Transpl Int (2000) 13: 385–401

REVIEW ARTICLE

Ewout A. Kouwenhoven
Jan N. M. IJzermans
Ron W. F. de Bruin

Etiology and pathophysiology of chronic transplant dysfunction

Received: 2 August 1999
Revised: 11 April 2000
Accepted: 27 June 2000

E. A. Kouwenhoven · J. N. M. IJzermans
R. W. F. de Bruin
Department of Surgery,
Erasmus University Rotterdam,
P. O. Box 1738, 3000 DR Rotterdam,
The Netherlands

R. W. F. de Bruin (✉)
Laboratory for Experimental Surgery
and Oncology,
Erasmus University Rotterdam,
PO Box 1738, 3000 DR Rotterdam,
The Netherlands
e-mail: debruin@heel.fgg.eur.nl
Tel.: + 31-10-408-7761
Fax: + 31-10-408-9471

Abstract Chronic transplant dysfunction (CTD) is the predominant cause of late graft failure. The common histopathological feature in all transplanted organs is intimal hyperplasia accompanied by organ specific lesions. The knowledge about CTD is incomplete, and there is no therapy to prevent or treat it. This review describes the current knowledge on the etiology of CTD, with emphasis on kidney transplants, and postulates a pathophysiologic route through which CTD may develop.

Keywords Chronic transplant dysfunction · Etiology · Pathophysiology · Review

The problem of chronic transplant dysfunction

Since it was first shown in 1954 that successful transplantation of a healthy kidney could completely rehabilitate an individual with renal failure, transplantation of several organs has become an increasingly successful medical treatment for patients with end-stage organ failure. In 1998, in the Eurotransplant area alone, more than 3000 kidneys, 750 hearts, about 1000 livers, 230 lungs, and about 100 pancreas from cadaveric donors were transplanted [9]. Worldwide, 56 intestinal transplantations were performed in 1996 [70]. The short-term results after clinical organ transplantation have improved progressively. This is principally due to refinements in tissue typing, advancements in organ preservation, operative techniques and ancillary care, more effective immunosuppressive agents, and better monitoring after engraftment. For example, one year survival of cadaveric kidneys has increased from approximately 50% by the end of the 1960s, to about 85% nowadays [67], and for living-related kidneys from 80% to

Despite improving early results, however, it has become clear that clinical transplantation has not achieved its goal as a long-term treatment. For the period beyond one year, the annual rate of graft loss has changed less since the beginning of the experience. The half-life of cadaveric kidney allografts, for instance, has remained consistent at 7.5–9.5 years, although the latest United States Renal Data System (USRDS) data suggest that half-life of first cadaveric kidney grafts is improving (Figure 1) [68, 146]. Similarly, the half-life beyond the first year of heart transplants is 10.5 years [146]. Other organ transplants generally show comparable results, with exception of the liver, which shows more favourable long-term results [10, 98].

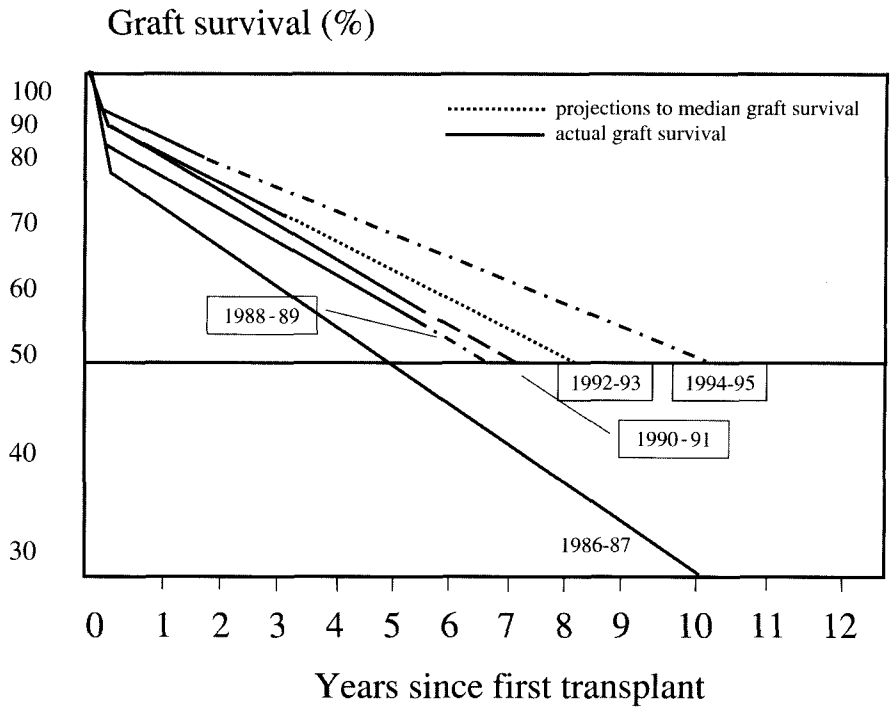

Fig. 1 Cadaveric kidney graft survival for first transplants, 1986–1995. Rates adjusted for sex, race, and cause of ESRD. Derived from: United States Renal Data System 1999 Annual Data Report

Chronic transplant dysfunction (CTD) is the most important, single cause of late graft deterioration and failure. Kidney graft loss is in 35%–58% due to CTD [53], more than 70% of lung allografts had CTD 5 years post-transplantation [166]; more than 50% of the heart transplants had severe coronary arteriosclerosis at five years [222, 231]; and about 9–26% of graft loss of liver transplants was due to CTD [1, 14, 194]. Moreover, a significant number of functioning grafts is lost due to death of the recipient. There is still no treatment to inhibit or prevent CTD, and a conclusive therapeutic strategy is not within hand's reach since its etiology and pathophysiology are poorly known.

Definition of chronic transplant dysfunction: functional and histopathological characteristics

CTD is a phenomenon in solid organ transplants displaying a gradual deterioration of graft function months to years after transplantation, eventually leading to graft failure, and which is accompanied by characteristical histological features. Clinically, CTD in kidney grafts manifests itself as a slowly progressive decline in glomerular filtration rate, usually in conjunction with proteinuria and arterial hypertension [150]. In heart transplants, CTD presents itself with congestive heart failure, acute infarction, arrythmias and, most dramatically, as sudden death [63]. The diagnosis of liver CTD should be based upon clinical evidence of chronic liver disease consisting of persistent enzyme abnormalities, elevated bilirubin, diminished synthesis of protein and blood clotting factors [46, 60]. Intractable diarrhoea and weight loss are the accompanying symptoms in intestinal transplants with CTD [191].

The cardinal histomorphological feature of CTD in all parenchymal allografts is fibroproliferative endarteritis [2]. The vascular lesion affects the whole length of the arteries in a patchy pattern. There is concentric myointimal proliferation resulting in fibrous thickening and the characteristic 'onion skin' appearance of the intima in small arteries [2]. Other findings include endothelial swelling, foam cell accumulation, disruption of the internal elastic lamina, hyalinosis and medial thickening, and presence of subendothelial T-lymphocytes and macrophages [91]. In addition, a persistent focal perivascular inflammation is often seen. Although intimal hyperplasia is very specific for CTD, the diagnosis of CTD in biopsies of allografts is frequently based on other, less specific abnormalities, since intimal hyperplasia is very patchy and affects mainly arteries larger than those seen in biopsies.

In addition to vascular changes, kidneys undergoing CTD also show interstitial fibrosis, tubular atrophy and glomerulopathy. Chronic transplant glomerulopathy – duplication of the capillary walls and mesangial matrix increase – has been identified as a highly specific feature of kidneys with CTD [196]. Less specific lesions are glomerular ischemic collapse, tubular atrophy, and interstitial fibrosis. Furthermore, peritubular capillary

Table 1 Risk factors for CTD

Alloantigen specific factors	Non-alloantigen specific factors
Histoincompatibility	Ischemia
Acute rejection episodes	Brain death
Suboptimal immunosuppression	Infection
Non-compliance	Hyperlipidemia
Anti-donor antibodies	Hypertension
	Age
	Gender
	Race
	Size

basement splitting and laminations are associated with late decline of graft function [136]. The criteria for histological diagnosis of CTD in kidney allografts are internationally standardised in the BANFF scheme for Renal Allograft Pathology [195].

Until now, such typically functional and histological changes of allografts are often diagnosed as 'chronic rejection'. However, the designation 'rejection' presumes a host alloimmune responsiveness to be basis for these changes. Since there are indications that non-alloimmune mediated factors involved in organ transplantation can cause similar functional and histopathological changes, calling the whole process chronic rejection is not satisfactory. As long as the result – dysfunction and characteristic histological changes – cannot be exclusively attributed to an alloimmune-mediated pathway, it is recommended to name the process CTD, leaving any causative factor out of consideration.

Etiology of chronic transplant dysfunction

In 1963, Porter *et al* reported four human cadaveric kidney allotransplants in which striking obliterative vascular lesions developed a few months after transplantation [158]. All patients had experienced early episodes of acute rejection, and the subsequent vascular lesions were thought to have an immunological basis. These cases suggested that the process of allograft rejection can evolve from early acute cellular infiltration of the engrafted organ to a more chronic process, ultimately resulting in intimal arterial thickening, with interstitial fibrosis. However, to the present day the cause of CTD remains ill defined. Two working hypotheses are proposed to understand the process: 1) the phenomenon leading to CTD is the result of an ongoing host alloimmune response. 2) Non-alloimmune responses-to-injury, such as ischemia, can cause or aggravate the process.

Alloantigen-specific factors

Several data indicate that CTD is the result of the recipient's immune response to incompatible donor tissue antigens. In this view, the relationships between the following identified risk factors and CTD all reflect an alloimmunologic mechanism: 1) Histoincompatibility, 2) Acute rejection, 3) Suboptimal immunosuppression/non-compliance, and 4) Anti-donor specific antibodies. Antigenic disparity in humans between donor and host is associated with the occurrence of CTD, as demonstrated in kidney, heart, and lung transplant studies. Long-term graft survival appeared to be strongly correlated with the degree of histocompatibility matching between donor and recipient [67, 89, 146, 194, 214]. Cadaveric kidneys with zero HLA-mismatches have a half-life of 13.2 years compared to 7.0 years in grafts with six-allelic mismatches [146]. Interestingly, some large unicentre studies are unable to demonstrate the benefit of histocompatibility matching for the development of CTD in kidneys and hearts, independently of the effect of acute rejection [88]. It is presently unclear whether matching directly affects the development of CTD or whether this results from a decreased incidence of acute rejection episodes [20, 38, 155, 193].

Graft survival studies from uni- and multicentres alike show a strong correlation between acute rejection episodes and the lifespan of a graft [115, 125, 147, 224]. For instance, Matas *et al* [125] showed in a group of 278 cadaver kidney graft recipients that a single rejection episode in the first post-transplant year reduces the estimated graft half-life from 33 years to 22 years, whereas multiple rejections or a single rejection after the first year decreases the half-life to less than 5 years. Several retrospective analyses of organ grafts with CTD demonstrate that acute rejection is strongly related to the development of CTD in all types of organ transplants [17, 28, 57, 88, 105, 101, 195]. Basadonna *et al* reported that in a cohort of 205 cadaveric renal transplant recipients, the incidence of biopsy-proven CTD was 0% in the 109 patients without acute rejection, 36% in the 69 patients with an acute rejection within the first 2 months after transplantation ($P < 0.001$), and 63% in the 27 patients with acute rejection 60 days after transplantation ($P < 0.001$) [45]. Other clinical studies have corroborated and refined these findings: The onset, frequency, and severity of an acute rejection episode are independent risk factors for CTD [19, 57, 204, 224]. Acute rejections with complete functional recovery do not have a deleterious effect on the long-term outcome [39, 226], whereas an increased baseline serum creatinine level after treatment of an acute rejection episode is associated with CTD [92, 147] In addition, the vascular type of acute rejection appears to be a stronger risk factor for the occurrence of CTD than interstitial rejection [223]. Experimental studies in kidney-, heart-, and lung trans-

plantation models confirm these clinical observations [86, 90, 141, 232, 233, 235]. Nonetheless, acute rejection is not a prequisite for CTD: patients may also develop CTD without prior acute rejection episodes [41, 45, 54]. Reviewing the literature, it can be stated that at present, acute rejection is the most consistently identified clinical risk factor for the occurrence of CTD.

A low dose of maintenance Cyclosporine (CsA) medication in some clinical studies has been associated with CTD [6, 194, 177], but not in others [68]. At 5 years post-transplantation, the percentage of recipients who were free of CTD as demonstrated by biopsy was 86% for those using CsA > 5 mg/kg per day *versus* 77% for those on < 5 mg/kg per day [6]. Additional evidence that CTD may be related to inadequate immunosuppression was provided by the histopathological studies of Isoniemi *et al* [96]. They found that CTD-lesions were less apparent in patients given protocols of triple- versus double-dose immunosuppressive therapy. Experimentally, we and others have demonstrated that in the rat aortic allograft model, both high dose CsA as well as other immunosuppressive agents were able to prevent the inflammatory response, and concomitantly inhibit the generation of intimal lesions during the 4-weeks follow-up period [65, 103, 199]. However, in man it would be impossible to maintain high doses of immunosuppressants on the long-term, because of the associated toxic side effects [203].

Noncompliance also indicates that CTD may result from inadequate immunosuppression [24, 51, 217]. In a study by the Minneapolis group, 34% patients were noncompliant, and this was associated with late deterioration of graft function [124].

Many studies have shown that following transplantation, the majority of patients produce antibodies [49, 75, 99, 121, 122, 149, 154, 165, 168, 192, 202]. Both, preformed antibodies reactive against donor tissue, and antibodies produced after transplantation against HLA class I antigens and against tissue, (endothelial cells, smooth muscle cells) are found. A correlation between antibodies and CTD, however, is not consistently found [45, 49, 54, 58, 90, 149, 166, 179]. No difference in panel-reactive antibody levels was found between those of patients whose grafts were still functioning, *versus* those of patients who lost their graft due to CTD [59, 179] Likewise, Hosenpud *et al* found no differences in the presence of IgM antibodies against endothelial cells of kidney grafts with or without CTD [90]. Other investigators, however, observed significantly more anti-donor reactivity against both HLA class I and II in sera of patients with biopsy-proven CTD in kidneys (94.4%) than in sera of patients with a normal functioning graft (12.8%) [144]. In 70% of the liver allografts with CTD, patients had non-HLA anti-smooth muscle and anti-nucleus antibodies, which were not present in patients with a healthy liver transplant [77].

Experimentally, Paul *et al* demonstrated IgG antibodies against the glomerular and tubular basement membrane, the mesangial cell, and endothelial cell antigens in sera of rats with a kidney allograft with CTD, whereas such antibodies were not found in sera from animals that had received a syngeneic graft [85, 151]. In other experimental models of CTD, the presence of antibodies was noted in areas with intimal hyperplasia [64, 78].

Non-alloantigen associated factors

In the late 1980-ies, attention was redrawn to the fact that in the pre-immunosuppression era even human kidney transplants between identical twins developed late morphological changes. Two-thirds of these kidney isografts developed glomerular lesions between 2 months and 16 years post-transplantation, which were classified as a recurrence of the original disease, glomerulonephritis [69]. Two of these grafts with glomerular lesions developed in a later stage additional vascular lesions. It was also suggested that such changes observed in human renal isografts might have been a consequence of the transplantation injury *per se* [42]. Nowadays, surgical injury and other, non-alloimmune specific factors related to the donor and the graft have been associated to the development of CTD [54, 104, 220]. These risk factors include: ischemia, brain death, viral infections, hyperlipidemia, hypertension, age, gender, race, and the amount of functional tissue.

In clinical transplantation it is still unclear if ischemia participates in the development of CTD. While some studies reported that prolonged cold ischemia reduces graft survival [38, 67, 218], others found no correlation [153, 155]. For instance, the UNOS registry showed that preservation for > 24 hours significantly impaired late kidney graft survival rates compared to cold ischemic times between 0–24 h [67]. In cardiac transplants, a prolonged ischemic time was a risk factor for transplant arteriosclerosis [13]. Experimental transplant studies have demonstrated that ischemia *per se* can cause CTD-like lesions in the absence of allogenicity [225]. We [104], and others [220] have demonstrated that rat kidney isografts develop the same functional and morphological changes as allografts, including vasculopathy, albeit over a much longer time interval. These changes appeared to be triggered mainly by ischemia. Similarly, on the long-term, syngeneic aorta and heart transplants develop intimal hyperplasia, in which the degree of intimal hyperplasia correlates with the duration of the ischemia period [178, 227]. Nonetheless, it is much less clear whether the length of the ischemic period plays a role in the onset of CTD in allografted organs. While Hayry's group showed that in renal allografts a cold ischemic time of 60 min led to in-

creased intimal proliferation and glomerulosclerosis, compared to kidneys subjected to 30 min cold ischemia [236], in heart and aortic allografts the duration of the cold ischemic period did not have an influence on the degree of CTD [8, 101, 227].

It has also been suggested that in allografts the effect of ischemia on CTD is indirect by predisposing for acute rejection. Organ grafts with prolonged cold ischemia or with delayed graft function experience more often an early acute rejection episode than grafts that functioned immediately [72, 73, 145, 188, 218]. We showed that, following 24 h of cold ischemia, increased numbers of $CD4^+$ cells and macrophages infiltrated the kidney grafts, compared to non-ischemic controls. Importantly, ischemic grafts still showed significantly increased numbers at one year post-transplant. Histologically, these grafts showed more glomerulopathy and intimal hyperplasia than non-ischemic controls [104]. These data presume a direct effect of ischemia on long-term outcome.

The striking divergence in clinical long-term results between kidney grafts from cadavers and those from living-related and unrelated donors [212], has drawn attention to the health of an organ before procurement. The hypothesis has been put forward that brain death activates surface molecules on peripheral organs via cytokines. In brain death donors, increased serum cytokine levels are found before organ procurement [161]. In experimental models of brain death, peripheral organs show increased endothelial cell activation [87, 208] and a more accelerated tempo of acute rejection in organs from brain dead animals is observed [160, 229]. The relevance for CTD still has to be proved.

While infection with cytomegalovirus (CMV) has shown to be related to CTD in cardiac-, liver-, and lung transplantation [71, 105, 108, 128, 143], its association with CTD in kidney transplants is not yet clear. A multivariate analysis on risk factors for CTD performed on 675 renal allograft recipients showed no difference in the incidence of CMV infection in patients who did or did not loose their grafts to CTD [122]. Experimentally, CMV infection has been identified as promotor of CTD in aorta, kidney and heart transplants [110, 111, 235]. CMV infection directly affects intercellular adhesion molecule-1 (ICAM-1) expression on endothelial cells, [159, 234] and induction of MHC class II antigens is observed, together with a prolonged and increased acute cellular infiltration of T cells and macrophages [109].

Hyperlipidemia is a controversial risk factor for allograft arteriosclerosis [18, 52, 180]. The relevance of hyperlipidemia in animal transplant arteriosclerosis models has also been a matter of controversy [3, 7, 48, 56, 133, 211].

Systemic hypertension in clinical kidney and heart transplants is associated with CTD [30, 148, 157, 162]. In heart transplant recipients, hypertension was associated with an earlier onset of CTD [162]. In renal allograft recipients, hypertension is a common event (75%), although its role as a causative factor or a consequence of renal dysfunction is difficult to define since a vicious circle is created where the worsening of one parameter leads to the worsening of the other [163]. Experimental studies showed that systemic hypertension accelerates CTD in kidney allografts [106], whereas antihypertensive drugs inhibited the progression of chronic allograft dysfunction [22]. Similarly, in rat aortic transplants, hypertension was associated with a significant increase of intimal thickness, whereas ACE-inhibition was able to decrease systolic blood pressure by 30%, and concomitantly reduce intimal lesions by 40% [134].

Donor age is a controversial risk factor. Some investigators have found that grafts from donors over 60 years of age are associated with poorer survival rates [33, 79, 123]. Cardiac transplants from an older aged donor had an earlier onset of CTD [23, 40].

In male recipients, solid organ grafts appeared to be more vulnerable for the development of CTD. In cardiac allografts, the onset of arteriosclerosis was earlier in males than in females [40] and the prevalence of CTD was reported to be higher in male- than in female recipients: 30% versus 50% free of coronary artery disease at 5 years ($P = 0.01$) [129]. The UNOS Transplant Registry reported a similar observation for kidney grafts [67]. Experimental studies have corroborated these observations: In rat syngeneic aorta transplants, female gender protects against myointimal hyperplasia [59]. This gender effect could reflect oestrogen. Oestrogen protects against cardiovascular disease, and it has been demonstrated that oestradiol effectively inhibits transplant arteriosclerosis in experimental models [32, 116, 175].

Long-term survival of cadaveric renal transplants appeared to be related to race: Five-year graft survival rates were 66% for Asians, 61% for Caucasians and Hispanics, and 47% for Black recipients [100]. Black recipients of heart transplants developed CTD earlier than non-blacks [40]. The absence of the Duffy antigen Receptor for Chemokines on erythrocytes in African Americans seems an important risk factor for the development of CTD [44].

A risk factor reserved to the kidney is the contribution of reduced numbers of nephrons to the progression of CTD. In non-transplant models in the rat, it is well established that kidneys with significantly reduced numbers of nephrons, such as in the 'remnant kidney model', develop glomerulosclerosis, tubular atrophy, and interstitial fibrosis in response to an increased workload of the remaining nephrons, i.e. hyperfiltration [142, 186]. In a chronic kidney allograft model, Heemann *et al* demonstrated that reduction of renal mass led to earlier onset of CTD and shortened survival. Moreover, iso-

grafts and non-transplanted, ablated kidneys having only 1/6 of total mass experienced proteinuria in the same tempo as allografts, whereas 2/6 or 3/6 nephrectomized native and isografted kidneys had negligible damage [83]. Thus, the reduction of functioning renal mass accelerated the changes characteristic for CTD, and after a substancial reduction, hyperfiltration plays an overriding role in further deterioration [117]. Nonetheless, in clinical kidney transplantantion, the significance of a mismatch between donor nephron supply and functional metabolic demand of the recipient in the development of CTD is unclear. Poorer survival of grafts from very young, elderly, black, or female donors, compared to grafts from donors aged 15–55, non-black or from male donors has been ascribed to hyperfiltration damage [25]. None of these CTD-prone conditions, however, are uniformly found. Miles *et al* did not find that the donor kidney size was different in patients who lost their graft due to CTD compared with the kidney size of patients with stable function [135]. Others did not see differences in CTD between pediatric kidney recipients and adult-kidney recipients either [5]. Paired pediatric kidney transplantation did not improve renal function compared to small single pediatric kidneys [164].

Pathophysiology of chronic transplant dysfunction

As already outlined, CTD is characterized by morphological evidence of destruction of the transplanted organ [191]. The common denominator of all parenchymal organs is the development of intimal hyperplasia. Whether the parenchymal changes with fibrosis occurs secondarily to gradual arterial insufficiency and ischemia, or if they develop from ungoing subclinical host immunological attacks or other factors, remains undefined.

Immunohistochemistry of allografts with CTD has shown that T cells and macrophages are the predominant graft-invading cell types, with an excess of $CD4^+$ over $CD8^+$ T cells [4, 47, 50, 82, 104, 176, 191, 198]. Increased expression of adhesion molecules (ICAM-1, VCAM-1) [77, 114], and MHC antigens [81, 114] are seen in allografts with CTD. Also, complement and immunoglobulin deposits are seen in areas with intimal hyperplasia [77, 78, 90, 114]. Little consistent information is available on the expression of growth-regulating factors and their receptors in organ transplants with CTD. An increased TGF-β expression, however, is frequently found [152, 185, 206].

The histologic lesions, including intimal hyperplasia, the infiltrating cells, upregulated adhesion molecules, and cytokines in organ transplants with CTD do not necessarily reflect an alloimmune-mediated response. As already mentioned, syngeneic transplants, ischemia- or mechanically-injured organs also show cell infiltration, upregulation of cytokines and develop CTD-like lesions [104, 220, 227]. Notwithstanding, the development of the lesions occurs much more rapidly in allografts, suggesting that alloimmune responses play a role [104]. The most consistent clinical risk factor 'acute rejection' also indirectly indicates that an alloimmune response is involved in CTD and suggests that CTD is, for the main part, the result of insufficient immunosuppression. More evidence to support this hypothesis comes from experiments that have demonstrated that pretransplant immunizations with donor splenocytes accelerate CTD [41], whereas manipulations aimed at induction of tolerance delay the process [36, 187]. In the following subparagraphs, we suggest the route through which a graft may develop CTD.

Initial response-to-injury

Endothelial cell activation

The specific adhesion of cells to other cells or to particular tissues is a basic function of cell migration and recognition. Under normal conditions, contact between leukocytes and vascular endothelium is random if both cell types are inactive and at rest, the cells touch vessel walls indiscriminately. In organ transplantation, the endothelial cells are activated by ischemia, surgical manipulation, and reperfusion injury, events inherent to the procedure. After ischemia and reperfusion, endothelial cells produce oxygen free radicals predominantly via the xanthine-oxidase pathway, which *in vitro* activate and damage the cells [21]. Upon activation, the endothelial cells retract and release increased amounts of the cytokines IL-1, IL-6, IFN-γ, TNF-α, the chemokines IL-8, macrophage chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α and MIP-1β, colony stimulating factors, and multiple growth factors such as, platelet derived growth factors (PDGF), insulin growth factor-1(IGF-1), transforming growth factor (TGF)-β, and pro-thrombotic molecules (tissue factor, plasminogen activator inhibitor). This secretion enhances migration of neutrophils, monocytes/macrophages and T lymphocytes to the site of injury [27]. The release of cytokines also leads to upregulation of adhesion molecules on the vascular endothelium [27, 62]. The proinflammatory cytokines IL-1 and TNFα induce the expression of the adhesion molecules P- and E-selectin on the endothelium [167, 230], by which circulating leucocytes begin to adhere via binding to their surface carbohydrates [112, 127, 197]. Leucocytes are then triggered by the chemokines released by the endothelium, which causes upregulation of the affinity of the β_2-integrin receptors LFA-1 and MAC-1 on their surface. This enables a permanent adherence of leucocytes to the endothelial adhesion molecules ICAM-1

and VCAM-1 [118], the expression of which is induced by the released cytokines IL-1β, IFNγ, TNFα [26, 156]. Activated complement also plays a role in the adhesion of neutrophils and monocytes to endothelium [16]. Finally, extravasation of leucocytes occurs to the extracellular matrix and graft tissue, presumably facilitated by activated complement [209, 229] and oxygen-free radicals that increase the permeability between endothelial cells [94]. The first cells that infiltrate the graft are neutrophils. They further aggravate the inflammatory response through release of oxygen-free radicals and inflammatory mediators, including platelet activating-like factors and leukotrienes. Direct evidence that oxygen free radicals, adhesion molecules, and neutrophils play a role in the pathogenesis of CTD is shown by interference studies [29, 107, 210]. One recent study, for instance, revealed that carotid allografts from donor mice deficient in ICAM-1 had a 52% reduction of intimal hyperplasia compared to controls [183].

In addition to the increased expression of adhesion molecules on the endothelium, after reperfusion of a transplanted organ, a dramatic upregulaton of MHC class I and II antigens on the endothelium occurs [37, 93], which appears to be induced by release of cytokines IFN-γ, TNF-α and TNF-β [74, 181]. Alterations in tissue density of MHC class II antigens are likely to influence the alloimmune response against the tissue [76]. Parenchymal cells are also activated after ischemia. In non-transplanted kidneys, MHC class I and II antigens are upregulated on the tubular epithelium [93, 189]. Epithelial cells in lung autotransplants showed a mild expression of MHC class II after cold ischemia [181].

$CD4^+$ T-lymphocytes infiltrate ischemic allografts, isografts and non-transplanted organs [11, 93, 104, 220]. In addition, T cell associated cytokines, such as IFN-γ and TNF-α are produced [93] and blockade of the C28-B7 costimulatory pathway decreased early influx of T cells and expression of T cell associated cytokines [207]. We showed that cyclosporine was able to overcome the deleterious effects of ischemia in syngeneic transplants with a concomitant decrease in infiltrating $CD4^+$ T-cells [104]. The role of $CD4^+$ T-lymphocytes in ischemia has been elegantly demonstrated. In a liver ischemia model, $CD4^+$ T cell deficient mice had significantly less hepatic damage [236]. This response to ischemic injury is initially independent from allogenicity: Heemann *et al* have demonstrated that the pattern of cellular infiltration and cytokine expression in both syngeneic and allogeneic cardiac grafts was similar if not identical within the first 48–72 h after engraftment [84]. Thus, as result of the transplant procedure, a complete network of cytokines is already activated, even before allogeneic reactions develop. Some pretransplant conditions of both donor and recipient, as discussed in the etiology section, appear to aggravate this initial injury.

Alloimmune response

The recognition of histoincompatible MHC alloantigens will provoke an alloimmune response. Class I antigens, constitutively expressed on nucleated cells, interact with $CD8^+$ cells, and class II antigens, constitutively expressed on lymphoid cells and inducible on endothelial cells, macrophages and fibroblasts are recognised by $CD4^+$ cells. Intact foreign MHC molecules on donor cells may be directly recognised by T cells, either in combination with an allopeptide or a selfpeptide, which results in an exceptionally strong immune response. Frequencies of T cell precursors that respond to alloantigens are 10–100 fold higher than for other nominal antigens [182]. In draining lymph nodes and spleen, alloreactive T-cells recognise donor MHC indirectly, presented by self-MHC molecules on recipient antigen presenting cells [190].

In allorecognition, the MHC antigen is bound to the T cell receptor. For activation of T-cells, costimulatory pathways as the CD28 receptor on T cells with its ligand B7, and CD40 with its T-cell based ligand, CD40L are mandatory for the promotion of T-cell effector function and proliferation. The adhesion molecules ICAM-1, VCAM-1 and LFA-3 have also been shown to co-stimulate T cell activation. Once the $CD4^+$ T cell is activated, a cascade of events amplifies the alloimmune response: Secreted IL-2 leads to clonal proliferation of alloreactive cells and stimulates $CD8^+$ T cells to develop into mature cytotoxic effector cells. Release of cytokines such as IFNγ and TNFα may further increase the expression of adhesion molecules, and MHC antigens on the endothelium, smooth muscle cells and parenchymal cells. IFNγ is also responsible for the activation of macrophages, which together with $CD8^+$ cells are cytotoxic to the graft cells, leading to acute graft failure, when no immunosuppressive intervention is given to prevent or to overcome this $CD4^+$ T-cell mediated alloimmune response.

Despite inhibition of T cell activation by cyclosporine, FK 506, or anti-IL2 monoclonal antibodies, these therapies do not prevent the development of CTD in clinical transplantation, probably due to too low doses of these drugs. In experimental models, continuously high doses of cyclosporin A or blockade of CD28/B7 and CD40/CD40L costimulatory pathways decrease early infiltration and almost completely inhibit intimal hyperplasia in murine aortic and cardiac allografts [65, 171, 199, 205]. Evidence that the $CD4^+$ T cell is involved in the genesis of intimal hyperplasia is elegantly exemplified by Shi *et al*: Carotid allografts in mice that were genetically deficient for the CD4 + T cell developed intimal thickening to only 40% of that seen in controls [184].

Anti-donor specific antibodies

The cytokines IL-4, IL-6, and IL-10 released by activated $CD4^+$ cells are growth- and differentiation factors for B cells. Activation of B cells may result in maturation into plasma cells with allospecific antibody production. Since immunoglobulin, complement, and antigen-antibody complexes have been found in areas of intimal hyperplasia [15, 170, 216], humoral activity has long been thought to be primarily responsible for CTD. A recent finding of upregulated immunoglobulin J chain in arteriosclerotic lesions suggests the presence of IgM- or IgA-producing plasma cells in such grafts [31]. Donor-specific antibodies are found against HLA antigens, endothelial cells, mesangial cells, glomerular and tubular basement membrane, smooth muscle cells and the nucleus [99, 201].

The precise significance of antibody deposition that mitigates over time, as shown in many animal models [64, 77, 78], remains to be established. In experiments with SCID mice, which lack T and B cell mediated cellular responses, passive transfer of anti-donor specific antibody was sufficient to produce graft arteriosclerosis with a perivascular mononuclear cell infiltrate in long-standing cardiac allografts [174]. While some investigators found that the degree of intimal hyperplasia aortic and cardiac allografts in mice recipients with a defect of humoral antibody production was comparable to that seen in immunocompetent mice [34], Russell *et al* showed that cardiac allografts in B cell deficient mice did not develop fibroproliferative arteritis [173]. These investigators also demonstrated that in two donor-recipient mice combinations in which anti-donor antibodies are generally undetectable, intimal fibrosis was uncommon, whilst these recipients became capable of producing fibrous lesions in allografted hearts when given anti-donor, class I antibody [173]. Similarly to Russell's report, Shi *et al* showed that $CD4^+$ cells, humoral antibodies and macrophages together were necessary for intimal hyperplasia in a mouse carotid allograft model. Arteries allografted into mice, deficient in both T cell receptors and humoral antibody, showed almost no neointimal proliferation, whereas those grafted into mice, deficient only in humoral antibody, developed minimal intimal hyperplasia [184].

The mechanism by which antibodies contribute to CTD is rather speculative. One recent study has shown that anti-HLA antibodies, when attached to their HLA class I antigen on cultured endothelial cells, induce increased gene expression of bFGF receptor and ligand binding, and a 4–6 fold cell proliferation, as it does for smooth muscle cells [80]. Marsh *et al* hypothetized that IgG induces the accumulation, differentiation and subsequent cytokine production by intimal macrophages via crosslinking of FcγR thereby preventing apoptosis of monocytes. FcγR crosslinking induces the production of MCP-1 and IL-8, which can promote both macrophage and lymphocyte accumulation [119, 120].

Chronic response-to-injury

It is not clear why this response to the initial injury does not disappear over time, as seen in normal healing processes. In allografts, it is conceivable that the alloantigens are responsible for an ongoing cellular and/or humoral response. T cells decline to relatively low numbers as the process enters its chronic phase, they and their products may continue to provide a persisting low grade immunological response and ongoing subclinical injury to the graft's endothelium and parenchyma over time [221]. Since there is a continuous supply of donor allopeptides processed and presented by host professional APCs (dendritic cells, macrophages, B cells), self-MHC restricted T cells may perpetuate a chronic alloimmune response. Suciu-Foca and collaborators demonstrated a persistent allopeptide reactivity in patients developing CTD [35, 201]. The continued alloimmune recognition in long term graft recipients is evidenced by the presence of graft reactive cytotoxic T splenocytes in long term recipients of cardiac allografts. Anti-donor specific antibodies may also maintain a chronic alloimmunologic injury: Donor reactive alloantibodies in the recipient's circulation have been demonstrated long-term after engraftment [149, 228].

The significance of donor alloantigens on 'non-professional' antigen presenting cells, like the endothelial cells for T cell recognition is unclear. An indication that donor MHC class I and II antigens play a role in the chronic phase has recently been obtained. Carotid allografts from donor mice deficient in MHC II molecules showed a reduction of intimal hyperplasia formation of 33%, primarily due to a reduction in smooth muscle cell accumulation [183]. The absence of such a continuous alloantigeneic stimulus in syngeneic transplants might explain the much more rapid development of CTD in allografts.

Thus, the strength of the initial trigger, the length of the trigger, and the presence of additional factors, and under which alloantigens, determine the onset and the pace of progress of irreversible chronic lesions

Macrophages

Activated T cells produce, amongst others, the cytokine RANTES (Regulated upon activation, normal T cell expressed and secreted), a macrophage chemoattractant [137]. Other cytokines, such as IL-8, MCP-1 and osteopontin released by interstitial cells and smooth muscle cells are chemotactic for macrophages as well. Upregulated adhesion molecules contribute to their localisation

in areas of injury. Macrophages invade the graft and become activated by IFN-γ. The continuous presence, the activated state, and the upregulation of macrophage associated cytokines in long-term allografts with CTD and, in other chronic diseases, with fibrotic features, suggest a pivotal role for the macrophages [12, 172, 198].

The importance of macrophages was demonstrated by the prevention of CTD by treatment with gammalactone, a synthetic inhibitor of macrophage activity, in a rat renal allograft model [12], and by the observation that carotid allografts in mice deficient in macrophages, developed only slight intimal hyperplasia [184]. Activated macrophages produce a number of cytokines including TNF-α, IL-1β, PDGF, bFGF, and TGF-β. This perpetuates and amplifies the fibrogenic signals.

Cytokines and growth factors

Cytokines and growth factors play an important role in the chronic phase. They have profound effects on cells of the graft and on the immune system. Cytokines and growth factors are pleiotropic, with biological effects on many cell subpopulations, are, furthermore, regulated via autocrine, paracrine or systemic pathways, and there is a great deal of redundancy in the cytokine networks. The advent of the transgenic and knock-out technology has allowed dissecting of the molecular pathways causally involved in allograft arteriosclerosis [200]. No cytokine has been unequivocally identified as specific to alloimmune response.

The redundancy of the cytokine system has been stressed by gene knockout technology: IL-4 is not necessary for the development of graft coronary arteriosclerosis, nor does its absence appear to augment the development of vascular lesions. In addition, TNFα-R1 deficiency in either donor heart or recipient does not abrogate the development of graft arteriosclerosis [140]. The increased expression of TGF-β_1 has been linked to transplant arteriosclerosis both by clinical and experimental studies, and transfection of TGF-β to the kidney led to increased accumulation of the extracellular matrix and glomerulosclerosis [95]. Interestingly, cardiac allografts in TGFβ_1 deficient recipients developed significantly more intimal hyperplasia than controls [102].

In 1989, IFN-γ has already been postulated by Libby *et al* to play a central role in CTD because of its effects on T cells and macrophages, as outlined above [113]. The availabilty of IFN-γ deficient mice permitted this group to test critically the contribution of IFN-γ to the development of CTD [138, 139]. Cardiac allografts in IFN-γ deficient mice developed only minimal or no transplant arteriosclerosis as compared to controls. In addition, similar results on graft arteriosclerosis were found after the administration of IFN-γ neutralizing antibody in normal rats.

Chronic remodelling

The process eventually becomes irreversible, but the period in which this occurs is variable: Retransplantation of allogeneic kidney grafts back into the original donor strain prevents CTD, when the retransplant is performed within 12 weeks, but not after this period [219]. In aorta- and cardiac allografts Mennander *et al* and Izutani *et al* reported a much shorter time interval after which intimal hyperplasia continues, when the graft was transplanted back into the donor strain [97, 132].

Smooth muscle cells

Once the endothelial cells are injured, the secreted cytokines, i.e. IL-1, PDGF, IGF-1, TGF-β and bFGF, and metabolic products such as prostaglandin, nitric oxide, and oxidized low-density lipoproteins induce smooth muscle cell (SMC) proliferation, as reviewed by Ross [169]. Activated T cells and macrophages, often in close anatomical association with the replicating SMC, produce also a whole wealth of these factors. Platelets deposited along the injured vascular wall contribute by secreting PDGF, EGF, TGF-β and tromboxane-A_2. When SMC migrate to the intima, they transform their phenotype from 'contractile' to 'secretory' and the cells become capable of replication [169, 215]. In addition, SMC can produce many of these growth factors and may generate similar autocrine or paracrine loops of stimulation for cell replication, as seen in 'classical' atherosclerosis [169]. These factors also may modulate extracellular matrix synthesis, angiogenesis, and leucocyt adhesion. Moreover, activated SMC can express MHC class I and II and may act as antigen presenting cells. Numerous drugs inhibit SMC proliferation, and some, such as angiopeptin, have been shown to be of benefit in organ allografts [55, 130, 131].

Extracellular matrix

As the endothelium is damaged, the underlying extracellular matrix can become activated and act as costimulator for leucocytes to facilitate recruitment and extravasation. For instance, exposed collagens and fibronectin may act as costimulators for activated $CD4^+$ T-cells [43, 126]. After activation by antigens, T cells synthesize heparanase, which facilitates migration through tissue [61]. The cleavage of heparan sulphate by this enzyme also activates and releases fibrogenic growth factors, such as basic fibroblast growth factor in the extracellular matrix [66]. TGF-β, produced by the activated T cells and macrophages, stimulates the production of ECM molecules and inhibits the matrix degrading enzymes. The thickening of basal membranes,

such as that of the pericapillary and glomerular endothelium in the transplanted kidney, interstitial fibrosis and sclerosis, and in intima hyperplasia smooth muscle cell proliferation is accompanied by excessive synthesis of connective tissue proteins.

Conclusion

CTD is currently the main cause of late graft failure. It is usually associated with previous acute rejection episodes, although several non-alloantigen-associated factors, like ischemia, hyperlipedimia, and hypertension may enhance the process. We propose that the process leading to CTD in allografts begins at the time of graft retrieval, is enhanced by ischemic injury, which provokes an alloimmune response to the endothelial cells, the extracellular matrix and parenchyma. An ongoing alloimmune response, in which several non-alloimmune factors may interfere, eventually leads to irreversible lesions of the graft.

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