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TGF-β, IL-6, IL-17 and CTGF direct multiple pathologies of chronic cardiac allograft rejection

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Abstract

Cardiac transplantation is an effective treatment for heart failure refractive to therapy. Although immunosuppressive therapeutics have increased first year survival rates, chronic rejection remains a significant barrier to long-term graft survival. Chronic rejection manifests as patchy interstitial fibrosis, vascular occlusion and progressive loss of graft function. Recent evidence from experimental and patient studies suggests that the development of cardiomyocyte hypertrophy is another hallmark of chronic cardiac allograft rejection. This pathologic hypertrophy is tightly linked to the immune cytokine IL-6, which promotes facets of chronic rejection in concert with TGF-β and IL-17. These factors potentiate downstream mediators, such as CTGF, which promote the fibrosis associated with the disease. In this article, we summarize contemporary findings that have revealed several elements involved in the induction and progression of chronic rejection of cardiac allografts. Further efforts to elucidate the interplay between these factors may direct the development of targeted therapies for this disease.

Keywords

chronic allograft vasculopathy; chronic rejection; CTGF; fibrosis; hypertrophy; IL-6; IL-17; TGF-β

The advent of effective immunotherapeutic agents allowed cardiac transplantation to become a realistic treatment modality for end-stage cardiac diseases refractive to other therapies. Modern immunosuppressant regimens effectively limit acute rejection and prolong short-term survival of solid organ grafts. Indeed, the 1-year survival rate is approaching 90% for heart transplant recipients [1]. However, comprehensive evaluation of the success of clinical transplantation must take long-term survival, with its less favorable prospects, into account. For well over a decade, chronic rejection has been recognized as the most significant barrier to long-term graft survival [2–8] and has been defined by hallmarks of occlusive vasculopathy, interstitial fibrosis and progressive loss of graft function.

Cardiac allograft vasculopathy

In cardiac grafts undergoing chronic rejection, vessels undergo occlusive remodeling characterized by neointima development (Figure 1). This process is referred to by many names, although herein we will use cardiac allograft vasculopathy (CAV). CAV in humans was first

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reported in 1970 [9]. It has been suggested that some level of intimal thickening can be observed in 75% of cardiac transplants within the first year post-transplant [10,11], which may then develop CAV, estimated to occur in up to 80% of cardiac transplants within the first 5 years post-transplant [12,13]. Currently, no effective therapeutic exists for CAV other than retransplantation. Hence, the current approach to CAV is prevention. While treatment regimens utilizing cyclosporine A, azathioprine, steroids and antilymphocyte antibodies have not successfully prevented the incidence of the disease [8], recent findings suggest that newer immunosuppressive treatments may decrease the incidence and severity of CAV [8,14,15]. However, these effects may be attributable to more robust immunosuppression, as incidence of acute rejection has been decreased by these agents in some circumstances as well [16,17]. Although numerous factors may contribute to the development of CAV, it appears that graft/host incompatibility plays a central role, as CAV affects graft vessels up to, but not beyond, the suture line [8]. This supports the widely held notion that graft-derived factors, probably donor alloantigens, are critical for the disease [3,4,6–8,18].

Graft fibrosis

Another hallmark of chronic rejection is the development of patchy interstitial fibrosis (Figure 1). Fibrosis of cardiac grafts is characterized by the accumulation of thick web-like fibers of extracellular matrix (ECM) surrounding cardiomyocytes, readily visible in stained myocardial biopsy sections [19]. It has been suggested that graft fibrosis occurs largely in response to CAV [8], however the relationship between these elements of graft pathology is uncertain. Although its origins are not fully understood, fibrosis can have detrimental effects on organ function and survival. Ultimately, enhanced ECM accumulation observed in tissue fibrosis is the result of competition between programs that promote ECM degradation and those that promote ECM synthesis [20,21]. The balance between these two programs is regulated by numerous factors in the context of cardiac allograft fibrosis. Indeed, initiating factors for fibrotic responses can include both alloantigen-dependent (cellular and humoral immune attack) and alloantigen-independent factors (health of graft, ischemia reperfusion injury and infections), but both provide the common physiologic effect of tissue damage (Figure 1). Tissue damage can then prompt the production of cytokines, chemokines and growth factors [22]. Some of these mediators promote infiltration by immune cells, fibroblasts [23] and progenitor cells [24,25]. Infiltrating cells can then elaborate production of cytokines and growth factors that drive proliferative responses in inflammatory cells, fibroblasts and epithelial cells. Cytokines and growth factors subsequently promote cellular differentiation [26].

One specific type of cellular differentiation that has been recently reported to contribute to cardiac fibrosis is endothelial to mesenchymal transformation [27,28]. However, an essential contribution of such developmental reprogramming in organ fibrosis is controversial, as the protein used to define mesenchymal fibroblasts in these studies has been reported to be expressed by numerous cell types in other systems [29]. A role for endothelial to mesenchymal transformation in cardiac fibrosis may seem more plausible in light of the more established epithelial to mesencymal transformation hypothesis of developmental reprogramming in kidney fibrosis. However, recent observations maintaining that epithelial to mesenchymal transformation readily occurs *in vitro* have challenged whether the process occurs *in vivo* [30,31].

Regardless of their etiology, the cells that differentiate to myofibroblasts are probably the most important cell type with respect to accumulation of excessive ECM [32,33]. Myofibroblasts are characterized morphologically [34] and by the expression of fetal isoform α-smooth muscle actin, extradomain-A-containing fibronectin and type I collagen [35–38]. In addition to myofibroblasts, it has been reported that cardiac myocytes can contribute to the production of collagen type I [39,40]. However, it is generally thought that the cell that regulates homeostasis

of the ECM within the heart is the fibroblast [41], an abundant cell type that facilitates structural and functional connections in healthy cardiac tissue [42–44].

Cardiac fibrosis can occur in a reactive fashion to stimuli such as cytokines or hypertension, as well as a reparative fashion in response to cell death [45–50]. In both cases, fibrosis has significant implications for graft function, as it provides increased tensile strength but also stiffness to the myocardial wall. Furthermore, the sheathing of individual cardiomyocytes with ECM alters cell-to-cell contacts, which can result in disruption of the electophysiology of cardiac myocytes [49] and probably decrease the energy supply for cardiomyocytes. If this occurs while the workload for graft contractility is increased [50], the intense stress of such conditions triggers cell death and further reparative fibrosis. Hence, breaking this positive feedback loop of cardiac remodeling should be a priority for chronic rejection therapeutics.

Graft dysfunction & pathologic remodeling

Progressive loss of graft function in chronic rejection might occur in response to CAV-mediated impedance of vascular flow and tissue stiffening associated with fibrosis. Recent findings from the use of noninvasive echocardiographic imaging in patients and a murine model of chronic rejection have revealed an association between the development of cardiac hypertrophy and chronic rejection [51,52]. In murine studies, the heterotopic cardiac allograft model alters the hemodynamic load of cardiac grafts. Hence, even in the presence of appropriate controls, judicious interpretation must be exercised with regard to the physiologic implications of cardiac hypertrophy in these studies. However, the concommitance of hypertrophy with the development of fibrosis suggests a pathologic phenomenon [51]. This is consistent with previous *in vitro* demonstrations that hypertrophic stimuli induce cardiac myocytes to produce CTGF [53] and TGF-β [54], factors known to promote fibrosis of cardiac allografts [55,56]. In patient studies, hypertrophy was associated with graft vasculopathy, and it has been suggested that hypertrophy could provide a noninvasive surrogate marker for patient survival [52,57]. Hence, cardiac hypertrophy is concomitant with fibrosis and vascular pathology. Although causal relationships between these factors remain to be uncovered, echocardiographic analysis may provide a surrogate marker that is valuable for monitoring and diagnosing chronic rejection.

Etiology of chronic rejection

Although chronic rejection is highly prevalent, the etiology of the disease is less clear. Chronic rejection has been used to describe late graft loss from antigraft immunity [58]. However, both immune and nonimmune parameters indicate risk of chronic rejection [18], and contributions by alloantigen-dependent and -independent factors are well established [3,6,8,59]. The multifaceted nature of factors contributing to chronic rejection (Figure 1) may partially explain why correlative associations abound while causative relationships have been more elusive.

TGF-β: a key agent in chronic rejection

Perhaps no factor has been associated with chronic rejection more frequently than TGF-β – a cytokine whose effects are linked to both graft acceptance and the development of chronic rejection. TGF-β overexpression is linked with chronic rejection [56,60] and may negatively impact graft survival through chemotactic and profibrotic effects [61]. TGF-β plays an important role in fibrosis of various causes in multiple organs [62] and is reported to induce the differentiation of cardiac myofibroblasts [63]. Indeed, fibroblasts themselves can make TGF-β [64] and myofibroblasts are rescued from apoptosis by TGF-β [65].

However, in addition to its deleterious fibrotic effects on the graft, TGF-β mediates immunosuppressive and antiproliferative functions [61,66] that may be indispensable for graft

and host survival [67]. The importance of TGF-β in establishing graft tolerance has been recently demonstrated by the premature rejection of allografts in $CD4^+$ cell-depleted recipients with abrogated T-cell TGF-β signaling [68]. This may be explained in part by the critical role TGF-β plays in the induction and function of regulatory T cells, which are believed to contribute to graft acceptance [69–71]. Somewhat paradoxically, regulatory T cells that prevent acute allograft rejection could be a significant source of TGF-β that drives chronic rejection. Hence, while TGF-β promotes chronic rejection, TGF-β signaling in T lymphocytes is required for some mechanisms of graft tolerance. Thus, global disruption of TGF-β-dependent mechanisms of allograft acceptance may prevent manifestations of chronic rejection, but do so at the cost of accelerated immune-mediated rejection.

One approach to the contradicting roles of TGF-β has been through the local neutralization of TGF-β using decorin. Decorin is able to bind active TGF-β and sequester it in the ECM, which inhibits the interaction of TGF-β with its receptor [72,73]. It should be noted that decorin can inhibit TGF-β-mediated upregulation of α-smooth muscle actin and decrease TGF-β-induced collagen gel contraction *in vitro* [74]. This indicates that decorin is able to suppress myofibroblast differentiation, a process thought to be critical in the fibrotic lesions of chronic rejection [75]. Previous studies utilizing decorin gene transfer have shown promise in limiting the development of fibrotic lesions in both the kidney and lung [76,77]. Recent observations by our group revealed that ectopic decorin expression within the graft was able to ameliorate fibrosis in a murine model of chronic cardiac allograft rejection [78]. These findings cumulatively raise the possibility that targeting TGF-β in a local milieu might selectively block its deleterious functions while sparing the graft-protective functions. While decorin gene transfer appears hopeful as a therapeutic, it remains to be seen if localized TGF-β suppression will disrupt protective activities of TGF-β within the graft. Because of this potential limitation, complimentary approaches have aimed to identify facilitators and downstream mediators of deleterious TGF-β effects in chronic rejection. If identified, these factors may prompt the development of therapeutics that are able to negate the fibrosis-inducing activity of TGF-β while sparing its anti-inflammatory and antiproliferative effects.

CTGF is a downstream mediator of fibrosis in chronic rejection

CTGF is induced by TGF-β in multiple cell types [79], including cardiac myocytes and fibroblasts [80], and has been frequently implicated in cardiac disease [81]. Recent investigations have highlighted an association of CTGF with the development of vascular injury. Adventitial application of recombinant CTGF stimulated neointimal hyperplasia associated with vascular injury, which phenotypically recapitulates *smad3* (a TGF-β signaling mediator) gene transfer [82]. Furthermore, it has been reported that the C-terminal domain of CTGF can induce cardiomyocyte hypertrophy [83]. CTGF drives connective tissue development and scar tissue formation [84,85]. CTGF is also upregulated in fibrotic disorders, including chronic rejection of cardiac and kidney grafts [56,81,86,87]. CTGF can mediate a number of profibrotic effects attributed to TGF-β such as enhanced accumulation of ECM and fibroblast proliferation [81]. Because CTGF can be induced by TGF-β and the two share similar profibrotic and remodeling effects, CTGF has been a target for limiting the downstream fibrotic effects of TGF-β, while hopefully sparing its immune-modulatory functions [5,56,88]. Indeed, recent findings by our group in a murine model of chronic cardiac allograft rejection indicate that CTGF neutralization can limit the development of interstitial fibrosis [55], suggesting that CTGF-targeting therapeutics might be effective at limiting the development of interstitial fibrosis in patients.

It should be noted that although transduction of cardiac allografts with TGF-β induces CTGF and chronic rejection, transduction of syngeneic grafts with TGF-β is insufficient to induce CTGF or chronic rejection [56]. Thus, the *in vivo* induction of CTGF by TGF-β depends on

factors associated with the transplant setting (Figure 2). An obvious demarcation between allogeneic and syngeneic grafts is the development of alloimmune responses. In turn, alloimmune responses can be associated with the production of some factors known to crosstalk with TGF-β signaling [89]. One such factor is IL-6 (Figure 2), which has been reported to modulate TGF-β-mediated effects in multiple cell types [90–92].

IL-6 in chronic rejection

IL-6 is a pleiotropic cytokine with effects on cardiac biology [93] and broad effects upon immunologic responses [94–97]. Among its immune-stimulating functions, IL-6 enhances immune cell differentiation and lineage commitment while promoting inflammation through leukocyte recruitment and survival [98–105]. Recent observations have invoked a renaissance of interest in IL-6 as a modifier of immune responses and usurper of immune tolerance [106–108]. As is often the case, these new observations have reframed our understanding of historic data and brought new questions to the forefront. This is especially true regarding the associations of IL-6 with transplant pathology, as an association of IL-6 with TGF-β in rejecting cardiac grafts was observed more than a decade ago [109]. If not fully realized at the time, it is clearer now that IL-6 can instigate numerous phenomena associated with transplant rejection.

Several recent investigations have implicated a role for IL-6 in acute rejection. Studies placing *IL-6*$^{-/-}$ donor grafts in wild-type recipients and wild-type grafts in *IL-6*$^{-/-}$ recipients suggested that graft-origin IL-6 may be more essential than recipient-origin IL-6 in promoting acute rejection [110]. As the authors suggest, IL-6 may serve as an immune ‘danger’ signal in this context, consistent with recent demonstration of the ability of IL-6 to mediate disruption of established allograft tolerance by Toll-like receptor signals [111]. Whether similar functions of IL-6 are operating in the etiology of chronic rejection remains to be explored; however, a critical role for IL-6 in the onset and progression of chronic rejection has now been reported [51]. In cardiac allografts transiently depleted of $CD4^+$ cells, which normally undergo chronic rejection, neutralization of IL-6 prevented chronic rejection. Though enumeration of graft-reactive cytokine production by recipient splenocytes did not reveal significant differences [51], intragraft expression of IL-6 and IL-17 were decreased in response to anti-IL-6 monoclonal antibodies (mAbs) [55].

IL-6 effects in chronic rejection are likely to extend beyond the alloimmune response. As summarized above, cardiac hypertrophy is emerging as a new hallmark of chronic rejection in cardiac grafts, associated with the onset and progression of chronic cardiac allograft rejection in patients [57] as well as experimental systems [51]. Previous findings have revealed an association between elevated IL-6 levels and pathological cardiac hypertrophy [112–116], and increased myocardial IL-6 levels correlate with donor heart dysfunction [117]. Indeed, IL-6 upregulation appears to extend beyond the heart, as several reports have correlated elevated levels of IL-6 in serum with cardiac dysfunction [118–121]. In chronic rejection of murine cardiac allografts transiently depleted of $CD4^+$ cells, IL-6 was required for hypertrophic remodeling, as IL-6-neutralizing mAb normalized contractile parameters and prevented left ventricular wall thickening associated with hypertrophy [51].

IL-6 neutralization was also associated with minimal development of interstitial fibrosis, which might be due to its roles in immune function and hypertrophic remodeling [51]. Although IL-6 might promote fibrosis in chronic rejection indirectly through inflammation and cardiomyocyte hypertrophy, several lines of evidence indicate that IL-6 may itself have profibrotic effects (Figure 2). IL-6 upregulated collagen transcripts in cardiac fibroblast and cardiac myocyte co-culture experiments [122], while IL-6-neutralizing mAbs decreased cardiac fibroblast proliferation [123]. Related activities of IL-6 include enhanced fibroblast survival [124] and augmentation of TGF-β signaling through altered turnover and compartmentalization of its

receptor [92]. In summary, recent findings implicate IL-6 to be an important player in alloimmunity, hypertrophy and fibrosis associated with chronic cardiac allograft rejection. Because IL-6 is involved in so many facets of the disease, it may present a unique target for future studies and perhaps therapeutics.

IL-17

The presence of IL-6 shunts T-cell responses to TGF-β toward the Th17 lineage, while TGF-β in the absence of IL-6 promotes the generation of $Foxp3^+$ regulatory cells [90]. As both IL-6 and TGF-β are tightly associated with chronic rejection, the role of IL-17 in these effects must be considered (Figure 2). Several previous investigations have associated Th17 responses with chronic remodeling pathologies of the lung. First, Th17 responses against collagen type V have been correlated with the severity of obstructive modeling in human lung transplant patients with bronchiolitis obliterans syndrome [125]. More recently, Th17 cellular immune responses have been demonstrated to facilitate lung fibrosis in response to transferred MHC class I immunity [126]. Furthermore, Th17 responses were implicated in the development of inflammation and fibrosis in a murine model of hypersensitivity pneumonitis [127]. Two recent investigations have highlighted a role for IL-17 in chronic rejection of cardiac grafts. In a model of CAV, graft recipients lacking the Th1 transcription factor Tbet had exacerbated vasculopathy associated with enhanced infiltration by IL-17-producing $CD4^+$ cells [128]. More recently, it has been described that *IL-17*$^{-/-}$ mice are protected from fibrosis in a model of chronic cardiac allograft rejection following transient depletion of $CD4^+$ cells [68].

Beyond its roles in the control of immune responses described above, evidence suggests that IL-17 may more directly elicit fibrotic responses. IL-17 has been reported to promote collagen production by primary mouse cardiac fibroblasts [129], and these effects may involve modulation of the balance of matrix metalloproteinases and tissue inhibitors of metalloproteinases [130,131]. A profibrotic role for IL-17 is further supported by the ability of IL-17 neutralization to ameliorate the degree of fibrosis resulting from drug-induced heart failure 130]. Our group has recently reported an association of elevated intragraft IL-17 expression with chronic rejection and fibrosis in response to *TGF*-β gene transfer [55]. Furthermore, cardiac allografts in IL-17-deficient recipients transiently depleted of $CD4^+$ cells develop significantly less fibrosis than wild-type controls [68]. It should be noted that Th17 responses can elaborate the production of IL-6 [132,133], which can directly or indirectly promote ECM accumulation in chronic rejection (Figure 2).

In summary, recent investigations have highlighted a complex interplay between the quadrumvirate of TGF-β, IL-6, IL-17 and CTGF in the pathology of chronic cardiac allograft rejection. Further studies are necessary to better understand both the interrelationships between these cytokines and the associations of each with chronic rejection of cardiac grafts in patients. It should be noted that while individual associations of TGF-β, IL-6, IL-17 and CTGF with chronic rejection of multiple organs have been established, the cytokine interactions discussed here for cardiac fibrosis may or may not be operative in other organs. Indeed, the evolution of hypertrophy and associated responses are likely to be unique to chronic remodeling of cardiac grafts. Hence, advancements in our understanding of these factors and their interrelationships in chronic rejection may facilitate the development of future therapeutics that breach the impasse of chronic rejection and make the transplantation of solid organs an even more effective therapy.

Future perspective

Current immunotherapeutics for transplant rejection have extreme side effects and have generally been ineffective against the development of chronic rejection. By contrast to broad immunosuppressive agents, the ‘holy grail’ of donor-specific tolerance in allograft recipients

remains elusive, although our understanding of the mechanisms underlying immune tolerance is rapidly expanding. Until that goal is reached, targeted therapeutics against the pathologic manifestations of chronic rejection should be considered. Immunotherapeutic agents specifically targeting the factors described herein may provide alternate or supplementary treatments that are more efficacious in ameliorating the hallmark pathologies of chronic rejection. While it is ultimately uncertain whether therapeutics effective for treating the onset and development of chronic cardiac allograft rejection in experimental models will be efficacious clinically, it is clear that these factors have provided targets for future investigations.

Executive summary

Hypertrophy should be considered as a new hallmark of chronic cardiac allograft rejection

- Cardiomyocyte hypertrophy is an indicator of the onset and progression of chronic rejection, evidenced by echocardiographic evaluation of ventricular wall thickening in patients and animal models.
- Echocardiographic analysis of cardiac hypertrophy may provide a noninvasive assay that helps predict the onset and progression of chronic rejection.

CTGF is a downstream mediator of fibrosis in chronic cardiac allograft rejection

- Targeting CTGF may provide a fibrosis-specific therapeutic.
- CTGF neutralization may ameliorate the fibrosis-associated chronic transplant rejection, and may do so without inflicting additional immune disruption to highly immunosuppressed patients.

IL-6 is a critical mediator of chronic rejection

- IL-6 neutralization prevented the onset of hypertrophy and fibrosis in an experimental model of chronic rejection.
- In transplant settings, IL-6 can disrupt established tolerance and promote the induction of Th17 responses.
- IL-6 potentiates TGF-β-mediated induction of CTGF in experimental models of chronic cardiac allograft rejection.

Growing evidence suggests an involvement of IL-17 in the development of chronic rejection pathology, particularly fibrosis

- IL-17 has been associated with the development of multiple fibrotic remodeling pathologies of the lung.
- IL-17 upregulation has been observed in murine models of chronic cardiac allograft rejection. Furthermore, cardiac allografts in *IL-17*$^{-/-}$ recipients display reduced development of interstitial fibrosis.

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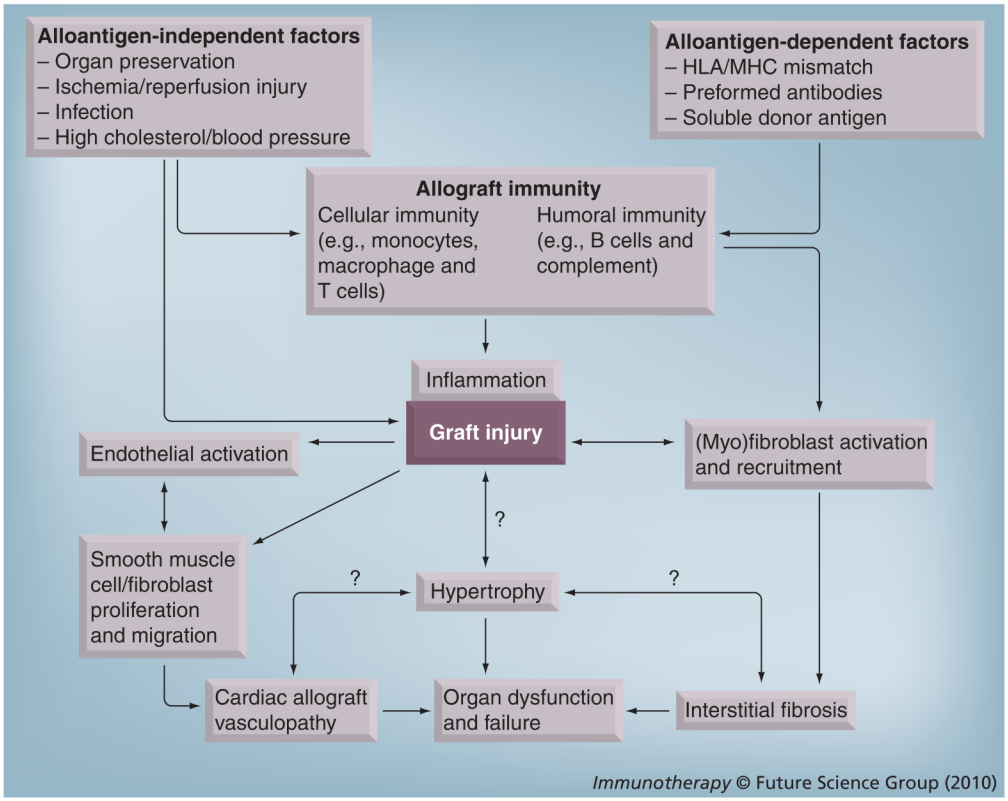

Figure 1. Multiple processes contribute to the development of chronic rejection

Both alloantigen-dependent and -independent factors promote immune responses against allografts and activation of graft endothelium. Complex interplay of these factors results in graft infiltration/inflammation and injury. Injury prompts reparative processes characterized by fibroblast activation and recruitment, as well as proliferation and migration of smooth muscle-like cells in the vasculature. These processes lead to the development of chronic rejection hallmarks of chronic allograft vasculopathy and interstitial fibrosis. Graft hypertrophy, characterized by increased cardiomyocyte size and thickening of the left ventricle wall, accompanies these pathologies, although the interrelationship between these processes is not yet understood. Ultimately, these graft pathologies lead to organ dysfunction and failure.

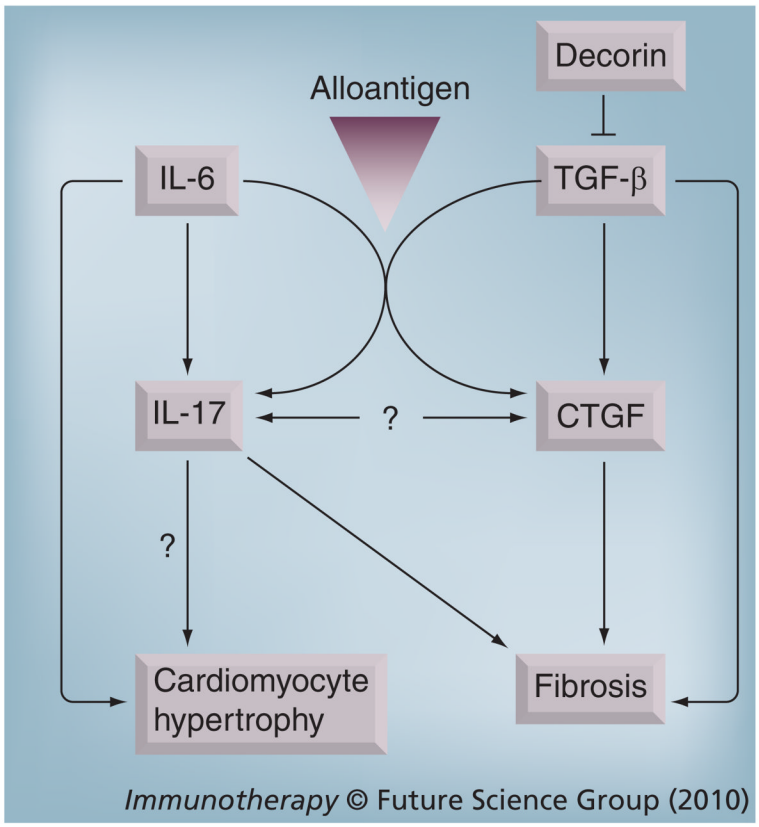

Figure 2. Proposed interactions of TGF-β, IL-6, IL-17 and CTGF in the evolution of cardiac allograft hypertrophy and fibrosis

In the context of alloantigen, TGF-β and IL-6 induce CTGF and IL-17. The relationship between IL-17 and CTGF remains to be established, although both of these factors, along with TGF-β, promote graft fibrosis. IL-6 induces cardiomyocyte hypertrophy, which might involve induction of IL-17.