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Impact of Hyperlipidemia on Alloimmunity

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Abstract

Purpose of Review—Hyperlipidemia is a co-morbidity affecting a significant number of transplant patients despite treatment with cholesterol lowering drugs. Recently it has been shown that hyperlipidemia can significantly alter T cell responses to cardiac allografts in mice, and graft rejection is accelerated in dyslipidemic mice. Here we review recent advances in our understanding of hyperlipidemia in graft rejection.

Recent Findings—Hyperlipidemic mice have significant increases in serum levels of pro-inflammatory cytokines, and neutralization of IL-17 slows graft rejection, suggesting that IL-17 production by Th17 cells was necessary but not sufficient for rejection. Hyperlipidemia also causes an increase in alloreactive T cell responses prior to antigen exposure. Analysis of peripheral tolerance mechanisms indicated that this was at least in part due to alterations in FoxP3⁺ T cells that led to reduced Treg function and the expansion of FoxP3⁺ CD4 T cells expressing low levels of CD25. Functionally, alterations in Treg function prevented the ability to induce operational tolerance to fully allogeneic heart transplants through costimulatory-molecule blockade, a strategy that requires Tregs.

Summary—These findings highlight the importance of considering the contribution of inflammatory co-morbidities to cardiac allograft rejection, and point to the potential importance of managing hyperlipidemia in the transplant population.

Keywords

Hyperlipidemia; Cardiac allograft; Rejection

Introduction

Organ transplantation is currently the only treatment for end-stage organ failure, and development of modern immunosuppressive drugs has resulted in impressive one-year survival rates (1). However, elucidating immune and non-immune factors that affect long-

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term organ survival remain some of the most challenging and complex areas of medicine. Indeed, despite the improvements in short-term survival, long-term survival rates have not changed over the last twenty years, and late graft rejection remains a major cause of mortality in patients more than one year after transplantation (1).

The field of transplantation immunology has traditionally relied on the use of inbred animal models to study rejection. However, it is important to recognize that the majority, if not all, of animal models fall short in their ability to model clinical transplantation conditions. For example, standard mouse transplant models do not take into consideration effects on donor organs of brain death or prolonged ischemic time as a result of transplant harvest, factors that can significantly impact rejection and organ survival (2, 3). Nor do standard transplant models address preexisting or concomitant health conditions present in the human transplant population that might affect outcomes. Indeed, transplant patients typically suffer from preexisting health conditions that either result from or lead to systemic inflammation such as diabetes, obesity and atherosclerosis (4). Increased inflammation in the recipient could significantly impact responses to alloantigen, modify mechanisms of rejection and negatively impact long-term survival of the transplanted organ. Consideration of these comorbidities in terms of how they affect rejection and acceptance has not been studied in depth until recently. Analyzing transplant rejection and tolerance induction in the context of concomitant health conditions prevalent in the human transplant population has revealed that our canonical understanding of rejection and tolerance may have to be revised to incorporate the influence of co-morbidities that affect outcomes in transplantation.

Effects of hyperlipidemia on graft rejection in humans

One example of a preexisting or concomitant condition that might affect transplant outcome is hyperlipidemia, a condition affecting a majority of transplant patients (5, 6).

Hyperlipidemia is an increased level of lipids in the blood including increased cholesterol and triglycerides. Increases in serum cholesterol levels, especially the low-density lipoprotein (LDL) fraction, correlates with development of atherosclerosis (7).

Atherosclerotic coronary artery disease resulting in ischemic cardiomyopathy is the cause of end-stage heart disease in approximately 40% of all patients requiring a heart transplant (8). Atherosclerosis resulting from high cholesterol pre- or post-transplant is well understood to be a chronic inflammatory disease (9–17). Humans with atherosclerosis exhibit increased serum cytokine levels, in particular inflammatory cytokines such IL-6, IL-17, IL-18, IL-23, IL-27 and IFN- γ . High levels of cholesterol and triglycerides also develop in 50% of heart transplant patients after the first year of transplant, and as high as 95% of patients within 5 years. (www.nhlbi.nih.gov). In spite of treatment, two-thirds of transplant patients remain dyslipidemic and a significant number of heart transplant patients are statin intolerant (18, 19). The net result is that the majority of transplant patients experience a significant length of time with elevated lipid levels, and therefore any alteration in anti-donor responses will be highly relevant in a clinical setting.

One clue suggesting that hyperlipidemia affects transplant survival can be found in chronic rejection of cardiac transplants. Chronic rejection manifests itself as cardiac allograft vasculopathy (CAV), characterized by obliterative vasculopathy, infiltration of leukocytes,

luminal occlusion, and fibrosis (20). CAV affects approximately 8%, 30%, and 50% of patients who survive 1, 5, and 10 years post-transplant, respectively (1). Survival after development of CAV is significantly lower compared to patients that do not develop CAV (1). Graft failure from CAV accounts for 30% – 50% of deaths of heart transplant patients after one year (20, 21). A major recipient characteristic associated with cardiac allograft rejection after the first year is a history of ischemic heart disease resulting from coronary artery disease caused by hyperlipidemia (8). Several studies have found a direct correlation between dyslipidemia and development of late graft rejection. Increases in the ratio of triglycerides to HDL is correlated with increased frequency and severity of CAV (22). Similarly, preexistent dyslipidemia at the time of heart transplant has been found to be a significant risk factor for the development of CAV (23). Progression of CAV monitored using three-dimensional intravascular ultrasound correlates with increases in total cholesterol and LDL (24). And total cholesterol levels after one year appear to have prognostic value in determining which patients will develop CAV (25). Thus, there is a significant body of evidence suggesting that hyperlipidemia in human transplant patients has effects on allograft survival.

While hyperlipidemia can promote CAV, reducing lipids can reduce incidences of rejection. Indeed, the standard treatment for hyperlipidemia is administration of cholesterol-lowering statins (26). Statins decrease the incidence of acute rejection, improve one-year survival, and reduce the development of CAV (27–43). Although these effects may be related to their ability to lower lipid levels, statins also have immunomodulatory properties that are independent of lipid lowering (44–46). Indeed, statins have immunomodulatory properties in monocytes (34–42) and T cells (36, 37, 47, 48). Nevertheless, although the mechanisms by which statins improve transplant outcome are unclear, it is reasonable to suggest that lipid lowering protects against the effects of hyperlipidemia on transplant survival. However, it is important to point out that because of problems with statin usage, two-thirds of transplant patients remain dyslipidemic and many transplant patients are statin intolerant (18, 19). This raises the clinically relevant issue of whether more aggressive statin therapy, or new approaches to control hyperlipidemia may improve outcomes.

Modeling effects of hyperlipidemia on transplant survival in mice

Most mouse strains commonly used in transplantation studies, such as C57BL/6 mice, have low plasma lipid levels, including low levels of LDL, and do not naturally develop atherosclerosis. When fed a high-fat diet meant to mimic the typical western diet, C57BL/6 mice experience increased blood lipid levels and development of atherosclerotic lesions (49, 50). However, even in mice fed a high fat diet, plasma lipid levels of LDL and VLDL never approach levels observed in humans. Several models of altered plasma lipids have been developed for the study of atherosclerosis, including apolipoprotein E (ApoE) deficient mice (51). ApoE together with apolipoprotein B, are the major protein constituents of low-density lipoprotein (LDL) and very low LDL (VLDL). ApoE mediates the uptake of VLDL particles through the LDL and LDL receptor–related protein (LRP) pathways. Deletion of ApoE therefore results in a large increase in the plasma levels of LDL and VLDL due to the failure to clear lipoproteins from plasma. Ratios of plasma cholesterol, LDL, VLDL, HDL, and triglycerides are more similar to that seen in hyperlipidemic humans (10, 51–53). Feeding

ApoE^{-/-} a high-fat diet leads to a further increase in serum cholesterol (51–54). And, unlike wild-type mice fed a high fat diet, ApoE deficient mice do not become obese or hyperglycemic allowing the study of the effects of high plasma lipid levels without these confounding comorbidities which have been shown to have independent effects on immunity (55, 56).

Several studies have indicated that hyperlipidemic ApoE^{-/-} mice have systemic immune system changes, similar to those seen in hyperlipidemic patients. ApoE knockout mice have increased T-helper type 1 (Th1) and Th17 responses (15–17) and show changes in response to pathogens (57–59). Thus, ApoE^{-/-} mice display immunological changes typical of those seen in humans with atherosclerosis secondary to hyperlipidemia. We therefore used ApoE deficient mice as a model to study the effects of hyperlipidemia on transplant rejection (54, 60). To examine the effects of hyperlipidemia on graft survival, we examined survival of allogeneic hearts heterotopically transplanted into hyperlipidemic recipients. Fully allogeneic heart grafts are rapidly rejected when transplanted into normal recipients. Indeed, BALB/c hearts transplanted into control C57BL/6 recipients were rejected with a median survival time (MST) of eight days. Transplantation of BALB/c hearts into hyperlipidemic recipients resulted in rejection with a MST of six days. These data provided the first indication that hyperlipidemia promotes rejection. However, while this was significant difference, the rapid rejection response made it difficult to study changes in rejection kinetics. We therefore took advantage of a murine model of chronic rejection to study how hyperlipidemia alters transplant rejection in which MHC class II disparate C57BL/6.C-H2^{bm12} hearts (bm12) are transplanted into C57BL/6 mice. Bm12 hearts transplanted into control C57BL/6 mice fed normal chow survived long-term as expected (>100 days) but displayed signs of chronic allograft vasculopathy by day 60 when examined by histology as reported previously (61). In contrast, bm12 hearts transplanted into ApoE^{-/-} mice fed a high-fat diet were acutely rejected and stopped beating with a MST of 21.5 days. Acute rejection in hyperlipidemic hosts resulted from alloreactivity, as syngeneic grafts survived long-term (>100 days). This startling change in the kinetics of rejection was not due to the immunomodulatory effects reported for ApoE (54). ApoE^{-/-} mice fed normal chow rejected bm12 heart grafts more slowly than ApoE^{-/-} mice fed a high fat diet that have much higher blood lipid levels due to diet (55). Thus, rejection appeared to correlate with the degree of hyperlipidemia rather than ApoE status. We further examined whether inducing hyperlipidemia in wild-type mice would affect graft rejection. C57BL/6 mice fed a high-fat diet were hyperlipidemic after four weeks, and exhibited accelerated rejection of transplanted H-2 K^{bm12} hearts. Thus, rejection of heart grafts is accelerated independently of obesity, hyperglycemia, high fat diet and ApoE^{-/-} mutation status, but is correlated with degree of hyperlipidemia. Accelerated rejection of cardiac grafts in mice on a high fat diet has recently been confirmed by a study performed comparing mice on a high fat diet with mice given a low fat diet (62). Together, these data point to a role for hyperlipidemia in transplant rejection.

Mechanisms of rejection in hyperlipidemia

Th1 cells (63–65) are considered the main CD4 T cell subset that mediates rejection (66–69). Th17 cells represent a unique CD4 T cell lineage derived from naïve T cells stimulated

in the presence of TGF- β plus IL-6 or IL-21 (70–84). We and others have suggested that Th17 cells may be involved in transplant rejection, however their role is controversial because the majority of studies implicating Th17 cells in rejection have relied on models with questionable physiological relevance such as T-bet deficient mice (85–99). In hyperlipidemic mice that rapidly rejected transplanted bm12 hearts, we observed an increased frequency of T cells producing IL-17 in the periphery. We also observed that a significant number of graft infiltrating cells observed in bm12 as well as fully allogeneic BALB/c hearts transplanted into hyperlipidemic recipients produced IL-17. Interestingly, IL-17 producing graft infiltrating cells were not observed in hearts undergoing rejection in control recipients. Mechanistically, IL-17 production contributed to rejection as survival of bm12 hearts was significantly prolonged when IL-17 was neutralized, or genetically deleted. These data suggest that the condition of hyperlipidemia promotes a rejection response that involves a TH17 component not observed in mice with normal lipid levels.

Cholesterol in T cell activation

It is well established that T cell activation and clonal expansion require significant synthesis of cholesterol containing membranes (100). T cells accumulate cholesterol either through cellular synthesis or through the uptake of exogenous cholesterol via low-density lipoprotein receptor (LDLR) or alternate receptors (100). Cellular cholesterol is regulated by transcription factors that either promote cholesterol efflux (the Liver X Receptors (LXR α and LXR β)) and degrade LDLR or through factors that promote cholesterol accumulation (the Sterol Response Element Binding Proteins (SREBPs)). The presence of oxidized cholesterol, and cholesterol itself activates LXRs and suppresses SREBPs to maintain cholesterol homeostasis in T cells. When cellular cholesterol homeostasis is perturbed, T cell responses are significantly altered. For example, when ATP-binding cassette transporter G1 (ABCG1) which promotes the cellular efflux of cholesterol is deleted in T cells, ABCG1-deficient CD4 T cells have increased cellular accumulation of cholesterol which results in enhanced TCR signaling (101). SREBP-deficient CD8 T cells display defective proliferation and deficient clonal expansion during viral infection (102). Pharmacological inhibition of ACAT1, a key cholesterol esterification enzyme, leads to increased CD8 T cell cytotoxicity, TCR clustering, and TCR signaling (103). In addition to the effects of cholesterol on T cell proliferation, mounting evidence suggests that cholesterol is involved in TCR mediated signal transduction. Cholesterol binds to the TCR- β chain (104), and the ratio of cholesterol to inhibitory cholesterol derivatives can potentiate TCR receptor mediated activation (105).

Cholesterol has also been shown to play a role in T cell polarization following activation. While oxysterol induced LXR prevents Th-17 T cell generation through inhibiting aryl hydrocarbon receptor-dependent IL-17 transcription (106), several non-LXR agonist oxysterols induce ROR γ t, the master transcriptional element controlling Th-17 development (107). Exogenous supplementation of cultures with these oxysterols result in preferential development of Th-17 cells (107). In addition, regulatory T cells appear to be particularly sensitive to cholesterol for proper function. Inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), which controls cholesterol synthesis, prevents Treg proliferation and impairs Treg function (108). Similarly, specific deletion of ABCG1

increases Treg proliferation (109). In the LDL receptor knockout model of hyperlipidemia increases in the splenic frequency of regulatory T cells was correlated with changes in phenotype, and their functional inability to control atherosclerotic lesion (110).

While lipids such as cholesterol play a role in T cell activation as discussed above, in order to be applicable to patients with hyperlipidemia, it would have to be shown that disruptions in normal cholesterol homeostasis in T cells can be caused by excessive concentrations of exogenous lipid in the plasma. While the connection has not yet been proven, there are several lines of evidence suggesting that in addition to the endogenous pathways of cholesterol control, the uptake of exogenous cholesterol also plays a critical role in T cell mediated immunity. Blocking cholesterol uptake by culturing cells in media depleted of LDL or genetic deletion of LDL receptors reduces T cell proliferation (111, 112), suggesting that lipids must be present in the culture media to facilitate optimal T cell activation. Also, evidence exists that genetic deficiencies in the cholesterol synthesis pathway can be partially rescued by the presence of exogenous cholesterol. Exogenous cholesterol supplementation of T cells deficient in the SREBP can restore both clonal expansion and effector cytokine production, in T cells (102). In vivo administration of squalene, a precursor of cholesterol, to mice also increases membrane cholesterol CD4 T cells, and promotes raft localization of cytokine receptors (113). Given these data, it appears likely that many of the immunological alterations observed in hyperlipidemic mice may be due to effects of altered cholesterol levels on T cell function. It is therefore of major importance to determine whether these functional changes were reversible when lipid level are reduced. In at least one study, it has been reported that the effects of hyperlipidemia on T cell function are indeed reversible. In ApoE^{-/-} mice in which lipid levels were lowered through dietary intervention, it was found that T cell production of IL-10 and IL-12 were decreased in a manner that correlated with cholesterol levels (111).

Effects of cholesterol on antigen presenting cells

As is observed in T cells, cholesterol plays an important role in the maintenance of membrane fluidity essential for proper antigen-presenting cell (APC) function (114, 115). *Abcg1*^{-/-} macrophages, which have impaired cholesterol efflux and elevated cholesterol levels exhibit an intrinsic bias towards “M1” polarization with increased NF- κ B activation (116). Furthermore, *Abcg1*^{-/-} macrophages have been shown to display enhanced proinflammatory cytokine production (117, 118). OxLDL induces autophagosome formation, MHC-II expression, and phosphorylation of SYK in macrophages (119). Several studies have suggested a role for cholesterol in the development and maturation of dendritic cells. Oxidized cholesterol can promote the differentiation of monocytic precursors into phenotypically mature dendritic cells (120). Treatment of dendritic cells in vitro with ox-LDL correlated with the up-regulation of the costimulatory molecules CD86 and MHC-II and the down-regulation of the co-inhibitory molecule programmed death ligand-1 (PD-L1) (121). Thus, alterations in cholesterol transport and metabolism have intrinsic effects on antigen presentation.

However, when antigen presentation is studied in vivo, results have been contradictory. When dendritic cell subsets are isolated from hyperlipidemic ApoE^{-/-} mice, they do not

have altered antigen presenting function (122, 123). It has been suggested that ApoE^{-/-} macrophages are more activated (124, 125), and have reduced scavenging capacity (126). In a model of high fat diet induced obesity, hyperglycemia and hyperlipidemia, increased percentages of CD11c^{high} dendritic cells, CD11c^{low}/MHC II⁺/B220⁺ plasmacytoid DC were found in the spleen, however these cells had decreased stimulatory capacity (127). Similarly, in a recent study, dendritic cells isolated from C57BL/6 mice fed a high fat diet for eight weeks showed no changes in their ability to stimulate CD4⁺ CD25⁻ effector cells *in vitro* (128). Thus overall antigen presentation in hyperlipidemic mice remains unchanged, or slightly impaired. These results differ from a recent study in which antigen presenting cells derived from mice fed high fat diet were suggested to have greater stimulatory capacity *due to upregulation of co-stimulatory molecules* (62). However in this study control mice were fed a low fat diet, rather than normal chow, possibly decreasing the stimulatory capacity of APC from these control mice.

Hyperlipidemia and regulatory T cells

We found a significant expansion of CD4⁺ FoxP3⁺ Treg in hyperlipidemic mice, however, these cells have down-regulated expression of CD25 (60), a finding that resolves the contradictions in previous studies in ApoE^{-/-} mice (110, 129, 130) where authors have reported either increased or decreased frequencies of Treg depending on whether FoxP3⁺CD25⁻ cells were measured. We also observed that Treg derived from hyperlipidemic animals were less suppressive *in vitro* than Treg from C57BL/6 mice fed normal chow. Interestingly, previous studies have also suggested that incubation with OxLDL can significantly reduce the suppressive properties of CD4⁺CD25⁺Foxp3⁺ T cells (130). T cells from hyperlipidemic mice also expressed significantly lower levels of the pro-apoptotic molecule Bim, which has previously been implicated in Treg function (131). Given the importance of Tregs in tolerance induction, we reasoned that alterations in Tregs in hyperlipidemic mice might affect the ability to induce tolerance using approaches that require Tregs, such as costimulatory molecule blockade (132–136). Indeed, costimulatory molecule blockade using CTLA4-Ig and anti-CD154 failed to induce tolerance to fully allogeneic cardiac transplants in hyperlipidemic mice. Insofar as the majority of transplant patients become hyperlipidemic, we hypothesize that hyperlipidemia represents a barrier to costimulatory molecule blockade induced tolerance in patients.

Conclusion: Implications for comorbidities in transplantation

The data suggest that hyperlipidemia profoundly changes the host's immune response to donor antigens, the ability to regulate immune responses and establish immunological tolerance. These studies indicate the importance examining whether similar changes are observed in humans with hyperlipidemia. Furthermore, it raises the important question of whether our inability to improve mortality rates beyond the first year of heart transplantation in the last two decades may be related to a failure to consider how concomitant health conditions affect the transplant population. Conditions such as hyperlipidemia, obesity and hyperglycemia are both prevalent in the human transplant patient, and are known to be pro-inflammatory. These conditions may therefore affect responses to donor antigen and their regulation. If hyperlipidemia leads to similar alterations in humans it may be possible to

improve transplant outcomes by targeting T cell subsets that contribute to rejection in hyperlipidemic hosts, or by developing therapies that allow for maintenance of full Treg function. Indeed, it is possible that the inability to induce tolerance or long-term allograft survival in humans using costimulatory molecule blockade may be due at least in part to the effects of hyperlipidemia on anti-donor responses and the ability to regulate them. While the effects of hyperlipidemia on immune status in humans is poorly understood, it is becoming clear that hyperlipidemia can promote IL-17 responses and inflammation (10, 54, 137). Improving control of hyperlipidemia, or developing new approaches that target novel effectors and promote regulation may allow for the establishment of transplant tolerance.

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- Hyperlipidemia, a common condition in organ graft recipients, can accelerate rejection in a mouse model.
- Hyperlipidemia prevents tolerance induction through co-stimulatory molecule blockade
- Alterations in cholesterol metabolism alter T cell effector function