischemia-reperfusion injury in mice, and overexpression of TGF-beta 1 increases the resistance of cultured human tubular epithelial cells to TNF-alpha-mediated apoptosis (Guan et al., 2010).

The renal protection of TGF-beta in renal ischemia-reperfusion injury may be contributed by its two activities: stimulation of cellular growth and induction of anti-apoptosis. It has been known that many growth factors, such as epidermal growth factor (Danielpour et al., 1991), platelet-derived growth factor (Phillips et al., 1995; Di Paolo et al., 1996; Yamabe et al., 2000) and basic fibroblast growth factor (Phillips et al., 1997; Yamabe et al., 2000), stimulate TGF-beta 1 production in various renal cell cultures, and co-upregulated with TGF-beta in the proliferating or regenerating tubular cells during renal ischemia-reperfusion injury (Schaudies et al., 1993; Toubeau et al., 1994; Nakagawa et al., 1999; Villanueva et al., 2006). The treatment with epidermal growth factor or basic fibroblast growth factor or disruption of platelet-derived growth factor signaling indicate that these factors enhances renal tubule cell regeneration or repair and consequently accelerates the recovery of renal function after renal ischemia-reperfusion injury (Humes et al., 1989; Nakagawa et al., 1999; Villanueva et al., 2006). In addition, TGF-beta 1 in renal cells is upregulated by an autoinduction mechanism (Nowak and Schnellmann, 1996; Grande et al., 2002; Dockrell et al., 2009). Data from all these studies simply imply that TGF-beta may be one of key growth factors for renal regeneration or repair post ischemia-reperfusion injury.

In the kidney, anti-apoptotic Bcl-2 may be pivotal for renal cell survival as in fetal kidneys, the distribution of apoptotic cells is inversely correlated with expression of Bcl-2, and augmented metanephric apoptosis occur in Bcl-2–deficient mice (Winyard et al., 1996). In a rat model of renal ischemia-reperfusion injury, Bcl-2 expression markedly increases in the distal tubules and is associated with increased survival of both the distal and adjacent proximal segment at acute phases (0 to 2 days). After renal injury, expression of both TGF-beta 1 and Bcl-2 is enhanced in regenerating proximal tubule cells relining the basement membrane (Gobe et al., 1999b). Our data also indicate that in cultures of renal TECs, TGF-beta 1 induces Bcl-2 expression and prevents TNF-alpha-mediated apoptosis (Guan et al., 2010). All these studies suggest that Bcl-2 may mediate renal protective role or anti-apoptotic activity of TGF-beta in renal ischemia-reperfusion injury.
2.2 TGF-beta, a FOXP3⁺ Treg cells inducer for suppression of alloimmune response

It has been well-known for a while that TGF-beta is a potent immunosuppressive cytokine with multiple suppressive actions on a variety of immune cells including T cells, B cells, macrophages, and other cells, and acts with some other inhibitory molecules to maintain a state of immune tolerance in peripheral tissues (Prud'homme and Piccirillo, 2000). Mice with homozygous for Tgfb1 gene mutation die due to a massive multifocal mixed inflammatory cell infiltration and tissue necrosis in numerous organs (Shull et al., 1992; Christ et al., 1994) through autoimmune responses, such as antibody deposit in renal glomeruli (Yaswen et al., 1996). However, the cellular mechanisms by which TGF-beta suppresses immune responses are not fully understood. Recent findings suggest that TGF-beta is required for regulatory T (Treg) cell development; TGF-beta induces FOXP3 (forkhead box P3) expression in nonregulatory CD4⁺CD25⁻ T cells, and consequently converts these cells to CD4⁺CD25⁺FOXP3⁺ Treg cells in vitro (Chen et al., 2003), and in vivo is required for expansion of this phenotype of Treg cells (Peng et al., 2004). TGF-beta-dependent FOXP3⁺ Treg cells, including both CD4⁺ and CD8⁺ phenotypes, can induce immune tolerance to allografts in animal models (Cobbold et al., 2004; Kapp et al., 2006). However, it is also suggested that in the presence of IL-6, TGF-beta induces differentiation of naïve CD4⁺ T cells to effector interleukin (IL)-17-producing Th17 cells (Bettelli et al., 2006; Veldhoen et al., 2006), but the evidence for TGF-beta-dependent Th17 cell development in vivo has not been confirmed yet. Indeed, recent studies suggest that TGF-beta does not directly stimulate Th17 cell differentiation, instead it inhibits Th1 cells development that indirectly favors Th17 cell expansion (Santarlasci et al., 2009), and Th17 cells can be generated in the absence of TGF-beta signaling (Ghoreschi et al., 2010). Thus, TGF-beta may not have any direct effect on effector Th17 cells, and it may only act as an immuno-down regulatory cytokine by its induction of FOXP3⁺ Treg cell as well as directly and indirectly in the suppression of other types of immune cells.

The positive correlation of TGF-beta expression at early phase of transplantation with kidney transplant survival has reported in literature. A higher level of TGF-beta in the biopsies within 6 months of transplantation or during acute rejection episodes is associated with a decreased risk of chronic rejection development (Eikmans et al., 2002), and better graft function (Ozdemir et al., 2005). In the early antibody-mediated rejection, occurring within the first 3 weeks after transplantation, there is a strong correlation of intrarenal expression of TGF-beta 1 with FOXP3 mRNA, and importantly the low intrarenal TGF-beta 1 and FOXP3 have significantly shorter graft survival, implied by an increased risk for renal graft failure within next 12 months (Viklicky et al., 2010). The beneficial effect of immunoregulatory TGF-beta on early survival of kidney transplants is further supported by a recent experimental study, demonstrating that only the early renal allograft acceptance is associated with TGF-beta-induced immune regulation, both peripherally by splenocytes as well as locally by graft-infiltrating cells (Cook et al., 2008). All these studies may indicate that TGF-beta may benefit kidney transplant survival at the early phase of transplantation by its immunoregulatory activities, including induction of FOXP3-expressing Treg cells.

3. The adverse effects of TGF-beta on kidney transplant survival

3.1 TGF-beta, a fibrotic factor for chronic rejection of kidney transplants

Chronic rejection in kidney transplants is a major cause of long-term graft dysfunction and ultimate failure, and is characterized as a progressive process of interstitial fibrosis, tubular atrophy, and glomerulosclerosis and vascular sclerosis (Racusen et al., 1999; Nankivell et al.,
Although the pathogenesis of chronic rejection is not fully understood, it is proposed that these pathologies may result from chronic repair response towards injurious and inflammatory stimuli. As a result, extracellular matrix (ECM) accumulates in functional tissue leading to successive tissue fibrosis in the vascular (vascular sclerosis), tubulointerstitium (interstitial fibrosis) and glomeruli (glomerulosclerosis), and the excessive interstitial fibrosis progressively consequentially leads to tubular atrophy in kidney transplants. It has been reported that much of this ECM is produced by alpha-smooth muscle actin (alpha-SMA)-expressing myofibroblasts (Simonson, 2007; Wynn, 2008), and early presence of alpha-SMA expression predicts the progression toward pathologic changes for chronic rejection in kidney transplants (Badid et al., 2002; Hertig et al., 2008), suggesting that myofibroblasts are the primary effector cells for chronic rejection of kidney transplants.

Numerous studies have reported a significant correlation of the up-regulation of intragraft TGF beta 1 and active plasma TGF-beta 1 with chronic rejection in kidney transplants (Sharma et al., 1996; Ozdemir et al., 2005; Harris et al., 2007; Del Prete et al., 2009) and with cyclosporine A (CsA) toxicity (Ozdemir et al., 2005). In kidney cell cultures, in addition to the growth factors as discussed above, many injury or pro-inflammatory factors (e.g. platelet-activating factor, hydrogen peroxide, IL-1beta and TNF-alpha) and CsA induce TGF-beta 1 expression (Ruiz-Ortega et al., 1997; Iglesias-De La Cruz et al., 2001; Vesey et al., 2002a; Vesey et al., 2002b; Slattery et al., 2005; Guan et al., 2010). Thus, TGF-beta has been considered as a fibrogenic cytokine, involved in fibrosis or chronic rejection of kidney transplants (Morris-Stiff, 2005), and has been proposed as a therapeutic target for this problem (Mannon, 2006). However, the pathways of fibrotic activity of TGF-beta in chronic rejection of kidney transplants are not completely understood.

TGF-beta is a pivotal factor for the normal process of tissue homeostasis in every part of our body (Siegel and Massague, 2003). Hence, it is easy to understand why TGF-beta is up-regulated and involved in chronic tissue repair when kidney transplants are exposed to chronic inflammation/injury as well as nephrotoxicity of immunosuppressive drugs, but how TGF-beta-mediated chronic repair responses leads to the pathologic changes of chronic rejection in kidney transplants is not exactly known. It has been documented that epithelial-to-mesenchymal transition (EMT) can be induced by TGF-beta and is considered as a continuous supply to myofibroblast population during the progression of renal fibrosis (Iwano, 2010). Indeed, EMT has been detected in kidney transplant biopsies with chronic rejection but not in those with stable function (Vongwiwatana et al., 2005). However, recent experimental studies demonstrates that in the kidneys with unilateral ureteral obstruction a large majority of myofibroblasts for kidney fibrosis actually comes from the phenotypic transition of existing normal interstitial fibroblasts, whereas there is no evidence indicating that epithelial cells migrate outside of the tubular basement membrane and differentiate into interstitial myofibroblasts or EMT (Humphreys et al., 2010), and overexpression of TGF-beta 1 in renal TECs induces fibrosis in the kidney that is associated with interstitial fibroblast proliferation but not with EMT (Koesters et al., 2010). This notion may be also applied to the chronic rejection of kidney transplants that remains further elusive. At the molecular level, TGF-beta stimulates ECM production and/or inhibits ECM degradation in various kidney cells including TECs, interstitial fibroblasts and mesangial cells (Ruiz-Ortega et al., 1997; Iglesias-De La Cruz et al., 2001; Bottinger and Bitzer, 2002; Vesey et al., 2002a; Vesey et al., 2002b; Tian et al., 2006; Huang et al., 2008). All these data suggest that the fibrotic effect of TGF-beta in the chronic rejection of kidney transplants may be mediated simply by its stimulation of fibroblast growth and ECM remodeling leading to ECM accumulation or fibrosis.
Following ischemia-reperfusion injury, renal tubular epithelial cells and other types of renal cells are programmed to death (apoptosis and necrosis). TGF-beta may protect cells from apoptosis and stimulate proliferation of surviving renal cells to repair or regenerate the damaged tissue of kidney transplants. When naïve T cells are primed by alloantigens from the kidney transplants, TGF-beta may induce the development of FOXP3+ Treg cells that suppress alloimmunity against the kidney transplants. However, chronic up-regulation of TGF-beta production in the kidney transplants may induce ECM-producing myofibroblasts and chronic stimulation of cell growth of myofibroblasts in the tubulointerstitium, glomeruli and vascular tissue may result in chronic rejection, indicated by interstitial fibrosis, tubular atrophy, glomerulosclerosis, and vascular fibrosis. DC: dendritic cells; NT: naïve T cells; Th: T helper cells; B: B and plasma cells; CTL: CD8+ cytotoxic T cells.
4. Conclusion

TGF-beta affects kidney transplant survival in many ways; it is a growth factor for tissue regeneration and tissue remodeling when kidney transplants are damaged, and is an immunosuppressive factor when cellular immune response to kidney transplants is activated. At the beginning of transplantation, when kidney transplants are damaged by ischemia-reperfusion injury and recipient’s immune response is activated, TGF-beta may repair kidney transplants by stimulation of tissue regeneration, protection of renal cells from apoptosis and negatively regulates cellular immune response to kidney transplants by induction of FOXP3+ Treg cells. Later on, when kidney transplants are attacked by chronic inflammation including drug-resistant immune response and virus infection, and nephrotoxicity of immune suppressive drugs, the chronic repair response of TGF-beta may induce tissue remodeling of kidney transplants leading to chronic rejection (Figure 1). Thus, despite of the short-term beneficial effects of tubule-repairing and immune-down-regulation immediately posttransplantation, the long-term effects of TGF-beta on kidney transplant survival under current immune therapies seem to be negative as increased expression of TGF-beta1 promotes growth of fibroblasts and ECM accumulation leading to tissue remodeling in the tubulointerstitium, vascular tissue and glomeruli or chronic rejection.

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6. References

Ando, T.; Okuda, S.; Yanagida, T. & Fujishima, M. (1998). Localization of TGF-beta and its receptors in the kidney. Mineral and Electrolyte Metabolism, Vol.24, No.2-3, pp. 149-153

Badid, C.; Desmouliere, A.; Babici, D.; Hadj-Aissa, A.; McGregor, B.; Lefrancois, N.; Touraine, J. L. & Laville, M. (2002). Interstitial expression of alpha-SMA: an early marker of chronic renal allograft dysfunction. Nephrology Dialysis Transplantation, Vol.17, No.11, (November 2002), pp. 1993-1998

Basile, D. P.; Rovak, J. M.; Martin, D. R. & Hammerman, M. R. (1996). Increased transforming growth factor-beta 1 expression in regenerating rat renal tubules following ischemic injury. American Journal of Physiology, Vol.270, No.3 Pt 2, (March 1996), pp. F500-509

Bettelli, E.; Carrier, Y.; Gao, W.; Korn, T.; Strom, T. B.; Oukka, M.; Weiner, H. L. & Kuchroo, V. K. (2006). Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature, Vol.441, No.7090, (May 2006), pp. 235-238

Bhaskaran, M.; Reddy, K.; Radhakrishanan, N.; Franki, N.; Ding, G. & Singhal, P. C. (2003). Angiotensin II induces apoptosis in renal proximal tubular cells. American Journal Physiology - Renal Physiology, Vol.284, No.5, (May 2003), pp. F955-965
Bottinger, E. P. & Bitzer, M. (2002). TGF-beta signaling in renal disease. *Journal of American Society of Nephrology*, Vol.13, No.10, (October 2002), pp. 2600-2610

Chapman, J. R.; O'Connell, P. J. & Nankivell, B. J. (2005). Chronic renal allograft dysfunction. *Journal of American Society of Nephrology*, Vol.16, No.10, (October 2005), pp. 3015-3026

Chen, W.; Jin, W.; Hardegen, N.; Lei, K. J.; Li, L.; Marinos, N.; McGrady, G. & Wahl, S. M. (2003). Conversion of peripheral CD4+CD25− naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. *Journal of Experimental Medicine*, Vol.198, No.12, (December 2003), pp. 1875-1886

Christ, M.; McCartney-Francis, N. L.; Kulkarni, A. B.; Ward, J. M.; Mizel, D. E.; Mackall, C. L.; Gress, R. E.; Hines, K. L.; Tian, H.; Karlsson, S. et al. (1994). Immune dysregulation in TGF-beta 1-deficient mice. *Journal of Immunology*, Vol.153, No.5, (September 2004), pp. 1936-1946

Cobbold, S. P.; Castejon, R.; Adams, E.; Zelenika, D.; Graça, L.; Humm, S. & Waldmann, H. (2004). Induction of FOXP3+ regulatory T cells in the periphery of T cell receptor transgenic mice tolerized to transplants. *Journal of Immunology*, Vol.172, No.10, (May 2004), pp. 6003-6010

Cook, C. H.; Bickerstaff, A. A.; Wang, J. J.; Nadasdy, T.; Della Pelle, P.; Colvin, R. B. & Orosz, C. G. (2008). Spontaneous renal allograft acceptance associated with "regulatory" dendritic cells and IDO. *Journal of Immunology*, Vol.180, No.5 (March 2008), pp. 3103-3112

Dai, C.; Yang, J. & Liu, Y. (2003). Transforming growth factor-beta1 potentiates renal tubular epithelial cell death by a mechanism independent of Smad signaling. *Journal of Biological Chemistry*, Vol.278, No.14, (April 2003), pp. 12537-12545

Danielpour, D.; Kim, K. Y.; Winokur, T. S. & Sporn, M. B. (1991). Differential regulation of the expression of transforming growth factor-beta s 1 and 2 by retinoic acid, epidermal growth factor, and dexamethasone in NRK-49F and A549 cells. *Journal of Cellular Physiology*, Vol.148, No.2, (August 1991), pp. 235-244

de Fijter, J. W. (2010). Rejection and function and chronic allograft dysfunction. *Kidney International*, Supplements, No.119, (December, 2010), pp. S38-41

Del Prete, D.; Ceol, M.; Anglani, F.; Vianello, D.; Tiralongo, E.; Valente, M.; Graziotto, R.; Bonfante, L.; Scaparrotta, G.; Furian, L.; Rigotti, P.; Gambaro, G. & D'Angelo, A. (2009). Early activation of fibrogenesis in transplanted kidneys: a study on serial renal biopsies. *Experimental and Molecular Pathology*, Vol.87, No.2, (October 2009), pp. 141-145

Di Paolo, S.; Gesualdo, L.; Ranieri, E.; Grandaliano, G & Schena, F. P. (1996). High glucose concentration induces the overexpression of transforming growth factor-beta through the activation of a platelet-derived growth factor loop in human mesangial cells. *American Journal Pathology*, Vol.149, No.6, (December 1996), pp. 2095-2106

Dockrell, M. E.; Phanish, M. K. & Hendry, B. M. (2009). TGF-beta auto-induction and connective tissue growth factor expression in human renal tubule epithelial cells requires N-ras. *Nephron Experimental Nephrology*, Vol.112, No.3, pp. e71-79

Eikmans, M.; Sijpkes, Y. W.; Baelde, H. J.; de Heer, E.; Paul, L. C. & Bruijn, J. A. (2002). High transforming growth factor-beta and extracellular matrix mRNA response in renal allografts during early acute rejection is associated with absence of chronic rejection. *Transplantation*, Vol.73, No.4, (February 2002), pp. 573-579
Einecke, G.; Reeve, J.; Sis, B.; Mengel, M.; Hidalgo, L.; Famulski, K. S.; Matas, A.; Kasiske, B.; Kaplan, B. & Halloran, P. F. (2010). A molecular classifier for predicting future graft loss in late kidney transplant biopsies. *Journal of Clinical Investigation*, Vol.120, No.6, (June 2010), pp. 1862-1872

Ghoreschi, K.; Laurence, A.; Yang, X. P.; Tato, C. M.; McGeachy, M. J.; Konkel, J. E.; Ramos, H. L.; Wei, L.; Davidson, T. S.; Bouladoux, N.; Grainger, J. R.; Chen, Q.; Kanno, Y.; Watford, W. T.; Sun, H. W.; Ebel, G.; Shevach, E. M.; Belkaid, Y.; Cua, D. J.; Chen, W. & O'Shea, J. J. (2010). Generation of pathogenic Th17 cells in the absence of TGF-beta signalling. *Nature*, Vol.467, No.7318, (October 2010), pp. 967-971

Gobe, G.; Willgoss, D.; Hogg, N.; Schoch, E. & Endre, Z. (1999a). Cell survival or death in renal tubular epithelium after ischemia-reperfusion injury. *Kidney International*, Vol.56, No.4, (October 1999), pp. 1299-1304

Gobe, G.; Zhang, X. J.; Cuttle, L.; Pat, B.; Willgoss, D.; Hancock, J.; Barnard, R. & Endre, R B. (1999b). Bcl-2 genes and growth factors in the pathology of ischaemic acute renal failure. *Immunology & Cell Biology*, Vol.77, No.3, (June 1999), pp. 279-286

Grande, J. P.; Warner, G. M.; Walker, H. J.; Yusufi, A. N.; Cheng, J.; Gray, C. E.; Kopp, J. B. & Nath, K. A. (2002). TGF-beta1 is an autocrine mediator of renal tubular epithelial cell growth and collagen IV production. *Experimental Biology and Medicine (Maywood)*, Vol.227, No.3, (March 2002), pp. 171-181

Guan, Q.; Nguan, C. Y. & Du, C. (2010). Expression of transforming growth factor-betalpha1 limits renal ischemia-reperfusion injury. *Transplantation*, Vol.89, No.11, (June 2010), pp. 1320-1327

Harris, S.; Coupes, B. M.; Roberts, S. A.; Roberts, I. S.; Short, C. D. & Brenchley, P. E. (2007). TGF-beta1 in chronic allograft nephropathy following renal transplantation. *Journal of Nephrology*, Vol.20, No.2, (March-April 2007), pp. 177-185

Hertig, A.; Anglicheau, D.; Verine, J.; Pallet, N.; Toutot, M.; Ancel, P. Y.; Mesnard, L.; Brousse, N.; Baugey, E.; Glotz, D.; Legendre, C.; Rondeau, E. & Xu-Dubois, Y. C. (2008). Early epithelial phenotypic changes predict graft fibrosis. *Journal of American Society of Nephrology*, Vol.19, No.8, (August 2008), pp. 1584-1591

Horvath, L. Z.; Friess, H.; Schilling, M.; Borisch, B.; Deflorin, J.; Gold, L. I.; Korc, M. & Buchler, M. W. (1996). Altered expression of transforming growth factor-beta S in chronic renal rejection. *Kidney International*, Vol.50, No.2, (August 1996), pp. 489-498

Huang, W.; Xu, C.; Kahng, K. W.; Noble, N. A.; Border, W. A. & Huang, Y. (2008). Aldosterone and TGF-beta1 synergistically increase PAI-1 and decrease matrix degradation in rat renal mesangial and fibroblast cells. *American Journal of Physiology - Renal Physiology*, Vol.294, No.6, (June 2008), pp. F1287-1295

Humes, H. D.; Cieslinski, D. A.; Coimbra, T. M.; Messana, J. M. & Galvao, C. (1989). Epidermal growth factor enhances renal tubule cell regeneration and repair and accelerates the recovery of renal function in postischemic acute renal failure. *Journal of Clinical Investigation*, Vol.84, No.6, (December 1989), pp. 1757-1761

Humphreys, B. D.; Lin, S. L.; Kobayashi, A.; Hudson, T. E.; Nowlin, B. T.; Bonventre, J. V.; Valerius, M. T.; McMahon, A. P. & Duffield, J. S. (2010). Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis. *American Journal of Pathology*, Vol.176, No.1, (January 2010), pp. 85-97

Iglesias-De La Cruz, M. C.; Ruiz-Torres, P.; Alcami, J.; Diez-Marques, L.; Ortega-Velazquez, R.; Chen, S.; Rodriguez-Puyol, M.; Ziyadeh, F. N. & Rodriguez-Puyol, D. (2001).
Hydrogen peroxide increases extracellular matrix mRNA through TGF-beta in human mesangial cells. *Kidney International*, Vol.59, No.1 (January 2001), pp. 87-95

Iwano, M. (2010). EMT and TGF-beta in renal fibrosis. *Frontiers in Bioscience* (Scholar Edition), Vol.2, No.2, pp. 229-238

Kapp, J. A.; Honjo, K.; Kapp, L. M.; Xu, X.; Cozier, A. & Bucy, R. P. (2006). TCR transgenic CD8+ T cells activated in the presence of TGF beta express FoxP3 and mediate linked suppression of primary immune responses and cardiac allograft rejection. *International Immunology*, Vol.18, No.11, (November 2006), pp. 1549-1562

Koesters, R.; Kaisling, B.; Lehr, M.; Picard, N.; Theilig, F.; Gebhardt, R.; Glick, A. B.; Hahnel, B.; Hosser, H.; Grone, H. J. & Kriz, W. (2010). Tubular overexpression of transforming growth factor-beta1 induces autophagy and fibrosis but not mesenchymal transition of renal epithelial cells. *American Journal of Pathology*, Vol.177, No.2, (August 2010), pp. 632-643

Lario, S.; Mendes, D.; Bescos, M.; Inigo, P.; Campos, B.; Alvarez, R.; Alcaraz, A.; Rivera-Fillat, F. & Campistol, J. M. (2003). Expression of transforming growth factor-beta1 and hypoxia-inducible factor-1alpha in an experimental model of kidney transplantation. *Transplantation*, Vol.75, No.10, (May 2003), pp. 1647-1654

Laupacis, A.; Keown, P.; Pus, N.; Krueger, H.; Ferguson, B.; Wong, C. & Muirhead, N. (1996). A study of the quality of life and cost-utility of renal transplantation. *Kidney International*, Vol.50, No.1, (July 1996), pp. 235-242

Lee, H. T.; Kim, M.; Kim, J.; Kim, N. & Emala, C. W. (2007). TGF-beta1 release by volatile anesthetics mediates protection against renal proximal tubule cell necrosis. *American Journal of Nephrology*, Vol.27, No.4, pp. 416-424

Lee, H. T.; Ota-Setlik, A.; Fu, Y.; Nasr, S. H. & Emala, C. W. (2004). Differential protective effects of volatile anesthetics against renal ischemia-reperfusion injury in vivo. *Anesthesiology*, Vol.101, No.6, (December 2004), pp. 1313-1324

Li, C. & Yang, C. W. (2009). The pathogenesis and treatment of chronic allograft nephropathy. *Nature Reviews Nephrology*, Vol.5, No.9, (September 2009), pp. 513-519

Mannon, R. B. (2006). Therapeutic targets in the treatment of allograft fibrosis. *American Journal of Transplantation*, Vol.6, No.5 Pt 1, (May 2006), pp. 867-875

Massague, J. (1990). The transforming growth factor-beta family. *Annual Review of Cell Biology*, Vol.6, pp. 597-641

Morris-Stiff, G. (2005). TGF beta-1 and the development of chronic graft nephropathy: relative roles of gene, mRNA and protein. *Annals of The Royal College of Surgeons of England*, Vol.87, No.5, (September 2005), pp. 326-330

Nakagawa, T.; Sasahara, M.; Haneda, M.; Kataoka, H.; Nakagawa, H.; Yagi, M.; Kikkawa, R. & Hazama, F. (1999). Role of PDGF B-chain and PDGF receptors in rat tubular regeneration after acute injury. *American Journal of Pathology*, Vol.155, No.5, (November 1999), pp. 1689-1699

Nankivell, B. J.; Borrows, R. J.; Fung, C. L.; O’Connell, P. J.; Allen, R. D. & Chapman, J. R. (2003). The natural history of chronic allograft nephropathy. *New England Journal of Medicine*, Vol.349, No.24, (December 2003), pp. 2326-2333

Nowak, G. & Schnellmann, R. G. (1996). Autocrine production and TGF-beta 1-mediated effects on metabolism and viability in renal cells. *American Journal of Physiology*, Vol.271, No.3 Pt 2, (September 1996), pp. F689-697
Ozdemir, B. H.; Ozdemir, F. N.; Demirhan, B. & Haberal, M. (2005). TGF-beta1 expression in renal allograft rejection and cyclosporine A toxicity. *Transplantation*, Vol.80, No.12, (December 2005), pp. 1681-1685

Peeters, P.; Terryn, W.; Vanholder, R. & Lameire, N. (2004). Delayed graft function in renal transplantation. *Current Opinion in Critical Care*, Vol.10, No.6, (December 2004), pp. 489-498

Peng, Y.; Laouar, Y.; Li, M. O.; Green, E. A. & Flavell, R. A. (2004). TGF-beta regulates in vivo expansion of Foxp3-expressing CD4$^+$CD25$^+$ regulatory T cells responsible for protection against diabetes. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.101, No.13, (March 2004), pp. 4572-4577

Phillips, A. O.; Steadman, R.; Topley, N. & Williams, J. D. (1995). Elevated D-glucose concentrations modulate TGF-beta 1 synthesis by human cultured renal proximal tubular cells. The permissive role of platelet-derived growth factor. *American Journal of Pathology*, Vol.147, No.2, (August 1995), pp. 362-374

Phillips, A. O.; Topley, N.; Morrisey, K.; Williams, J. D. & Steadman, R. (1997). Basic fibroblast growth factor stimulates the release of preformed transforming growth factor beta 1 from human proximal tubular cells in the absence of de novo gene transcription or mRNA translation. *Laboratory Investigation*, Vol.76, No.4, (April 1997), pp. 591-600

Port, F. K.; Wolfe, R. A.; Mauger, E. A.; Berling, D. P. & Jiang, K. (1993). Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. *Journal of the American Medical Association*, Vol.270, No.11, (September 1993), pp. 1339-1343

Pribylova-Hribova, P.; Kotsch, K.; Lodererova, A.; Viklicky, O.; Vitko, S.; Volk, H. D. & Lacha, J. (2006). TGF-beta1 mRNA upregulation influences chronic renal allograft dysfunction. *Kidney International*, Vol.69, No.10, (May 2006), pp. 1872-1879

Prud’homme, G. J. & Piccirillo, C. A. (2000). The inhibitory effects of transforming growth factor-beta-1 (TGF-beta1) in autoimmune diseases. *Journal of Autoimmunity*, Vol.14, No.1, (February 2000), pp. 23-42

Qi, W.; Chen, X.; Holian, J.; Mreich, E.; Twigg, S.; Gilbert, R. E. & Pollock, C. A. (2006). Transforming growth factor-beta1 differentially mediates fibronectin and inflammatory cytokine expression in kidney tubular cells. *American Journal of Physiology - Renal Physiology*, Vol.291, No.5, (November 2006), pp. F1070-1077

Racusen, L. C.; Solez, K.; Colvin, R. B.; Bonsib, S. M.; Castro, M. C.; Cavallo, T.; Croker, B. P.; Demetris, A. J.; Drachenberg, C. B.; Fogo, A. B.; Furness, P.; Gaber, L. W.; Gibson, I. W.; Glotz, D.; Goldberg, J. C.; Grande, J.; Halloran, P. F.; Hansen, H. E.; Hartley, B.; Hayry, P. J.; Hill, C. M.; Hoffman, E. O.; Hunsicker, L. G.; Lindblad, A. S.; Yamaguchi, Y. et al. (1999). The Banff 97 working classification of renal allograft pathology. *Kidney International*, Vol.55, No.2, (February 1999), pp. 713-723

Ruiz-Ortega, M.; Largo, R.; Bustos, C.; Gomez-Garre, D. & Egido, J. (1997). Platelet-activating factor stimulates gene expression and synthesis of matrix proteins in cultured rat and human mesangial cells: role of TGF-beta. *Journal of American Society of Nephrology*, Vol.8, No.8, (August 1997), pp. 1266-1275

Santarlasci, V.; Maggi, L.; Capone, M.; Frosali, F.; Querci, V.; De Palma, R.; Liotta, F.; Cosmi, L.; Maggi, E.; Romagnani, S. & Annunziato, F. (2009). TGF-beta indirectly favors the
development of human Th17 cells by inhibiting Th1 cells. European Journal of Immunology, Vol.39, No.1, (January 2009), pp. 207-215

Savill, J. (1994). Apoptosis and the kidney. Journal of American Society of Nephrology, Vol.5, No.1, (July 1994), pp. 12-21

Schaudies, R. P.; Nonclercq, D.; Nelson, L.; Toubeau, G.; Zanen, J.; Heuson-Stiennon, J. A. & Laurent, G. (1993). Endogenous EGF as a potential renotrophic factor in ischemia-induced acute renal failure. American Journal of Physiology, Vol.265, No.3 Pt 2, (September 1993), pp. F425-434.

Schnuelle, P.; Lorenz, D.; Trede, M. & Van Der Woude, F. J. (1998). Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. Journal of American Society of Nephrology, Vol.9, No.11, (November 1998), pp. 2135-2141

Sharma, V. K.; Bologa, R. M.; Xu, G. P.; Li, B.; Mouradian, J.; Wang, J.; Serur, D.; Rao, V. & Suthanthiran, M. (1996). Intragraft TGF-beta 1 mRNA: a correlate of interstitial fibrosis and chronic allograft nephropathy. Kidney International, Vol.49, No.5, (May 1996), pp. 1297-1303

Shull, M. M.; Ormsby, I.; Kier, A. B.; Pawlowski, S.; Diebold, R. J.; Yin, M.; Allen, R.; Sidman, C.; Proetzels, G.; Calvin, D.; et al. (1992). Targeted disruption of the mouse transforming growth factor-beta 1 gene results in multifocal inflammatory disease. Nature, Vol.359, No.6397, (October 1992), pp. 693-699

Siegel, P. M. & Massague, J. (2003). Cytostatic and apoptotic actions of TGF-beta in homeostasis and cancer. Nature Reviews Cancer, Vol.3, No.11, (November 2003), pp. 807-821

Simonson, M. S. (2007). Phenotypic transitions and fibrosis in diabetic nephropathy. Kidney International, Vol.71, No.9, (May 2007), pp. 846-854

Slattery, C.; Campbell, E.; McMorrow, T. & Ryan, M. P. (2005). Cyclosporine A-induced renal fibrosis: a role for epithelial-mesenchymal transition. American Journal of Pathology, Vol.167, No.2, (August 2005), pp. 395-407

Tian, Y. C.; Chen, Y. C.; Hung, C. C.; Chang, C. T.; Wu, M. S.; Phillips, A. O. & Yang, C. W. (2006). Leptospiral outer membrane protein induces extracellular matrix accumulation through a TGF-beta1/Smad-dependent pathway. Journal of American Society of Nephrology, Vol.17, No.10, (October 2006), pp. 2792-2798

Toubeau, G.; Nonclercq, D.; Zanen, J.; Laurent, G.; Schaudies, P. R. & Heuson-Stiennon, J. A. (1994). Renal tissue expression of EGF and EGF receptor after ischaemic tubular injury: an immunohistochemical study. Experimental Nephrology, Vol.2, No.4, (July-August 1994), pp. 229-239

Veldhoen, M. Hocking, R. J.; Atkins, C. J.; Locksley, R. M. & Stockinger, B. (2006). TGF beta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity, Vol.24, No.2, (February 2006), pp. 179-189

Vesey, D. A.; Cheung, C.; Cuttle, L.; Endre, Z.; Gobe, G. & Johnson, D. W. (2002a). Interleukin-1beta stimulates human renal fibroblast proliferation and matrix protein production by means of a transforming growth factor-beta-dependent mechanism. Journal of Laboratory and Clinical Medicine, Vol.140, No.5, (November 2002), pp. 342-350

Vesey, D. A.; Cheung, C. W.; Cuttle, L.; Endre, Z. A.; Gobe, G. & Johnson, D. W. (2002b). Interleukin-1beta induces human proximal tubule cell injury, alpha-smooth muscle
actin expression and fibronectin production. *Kidney International*, Vol.62, No.1, (July 2002), pp. 31-40

Viklicky, O.; Hribova, P.; Volk, H. D.; Slatinska, J.; Petrasek, J.; Bandur, S.; Honsova, E. & Reinke, P. (2010). Molecular phenotypes of acute rejection predict kidney graft prognosis. *Journal of American Society of Nephrology*, Vol.21, No.1, (January 2010), pp. 173-180

Villanueva, S.; Cespedes, C.; Gonzalez, A. & Vio, C. P. (2006). 

bFGF induces an earlier expression of nephrogenic proteins after ischemic acute renal failure. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology*, Vol.291, No.6, (December 2006), pp. R1677-1687

Vongwiwatana, A.; Tasanarong, A.; Rayner, D. C.; Melk, A & Halloran, P. F. (2005). Epithelial to mesenchymal transition during late deterioration of human kidney transplants: the role of tubular cells in fibrogenesis. *American Journal of Transplantation*, Vol.5, No.6, (June 2005), pp. 1367-1374

Winyard, P. J.; Nauta, J.; Lirenman, D. S.; Hardman, P.; Sams, V. R.; Risdon, R. A. & Woolf, A. S. (1996). Deregulation of cell survival in cystic and dysplastic renal development. *Kidney International*, Vol.49, No.1, (January 1996), pp. 135-146

Wynn, T. A. (2008). Cellular and molecular mechanisms of fibrosis. *Journal of Pathology*, Vol.214, No.2, (January 1996), pp. 199-210

Yamabe, H.; Osawa, H.; Kaizuka, M.; Tsunoda, S.; Shirato, K.; Tateyama, F. & Okumura, K. (2000). Platelet-derived growth factor, basic fibroblast growth factor, and interferon gamma increase type IV collagen production in human fetal mesangial cells via a transforming growth factor-beta-dependent mechanism. *Nephrology Dialysis Transplantation* Vol.15, No.6, (June 2000), pp. 872-876

Yaswen, L.; Kulkarni, A. B.; Fredrickson, T.; Mittleman, B.; Schiffman, R.; Payne, S.; Longenecker, G.; Mozes, E. & Karlsson, S. (1996). Autoimmune manifestations in the transforming growth factor-beta 1 knockout mouse. *Blood*, Vol.87, No.4, (February 1996), pp. 1439-1445

Yu, L.; Border, W. A.; Huang, Y. & Noble, N. A. (2003). TGF-beta isoforms in renal fibrogenesis. *Kidney International*, Vol.64, No.3, pp. 844-856
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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