Literature review

The role of human leucocyte antigen in nasopharyngeal carcinoma

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ABSTRACT

Background: The cause of Nasopharungeal Carcinoma (NPC) is an interaction of multiple factors. The main etiologic factors are Epstein-Barr virus (EBV) infection which interacts with genetic susceptibility, and environmental factors. The growth of malignancy due to the virus is largely determined by the host immune response. Human leukocyte antigen (HLA) plays a significant role in presenting viral antigens, which is the key in determining the impact of the host immune response against this viral infection. **Purpose:** To discuss the role of HLA in NPC. **Literature review:** Individuals with specific HLA alleles may experience a decreased ability to present viral antigens and be less efficient in triggering an immune response against EBV-infected cells resulting in increased susceptibility to NPC and vice versa, so those specific HLA alleles may be protective. Various studies have reported the association of HLA alleles with NPC. The results of these studies are not always consistent. In the study of HLA class I, HLA-A2 and HLA-B46 alleles were the most consistently increasing frequency in NPC, while HLA-A11, HLA-B13, and HLA-B27 alleles were associated with a decreased risk of NPC. The HLA-DRB1*03, *08, *09, and *10 alleles contributed to susceptibility to NPC, while the HLA-DRB1*11 and *12 alleles were protective factors against NPC. **Conclusion:** Genetic factors are important risk factors for NPC, many studies have consistently reported the role of HLA in the pathogenesis of NPC, where specific HLA alleles cause susceptibility to NPC growth, but several HLA alleles are also associated with a reduced risk of NPC.

Keywords: HLA, alleles, nasopharyngeal carcinoma

ABSTRAK

Latar belakang: *Penyebab terjadinya Karsinoma Nasofaring (KNF) merupakan interaksi dari beberapa faktor. Faktor etiologi utama adalah infeksi virus Epstein-Barr (EBV) yang berinteraksi dengan kerentanan genetik, dan faktor lingkungan. Pertumbuhan keganasan akibat virus sangat ditentukan oleh respon imun host.* Human Leucocyte Antigen (HLA) *berperan penting dalam penyajian antigen virus, yang merupakan kunci dalam menentukan dampak respon imun* host *terhadap infeksi virus ini.* ***Tujuan:*** *Membahas peran HLA pada KNF.* ***Tinjauan pustaka:*** *Individu dengan alel HLA spesifik dapat mengalami penurunan kemampuan untuk mempresentasikan antigen virus dan kurang efisien dalam memicu respon imun terhadap sel yang terinfeksi EBV yang mengakibatkan peningkatan kerentanan terhadap KNF dan sebaliknya, sehingga alel HLA tertentu mungkin bersifat protektif. Berbagai penelitian telah melaporkan hubungan alel HLA dengan KNF. Hasil dari berbagai penelitian tersebut tidak selalu konsisten. Pada studi HLA kelas I, alel HLA-A2 dan HLA-B46 adalah yang paling konsisten frekuensinya meningkat pada KNF, sedangkan alel HLA-A11, HLA-B13 dan HLA-B27 dikaitkan dengan penurunan risiko KNF. Alel HLA-DRB1*03, *08, *09 dan *10 berkontribusi terhadap kerentanan terhadap KNF, sedangkan alel HLA-DRB1*11 dan *12 merupakan faktor protektif terhadap KNF.* ***Kesimpulan:*** *Faktor genetik merupakan faktor risiko penting pada KNF, berbagai penelitian konsisten melaporkan peran HLA dalam patogenesis KNF, di mana alel HLA tertentu menyebabkan kerentanan terhadap pertumbuhan KNF, sementara beberapa alel HLA juga terkait dengan penurunan risiko KNF.*

Kata kunci: *HLA, alel, karsinoma nasofaring*

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INTRODUCTION

The etiology of nasopharyngeal carcinoma is multifactorial, consisting of viral infection, environmental and genetic factors. Epstein Barr virus (EBV) infection is the predominant etiology. Up to 90% of cases in endemic areas show involvement of EBV. The EBV as an etiologic factor is supported by high titers of antibodies and EBV antigens in both plasma and tumor cells.[1]

The growth of malignancy due to the virus is largely determined by the host immune response. Human leucocyte antigen (HLA) plays a major role in presenting viral antigens, which is the key in determining the impact of the host immune response against this viral infection. Inhibition of HLA expression may facilitate the evasion of tumor cells from host immunosurveillance. Various studies have found a relationship between the HLA complex and the immune response to EBV. Several studies support the hypothesis that EBV can down-regulate the expression of HLA alleles which will cause cancer cells to evade the immune response by reducing the expression of EBV antigens from cancer cells.[2] Individuals with specific HLA alleles may experience a decreased ability to present viral antigens and be less efficient in triggering an immune response against EBV-infected cells, resulting in increased susceptibility to NPC.[3]

Human Leucocyte antigens consist of class I and class II, which are major histocompatibility complexes located on the short arm of chromosome 6 (6p).[4,5] The HLA class II genes encode DR, DQ, and DP genes that are expressed on immune cells and are important in the regulation of the immune response to antigens and recognition of self and non-self. These genes produce T-cell-specific peptides to initiate cell-mediated immune responses against EBV infection.[5]

Various studies have reported the association of HLA class I allele with NPC in areas of a high incidence of NPC, HLA-A2, and HLA-B46 alleles were reported to be the most consistent with increased risk of NPC, and HLA-A11, HLA-B13, and HLA- B27 is associated with a reduced risk of NPC. Research to see the relationship between NPC and HLA was less intensive in areas with an intermediate incidence of NPC. Several studies report that it was completely different from areas with high incidence of NPC. HLA-A10, -B13, -B51, and -B18 were associated with an increased risk of NPC, and HLA-B14 was associated with a decreased risk of NPC in this region.[6] Study on HLA class I had also been carried out on the Indonesian population in Java where HLA-A24, HLA-A2, and HLA-B16 were increasing the susceptibility of NPC.[7]

Studies on the relationship between HLA class II and the incidence of NPC had also been reported, although not as many as HLA class I studies. Various studies of HLA-DRB1 in NPC had obtained inconsistent results. One meta-analysis that examined the association of the HLA-DRB1 allele with the incidence of NPC found that the HLA-DRB1*03, *08, *09, and *10 alleles contributed to susceptibility to NPC. In contrast, the HLA-DRB1*11 and *12 alleles were protective factors against NPC, especially in Asian populations.[5]

This article aimed to describe the role of HLA in NPC, whether it increases susceptibility or reduces susceptibility to NPC.

LITERATURE REVIEW

Human Leucocyte Antigen (HLA)

HLA is located at 6p21.3, which consists of class II, class III, and class I genes which are located sequentially from the centromere to the end of the telomere. Class I molecules are involved in the binding and presentation of endogenous peptides to cells $CD8^+$T, while class II molecules are involved in the binding and presentation of peptides exogenous cells into $CD4^+$T and class III molecules involved in innate immune or inflammatory response.[8]

Human Leucocyte Antigen Class I

HLA class I molecules are expressed on the surface of all nucleated cells. This protein consists of a trans-membrane heavy chain with three extracellular domains (α1-3) and β2-microglobulin light chain.[9] The α1 and α2 domains form a peptide-binding groove that accommodates 8-11 amino acids.[9,10]

Before migrating to the surface of the cell, HLA class I molecules are first to be loaded with high-affinity peptide immunodominant, the result of degradation cytosolic proteins by the proteasome in the endoplasmic reticulum (ER).[9] Peptide antigens produced by a virus that lives in the cytoplasm of infected cells, tumor protein, or non-functional cytoplasmic protein.[10] HLA molecule class I in the ER binds to the peptides in the cytoplasm assisted by the Transporter associated with Antigen Processing (TAP) in the surface of the ER. Peptides are bound by TAP and are actively pumped into the ER. Class I peptide-HLA complexes are stabilized by peptide-loading complexes (PLCs), such as Erp57, calnexin or calreticulin, and tapacin, which are then transported to the cell surface for recognition by $CD8^+$T lymphocytes.[10]

Human Leucocyte Antigen Class II

HLA class II molecules are present on antigen-presenting cells (such as dendritic cells, macrophages, or B cells) consisting of α and β chains.[11] Each chain has two extracellular domains that form a groove peptide-binding capable of accommodating 10-30 peptides.[9,10]

Antigen-presenting cells constantly synthesize HLA class II molecules in the endoplasmic reticulum. Each new HLA class II molecule carries a protein with an invariant chain known as a class II invariant chain peptide (CLIP). This class II CLIP-HLA complex is transported to the cell surface in an exocytic vesicle that fuses with endosomal vesicles containing peptides from extracellular proteins. Endosomal vesicles contain a class I-like protein, DM, which functions to release CLIP from class II HLA molecules. Once the CLIP is removed, the peptide-binding groove is ready to bind to the peptide. Complexes of peptide-HLA class II is transported to the surface of the cell to be recognized by cells T $CD4^+$.[9,10]

The role of HLA in antigen recognition and presentation

Exogenous pathway via HLA-II

Antigens generally enter the body through the skin, gastrointestinal epithelium, and respiratory tract. Antigens are captured and processed into small peptides by lysosome enzymes, carried by the Antigen Presenting Cell (APC) to the lymph nodes. Small peptides are bound by HLA-II molecules in endosomes and transported to the APC surface for presentation to $CD4^+$T cells. Phagocytosis is initiated by the adhesion of the antigen to the macrophage membrane. The fusion of pseudopodia surrounding the membrane-bound material eventually forms a pocket called a phagosome. The phagosome moves to the anterior of the cell and fuses with the lysosome, which contains various hydrolytic materials and digests the ingested material.[12]

The exogenous (endosomal) pathway supports the process of antigens to be presented to T cells by a regulated class II mechanism. Peptide molecules a and b produced in the endoplasmic reticulum combine and interact with special chains that prevent peptide bonding in the intracellular compartment. At the end of the exogenous pathway, the endosomes contain HLA-II, and the invariant chains fuse with the lysosomes. Enzymes in lysosomes destroy invariant chains that allow HLA-II bonds to bind to peptides.[9]

Endogenous pathway via HLA-I

Antigens that are processed through the endogenous pathway will be bound by HLA-I molecules, which will then be brought to the cell surface and presented to $CD8^+$ T cells. $CD4^+$ and $CD8^+$ cells can only recognize antigens when presented by HLA molecules (HLA restriction phenomenon). Multiple protein complexes in plasma known as proteasomes are involved in the proteolytic degradation of proteins presented via HLA. Antigen molecules are carried from the cytoplasm to the endoplasmic reticulum to interact with HLA-I. When the HLA-I molecule has been stabilized, the Antigen-HLA-I complex leaves the endoplasmic reticulum, enters the Golgi apparatus, and is then carried to the cell surface.[12]

The role of HLA in NPC

The incidence of different NPC based on ethnicity, indicates the important contribution of genetic susceptibility in the pathogenesis of NPC. The incidence of NPC in southern China is 20 to 50 times higher than the population in the west, second and third-generation ethnic Chinese who migrated to the United States, which is an area with a low incidence, still have a higher incidence of NPC than local residents despite cultural assimilation.[3] The same thing was also reported by McDermott et al.[13] A lower incidence of almost all malignancies in the immigrant population in Canada except for three malignancies, one of which was nasopharyngeal carcinoma, which remained higher in immigrant communities from northeast Asia.

The incidence of NPC in families with NPC is found in 10% of the Chinese ethnic population. This is made possible by the common environmental risk factors between patients and their families and also due to genetic susceptibility in these ethnic groups.[3] Genetic susceptibility to NPC had been reported to be primarily associated with HLA.[3,4,14] Genetic susceptibility to NPC had been reported to be primarily associated with HLA class I and class II at the HLA locus on chromosome 6p21.[3,4,14]

HLA class I genes encode proteins for identifying and presenting foreign antigens, including EBV peptides to cytotoxic T cells to trigger a host immune response against virus-infected cells. The difference in susceptibility to NPC in different ethnicities illustrates the different abilities of the HLA haplotype in controlling EBV infection in the infected population. Individuals with certain HLA alleles may be less efficient in enhancing the cytotoxic immune response against EBV-infected cells, resulting in increased susceptibility to NPC.[3] HLA class II genes encoded by the DR, DQ, and DP genes are expressed on immune cells that play an important role in the regulation of the immune response to foreign antigens and the recognition of self and non-self.[15]

Recent studies from genome-wide association studies (GWAS) on NPC had consistently obtained Single Nucleotide Polymorphism (SNP) in the MHC region where the HLA gene is located.[16,17] HLA class II genes will present antigenic peptides to specific T cells to initiate a cell-mediated immune response against EBV infection. Each class II antigen is a heterodimer consisting of one chain α and one β encoded by the gene A and B. gene products produced by the highly polymorphic class II genes. This

polymorphism is caused mainly by the difference in the chain β , but can also be due to differences in DQα and DPα chain.[5]

The EBV-induced carcinogenesis process depends on the expression of protein oncogenes, especially Latent Membrane Protein 1 (LMP1), which plays a role in preventing apoptosis and activating a number of signaling pathways, such as nuclear factor kappa B (NF-kβ), mitogen-activated protein kinases (MAPK), JNK/AP1 and phosphoinositol 3-kinase (PI3K) promotes cell motility and suppresses the immune response.[3,18] LMP1 is the main transforming protein of EBV that has a pleiotropic effect, which plays a role in the induction of cell surface adhesion molecules and antigen activation, upregulation of anti-apoptotic proteins, B-cell lymphoma 2 (Bcl-2), and stimulates the production of cytokines (IL-6, IL-8). Expression of LMP1 in epithelial cells is associated with phenotypic effects, such as hyperproliferation, induction of proinflammatory cytokines, anti apoptosis and increased motility.[18]

The Epstein Barr Nuclear Antibody 1 (EBNA1) protein plays an important role in the replication and segregation of EBV episomes that prevent cells from apoptosis, increase cell survival and directly contribute to a tumorigenic phenotype. This effect is manifested by various mechanisms, including p53 destabilization, disruption of promyelocytic leukemia (PML) nuclear bodies, and modulation of various signaling pathways.[18] The EBNA1 protein is important for viruses to maintain viral DNA during cell division. EBNA1 also regulates viral and cellular gene expression.

The Epstein Barr virus can manipulate the antigen recognition process by the immune system by developing immune evasion strategies. During the latent phase in B cells, EBV decreases the expression of immunogenic proteins, such as EBNA1, that play an important role in preventing proteasomal degradation and antigen presentation by HLA class I. During replication, the virus downregulates HLA I and HLA II modulation to evade infected cells from T cells. CD4+ and CD8+.[19]

Some studies had reported several alleles of the HLA class I gene associated with the incidence of NPC in areas of high incidence of NPC, the alleles HLA-A2 and HLA-B46 were reported to be the most consistent as HLA class I, which increased in frequency in NPC; and HLA-A11, HLA-B13, and HLA-B27 were associated with a reduced risk of NPC. Research to see the relationship between NPC and HLA was less intensive in areas with an intermediate incidence of NPC. Several studies reported that it was completely different findings from areas with a high incidence of NPC, i.e. HLA-A10, -B13, -B51, and -B18 were associated with an increased risk of NPC, and HLA-B14 was associated with a decreased risk of NPC in this region.[6]

Research on the relationship between HLA class II and the incidence of NPC had also been reported. Various studies of HLA-DRB1 in NPC obtained inconsistent results. One meta-analysis of the association of HLA-DRB1 with the incidence of NPC found that the HLA-DRB1*03, *08, *09, and *10 alleles contribute to susceptibility to NPC, while the HLA-DRB1*11 and *12 alleles may be protective factors against NPC. NPC is mainly in Asian populations.[15] A study in southern Tunisia also found the HLA-DRB1*03 allele increased 2.83 times the incidence of NPC.[14]

A study by Yang et al.[4] reported that HLA-DRB1*03, *09, and *10 increased the risk of NPC by 1.7; 1.3; 1.9 times respectively, while HLA-DRB1*01 was a protective gene. They also performed a meta-analysis of multilevel (stratified meta-analysis) classifying risks by ethnic groups into Tunisian, Chinese and Caucasians, who had HLA-DRB1*03 was associated with increased risk of NPC in

Tunisia (p<0:01, OR= 3.151, 95% CI 1.998–4.968) and Asian (p=0.045, OR=1.62, 95% CI 1.011–2.594), but not significantly related in the Caucasian group.

HLA allele associated with susceptible to NPC

Epidemiological studies have shown that HLA allele polymorphisms are closely correlated with NPC susceptibility. Chan quoted in Li[8] conducted a study on the relationship between HLA and NPC in residents of Singapore, Malaysia, Hong Kong, and southern China found that HLA Class I alleles, such as A*02, A*33, B*46, B*58, and Cw*1 often appears in NPC patients.

Studies by Goldsmith[20] in high incidence NPC found a positive relationship between NPC risk and HLA-A*02, B*14, and B*46. Another study using molecular typing found a positive relationship between the alleles A*33, B*38, and B*58 with NPC. A study by Hildesheim et al.[21] on the HLA-A*02 serogroup found a consistent relationship between HLA-A*02:07 and NPC. These results were consistent with a study conducted by Hsu et al.[22] in Taiwan which concluded that the risk of NPC was highest in individuals with HLA-A*02:07. Yu et al.[23] in Taiwan conducted a study on high-risk multiplex families, found that HLA-A*02:07, A*33:03, B*38:02, and HLA-B*58:01 increased the risk of NPC.

The risk of NPC will be higher if two HLA alleles are found, i.e. HLA-A*02:07 and HLA-B*46:01. Wang et al.[24] study on the Han ethnic group in Xinjiang found that the haplotype of A*02-B*46 was strongly associated with distant metastases in NPC. Tang et al.[25] conducted a study on the Han ethnic group in Guangxi province, southern China and found that the haplotype A*02:06-B*15:02 increased in NPC, HLA-A*02:07 alone or the combination A*02:07-B*46:01 is associated with NPC susceptibility, HLA-A*33:03 alone or a combination of A*33:03-B*58:01 is also associated with NPC susceptibility. Yu et al.[23] found individuals with HLA-A*02:07 allele with/without HLA-B*46:01 had 1.9 times and 2.1 times the risk of NPC, respectively.

Studies on populations in areas with an intermediate incidence of NPC, Heirat et al as cited by Li et al.[8] found that HLA-A*03, B*05, and B*15 were more frequently found in NPC patients in Algeria. Mokni-Baizig et al.[27] in Tunisia reported a higher HLA-A*26 in NPC patients than controls and patient's family members. Li et al.[8] reported that haplotypes HLA-B*18:01 and HLA-B*57:01 were positively associated with NPC. Research conducted in areas with low incidence of NPC such as the Caucasian found that the alleles HLA-A*31, B*13, and B*27 were more frequently found in NPC patients.

Research on HLA class II, a meta-analysis study by Yao et al.[5] found a significant relationship between the HLA-DRB1*03 allele and an increased incidence of NPC (OR=1.55; 95% CI 1.3-1.8). When grouped by ethnicity, this relationship was also seen in Asians and Tunisians, but not in Caucasians. Another meta-analysis study by Yang et al.[4] also found that the HLA-DRB1*03 allele increased the incidence of NPC (OR=1.70; 95% CI 1.04-2.76). When grouped, it also found an association between Asian and Asian ethnicity, Tunisians, but not Caucasians.

Studies from areas of intermediate incidence of NPC such as Tunisia also reported that the HLA-DRB1*03 allele was associated with an increased risk of NPC, including the Mokni-Baizig et al.[27] report, where the allele frequency in cases was 41.66% and in controls 21.53%, and there was a significant relationship between allele frequency with increased incidence of NPC (OR= 2.04; p<0.05).

HLA allele that protective to NPC

Most cases of NPC are EBV positive; therefore, it is concluded that individuals who have HLA with a low ability to present antigens to the immune system have a tendency to suffer from greater NPC and vice versa.[28] Several studies had shown that the frequency of alleles or haplotypes of HLA causes susceptibility or protection against NPC events. The pattern of alleles or haplotypes varies in different regions, characterized by different prevalences in each region. Thus it is stated that alleles or haplotypes may be associated with the development of diseases related to the immune system or genetic predisposition according to ethnicity and geography.[6]

Some HLA alleles had a more efficient ability to elicit the immune system, leading to protective of NPC. HLA A-11 allele had been reported to represent the EBV immunodominant epitope of EBNA-4 and EBNA-6. Efficient activation of the T-cell response as a result of the induction of EBV epitope presentation by HLA-11 may explain the reduced risk of NPC in HLA A-11 positive patients. The HLA-B13 and HLA-B27 alleles were associated with protection against NPC.[28]

The study by Yu et al.[28] in the population with a high risk in Taiwan also found HLA-A*1101 that is protective to NPC. Hildesheim et al.[17] in his study in the same region, found that HLA-A*1101, HLA-A83101, HLA-B*13, and HLA-B839 were significantly lower than the control group. Strong and efficient induction of cytotoxic T cells, which respond against EBV-infected cells, was stimulated by a presentation of EBV epitopes by HLA. Lu et al.[29] reported the distribution of HLA-A2 was higher in NPC than in controls. In contrast to HLA-A*11 distribution, which was significantly low in the patient group and high in the control group. Mokni-Baizig[27] study in the Tunisia reported that HLA-B13 was found as the highest frequency in NPC patients and, HLA-A23 decreased the risk of NPC. HLA-B13 was susceptible in this study, in contrast to studies in Chinese where HLA-B13 was protective.

DISCUSSION

Some studies have reported that several alleles of the HLA class I gene are associated with the incidence of NPC in areas of a high incidence of NPC. The alleles HLA-A2 and HLA-B46 were reported to be the most consistent as HLA class I with increased frequency in NPC (increased susceptibility), and HLA-A11, HLA-B13 and HLA-B27 were associated with a reduced risk of NPC. Research in areas with an intermediate incidence of NPC to see the relationship between NPC and HLA was less intensive, from several reports getting completely different findings from areas with high incidence of NPC i.e. HLA-A10, -B13, -B51, and -B18 were associated with an increased risk of NPC, and HLA-B14 was associated with a reduced risk of NPC in this region.[6]

Studies on the relationship between HLA class II and the incidence of NPC had also been reported. Various studies of HLA-DRB1 in NPC obtained inconsistent results. One meta-analysis of the association of HLA-DRB1 with the incidence of NPC found that the HLA-DRB1*03, *08, *09, and *10 alleles contributed to susceptibility to NPC. In contrast, the HLA-DRB1*11 and *12 alleles might be protective factors against NPC.[5] A study in southern Tunisia also found that HLA DRB1*03 allele increased 2.83 times the incidence of NPC.[14] Another meta-analysis reported that HLA-DRB1*03, *09, and *10 increased the risk of NPC by 1.7; 1.3; 1.9 times respectively, while DRB1*01 was a protective gene.[4]

The meta-analysis by Yang et al.[4] stratifying risk by ethnic into Tunisian, Chinese and Caucasian, reported that HLA-DRB1*03

was associated with an increased risk of NPC in Tunisian (p< 0.01, OR=3.151, 95% CI 1.998–4.968) and Asian (p=0.045, OR=1.62, 95% CI 1.011–2.594), but not significantly related in the Caucasian group.

In conclusion, Human Leucocyte Antigen (HLA) had an important role in presenting viral antigens. Individuals with specific HLA alleles were thought to have decreased ability to present viral antigens and were ineffective in triggering an immune response against EBV-infected cells. This could lead to increased susceptibility to NPC. On the other hand, there were several specific alleles of HLA which were thought to be able to present viral antigens and very effective and efficient in triggering the immune response, so that they were protective towards NPC.

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