Review Article

Human leukocyte antigen (HLA) and cancer immunotherapy: HLA-dependent and -independent adoptive immunotherapies

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Abstract: Cancer immunotherapy, including immune checkpoint inhibitors, adoptive cell therapies and tumor vaccines, has recently shown impressive results in the treatment of multiple cancers. The key step shared by these therapies requires T cells to recognize the specific peptides presented by the human leukocyte antigens (HLAs) on the membranes of tumor cells and subsequently kick off an immune response. HLA class I molecules exist in most human cell types and can interact with T cell receptors (TCRs) to activate T cells, which are important molecules that induce adaptive immune responses. In recent years, research on cell therapy has mainly focused on $CD8^+$ T cell therapy, such as tumor-infiltrating lymphocytes (TILs) therapy and TCR-engineered T cells (TCR-Ts) therapy, which are both HLA-dependent immunotherapy. However, tumor cells may escape T cell attack through HLA downregulation, which limits HLA-dependent immunotherapy to some extent. Thus, HLA-independent immune cell therapies such as chimeric antigen receptor T-cell therapy, natural killer cell therapy and $CD4^+$ T cell therapy shed new light on this issue. In this review, we summarized the mechanisms of antigen presentation by HLAs, the latest progress of HLA-presented peptides identification, and the current status of HLA-dependent and -independent adoptive immunotherapies.

Keywords: Human leukocyte antigen (HLA); cancer immunotherapy; peptides; T cell receptor (TCR)

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Cancer immunotherapy exploits the immune system to fight cancers. Although immunotherapy has been an important component of cancer treatment for decades, it does not attract too much attention until the past ten years, especially when the Nobel Prize in Physiology or Medicine was awarded for the discovery of cytotoxic T-lymphocyte-associated protein (CTLA-4) and programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/PD-L1) (1) in 2018. Nowadays, immune checkpoint inhibitors are used to treat various cancers, including the first line treatment of advanced non-small cell lung cancer (NSCLC), melanoma and renal cell carcinoma. In addition to immune checkpoint inhibitors, adoptive cell therapies and tumor vaccines are also common cancer immunotherapies. The basic mechanism for these cancer immunotherapies is that T cells exert an immune function via recognizing tumor antigens presented by the major histocompatibility complex (MHC) on the membranes of tumor cells (2,3).

MHC is a group of polymorphic genes expressed in nearly all the vertebrates, which determines histocompatibility between different individuals. MHC was first discovered during the first decade of the 20th century because of tumor rejection between genetically distinct mice (4). Human MHC is also known as human leukocyte antigen (HLA).

HLA class I molecules are expressed on most cell types

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including tumor cells in human, presenting endogenous antigens to the immune system. HLA class II molecules are mainly expressed by antigen-presenting cells (APCs), presenting exogenous antigens to T helper cells. Both HLA class I and class II molecules show high polymorphism, which means that they have many different alleles among human populations. This is why HLA mismatch between donors and recipients is the primary cause of transplant rejection (5). According to IMGT/HLA database, more than 12,000 alleles were identified as HLA class I genes (6). Evolutionarily, the diversity of HLA molecules ensures that the immune system could recognize as many antigens as possible and help us to defend various pathogens. Interestingly, while investigating the effect of HLA class I divergence on the efficacy of immune checkpoint inhibitor treatment for cancer (7), Chowell *et al.* found that greater sequence divergence of an HLA-I genotype is associated with higher diversity of self, tumor and viral immunopeptidomes. Furthermore, patients with high HLA-I divergence show better responses to immune checkpoint inhibitors than patients with low HLA-I divergence. These findings suggested that HLA polymorphism is critical for us to fight cancer.

Antigen presentation by HLA

HLAs presents tumor antigens to T cells to facilitate the immune system to recognize tumor cells. The process by which HLA molecules bind antigen peptides and present them on the cell membrane is called antigen presentation. Here we summarized three different pathways of antigen presentation (*Figure 1*). All of these processes occur during tumor development and mediate responses to immunotherapies.

The peptide binding groove of HLA class I molecules is closed at both ends by conserved tyrosine residues, which usually restricts the size of bound peptides to 8–10 residues (8,9). Endogenous antigens are degraded by proteasomes into short peptides in the cytoplasm, and these short peptides are transferred from the cytoplasm to the endoplasmic reticulum (ER) lumen through the antigen processing-related transporter protein (TAP) (*Figure 1A*). In the ER, empty class I molecules waiting for peptide loading is retained by a series of chaperones including a dedicated chaperone tapasin (also called TAP-binding protein, TAPBP) in the peptide-loading complex. With the help of several chaperones, appropriate peptides then bind to class I molecules and the peptide-HLA complexes become stabilized. The stable complexes continue to move along with the ER, pass through the Golgi apparatus, and finally reach the surface of the cell membrane. In addition to tapasin, a second MHC class I-specific chaperone, the tapasin-related protein TAPBP-R was identified in 2013 (10). Both tapasin and TAPBP-R function as a peptide exchange catalyst and a quality control checkpoint. They ensure MHC class I molecules are loaded with high-affinity peptides and prolong cell surface presence of MHC class I molecules (11).

HLA class II molecules usually bind peptides with 13–25 residues in length according to their open binding grooves (12). Exogenous antigens are taken up by endocytosis or phagocytosis and cleaved into peptides in endosome. HLA class II molecules are synthesized in ER where they pair with a third chain, the invariant chain (Ii) (*Figure 1B*). This interaction prevents the loading of endogenous peptides to the MHC class II cleft. Ii also guides HLA class II through the cells to a late endosomal MHC class II compartment (MIIC). In MIIC, Ii is proteolytically cleaved into a short peptide called class II-associated Ii peptide (CLIP), which continues to block the binding of peptides to the class II cleft. The CLIP is exchanged for an antigenic peptide with the help of chaperones such as HLA-DM and HLA-DO. Like tapasin and TAPBP-R in the HLA I process, HLA-DM and HLA-DO also shape the peptide repertoire of HLA II that is ultimately presented on the cell surface of $CD4^+$ T cells. Interestingly, Yamashita *et al.* recently found that HLA-DP molecules with β-chains encoding Gly84 (DP^{84Gly}) do not bind Ii through the CLIP region, nor present CLIP. DP^{84Gly} uniquely exploits both class I and II antigen pathways to present both endogenous and exogenous peptides (13).

Certain APCs such as dendritic cells (DCs) have the ability to process and present exogenous antigens with HLA class I molecules. This process is called cross-presentation. During cross-presentation, extracellular proteins or cell debris are internalized by DCs through endocytosis or phagocytosis and further degraded into peptides and presented onto HLA class I molecules (14,15). There are mainly two pathways that have been reported for cross-presentation: the vacuolar pathway and the cytosolic pathway (*Figure 1C*). In the vacuolar pathway, an extracellular antigen is taken by DCs into the endosome. The antigen is degraded by proteasome and then the derived peptides are loaded onto HLA class I molecules directly in the endosome. In the cytosolic pathway, like the vacuolar pathway, the extracellular antigen is also internalized into the endosome. However, the antigen may be degraded inside

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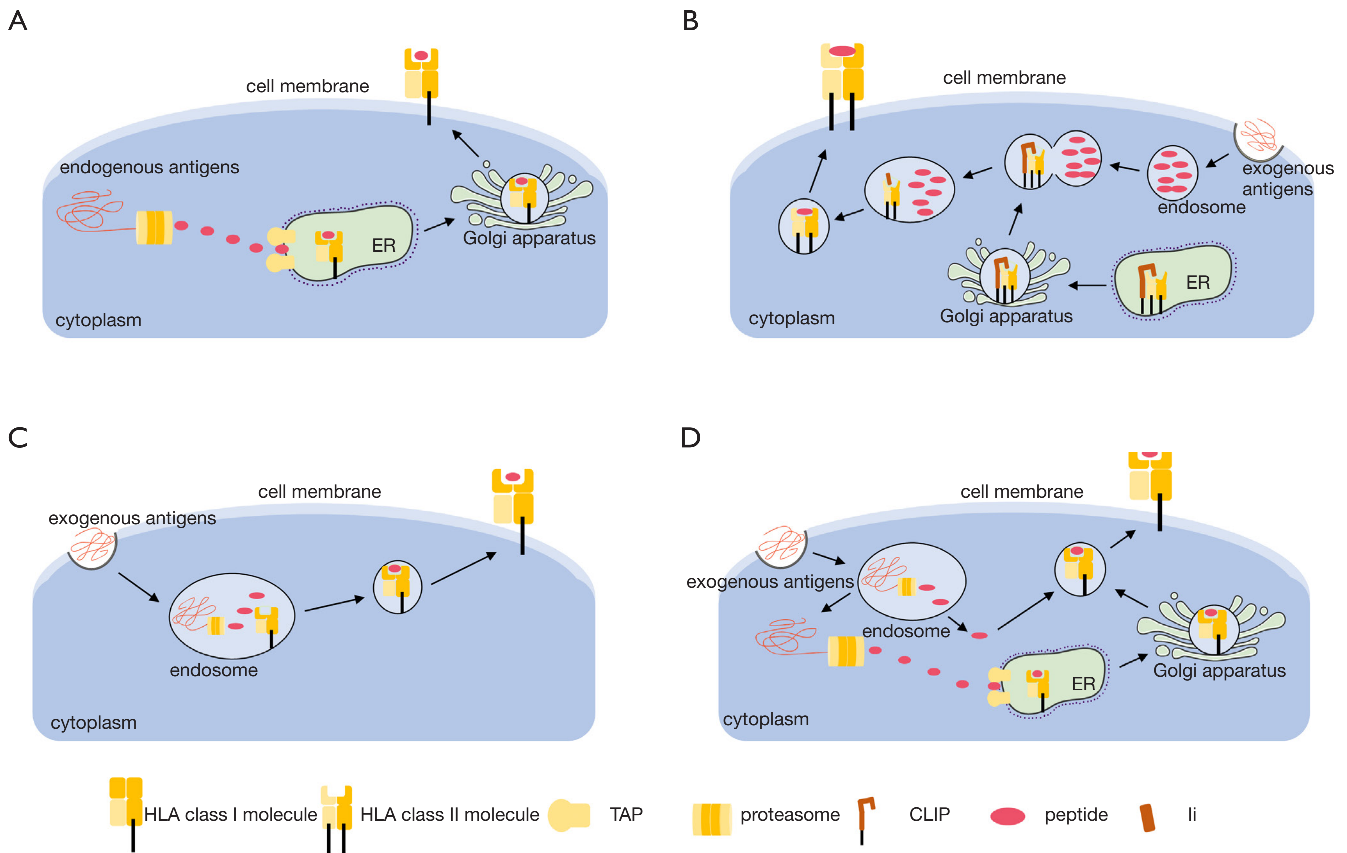

Figure 1 Three different pathways of antigen presentation. (A) Endogenous antigens are mostly presented by HLA class I molecular pathways; (B) exogenous antigens are mostly presented by HLA class II molecular pathways; (C) exogenous antigens can also be cross-presented by HLA class I molecules, including the vacuolar pathway (left) and the cytosolic pathway (eight). HLA, human leukocyte antigen.

the endosome or transported out of the endosome and then degraded in the cytoplasm. The derived peptides can either be transported by the TAP transporter into the ER, or back into the endosome for loading onto HLA class I molecules. Both pathways may occur in DCs during cross-presentation. The importance of cross-presentation is that it allows DCs to acquire antigens from other pathogen infected cells or cancer cells in the periphery and then report their presence to naive $CD8^+$ T cells in lymphoid organs (16).

HLA-dependent immunotherapy

$CD8^+$ cytotoxic T lymphocytes (CTLs)-based immunotherapy

$CD8^+$ cytotoxic T lymphocytes represent a crucial component of the adaptive immune system against tumors. Most cytotoxic T cells express T cell receptors (TCRs) that can recognize a specific antigen. After TCR binding to peptide-HLA complex expressed by tumor cells, CTLs are activated, accumulate at the tumor site, and release effectors to attack tumor cells. CTLs exert specific killing effects on tumor cells via two major pathways: (I) releasing cytotoxic substances such as perforin, granzymes, and cytokines to kill tumor cells; (II) activating death receptor pathway, e.g., FasL, expressed on the surface of T cells, binds to the death receptor Fas on the surface of tumor cells, to initiate apoptosis-related signals, which lead to tumor cell apoptosis.

Extensive evidence has suggested that adoptive transfer of CTLs could harness the cellular immune system and lead to the killing of tumor cells both in animal models and cancer patients (17). Over the past decades, many studies have transferred *in vitro* expanded tumor-infiltrating lymphocytes (TILs) back into patient donors and showed promising outcomes. The first one was reported by Rosenberg *et al.* in 1988 to treat patients with metastatic melanoma (18). Since then, TIL therapy has shown satisfactory efficacy

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in advanced melanoma. Favorable objective response rates up to 72% were reached with TIL therapy in several consecutive clinical trials, in which 10–20% of treated patients reached a complete remission and 40% of patients achieved durable clinical responses (19). In addition to melanoma, investigators also isolated TILs from other solid tumors such as renal cell, breast and cervical cancer. However, the tumor reactivity of TILs from these other tumors is usually lower when compared to melanoma (19). Although TIL treatment is effective, the biggest problem is that tissue samples for TIL production cannot be obtained from all cancer patients. Even worse, in some cases, TILs cannot be isolated from resected tumor tissues. Recently, with the help of lentivirus and other gene engineering technologies, a specific TCR recognizing tumor antigen was inserted into the genome of bulk T cells, which makes it possible to produce antigen-specific T cells for everyone. Thus, TCR-engineered T cells (TCR-Ts) are therefore considered as a more promising treatment for cancer patients.

Lots of TCR-Ts are currently tested in clinical trials as reviewed by other groups (20-22). In 2006, Morgan *et al.* is the first group to report clinical trial results to demonstrate the feasibility of treating tumors with TCR-Ts (23). In that study two patients showed a sustained objective regression of their metastatic melanoma and remained clinically disease-free for at least 20 months. In 2009, Johnson *et al.* used TCR-Ts to target MART-1 (melanoma antigen recognized by T cells 1) and gp100 for the treatment of melanoma (24). The response rate of targeting MART-1 was 30% (6/20), and the response rate of targeting gp100 was 19% (3/16). Moreover, in 2015, Robbins *et al.* reported that the response rates of NY-ESO-1 (New York esophageal squamous cell carcinoma 1)-specific TCR-engineered autologous T cells against synovial sarcoma and melanoma was 61% (11/18) and 55% (11/20), respectively (25,26). Nowadays, more clinal trials of TCR-Ts are ongoing. The majority of the TCR-T targets used in these trials are NY-ESO-1, MAGE family (melanoma antigen family), AFP (alpha fetoprotein), WT-1 (Wilms' tumor antigen 1), HPV (human papilloma virus), etc.

Expanding T cell epitope reservoir for CTLs-based cancer immunotherapy

The peptide-HLA complexes recognized by TCR are called T cell epitopes. Known T cell epitopes targeted by TCR-Ts which have been tested in clinical trials were summarized in *Table 1* of this review. Up to date, as shown in the list, a very limited number of T cell epitopes have been identified and targeted in immunotherapy. Most of known peptides are restricted by HLA*02:01. Therefore, identifying new targets for CTLs-based immunotherapy, especially peptides restricted by other HLA, is urgently needed in order to further enhance the therapeutic value of TCR-Ts. Although T cell epitopes can be identified by sequencing, bioinformatics and mass spectrometry, identifying new antigens that are immunogenic and can promote tumor rejection remains a major challenge (49).

Shared antigens expressed by broad types of cancers or individuals are considered limited. Therefore, targeting unique, patient-specific tumor mutations now has attracted a lot of attention and could become a promising alternative in the near future. Moreover, targeting "neoantigens", the somatic mutations expressed only by tumor cells, might enable specific tumor destruction without causing off-target damage to vital healthy tissues (50). Neoantigen-reactive T cells have been administered to cancer patients and shown objective response. In some cases, complete regressions in patients with different types of cancers were also observed (51-53). In order to identify neoantigens, tumor sections and corresponding normal tissues were sent for whole-exome sequencing to determine the tumor-specific non-synonymous mutations in protein-coding regions. After that, candidate neoantigens are selected according to HLA-binding affinity, expression level, variant allele frequency and several other criteria. Finally, the immunogenicity of the selected candidate peptides is evaluated with different immunological screening assays (54).

Next generation sequencing has greatly facilitated the progress of TCR-based immunotherapy. A large number of candidates neoepitopes could be identified through whole-exome sequencing. Moreover, TCR clones could also be discovered by high throughput single cell sequencing (55,56). The traditional immunological screening assays for T cell antigen discovery, such as interferon-γ (IFN-γ) ELISA/ELISPOT and pHLA multimer staining, are usually laborious and time-consuming. Recently several high throughput techniques have been developed to identify cognate antigens for T cells (57-64). The research team led by Dr. Stephen J. Elledge has developed a high throughput, whole-genome screening platform called T-Scan to identify antigens recognized by T cells (60). In this study, this technology was applied to identify multiple cytomegalovirus (CMV) antigens that can be recognized by memory T cells.

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Table 1 Known T cell epitopes targeted by TCR-T in clinical trials

Antigen	HLA	Sequence	Cancer (s)	Reference number
p53	HLA-A*02:01	LLGRNSFEV	Metastatic melanoma	(27)
MART1	HLA-A*02:01	AAGIGILTV	Metastatic melanoma	(28)
MART1	HLA-A*02:01	EAAGIGILTV	Stage IV skin melanoma, eye melanoma	(29)
gp100	HLA-A*02:01	KTWGQYWQV	Metastatic melanoma	(30)
NY-ESO-1	HLA-A*02:01, HLA-A*02:05, HLA-A*02:06	SLLMWITQC	Metastatic melanoma, Metastatic SCS, solid cancers	(25,31,32)
CEA	HLA-A*02:01	IMIGVLVGV	Metastatic CRC	(33)
MAGE-A3	HLA-A*02:01	KVAELVHFL	Melanoma, SCS; breast, cervical, renal, bladder cancers	(34)
MAGE-A3	HLA-A*01	EVDPIGHLY	High-risk or relapsed myeloma	(35)
MAGE-A4	HLA-A*24:02	NYKRCFPVI	Solid cancers	(36)
MAGE-A4	HLA-A*02	GVYDGREHTV	Solid and hematological malignancies	(37)
MAGE-A10	HLA-A*02:01, HLA-A*02:06	GLYDGMEHL	Advanced NSCLC	(38)
MAGE-A12	HLA-A*02:01	KMVELVHFL	Esophageal cancer	(34)
WT1	HLA-A*02:01	RMFPNAPYL	MDS, AML	(39)
Tyrosinase	HLA-A*02:01	YMDGTMSQV, YMNGTMSQV	Melanoma	(40)
HPV E6	HLA-A*02:01	TIHDIILECV	HPV-associated cancers	(41)
HPV E7	HLA-A*02:01	YMLDLQPET	HPV-associated cancers	(42)
Human thyroglobulin(hTG)	HLA-A*02:01	SKYISSLKTSADG	Metastatic thyroid cancer	(43)
PRAME	HLA-A*02:01, HLA-A2*02:01	VLDGLDVLL, SLYSFPEPEA, ALYVDSLFFL, SLLQHLIGL	AML, MDS, uveal melanoma	(44)
KRAS G12V	HLA-A*11:01	VVGAVGVGK	Pancreatic, gastric, gastrointestinal, colon, rectal cancers	(45)
KRAS G12D	HLA-A*11:01	VVGADGVGK	Pancreatic, gastric, gastrointestinal, colon, rectal cancers	(45)
HA-1	HLA-A*02:01	VLHDDLLEA	Relapsed or refractory acute Leukemia	(46)
TGFβRII frameshift protein	HLA-A*02	RLSSCVPVA	CRC	(47)
AFP	HLA-A*02:01, HLA-A*02:642	FMNKFIYEI	HCC	(48)

AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; HA-1, minor histocompatibility (H) antigen; HPV, human papilloma virus; HERV-E-derived antigen, human endogenous retrovirus-derived antigen; MART-1, melanoma antigen recognized by T cells 1; NY-ESO-1, New York esophageal squamous cell carcinoma 1; PRAME, preferentially expressed antigen in melanoma; TGFβRII, transforming growth factor beta receptor type II; WT1, Wilms' tumor antigen; AML, acute myeloid leukemia; ccRCC, clear cell renal cell carcinoma; CRC, colorectal cancer; HCC, hepatocellular cancer; MDS, myelodysplastic syndrome; SCS, synovial cell sarcoma.

Moreover, they also used this technology to successfully discover the genome-wide targets of self-reactive TCRs. David Baltimore's research team developed two cell-based platforms for TCR antigen discovery. One platform used chimeric receptors called signaling and antigen-presenting bifunctional receptors (SABRs) (58). These chimeric

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receptors are composed of an extracellular pHLA fused to an intracellular CD3ζ signaling domain and a CD28 co-stimulatory domain. When recognized by a specific TCR, this interaction triggers the expression of green fluorescent protein (GFP) and CD69 on Nuclear Factor of Activated T cells (NFAT)-GFP-Jurkat cells which can be selected and sequenced to identify the specific peptide recognized. The other platform exploits a membrane transfer phenomenon called trogocytosis, a rapid exchange of envelope fragments or related molecules between cells through cell-to-cell contact (59). Co-incubation of T cells expressing an orphan TCR with target cells led to specific labeling of cognate target cells, enabling isolation of these target cells and sequencing of the cognate TCR ligand. These high throughput techniques not only facilitate the screening of tumor antigen targets, but also can be used to discover the off-target reactivities of a therapeutic candidate TCR, making it a versatile tool for the development of T cell immunotherapy.

Tumor may escape CTLs-based immunotherapy through downregulation of HLA

Tumor immune escape refers to the phenomenon that in order to survive and proliferate in human bodies, tumor cells can escape from the surveillance of immune system. The downregulation or loss of HLA class I molecules is an important mechanism for tumors to escape from T cell-mediated immune responses.

HLA expression changes are a common event in the carcinogenesis process, and generally occur at the early stage (65,66). The downregulation or loss of HLA class I molecules can prevent tumor cells from being recognized by CTL. Besides, it was reported that class I molecules can be used as tumor suppressor genes in melanoma. Down-regulating the gene enhanced the carcinogenicity of cells, and allow melanoma cells to have a higher proliferation rate and greater migration and invasion potential (67). There are mainly two types of HLA downregulation. The first one is total HLA class I loss or downregulation, which may due to the mutation of beta-2 microglobulin (b2m) gene, complete loss of HLA class I locus or defects in antigen processing and transport pathway. The other one is partial HLA class I loss or downregulation, due to loss of one or several HLA alleles or epigenetically downregulated HLA gene expression. HLA downregulation is common in cancers (68). The percentage of total or partial HLA loss ranges from 65% to 90%, depending on the type of cancer (69). Carretero *et al.* examined the expression of HLA class I antigens in ten metastatic lesions obtained from a melanoma patient undergoing immunotherapy. The eight regressing metastases showed high level of HLA class I expression, whereas the two progressing lesions had low levels (70). Therefore, HLA class I downregulation may be barriers for effective CTLs-based immunotherapy.

Immunotherapies to overcome HLA downregulation

Chimeric antigen receptor (CAR) T-cell (CAR-T)

The discovery of CAR-T therapy provided a way to get around the limitation of the dependence on class I molecules. The main concept is to trigger T-lymphocyte cytotoxic reaction without the need for HLA recognition. CAR is a genetically engineered hybrid of an antibody and a TCR (71). CAR confers the T cells the abilities to recognize tumor cells with a chosen surface antigen and to trigger T cell activation with TCR signaling pathway.

The CAR structure consists of three parts, the extracellular antigen-binding region, the intracellular signal peptide region, and the transmembrane region. Its extracellular antigen-binding region is composed of single-chain variable fragments (scFv) derived from an antibody; the transmembrane region connects intracellular and extracellular structures, usually comprising CD8 or IgG4-Fc; and the intracellular signal peptide region, usually carrying a co-stimulatory domain and a CD3ζ chain, is mainly responsible for T cell activation. The CAR structure has gone through four generations of development so far. In the first-generation CAR, a scFv was fused to the gamma chain of an immunoglobulin or the zeta chain of a CD3 complex. There was no costimulatory molecule, and the survival time *in vivo* was short (72,73). The second generation was improved one step further by fusing a costimulatory molecule to the upstream region of a CD3 domain, mainly CD28 or 4-1BB (74,75). The third generation CAR combines multiple co-stimulatory domains, such as CD28 and 4-1BB or CD28 and OX40. The fourth-generation CAR-T further adds factors that enhance T cell expansion, persistence, and anti-tumoral activity, such as IL-2, IL-5, IL-12 and co-stimulatory ligands (76).

Immunotherapy with CAR-T cells has achieved tremendous successes in treatment of hematological malignancies. By targeting CD19, two second-generation CAR-Ts were approved by the US Food and Drug

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Administration (FDA) for treating leukemia and lymphoma in 2017, of which Kymriah uses 4-1BB as a co-stimulation domain and Yescarta uses CD28 as a co-stimulation domain. Researchers found that patients treated with tisagenlecleucel (Kymriah®) for relapsed/refractory B-cell precursor acute lymphoblastic leukemia (r/r ALL) showed a response rate that exceeds the response rate reported previously for standard chemotherapies. Moreover, clinical data showed that tisagenlecleucel has a continuous response without major safety concern (71,77).

There are also several ongoing clinical investigations about CAR-T therapy in solid tumors. The popular targets include glypican-3 (GPC3) (78,79), ganglioside GD2 (80,81), EGFR (82,83), EGFRvIII (84,85), etc. However, developing CAR-Ts for the treatment of solid tumors is challenging. Compared to the success in hematological malignancies, CAR-T therapy has to date been much less effective for solid tumors (86,87). The first obstacle in treating solid tumors with CAR-T cells is that there are limited antigens solely expressed on the cell surface of tumor cells but not normal cells. In the treatment of neuroblastoma, the fatal neurotoxicity was observed in high-affinity GD2-specific CAR-T cell therapy because of low amounts of GD2 expression in the cerebellum and basal regions of the brain (88). These results highlight the challenges associated with target antigens that exhibit shared expression on critical normal tissues. Therefore, to improve target specificity and eliminate toxicity are necessary in CAR-T cell therapy. Another problem for CAR-T therapy is the poor infiltration and survival of CAR-T cells in tumor microenvironment. To solve these problems, Ma *et al.* enhanced CAR-T cell activity against solid tumors by vaccine boosting. They used a CAR targeting EGFRvIII in combination with a vaccine containing an amphiphilic polymer linked to the EGFRvIII target antigen. In mice with EGFRvIII$^+$ gliomas, vaccination resulted in improved CAR-T cell proliferation and survival, and improved infiltration of activated CAR-T cells into tumor sites (89,90).

Natural killer cells (NK cells)

NK cells are another type of cytotoxic lymphocytes, whose function is also mediated by the interaction of cell surface receptors with HLA class I molecules (91).

NK cells circulate in peripheral blood and are larger than T cells in size, and their phenotypes are different from that of T cells. There are no immunoglobulins or TCRs on the surface of NK cells. Human NK cells are generally defined as cells that lack the cell surface marker CD3 and express CD16 and/or CD56 cell surface glycoproteins. Immediately after pathogen infection, NK cells migrate to the site of inflammation and release their immune function. In addition to cytotoxic functions, NK cells can also secrete certain cytokines to kill infected cells.

NK cell-mediated cell killing activity was inversely related to the expression of HLA class I molecules. The mechanism is that when the specific receptor of the HLA class I molecule on the surface of NK cells encounters its ligand molecule, it will send an inhibitory signal to prevent NK cells from being activated to exert cytotoxicity and secret cytokines (92), preventing NK cells from killing healthy cells. To that end, each NK cell expresses at least one inhibitory receptor that can specifically interact with type I molecules. There are two types of inhibitory receptors in human NK cells for HLA class I molecules, one is a heterodimer composed of membrane molecules CD94 and NKG2A that are covalently bound through disulfide bonds (93,94). The other type is called killer-cell immunoglobulin-like receptor (KIR) which are a family of transmembrane glycoproteins expressed on NK cells and a subset of T cells. The different ways used by NK cells and CD8$^+$ T cells to recognize and respond to class I molecules allow them to collectively generate complementary immune defense against infection.

Since 1970s, several studies have revealed the important role played by NK cells in anti-tumor cytotoxicity. For examples, NK cells can release CCL5, XCL1, and XCL2 to promote the aggregation of DCs inside solid tumors and to promote the antitumor effect of CD8$^+$ T cells (95). In a recent study, scientists transformed NK cells derived from patients with ovarian cancer into a cytotoxic CD56^{superbright}CD16$^+$ subset, which can effectively control the growth of autologous ovarian cancer xenografts in mice (96).

NK cells function through an antigen-independent pathway and can recognize the loss of HLA molecules as an activation signal, which effectively reduces the possibility of immune escape of tumor cells due to the downregulation of class I molecules. By exploiting this feature, we can then utilize NK cells to make up for the restriction on target recognition imposed by HLA class I molecules in TCR-T therapy.

CD4$^+$ T cells

At present, most TCR-T researches are focused on CD8$^+$ T cells. Since tumor cells often escape the surveillance of the immune system by down-regulating the expression of class I molecules, the application of CD8$^+$-associated TCR-T

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therapy is greatly limited. Therefore, some researchers have turned to CD4$^+$ T cells.

Class II molecules mainly present exogenous antigens and are only selectively expressed on specialized APCs that are functionally differentiated, such as macrophages, B cells, and DCs. One common feature shared by these cells is that class II molecules and antigen peptides form complexes before being transferred to the cell membrane surface and subsequently recognized and bound by CD4$^+$ T cells.

CD4$^+$ T cells are also called T helper cells, which help the activation of CTLs, B cells, macrophages and DCs. CD4$^+$ T cells can differentiate into different subsets such as Th1, Th2, Th17 and Treg cells. Although CD8$^+$ CTLs are the preferred tools to target tumors, CD4$^+$ T cells are also required for effective antitumor immunity (97,98). On one hand, CD4$^+$ T cells could kill tumor cells directly when HLA class II molecules expression were induced on certain tumor cells by IFN-γ stimulation (98). On the other hand, CD4$^+$ T cells can exert indirect cytotoxicity. Tumor antigen was processed by HLA class II positive APCs and presented to CD4$^+$ T cells. Tumor-specific CD4$^+$ T cells were activated and started to secrete cytokines (99,100). Vaccination with CD4$^+$ immunogenic mutations/neo-epitope induced cytotoxic T lymphocyte responses and conferred antitumor activity both in mice and patients, which revealed the participation of CD4$^+$ T cells in immunotherapy (100,101). Moreover, Robert D. Schreiber's group found that CD4$^+$ T cells were also required in immune checkpoint therapy and the expression of MHC class II-restricted antigens by tumor cells was required at the site of successful rejection, indicating that activation of CD4$^+$ T cells must also occur in the tumor microenvironment (102).

Up to date, several studies have shown that adoptive transfer of CD4$^+$ T cells can also induce tumor regression (103-105). Researchers have generated an MHC class II-restricted TCR transgenic mouse model in which CD4$^+$ T cells recognize one epitope in tyrosinase-related protein 1 (TRP-1), an antigen expressed by normal melanocytes and B16 murine melanoma (103). Both *in vitro* and *in vivo* experiments have confirmed that CD4$^+$ T cells can eliminate established B16 melanoma, and its therapeutic effect is mainly mediated by IFN-γ. In a clinical study (106) patients with metastatic melanoma were treated with autologous DP4-restricted NY-ESO-1 specific CD4$^+$ T cell clones and have achieved a long-term complete response for over 2 years, suggesting that CD4$^+$ T cells can also induce long-term tumor regression in human similar to what CD8$^+$ T cells have achieved.

Frequently found in a variety of cancer types, MAGE-A3 is a cancer germline antigen and is one of the best targets for cancer immunotherapy. In a clinical study conducted in 2017, 17 patients received adoptive transfer of CD4$^+$ T cells retrovirally transduced with MAGE-A3 TCR after lymphadenectomy plus systemic high-dose IL-2. The results showed that objective complete remission was observed in patients with metastatic cervical cancer. Patients with esophageal cancer, urothelial cancer, and osteosarcoma all had objective responses with durations ≥4 months. There were no treatment-associated adverse effects. Taken together, these findings have proven the safety and effectiveness of the MAGE-A3 specific CD4$^+$ TCR-Ts (107).

Summary

HLA molecules play a pivotal role in T cell-mediated adaptive immunity. HLA class I molecules exist on most types of human cells and interact with TCRs to activate T cells to induce adaptive immune responses. CD8$^+$ T cell-based therapies such as TIL therapy and TCR-T therapy are HLA-dependent immunotherapies (*Figure 2*). Although TIL has achieved significant results in the treatment of metastatic melanoma, it is still difficult to isolate and identify effective TILs for other malignant tumors. In addition, as a "personalized" treatment, its industrial manufacturing process is full of obstacles. The current researches on TIL therapy are focused on how to use a rapid method to isolate, identify, and expand TILs to the clinically required doses. In TCR-T therapy, antigen-specific TCRs are transduced into normal T cells using retrovirus or lentivirus making it more convenient compared to TILs. Currently, several TCR-Ts are under investigation in clinical trials to further explore the therapeutic value. However, tumor cells may escape T cell attacks through downregulation of HLA, which poses a greater challenge to HLA-dependent immunotherapy. Thus, HLA-independent immunotherapies such as CAR-T therapy, NK therapy and CD4$^+$ T cell therapy are discussed above (*Figure 2*). Interestingly, Crowther *et al.* recently found one TCR recognized and killed most human cancer types via the monomorphic MHC class I-related protein, MR1 (108). This MR1-restricted TCR mediated *in vivo* regression of tumor both in mice and in melanoma patients without the requirement of a specific HLA. These findings offered another opportunity for HLA-independent and pan-population immunotherapies. Considering great heterogeneity in tumor microenvironment, we believe that the combination of different immune cell therapies such as

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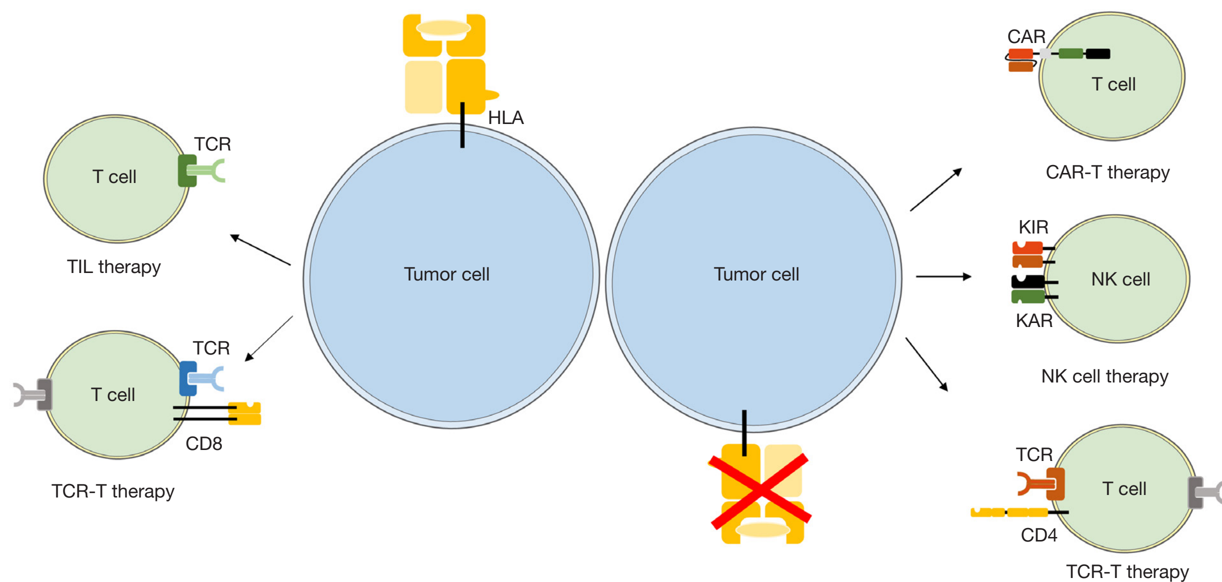

Figure 2 HLA and cancer immunotherapy. When HLA class I molecules exist and present antigens on tumor cells, $CD8^+$ T cell-based therapies such as TIL therapy and TCR-T therapy are useful tools of cancer adoptive immunotherapies. When tumor cells escape $CD8^+$ T cell attacks through downregulation of HLA, HLA-independent immunotherapies such as CAR-T therapy, NK therapy and $CD4^+$ T cell therapy can make up for the deficiency to a certain extent. HLA, HLA class I molecules; CD8, CD8 molecules; CD4, CD4 molecules; KIR, a killer cell inhibitory receptor; KAR, a killer cell activation receptor; CAR, chimeric antigen receptor; TCR, T cell receptor. Colorful TCR means the effective antigen-specific TCR, while grey TCR means the original expressed TCR of TCR-T cells; TCR-T, TCR-engineered T cell; CAR-T, chimeric antigen receptor T-cell; TIL, tumor-infiltrating lymphocyte.

$CD8^+$ T cells and $CD4^+$ T cells should be a trend of tumor adoptive immunotherapy in the future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aob-20-27). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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