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Infection, Rejection, and the Connection

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Abstract

Solid organ transplantation is a life-saving treatment for people with end-stage organ disease. Immune-mediated transplant rejection is a common complication that decreases allograft survival. While immunosuppression is required to prevent rejection, it also increases the risk of infection. Some infections, such as cytomegalovirus and BK virus, can promote inflammatory gene expression that can further tip the balance toward rejection. BK virus and other infections can induce damage that resembles the clinical pathology of rejection, and this complicates accurate diagnosis. Moreover, T cells specific for viral infection can lead to rejection through heterologous immunity to donor antigen directly mediated by anti-viral cells. Thus, viral infections and allograft rejection interact in multiple ways that are important to maintain immunologic homeostasis in solid organ transplant recipients. Better insight into this dynamic interplay will help promote long-term transplant survival.

Introduction

Allograft rejection is a major cause of graft damage and loss, with up to 25% of solid organ recipients experiencing rejection by the end of the first year after transplantation.[1-4] There are two main types of rejection, T cell mediated rejection (TCMR) and antibody-mediated rejection (AMR). TCMR is caused by infiltration of donor-reactive CD4 and/or CD8 T cells into the allograft, with concomitant inflammation and tissue damage.[5] AMR is caused by donor-specific antibodies (DSA) binding to the allograft endothelium, activating complement, and recruiting leukocytes that induce graft damage.[6] Chronic rejection is commonly associated with end stage disease in the allograft, and therefore is referred to as chronic allograft injury for kidney, cardiac allograft vasculopathy for heart, vanishing bile duct syndrome for liver, and chronic lung allograft dysfunction for lung.[7-12]

Rejection can also be categorized as hyperacute, acute, and chronic, which manifest at varying times post-transplant. Hyperacute rejection is rejection caused by pre-existing

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DSA, and occurs within hours of transplantation. It is exceedingly rare in the current era where panel-reactive antibody screening and histocompatibility testing are sophisticated and routine.[13,14] Acute rejection can occur at any time post-transplant but is most common within the first year. Recovery from acute rejection is variable depending on the severity and ability to treat promptly; acute rejection is a major risk factor for subsequent chronic rejection.[15] Chronic allograft rejection occurs months to years after transplantation. Chronic rejection causes graft vascular disease and is a leading cause of late graft failure.[16]

Rejection occurs through 3 primary T cell mediated pathways. The direct pathway involves direct recognition of donor allo-major histocompatibility complex (MHC) on donor cells and is commonly responsible for acute rejection. The majority of donor antigen-presenting cells die within weeks of transplantation, limiting the timeframe of this pathway.[17] The indirect pathway involves presentation of processed alloantigen on self-MHC. Chronic rejection is commonly mediated by the indirect pathway. The third pathway is semi-direct, in which donor MHC is presented intact on recipient antigen presenting cells.[18,19]

Advances in immunosuppressive therapies have significantly decreased the incidence of acute rejection.[20] However, escalation of cumulative immunosuppression also increases the risk of infection, and infection can contribute to allograft rejection both directly and indirectly. For instance, uncontrolled cytomegalovirus (CMV) infection is associated with elevated risk of acute rejection.[21] BK virus directly damages kidney allografts.[22] Other infections such as Epstein Barr virus (EBV) and adenovirus also contribute to rejection. Post-transplant infections are commonly treated through reduction of immunosuppressive therapy, which can indirectly increase the risk of acute, subacute or chronic rejection.[22-24] Because immunosuppression reduction is common to all viruses and the mechanism is straightforward, we do not discuss it separately for each virus. Of note, this treatment protocol is not standard of care for all infections, but is commonly selected as therapy for many viral infections without direct study of its efficacy. Interestingly, immune cross-reactivity to allograft and viral antigens can also result in pre-existing immune cells directing so-called heterologous responses to the allograft.[25] Potential viral-associated mechanisms of rejection are detailed below by infectious agent.

Cytomegalovirus

CMV is a DNA virus in the herpes family, which infects ~60% of people in the United States by adulthood.[26,27] It is a major infectious risk factor in transplant recipients.[28] After immune control, CMV establishes latency for the lifetime of the host and periodically reactivates, requiring an ongoing effective immune memory response to control it.[29,30] Recipients with no history of CMV infection (CMV seronegative) who receive CMV seropositive organs are considered at high risk of post-transplant CMV infection, with seropositive recipients at moderate risk.[31,32] CMV viremia, defined as detectable CMV virus in blood, is detected in up to 30% of kidney transplant recipients.[28,33] CMV disease resulting from uncontrolled viremia is associated with CMV syndrome and end organ disease including gastrointestinal disease, pneumonia, hepatitis, retinitis, and invasion of the allograft, with increased risk of allograft loss.[34,35] Thus, control of CMV infection is an important aspect of post-transplant health management.

In addition to the nonimmunological risks associated with CMV reactivation, this virus also increases the risk of allograft rejection (Table 1). Specifically, CMV viremia is associated with increased risk of acute rejection.[21,36-42] Consistent with this association, CMV antiviral prophylaxis and surveillance with pre-emptive therapy decrease the risk of rejection.[41,43-45] However, one large kidney transplant study indicates that CMV contributes to acute rejection only in recipients receiving 3-drug maintenance immunosuppression.[46] CMV infection (viremia or disease) and acute rejection are associated with other risk factors such as advanced donor age and delayed graft function, potentially confounding analysis of the relative contribution of CMV disease in registry-based clinical studies.[46] Therefore, further study will be important to contextualize the role of CMV relative to delayed graft function and other known factors associated with rejection.

CMV manipulates protein expression of infected and bystander cells in multiple ways that can directly increase the chance of acute rejection. First, CMV upregulates expression of adhesion molecules on infected cells, which can increase leukocyte infiltrate and inflammation in an allograft.[47] In rat models, CMV upregulated ICAM-1 expression in allograft tissue, leading to increased infiltration of inflammatory leukocytes.[48,49] Upregulated expression of adhesion molecules in allograft tissue has also been observed in human transplant recipients with CMV infection and rejection.[50] Second, CMV has complex effects on expression of MHC, a major alloantigen. CMV can downregulate MHC class I expression on infected cells by blocking intracellular transport, targeting MHC molecules for degradation, and blocking peptide loading of MHC.[51] CMV also downregulates MHC class II expression in infected monocytes by reducing MHC class II transcription, thereby limiting detection of CMV by CD4 T cells.[52] In contrast, uninfected bystander cells in infected tissues can upregulate MHC class I expression, likely in response to inflammatory infiltrate and cytokines. This bystander upregulation is hypothesized to provide a mechanism for CD8 T cells to control CMV despite cell-intrinsic decreases in MHC in infected cells, as high-MHC expressing bystander cells may be able to present CMV antigen to the T cells.[51] CMV infection can also upregulate MHC class II expression in allograft endothelium, again potentially enhancing allograft antigen presentation.[47,53] MHC class II upregulation is interferon (IFN) γ independent, and can be inhibited by ganciclovir, leading to the hypothesis that CMV DNA replication leads to the MHC class II upregulation.[53,54] Thus, through both direct and indirect effects, CMV can increase or decrease MHC expression, and the imbalance of these opposing activities can lead to lack of viral control or potentially rejection if the upregulation predominates.

CMV induces changes in immune cell activity that can promote rejection. For instance, CMV viremia induces highly inflammatory and cytotoxic cellular responses in transplant recipients, including natural killer (NK) cells, CD8 T cells and $\gamma\delta$ T cells.[55,56] CMV also has been associated with accelerated CD8 T cell aging after transplantation.[57,58] Aged CD8 T cells have a highly differentiated pro-inflammatory phenotype that can contribute to mortality in the aged.[59,60] T cell aging also involves accumulation of memory cells, altered MHC expression, and impaired regulatory T cell function, each of which can contribute to increased risk of rejection.[61] Thus, the T cell phenotypes observed in transplant recipients are associated with poor outcomes that could contribute to rejection. In addition, T cells that are cross-reactive for CMV and alloantigen have been detected in blood and kidney

of kidney transplant recipients, though they have yet to be proven to directly contribute to rejection.[62] This mechanism is discussed in greater detail in the later section on heterologous immunity. Of note, CMV has also been associated with decreased alloreactivity after liver transplant through upregulation of inhibitory receptor CD244, in contrast to the many other findings associating CMV with enhanced rejection.[63] The mechanism by which CMV contributes to acute allograft rejection is incompletely understood, so further study will be of great interest.

In addition to increasing the risk of acute rejection, CMV is associated with increased risk of chronic allograft rejection. Chronic rejection is often characterized as antibody-mediated with CD4 T cell help, and donor/recipient mismatch of HLA-DQ and -DR is associated with increased risk of DSA formation.[17] Of note, chronic rejection is commonly mediated through indirect and semi-direct MHC class II recognition by CD4 T cells, indicating the MHC class II modulation described above for acute rejection may impact chronic rejection as well.[18] Chronic rejection in the kidney results in interstitial fibrosis and tubular atrophy. Kidney transplant recipients with both acute rejection and CMV disease are potentially at elevated risk of chronic rejection compared to those with only acute rejection or CMV disease.[64] One study found elevated risk of chronic allograft injury in kidney transplant recipients who developed CMV disease within 12 weeks of transplantation;[65] another study found no association of CMV and chronic rejection risk.[66] In heart transplant recipients, chronic rejection is characterized by arteriosclerosis.[67] CMV infection increases the risk of arteriosclerosis after heart transplant, and this risk is mitigated by antiviral prophylaxis.[68] In liver transplantation, chronic rejection is characterized by bile duct atrophy and loss, and persistent CMV infection is a major risk factor.[10] In lung transplantation, chronic rejection is characterized by progressive airway obstruction that cannot be explained by acute rejection or infection.[36] Treatment with antiviral prophylaxis decreases the incidence of chronic rejection of the lung.[36] Rat models of chronic rejection have found that CMV accelerates chronic rejection of both aorta and kidney allografts.[7,69] In a heterotopic aortic allograft model, CMV infected grafts had elevated adhesion molecules, infiltration of inflammatory cells, and induction of tissue growth in the graft, suggesting that these pro-inflammatory factors contributed to rejection.[7,70] The kidney model demonstrated increased inflammation, macrophage infiltration, and fibrosis associated with CMV infection.[7] Thus, CMV is a significant contributor to chronic allograft rejection, with antiviral prophylaxis playing a major role in prevention across transplant types.

Another mechanism by which CMV is linked to chronic rejection is through macrophage infiltration. Monocytes, a macrophage precursor, are frequently infected with CMV.[71,72] In fact, CMV alters monocyte gene expression to a more pro-inflammatory state.[73,74] A rat CMV (RCMV) model of accelerated chronic rejection found upregulated chemokine expression in RCMV-infected allografts, concomitant with elevated T cell and macrophage infiltration and formation of tertiary lymphoid organs containing macrophages and T cells.[75,76] In the same rat model, pretransplant depletion of macrophages from CMV-infected cardiac allografts delayed the development of chronic rejection and extended graft survival.[77] Whole-genome transcriptional analysis from human kidney transplant biopsies found an inflammatory macrophage gene signature that correlated with both higher degree of subclinical allograft injury, and subsequent development of chronic rejection.[78] Thus, the

pro-inflammatory states induced by CMV-infected monocytes and macrophages contribute to chronic rejection.

Clinical implications of the role of CMV in rejection are multifold. First, monitoring and controlling CMV viral load is important to evaluating and mitigating the risk of allograft dysfunction and decline. Second, the risk of rejection suggests that matching donor to recipient for CMV serostatus may be appropriate to reduce rates of rejection.[79] Third, the findings on antiviral prophylaxis reducing rejection rates suggest that more extensive antiviral prophylaxis may be appropriate as a preventative measure for rejection. Indeed, prolonged CMV prophylaxis has been shown to significantly reduce the risk of chronic rejection in lung transplant recipients.[80,81] Each of these clinical implications is important to evaluate transplant health and therapies, and further study of rejection risk in particular will be very valuable.

BK Virus

BK virus (BKV) is a polyomavirus and a major infectious complication of kidney transplant, which infects >80% of people by adulthood.[82] BKV establishes latency in kidney tubular epithelia and bladder cells.[83,84] In healthy individuals, NK cell, CD4 T cell, and CD8 T cell cytotoxicity controls BKV infection.[85,86] Antibodies to BKV play an important role in control of primary BKV infection, but do not protect against BKV in secondary responses.[86,87] Self-resolving BKV infection in transplant recipients has been associated with rapid induction of BKV-specific IFNγ-producing T cells, and the presence of BKV-specific T cells early post-transplant correlates with protection against viral replication .[88] Multiple components of the immune system contribute to protection against BKV, but T cells appear to be the most important to memory responses.

BKV and other polyomaviruses have been associated with disease in immunocompromised and immunosuppressed people.[84] Immunosuppression can impair control of BKV leading to uncontrolled viremia and BK Virus Nephropathy (BKVN).[89] BKVN is characterized by viral shedding in the urine, detectable virus in kidney biopsy, direct viral cytopathic effects, interstitial inflammation and tubular atrophy.[84] In consequence of the kidney damage, BKVN increases the risk of allograft loss in both adult and pediatric kidney recipients (Table 1).[90,91] Higher BKV viral load and donor BKV infection have been associated with increased risk of BVKN in kidney recipients.[92,93] BKVN occurs predominantly in the context of kidney transplantation.[92] While the mechanism of specificity of BKVN to kidney transplantation is unknown, one hypothesis is that BKVN results when the recipient receives an different strain of BKV from the donor, with the result that recipient immunity cannot control the re-infection with the new strain. Because of kidney tropism of BKV, this mechanism would not affect transplantation of other organs.[94] BKV is a major cause of chronic kidney disease in kidney transplant recipients, with some evidence in other transplant types.[95] For example, liver recipients with chronic kidney disease have much higher rates of BKV viremia and viruria than liver recipients without chronic kidney disease.[94]

Recent studies have shown that BKVN is associated with elevated expression of immune related genes, including chemokine receptor signaling, suggesting that these proinflammatory genes promote the kidney damage associated with BKVN.[96] Specifically, CXCL10 and STAT1 were upregulated, both of which are associated with activated T cell responses.[96] A higher degree of HLA mismatch between donor and recipient is associated with elevated risk of both BVKN and acute rejection, suggesting that inflammatory pathways involved in rejection could also contribute to development of BKVN and vice versa.[97]

BKVN also complicates the diagnosis of acute rejection because the associated kidney pathology is very similar to that of rejection. Biopsy immunophenotype in BKVN and rejection are largely similar, but there may be greater infiltration of B cells and lower infiltration of T cells in BKVN specifically.[98] This is consistent with the high importance of T cell memory and lower importance of B cell memory to protective from BKV reactivation. Detection of SV-40 stain and BK viral load are crucial in distinguishing the two pathologies.[99,100] BKVN also may occur on a different time frame from acute rejection, with rejection occurring typically within the first 6 months and BKVN occurring around 1 year post-transplant.[100]

A major clinical implication of BKV is the importance of identifying the appropriate therapies in various settings. For instance, tacrolimus and prednisone treatment have been associated with risk of BKVN.[101] Tacrolimus has been associated with higher risk of BK viremia than cyclosporin A.[102,103] However, one recent study found that everolimus treatment with reduced dose of tacrolimus actually increased BK viremia rates relative to the standard dose of tacrolimus.[104] Thus, more study is needed to identify the most effective immunosuppression to prevent BKVN, if one exists. Studies addressing the efficacy of combined immunosuppression and antiviral therapy indicate that in cases where reduction of immunosuppression leads to rejection, this may be an appropriate therapy.[105,106] Management of BK nephropathy, BK viremia and BK viruria remains underexplored, especially in populations with high immunologic risk for rejection.

Epstein Barr Virus

In addition to CMV, another herpes family virus with implications for rejection is EBV, which infects over 90% of human adults.[107] Elevated immunosuppression for treatment of rejection can induce EBV viremia.[108] Lytic EBV infection has also been correlated with late acute rejection, though it remains to be determined whether EBV preceded rejection or vice versa (Table 1).[109] In addition, EBV causes another major complication of transplantation, post-transplant lymphoproliferative disorder (PTLD). PTLD is defined as abnormal proliferation of lymphoid cells in recipients of hematopoietic stem cell or solid organ transplantation, but is most commonly characterized by proliferation of EBV-infected B cells.[110] Upon infecting a B cell, EBV expresses genes LMP1 and 2A that mimic co-stimulatory and B cell receptor (BCR) signaling to drive proliferation and survival of the infected cells.[111] While sometimes benign, the proliferation in PTLD can drive malignant lymphoma.[110,112] EBV seronegative recipients of EBV seropositive organs have the highest risk of PTLD, but prolonged immunosuppression also increases PTLD

risk.[113] EBV-associated B cell lymphomas have also been described in other cases of immune deficits, including patients with AIDS and with primary immune deficiency.[110] As is the case for CMV infection, T cells are important to control EBV infection and to block proliferation of infected B cells.[110] Studies have shown mixed results as to whether reduced levels of EBV-specific T cells lead to PTLD, but recent data indicate that T cell polyfunctionality is reduced in PTLD patients, suggesting that PTLD occurs in patients with impaired T cell function.[110] A major clinical consideration for EBV is balancing relative risks of rejection and PTLD in determining appropriate immunosuppressive therapy, and then modifying therapies as needed in the event of PTLD or rejection events.

SARS-CoV-2

SARS-CoV-2, the virus responsible for the COVID-19 pandemic, has been linked to allograft rejection in several studies. Acute kidney injury is a common complication of COVID-19, necessitating dialysis for up to 45% of patients in intensive care, and chronic kidney disease is a major risk factor for COVID-19 mortality.[114] In a case study, a kidney transplant recipient with no pre-existing DSA developed TCMR subsequent to COVID-19, though this patient had immunosuppressive therapy substantially reduced during the infection.[115] Case studies have found AMR mediated by de novo DSA subsequent to COVID-19.[116,117] A study of 20 kidney transplant recipients with COVID-19 found that 70% had biopsy-proven acute or chronic AMR detected after recovery, including 9 patients with no prior history of AMR (Table 1), though the analysis was only at 1 post-recovery time point, so causality cannot be determined.[118] In contrast, a recent study of anti-HLA and anti-SARS-CoV-2 antibody responses in kidney transplant recipients found that SARS-CoV-2 infection did not increase DSA, even in the context of withdrawn antimetabolite.[119] Thus, the impact of SARS-CoV-2 on AMR is an important area for further study. These studies suggest a link between SARS-CoV-2 and allograft rejection, but did not exclude the possibility that rejection was induced by reduced immunosuppression. Further study will be important to fully understand the contribution of this infection to allograft rejection.

Hepatitis C

Similar to the other infections described above, Hepatitis C (HCV) has been associated with increased risk of rejection in kidney transplant recipients. This risk has been hypothesized to be linked to the use of interferons as treatment for HCV. However, kidney transplant recipients treated with direct acting antivirals (DAA) do not have any increase in risk of rejection.[120] In fact, DAA-treated recipients of HCV^+ kidneys have similar outcomes, with no increase in rejection, to recipients of HCV^- kidneys. Thus, in the current era of DAA treatment, the impact of HCV on rejection is minimal.

In contrast, HCV plays an unusual role in allograft rejection in that it has been associated with allograft tolerance in the context of liver transplantation. Withdrawal of immunosuppression and operational tolerance have been achieved in liver transplant recipients chronically infected with HCV. The tolerant patients had an expansion of exhausted HCV-specific T cells (Table 1).[121] A follow-up study found that HCV-specific T cells in liver recipients could cross-react with alloantigen, and therapeutic clearance of

virus with direct acting antivirals (DAA) was associated with increased reactivity to donor alloantigen.[122] However, this increased reactivity did not lead to increased rejection. These findings suggest that cross-reactivity between infection and allograft can actually modulate immunity in a graft-protective manner. Because the liver is the site of HCV infection, local inflammation may contribute to its tolerogenic effects in the liver. Cross-reactivity is further discussed in the section on heterologous immunity.

Additional viral infections

Human herpesvirus 6 (HHV-6) is another herpesvirus that infects over 90% of humans and has been linked to rejection.[123] HHV-6 has been associated with acute rejection in liver and kidney transplant recipients.[124,125] Rejection risk also increases with coinfection of multiple herpesviruses, including CMV, EBV, and HHV-6.[125] This may be caused by cross-reactivity, as outlined in the later section on heterologous immunity. Thus, understanding the role of a variety of infections as well as co-infection will be important to fully understanding the contribution of infections to allograft rejection.

Another viral infection that commonly affects transplant recipients is adenovirus. Adenovirus typically infects people during childhood and establishes latency. It is a common viral complication in transplant recipients that usually resolves without therapeutic intervention.[126] Adenoviral infection has been associated with acute rejection,[23,127] though whether adenovirus induces rejection remains unknown. Additionally, adenovirus nephropathy causes similar pathology to acute cell-mediated rejection, complicating differential diagnosis of the two.[128]

The infections outlined in this section demonstrate that there are clinical implications of many viral infections, not just the most common ones. Each infection and co-infection has a distinct impact on rejection risk with disparate clinical manifestations. This indicates that understanding the full scope of infection will be crucial to understanding rejection and other clinical manifestations of the infection-immunosuppression balance in various organ transplant populations.

Other infections

Bacterial infection can also contribute to allograft rejection. Organ transplants with the highest rates of rejection are those associated with higher loads of microbial exposure, including the skin, intestines, and lung.[129] A mouse model of allograft tolerance demonstrated that bacterial infection at the time of transplant can block induction of tolerance.[130] This block of tolerance was further determined to be mediated specifically by an individual Toll-like receptor (TLR).[131] TLRs are a type of pattern recognition receptor (PRR) adapted to form innate immune responses to microbial pathogens. TLR signaling is required for rejection based on minor antigen mismatch.[132,133] Further, polymorphisms of TLR4 have been associated with differential risk of rejection in human patients, with elevated or dampened TLR4 signaling respectively increasing or decreasing risk of rejection.[134,135] Other PRRs including RIG I-like receptors, Nod-like receptors, and C-type lectin receptors may also contribute to allograft rejection.[129] In addition to bacterial

infection, microbial colonization of the gut and mucosal surfaces has major impacts on immunity and in particular alloimmunity. This topic is beyond the scope of this review, but has previously been extensively reviewed.[136,137] Of note, TLRs can drive rejection in the absence of infection, through engagement of damage-associated molecular patterns (DAMPs), which are endogenous molecules released in response to cell damage or death, including the damage associated with ischemia-reperfusion injury.[129,138] DAMPs have been associated with increased risk of allograft rejection.[139,140] Thus, pathways involved in infection can contribute to rejection even in the absence of infection. Taken together, these animal model data offer enticing teleological narratives of infection and rejection. Yet caution is warranted in interpreting the relevance of animal models to clinical therapies. For example, specific-pathogen free mice do not accurately reflect microbial exposure in human patients, so a tolerance induction protocol that is effective in mice may not be as effective in patients. Similarly, how zoonotic infections might manifest in xenotransplantation in the clinical setting remains to be seen, an issue of particular importance in the context of recent experimental pig- to human kidney and heart transplantation.[141-143]

Heterologous immunity

Heterologous immunity is defined as the induction of an immune response to an antigen after exposure to an unrelated antigen/infection (Figure 1A) and has been associated with 1 T cell receptor (TCR) that responds to more than 1 antigen (Figure 1B, C).[144] These cross-reactive antigen receptors were first described in the context of responses to multiple pathogens (Figure 1B). Calculations based on theoretically possible TCRs and peptide-MHC have determined that any 1 TCR can theoretically bind up to a million peptide-MHC pairs.[145,146] Cross-reactivity can be mediated in 3 distinct ways. First, peptides from distinct viruses but with similar epitopes could lead to molecular mimicry in which the TCR binds both peptides at the same residues. Second, the TCR could bind with similar avidity to a distinct set of peptide contacts on 2 different peptides. Third, a T cell expressing 1 TCRβ and 2 distinct TCRα chains could have cross-reactivity for 2 different antigens mediated by TCRα binding.[145] Limiting dilution assays have been used to show cross-reactivity of the same cytotoxic T cell clone for 2 viruses, and in some cases cross-reactivity for alloantigen.[145] As described above for CMV, this is a major source of risk related to infection and rejection, as cells that proliferate to respond to an infection can then reject the allograft. It is difficult to study heterologous immunity in transplant recipients because of the need to identify responses to 2 distinct antigens, so the data described here are from a variety of *in vitro* and animal models. The data described here are not intended as an exhaustive list, but rather a summary of the range of studies completed on heterologous immunity (Table 2).

A common framework to study heterologous immunity is measurement of responses to known co-infection or vaccination (Table 2).[144] For instance, T cell lines from healthy volunteers expanded in response to EBV or influenza peptide cross-reacted to antigen from the other virus in 3 of 8 donors analyzed.[147] A study of infectious mononucleosis found that the population of CD8 T cells proliferating in response to EBV included pre-existing flu-responsive memory cells, suggesting that those cells were cross-reactive.[147] The EBV and flu epitopes stimulating the cross-reactive T cells shared only 3 amino acid overlap, indicating that a small degree of overlap is sufficient for cross-reactivity.[148] In a mouse

model, mice were infected first with Lymphocytic choriomeningitis virus (LCMV) and subsequently with vaccinia virus (VV). T cells that bound LCMV peptide-MHC proliferated in response to VV infection.[148] Infection with Pichinde virus subsequent to LCMV also led to expansion of cross-reactive epitopes.[149] Co-infection studies have shown that pre-existing immunity to a heterologous infection can promote protective responses to a new infection, though the protection was not always reciprocal.[145] There is also evidence that memory T cell pools are enriched for T cells that cross-react with multiple viruses, likely as a result of ongoing antigenic signaling.[145] Thus, studies in both humans and animal models have demonstrated the existence of T cell clones that react to 2 distinct viral infections (Table 2).

While the above studies provide substantial evidence for the existence of heterologous immunity, they do not measure heterologous immunity shared between viruses and alloantigen. Several mouse models demonstrate the existence of heterologous alloimmunity (Table 2, Figure 1C). Infection of mice with LCMV, VV or vesicular stomatitis virus (VSV) produces T cells that produce IFNγ in response to stimulation with cells presenting allogeneic MHC.[150,151] When treated with donor bone marrow infusion and costimulatory blockade, a protocol that tolerizes naïve mice to an allogeneic skin graft, mice previously infected with LCMV, VV, or VSV rejected their skin allografts.[150] Rejection mediated by cross-reactivity was further tested in a model of allogeneic skin graft in mice lacking adaptive immunity. In this model, allogeneic grafts are typically accepted long-term. When purified LCMV-MHC tetramer specific CD8 T cells were adoptively transferred into these mice, allogeneic skin grafts were rejected, demonstrating that these cells were sufficient to induce rejection.[151] Thus, antiviral T cells can exhibit reactivity against alloantigen.

Several studies have also identified allo-cross-reactivity in healthy humans (Table 2). One study identified T cells specific to CMV, influenza, and varicella zoster virus (VZV) with peptide-MHC tetramer, and found these cells proliferated in response to allogeneic stimulation with irradiated HLA-mismatched peripheral blood cells.[152] Eleven virus-specific T cell lines derived from healthy volunteers were stimulated with a panel of B cell lines expressing a range of HLA types, and 9 produced IFNγ in response to the cell lines.[153] In this study, for 2 T cell clones, it was demonstrated that an identical TCR was reacting to both virus and HLA.[153] HLA-C is an important target for immune tolerance because it is expressed at the maternal-fetal interface in pregnancy, and cross-reactivity for HLA-C by EBV-specific T cells has been identified in cell lines.[154] 3-4% of CD4 and CD8 T cells in healthy volunteers proliferate in response to alloantigen, and memory and virus specific T cells are significant contributors to this allo-response.[155] Because these studies are in healthy individuals they do not address whether the allo-reactive cells actually induce rejection, but they demonstrate the importance of further study in the context of transplantation.

The limited range of studies of heterologous immunity to alloantigen and virus in transplant recipients have produced some intriguing findings (Table 2). One study found a public CMV-specific TCR cross-reactive for HLA-B27 in 2 unrelated lung transplant recipients.[156] Another study found CMV-specific T cells proliferating in response to alloantigen in blood from kidney transplant recipients both pretransplant and transiently after transplantation, though these cells did not appear to impact allograft function during the study period.[157] A third study analyzed TCR of CMV-responsive T cells from heart and kidney transplant

recipients and identified TCRs with putative recognition for antigen in the context of donor HLA, suggestive of semi-direct alloreactivity.[158] A kidney transplant candidate vaccinated for VZV had a CD8 memory T cell clone that displayed cytotoxicity against HLA-B*055.[159] In lung transplant recipients, EBV-specific CD8 T cells have been shown to cross-react with alloantigen.[160] Of note, these studies have not typically found an association of cross-reactive T cells and enhanced risk of rejection. It has been hypothesized that this is because effects will be more likely to be present at the time of active viral infections, so follow up studies should address heterologous immunity in that context.[161] Another possibility is that the cross-reactive T cells are blocked from responding to the allograft by regulatory cells, potentially even regulatory T cells with the same TCR. It is also possible that the immunosuppression in the transplant recipients in these studies was adequate to block activity by these cross-reactive T cells. Because of the limited number of studies completed thus far, much more work in this area is needed to address these hypotheses. In particular, since previous infection and heterologous immunity can block tolerance induction in mice,[150,162] studies of cross-reactive T cells in protocols of allograft tolerance induction in humans are needed to determine whether these T cells can block tolerance in the human setting.

Heterologous immunity is a process that can apply to both T cell and B cell responses, and yet the vast majority of studies identifying heterologous immunity have focused on T cells. There is some evidence that viral infection leads to the production of HLA-specific B cells. This has been hypothesized to be the result of virally-produced TLR ligands and immune cell-produced cytokines leading to polyclonal B cell activation, including alloreactive B cells.[163] In kidney transplant recipients and patients on the kidney waitlist, viral infection and other pro-inflammatory events are associated with increased levels of HLA-specific antibody.[164] The above studies provide evidence of an association between B cell alloreactivity and infection, but do not directly address cross-reactivity. One recent study tested 51 human monoclonal antibodies specific to viruses (CMV, VZV, human immunodeficiency virus, and parvovirus) for reactivity against HLA, and 41 antibodies specific to HLA for reactivity against viruses. No cross-reactivity was detected, in stark contrast to the many studies showing T cell cross-reactivity.[165] This may be due to the differential selection processes of B and T cells. Thymic T cell development includes a positive selection checkpoint in which the TCR must interact with self-peptide loaded in MHC class I or II in order to survive.[166] In contrast, B cell positive selection is not mediated through MHC recognition.[167] Thus, the differential positive selection processes could lead to T cells having a much higher probability of cross-reactivity between virus and MHC. Intriguingly, TLR ligands have been shown to contribute to B cell positive selection, much like TLR signaling contributes to rejection.[168] Thus, positive selection may play a crucial role in development of both T and B cells that promote alloreactivity, though by different mechanisms. Further study will be needed to understand the mechanistic differences in T cell and B cell alloreactivity.

Heterologous immunity has several clinical implications for transplantation. First, the existence of cross-reactivity between anti-viral and anti-HLA T cells demonstrates that immune history is an important factor in evaluating sensitization of a transplant candidate to a putative donor organ, and that this sensitization can impact patient outcomes. Testing

dominant antiviral T cell repertoires for anti-donor responses could be a valuable addition to donor/recipient matching. While the complexity of these assays has currently limited their scope of use to the research setting, identification of clinical settings of unmet need may help develop strategies for refining the assays into future clinical practice. For example, heterologous immunity has significant implications for transplant tolerance. Animal models have found difficulty in maintaining stable tolerance in the presence of cross-reactive T cells, indicating that tolerance protocols may be more likely to fail in patients with these T cells. Knowledge gained through animal models of cross-reactivity and immune tolerance will be important to develop clinical immune tolerance protocols.

Conclusions

Infection remains an important consideration for the study and treatment of allograft rejection. Infections such as herpesviruses CMV, EBV, and HHV-6, are known to increase the risk of rejection. Hepatitis C in contrast may reduce the risk of rejection in liver recipients. Preliminary studies have linked SARS-CoV-2 to allograft rejection, but further study will be needed to fully elucidate this linkage. Treatment for viral infection often involves reduction of immunosuppressive therapy, which can also increase the risk of rejection. Clinical responses to infection in solid organ transplant recipients can invoke patterns of pathological responses similar to rejection. Such overlap, particularly in subclinical and indolent responses, complicates the process of diagnosis and treatment, as most notably demonstrated in the case of BK nephropathy in kidney transplant recipients. Immune cells that proliferate in response to viral infection can in some cases react to donor, potentially inducing an immune response against the allograft. In the face of severe and worsening organ shortage for patients awaiting solid organ transplantation, strategies to extend allograft survival have become an increased focus. Leveraging and expanding upon our current knowledge of infection-immunosuppression homeostasis in transplant recipients will contribute to improving patient and allograft survival.

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Abbreviations

AMR	Antibody-mediated rejection
BCR	B cell receptor
BKV	BK virus
BKVN	BK Virus Nephropathy
CMV	Cytomegalovirus
DAMP	Damage-associated molecular pattern
DSA	Donor-specific antibodies

EBV	Epstein Barr virus
HHV-6	Human herpesvirus 6
IFNγ	Interferon gamma
LCMV	Lymphocytic choriomeningitis virus
MHC	Major histocompatibility complex
NK cells	Natural killer cells
PRR	Pattern recognition receptor
PTLD	Post-transplant lymphoproliferative disorder
RCMV	Rat CMV
TCMR	T cell mediated rejection
TCR	T cell receptor
TLR	Toll-like receptor
VV	Vaccinia virus
VSV	Vesicular stomatitis virus

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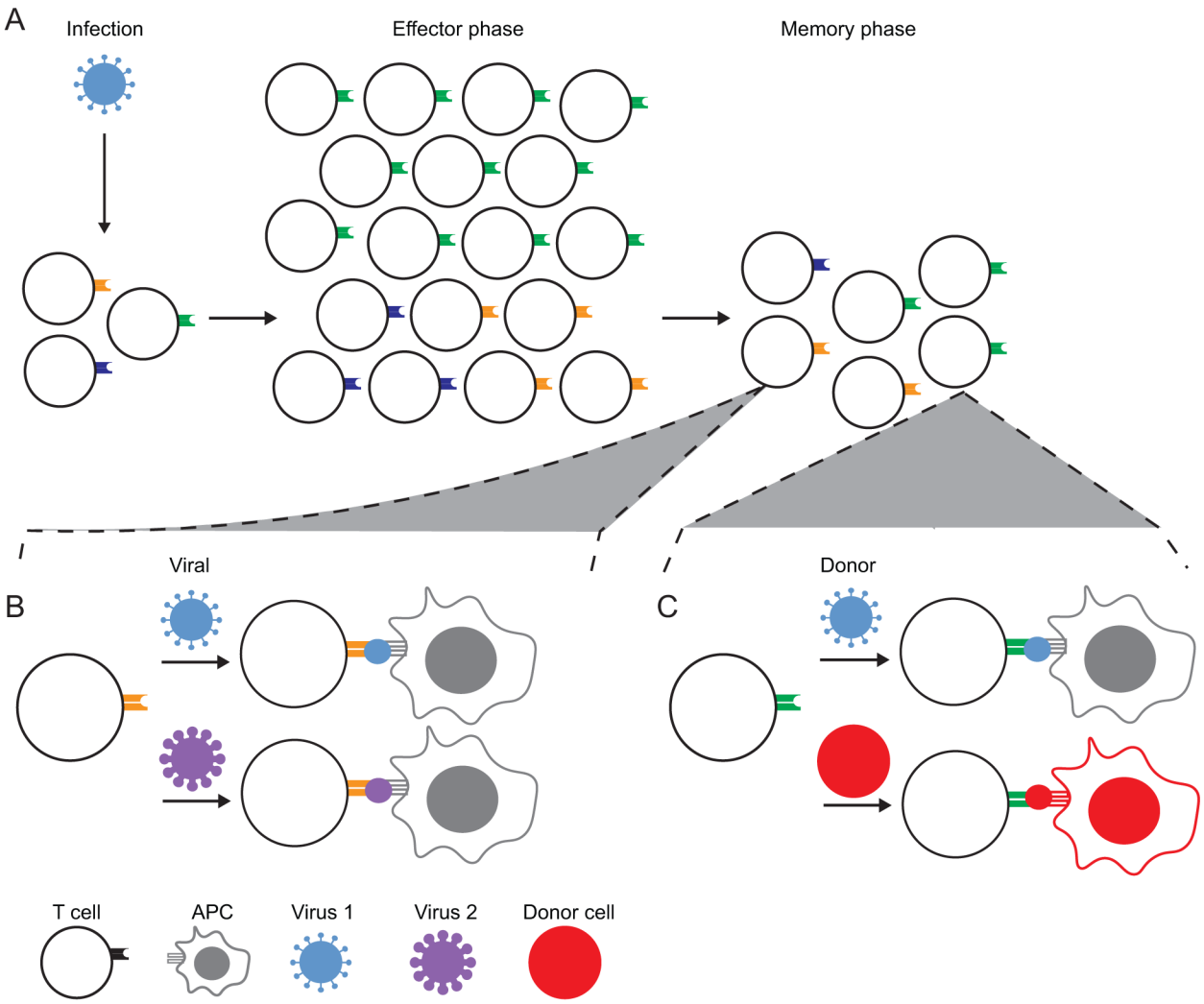

Figure 1: Development of heterologous immunity.

A) A naïve T cell pool encountering viral antigen will proliferate to form an effector response, and contract to the memory phase once the infection is under control. B) T cell receptor clones that cross-react with a different virus (orange TCR clone, purple virus) can mount a heterologous response to that virus. C) Upon exposure to alloantigen (red cell), T cell receptor clones (green) that cross-react to allo can mount a heterologous response to alloantigen. Note: allorecognition can be mediated through either direct or indirect antigen presentation, as described in the text. For simplicity, we only show direct presentation in this figure.

Table 1:

Summary of infectious contributions to allograft rejection.

Virus	Impact on immune function	Treatment
CMV	• Viremia associated with increased risk of acute rejection[21,36-42] • Antiviral prophylaxis decreases rejection risk[41,43-45] • History of viremia associated with increased risk of chronic rejection [7,10,64-66,68] • Upregulates adhesion molecules promoting allograft infiltration and inflammation[48-50] • Modulates MHC expression[47,51-54] • Induces inflammatory NK and T cells[55,56] • Induces pro-inflammatory T cell aging[57-60]	Reduction of immunosuppression • Antivirals: valganciclovir, ganciclovir, foscarnet, cidofovir, letermovir[169] • Donor/recipient serostatus matching[79]
BKV	• Kidney allograft direct cytopathic effects[84] • Inflammation[84,96-98] • Tubular atrophy[84] • BKVN and rejection have similar pathology, complicating diagnosis[99,100]	• Reduction of immunosuppression[105,106] • Antivirals: cidofovir[170] • Specific combinations of immunosuppressive drugs may be effective to treat BKVN while preventing rejection[101-104]
EBV	• EBV viremia induced by high dose immunosuppression[108] • Lytic EBV correlated with late acute rejection[109] • Treatment needs to counterbalance risks of rejection and PTLD[110]	• Modulation of immunosuppression • Patients who develop PTLD are treated for their hematogic malignancy[110]
SARS-CoV-2	• Several small studies have identified transplant recipients developing rejection subsequent to infection[115-119]	• Monoclonal antibodies[171,172] • Antivirals: remdesivir,[173] nirmatrelvir-ritonavir,[174] molnupiravir[174,175] • Vaccination[176]
HCV	• Chronic active infection associated with operational tolerance to liver transplant[121] • Viral clearance associated with donor reactivity, but no proven rejection, in liver transplant[122] • Pre-DAA therapies associated with rejection risk for kidney transplantation, but no elevated rejection risk for kidney recipients in DAA era[120]	• Direct acting antivirals (DAA)[122]

Summary provided for all viruses individually discussed in the text. References are listed for each individual point.

Table 2:

Summary of knowledge of heterologous immunity.

Organism	Form of cross-reactivity	Evidence of cross-reactivity
Mus musculus	**Two infections**	• LCMV-specific T cells proliferate in response to VV or Pichinde antigen[148,149]
	Virus and alloantigen	• LCMV-, VV-, or VSV-specific T cells produce IFNγ in response to allogeneic MHC[150,151] • Prior infection with LCMV, VV, or VSV blocks skin graft tolerance induction[150,151]
Homo sapiens	**Two infections**	• Memory flu-specific T cells can proliferate in response to EBV[147,148,152-155]
	Virus and alloantigen (healthy volunteers)	• T cells specific to CMV, influenza, VZV proliferate in response to alloantigen[152] • Virus-specific T cell lines produce IFNγ in response to HLA[153] • Memory CD4 and CD8 T cells from healthy volunteers proliferate in response to alloantigen[155]
	Virus and alloantigen (transplant recipients)	• T cells specific to CMV, VZV, EBV have been shown to react to HLA in transplant recipients[156-161] • These studies have not directly addressed rejection risk

Summary for mouse and human models, subdivided based on nature of heterologous challenge. References are listed for each individual point. This list is not intended to be exhaustive.