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Hyperlipidemia and Allograft Rejection

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Abstract

Purpose of review: Advances in the development of immunosuppressive drug regimens have led to impressive survival rates in the year following organ transplantation. However rates of long-term graft dysfunction remain undesirably high. Recently it has been shown that co-morbidities in the patient population may affect graft survival. In mouse models, hyperlipidemia, a co-morbidity present in the majority of cardiac transplant patients, can significantly alter T cell responses to cardiac and skin allografts, and accelerate graft rejection. Here we review recent advances in our understanding of how alterations in lipids affect immune function and graft survival.

Recent Findings: Recent work in humans has highlighted the importance of controlling low density lipoprotein (LDL) levels in transplant recipients to reduce the development of chronic allograft vasculopathy (CAV). High serum levels of cholesterol containing particles leads to extensive immune system changes to T cell proliferation, differentiation and suppression. Changes in B cell subsets, and the ability of antigen presenting cells to stimulate T cells in hyperlipidemic animals may also contribute to increased organ allograft rejection.

Summary: Cholesterol metabolism is a critical cellular pathway for proper control of immune cell homeostasis and activation. Increasing evidence in both human, and in mouse models shows that elevated levels of serum cholesterol can have profound impact on the immune system. Hyperlipidemia has been shown to increase T cell activation, alter the development of T helper subsets, increase the inflammatory capacity of antigen presenting cells (APC) and significantly accelerate graft rejection in several models.

Keywords

Transplantation; T cells; regulatory T cells; co-morbidity

Introduction:

Despite advances in short-term outcomes after transplantation, long-term allograft survival has improved only nominally in the era of modern immunosuppressive regimens. The yearly rate of allograft failure at 5–10 years after transplant changed between 1989 and 2008,

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respectively, from 4.7% to 4.3% for liver, from 10.9% to 10.1% for lung and from 6.4% to 5.1% for heart transplant recipients (1). Hence, elucidating immune and non-immune factors that affect long-term organ survival remains a critical area of research. Recent work modelling co-morbidities present in the human patient population has shown that environmental factors, such as obesity, salt intake, and hyperlipidemia can have significant impacts on the nature of the anti-donor immune response, and on graft rejection (2).

Hyperlipidemia is an increased level of lipids in the blood including increased cholesterol and triglycerides, and is a significant co-morbidity in the organ transplant patient population. 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 (3). Atherosclerosis resulting from high cholesterol pre- or post-transplant is well understood to be a chronic inflammatory disease (4–9) (10). High levels of cholesterol and triglycerides also develop in 50% of heart transplant patients after the first year of transplant, and as many as 95% of patients within 5 years, (www.nhlbi.nih.gov). Thus, the effects of altered lipid levels on immune responses to allogeneic organ grafts will be highly relevant clinically.

Effects of hyperlipidemia on graft rejection in humans

A significant body of evidence suggests that hyperlipidemia in transplant recipients has effects on allograft survival. Dyslipidemia at the time of heart transplant has been found to be a significant risk factor for the development of CAV (11). Increases in the ratio of triglycerides to HDL (12, 13) and LDL level (14) is correlated with increased frequency and severity of CAV while decreases in HDL mediated cholesterol efflux is negatively correlated with development of CAV (15). Hyperlipidemia appears to have prognostic value in determining which patients will develop CAV (16, 17). In addition, the use of lipid lowering agents such as statins can prevent or delay the development of CAV. Statins decrease the incidence of acute rejection, improve one-year survival, and reduce the development of CAV (18–34). Statins significantly lower serum low density lipoprotein (LDL) cholesterol levels, but also have been suggested to have other immunomodulatory properties such as modulation of antigen presenting cell function, T cell activation and cytokine production, and immune cell migration (35–37). Thus it has remained an open question whether the effects of statin treatment on graft survival are mediated through lowering lipid levels, or other immune modulatory effects. A recent study by Harris et al. (38) showed in a retrospective analysis of 194 cardiac transplant patients that LDL levels below 100 mg/dl were associated with delays in the development of CAV. Since 98.5% of these patients were receiving statin treatment, these data suggest that lower lipid levels are intrinsically protective, regardless of the other immunomodulatory effects of statins on development of CAV. Thus, evidence is mounting that elevated lipid levels have negative consequences for cardiac allograft outcomes.

Modeling effects of hyperlipidemia on graft rejection.

Most mouse strains commonly used in transplantation studies, such as C57BL/6 mice, have low plasma lipid levels, including levels of LDL much lower than those observed in humans. 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 (39, 40). However, even in mice fed a high fat diet, plasma lipid levels of LDL and VLDL never approach levels observed in humans. The genetic disruption of a key component of the cholesterol transport pathway, apolipoprotein E (ApoE) results in mice with significantly increased levels of LDL and VLDL, and reduced HDL as seen in hyperlipidemic humans (4, 41–43). ApoE is one of the major proteins low-density lipoprotein (LDL) and very low LDL (VLDL) particles. ApoE mediates the uptake of cholesterol 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. Feeding ApoE^{-/-} a high-fat diet leads to a further increase in serum cholesterol (41–44). 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 (45, 46). Similarly, deletion of the LDL receptor leads to large increases in serum cholesterol. However, LDL receptor is expressed on antigen presenting cells, and it is rapidly upregulated on stimulated T and B cells (47) suggesting that LDL receptor may be involved in adaptive immune responses. In contrast, ApoE is made predominantly by macrophages, but not expressed in T or B cells.

When we studied the effect of ApoE deletion on graft rejection, we found that both fully allogeneic grafts, and MHC class II mismatched grafts displayed accelerated rejection in ApoE^{-/-} mice when compared with wild-type controls. Similarly, both wild-type and ApoE^{-/-} mice exhibited accelerated rejection of allografts when placed on a high fat diet, which increases serum cholesterol. Thus, rejection appeared to correlate with the degree of hyperlipidemia rather than ApoE status. 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 (48). Furthermore, skin allografts in CD8 depleted ApoE deficient mice are more rapidly rejected than in wild type mice (49). Together, these data point to a role for hyperlipidemia in potentiating allograft rejection.

Mechanisms of rejection in hyperlipidemia

While the role of Th17 cells in allograft rejection remains controversial (50–64), we observed a striking increase in the presence of IL-17 producing cells in cardiac allografts in hyperlipidemic mice. Mechanistically, IL-17 production contributed to rejection as survival of bml2 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. Furthermore, we observed an increase in the frequency of regulatory T cells expressing low levels of the IL-2 receptor CD25, and these cells were unable to mediate costimulatory blockade induced tolerance, suggesting a role for decreased T cell regulation in the acceleration of rejection in hyperlipidemic mice. Other reports have suggested that changes to the antigen presentation capacity of APC may exacerbate graft rejection (48, 49). Thus, hyperlipidemia appears to mediate changes to several types of immune system cells required for anti-donor immune responses.

Effects of hyperlipidemia on immune cell activation

T cells

Cholesterol is a critical component of the plasma membrane, and provides structural integrity on the absence of a cell wall. In T cells in particular, cholesterol acts to maintain appropriate membrane fluidity, and regulate the formation of lipid rafts and T cell signaling. Cholesterol can additionally directly bind to the transmembrane domain of TCR- β chain to mediate TCR clustering on T cell surface, which can increase the avidity of TCR to foreign antigens and therefore augment TCR signaling (65). So, the presence of cholesterol can affect multiple aspects of T cell biology – proliferation, migration and T cell signaling.

T cells obtain cholesterol in a tightly controlled fashion, both through de novo cellular synthesis of cholesterol and through the uptake of exogenous cholesterol present in serum. There are at least two families of cholesterol sensing proteins in T cells that modulate this process. Sterol regulatory element-binding proteins (SREBP) reside on the membrane of the endoplasmic reticulum until their activation by low cholesterol levels, when they are ultimately transported to the nucleus. There they control gene expression of a variety of components of the cholesterol pathway including hydroxymethylglutaryl (HMG)-CoA reductase (*HMGCoR*) which controls cholesterol synthesis and the LDL receptor (*LDLR*) and enhances uptake of endogenous cholesterol. When cellular cholesterol levels become high enough, the cholesterol sensing liver X receptors (LXR α and LXR β) are activated, and regulate the expression of various negative modulators of cholesterol synthesis and uptake, such as sterol transporters ATP-binding cassette transporters (ABCA1/ABCG1) which promotes efflux of cholesterol from the cell, and upregulation of the inducible degrader of the low density lipoprotein receptor (IDOL), thereby suppressing exogenous cholesterol uptake.

Disruption of normal cholesterol homeostasis can fundamentally alter the T cell immune response. Genetic deletion of ABCG1, preventing LXR mediated control of cholesterol content, increased the cellular cholesterol content, and resulted in increased proliferation of CD4 T cells upon TCR stimulation (66, 67). Paradoxically, when ABCA1 was specifically deleted in T cells, no changes were seen in CD4 T cell proliferation while the frequency of Treg drastically increased (68). This suggests a role for T cell extrinsic factors in the whole body knockout that are not present in T cell specific knockouts.

In contrast to genetic deletion of ATP-binding cassette transporters, which promotes cholesterol accumulation in T cells, activation of LXR using LXR agonists decreases cellular cholesterol. Pharmacological activation of LXR prevents pro-inflammatory T cell polarization while increasing Treg differentiation and suppressive capacity (69). Pharmacological activation of LXR inhibits Th-17 cell development and proliferation, an effect that can be overcome by the addition of mevalonate, a cholesterol precursor (67, 70, 71). Activation of LXR can not only decrease effector T cell responses but also inhibit IL-23 receptor and IL-17 expression (71).

These studies have demonstrated that T cells are profoundly affected by alteration of intrinsic pathways that control cholesterol content. Similar effects on T cells of increased

serum cholesterol, as would be observed in hyperlipidemic patients, have also been demonstrated. As in T cells genetically modified to accumulate cholesterol, exposure to excess serum cholesterol appears to modify the differentiation of specific T cell subsets. The addition of exogenous oxysterols to cell cultures results in a preferential development of Th-17 cells (72), and our studies in hyperlipidemic ApoE^{-/-} mice indicate an increase in Th17 mediated rejection in mice with high serum cholesterol levels. A recent report demonstrated a significant effect of cholesterol modification on IL-9 producing CD8 T cell differentiation. Addition of cholesterol to cell cultures activated LXR sumoylation and reduced IL-9 production through p65 (73). Treatment of cells with β -cyclodextrin to reduce cellular cholesterol enhanced Tc9 differentiation, IL-9 production and Tc9 cell persistence and anti-tumor activity in vivo. While the focus of this study was Tc9 cells, the authors also noted a modest effect on IL-9 production in Th9 CD4 T cells. This suggests that cholesterol-mediated suppression of IL-9 expression through LXR may more generally suppress IL-9 production. Since IL-9 has been suggested to be critical for the maintenance of graft specific tolerance (74), and enhances the suppressive function of Treg (75) these studies suggest a potential role for hyperlipidemia in preventing tolerance induction.

Similarly, serum cholesterol has also been shown to affect regulatory T cells (Treg). In hyperlipidemic ApoE^{-/-} and LDLR^{-/-} mice, the frequency of FoxP3 expressing cells increases (76–78). However, Treg from these mice express low levels of IL-2 receptor, increased Akt activation, and decreased function (79). Recently it was shown that exogenous oxidized LDL cholesterol can reduce the differentiation of Treg in vitro through limitation of available IL-2 (80). Treg from ApoE^{-/-} mice fed a high fat diet, have a substantially increased frequency of Treg that lose FoxP3 expression and suppressive capacity when compared with ApoE^{-/-} mice with lower levels of hyperlipidemia. This conversion from regulatory T cell to effector T cell could be reduced in vivo by increasing the efflux of cholesterol through the addition of apolipoprotein A-I, which promotes cellular cholesterol efflux (80). Together these data suggest that in the presence of high serum cholesterol, Treg have decreased suppressive function, leading to increased effector T cell proliferation in hyperlipidemic mice (76, 81). Importantly, these effects appear to be reversible with reduction of serum cholesterol. When lipid levels were lowered in ApoE^{-/-} mice through dietary intervention the presence of inflammatory T cells in atherosclerotic plaque was decreased, and IL-10 and IL-12 expression in CD4 and CD8 T cells was also decreased (81). That the changes to T cell differentiation, proliferation and regulation may be reversible through lowering cholesterol levels has significant implications for clinical care of organ transplant recipients with hyperlipidemia.

B cells

With the development of powerful immunosuppressive drugs targeting T cell activation, the role of B cells in promoting graft failure has become more apparent. Numerous clinical studies have highlighted the role of generation of anti-donor specific antibodies in the decline of graft function over time (82). Cardiac transplant recipients who experience antibody mediated rejection have an almost 10-fold increase in the incidence of CAV compared with patients who only experience cellular rejection without antibody production (83). Preemptive B cell depletion can decrease the incidence of chronic graft rejection in a

non-human primate model (84) B cells may also play a role in antigen presentation to alloreactive T cells, and the development of memory T cell responses (85). Thus it is apparent that B cells can play a significant role in allograft rejection, raising the question of whether changes in lipid levels affect this population.

Recent evidence has shown that significant alterations in B cells subsets and activation can be observed in hyperlipidemic mice (86). Increasing levels of serum cholesterol were correlated with an increase in B cell activation including higher surface expression of CD80, CD86, and CD40. When ApoE $-/-$ mice were fed a high fat diet, significant increases in the basal level of IgG in the serum were noted when compared with either ApoE $-/-$ or wild type mice fed a normal diet, indicating that IgG levels rise in concert with levels of hyperlipidemia, which may be of particular interest in the setting of antibody mediated graft dysfunction. Further study of B cell subsets in hyperlipidemic mice indicate that while at 6 weeks of age, wild type and ApoE deficient mice have similar B cell subset distribution, by 24 weeks of age, the hyperlipidemic mice demonstrate a two fold increase in the total number of marginal zone B cells in comparison with wild type mice (87). Marginal zone B cells have been implicated in the generation of T independent antibody responses to lipoproteins (88) and xenoantigens. Recently, it has been reported that marginal zone B cells upregulate the immunoregulatory ligand PDL1, and control T follicular helper differentiation and activation in response to high cholesterol diet (89). While only MZB cells were altered in these studies, it is interesting to note that resting MZB express the LDL receptor CD36, unlike follicular B cells which only upregulate CD36 following activation (90). It remains to be determined what effect ligation of CD36 in the presence of excess LDL might have on activated B cells.

Macrophages

The role of macrophages in hyperlipidemic mice has been intensively investigated as the causative agents in the development of atherosclerosis in mice with high lipid levels. Like T cells, macrophages in which cholesterol efflux has been impaired by genetic deletion of ABCA1 have an increased pro-inflammatory phenotype, NF- κ B activation and pro-inflammatory cytokine production (91–93). Genetic deletion of the ABCA1/G1 cholesterol efflux proteins in macrophages increases production of IL-1 and IL-18 via activation of the NLRP3 inflammasome pathway, and increased accumulation of neutrophils at the site of atherosclerotic plaque, indicating that elevated cholesterol levels in macrophages triggers systemic inflammation (94).

Macrophages are critical mediators of cholesterol clearance, and efficiently phagocytose oxidized LDL. Therefore, substantial work has been done examining the changes to macrophages as a result of cholesterol uptake in high lipid environments. Macrophages are a major cellular source of ApoE production, along with the liver, and deletion of ApoE increases macrophage activation (95). Conversely expression of ApoE on mouse macrophage cell lines induces more anti-inflammatory M2 macrophages (96). Production of inflammatory cytokines such as tumor necrosis factor and interferon gamma act to downregulate ApoE production by macrophages, and increase their ability to stimulate T cell activation (95).

Mindin/spondin 2 is an extracellular matrix (ECM) component that is a pattern-recognition molecule for microbial pathogens (97), serves as an integrin ligand and is involved in inflammatory cell recruitment (98). A recent report has demonstrated that mindin plays a role in macrophage cholesterol homeostasis, and that Mindin directly suppresses LXR β (99). Suppression of LXR by mindin prevents cholesterol efflux, and promotes macrophage expression of pro-inflammatory genes (99). This observation directly connects innate immune mediators with the control of cholesterol homeostasis in immune cells.

Dendritic cells

While the reported effects of hyperlipidemia on macrophages are almost uniformly pro-inflammatory, the effects on dendritic cells are less clear. Oxidized LDL can promote the maturation of monocyte precursors into mature dendritic cells and increase the expression of MHC class II and the co-stimulatory molecule CD86 (100). However, when the ability of dendritic cells to stimulate T cells in vivo was analyzed there was no significant difference when cells derived from LDL receptor or ApoE knockout mice fed a high fat diet were compared (101). In contrast, it was recently reported that an increase in cellular cholesterol as a result of ApoE deficiency increases the antigen presentation capacity of dendritic cells, and increases localization of MHC class II to lipid rafts in dendritic cells (49). This study also reports that DCs from human carriers of the ApoE4 isoform exhibit increased cellular cholesterol levels and mediate increased polarization of naive CD4 T cells toward the effector memory phenotype. These results build on the previously reported increased antigen presenting capacity of APC from ApoE $-/-$ mice, although this study implicated changes in lipid raft components rather than increased co-stimulatory molecule expression (48). Thus, the effects of high serum cholesterol levels on dendritic cells would benefit from more study.

Neutrophils

Neutrophils are one of the first types of lymphocytes observed infiltrating transplanted organs (102). Neutrophils can migrate to lymph nodes, present MHC-II restricted antigens and crosspresent endogenous antigen to prime cytotoxic CD8 cells (103, 104). It has been reported that bacterial infection can upregulate co-stimulatory molecules on neutrophils and precipitate lung allograft rejection (105). While a role for neutrophils in graft rejection in hyperlipidemic recipients has not been described, as discussed above, increased serum cholesterol promotes Th17 responses and IL-17 promotes endothelial production of neutrophil chemoattractants CXCL1, CXCL2, and CXCL5 (106), suggesting this cell type may be preferentially recruited to grafts in hyperlipidemic recipients. Neutrophils also produce the serine protease Neutrophil Elastase (NE), and NE is upregulated in the serum and aortas of hyperlipidemic mice. Wen et al. demonstrated that NE promotes cholesterol accumulation in macrophages through ABCA1 degradation (107). Thus neutrophils may play a role in the immune changes to macrophages observed in hyperlipidemic mice as a result of increased cholesterol levels.

Conclusion:

As these studies clearly indicate, hyperlipidemia, a co-morbidity present in a majority of transplant patients, has profound effects on multiple immune system cells. The culmination

of these changes is a potentiated alloimmune responses that leads to increased rejection. One major implication of this research is the necessity of taking inflammatory comorbidities into consideration when attempting to develop clinically beneficial immunomodulatory therapies. In mouse models for example, hyperlipidemia appears to decrease the effectiveness of co-stimulatory blockade in the induction of immune tolerance. Further investigation into the changes effected by hyperlipidemia in human patients, and the degree to which these changes are reversible under normal lipid conditions may allow for improved efficacy of immune intervention. One of the major roadblocks to the development of effective immunotherapy has been the difficulty of translating approaches which have been tremendously effective in animals, into humans where frequently these therapies fail to result in durable graft survival. Increases in our understanding of the effects that co-morbidities, present in humans and absent in most animal models, have on immune function suggest that a better comprehension of the mechanisms of these changes may lead to more successful translation of clinically effective treatment modalities.

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Conflict of Interest

John Iacomini and Jessamyn Bagley report grants from the NIH and the American Heart Association. Christian Rosa Birriel and Linus Williams declare grants from the NIH. Michael Hyde declares grants from the NIH and the FASEB.

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•• Of major importance

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