

Using Human Cytomegalovirus Glycoproteins to Prevent Graft versus Host Disease through Downregulation of Major Histocompatibility Complex Class I and Class II: A Novel Approach

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Abstract

Graft Versus Host Disease (GVHD) is an immune-mediated disease occurs as a complication of allogeneic Hematopoietic Stem Cell Transplantation (HSCT). Differences between donor and recipient Major Histocompatibility Complex (MHC) antigens initiate the disease. The immunocompetent cells of the donor recognize the cells of the immunocompromised host as non-self, thus commencing an immune response against them.

The human Cytomegalovirus (hCMV) is a member of the herpesvirus family that has developed strategies to escape the immune surveillance and defense system via encoding a series of glycoproteins that down regulate host MHC antigens. The Unique Short (US) hCMV glycoproteins US2, US3, US6, US10 and US11 have shown variable capabilities to downregulate MHC class I and II. Theoretically, these capabilities could be utilized to downregulate the expression of host MHC antigens, thus inhibiting the allograft recognition and the subsequent immune response, which would prevent GVHD. In this systematic review, 620 literatures have been identified through a PubMed, Epistemonikos, and Google Scholar search. An inclusion criterion has been applied to these studies, of which 27 have been selected.

This review found that the hCMV glycoproteins act as partner to downregulate MHC class I and class II, CMV glycoproteins regulate destruction of class I MHC molecules, and degrade MHC class II.

The Preferred Reporting Items for Systematic Reviews (PRISMA) Statement has been used to increase the quality of the review, and thus a Population Intervention Comparison Outcome Study design (PICOS) model has been formulated.

The findings of this research could be further studied and validated to offer an alternative approach to the current pharmacological preventive measures of GVHD, possibly without compromising patients' immunity.

Keywords: Graft Versus Host Disease (GVHD); Human Cytomegalovirus (hCMV); Unique Short (US) glycoproteins US3/US2/US6/US11; Major Histocompatibility Complex (MHC); Antigen presentation pathway; Hematopoietic Stem Cell Transplantation (HSCT); Bone Marrow Transplant (BMT)

Abbreviations: hCMV: Human Cytomegalovirus; MHC: Major Histocompatibility Complex; HLA: Human Leukocyte Antigen; BMT: Bone Marrow Transplantation; HSCT: Hematopoietic Stem Cell Transplantation; DC: Dendritic Cells; HC: Heavy Chain; mHAGs: Minor Histocompatibility Antigens; ER: Endoplasmic Reticulum; TAP: Transporter Associated with Antigen Processing

Background

GVHD develops in 20 to 80% of those underwent a Bone Marrow Transplantation (BMT), regardless of HLA donor-recipient matching [1]. The Major Histocompatibility Complex (MHC), also known as Human Leukocyte Antigens (HLA), is a major determinant of GVHD. The extreme polymorphism of HLA genes complicates finding a compatible donor. Matching donor-recipient HLA antigen lowers the risk of acute and chronic GVHD. The greater the disparity between donor and recipient HLA, the greater is the likelihood of GVHD complication [2,3]. The immunocompetent cells of the donor recognize the HLA antigens on cells of the immunocompromised host as non-self, thus initiate immuneresponse that ultimately lead to destruction and rejection of host cells. Core pathology of GVHD includes organ damage affecting skin, liver, and the mucosa of the gastrointestinal (GI) tract [1]. Prevention of GVHD will greatly enhance transplant outcomes and patient survival. Many of the treatment options that are widely used to

prevent and treat GVHD are general immunosuppressive medications that cause weakening of the patient's immune system, leading to increased susceptibility to opportunistic infections and malignancies with increasing morbidity and mortality. T-cell depletion, one of the most common immunosuppressive mechanisms, leaves the patient at a risk of graft failure, cancer relapse, and general health deterioration [4].

The human Cytomegalovirus (hCMV), a member of the herpes virus family, is a worldwide human pathogen with the ability to persist as a lifelong latent infection [5]. The virus targets the innate and acquired host immune system by encoding immune evasion mechanisms; one of which is the inhibition of antigen presentation by the expression of several glycoproteins in its Unique Short (US) genomic region. These glycoproteins are found to down regulate MHC class I and class II, as described by several published studies [6-14].

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hCMV inhibits peptide import into the Endoplasmic Reticulum (ER) by the MHC-encoded TAP peptide transporter [13].

The capability of immune evasion can be utilized to reduce surface expression of the MHC classes I and II and hence down regulation of host's antigen presentation pathway preventing allorecognition of host antigens by the donor's cells which triggers GVHD.

Preventing GVHD using the hCMV glycoproteins US2, US3, US6 and US11 will potentially eliminate the drawbacks of all other treatment options and decrease treatment-related mortality. This approach will also decrease health-care costs, and could additionally be used to prevent other immune-mediated diseases and diseases related to transplant failure, provided the conclusions of this review are validated in experimental trials and *in vivo* studies on animal models. Because hCMV infection requires the virion envelope proteins to initiate pathogenesis and disease production potential hCMV infection is not possible, however, the safety of this approach must be first vigorously scrutinized and validated in clinical trials.

It was found that despite the presence of numerous donor antigen-presenting cells, only host-derived antigen-presenting cells initiated graft versus host disease in a murine allogeneic bone marrow transplantation model [15]. Thus, strategies for preventing graft versus host disease could be developed that are based on inactivating host antigen-presenting cells. This systematic review for the included literatures [5-26] has been conducted to explore the potential use of hCMV glycoproteins US2, US3, US6 and US11 to prevent GVHD.

Objectives

The research question is formulated based on the Population Intervention Comparison Outcome Study design (PICOS) model, as suggested in the Preferred Reporting Items for Systematic Reviews (PRISMA) Statement checklist –checklist item #4.

Research questions

- Is MHC class I and class II antigen presentation pathway downregulation possible?
- Can the HCMV glycoproteins US2, US3, US6 and US11 be used to downregulate MHC class I and class II antigen presentation pathways?
- In patients having an allogeneic BMT would the downregulation of host MHC classes I and II antigen presentation pathways using hCMV glycoproteins US2, US3, US6 and US11, compared to no intervention, prevent GVHD partially or completely?
- Can the hCMV glycoproteins US2, US3, US6 and US11 initiate cytomegalovirus infection if used for MHC class I and class II downregulation?

Methods

Information sources and study tools

Studies have been identified by a PubMed, Epistemonikos and Google Scholar search, and by the reference lists of the given articles. The research is formulated based on the PICOS model as suggested by the PRISMA Statement.

A. PICOS

- P (population): Patients having an allogeneic HSCT.
- I (intervention): Downregulation of MHC classes I and class II

antigen presentation pathway using HCMV glycoproteins US2, US3, US6 and US11.

- C (comparison): Compared to no intervention.
- O (outcome): Prevent GVHD partially or completely.
- S (study design): Prospective randomized controlled trial (RCT).

Eligibility criteria

Novel studies, case-studies, and all types of evaluative studies of all methodological approaches were eligible for inclusion in the review. Grey literature (literature “which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers”, as defined by Grey Literature Report) will also be included to eliminate the risk of bias. The aforementioned literatures will be included if its major title is concerned with the review question (MHC downregulation using the HCMV glycoproteins US2, or/and US3, or/and US6 or/and US11, or GVHD prevention via MHC downregulation).

Search

PubMed search strategy: “Graft vs. Host Disease/immunology” [Mesh] OR “Graft vs Host Disease/prevention and control” [Mesh]) and “Graft vs. Host Disease” [Majr:NoExp] and (“Cytomegalovirus” [Mesh] OR “US2 protein, Varicella virus” [Supplementary Concept] OR “US3 protein, cytomegalovirus” [Supplementary Concept] OR “US11 protein, herpesvirus” [Supplementary Concept]) OR “Major Histocompatibility Complex/immunology” [Majr:NoExp]

Data collection process

Data has been extracted from reports using the piloted forms. The reports were assessed for eligibility before inclusion, and any report that fails to meet the eligibility criteria has been excluded.

Risk of bias in individual/across studies

A table will be used to assess the quality of the studies included in the review by analysis of their conclusions, and reasons of exclusion will always be addressed and mentioned using the flowchart. This will be done at the outcome level.

Results

Study selection: Represented in a flowchart in Figure 1.

Study characteristics: Represented in Table 1.

Discussion

hCMV glycoproteins partner to downregulate MHC class I

Results of Noriega and Tortorella experiments showed that HCMV glycoproteins US2 and US3 robustly downregulate surface class I molecules [5]. Their data shows that US3 may augment US2-mediated class I protein degradation by enhancing the association between class I molecules and US2. Noriega et al., showed that co-expression of US3 and US11 resulted in a decrease of surface expression of class I molecules. Human astrocytoma cells, transfectants, and fibroblasts infected with both US3 and US11 expressing viruses demonstrated enhanced retention of MHC class I complexes within the ER [6]. Cells co-infected with both US3 and US11 have presented results similar to increased downregulation of surface class I molecules observed in US3/US11-expressing cells. The data suggests that during HCMV infection, US3 and US11 are able to effectively downregulate class I molecules.

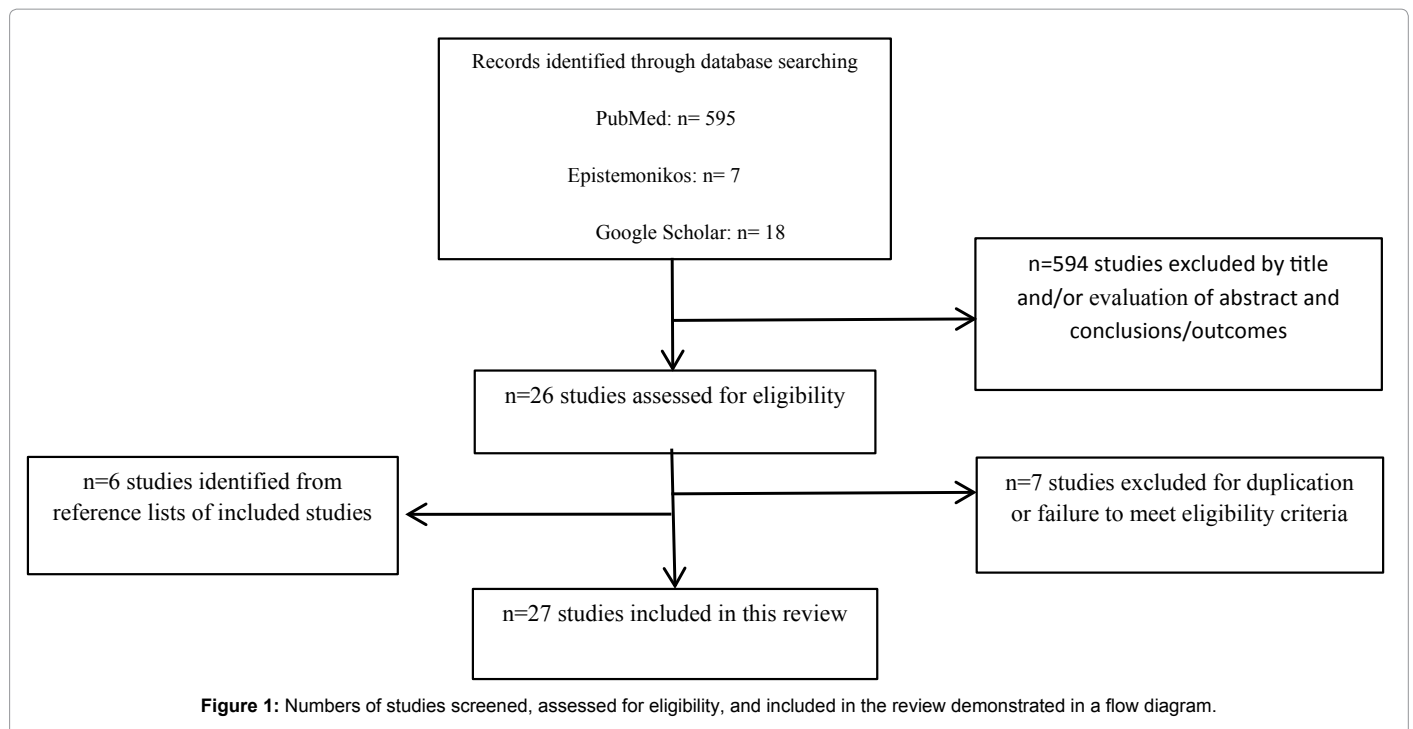


Figure 1: Numbers of studies screened, assessed for eligibility, and included in the review demonstrated in a flow diagram.

hCMV glycoproteins US2, US3, US6 and US11 regulate demolition of class I MHC molecules

Jun et al., on his experiment using human trophoblast cell lines as well as other cell lines stably transfected with the human class I genes, have demonstrated that HCMV US3 and US6 down-regulate the cell-surface expression of both HLA-G and HLA-C by two different mechanisms. HCMV US3 physically associates with both trophoblast class I MHC species, retaining them in the endoplasmic reticulum [7]. In contrast, HCMV US6 inhibits peptide transport by TAP and thus prevents intracellular trafficking of class I molecules which might explain the underlying HCMV-related spontaneous pregnancy loss. Their study has also revealed that US6 inhibits TAP-mediated peptide translocation from the cytosol to the ER. Additionally, their results indicate that the ER retention of the class I MHC molecules mediated by the US3 is neither cell type nor allotype specific.

Noriega and Tortorella established that US2 modulates surface expression of class I MHC products by targeting class I heavy chains for dislocation from the ER to the cytosol, where they undergo proteasomal degradation [5,8]. ER-luminal domain alone is sufficient to mediate tight binding to HLA-A2 in the absence of other cellular or viral proteins. They have examined the ability of US2 to bind to HLA-A2 complexes containing different peptides of certain sequences, and have concluded that US2 binds peptide-loaded class I molecules regardless of the peptide sequence.

hCMV glycoproteins US2 and US3 degrade MHC class II

Johnson and Hegde have shown that both US2 and US3 can inhibit presentation of exogenous protein antigens to CD4+ T lymphocytes in vitro assays [9]. The HCMV glycoprotein US2 causes degradation of two essential proteins in the MHC class II antigen presentation pathway: HLA-DR- β and DM- β . Expression of US2 in cells reduced or abolished their ability to present antigen to CD4+ T lymphocytes. US2 causes degradation of MHC class II molecules: HLA-DR-alpha

and HLA-DM-alpha, as well as class I heavy chain (HC), but does not affect DR-beta or DM-beta chains [10,11]. hCMV also disturb expression of HLA II molecules by altering the regulatory factors at transcriptional level [12].

Unlike US2, US3 binds newly synthesized class II alpha/beta complexes, reducing the association with the invariant chain (Ii) and causing mislocalization of class II complexes in cells. Since US2 and US3 are expressed solely within HCMV-infected cells, it appears that these viral proteins have evolved to inhibit presentation of endogenous, intracellular viral antigens to anti-HCMV CD4+ T cells.

Conclusions

The results suggest that HCMV glycoproteins US2, US3, US6 and US11 have sufficient functional roles to downregulate MHC class I and class II thus interfering with antigen presentation pathways. Preventing antigen presentation to cytotoxic T-cells through the potential use of CMV glycoprotein will avert the immune response initiated after non-self-antigen recognition of the host cells by the donor cells from the HPSC graft, thus hindering the commencement of GVHD. As the host antigen presentation pathway is the major triggering of GVHD, MHC antigens on host cells; APC should be the target for immunomodulation through possibly vaccination by viral glycoproteins at one stage before donor cell recognition. The study on the viral protein and the mechanisms of immune modifications should enhance further the findings of this research which should also be validated both *in vitro* and *in vivo*. The HCMV gene products US2, US3, US6 and US11 could be expressed in primary cell lines by cloning the cDNA of the aforementioned gene products. Development of xenogeneic transplant model will facilitate the expression of the HCMV gene products (US2, US3, US6 and US11) in the host using a recombinant HCMV vector.

If the outcomes of this research are validated accordingly, the suggested intervention could be eventually applied to humans. The intervention could be introduced to the host cells via cell vaccination after the conditioning regimen is done and prior to transplantation.

Author(s)	Title	Study type	Results/summary/conclusions
Petersdorf E [2]	The major histocompatibility complex: a model for understanding graft-versus-host disease	Review article	The MHC remains a model system for understanding the immunogenetic basis of GVHD and transplant outcomes. GVHD is a polygenic disease where risk is contributed by the MHC haplotypes of the patient and the transplant donor. A new paradigm is emerging that includes consideration for both HLA coding and HLA haplotype-linked variation as important factors in unrelated donor HCT. The identification of specific novel variants within the MHC that play a role in GVHD underscores the need for more complete information on MHC haplotype diversity and the organization of sequence
1. Ho VT, Soiffer RJ [4]	The history and future of T-cell depletion as graft-versus-host disease prophylaxis for allogeneic hematopoietic stem cell transplantation	Journal article	The authors state that it is frustrating that after 2 decades, we have not been able to establish the role of TCD in transplantation. We still do not have a clear idea of who should receive a TCD BMT, or how marrow or stem cells should be purged. It remains unclear whether additional medications are needed to promote engraftment or control GVHD, or what the nature and timing of immunomodulating manipulations to reduce the risk of relapse should be. There have been no definitive randomized trials to answer these questions to date, partly because researchers have not been able to agree on a single TCD strategy or the best way to engineer a graft. The optimal number of T cells to include in the graft remains unknown and may in fact vary among donor-recipient pairs. It would be ideal to be able to manipulate different lymphoid subgroups responsible for GVHD and GVL. Being able to do so will be critical to the future success of allogeneic stem cell transplantation.
Slobedman B, Cao JZ, Avdic S, Webster B, McAllery S, et al. [5]	Human cytomegalovirus latent infection and associated viral gene expression	Review article	This article covers several aspects of HCMV latency, with a focus on current understanding of viral gene expression and functions during this phase of infection.
Noriega V, Tortorella D [6]	Human Cytomegalovirus-Encoded Immune Modulators Partner To Downregulate Major Histocompatibility Complex Class I Molecules	Journal article	-U373-MG astrocytomas support expression of HCMV US2 and US3 -HCMV US2 and US3 robustly downregulate surface class I molecules -Class I molecules are efficiently degraded in cells expressing US2/US3 -US2/US3 increase the degradation rate of class I molecules -Retention of class I molecules in the ER does not mimic US2/US3-mediated class I protein degradation -US3 prolongs the association of a class I molecule/US2 complex
Noriega VM, Hesse J, Gardner TJ, Besold K, Plachter B, et al. [7]	Human cytomegalovirus US3 modulates destruction of MHC class I molecules	Author manuscript	-Surface class I expression is reduced in US3/US11-expressing cells -Class I molecules in US3/US11 cells are not targeted for proteasome destruction -HCMV US3 attenuates US11-mediated class I destruction -US3/US11-induced MHC class I down-regulation in HCMV infected cells
Jun Y, Kim E, Jin M, Sung H, Han H, et al. [8]	Human Cytomegalovirus Gene Products US3 and US6 Down-Regulate Trophoblast Class I MHC Molecules	Journal article	-The HCMV gene products US3 and US6 independently downregulate surface presentation of trophoblast class I Ags -Infection of JEG-3 cells either with vvUS3 or vvUS6 inhibits intracellular transport of both HLA-G and HLA-C -The inhibition of the intracellular HLA-G transport by US3 and US6 is not cell type specific -US3 binds directly to HLA-G and HLA-C -Peptide translocation by TAP is inhibited by US6 in JEG-3 cells
Gewurz B, Wang E, Tortorella D, Schust D, Ploegh H [9]	Human Cytomegalovirus US2 Endoplasmic Reticulum-Lumenal Domain Dictates Association with Major Histocompatibility Complex Class I in a Locus-Specific Manner	Journal article	-Production of soluble US2 -US2 ₁₅₋₁₄₀ associates with class I molecules in vitro -US2 recognizes class I molecules independently of peptide sequence -US2 ₁₅₋₁₄₀ maintains locus-specific binding. -US2 ₁₅₋₁₄₀ and TCR can simultaneously interact with MHC class I. It -US2 ₁₅₋₁₄₀ does not interact with HLA-DR or HLA-DM
Johnson DC, Hegde NR [10]	Inhibition of the MHC class II antigen presentation pathway by human cytomegalovirus	Review article	Both US2 and US3 can inhibit presentation of exogenous protein antigens to CD4+ T lymphocytes in in vitro assays. US2 causes degradation of MHC class II molecules: HLA-DR-alpha and HLA-DM-alpha, as well as class I heavy chain (HC), but does not affect DR-beta or DM-beta chains. Unlike US2, US3 binds newly synthesized class II alpha/beta complexes, reducing the association with the invariant chain (Ii) and causing mislocalization of class II complexes in cells. US3 expression reduces accumulation of class II complexes in peptide-loading compartments and loading of peptides.
Tomazin R, Boname J, Hegde NR, Lewinsohn DM, Altschuler Y, et al. [11]	Cytomegalovirus US2 destroys two components of the MHC class II pathway, preventing recognition by CD4+ T cells.	Journal article	HCMV protein US2 causes degradation of two essential proteins in the MHC class II antigen presentation pathway: HLA-DR-alpha and DM-alpha.
Oresic K, Noriega V, Andrews L, Tortorella D [12]	A Structural Determinant of Human Cytomegalovirus US2 Dictates the Down-regulation of Class I Major Histocompatibility Molecules	Journal article	-Sequence Specificity of the HCMV US2 Cytoplasmic Tail Is Essential for Class I Degradation -Identification of the HCMV US2 -Cytoplasmic Tail Region Important for Class I Degradation -Analysis of Site-directed Alanine Mutants of the US2 Cytoplasmic Tail
Lin A, Xu H, Yan W [13]	Modulation of HLA expression in human cytomegalovirus immune evasion.	Review article	-Down-regulation of the expression of HLA class I molecules -Inhibition of NK cell-mediated lysis -Modulation of the non-classical HLA I molecule expression in pregnancy -Modulation of the HLA class II molecule expression

del Val M, Hengel H, Häcker H, Hartlaub U, Ruppert T, et al. [14]	Cytomegalovirus prevents antigen presentation by blocking the transport of peptide-loaded major histocompatibility complex class I molecules into the medial-Golgi compartment	Journal article	<ul style="list-style-type: none"> -Lack of Selectivity in the Inhibition of Antigen Presentation by MCMV E Gene Products -Correct Processing of pp89 in Absence of Antigen Presentation -Naturally Processed Peptides Are Bound to the MHC Class I Heavy Chain L⁹ -Correct Assembly of MHC Class I Complexes -Defective Glycosylation of MHC Class I Complexes -Defective Transport of MHC Class I Molecules
Shlomchik WD, Couzens MS, Tang CB, McNiff J, Robert ME, et al. [15]	Prevention of graft versus host disease by inactivation of host antigen-presenting cells	Journal article	The authors suggest that strategies for preventing graft versus host disease could be developed that are based on inactivating host antigen-presenting cells. Such strategies could expand the safety and application of allogeneic bone marrow transplantation in treatment of common genetic and neoplastic diseases.
Arieh S, Laham N, Schechter C, Yewdell JW, Coligan JE, et al. [16]	A single viral protein HCMV US2 affects antigen presentation and intracellular iron homeostasis by degradation of classical HLA class I and HFE molecules	Journal article	<ul style="list-style-type: none"> -TfR synthesis is induced and ferritin synthesis is reduced in HFE-transfected HEK 293 cells -HCMV US2 down-regulates the expression of HFE and class I molecules via a similar mechanism -HCMV US2 targets HFE to proteasome-dependent degradation -Expression of US2 HCMV reconstitutes TfR and ferritin levels
Barel M, Rensing M, Pizzato N, van Leeuwen D, Le Bouteiller P, et al. [17]	Human Cytomegalovirus-Encoded US2 Differentially Affects Surface Expression of MHC Class I Locus Products and Targets Membrane-Bound, but Not Soluble HLA-G1 for Degradation	Journal article	<ul style="list-style-type: none"> -Allelic differences in US2-mediated down-regulation of MHC class I surface expression -Cytoplasmic tail of MHC class I H chains is not essential for US2-mediated down-regulation -HLA-G and short-tailed HLA-A2 are efficiently targeted for degradation by US2 -Evaluation of US2-mediated down-regulation of HLA-G in cell lines of human origin -Soluble HLA-G1 is resistant to US2-mediated degradation
Bevan MJ [3]	Pillars article: the major histocompatibility complex determines susceptibility to cytotoxic T cells directed against minor histocompatibility antigens	Pillars article	<ul style="list-style-type: none"> -Primary In Vivo Cytotoxic Response of BALB/C to P815 -Anti-Thy-1 .2 Sensitivity of Primary and Secondary Cytotoxic Cells -Nonspecific Lysis of Tumor Cells -The H-2 Haplotype of the Target Determines Its Susceptibility to Lysis -Discrimination between the Hypotheses: F₁ Cytotoxic Effector Cells -Discrimination between the Hypotheses: The Cold Target Competition Experiment -The Regions of H-2 Important in Restricting Target Susceptibility
Elkington R, Khanna R [19]	Cross-recognition of human alloantigen by cytomegalovirus glycoprotein-specific CD4 ⁺ cytotoxic T lymphocytes: implications for graft-versus-host disease	Brief report	This study confirms the existence of cross-reactive memory T cells capable of recognizing both a HCMV gB-specific epitope and the HLA-DR4 molecule. Considering the fact that pre-transplantation serologic studies have established that HCMV exposure is an important risk factor for various clinical complications in patients who receive solid organ or stem cell transplants, it will be interesting to explore the role of this cross-reactivity and the incidence of graft-versus-host disease (GvHD) in patients who receive transplants.
Falk C, Mach M, Schendel D, Weiss E, Hilgert I, et al. [28]	NK Cell Activity During Human Cytomegalovirus Infection Is Dominated by US2-11-Mediated HLA Class I Down-Regulation	Journal article	<ul style="list-style-type: none"> -Deletion of the US2-11 region or gpUL40 does not impair viral infectivity and growth characteristics -HCMV US2-11 genes down-regulate MHC class I during infection and govern the cytotoxic activity of NK cells -Reintroduction of the US2-6 region reconstitutes AD169-WT characteristics -US2-11 genes dominate in the hierarchy of viral MHC class I modulating genes
Gao L, Yang TH, Tourdot S, Sadovnikova E, Hasserjian R, et al. [20]	Allo-major histocompatibility complex-restricted cytotoxic T lymphocytes in bone marrow transplant recipients without causing graft-versus-host disease	Journal article	The authors used cloned allo-restricted CTL isolated from BALB/c mice (H-2 ^d) that killed H-2 ^b -derived tumor cells expressing elevated levels of the mdm-2 target protein. When these CTL were injected into bone marrow transplanted (BMT) C57BL/6 (H-2 ^b) recipients, they consistently engrafted and were detectable in lymphoid tissues and in the bone marrow (BM). Long-term survival was most efficient in spleen and lymph nodes, where CTL were found up to 14 weeks after injection. The administration of CTL did not cause graft-versus-host disease (GVHD) normally associated with injection of allogeneic T cells. These data show that allo-restricted CTL clones are promising reagents for antigen-specific immunotherapy in BMT hosts, because they engraft and retain their specific killing activity without causing GVHD.
Hennecke J, Wiley DC [21]	T Cell Receptor-MHC Interactions up Close	Mini review	X-ray crystal structures of TCRs bound to MHC I and MHC II molecules with bound antigenic peptides reveals the atomic contacts upon which MHC restricted T cell recognition is based. Very different signals can result from very similar structures and identical signals can result from different structures. An important caveat is that the CD3 and zeta chains of the TCRs and all of the transmembrane anchors and cytoplasmic segments were absent from all of the crystal studied to date. The possibility, for example, that the cell surface TCR contains two αB TCR units (Fernandez- Miguel et al., 1999) suggests that until the full TCR with CD3 and zeta chains is assembled and crystallized, choosing among signal initiation mechanisms involving oligomerization or allosteric switches will be difficult.
Parham P [22]	Putting a face to MHC restriction	Pillars article	Excerpt from 'Outcome': The first HLA class I structures showed that the peptides bound by MHC class I were mostly no namers that were bound tightly in register within the binding groove. Once bound they literally be- came restricted! This knowledge opened up a new cottage industry in which peptide pools were extracted from purified MHC class I and analyzed by high performance liquid chromatography, mass spectrometry, and protein sequencing (18, 19).

Rehm A, Engelsberg A, Tortorella D, Korner I, Lehmann I, et al. [23]	Human Cytomegalovirus Gene Products US2 and US11 Differ in Their Ability To Attack Major Histocompatibility Class I Heavy Chains in Dendritic Cells	Journal article	-Adenoviral expression of US2 and US11 induces class I HC degradation in astrocytoma cells -US11 efficiently targets MHC class I HCs for destruction in DCs -MHC class II molecules are unaffected by US2 mediated degradation
Rinaldo CR [24]	Modulation of major histocompatibility complex antigen expression by viral infection	Commentary	-Decrease in MHC Antigen Expression by HCMV and Other Viruses: Downmodulation of MHC Class II Downmodulation of MHC Class I -Increase in MHC Antigen Expression by HCMV and Other Viral Infections: Upmodulation of MHC Class II Upmodulation of MHC Class I
Warren EH, Zhang X, Li S, Fan W, Storer BE, et al. [25]	Effect of MHC and non-MHC donor/recipient genetic disparity on the outcome of allogeneic HCT	Review article	Matching the donor and recipient for the short DNA sequences that encode the peptide-binding regions of HLA-A, -B, -C, and -DRB1 does not also match them for the diverse set of peptides presented by those molecules on the surface of donor and recipient cells. It seems probable that the specific pairing of donor KIR and NKC genotypes with recipient MHC genotype will be a more important determinant of transplantation outcome than the identity or nonidentity between donor and recipient KIR and NKC genotypes.
Perreault C, Decary F, Brochu S, Gyger M, Belanger R, et al. [26]	Minor Histocompatibility Antigens	Review article	The authors conclude that most of our knowledge concerning MiHA has been acquired very recently and major advances are expected in the near future. There is now compelling evidence that MiHA are small endogenous peptides that occupy the antigen-binding site of self-MHC molecules. Their recognition by T cells is MHC restricted and shows features of antigen competition. Latent viral sequences may encode for some MiHA or control their expression. MiHA contribute to the definition of our immunologic self and to the shaping of our T-cell repertoire. Immune responses to MiHA raise number of concerns in transplantation because they may cause graft rejection or GVHD. However, their potential role in the crucial GVL effect is of utmost importance. A better understanding of MiHA biology could be exploited to reach a major goal in bone marrow transplantation: prevention of GVHD with amplification of the GVL effect.
Mori S, El-Baki H, Mullen CA [27]	Analysis of Immunodominance among Minor Histocompatibility Antigens in Allogeneic Hematopoietic Stem Cell Transplantation	Journal Article	-The mHAg B6dom1 is immunodominant relative to the H3 and H13 mHAg -The immunodominance of B6dom1 over H3 and H13 cannot be explained by peptide/MHC affinity or avidity -Comparison of Vb clonotypes responding to mHAg -Hematopoietic stem cell donor immunity to the immunodominant mHAg B6dom1 is neither sufficient nor necessary for the induction of severe GVHD

Table 1: Study characteristics.

Limitations

Minor histocompatibility antigens (mHAg) have not been widely considered in this review. mHAg are cell membrane alloantigens that are unlike MHCs which are recognized by both B cells and T cells, they are only recognized by T cells [27]. Although they cause far less rejection problems than those of the MHC, they can sometimes cause GVHD in cases where there are dissimilarities between the immunodominant mHAg of the donor and the host [28]. Therefore, matching mHAg, precisely the immunodominant ones, along with the downregulation of MHC class I and II antigen presentation pathway using the HCMV glycoproteins US2, US3, US6 and US11 in allogeneic HSCTs will attenuate GVHD and possibly lead to the full elimination of the disease.

NK –cell lyses mechanisms have also been found to contribute to or protect from GVHD through self-antigen recognition, this mechanism were not touched in our review. Strategies that block expression of ligands that activate NK cells or preserve expression of legends that inhibit NK cell triggering have been developed also by CMV and should be considered for any attempts to prevent GVHD.

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