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Transforming Growth Factor-Beta in Kidney Transplantation: A Double-Edged Sword

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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 H_2O_2-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.,

2003). 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 consequently 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 mesanglial 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.

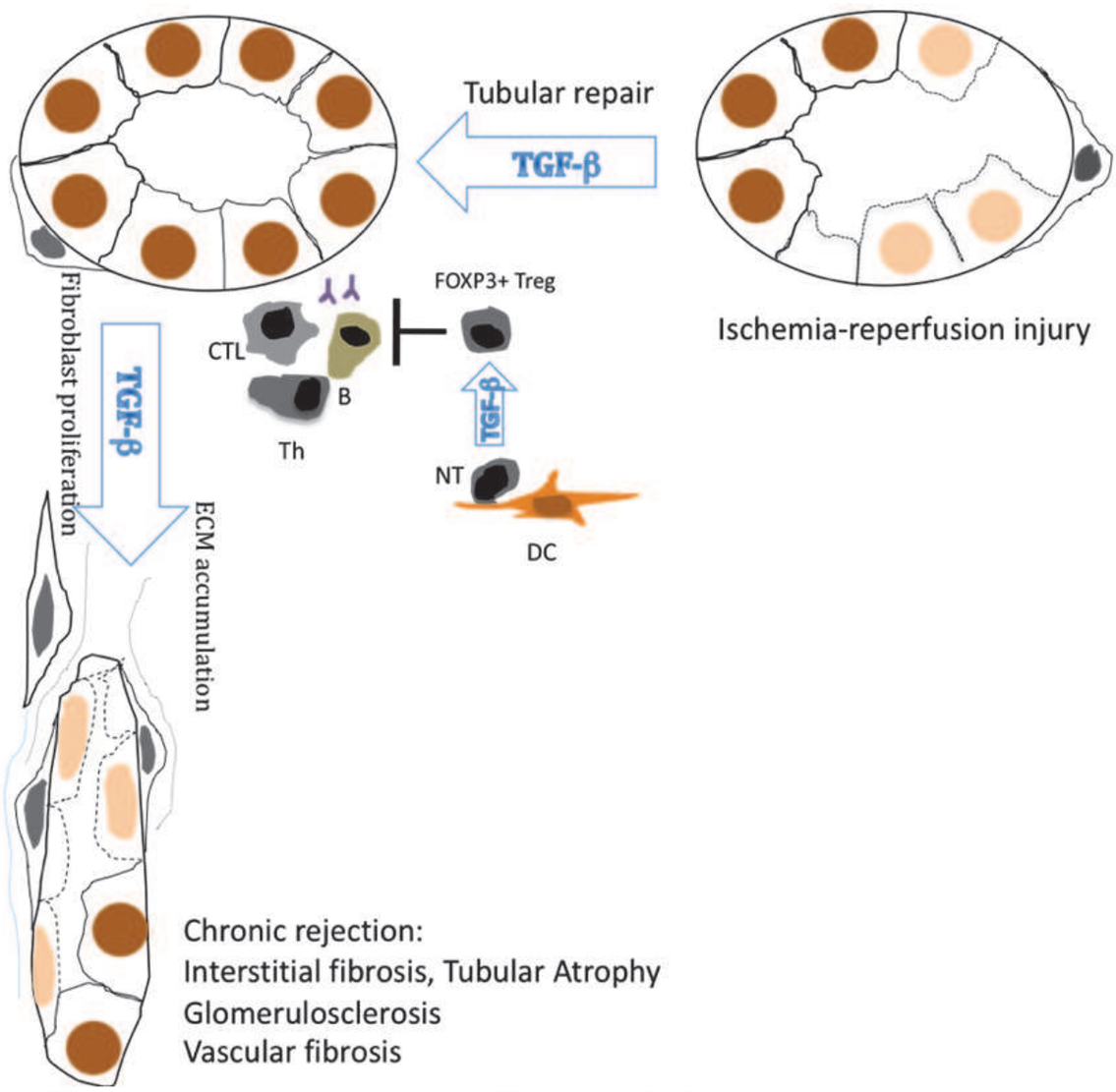

Fig. 1. A simple scheme for cellular pathways of TGF-beta in renal repair/regeneration, immune-modulation and renal fibrosis in kidney transplants.

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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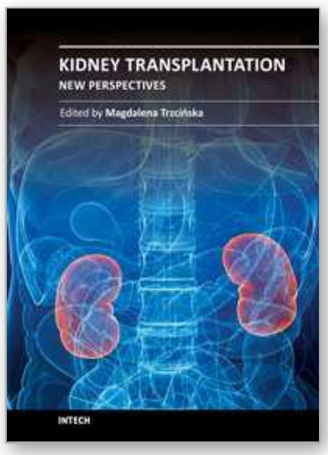

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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and thatâ€™s why conscious 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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