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Epstein-Barr Virus and the Human Leukocyte Antigen Complex

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Abstract

Purpose: While most adults are infected Epstein-Barr virus (EBV), 3-5% remain uninfected. The human leukocyte antigen (HLA) complex, which controls many pathogens, may influence infection and disease associated with EBV.

Recent Findings: Numerous EBV proteins and miRNAs down-regulate HLA class I and II expression on the cell surface. HLA class II functions as a receptor for EBV entry into B cells. Specific HLA class II alleles correlate with the susceptibility of B cells to EBV infection *in vitro* and with EBV seropositivity or seronegativity of humans. HLA class I polymorphisms correlate with development and severity of EBV infectious mononucleosis and with the risk of several virus-associated malignancies including nasopharyngeal carcinoma, Hodgkin lymphoma, and post-transplant lymphoproliferative disease.

Significance: These findings indicate that while EBV has evolved to use MHC class II as a receptor for virus entry, polymorphisms in MHC class II and class I influence virus infection and disease.

Keywords

Epstein-Barr; HLA; MHC; infectious mononucleosis; nasopharyngeal carcinoma; Hodgkin lymphoma

Introduction

The human leukocyte antigen (HLA) complex encodes the major histocompatibility complex (MHC) proteins in humans. The major function of the HLA complex is to present

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Conflict of Interest

Qingxue Li and Jeffrey I. Cohen each declare no potential conflicts of interest.

Human and Animal Rights

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

antigens derived from pathogens, tissue-specific differentiation antigens, or mutated proto-oncogenes on the cell surface for recognition by T cells in response to infection or to malignancy (1). HLA serves as a key determinant for resistance to infections. The major HLA class I genes (HLA-A, HLA-B and HLA-C) and class II genes (HLA-DR, DP and DQ) are located on chromosome 6 (2). The current number of HLA and related alleles is 22,548, which give rise to tens of thousands of possible combinations (http://hla.alleles.org/alleles/index.html (3). The evolution of diversity of HLA molecules is thought to be the result of selection and adaption from combating infection by modulating host immunity (4). Consequently, there are strong associations between HLA alleles and various diseases, including infection, autoimmune diseases and cancer.

Over 90% of world's adult population is infected with Epstein-Barr virus (EBV). Both social/economic factors and genetic composition of individuals affect susceptibility to virus infection and the outcome of infection. While most infections occur in infants and young children who present with nonspecific symptoms or no symptoms, in young adults EBV frequently causes infectious mononucleosis (5). EBV is associated with several malignancies, including lymphomas (Burkitt and Hodgkin lymphoma) and epithelial cell cancers (nasopharyngeal carcinoma and gastric carcinoma). In patients with acquired immune deficiencies, such as HIV and persons receiving bone marrow transplants, or patients with congenital immunodeficiencies such as X-linked lymphoproliferative disease, EBV can result in lymphoproliferative disease or lymphoma.

Modulation of HLA class I and II molecules by EBV

Since HLA determines the efficiency of the presentation of EBV peptides to T cells, down-regulation of HLA by the virus is an important mechanism for immune invasion by EBV (6–8). Several EBV lytic and latent proteins down-regulate HLA class I as part of the virus' immune-evasion mechanisms. BILF1 binds to MHC class I resulting in degradation of the latter protein and reduced expression on the cell surface (9). BNLF2 interacts with the transporter associated with antigen processing resulting in reduced MHC class I expression at the surface of cells (10). BDLF3 increases internalization of surface MHC class I with reduced expression of MHC I on the cell surface (11). BGLF5 inhibits host protein synthesis, including expression of MHC class I (12). BZLF1 inhibits upregulation of MHC class I expression by LMP1 (13). EBNA1 inhibits its own presentation to the MHC class I complex through glycine-alanine repeats in the protein (14, 15). Analysis of nasopharyngeal carcinoma cells indicated that levels of EBNA1, EBNA2, EBNA3A, EBNA3B, LMP1, and LMP2A are inversely correlated with expression of MHC class I (16).

Several EBV proteins modulate MHC class II expression or interfere with its activity. BZLF1 inhibits expression of MHC class II (17). BCRF1inhibits both constitutive and IFN-γ induced expression of MHC class II (18). BDLF3, BGLF5, BZLF1, and LMP2A each has been found to downregulate expression of MHC class II (11, 12, 17, 19). BZLF2 interferes with MHC class II presentation of antigens to T cells (20).

EBV encodes at least 44 microRNAs (miRNA), several of which directly or indirectly control antigen presentation by down-regulating HLA class I and class II and reducing immune surveillance by virus-specific CD4+ and CD8+ T cells (21–23).

The role of HLA class II in EBV infection in vitro

EBV establishes latency in B lymphocytes. The virus displays many glycoproteins on its envelope including glycoprotein gp350, gB, gH/gL, and gp42 (24, 25). Each of these five glycoproteins is important for entry into cells. The virus attaches to B cells using EBV gp350 which binds to one of two receptors CD21 (also termed CR2) or CD35 (also termed CR1) (26–28). EBV gp42 is essential for infection of B cells and uses HLA class II molecules as a receptor (29–32). The C-terminus of gp42 binds to the β chain of HLA class II (33–36). Antibodies to gp42, HLA class II, or soluble gp42 inhibit EBV infection of B cells (29, 37). gp42 is a type II membrane protein. The functional form lacks the N-terminal domain of the gp42, which is cleaved during processing of the protein. EBV gp42 interacts with gH/gL and consequently recruits gB, a fusion protein (37, 38). EBV gH/gL, gB, and gp42 are essential for fusion of the virus to B cells during EBV entry. The role of gp42 in fusion is distinct from its interaction with HLA class II, since a gp42 monoclonal antibody (CL40) that does not block gp42 binding to MHC class II still blocks fusion (39).

HLA class II molecules are encoded by 5 genes, *HLA-DR, HLA-DP, HLA-DO, HLA-DM, and HLA-DO*. HLA-DP, HLA-DQ, HLA-DR present antigens that are outside the cell to T cells; HLA-DM, and HLA-DO are important for internal processing of antigens. HLA class II molecules are comprised of a and β polypeptide chains. Each a and β chain of HLA-DR, -DP, or -DQ has a highly conserved a2 and β2 region and a polymorphic al and β1 region. HLA class II proteins consist of HLA-DR, -DQ, or -DP molecules and are inherited as haplotypes which share about 70% sequence similarity to each other. EBV gp42 can bind to any of the three HLA class II molecules (34, 40), although their binding affinities may not be identical. Unlike HLA class II mediated antigen presentation, in which the peptide binding groove consists of both α1 and β1 chains, EBV gp42 interacts only with the β chain of HLA class II (33, 34, 41, 42), although the gp42 binding site is near the peptide grove. This may help to explain how soluble gp42 can interfere with antigen presentation (20, 34, 43).

CD21-positive B or T cells lacking MHC class II are only infectible if HLA-DR, -DP, or DQ are exogenously expressed in the cells (44). Since EBV gp42 is critical for virus infection through its interaction with HLA class II and fusion to B cells, B cells with different HLA sequences might show different susceptibility to EBV infection. An in vitro study in which HLA-DQ was transiently expressed in a B cell line lacking HLA class II showed that cells expressing HLA-DQ3.3 (α*0301 × β*03032) cells were less susceptible to EBV infection, while cells expressing HLA-DQ2 (a*0501 × β*0201) were more susceptible to virus infection (44).

The role of HLA class I in EBV infection in vitro

HLA class I molecules are encoded by 6 genes, *HLA-A, HLA-B, HLA-C, HLA-E, HLA-F and HLA-G*, and 12 pseudogenes (3). HLA class I molecules bind to β_2 microglobulin and present peptides that are inside the cell onto the surface of the cells.

Lai et al. used monoclonal antibodies with T cell receptor-like epitopes to show that antibody binding to peptides from HLA A*02:01, A*02:03, A*02:06 and A*02:07 alleles mediates both complement-dependent and antibody-dependent cellular cytotoxicity on EBV-transformed human B lymphoblastoid cell lines (45).

The role of HLA class II in EBV infection of humans

About 3-5% of adults in the general population are seronegative for EBV. The ability of EBV to bind to B cells has been correlated with the EBV serostatus in several studies. Gervis et al. observed relatively low EBV binding to B cells in EBV seronegative adults (46). CD21 and MHC class II serve as receptors for EBV infection of B cells through their interactions with EBV gp350 and gp42, respectively. CD21 is highly conserved; thus, the reduction in EBV binding to B cells in seronegative individuals is likely a result of variation in HLA. A significant correlation was observed between HLA-DR 13 and seronegativity to EBV in a study of 52 individuals (47). HLA-DR 13 is associated with HLA-DQ6 β1 *06 in Caucasians (48); thus, the increased EBV seronegativity found in the HLA-DR β 1 * 13-DQ β1 *06 haplotype may be primarily due to DQ β1 *06. We found that individuals with DQ β1 *06/*06 were also more likely to be EBV seronegative (49). Hocker et al. found that HLA-DR7 was an independent risk factor for EBV infection in pediatric allograft recipients (50). HLA-DR7 is strongly associated with DQ β1 *02/*02; thus, the findings of Hocker et al. are consistent with our findings of an increased frequency of EBV seropositivity in persons with HLA-DQ β1 *02 (49).

To determine if the HLA DQ restriction for EBV infection is also seen in infection of humans in the general population, we collected 106 EBV-seronegative individuals from a pool of about 3,300 healthy blood donors (49). We found that Caucasians were more likely to be seronegative for EBV than African Americans and other non-white persons, suggesting that genetics in addition to socio-economic factors may be at play (49). These seronegative individuals, together with 218 randomly selected EBV seropositive controls, were genotyped for the HLA-DQ β chain. All four DQ β1 *04/*05 positive subjects were EBV seronegative, while all 12 DQ β1 *02/*02 positive subjects were EBV seropositive. There was an increased frequency of subjects with DQ β1 *06/*06 and DQ β1 *02/*03 than expected in the EBV seronegative group than the seropositive controls. The data were then analyzed for an association between EBV serostatus and the expression of any single HLA-DQ β 1 allele. We found that persons with at least one HLA-DQ β1 *03 allele had the highest chance of being seronegative, compared with other HLA-DQ β1 alleles. In addition, a higher than expected proportion of EBV seropositive individuals carried at least one DQ β1 *02 or one DQ β1 *04 allele. Subsequent in vitro binding and infectivity assays showed that the efficiency of EBV gp42 to bind to specific HLA-DQ alleles was sufficient to account for the allele-specific correlations with EBV seropositivity and seronegativity in naturally infected

humans. In the presence of HLA DR and DP, gp42 protein binds more efficiently to HLA-DQ β1 *02/*02 positive B cells than to either HLA-DQ β1 *03/*03 or *04/*05 positive B cells. In the absence of HLA DR or DP, gp42 protein binds more efficiently to HLA-DQ β1 *02/*02–positive and *05/*05–positive retrovirus transduced mouse cells than to HLA-DQ β1 *03/*03–positive and *06/*06–positive mouse cells. Thus, both in vivo and in vitro data provide evidence that different HLA alleles in individuals can account for differences in susceptibility to EBV infection based on the role of HLA class II for entry of EBV into cells.

In a series of studies involving students in Edinburgh, HLA-DRB1*01:01 was associated with an increased risk of infectious mononucleosis, while HLA-DRB 1*04:01 and HLA-DQB1*03:01were associated with a decreased risk compared with students who seroconverted to EBV without symptoms (51).

The role of HLA class I in EBV infection of humans

McAulay et al. reported that HLA class I polymorphisms were associated with both development and severity of infectious mononucleosis (52). However, in contrast with HLA class II, there is no evidence suggesting that HLA class I is important for entry of EBV into B cells. Therefore, the association of HLA class I polymorphisms with EBV is more likely due to genetic variation in T cell responses that control the course of primary EBV infection, the level of virus in the blood, virus reactivation, and control for EBV-associated oncogenesis (53). HLA A10, A29 and B15 were less frequent in EBV seronegative persons than those who were seropositive (54). Boyer et al. found a significantly decreased prevalence of EBV seropositivity in healthy donors who carry an HLA-A1 locus; however, the Al alleles were not able to be further defined by serology (55). EBV seronegativity was associated with HLA-C and HLA-Bw4 variants in persons over age 60 (56).

Ramagopalan et al. found that HLA-C*04:01 was associated with an increased risk of infectious mononucleosis, while HLA-C*02:02 and HLA-B* 15:01 were associated with a decreased risk compared with students who seroconverted to EBV without symptoms (51).

The Role of HLA in EBV-associated malignancies

Several cancers that are associated with EBV are more common in specific geographic areas. While environmental factors, including malaria or HIV, and dietary habits, may be risk factors for EBV diseases, genetic factors including HLA have been associated with EBV diseases. HLA is important for presentation of viral peptides to T cells and certain tumors, including EBV-positive Burkitt lymphoma cells down-regulate HLA antigens which may lead to tumor escape (57).

Virtually all cases of anaplastic nasopharyngeal carcinoma are associated with EBV and the disease is more common in Southern China and in Inuit populations. Certain HLA types, particularly HLA-A*02:07, A*33:03, and B*38:02, followed by A*02:06, B*58:01, and C*03:02 and C*07:02, are associated with an increased risk of nasopharyngeal carcinoma; other HLA types- HLA-A* 11:01, A*31:01, B*13:01, and B*55:02, followed by C*12:02 and C*12:03, are associated with a reduced risk of the disease (58, 59). Genome-wide association studies (GWAS) have also demonstrated strong links between HLA-A and

nasopharyngeal carcinoma, with weaker links between HLA-B and -C loci and disease (59–63). In addition to germline mutations, somatic mutations in HLA-A, -B, and -C have been reported in nasopharyngeal carcinoma (64).

HLA-A*01 is associated with an increased risk of EBV-positive Hodgkin lymphoma, while HLA-A*0201 correlates with a lower risk of the disease in Europeans (65–67). HLA-A*02:07 is associated with an increased risk of EBV-positive Hodgkin lymphoma in Chinese (67). However, the increased risk of HLA-A*01 and decreased risk of HLA-A*0201 for EBV-positive Hodgkin lymphoma was not observed in Hispanic patients (68). HLA-B37 and HLA-DR10 were associated with an increased risk of EBV-positive Hodgkin lymphoma in Europeans (67). HLA-wide and GWAS studies of EBV-positive Hodgkin lymphomas showed a positive correlation between HLA-A and a locus near the HLA-DPB1 gene with EBV-positive Hodgkin lymphoma (69–71). Expression of HLA class I (72) and II on the surface of Reed-Sternberg cells (the tumor cells of Hodgkin lymphoma) is more common in cases of EBV-positive than EBV-negative Hodgkin lymphoma.

A small in vitro study showed that EBV-specific CD8 T cell responses to HLA-A*01-restricted epitopes were much weaker than virus-specific CD8 T cell responses to other HLA class I restricted epitopes (73). In addition, EBV-specific CD4 and CD8 T cell responses restricted to HLA-A*01 epitopes have not been detected (53). These findings might explain the increased risk of EBV-positive Hodgkin lymphoma associated with HLA-A*01. While responses to EBV EBNA3 antigens which dominate EBV-specific CD8 T cell response were associated with multiple HLA class I molecules, responses to EBV LMP1/2A which are subdominant were mostly restricted with HLA-A*02 (74).

An increased risk of developing EBV post-transplant lymphoproliferative disease was associated with HLA-B51 in bone marrow transplant recipients (75). A study in solid organ transplant recipients showed increased risk of EBV post-transplant lymphoproliferative disease in patients who were HLA-B18 and a reduced risk in those who were HLA-A03 or HLA-DR7 (76). Post-transplant lymphoproliferative disease was higher in solid organ transplant recipients who were homozygous for HlA-A1 and lower in those who were homozygous for HLA-A2 (77).

Conclusions

HLA class I and II are highly polymorphic molecules that present antigens from pathogens to the immune system for recognition by T cells. EBV has evolved a number of viral proteins to block the activity of HLA class I and II molecules. HLA class II has a critical role in EBV infection, since it is required for the initial stage of virus infection of B cells, which are the site of virus latency. Specific HLA class II alleles are associated with increased or reduced susceptibility to EBV infection, which also correlates with their ability to bind to EBV gp42. In contrast, while HLA class I is not required for virus entry, polymorphisms in HLA class I alleles are associated with development and severity of infectious mononucleosis. Specific HLA class I alleles have been associated with several EBV malignancies including nasopharyngeal carcinoma, Hodgkin lymphoma, and post-transplant lymphoproliferative disease. Thus, while EBV has evolved to require HLA class

II for infection, both class II and class I affect susceptibility to infection and EBV-associated disease.

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