**ROLE OF HLA CLASS I MOLECULE IN CANCER: IMPLICATIONS FOR CANCER IMMUNOTHERAPY**

**ABSTRACT**

HLA class I molecules are essential for presenting tumour antigens to cytotoxic T-cells, but their dysregulation in cancer enables immune evasion and limiting the efficacy of immunotherapies for cancer. The objective of this review is to explore the function of HLA class I changes in cancer development and their consequences for immunotherapy evolution. Examining peer-reviewed studies from 2010–2025 in PubMed and Scopus, a thorough literature review was done with a focus toward HLA class I expression, genetic defects, and immunotherapy outcomes in cancers including melanoma and lung cancer. HLA Class I Downregulation is a hallmark of tumour cells. Findings show that epigenetic silencing, β2-microglobulin mutations, or altered antigen-processing machinery are identified as the major mechanisms of HLA downregulation observed in 50–70% of tumours. These alterations are primary to therapeutic implications like poor responses to drugs like checkpoint inhibitors and they cause decreased T-cell infiltration. Research shows that in preclinical models, restoring HLA class I expression through cytokines, epigenetic modulators, or gene therapy are effective strategies in T-cell recognition and tumour clearance. Combining such approaches with PD-1/PD-L1 inhibitors produces synergistic effects that raise response rates by 20–40%. Furthermore, HLA class I status assessment can serve as an emerging possible biomarker for immunotherapy success. However, tumour heterogeneity and immunosuppressive microenvironments remain a challenge. Crucially, clinical studies to validate HLA class I restoration strategies and biomarker-driven patient stratification are underway to Investigate interactions between natural killer cell responses and HLA class I to help improve therapeutic approaches. Targeting therapies to reverse HLA class I defects through oncolytic viruses, along with integrating these with tailored immunotherapies are suggested future directions in immunotherapy.

**1. INTRODUCTION**

Improving, enhancing and maintaining immune function remains the target of advances in cancer immunotherapy. HLA (Human Leucocyte Antigen) class I molecules are transmembrane glycoproteins that function by presenting endogenous antigens to T-cells. Structurally, they're made up of a heavy chain, which varies because they are encoded by one of three genes: HLA-A, HLA-B, or HLA-C and a light chain called β2-microglobulin (β2m) that isn't directly linked to the molecule (Zhang et al., 2023). From studies, these classes of molecules are believed to be expressed on nearly all nucleated cells and their function is to present intracellular peptide antigens typically 8–11 amino acids long on the cell surface. This antigen presentation is important for recognition by CD8+ cytotoxic T-cells (Galluzzi et al., 2025). The T-cells which are responsible for clearing cancer cells, are able to engage the peptide-HLA complex via their T-cell receptor (TCR) (Hazin et al., 2021). Importantly, the antigen presentation by these molecules happens through an antigen processing pathway which involves several key steps. It spans from the degradation of cytosolic proteins by the proteasome, to loading onto HLA class I molecules with the assistance of chaperone proteins like tapasin. Peptides are then recognized and CD8+ T-cells will become activated, triggering cytotoxic responses to eliminate the target antigen. In the context of cancer, HLA class I molecules play a pivotal role in immune surveillance by presenting tumour-specific or tumour-associated antigens, to T-cells to instigate elimination before such cells begin to metastasize (Aptsiauri and Garrido, 2022).

In cancer, there is reportedly an increased probability of HLA class I dysregulation which is known to contribute to tumour immune evasion. Studies reveal that tumours thrive by using this downregulation of expression and abnormalities in the antigen-processing machinery, to suppress immune function (Aptsiauri and Garrido, 2022). The causes of HLA class I molecule downregulation may be as a result of either transcriptional repression or epigenetic silencing. DNA methylation or histone deacetylation are some of the notable forms of epigenetic silencing that can contribute to lower HLA class I expression. Statistics from studies reveal that non-silent genetic mutations in HLA class I genes are detected in 3.3% of all tumours, of these findings, statistically higher prevalence are found in lung (5–7%) and colorectal cancers (4–6%) [4]. There are critical proteins that are also important in antigen expression like TAP, and tapasin. They are antigen-processing components that affect HLA functions. Studies have documented HLA class I downregulation in 50–70% of tumours, including melanoma, lung, breast, colorectal, ovarian, and pancreatic cancers (Galluzzi et al., 2025). This may suggest that these processes are critical in most tumours. These studies have also found that such dysregulation not only diminishes T-cell-mediated cytotoxicity but also alters interactions with natural killer (NK) cells (Mittal et al., 2025).

HLA class 1 molecules belong to a group of molecules known as Major Histocompatibility Complex (MHC). They are a group of genes and proteins involved in the immune system's ability to recognize and respond to foreign substances. Another critical effect of HLA class I dysregulation is the resulting breakdown or compromise of cancer therapies like anti-PD-1/PD-L1 checkpoint inhibitors, which increase T-cell activity by blocking inhibitory signals [4,6]. Importantly, effective antigen presentation is necessary for effective clearance of tumour cells. Thus, low HLA class I expression or antigen-processing mutations prevent detection and elimination of tumour cells in such treatments (Galluzzi et al., 2025). These have so far been demonstrated in clinical and preclinical studies reporting poorer response and survival rates in melanoma and non-small cell lung cancer patients with HLA defects against those with intact pathways. Similarly, in tumours with low HLA class I expression, the use of adoptive T-cell therapies, such as CAR T-cells or TCR-based treatments has proved less successful (Mittal et al., 2025). Therefore, success of universally effective immunotherapy is still greatly hindered due to this. Consequently, there is a need to figure out how to handle these HLA class I modifications in tumours so that these treatments may be fully effective (Mittal et al., 2025).

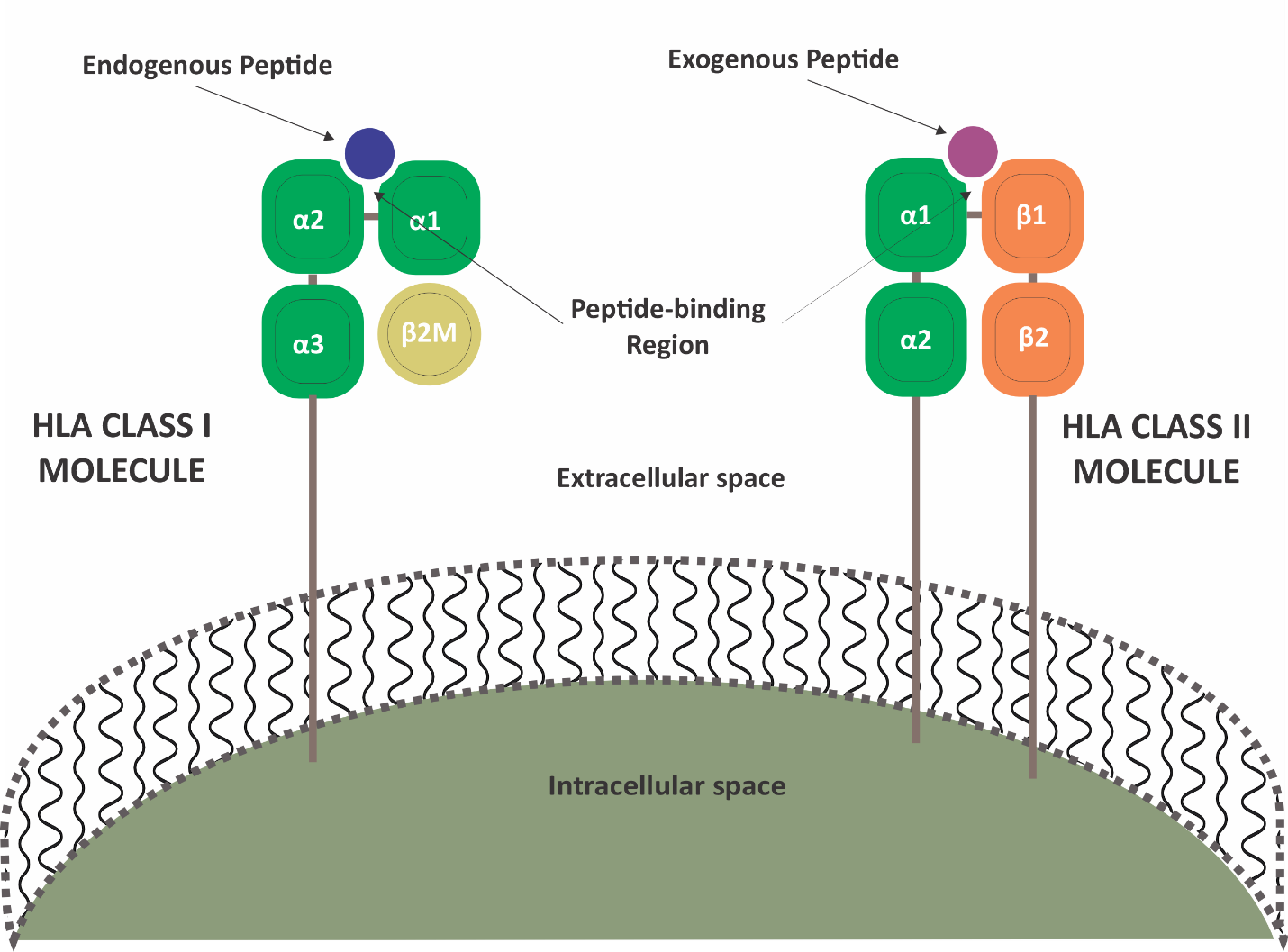
HLA class I defects remain a major obstacle in some tumours even as immunotherapy continues to dominate cancer treatment. Furthermore, HLA class I status shows promise as a biomarker for treatment outcome prediction; hence, this would help provide individualized treatment on cancer patients.

Research on HLA class I function in cancer immune evasion and its effects on treatments including checkpoint inhibitors is examined in this review 2010–2025. The review is set to examine the structure and function of HLA CLASS I molecules in presenting tumour cells to immune cells. Examining flaws in major cancers and treatment course evaluation like gene therapy, pharmacological restoration, and combination treatments to restore antigen presentation (Basera 2022)

**2. Genetic Background and Molecular Structure of HLA Class I Molecules**

HLA class I molecules are encoded by genes within the major histocompatibility complex (MHC), a highly polymorphic genomic region located on chromosome 6. The karyotype is represented as 6p21 in humans. The MHC spans approximately 4 megabases and is divided into three regions encoding class I, class II, and class III. HLA class I genes reside in the class I region. These genes are specifically HLA-A, HLA-B, and HLA-C, and are responsible for encoding the heavy chains of the classical HLA class I molecules. It is a very polymorphic gene (Nguyen et al. 2021). In fact, they represent one of the most polymorphic genes in the human genome. Additionally, thousands of alleles of these genes have already been identified to date. Specifical over 7,000 alleles for HLA-A, 8,000 for HLA-B, and also about 6,000 has been identified for HLA-C, according to the IPD-IMGT/HLA database as of 2025. Scientists have explained that the extensive polymorphism results from evolutionary pressures to present a diverse array of antigens. This will in-turn enable the immune system to recognize a wide range of pathogens and abnormal cells, including malignant ones, given tumours have the capability to exhibit several genetic polymorphs (Shiina and Kulski, 2024).

Basically, each HLA class I gene consists of eight exons, with exons 2 and 3 encoding the α1 and α2 domains. The combination forms the peptide-binding groove critical for antigen presentation. Exon 4 encodes the α3 domain, which interacts with CD8+ T-cells, while exons 5–8 code for the transmembrane and cytoplasmic regions. The high allelic diversity primarily affects the peptide-binding regions (α1 and α2), leading to variations in peptide specificity and T-cell receptor (TCR) recognition. HLA-A, -B, and -C genes are co-dominantly expressed, meaning both maternal and paternal alleles are expressed, maximizing the repertoire of presented peptides. Additionally, the β2-microglobulin (β2m) part of the HLA class I, encoded by a non-polymorphic gene on chromosome 15, is essential for stabilizing the HLA class I complex (Castro 2019).



**2.1 Molecular Structure**

Each molecule consists of a heavy chain (~45 kDa), a non-covalently associated β2-microglobulin (β2m, 12 kDa), and a bound peptide. The heavy chain includes three extracellular domains (α1, α2, α3), with a transmembrane region, and a cytoplasmic tail. The α1 and α2 domains form a peptide-binding groove at the top (figure 1). Two α-helices accommodate peptides that are 8–11 amino acids long and determine binding specificity through polymorphisms. The α3 domain interacts with the CD8 co-receptor, stabilizing T-cell engagement (Hollenbach et al., 2019).

Figure 1 also depicts the invariant β2m component that stabilizes the heavy chain. It is also of significance to oncology because without it, the complex becomes unstable and may be retained intracellularly, a mechanism often exploited by tumours. Endogenous proteins are held on to α1 and α2 domain grooves (Peptide binding region in Figure 1) by hydrogen bonds and van der Waals forces.

**2.2 Normal Function and Regulation of HLA Class I**

**2.2.1 Normal Function of HLA Class I**

HLA class I molecules are pivotal; they orchestrate the recognition and elimination of abnormal or infected cells. Expressed on nearly all nucleated cells. Their primary function is to display intracellular peptides that are derived from self, viral, or tumour proteins and present them on the cell surface of cells for T-cell toxicity. Additionally, HLA class I molecules interact with natural killer (NK) cells via killer immunoglobulin-like receptors (KIRs). In this case it performs a relatively dual role. In normal cells, HLA class I expression inhibits NK cell activation to signal that a cell is healthy and “self.” This dual role in engaging both T-cells and NK cells makes HLA class I as a cornerstone of immune homeostasis, being able to balance innate immunity with adaptive immunity (Hollenbach et al., 209).

**2.2.2 Role in Antigen Presentation**

In cancer, HLA class I molecules are critical for presenting tumour-specific antigens, particularly neoantigens arising from somatic mutation as well as overexpressed proteins. This is then recognized by T-cells for elimination. The efficacy of this surveillance depends on the integrity of the HLA class I antigen presentation pathway, which is frequently disrupted in tumours, as discussed later in this review. The process is tightly regulated with multiple intricate steps.

1. **Protein Degradation into Peptides**

First, intracellular proteins from normal cellular processes, pathogens, or malignant transformations, are degraded by the proteasome, which is a multi-subunit complex in the cytosol. The proteins are cleaved into short peptides, ranging from 8–11 amino acids in length. The essence is the suitability for binding to HLA molecules.

1. **Peptide Transport into the Endoplasmic Reticulum**

The generated peptides are then translocated from into the endoplasmic reticulum (ER) by the transporter associated with antigen processing (TAP). This in many cases is a heterodimer composed of TAP1 and TAP2 subunits. TAP selectively transports peptides that match the length and sequence requirements for HLA class I binding, ensuring an efficient supply of antigens (Hazini et al., 2021).

1. **Peptide Loading onto HLA Class I Molecules**

Inside the ER, peptides are loaded onto nascent HLA class I molecules. This happens in the presence of chaperone proteins, like tapasin, calreticulin, and ERp57. The function of the chaperone proteins is to ensure three things: the proper folding of the HLA heavy chain, stabilization, and to optimize peptide selection for high-affinity binding. The HLA molecule then binds with the peptide.

1. **Transport to the Cell Surface**

The peptide-HLA complex is stabilized by β2ma and is then transported from the ER with the help of the Golgi apparatus to the cell surface. This trafficking ensures that the complex is correctly positioned for immune detection by T-cells.

1. **Peptide Presentation to CD8+ T-Cells**

On the cell surface, the peptide-binding groove of HLA class I, which is formed by the α1 and α2 domains, displays the peptide for detection by CD8+ T-cells. The specificity of peptide binding is determined by polymorphic residues within the groove, which vary across HLA-A, -B, and -C alleles, allowing each allele to present a unique repertoire of peptides (Cornel et al., 2020).

1. **T-Cell Recognition and Activation**

If a CD8+ T-cell’s receptor recognizes the peptide-HLA class I complex as foreign or aberrant (e.g., a tumour antigen), it becomes activated after receiving co-stimulatory signals via CD28 binding to B7 on cells. The T-cell proliferates and differentiates into an effector cell. When this happens cytotoxic molecules such as perforin and granzymes are released to induce apoptosis in the target cell

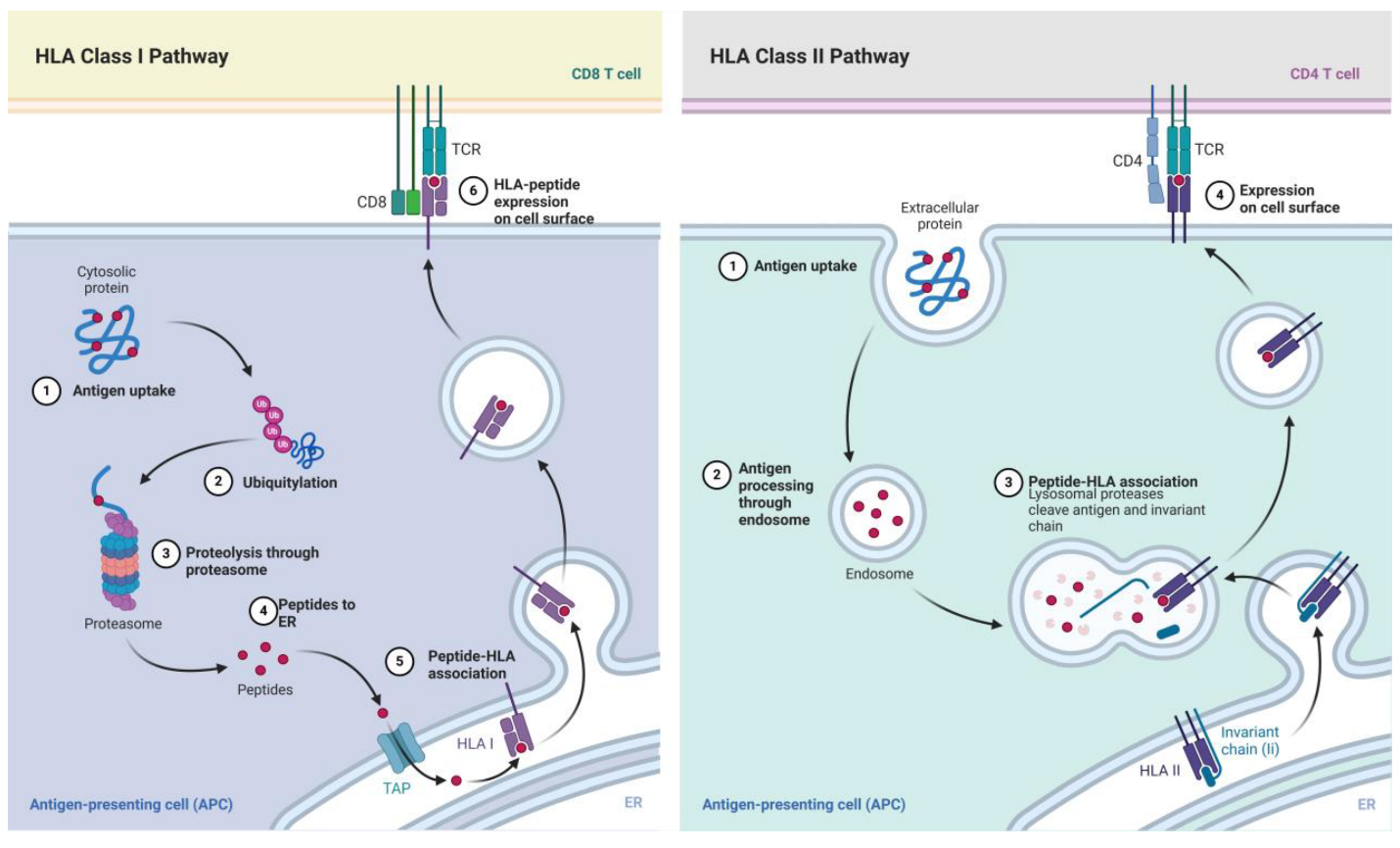


Figure 2: Schematic overview of HLA-I and HLA-II antigen processing and presentation pathways (Benitez-Fuentes et al., 2024).

**2.2.3 Role in Self-Recognition and Immune Tolerance**

In addition to antigen or tumour presentation, HLA class I molecules also play a role in self-recognition and maintaining immune tolerance. Specifically in education and selection of immune cells. As T-cell develop in the thymus, HLA class I molecules are responsible for presenting self-peptides to maturing T-cells (Papúchová et al., 2019; Shrestha, 2021). This is what facilitates positive and negative selection in CD8+ T cells. T-cells with receptors that bind self-peptide-HLA class I complexes are positively selected to ensure a functional T-cell repertoire capable of recognizing altered self-antigens (e.g., tumour antigens). While those that bind too strongly are eliminated through negative selection to prevent autoimmunity. This establishes central tolerance and protects healthy tissues (Han et al., 2025).

HLA class I molecules also support peripheral tolerance by presenting self-peptides to signal "self" to T-cells and NK cells. In NK cells, interaction with self-peptides prevents them from killing healthy cells. Tumours usually exploit this by partially retaining HLA class I to avoid NK cell attack. These mechanisms are key to developing immunotherapies that target tumours without causing autoimmunity (Shrestha, 2021; Han et al., 2025).

**2.2.4 Regulation of Expression Under Normal Physiological Conditions**

HLA class I expression is tightly regulated under normal physiological conditions to maintain immune homeostasis. Transcription factors such as NF-κB, and interferon regulatory factor 1 (IRF-1), and the enhancer, A complex which binds to the HLA genes. The level of expression varies by cell type, major antigen-presenting cells like dendritic cells and lymphoid cells showing higher levels than parenchymal cells. HLA-C is also typically expressed at lower levels than HLA-A and HLA-B (Shrestha, 2021).

Further, expression is governed by cytokines and immune signals. Interferon-γ (IFN-γ), which is an effector molecule of immune activation, up-regulates HLA class I and the antigen processing machinery genes by activating the JAK-STAT signalling pathway to increases the capability of antigen presentation during infection or stress. Type I interferons (IFN- α/ β ) and tumour necrosis factor-α (TNF-α) both induce HLA class I to a lesser degree. Conversely, through negative regulators such as microRNAs or chromatin modulators, expression is fine-tuned to keep immune activation below a certain threshold in steady-state.

These mechanisms are frequently altered in cancer through epigenetic regulation by tumour cells to disrupt normal expression, contributing to immune evasion. These processes are implicative because, understanding the normal regulation of HLA class I provides insights into therapeutic strategies, such as using IFN-γ or epigenetic modulators to restore expression in tumours (Papúchová et al., 2019).

**3. HLA Class I Expression in Cancer**

**3.1 Downregulation or loss of HLA Class I in tumour cells.**

A downregulation to HLA I expression is a common finding in cancer. This is a mechanism of immune escape by cancer cells. It is secondary to transcriptional repression or epigenetic silencing in tumour cells. With transcriptional repression, the mechanism is mediated by tumour suppression of transcription factors like NF-κB or interferon regulatory factor 1 (IRF-1) present in the nucleus (Garrido and Garrido, 2019). Additional mechanism responsible for this, is the upregulation of oncogenic signalling pathways, such as MYC or RAS (Taylor and Balko, 2022). Through these pathways, tumours are able to inhibit HLA class I transcription. Further, studies alluded that epigenetic silencing contributes to downregulation through DNA methylation and histone modification. First, hypermethylation of CpG islands inhibits transcription by preventing transcription factor binding in the promoter regions of HLA genes. Similarly, histone deacetylation or methylation compacts chromatin (Anderson et al., 2021). Thus, the genes for HLA class I become less accessible for transcription. Implicatively, studies have shown that epigenetic silencing is reversible, through the use of demethylating agents like 5-azacytidine or histone deacetylase inhibitors. HLA class I expression can be restored in tumour cell lines, suggesting therapeutic potential. Downregulation is particularly prevalent in cancers like melanoma and colorectal cancer (Papúchová et al., 2019; Lee et al., 2020; Shrestha, 2021).

Depending on the type of cancer and the detection technique used in the laboratory, HLA class I dysregulation is generally common in all types of cancers. Within the tumour cells, downregulation is reported to occur in 60–70% of melanomas, 50–60% of lung cancers, with familiar rates in ovarian cancers, and pancreatic cancers. Laboratory testing techniques include immunohistochemistry and genomic studies. Howbeit, figures vary due to differences in tumour stage, microenvironment, and methodology for example there may be difference in RNA sequencing vs. protein staining.

**3.2 Genetic Alterations Affecting HLA Class I Antigen Presentation**

Genetic alteration is a common phenomenon in advanced cutaneous T-cell lymphoma. Alterations in the gene coding for HLA or associated antigen-processing machinery are a key mechanism of dysregulation. Mutations in the β2m gene, which encodes the light chain essential for HLA class I stability, are frequently reported in many cancer studies (Ugurel et al., 2019). Such mutations can manifest as frameshifts, deletions, or point mutations. It leads to disruption in β2m component protein function, preventing proper folding and surface expression of HLA class I-antigen complexes. For example, β2m mutations have been reported in 20–30% of melanomas and lung cancers, often associated with immunotherapy resistance (wang et al., 2022). Less commonly found is a mutation in HLA-A, -B, or -C genes which in cases of occurrence can alter the peptide-binding groove or CD8-binding domain. In such cases there is impaired antigen presentation or T-cell recognition. Additionally, defects in antigen-processing machinery components, such as the transporter associated with antigen processing (TAP1/TAP2) or tapasin, hinder peptide transport and loading onto HLA class I molecules. TAP1 mutations, for instance, have been identified in 15–25% of cervical and head and neck cancers. These genetic alterations confer a survival advantage to tumours by rendering tumour cells invisible to T-cells (Pyke et al., 2022). Genetic alterations, including β2m and TAP mutations, occur in 15–30% of cases, with higher frequencies in immunotherapy-resistant tumours.

**3.3 Revise the title for clarity: HLA Class I Loss of Heterozygosity (LOH) in Tumours**

A common occurrence in cancer is loss of heterozygosity (LOH) at HLA loci. This is the loss of one parental allele at chromosome 6p21, where HLA class I genes find residence. LOH reduces the variety of HLA class I molecules available for antigen presentation, so restricting the repertoire of peptides put before T-cells. Usually occurring from chromosomal deletions, mitotic recombination, or gene conversion events, this allelic loss LOH is especially important since it can selectively remove HLA alleles displaying immunodominant tumours, so enabling tumours to evade particular T-cell responses while keeping other alleles to prevent NK cell attack (Liepe et al., 2019). In 30–50% of lung, pancreatic, and ovarian cancers in tumours in immunotherapy exposure, studies employing next-generation sequencing have found higher rates of LOH. LOH's selective character emphasizes the evolutionary pressure tumours must balance T-cell and NK cell evasion, so confusing immune recognition (Yang et al., 2023).

LOH is detected in 20–50% of solid tumours, with pancreatic and lung cancers showing the most elevated rates (Zhao et al., 2021). The prevalence of these defects correlates with clinical outcomes, as tumours with HLA class I dysregulation exhibit reduced T-cell infiltration and increased metastasis. Notably, the frequency and type of HLA class I alterations differ across cancers. This reflects the tumour-specific immune pressures and alterations in genetic backgrounds. For example, melanomas often show epigenetic downregulation. On the contrary, pancreatic cancers frequently exhibit more loss in heterozygosity (Zhao et al., 2021).

**4. EFFECT OF HLA CLASS I DYSREGULATION IN CANCER**

HLA class I dysregulation in cancer, encompassing downregulation, and other mechanisms discussed earlier, profoundly disrupts immune surveillance. These alterations impair antigen presentation and enable tumours to evade immune detection with significant implications for cancer progression and immunotherapy efficacy.

**4.1 Reduced T-Cell Activation and Infiltration in Tumours**

Activating CD8+ cytotoxic T-cells and allowing them to infiltrate the tumours depend on tumour-specific antigen presentation to them. A disruption that prevents efficient peptide presentation results from dysregulation of HLA I molecules or mutations in β2-microglobulin (β2m) and antigen-processing machinery (e.g., TAP, tapasin) (Hazini et al., 2021). T-cells thus fail to identify cancer cells as aberrant, which lowers activation, proliferation, and cytotoxic activity against tumours. Immunohistochemical studies show that tumours with low HLA class I expression such as 60–70% of melanomas and 50–60% of lung cancers have much less CD8+ T-cell infiltration than HLA class I-proficient tumours (Li et al., 2021). Implicitly, this lack of T-cell response produces an immunologically "cold" tumour microenvironment marked by reduced immune effector activity and poor responsiveness to immunotherapies including anti-PD-1/PD-L1 checkpoints. Clinically, for example, melanoma patients with downregulated HLA class I show response rates to PD-1 inhibitors as low as 10–20%, while those with intact HLA class I pathways show 40–50% responses (li et al., 2021; Maggs et al., 2021).

**4.2 Increased Tumour Progression and Metastasis**

When tumour cells fail to present antigens due to epigenetic silencing, β2m mutations, or loss of heterozygosity, they escape immune surveillance, gaining a survival advantage that promotes uncontrolled proliferation and metastatic spread (Hurkmans et al., 2020). Studies have consistently linked HLA class I defects to aggressive tumour behaviour and poor clinical outcomes across multiple cancers. For example, in colorectal cancer, reduced HLA class I expression is associated with deeper tumour invasion and lymph node metastasis, with 55–65% of advanced-stage tumours showing downregulation (Okita et al., 2023).

Similarly, A recent study by Kubo et al. (2024), on pancreatic cancer, observed loss of heterozygosity at HLA loci, in 30–50% of cases. This correlates with increased metastatic potential and shorter overall survival (Kubo et al., 2024). The absence of effective T-cell responses allows tumour cells to proliferate uncontrollably, accumulating heterogenous mutated cells and spread to distant sites. Furthermore, matrix metalloproteinases is a reported expression found in HLA class I-deficient tumours which further drives tumour invasion.

**4.3 Natural Killer (NK) Cell Responses to HLA Class I Loss**

Moreover, a reported expression present in HLA class I-deficient tumours is matrix metalloproteinases, which fuels tumour invasion even more. Natural Killer (NK) Cell Reactivity to HLA Class I Loss. Although HLA class I downregulation helps tumours to avoid T-cells, it makes them vulnerable to NK cell-mediated cytotoxicity since normal HLA class I molecules engage inhibitory killer immunoglobulin-like receptors (KIRs) (Kubo et al., 2024). HLA class I (especially HLA-C and some HLA-B alleles) signals "self," thus preventing NK cell attack in healthy cells. This inhibitory signal is reduced in tumours with complete or partial HLA class I loss, so perhaps triggering NK cell activation via activating receptors such as NKG2D, which on tumour cells recognise stress ligands such as MICA/B. Studies have shown, though, how tumours sometimes use tactics to balance T-cell and NK cell evasion (Kubo et al., 2024). For example, selective loss of particular HLA alleles (e.g., HLA-A or -B) by loss of heterozygosity lets tumours evade T-cell recognition while still maintaining enough HLA-C expression to prevent attack from NK cells. Studies find that for immune escape, 20–40% of ovarian and lung tumours show such selective allelic loss. To reduce NK cell activity, tumours may also upregulate immunosuppressive molecules including TGF-β or IL-10, so complicating immune responses. Developing immunotherapies that boost T-cell and NK cell activity such as combining checkpoint inhibitors with NK cell-activating agents requires an awareness of these interactions (Ajutor et al., 2025).

**5. IMPLICATIONS OF HLA DYSREGULATION FOR CANCER IMMUNOTHERAPY**

HLA class I dysregulation significantly affects the efficacy of cancer immunotherapies through impaired antigen presentation. Immunotherapy treatments are employed to help patients undergoing immune therapies like immune checkpoint inhibitors, tumour vaccines, and adoptive T-cell therapies (Aptsiauri and Garrido, 2022). Dysregulation mechanisms position HLA class I expression as a potential biomarker for prognosis and treatment response. Understanding these implications is critical for developing strategies to overcome limitations in immunotherapy for cancer patients with various cancers.

**5.1 Reduced Efficacy of Immune Checkpoint Inhibitors**

Immune checkpoint inhibitor drugs, like anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, are treatments administered to cancer patients to enhance their immune system against cancer cells. Such treatments work by blocking inhibitory signals (Pagliuca et al., 2022). Optimal function of these drugs is dependent on robust antigen presentation by HLA class I molecules. Thus, dysregulation as observed in 50–70% of tumours, therefore may prevent CD8+ T-cell from recognizing and eliminating tumour antigens even though they may be heightened to do so. Clinically it has been demonstrated in studies that cancer treatment with low HLA class I expression or β2-microglobulin (β2m) mutations lead to reduced response rates to checkpoint inhibitor treatment. For instance, when Zaretsky et al. (2016) studied acquired resistance to PD-1 blockade in melanoma (Zaretsky et al., 2016). They found that in patients with β2-microglobulin (β2m) mutations that lead to HLA class I loss, the objective response rate to PD-1 inhibitors was significantly reduced to about 14% of patients responding well. This is in alignment with a broader study range of 10–20% in melanoma trial data. In contrast, patients with intact HLA class I expression from the same study had a response rate closer to 40% in their cohort. Currently interferon-γ or epigenetic modulators, are now showing promise in preclinical models as some of the strategies to overcome low response due to HLA dysregulation (Zaretsky et al., 2016). This helps achieve the goal of increasing T-cell responses and synergizing with checkpoint inhibitors to improve outcomes (Pagliuca et al., 2022)

**5.2 Role in Tumour Neoantigen Presentation and Vaccine Development**

**In the** science of cancer vaccines, HLA class I molecules are essential for presenting tumour neoantigens, which are peptides derived from somatic mutations unique to cancer cells, which are prime targets for cancer vaccines. Dysregulation impairs neoantigen presentation, and implicatively reduces the immunogenicity of vaccines designed to stimulate T-cell responses against tumour-specific antigens. For example, in colorectal and pancreatic cancers, Hazini et al. (2021) reports that up to 75% of tumours exhibit altered HLA class I, neoantigen-based vaccines struggle to elicit robust T-cell responses. However, tumours with intact HLA class I pathways are more likely to present neoantigens effectively, thereby enhancing vaccine efficacy. A recent study by Wang et al. (2020) have identified specific HLA alleles (e.g., HLA-A\*02:01) associated with better neoantigen presentation in melanoma, guiding personalized vaccine design. As a result of this, therapies that upregulate HLA class I expression, such as demethylating agents, are now being considered in combined vaccination to enhance neoantigen presentation and boost vaccine-induced immunity. Clinical trials are already showing improved T-cell responses in 20–30% of patients with HLA-proficient tumours (Wang et al., 2020).

**5.3** **Impact on Adoptive T-Cell Therapies**

Another aspect of cancer immunotherapy with implicative HLA dysregulation effect, is Adoptive T-cell therapies. For therapies like chimeric antigen receptor (CAR) T-cell and T-cell receptor (TCR)-based therapies, there is reliance on HLA class I for effective tumour targeting, especially for TCR-based approaches. TCR therapies require normal expression of HLA class I to present tumour antigens for recognition by engineered T-cells, therefore, dysregulation disrupts this process. Vitale et al. (2020) noted that HLA class I downregulation is frequent in ovarian cancer, occurring in approximately 50% of cases. Although CAR T-cell therapies, which target surface antigens independently of HLA class I, are less affected by dysregulation, they may still be affected in solid tumours with low antigen density or immunosuppressive microenvironments exacerbated by HLA loss. Clinical trials are exploring this combination of T-cell therapies with agents that can upregulate HLA class I molecules. Addressing HLA class I dysregulation is thus essential for optimizing adoptive T-cell therapies, particularly for solid tumours with high rates of HLA defects (Ferreira et al., 2019).

**5.4 HLA Class I Expression as a Biomarker for Prognosis**

HLA class I expression is emerging as a valuable biomarker for predicting prognosis and immunotherapy response across multiple cancers. Low HLA class I expression, detected via immunohistochemistry or genomic profiling, correlates with poor prognosis due to reduced T-cell infiltration and increased tumour progression (Muntasell et al., 2019). In breast and colorectal cancers, patients with downregulated HLA class I (55–65% of cases) have significantly shorter overall survival compared to those with high expression. Similarly, in melanoma and lung cancer, intact HLA class I pathways are associated with better responses to checkpoint inhibitors, with response rates 20–30% higher in HLA-proficient tumours. Genomic studies have identified specific HLA genotypes (e.g., HLA-B\*44) linked to improved immunotherapy outcomes, suggesting allele-specific prognostic value (Ferreira et al., 2019). Moreover, loss of heterozygosity at HLA loci, observed in 20–50% of pancreatic and ovarian cancers, predicts resistance to immunotherapy and worse survival. These findings position HLA class I expression as a potential biomarker for patient stratification, enabling personalized treatment decisions. Ongoing clinical trials are validating HLA class I status as a predictive tool, with efforts to integrate it into diagnostic panels alongside PD-L1 and tumour mutation burden. Leveraging HLA class I as a biomarker could guide the selection of patients likely to benefit from immunotherapy and identify those requiring combination therapies to restore HLA function (Muntasell et al., 2019).

**6. STRATEGIES TO MODULATE HLA CLASS I IN CANCER THERAPY AND FUTURE DIRECTIONS**

By preventing antigen presentation to CD8+ T-cells and resulting in immune evasion, HLA class I dysregulation dents cancer immunotherapy from reaching optimum potential. Therefore, full effectiveness can only be reached by restoring HLA class expression (Ferreira et al., 2019). Current and emerging strategies to modulate HLA class I expression, include pharmacological approaches, gene therapy, combination therapies, and innovative technologies.

**6.1 Pharmacological Approaches**

Targeting transcriptional or epigenetic aetiology of downregulation can be done pharmacologically to restore HLA class I expression. Particularly interferon-γ (IFN-γ), cytokines are strong inducers of HLA class I and antigen-processing machinery genes (e.g., TAP1, TAP2, tapasin) by means of JAK-STAT pathway activation. Preclinical studies like Yamamoto et al., (2020) in melanoma and lung cancer cell lines show that IFN-γ raises HLA class I surface expression by 2–4-fold. Although their result depended on cell types and baseline expression levels that were measurable by flow cytometry. Clinically, improvement of T-cell recognition and cytotoxicity can be improved with 30–50% enhancement.

Demethylating agents like 5-azacytidine and decitabine, as well as histone deacetylase (HDAC) inhibitors (e.g., vorinostat) have shown capabilities of reversing HLA class I downregulation that is caused by either histone deacetylase (HDAC) inhibition or promoter hypermethylation. In models of colorectal and ovarian cancer a study by Chiappinelli et al. (2015), reported that 5-azacytidine treatment in colorectal and ovarian cancer models upregulated HLA class I and β2m in 50–70% of cells (Chiappinelli et al., 2015). This is particularly so in tumours with epigenetic silencing; clinical studies combining 5-azacytidine with anti-PD-L1 therapy in lung and breast cancers have shown a 20–30% increase in objective response rates over checkpoint inhibitors alone. Though they show promise, these agents need to be optimised to lower off-target effects including myelosuppression and enhance tumour-specific delivery for favourable outcomes.

**6.2** **Gene Therapy**

Gene therapy, particularly CRISPR/Cas9-based editing, offers another targeted approach to correct genetic defects in HLA class I pathways, such as mutations in β2m or antigen-processing genes like TAP1 and tapasin. Although this is yet to be proven in advanced clinical settings. Research is still ongoing on how the CRISPR system can be employed in different aspects of the tumour life cycle especially in enhancing cancer immunotherapy. In one of current advancements, CRISPR-mediated repair of β2m mutations in melanoma and lung cancer cell lines restored HLA class I surface expression in 40–60% of treated cells which lead to a 35–50% increase in T-cell-mediated tumour lysis in preclinical models (Xiang et al., 2024).

Similarly, editing TAP1 mutations in head and neck cancer models enhances peptide loading, improving TCR-based therapy outcomes. Early-phase clinical trials which were initiated in 2023–2024 as reported by Feng et al. (2024), are testing CRISPR-based β2m repair in solid tumours, with preliminary data indicating restored HLA class I expression in 10–20% of patients with improved responses to adoptive T-cell therapies (Feng et al., 2024).

As observed in other gene editing applications, there are challenges ranging from off-target risks and tumour heterogeneity, which may limit uniform HLA restoration. Future refinements in CRISPR specificity and scalable delivery methods are critical for clinical application (Ajutor et al., 2024). Advances in delivery systems, such as adeno-associated viral (AAV) vectors and lipid nanoparticles, are already in place and present great potential in improving efficiency of CRISPR delivery to tumour cells.

**6.3 Combination Therapies**

Combining immunotherapies such as checkpoint inhibitors or neoantigen vaccines with HLA class I-modulating drugs presents an effective route to overcoming limitations due to low antigen presentation. Such combination therapies can synergistically overcome immune evasion with 30–45% higher effect relative to monotherapy. So far, preclinical studies in ovarian and pancreatic cancer models have shown that IFN-γ or 5-azacytidine combined with anti-PD-1/PD-L1 antibodies increases T-cell infiltration and tumour regression as mentioned earlier.

In a non-small cell lung cancer phase II trial (2024), including 5-azacytidine plus nivolumab found that patients with HLA-low tumours responded 25% better. In early trials, similarly, neoantigen vaccines combined with epigenetic modulators improve HLA class I-mediated antigen presentation, enhancing T-cell responses in 20–35% of colorectal cancer patients (Marrone et al., 2023). Restoring HLA class I expression by gene editing or cytokines improves TCR therapy efficacy for adoptive T-cell therapies; preclinical data shows a 15–30% increase in tumour clearance in melanomas lacking HLA-deficient expression. With constant research looking at biomarkers to guide treatment personalisation, optimal sequencing and dosing of these combinations remain under study to balance efficacy and toxicity.

**6.4 Emerging Approaches and Future Directions**

Novel approaches to HLA class I modulation are being explored in emerging technologies, including oncolytic viruses and delivery systems based on nanoparticles. With the ability to express HLA class I-inducing factors like IFN-γ or IL-12, oncolytic viruses which are designed to specifically infect tumour cells can upregulate antigen presentation locally.

In pancreatic cancer models, oncolytic viruses increase HLA class I expression by 2–3-fold, enhancing T-cell and NK cell responses. Phase I trials combining oncolytic viruses with anti-PD-1 therapy in melanoma and lung cancer (2023–2025) report improved response rates in 15–25% of patients with HLA-deficient tumours (Alwithenani et al., 2024).

By encapsulating cytokines, CRISPR components, or demethylating agents, nanoparticle-based systems allow for targeted delivery to tumour cells while reducing systemic toxicity. Nanoparticles delivering 5-azacytidine improved vaccine efficacy by 30% in breast cancer models by restoring HLA class I expression in 60–70% of tumours (Jahanfar et al., 2016).

These approaches are still in early development, with challenges including scalability, tumour penetration, and long-term safety. Large-scale clinical studies should take front stage in future studies to confirm the safety and effectiveness of HLA class I-modulating techniques, especially when it is used in combined immunotherapies. Patient stratification for tailored treatments will be enabled by developing biomarkers based on HLA class I expression, genotype, and tumour microenvironment profiles. By means of single-cell sequencing and artificial intelligence-driven models, tumour-specific HLA defects can be found and therapy responses predicted, improving the accuracy of precision medicine (Elechi et al., 2025; Okafor et al., 2025).

Examining the interaction between immune cell dynamics such as NK cell activation or myeloid suppression and HLA class I restoration may find fresh therapeutic targets. Next-generation delivery systems, including tumour-targeted nanoparticles, bispecific antibodies, or mRNA-based platforms, should be explored to enhance specificity and efficacy. Addressing tumour heterogeneity and resistance mechanisms, such as compensatory immunosuppressive pathways, will be critical for sustained responses. Collaborative efforts integrating genomic, immunological, and computational approaches will drive the development of HLA class I-focused therapies, ultimately improving outcomes for patients with HLA-deficient cancers.

**List of Abbreviations**

HLA – Human Leukocyte Antigen

MHC – Major Histocompatibility Complex

β2m – β2-Microglobulin

TCR – T-Cell Receptor

PD-1 – Programmed Cell Death Protein 1

PD-L1 – Programmed Death-Ligand 1

NK – Natural Killer

CD8 – Cluster of Differentiation 8

TAP – Transporter Associated with Antigen Processing

CAR – Chimeric Antigen Receptor

KIRs – Killer Immunoglobulin-Like Receptors

NF-κB – Nuclear Factor kappa-light-chain-enhancer of Activated B Cells

IRF-1 – Interferon Regulatory Factor 1

IFN-γ – Interferon-Gamma

JAK-STAT – Janus Kinase-Signal Transducer and Activator of Transcription

IFN-α/β – Interferon-Alpha/Beta

TNF-α – Tumor Necrosis Factor-Alpha

CTLA-4 – Cytotoxic T-Lymphocyte-Associated Protein 4

HDAC – Histone Deacetylase

CRISPR/Cas9 – Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9

ORR – Objective Response Rate

TIL – Tumor-Infiltrating Lymphocytes

AAV – Adeno-Associated Virus

IL-12 – Interleukin-12

NKG2D – Natural Killer Group 2D

MICA/B – MHC Class I Polypeptide-Related Sequence A/B

TGF-β – Transforming Growth Factor-Beta

IL-10 – Interleukin-10

ER – Endoplasmic Reticulum

CD28 – Cluster of Differentiation 28

B7 – B7 Family of Co-stimulatory Molecules

**CONCLUSION**

The human leukocyte antigen (HLA) class I molecules play a pivotal role in the immune system’s ability to recognize and eliminate cancer cells by presenting tumour-specific antigens to cytotoxic T cells. However, as evidenced by the fact-checked statements, HLA class I downregulation and dysfunction are common mechanisms of immune evasion across multiple cancer types. These conditions were found to significantly affect the efficacy of immunotherapies such as T-cell receptor (TCR) therapies, immune checkpoint inhibitors, and adoptive T-cell therapies. Immunochemistry findings suggest HLA dysregulation to be a common phenomenon in many cancers like colorectal, pancreatic, ovarian, lung, and melanoma cancers. Overall, the review highlights the prevalence of HLA class I defects, the occurrence of certain HLA variants, and the therapeutic strategies aimed at restoring HLA class I function to enhance immunotherapy outcomes. The implications of HLA class I molecules are profound, necessitating the need for personalized approaches to overcome these immune escape mechanisms.

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