Human leukocyte antigen and tumor immunotherapy (Review)

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Abstract. Malignant tumors seriously endanger human health and life, and restrict economic development. Human leukocyte antigen (HLA) is the expression product of the human major histocompatibility complex, which, at present, is the most complex known polymorphic system. The polymorphism and expression of HLA molecules have been demonstrated to be associated with the occurrence and development of tumors. HLA molecules can regulate the proliferation of tumor cells and inhibit antitumor immunity. In the present review, the structure and function of HLA molecules, the polymorphism and expression of HLA in tumor tissue, the roles of HLA in tumor cells and tumor immunity, and the potential clinical application of HLA in tumor immunotherapy are summarized. The overall aim of the present review is to provide relevant information for the development of antitumor immunotherapies involving HLA in the clinic.

Contents

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1. Introduction

Human leukocyte antigen (HLA) is the expression product of human major histocompatibility complex (MHC), which is located on the short arm of chromosome 6p21.31 (1). HLA genes have a complex polygenic architecture and are highly polymorphic (1). To date, based on the IPD-IMGT/HLA database (https://www.ebi.ac.uk/ipd/imgt/hla/), >35,000 alleles of HLA have been identified, of which >15,000 functional genes have been demonstrated to express proteins. The arrangement of HLA genes on chromosomes is divided into three regions, namely the class-I, -II and -III gene regions (2). HLA-I molecules are widely distributed on the surface of human nucleated cells and participate in the processing and presentation of endogenous antigen peptides (3). The presentation of endogenous antigens by HLA-I molecules involves three important steps: i) The production of antigen polypeptides by proteasome cleavage; ii) transportation of polypeptides to the endoplasmic reticulum by transporter associated with antigen processing (TAP); and iii) polypeptides bind to HLA-I molecule binding channels and are transported to the cell surface for display (3). By contrast, HLA-II molecules are predominantly expressed on the surface of antigen-presenting cells and activated T cells (4). These HLA-II molecules are mainly involved in the processing and presentation of exogenous antigens (4). In the endoplasmic reticulum, HLA-II molecules bind to a peptide chain named the invariant chain to form a complex to prevent the binding of endogenous antigenic peptides to HLA-II molecules. In this process, after the constant chain is degraded by proteases, the exogenous antigen polypeptide binds to the empty HLA-II molecule to form a complex that is expressed on the cell surface (4). The immune response of cytotoxic T cells has been demonstrated to be restricted by HLA-I molecules (5). By contrast, HLA-II molecules are involved in immune regulation through the action of restricted helper T cells (5). HLA-III genes are located between the class-II and class-I genes, and mainly include genes associated with the complement system, and tumor necrosis factor (TNF) and heat shock protein (HSP) genes (6,7). The abnormal expression of HLA molecules has been demonstrated to affect antigen processing and presentation, leading to immune escape and lack of recognition of tumor cells by the body (8,9). In recent years, an increasing number of studies have focused on HLAs as potential targets for tumor immunotherapy (8-10). The effective binding of HLA to antigen epitopes is the key to immunotherapy. Tumor

polypeptide vaccines targeting peptides recognized jointly by HLA-I and HLA-II molecules can produce more potent and long-lasting antitumor effects (10). In the present review, the roles and mechanisms of HLAs in tumor immunotherapy are summarized.

2. Physiological function and structure of HLA

HLA-I genes can be divided into three classical groups (HLA-A, HLA-B and HLA-C) or the non-classical groups (for example, HLA-E, HLA-F and HLA-G) (11). HLA-I molecules are composed of a heavy chain (the α-chain) and a light chain (the β2m chain) (12). The α-chain is encoded by HLA-A, B and C alleles, and is divided into the extracellular, transmembrane and intracellular regions (12). The extracellular region of the α-chain is formed by the folding of the three functional regions (namely, α1, α2 and α3), where CD8 binding sites are located on α3 (12). By contrast, the β2m chain, encoded by the β2 microglobulin gene, is attached to the α3 region by non-covalent bonds (13).

HLA-II molecules are heterodimers, located near to the centromeres of chromosomes, which are composed of an α- and a β-chain (14). HLA-D alleles of HLA-II are divided into HLA-DR, HLA-DQ and HLA-P isotypes, and there are also DMA, DMB, latent membrane protein 2 (LMP2), LMP7, TAP1 and TAP2 gene loci (15). At least 36 genes have been mapped in the class III gene region, among which the genes associated with the immune system include C4B, C4A, C2, BF, TNF and HSP70, which encode the C4, C2, factor B, TNF-α, TNF-β and HSP70 proteins (16-18).

In recent years, greater attention has been paid to HLA-G and HLA-E, which belong to the group of non-classical HLA-I molecules and are located at chromosome 6p21.3 (19,20). During embryonic development, HLA-G is secreted by amniotic cells, erythroid precursor cells and cytotrophoblasts (21); its main role is to inhibit the function of maternal natural killer (NK) cells and to prevent NK cells from attacking allogeneic fetuses with antigenicity (22). Compared with those in normal pregnancy, the expression levels of HLA-G mRNA and protein in the placenta of patients with pre-eclampsia and recurrent miscarriages have been demonstrated to be decreased (23). HLA-G is expressed in immune privilege sites, including the cornea, thymus, pancreatic islets, erythroblasts and epithelioid progenitor cells, in healthy individuals (24). By contrast, HLA-E has been demonstrated to be mainly expressed on the surface of endothelial cells, T and B lymphocytes, monocytes and macrophages, and also at a high level in the amniotic membrane and trophoblast cells at the maternal-fetal interface (25,26). HLA-E molecules are the ligands of C-type lectin family receptors (27). The inhibitory receptors of C-type lectin family receptors are the CD94/NKG2A receptors, and the activating receptors are the CD94/NKG2C receptors (28). Under physiological conditions, the affinity between HLA-E and CD94/NKG2A is significantly higher than that between HLA-E and CD94/NKG2C (28). Upregulation of HLA-E expression can protect target cells from being killed by NK cells (29). HLA-G and HLA-E have been found to be abnormally expressed in autoimmune diseases, viral infections and inflammation (30-32).

HLA molecules have two main biological functions: A target function and a recognition function (33). The antigenic specificity of the HLA-I antigen lies in the specific amino acid sequence of the antigenic determinant of the peptide chain (34,35). The recognition function of HLA is associated with the unique synergy of the immune response (36). Antibodies are produced in B cells, although, in the majority of cases, macrophages and T lymphocytes are required to participate in antibody production (8). After the antigen has been processed by macrophages, the antigen information is transmitted to helper T cells, which then transmit the information to B cells to ensure that they can further secrete specific antibodies (37). During this process, helper T cells not only recognize antigens on sensitized macrophages, but also recognize whether the macrophages are consistent with their own class II antigens (38). Helper T cells are activated only when the haplotypes of macrophages and helper T cells match consistently, and this mechanism ensures that the immune response is regulated under strict genetic control (39).

The majority of febrile non-hemolytic blood transfusion reactions are caused by HLA, especially in patients who have multiple blood transfusions (40,41). HLA matching is the most important standard prior to organ transplantation, and this is significant in terms of improving the survival rate for patients with transplanted organs and ensuring the success of organ transplantations for patients with high sensitivity to anti-HLA antibodies (42-45). The purpose of bone marrow transplantation (BMT) is to transplant hematopoietic stem cells (46,47). Stem cells have the ability to replicate and differentiate into hematopoietic and immune active cells (48). BMT is associated with HLA and it is therefore a requirement that the HLA-A, B, DR and DQ isotypes of the donor and recipient are as compatible as possible (49).

The HLA complex is highly polymorphic, and the probability of matching identical phenotypes among unrelated individuals is extremely low. Therefore, this characteristic may be used for individual identification in forensic medicine (50). The HLA complex is regarded as a specific genetic marker that accompanies an individual for life (50). To date, >60 diseases have been found to be associated with HLA (51). The precise etiology or pathogenesis underlying this involvement of HLA with disease remains unknown, although it is known to be associated with immune abnormalities, familial tendencies and environmental induction (51). The most notable example is that >91% of white patients with ankylosing spondylitis carry the HLA-B27 antigen (52). In addition, 40% of patients with Hodgkin's are HLA-A1$^+$ (53), 76% of patients with skin pigmentation conditions are HLA-A3$^+$ (54) and 40% of patients with Behcet's disease are HLA-B5$^+$ (55).

It can therefore be noted that the physical and chemical properties and the biological functions of HLA, not only have important theoretical significance, but they are also of great biomedical value.

3. HLA polymorphism and cancer

The degree of the association between HLA polymorphism and tumor risk is affected by ethnicity, and even results obtained from the same population can be quite different. The results obtained from Spanish patients with liver disease

demonstrated that the frequency of the HLA-DR11 gene in hepatitis C virus (HCV) carriers was significantly higher than that in patients with end-stage liver disease and liver cancer (56). The frequency of the HLA-B18 allele was significantly increased in patients with hepatocellular carcinoma (HCC), although the HLA-B18 allele was found to be absent in HCV carriers (56). Compared with that in HCV carriers, the frequency of the HLA-A4 allele was also found to be significantly higher in patients with HCC (56). In a different study, the frequency of the HLA-B15 antigen in Yugoslav patients with $HBsAg^+$ hepatoma was found to be significantly higher than that in other chronic liver disease control groups and hepatitis B virus carriers (57). CW7, B8 and DR3 antigens were found to be significantly elevated in Italian patients with HCC (58). The frequencies of DRB1*07, DRB1*04 and DQB1*02 of Egyptian patients with HCC were found to be significantly higher than those of healthy controls, whereas the frequencies of DQB1*06 and DRB1*15 in the patient group were significantly lower than those in the control group (59). These findings suggested that DRB1*07, DRB1*04 and DQB1*02 are risk factors for HCC, whereas DQB1*06 and DRB1*15 act as protective factors (59). In a study by De Re *et al* (60), the DRB1*1101 and DQB1*0301 haplotypes were found to be associated with the natural clearance of HCV. In the same study, the DQB1*0301 allele was also demonstrated to have a protective role in the development of HCV infection associated with HCC, whereas DRB1*1101 exerted the opposite effect (60).

The frequency of HLA-A1 and HLA-A2 in patients with ovarian cancer was found to be higher than that in healthy controls, although the frequency of HLA-A3 was lower than that in healthy controls (61). HLA-A2:B8 haplotypes, such as A2, B5, DRB1*03, DRB1*04 and CW3, and HLA-II haplotypes, namely DRB1*0301, DQA1*0501, DQB1*0201, DRB1*1001, DQA1*0101 and DQB1*0501, were significantly higher compared with those in the control group (62). A study by Kübler *et al* (62) also demonstrated that the HLA-A2:B8 and HLA-II haplotypes may be significantly associated with the pathogenicity of ovarian cancer. The HLA-DRB1*04, HLA-DRB1*07, HLA-DRB1*11 and HLA-DRB1*15 alleles are associated with the occurrence of cervical squamous cell carcinoma and $HPV16^+$ cervical squamous cell carcinoma in women (63). In a different study, the alleles, HLA-DRB1*1402 and HLA-A*02 were demonstrated to decrease the incidence of cervical cancer, whereas DRB1*1501 and DQA1*0102 increased the incidence of cervical cancer (64). A study by Guerini *et al* (65) demonstrated that HLA-DRB1*14 was significantly associated with the occurrence of glioma. By contrast, the HLA-CW7, DRB1*1104, DRB1*1302, DQA1*0302 and DQB1*0604 haplotypes were significantly associated with the occurrence of Kaposi's sarcoma (66). Reinders *et al* (67) demonstrated that HLA-B*35 could inhibit the metastasis of head and neck squamous cell carcinoma, whereas HLA-B*40 was associated with the occurrence of oral tumors, and the HLA-B*40 and DRB1*13 haplotypes were susceptibility factors for oral tumorigenesis (67). The HLA polymorphisms associated with tumors are summarized in Table I.

The expression of HLA-G was demonstrated to be highly correlated with tumor size, lymph node metastasis and the Tumor-Node-Metastasis (TNM) stage of patients with breast cancer (68). The survival rate of patients with positive HLA-G expression was found to be lower than that of patients with negative HLA-G expression (68). The level of serum HLA-G (sHLA-G) in patients with breast cancer was demonstrated to be significantly higher than that in healthy individuals, and this was found to be significantly correlated with an increase in the $CD4^+CD25^{high}Foxp3^+$ to regulatory T cells ratio (69). The mRNA and protein levels of HLA-G in the tumor tissues of patients with advanced ovarian cancer were demonstrated to be significantly higher than those of early disease patients and healthy volunteers (70). The expression of HLA-G was also demonstrated to be associated with poor prognosis in patients with ovarian cancer (70). In a study by Lin *et al* (71), the expression of HLA-G in non-small cell lung cancer (NSCLC) was demonstrated to be significantly correlated with TNM stage, lymph node metastasis and the immune response. In addition, it was accompanied by an increase in the level of interleukin-10 (IL-10) and the gene deletion of classical HLA-I (71). In a different study, HLA-G expression in renal cancer tissue was demonstrated to be significantly higher than that in adjacent normal tissue, and the frequency of upregulated expression of HLA-G was significantly higher than that of other HLA antigens (72). HLA-G expression in patients with esophageal cancer, HCC and colorectal cancer has also been demonstrated to be significantly higher than that in healthy volunteers, and this was correlated with TNM stage, tumor histological grade, invasion degree, lymph node status and the immune response (73-75). The postoperative survival time of patients with HCC and with $HLA\text{-}G^+$ expression was significantly shorter than that of patients with $HLA\text{-}G^-$ expression. Furthermore, compared with the patients without HLA-G expression, the recurrence rate of HCC was also higher in the patients with HLA-G expression (74). The level of sHLA-G in patients with colorectal cancer and NSCLC was also found to be significantly higher than that in healthy volunteers, suggesting that sHLA-G may be used as a diagnostic marker for malignant tumors (76,77).

The expression levels of the HLA-E and HLA-G proteins and the levels of human papillomavirus (HPV) in cervical cancer tissues were demonstrated to be higher than that in cervical intraepithelial neoplasia (CIN) and chronic cervicitis tissues (78). The expression levels of HLA-E and HLA-G were positively correlated with differentiation, CIN grade, TNM stage and HPV infection (78). The levels of sHLA-E and sHLA-G in patients with gastric cancer were significantly higher than those of the healthy volunteers (79). In addition, the same study revealed that the level of HLA-E in patients with stage III gastric cancer was significantly higher than that in patients with stages I and II (79). HLA-E expression in HCC was found to be higher than that in adjacent liver tissues, and this expression was demonstrated to be positively correlated with tumor recurrence (80). A study by Zhou *et al* (81) revealed that the distribution frequency of HLA-E*0103 in patients with breast cancer was significantly higher than that in healthy controls, and the risk of breast cancer was significantly increased in patients that carried the HLA-E*0103 allele. The same study also demonstrated that the sHLA-E level of patients with HLA-E*0103 was significantly higher than that of healthy controls (81).

Table I. HLA polymorphisms associated with tumors.

Cancer type	HLA polymorphisms	Patient background	First author, year	(Refs.)
Hepatocellular carcinoma	HLA-DR11	Spanish	López-Vázquez *et al*, 2007	(56)
	HLA-B18			
	HLA-A4			
	HLA-B15	Yugoslav	Golubovic *et al*, 1996	(57)
	HLA-CW7	Italian	Ricci *et al*, 1995	(58)
	HLA-B8			
	HLA-DR3			
	HLA-DRB1∗07	Egyptian	El-Chennawi *et al*, 2008	(59)
	HLA-DRB1∗04			
	HLA-DQB1∗02			
	HLA-DRB1∗1101	Italian	De Re *et al*, 2004	(60)
Ovarian cancer	HLA-A1	Swedish	Gamzatova *et al*, 2007	(61)
	HLA-A2			
	HLA-A2	Caucasian	Kübler *et al*, 2006	(62)
	HLA-B5			
	HLA-DRB1∗03			
	HLA-DRB1∗04			
	HLA-CW3			
	HLA-DRB1∗0301			
	HLA-DQA1∗0501			
	HLA-DQB1∗0201			
	HLA-DQA1∗0101			
	HLA-DRB1∗1001			
	HLA-DQB1∗0501			
Cervical cancer	HLA-DRB1∗04	Chinese	Yang *et al*, 2006	(63)
	HLA-DRB1∗07			
	HLA-DRB1∗11			
	HLA-DRB1∗15			
	HLA-DRB1∗1501	American Indian	Schiff *et al*, 2005	(64)
	HLA-DQA1∗0102			
Glioma	HLA-DRB1∗14	Italian	Guerini *et al*, 2006	(65)
Kaposi's sarcoma	HLA-CW7	Italian	Masala *et al*, 2005	(66)
	HLA-DRB1∗1104			
	HLA-DRB1∗1302			
	HLA-DQA1∗0302			
	HLA-DQB1∗0604			
Oral tumor	HLA-B∗40	Dutch	Reinders *et al*, 2007	(67)
	HLA-DRB1∗13			

HLA, human leukocyte antigen.

To avoid the bias of single studies due to ethnic differences, the expression levels (Fig. 1A) and prognostic roles (Fig. 1B) of HLA subtypes in solid tumors were analyzed. Gene Set Cancer Analysis (GSCA) (http://bioinfo.life.hust.edu.cn/GSCA) was used to analyze and visualize the RNA-sequencing expression profiles [fragments per kilobase of transcript per million (FPKM)] (false discovery rate <0.05, $\log_2$ fold change >2) and corresponding clinical information of 33 types of cancer in The Cancer Genome Atlas (TCGA) database (https://www.cancer.gov/ccg/research/genome-sequencing/tcga). The results obtained revealed that the majority of HLAs were expressed at lower levels in human lung squamous cell carcinoma and lung adenocarcinoma (LUAD), whereas the expression levels were higher in kidney renal papillary cell carcinoma and kidney renal clear cell carcinoma (Fig. 1A). Most HLAs were found to be useful as favorable prognostic markers for the overall survival and progression-free survival rates of LUAD and skin cutaneous melanoma, although HLAs were generally found to be unfavorable prognostic markers for

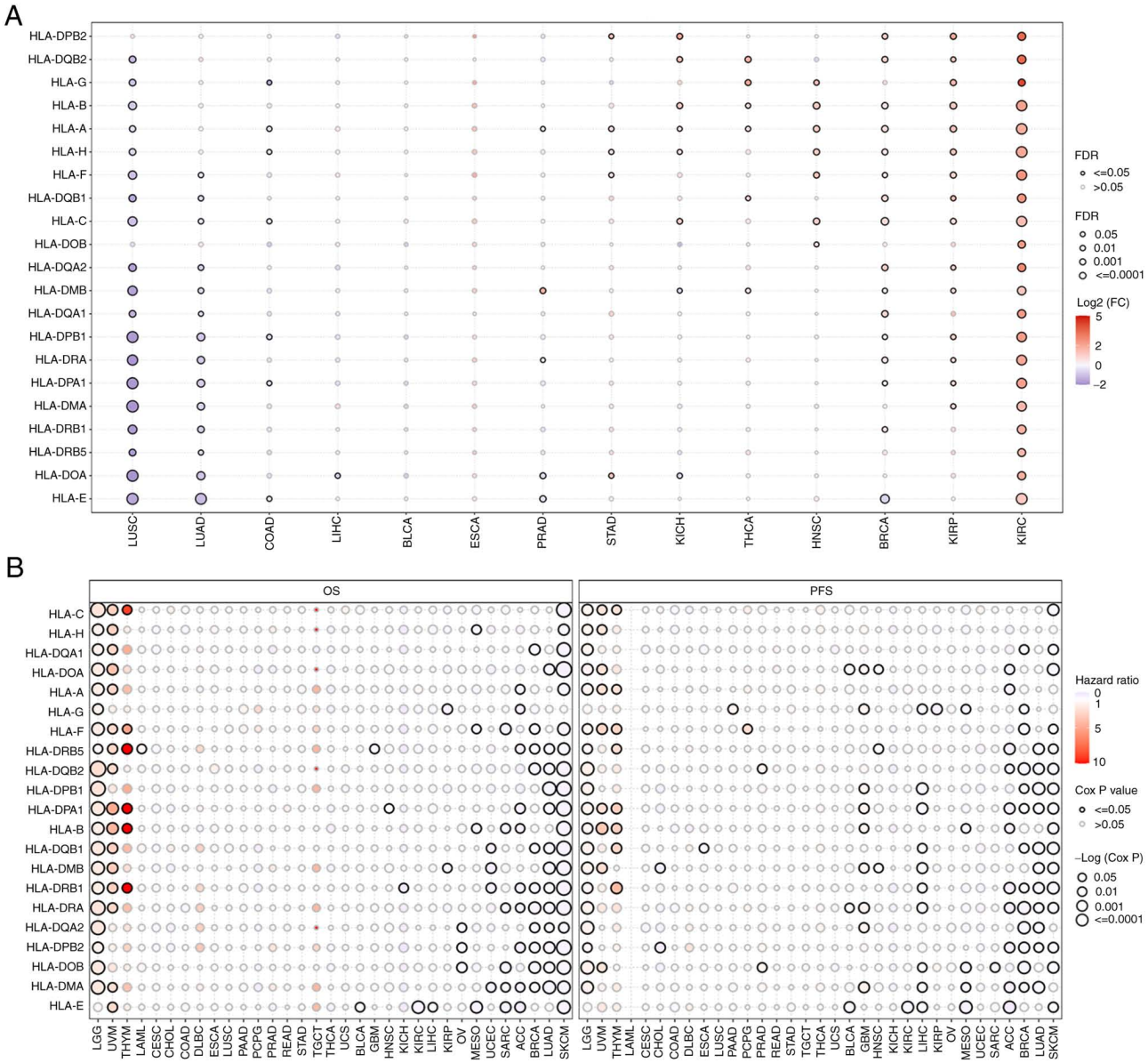

Figure 1. (A) Expression levels and (B) prognostic roles of HLA subtypes in tumors based on The Cancer Genome Atlas database. Sample set: ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; FC, fold-change; FDR, false discovery rate; GBM, glioblastoma multiforme; HLA, human leukocyte antigen; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, malignant mesothelioma; OS, overall survival; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PFS, progression-free survival; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

lower-grade glioma, uveal melanoma and thymoma (Fig. 1B). Based on the current published data, the reasons why HLAs play different roles in different types of cancer cannot be explained. However, our hypothesis is that tumor heterogeneity and the immune microenvironment are the main factors affecting HLA-regulated tumor prognosis. In addition, the mutation status of HLA in solid tumors was also analyzed (Fig. 2). The single nucleotide variation (SNV) summary and oncoplot waterfall plot were generated by GSCALite software (http://bioinfo.life.hust.edu.cn/web/GSCALite/) based on 33 types of cancer in TCGA database. In cancer tissues, the percentage variations of HLA-B, HLA-A, HLA-G and HLA-DRA were ≥10%. The most common SNV class of HLAs in cancerous tissues was found to be C>T.

Considered together, the available evidence has demonstrated that HLA polymorphisms can affect the survival rate of, and influence the curative effects on, patients with tumors, and these may therefore be used as an indicator of individualized treatment plans for these patients. Nonsynonymous mutations in the HLA gene affect antigen presentation and the expression of HLA in cancer cells, which therefore induces immune escape.

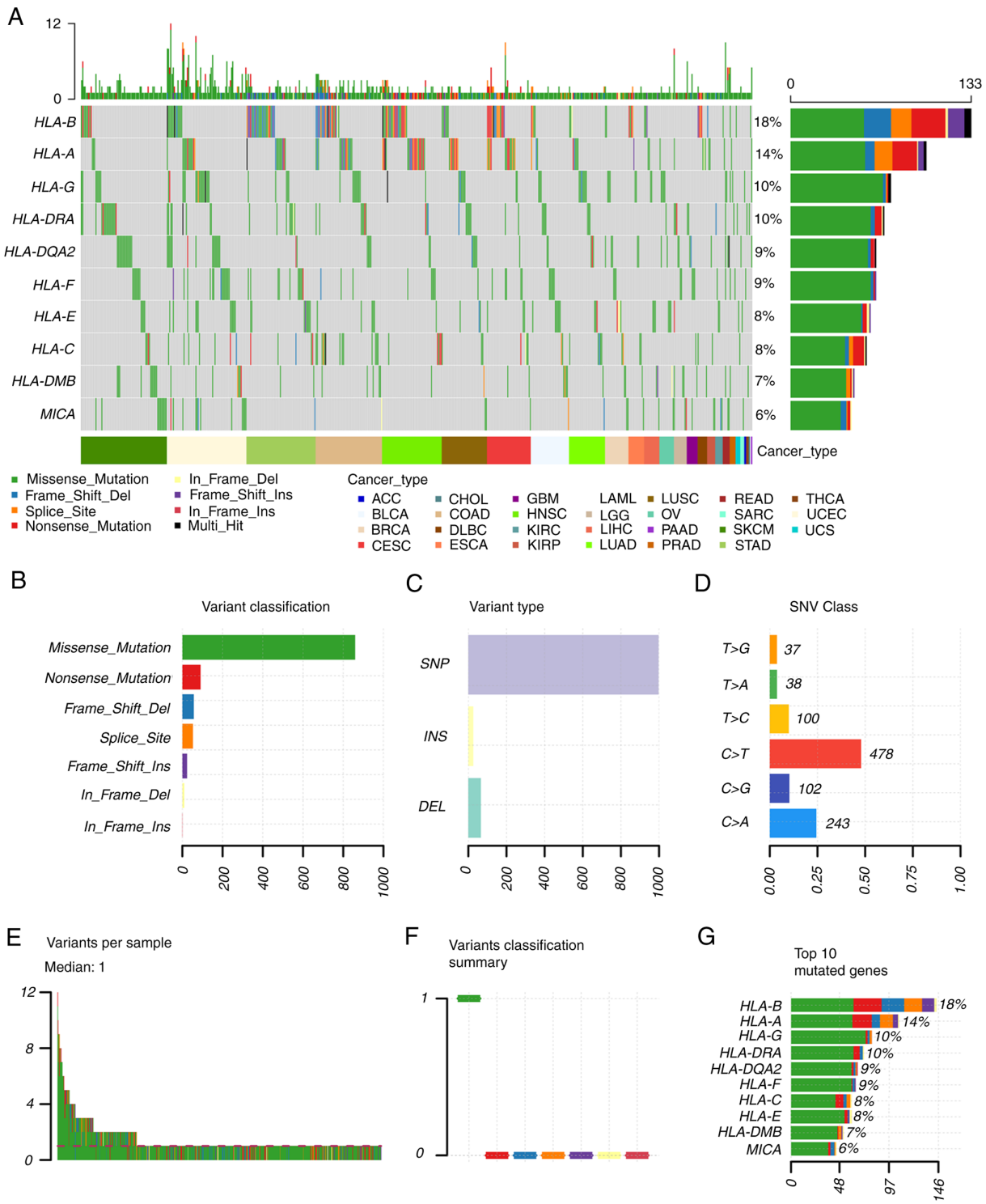

Figure 2. Mutation status of HLA subtypes in tumors based on The Cancer Genome Atlas database. (A) Mutation distribution of the top 10 mutated genes from the inputted gene set in the sample set of all 33 cancer types. (B) Count of Missense_Mutation, Nonsense_Mutation, Frame_Shift_Ins, Splice_Site, Frame_Shift_Del, In_Frame_Del and In_Frame_Ins of the inputted gene set in all 33 cancer types. (C) SNP, INS and DEL count of the inputted gene set in all 33 cancer types. (D) Count of each SNV (single nucleotide variation) class of the inputted gene set in all 33 cancer types. (E) Count of variants in the inputted gene set in all 33 cancer types. (F) Distribution of the count of each variant classification in the inputted gene set in all 33 cancer types. (G) Count and percentage of variants in the top 10 mutated genes. Inputted gene set: HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-E, HLA-G, HLA-DQB1, HLA-DQA1, HLA-DPB1, MICA, HLA-DRA, HLA-DQA2, HLA-DPA1, HLA-DRB5, HLA-DOA, HLA-DRB3, HLA-DRB4, HLA-DMB, HLA-DMA, HLA-DPB2, HLA-DOB, HLA-DQB2, HLA-F, HLA-H. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DEL, deletion; DLBC, lymphoid neoplasm diffuse large B cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HLA, human leukocyte antigen; HNSC, head and neck squamous cell carcinoma; INS, insert; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MICA, major histocompatibility complex class I-related chain A; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; SNP, single nucleotide polymorphism; SNV, single nucleotide variation; STAD, stomach adenocarcinoma; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma.

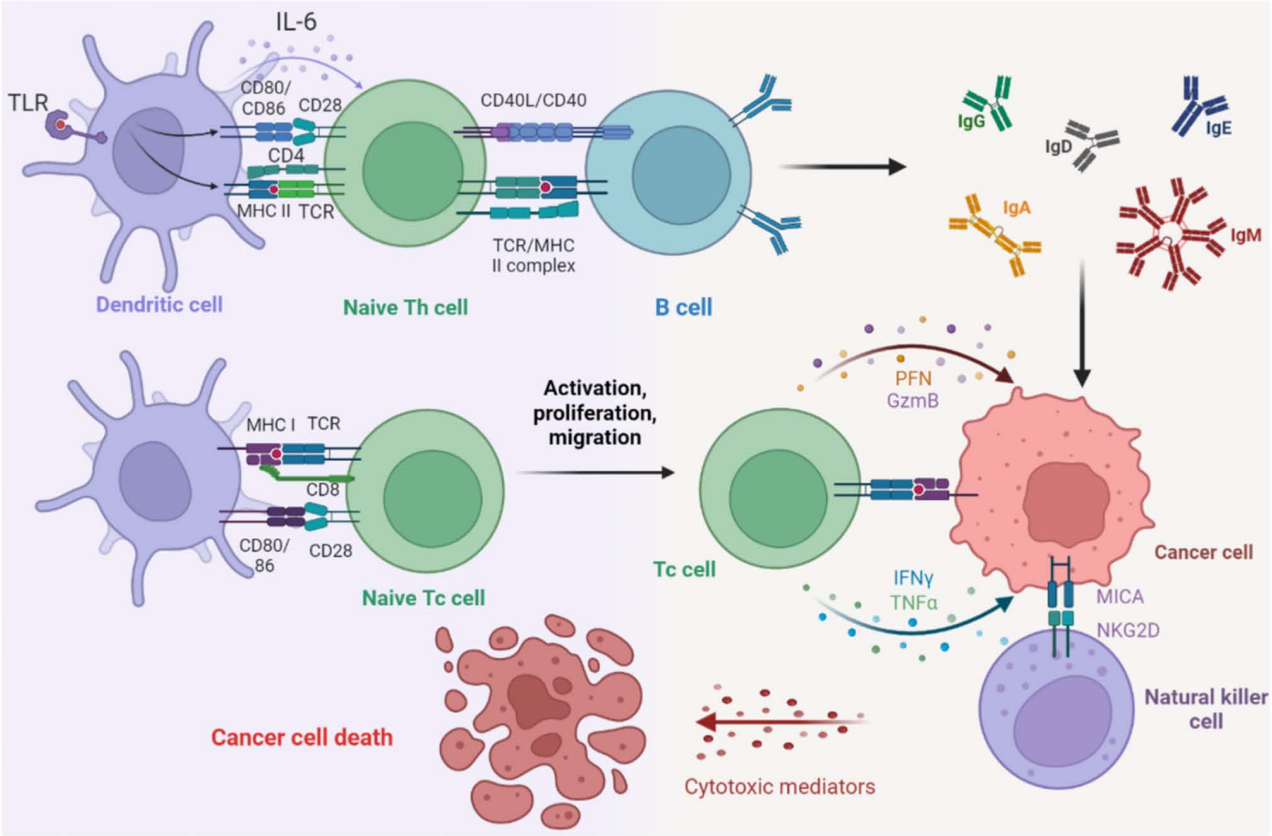

Figure 3. Ideograph of HLA-I and HLA-II in regulating antitumor immunity. GzmB, granzyme B; HLA, human leukocyte antigen; IL-6, interleukin 6; MHC, major histocompatibility complex; MICA, MHC class I-related chain A; PFN, perforin; Tc, cytotoxic T cell; TCR, T-cell receptor; Th, helper T cell; TLR, toll-like receptor; TNFα, tumor necrosis factor α. This figure was created by Biorender (https://biorender.com/).

4. Function of HLA in tumor immunity

HLA-I molecules present endogenous antigenic peptides to the cell surface, enabling the immune system to recognize tumor-specific neoantigens and to eliminate them before the tumor develops further (82). The expression of the HLA-I gene in tumor cells is one of the determinants of the recognition and destruction of tumor cells by $CD8^+$ cytotoxic T lymphocytes (CTLs) (83) (Fig. 3). However, mutation of the HLA-I gene often occurs in tumor cells, resulting in a partial or total deletion of HLA-I on the tumor surface, which decreases the secretion of perforin, Granzyme B, IFN-γ and TNF-α from CTLs and promotes immune escape of tumor cells (84) (Fig. 3). HLA-I gene expression on the surface of pancreatic ductal gland tumor cells has been demonstrated to improve the effect of antigen presentation, leading to enhanced antitumor effects of T cells and consequently slower tumor growth (85). In a study by Yang *et al* (86), the activation of the Wnt/β-catenin signaling pathway was demonstrated to lead to a decrease in HLA-I gene expression, which in turn decreased the CTL-mediated immune response to cancer cells. Tumor cells have collectively selected the evolutionarily conserved and lineage-specific functions of polycomb repressive complex 2 (PRC2) to silence MHC class I molecular antigen processing and presentation pathways, thereby escaping immune surveillance (87). Notably, after pharmacological inhibition of *Drosophila* zeste gene enhancer human homolog 1 (EZH1) and EZH2, the PRC2-mediated silencing of MHC class I molecule-dominated antigen processing pathway-associated genes becomes reversible, thus re-establishing T cell-mediated antitumor immunity (87). The early embryonic transcription factor, double homeobox 4, which is silenced in somatic tissues, is expressed in a variety of solid tumors, where it inhibits HLA-I molecules to promote tumor immune escape (88). Radiotherapy has also been demonstrated to improve the efficacy of $CD8^+$ T cells in killing tumor cells via enhancement of the expression of HLA-I molecules (89).

NK cells contribute significantly towards the natural immune system and provide the first line of defense against pathogens and tumors (90). These cells not only serve an important role in the process of immune surveillance, but also fulfill the functions of being antivirus and anti-infection molecules, and killing tumor cells (91). Due to their property of being unrestricted by MHC molecules, NK cells can recognize and kill MHC-I-deficient tumor cells (92). However, the immune function of NK cells is still regulated by MHC class I-related chain A (MICA) (93). MICA is a non-classical HLA-I gene, located between solute carrier superfamily 6 member 19 and HLA-B genes, positioned 46 kb away from HLA-B with a total length of 11,772 bp, including 6 exons, and is highly polymorphic (94). It has been demonstrated that the occurrence of multiple tumors is associated with the polymorphism of MICA (95). MICA A9 is a high-risk factor of gastric cancer (96), whereas MICA A6 has been demonstrated to be a high-risk factor of oral squamous cell carcinoma (97). The activated receptor NKG2D fulfills an important role

in the antitumor immunity of NK cells (98,99). There is no currently recognized signal transduction domain in the cytoplasmic region of NKG2D, and the receptor mainly relies on YXXM, an immunoreceptor tyrosine activation motif in the cytoplasmic region of DNAX-activating protein 10 (DAP10), for its ability to activate signal transduction (98,99). The NKG2D-DAP10 dimer binds to p85, a subunit of phosphoinositide 3-kinase, and transmits an activation signal (100). When MICA binds to the NKG2D-DAP10 dimer, this leads to the activation of numerous signal transduction pathways, such as those involving lactaldehyde-derived lysine dimer, signal transducer and activator of transcription 5, and AKT in effector cells, thereby activating the antitumor immunity of NK cells (100). The sensitivity of $MICA^+$ leukemia cells to NK cells has been demonstrated to be significantly higher than that of $MICA^-$ leukemia cells (101). *In situ* tumor cells of myeloma highly express MICA, although myeloma cells with pleural effusion show little or no expression of MICA (102). NK cells are only able to recognize myeloma cells that kill tumor sites, and not myeloma cells with pleural effusion (102). Another study published by Zhang *et al* (103) revealed that MICA on the surface of lung, colorectal and cervical cancer cells can upregulate NKG2D activity and downregulate the expression of the inhibitory receptors, NKG2A and KIR2DL1 (103). Although $V\delta1^+\gamma\delta$ T cells also express NKG2D receptors, a low level of MICA expression is insufficient to activate the $V\delta1^+\gamma\delta$ T cell immune response (104). HeLa cells were found to highly express the MICA membrane protein, while the ovarian cancer cell line, SKOV3, expressed MICA plasma protein in large quantities, which was unable to bind to NKG2D and activate $V\delta1^+\gamma\delta$ T cells. Therefore, the killing effect of $V\delta1^+\gamma\delta$ T cells on HeLa cells was found to be much stronger than that of SKOV3 cells (105). For the present review, R programming (version 4.1.1, https://cran.r-project.org/) was used to analyze and visualize the RNA-sequencing expression profiles and corresponding clinical information of the 33 types of cancer in TCGA database. GTEx samples were collected from 54 non-diseased tissue sites across nearly 1,000 individuals. Pan-cancer analysis revealed the levels of MICA mRNA in solid tumors using the Wilcoxon rank-sum test (Fig. 4). Compared with tumoral tissues, higher levels of MICA mRNA were found in normal tissues of most cancers, such as bladder urothelial carcinoma, breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma, colon adenocarcinoma, esophageal carcinoma, lung adenocarcinoma and lung squamous cell carcinoma (Fig. 4). By contrast, higher MICA expression was detected in tumoral tissues compared with in normal tissues for cholangiocarcinoma (CHOL), glioblastoma multiforme, kidney renal papillary cell carcinoma, head and neck squamous cell carcinoma and pancreatic adenocarcinoma (Fig. 4). $P<0.05$ was considered to indicate a statistically significant difference.

Tumor cells generally express MHC class I molecules, and rarely express MHC class II molecules (106). Therefore, clinical research on neoantigens and other types of tumor antigens has mainly focused on MHC class I molecule-restricted antigens (106). However, given the in-depth studies that have enabled an increase in the understanding of tumor immunity, the regulatory effects of MHC class II molecular restriction antigens on $CD4^+$ T cells have been paid a greater level of attention with respect to tumor immunity (107) (Fig. 3). The activation of toll-like receptor 2 leads to a decrease in the expression of MHC class II molecules in microglia, an inhibition of the proliferation and functional activation of $CD4^+$ T cells, and the promotion of immune escape of microglia cells (108). Interferon-γ stimulation was demonstrated to lead to the upregulation of MHC class II molecules in chronic myeloid leukemia (CML) stem cells (109). However, the JAK1/2 inhibitor, ruxolitinib, inhibited the proliferation of CML stem cells, resulting in a significant increase in the expression level of MHC class II molecules (109). These results suggest that the JAK-mediated signaling pathway is driven by cytokines provided by CML cells and the immune microenvironment antagonizes MHC class II molecule expression, thereby escaping immune surveillance. In a different study, MHC class II molecules expressed in murine breast tumor cells were found to promote the local activation of $CD4^+$ T cells, indirectly aiding the activation and expansion of $CD8^+$ T cells, delaying T-cell exhaustion and inhibiting tumor cell proliferation (110). MHC class II molecules are expected to stimulate more powerful and lasting immune responses, either alone or in cooperation with MHC class I molecules. In melanoma, colon cancer and breast cancer, tumor cells may be recognized by $CD4^+$ T cells instead of $CD8^+$ T cells, which suggests that, compared with MHC class I molecules with a stricter restriction, tumor individualized neoantigens may be more likely to bind to MHC class II molecules (111). Therefore, MHC class II molecules have been demonstrated to be promising immunotherapeutic targets.

Tumor cells express and secrete HLA-G, which inhibits NK cell- and CTL-mediated cell lysis, thereby causing tumor cells to escape from human immune surveillance and killing (112). The mechanism of action of HLA-G in tumors involves three steps of tumor immune escape: Elimination, equilibrium and escape (113). In the elimination stage, HLA-G expressed by tumor cells binds to the immunoglobulin-like transcript 2 (ILT2) and ILT4 receptors on immune cells, inhibits the cytolytic function of T and NK cells, and enables tumor cells to escape recognition and elimination of immune cells (113). In addition, HLA-G can also inhibit the secretion of cytokines, induce antigen-presenting cells to secrete HLA-G and further inhibit immune function (113). In the equilibrium stage, most of the tumor cells have been eliminated, and individual monoclonal cells survive through mutation (113). At this stage, HLA-G expression occurs at a low level, although it can still weaken the activity of immune cells and promote the production of regulatory cells and immunosuppressive factors, such as IL-10 (113). In the final escape stage, various factors, such as hypoxia inducible factor 1 produced by hypoxia, promote the expression of HLA-G, inhibiting the activity of immune cells to the maximal possible extent, thereby causing rapid tumor progression and local microenvironment hypoxia, which further promotes the production of IL-10 and other cytokines, and upregulates the expression of HLA-G to promote tumor formation (113).

HLA-E fulfills an important role in regulating the antitumor immune response, mainly by binding to the inhibitory NKG2A receptors of NK cells or T cells (114). After NKG2A/CD94 binds to the HLA-E/antigen polypeptide complex, it can cause the protein tyrosine phosphatase, Src homology region

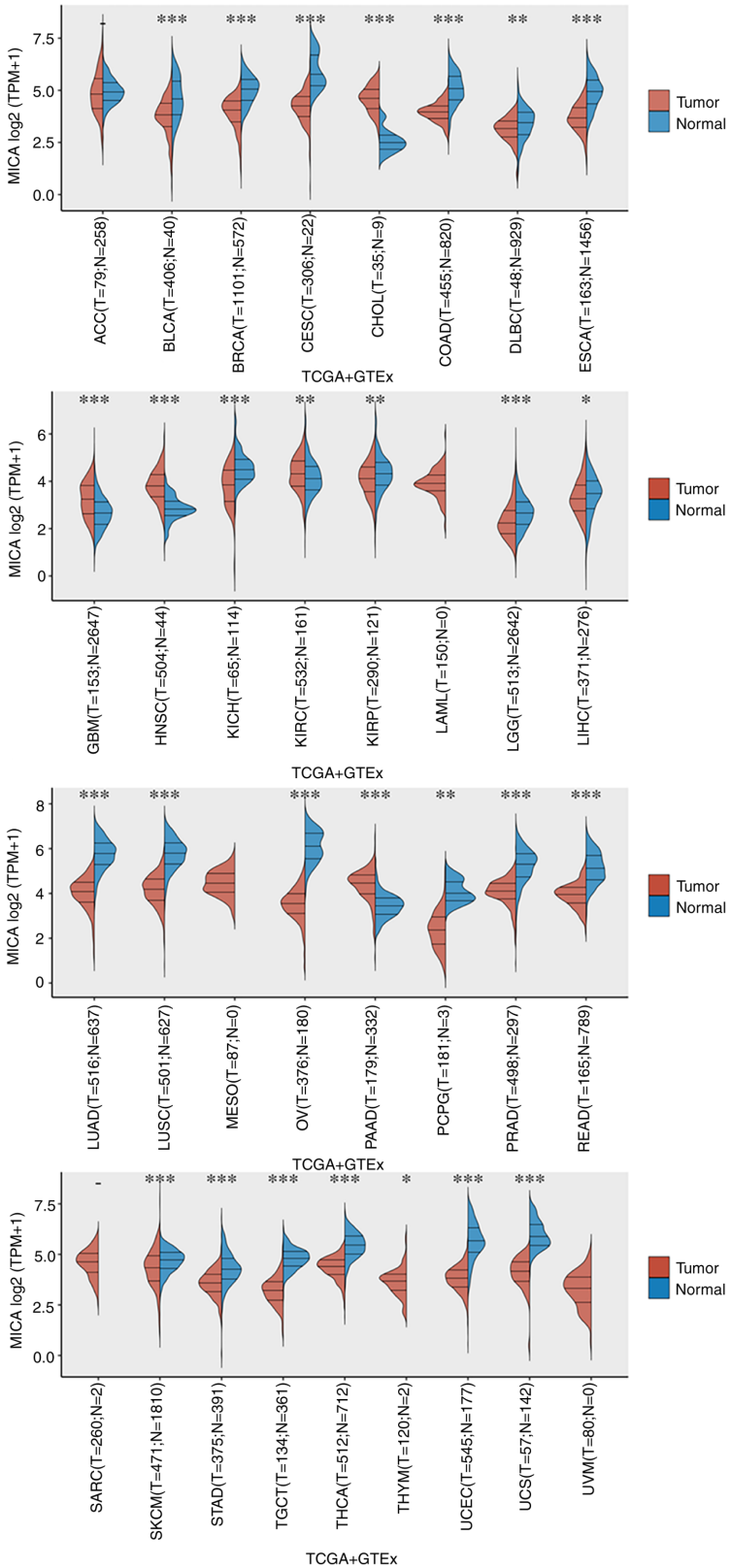

Figure 4. Expression distribution of MICA gene in tumor tissues and normal tissues. The statistical differences between two groups were compared using the Wilcoxon rank-sum test. *P<0.05, **P<0.01, ***P<0.001. Sample set: ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, malignant mesothelioma; MICA, major histocompatibility complex class I-related chain A; N, normal; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; SNP, single nucleotide polymorphism; SNV, single nucleotide variation; STAD, stomach adenocarcinoma; T, tumor; TCGA, The Cancer Genome Atlas; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; TPM, transcripts per million; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

2 domain-containing phosphatase-1, to be recruited to the vicinity of the immunoreceptor tyrosine-based inhibitory motif in the intracellular domain of NKG2A, thereby causing the signaling molecules upstream and downstream of the pathway to undergo dephosphorylation, which effectively inhibits NK cell activation (115). Tumor cells upregulate the expression of HLA-E, interact with CD94/NKG2A and inhibit the antitumor activity of IL-2 receptor-dependent $CD8^+$ T cells through inhibiting the proliferation, activity and secretion of cytokines (116). The study conducted by Chen *et al* (117) demonstrated that blocking NKG2A could significantly enhance the killing ability of $CD8^+$ T cells against tumor cells.

Further studies on the role and mechanism of HLA-G and HLA-E in tumorigenesis and development will contribute towards the application of HLA-G and HLA-E in the clinic, especially with regards to clinical disease diagnosis, prognosis and immunotherapy.

5. Clinical significance of HLA in tumor immunotherapy

During the process of T cells initiating the immune reaction, the recognition of weak binding peptides by T-cell receptors may lead to an unstable interaction between the peptide and the MHC molecule antigen-binding groove, thereby causing tumor immune escape (118). The analysis and screening of tumor antigen peptides that efficiently bind to MHC molecules is of great significance for the rapid development of safe and effective tumor vaccines (119). Mass spectrometric analysis of tumor antigen peptides has been used to identify effective tumor neoantigen peptides from tumor cells or tissues (120). Oncolytic viruses induce tumor cells to produce new MHC class I molecular ligands to activate $CD8^+$ T-cell responses (121). A peptide MHC class I molecule IgG-antibody fusion protein-redirected vaccine was demonstrated to target lung cancer cells *in vivo* and endow them with viral antigenicity, thereby activating antiviral $CD8^+$ T cells induced by the vaccine and inhibiting tumor growth (122). Tumor vaccines are designed to target tumor neoantigens as a part of MHC molecule-binding neoantigen immunotherapy (123). Duperret *et al* (124) used DNA vaccines to target tumor neoantigens for preclinical research and found that the optimized tumor neoantigens were immunogenic and mainly produced MHC I molecule-restricted $CD8^+$ T-cell responses. DNA neoantigen vaccines have also been demonstrated to induce therapeutic antitumor immune responses *in vivo*, and the neoantigen-specific T cells expanded *in vivo* were demonstrated to kill tumor cells *in vitro* (125). At present, research on tumor antigens, including neoantigens, has mainly focused on MHC class I molecules, but with the gradual deepening of the understanding of tumor immunity and the accumulation of clinical and experimental data, researchers are also gradually shifting their attention towards $CD4^+$ T cells and MHC class II molecular antigen peptides (126). The selective pressure against MHC class II-restricted neoantigens is stronger than that against MHC class I molecules, indicating that the immune monitoring of $CD4^+$ T cells is an important limiting factor in tumorigenesis and development (127). MHC class II molecule-restricted neoantigens can be recognized from their own tumor-infiltrating lymphocytes from patients with metastatic CHOL, and $CD4^+$ T-cell reinfusion treatment has been performed to effectively alleviate the condition of patients (128).

Immune checkpoint inhibitors (ICIs) fight cancer by reactivating the adaptive immune system of the patient (129). Selective autophagy of MHC class I molecules mediated by the selective autophagy substrate receptor/ATG8 interacting protein neighbor of BRCA1 is a novel mechanism that has been discovered, which enables pancreatic ductal gland tumor cells to evade immunity (130). Autophagy or lysosomal inhibition can restore the expression of MHC class I molecules, enhance the immune effect of antitumor T cells and improve the response to immune checkpoint blockade therapy (131). Friedman *et al* (132) found that the decreased expression of MHC class I molecules in patients with endometrial cancer is a potential mechanism through which patients develop resistance to ICIs. The induced expression of MHC class I molecules further increases the therapeutic potential of ICIs in breast cancer (133). In a different study, the expression of chemokine (CXC motif) ligand 14 was demonstrated to inhibit human HPV^+ cervical cancer by restoring the expression of MHC class I molecules on tumor cells and promoting antigen-specific $CD8^+$ T-cell responses (134). Taken together, these studies have collectively demonstrated that the increased expression of MHC class I molecules can enhance the efficacy of ICIs in treating tumors.

6. Future perspectives

In the present review, the relationship between HLA polymorphism and tumorigenesis has been considered, and the key role and mechanism of HLA in tumor immunity and treatment has been focused on. Effective tumor immunotherapy is based on the synergy of various components of the immune system. In order to establish effective immunotherapy for patients with tumors, NK cells, $CD4^+$ T cells and $CD8^+$ T cells have an indispensable role. Although tumor vaccines and adoptive cell therapy based on MHC-restricted antigens have achieved significant efficacy in preclinical and clinical studies, they still cannot completely cure tumors, and the efficacy needs to be strengthened further. Previous studies have demonstrated that HLA serves an important role in the occurrence and development of a variety of tumors, including in gastric, lung and liver cancer. Due to the high degree of polymorphism of HLA, the research results obtained on the association between HLA and human tumors have not proven to be entirely consistent, and future studies incorporating big data analysis are required. In addition, recent studies demonstrated that HLA affects the survival rate of patients undergoing ICI therapy (135-137). These studies have suggested that HLAs could be used to improve the efficacy of individualized treatments of patients with cancer in the future.

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Availability of data and materials

All data generated or analyzed during this study are included in the published article.

Authors' contributions

This review was conceptualized by PX; DHL, FFM and MA performed the software analysis; MA, DHL and PX were responsible for the original draft preparation; FFM and PX wrote the review and subsequently edited it; PX supervised the project and was also the project administrator; PX was responsible for the funding acquisition. DHL, FFM, MA and PX confirm the authenticity of all the raw data. All authors, read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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