Front. Med. 2011, 5(3): 248–253
DOI 10.1007/s11684-011-0149-3

REVIEW

Mechanism of arterial remodeling in chronic allograft vasculopathy

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Abstract **Chronic allograft vasculopathy (CAV) remains a major obstacle for long-term survival of grafts even though therapeutic strategies have improved considerably in recent years. CAV is characterized by concentric and diffuse neointimal formation, medial apoptosis, infiltration of lymphocyte or inflammatory cells, and deposition of extracellular matrix both in arteries and veins. Recent studies have shown that stem cells derived from the recipient contribute to neointimal formation under the regulation of chemokines and cytokines. Arterial remodeling in allografts eventually causes ischemic graft failure. The pathogenesis is multi-factorial with both immunologic and non-immunological factors being involved. The immunological factors have been discussed extensively in other articles. This review focuses mainly on the arterial remodeling that occurs in 3 layers of vessel walls including intimal injury, accumulation of smooth muscle-like cells in the neointimal, medial smooth muscle cell apoptosis, adventitial fibrosis, and deposition of extracellular matrix.**

Keywords transplantation; chronic rejection; neointimal; immunology; arterial remodeling; allograft vasculopathy

Introduction

Half a century has elapsed since the first organ transplantation was successfully conducted [1]. At present, transplantation is the mainstream therapy for patients with end-stage organ failure. The rate of acute rejection has been reduced significantly after the introduction of immunosuppressive therapy and tissue matching techniques. However, long-term survival of grafts is still a challenge for doctors. Chronic rejection remains a major cause of late mortality in patients receiving organ transplantation [2]. Elucidating the pathogenesis of chronic allograft vasculopathy (CAV) is vital for establishing proper and effective therapeutic strategies against CAV [3]. Some of the most common and distinctive features of chronic rejection are also presented in CAV. One of them is intimal thickening [4]. Diffusive intimal hyperplasia modifies blood flow, eventually leading to ischemia and loss of function. Recent findings from basic and clinical studies show that CAV is multi-factorial and is regulated by forces interacting at different stages.

Received April 11, 2011; accepted July 7, 2011
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Both immunologic and non-immunologic factors are involved in CAV. Immunologic factors include HLA mismatch and acute rejection. At present, it has been widely accepted that allograft rejection is preceded in a Th1-dependent manner. On the contrary, Th2 phenotype facilitates long-term allograft tolerance and prolongs survival of the transplant organs [5]. The differentiation of $CD4^+$ T lymphocytes into either Th1 or Th2 is determined by various factors, such as the type of antigen presenting cells and the cytokine milieu [6]. IFN-γ plays a key role in the pathogenesis of arterial remodeling. IFN-γ deficient mice are unable to develop the proliferation of arteries intimal [7]. However, IFN-γ is not the only factor involved in the mediation of CAV. Antibodies also play a role in this process in a similar manner [8]. Further evidence shows that $CD8^+$ T cells can promote CAV without other T cell populations. Ablation of either $CD4^+$ or $CD8^+$ T cells only reduces but does not prevent CAV in allografts [9], indicating that both of them are involved in arterial remodeling.

Non-immunologic factors involved in CAV include ischemia/reperfusion [10], virus infections, old donor age and hyperlipidemia. All of these risk factors cause endothelial injury, promote endothelial cell permeability and increase the adhesion of leukocytes [11]. The contributions of these factors to CAV have been discussed comprehensively in other

articles [12, 13]. This review focuses mainly on the views of arterial remodeling that have been put forward in recent years in graft vasculopathy.

Characteristics of CAV

The common and distinctive features of CAV are intimal thickening, medial apoptosis, adventitial fibrosis and deposition of extracellular matrix (Fig. 1). Infiltration of lymphocyte cells and accumulation of macrophages are observed in vascular lesions. Blood flow resistance is associated with the vascular tone (the resistance increases 16-fold with 50% reduction in the radius). Therefore, arterial remodeling in small vessels, capillaries and large vessels is different. Relatively small changes in vascular tone can profoundly influence myocardial perfusion pressures. In the process of CAV development, arterial remodeling occurs in the vascular walls as early as 1 or 2 weeks after transplantation. Unlike native atherosclerosis, calcification and internal elastic lamina rupture are uncommon in CAV [14]. The assault of immunologic and non-immunologic factors lead to body shrinkage, chromatin condensation and formation of apoptotic bodies in intimal and medial cells. The apoptotic bodies are quickly cleared by nearby phagocytes. As the disease progresses, the media is gradually replaced by fibrous tissue [15]. Another key property of CAV is microvascular formation in the neointima. Normally, microvasculature is located only within the adventitia. However, in the neointima of allograft arteries, substantial proliferation of microvessels is observed [16]. Thus, it appears likely that, preceding neointimal formation, vasculogenesis within the intima plays an indispensable role in the progress of CAV. In the following sections, we discuss the individual steps of remodeling in the course of CAV in greater detail.

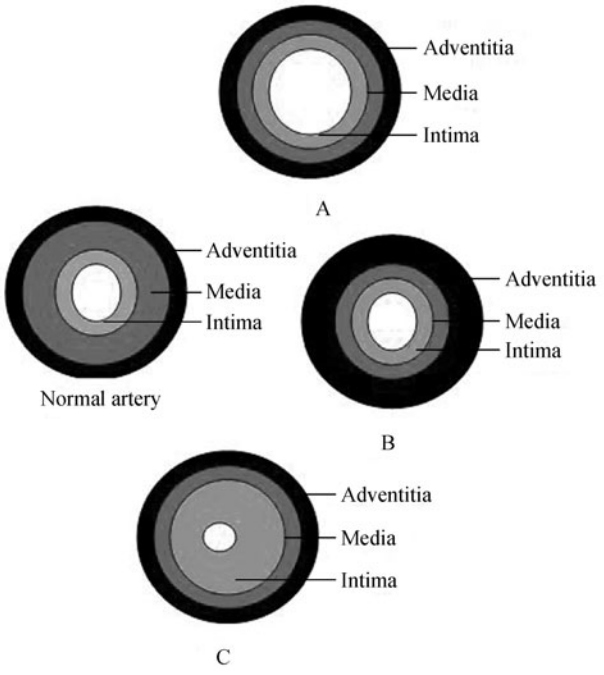

Fig. 1 Types of allograft vascular remodeling. (A) Medial apoptosis and vessel expansion; (B) Constrictive remodeling; (C) Intimal thickening.

Intimal thickening

The intima, located in the innermost vascular walls, consists of a layer of endothelium. It inhabits a basement membrane which overlies a thin extracellular matrix (ECM) substrate. Healthy endothelium inhibits platelet aggregation, maintains hemodynamic stability, and regulates vasodilatation and vasoconstriction [17]. As the first allogenic surface encountered by the recipient's immune system, endothelial cells actively regulate vascular biology. They participate in arterial remodeling and co-agulation. Endothelial cells initiate inflammatory and immunologic reactions by releasing factors that influence cellular growth, death and migration. The integrity of the vascular endothelium is critical for the health of an organ. Disorder of endothelial cells is now regarded as a characteristic feature of chronic allograft rejection.

Immunologic responses, surgical procedures and ischemia/reperfusion of the associated graft can cause endothelial cell damage. Such damages result in the release of endothelium-derived active agents such as endothelin and nitric oxide (NO) [18], which are responsible for hemodynamic disturbance and ischemia of allografts. It has been shown that inhibition of inducible NO synthase expressed in the vessel wall can significantly accelerate intimal hyperplasia [19]. As a major vasodilator released from endothelial cells, NO serves a critical role in the inhibition of platelet aggregation, leukocyte adhesion, smooth muscle cell proliferation, and atherosclerosis via a cGMP-dependent mechanism [20]. NO is also an important mediator in the process of releasing progenitor cells from the bone marrow. However, the role of NO in the pathogenesis of allograft vasculopathy needs further investigation. It has been reported that allograft inflammatory factor-1 (AIF-1), a 143 amino acids long calcium-binding protein secreted by a subset of activated macrophages, plays a central role in endothelial cell activation [21]. Furthermore, there is evidence for a causal relationship between the expression of AIF-1 and activation of signal transduction pathways [21].

Endothelial function can be evaluated using various soluble markers. CD146 is a marker for mature endothelial cells. Woywodt *et al.* found that the number of circulating $CD146^+$ endothelial cells increased in recipients with acute rejection and that their number was also higher in transplant recipients than in healthy control subjects [22]. Therefore, the level of $CD146^+$ endothelial cells in peripheral blood may be used as a biomarker for endothelial damage that might occur

after transplantation.

Role of endothelial progenitor cell

The repair of damaged endothelium occurs not only through proliferation of adjacent endothelial cells, but also through recruitment of circulating endothelial progenitor cells [23]. Endothelial progenitor cells play an important role in re-endothelialization and restoration of injured blood vessels [24]. In CAV, persistent agents promote the recruitment of endothelial progenitor cells, contributing to endothelial expansion. There is a rapid increase in the number of endothelial progenitor cells in peripheral blood after traumatic vascular injury. Normally, these vascular progenitor cells reside quiescently in different locations such as the bone marrow, skeletal and cardiac muscles, the spleen, and normal arterial walls [25]. They mobilize and migrate to sites of damage when activated by injury or other factors. Mobilization of progenitor cells is a part of the response to vascular injury, and is followed by recruitment of these cells to the injured sites, and their differentiation into cells of arterial walls [26, 27]. Accumulating evidence indicate that mobilization of endothelial progenitor cells may help vascular repair. However, it can also be a potential contributor in the development of chronic rejection by altering the immunologic properties of the graft. Chronic replacement of donor endothelial cells by recipient endothelial progenitor cells results in immunologic injury [28]. Progenitor cells can also contribute to the formation of micro-vessels in the neointimal of the allograft. However, the role of the neointimal microvascularization in the development of CAV is still unknown [29]. In the process of neointima formation, the endothelium loses the properties of normal anti-coagulation and anti-thrombogenesis, which facilitates infiltration of inflammatory factors and promotes the expression of transforming growth factor-β1 [30]. It has been proposed that studying endothelial function may provide more prognostic information on the development of CAV after transplantation [13]. Additionally, endothelium injury activates a cascade of immunologic processes. This activation can induce inflammatory reaction, thrombosis, smooth muscle cell proliferation and blood vessel constriction. Many contemporary studies show that there is a direct relationship between vascular endothelial cell loss and allograft function disorder [31].

Smooth muscle cells and smooth muscle-like cells

Proliferation of smooth muscle cells (SMCs) in the vascular intima leads to intimal hyperplasia and thickening. Proliferating cell nuclear antigen (PCNA), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) can be detected in the thickened arterial intima of the allograft. The intimal SMCs have different morphological phenotypes, and gene expression and chemokine receptor expression profiles from medial SMCs. Medial SMCs primarily show contractile property in regulating vascular tone, while neointimal SMCs show embryonic, synthetic phenotypes [32]. Sata *et al*. observed that progenitor cells derived from the host bone marrow do not express the markers for SMCs or endothelial cells when they are attached to the injured vascular sites one week after the physical damage [33]. Instead, they express hematopoietic markers, including CD34, Thy-1, c-kit and flt-3 [34]. We refer to the neointimal SMCs as smooth muscle-like cells (SMLCs) to distinguish them from medial SMCs since there are many important functional differences between them. Migration of medial SMCs, proliferation of pre-existing intimal clones, emigration of adventitial fibroblasts, and infiltration of circulating progenitor cells are potential sources of SMLCs [35]. Traditionally, neointimal SMLCs have been believed to originate mainly from the SMCs of the medial layer [36]. However, this viewpoint has been challenged by recent studies showing that SMLCs are mainly host-derived [37, 38] and bone marrow stem cells attach to the luminal side of injured artery before development of neointimal hyperplasia [33,39]. We performed sex-mismatched bone marrow transplantation from male SD rats to female SD rats and then established the rat aortic transplantation model. Eight weeks after transplantation, aortic grafts were harvested for histological evaluation, immunohistochemistry and Sry gene-specific PCR. The results suggested that recipient bone marrow cells were the major origin of neointimal smooth muscle cells, and they contributed to the neointimal hyperplasia of aortic allografts. It has been reported that the amount of host-derived SMC proliferation in neointima correlates with the number of infiltrating leukocytes and acute rejection [40]. Stem cells have been found to perform similarly as leukocytes in many ways. Like leukocyte recruitment, the migration of stem cells involves chemo-attraction, adhesion and transmigration. The CXCR4 receptor on leukocytes and its ligand CXCL12/sromal derived factor-1 (SDF-1) on endothelial cell or stromal cells seem to play an indispensable part in this process [41]. The role of SDF-1 in mobilization is primarily mediated by its receptor CXCR4. Inhibiting SDF-1 expression by endothelial nitric oxide synthase can suppress SMC proliferation. It has been shown that local presentation of E-selectin and SDF-1 on the luminal side determines site specificity of recruitment and homing [42]. E-selectin expression is induced by injured tissue in endothelial beds. Sackstein and colleagues have reported that CD44, a ligand for E-selectin, promotes efficient adhesive interaction of stem cells with injured vascular endothelial cells. They found that CD44 in stem cells enables them to bind to E-selectin [43]. Other molecules and chemokines that are involved in migration of stem cells to sites of damaged tissue are VCAM-1, ICAM-1, ICAM-2, transforming growth factor-β (TGF-β) and MCP-1 [27, 44]. The amount of host-derived stem cells contributing to graft neointima has not been assessed accurately. A more precise quantitative assessment of stem cells is necessary, because it

determines the need to establish therapeutic regimen to prevent the host-derived stem cell involvement.

Medial apoptosis

Deep in the intima is the medial which is composed of SMCs and ECM. The principle function of medial SMCs is contracting and relaxing to regulate the blood vessel diameter in response to a variety of vasodilators and vasoconstrictors. The traditional view that medial SMCs are relatively quiescent has changed in recent years. Medial SMCs are significant immunological targets and play a dominant role in the progression of CAV [45]. It has been reported that marrow-derived stem cells circulating in the blood are recruited only when the medial is attacked persistently [46]. Current evidence shows that it is the apoptosis of SMCs but not migration that is responsible for medial loss, and the extent of medial injury predicts, to some degree, the extent of intimal thickening. Apoptosis of SMCs is a signal for the differentiation of vascular progenitor cells to compensate for the loss of cells. Matyas reported that IFN-γ, secreted by $CD8^+$ T cells, induces apoptosis of SMCs by activating the Fas/Fasl killing pathway [47]. The events that mediate the destruction of SMCs occur in a loop — they continue to promote arterial remodeling even in the absence of persistent allogeneic exposure after an initial exposure. Nevertheless, the molecular mechanism of SMCs apoptosis in CAV still remains to be established. One hypothesis that has been proposed is that loss of SMCs in media is essential for upregulating SDF-1 expression [48]. SMCs can be changed from quiescent cells into synthetic and migratory ones under the influence of inflammatory factors. Such SMCs show properties of proliferation, migration and synthesis of ECM [49]. Activation and proliferation of SMCs plays a critical role in the formation of neointima. Inhibiting the proliferation of SMCs can therefore significantly reduce CAV [50].

SMCs and endothelial cells can be differentiated from a common vascular progenitor under the regulation of local microenvironment. The molecular mechanisms directing the differentiation of these cells are complicated and poorly understood [51]. Mesenchymal stem cells (MSCs) are characterized by the potential for multilineage differentiation when cued by the appropriate microenvironment. MSCs play an important role in allograft arterial remodeling. Differentiation of MSCs into either SMCs or endothelial cells is significant for the progression of CAV [51]. Once we have a better understanding of the mechanisms of MSC differentiation, we can build a therapeutic strategy to direct the differentiation of progenitor cells for favorable prognosis. Vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β1 are both essential in the differentiation of endothelial cells. However, smooth muscle progenitor cell differentiation is still incompletely understood [52]. TGF-β1, TGF-β3 and platelet-derived growth factor (PDGF)-BB may be involved in this process. PDGF-BB also stimulates SMC proliferation and migration by activating the extracellular signal-regulated kinase (ERK) pathway.

Adventitial fibrosis and ECM deposition

Adventitia, the outer layer of vessel walls demarcated from the media by external elastic lamina, is comprised of fibroblasts, macrophages, and associated ECM. The adventitial layer is also a potential source of progenitor cells that can be differentiated into SMLC. Besides being a supportive tissue, adventitia also directly participates in the regulation of vasomotor tone. However, research on inflammatory response in the adventitia is scarce. The adventitia of CAV is characterized by fibroblasts-to-myofibroblasts conversion, deposition of ECM, and infiltration of inflammatory cells [53]. Endothelin receptors, which are expressed in the adventitial fibroblasts, can induce cell contraction, promote mitogenic activity and enhance ECM formation [54]. The proliferation of myofibroblast and synthesis of ECM are responsible for adventitial fibrosis, which then inhibits lumen expansion. Neurotransmitters secreted by the sympathetic and vagal fibers can decrease vascular tone and partially dilate the vessels when endothelial function is impaired [55]. C-reactive protein, IL-6 and TNF-α contribute to the development of allograft adventitial inflammation and arteriosclerosis [56]. As one of the major components of adventitia, the ECM consists of collagen and elastic fibers. It participates in arterial remodeling by interacting with vascular cells. There is an imbalance between ECM degradation and production when chronic rejection occurs. Initially, ECM degradation neutralizes neointimal thickening and maintains luminal diameter. With the progress of CAV, overexpression of protease inhibitors reduces ECM degradation and thus leads ECM to be deposited in the vessel wall [57]. Moreover, collagenous scarring limits vascular elasticity. TGF-β2 is reported to increase the synthesis of collagen type 1, which represents the most abundant ECM protein in the neointima. Administration of TGF-β2 antibody can decrease ECM protein production [58]. The composition of ECM can be changed by injured endothelial cells. Interestingly, Religa *et al*. observed that activation of medial SMCs was accompanied by increased expression of the ECM proteins fibronectin and osteopontin [4].

Conclusions

Arterial remodeling is a dynamic process. Lumen constriction in CAV results from remodeling in the 3 layers of the vessel wall. Endothelium injury initiates the progress of CAV, followed by the actions of progenitors cells released from different sources. Accumulation of SMLCs in the vascular intima leads to intimal expansion, which is the major cause of concentric vascular narrowing. In adventitia, adventitial

fibrosis deposition of ECM, and infiltration of inflammatory cells limit vascular elasticity, which indirectly contribute to luminal loss. At present, there is no scientific strategy to prevent the progress of CAV in grafts. The molecular mechanisms underlying the mobilization, recruitment and differentiation of host-derived stem cells are complicated and poorly known. Similarly, the mechanisms of immunological and non-immunologic attacks, infiltration by inflammatory cells and turnover of the extracellular matrix are unclear. More efforts are required to further elucidate the etiology of CAV in order to establish preventive and therapeutic strategies.

Acknowledgements

This study was supported by grants from the National Natural Science Foundation of China (No. 30700798) and from the Ph.D. Programs Foundation for Young Teachers of Ministry of Education of China (No. 20070487158). We thank Peng Fu, MM (Department of Cardiac Surgery, Union Hospital, Huazhong University of Science and Technology) for his suggestions.

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