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Review

Playing hide and seek: Tumor cells in control of MHC class I antigen presentation

M.L.M. Jongsma [a], J. Neefjes [a], R.M. Spaapen [b,c,d,*]

[a] Department of Cell and Chemical Biology, Oncode Institute, Leiden University Medical Center, Leiden, the Netherlands
[b] Department of Immunopathology, Sanquin Research, Amsterdam, the Netherlands
[c] Landsteiner Laboratory, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[d] Cancer Center Amsterdam, Amsterdam, the Netherlands

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ABSTRACT

MHC class I (MHC-I) molecules present a blueprint of the intracellular proteome to T cells allowing them to control infection or malignant transformation. As a response, pathogens and tumor cells often downmodulate MHC-I mediated antigen presentation to escape from immune surveillance. Although the fundamental rules of antigen presentation are known in detail, the players in this system are not saturated and new modules of regulation have recently been uncovered. Here, we update the understanding of antigen presentation by MHC-I molecules and how this can be exploited by tumors to prevent exposure of the intracellular proteome. This knowledge can provide new ways to improve immune responses against tumors and pathogens.

1. Loss of tumor MHC class I is associated with poor outcome

Solid tumors are often infiltrated by a wide variety of adaptive and innate immune cells including $CD4^+$ T cells, $CD8^+$ T cells (cytotoxic T cells), γδ T cells, natural killer cells (NK), macrophages, neutrophils and dendritic cells (DCs), some of which possess tumor-specific killing capacity (Cali et al., 2017). In return, tumor cells can activate various intrinsic mechanisms and modulate extrinsic factors to successfully escape from control by the infiltrating immune system. The current belief is that immune escape represents one of multiple strategies for tumors to safeguard survival and proliferation, also known as the hallmarks of cancer (Hanahan and Weinberg, 2011). At a molecular level, these immune escape mechanisms include but are not limited to i) the interference in major histocompatibility complex (MHC; HLA in humans) mediated antigen presentation to prevent T cell surveillance, ii) the secretion of broadly immunosuppressive cytokines such as TGF-β and IL-10 (Batlle and Massague, 2019), and iii) the expression of inhibitory receptors at the cell surface such as PD-L1 and PD-L2 which limit T cell activation (Seliger, 2019).

The success of therapeutic application of immune checkpoint antibodies (e.g. anti-PD-L1) to intervene in tumor immune suppression emphasizes the importance of the immune system to limit tumor outgrowth. A major factor for immunogenic tumors to escape this immunotherapy is the negative modulation of antigen presentation by MHC class I (MHC-I) (Chowell et al., 2018; Gettinger et al., 2017; Restifo et al., 1996; Sade-Feldman et al., 2017; Zaretsky et al., 2016). Even without immunotherapy, the loss of effective MHC-I antigen presentation by tumor cells is associated with poor clinical outcome in the majority of human cancer types (reviewed by (Garrido et al., 2016; Leone et al., 2013)). Of note, MHC class II (MHC-II) is in principle not expressed by healthy non-hematopoietic cells, but surprisingly often by their malignant counterparts (solid tumors). Tumor-specific $CD4^+$ T cells are present in such tumors (Linnemann et al., 2015; Yossef et al., 2018), which explains the need of tumors to downregulate MHC-II or shift their antigenic landscape (Marty Pyke et al., 2018). It is currently unclear why non-hematopoietic cells upregulate MHC-II in the transformation process and unknown whether they subsequently downregulate MHC-II. In leukemia however, downregulation of MHC-II transcription is regularly induced by immunotherapy in the form of stem cell transplantation (Christopher et al., 2018; Toffalori et al., 2019). In addition, MHC-II expression by different tumor types is associated with favorable outcome, also in response to anti-PD-1 or anti-PD-L1 immunotherapy (reviewed by (Axelrod et al., 2019)). Much more is known about alterations in the MHC-I pathway, which is therefore the focus of this review.

* Corresponding author at: Department of Immunopathology, Sanquin Research, Amsterdam, the Netherlands.
E-mail address: r.spaapen@sanquin.nl (R.M. Spaapen).

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2. MHC-I peptide processing and presentation

MHC-I molecules are ubiquitously expressed at the cell surface of all nucleated cells, although not at equal levels. For example, immune cells like mature DCs are specialized antigen presenting cells and express up to 20-fold more MHC-I than other somatic cells (Ackerman and Cresswell, 2003; Wu et al., 2016). MHC-I expression obviously starts at the transcriptional level, which is controlled at the MHC-I promotor region by NF-κB (binds to Enhancer A region), interferon (IFN)-γ induced IRF-1 (binds to the ISRE element) and a complex called the enhanceosome, which consist of NLRC5, RFX-complex (RFX5/RFXAP/RFXANK), ATF1/CREB and the NFY-complex (NFYa/b/c) (binds the SXY-module) (Jongsma et al., 2019) (Fig. 1A). The resulting MHC-I mRNA is either used for translation or degraded after MEX-3C-mediated ubiquitination (Cano et al., 2012). The MHC-I heavy chain is translated by ER associated ribosomes by virtue of an N-terminal signal sequence. In the ER, the synthesized polymorphic MHC-I heavy chain interacts with the chaperone calnexin, which supports assembly of the heavy chain and a light chain named β-2-microglobulin (β2 M), as occurring within 4 min after translation (Neefjes et al., 1993). This MHC-I heterodimer is now ready for loading with peptides originating from degraded proteins, signal sequence fragments or misfolded defective translation products (DRiPs) (Anton and Yewdell, 2014; Wei and Cresswell, 1992; Yewdell et al., 1996). These DRiPs are derived from prematurely terminated or misfolded proteins, which may be increased under pathogenic conditions. The peptide fragments to be loaded in MHC-I are produced by the proteasome or immunoproteasome (LMP2 and LMP7) and often further trimmed to single amino acids by cytosolic peptidases that will eliminate many of these peptides before they can be translocated to the ER (Ferrington and Gregerson, 2012; Michalek et al., 1993; Reits et al., 2003; Rock et al., 1994). Some of the remaining peptides can then be transported into the ER by the heterodimeric TAP1/TAP2 transporter (Parcej and Tampe, 2010). Inside the ER lumen, ERp57, calreticulin, tapasin and the MHC-I heterodimer have gathered around the TAP transporter, forming the peptide loading complex (PLC) (Cresswell et al., 1999). ERp57 stabilizes the peptide free MHC-I molecule, while tapasin interacts with TAP coupling peptide translocation to peptide loading (Wearsch and Cresswell, 2007). The length of peptides to be stably loaded onto MHC-I complexes is usually 8–12 amino acids, but TAP allows translocation of peptides from 8 amino acids to over 40 amino acids that then require further trimming (Momburg et al., 1994). Peptides entering the ER have different fates. They can be trimmed to either or not fit MHC-I or otherwise are efficiently removed by transport into the cytosol where cytosolic peptidases trim or completely destroy such peptides (Roelse et al., 1994). Peptide trimming in the ER is performed by the aminopeptidases ERAAP/ERAP1 and ERAP2 till an optimal length to fit in the MHC-I peptide binding groove (Saric et al., 2002; Saveanu et al., 2005; Serwold et al., 2002). In fact, most peptides can bind with equal on-rates but then leave MHC-I when considered not perfectly fitting. MHC-I undergoes a conformational change every time a

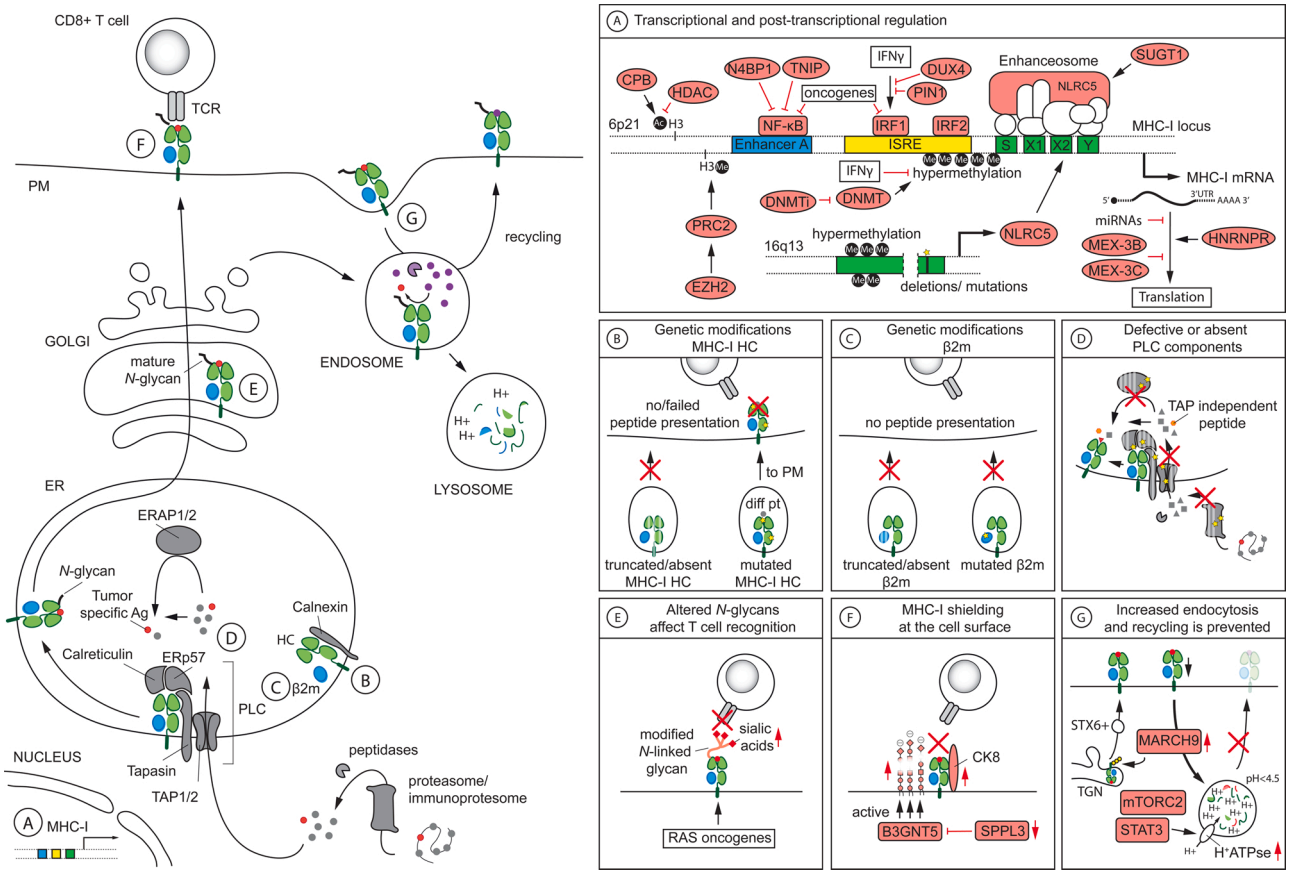

Fig. 1. Schematic overview of MHC-I antigen presentation. MHC-I heterodimers are assembled in the ER from a MHC-I heavy chain and β2 m supported by calnexin. Cytosolic peptides, generated by the (immune)-proteasome enter the ER lumen through the TAP1/2 transporter. In the ER these peptides can be further processed by ERAP1/2 and loaded on the MHC-I heterodimer with help of the PLC, which consists of Calreticulin, ERp57, Tapasin and TAP1/2. The peptide loaded MHC-I heterotrimer is further modified by the addition of a N-glycan, which is processed in the ER and the Golgi. At the cell surface, MHC-I can present its peptide to $CD8^+$ T cells. At a certain point in time, MHC-I gets internalized after which it is either recycled back to the cell surface to present a newly acquired peptide or degraded in the lysosome. Right panels: Tumor cells can modulate different steps of the pathway: on a transcriptional or post-transcriptional level (A), by genetically modifying the heavy chain (B), β2 m light chain (C) or PLC components (D), by post-translational mechanisms affecting the N-glycan (E), affecting the accessibility at the cell surface, e.g. by upregulation of nsGSLs (F) and affecting MHC-I endocytosis and recycling (G).

peptide binds until a high affinity peptide is catched (Garstka et al., 2015). The resulting stable MHC-I trimers are released from the ER quality control system for transport to the plasma membrane to finally present an intracellular peptide to $CD8^+$ T cells (Neefjes et al., 2011) (Fig. 1).

3. Are all MHC-I molecules equal?

During viral infections, MHC-I molecules present virus-derived peptides to initiate anti-viral T cell immune responses. Given the high capacity of viruses to adjust their genome for their own benefit, one may expect that sequences coding for immunogenic antigens should have been depleted from their genomes by now. This may have occurred if mammalian species would have had one single MHC-I protein, however this is considerably more difficult since many mammals express multiple MHC-I genes that are also polymorphic within the population. For example, humans have protected themselves by duplications within the MHC-I locus on chromosome 6, which yielded three genes (HLA-A, HLA-B and HLA-C) on each copy of the chromosome, giving rise to the expression of three to six different classical MHC-I proteins, dependent of the polymorphic HLA-types of the biological mother and father. β2 m is not polymorphic. Of note, MHC-I is by far the most polymorphic human gene with more than 20.000 different alleles across the human population (Robinson et al., 2020), although some HLA-types are dominant in different human populations. HLA-A2 -for example- is present in about 60 % of the Caucasian population and it is believed that this could be the result from some infection in the past that was best controlled by HLA-A2 positive human. Along the same lines, HLA-B57 is claimed to protect people from HIV and HLA-B57 positive people will likely become dominant in populations with a strong selection pressure due to HIV infection (Martin and Carrington, 2013). How does polymorphism translate into immune responses? Non-synonymous MHC-I polymorphisms concentrate in the peptide-binding groove. The amino acid characteristics in the peptide-binding groove determine the charge and size of pockets where peptide amino acid side chains dock into. Consequently, amino acid polymorphisms alter the peptide binding sites of MHC-I resulting in the binding of different peptides (Falk et al., 1991; Trowsdale, 2005). From a single virus -for example- HLA-A2 will present certain peptides. A virus may alter the amino acids required for binding to HLA-A2 and thus escape immune surveillance but the virus is then still recognized by the immune system of another individual who presents another set of viral peptides by another allele, for example HLA-A1. As a result, polymorphism protects the population and not necessarily the individual albeit the expression of three to six different HLA alleles per individual certainly helps. In cancer cells, some HLA alleles will present many immunogenic tumor-specific peptides, while others will not present any immunogenic antigens at all. For example downregulation of a single HLA-allele in a Burkitt lymphoma and a lung carcinoma, HLA-A11 and HLA-B39 respectively, was sufficient to escape $CD8^+$ T cell recognition (Gavioli et al., 1992; So et al., 2005). Variation in peptide-selection is not the only difference between HLA-allotypes, because also differences are found in expression levels, their dependence on the PLC for peptide loading and the rate of transport to the cell surface. First, HLA-A and -B are usually highly expressed, HLA-C levels are much lower due to poor peptide loading or low HLA-C gene expression (Neefjes and Ploegh, 1988; Neisig et al., 1996). However, the low expression of peptide HLA-C complexes is still sufficient to activate some tumor-specific T cells (Tran et al., 2015). HLA-C has another function as well as it conveys signals through inhibitory leukocyte and killer cell Ig-like receptors (LIRs and KIRs) to suppress undesired immune cell activation (Saverino et al., 2000; Valiante et al., 1997). Next, HLA-A and HLA-C bind much more efficient to the PLC than HLA-B (Neisig et al., 1996). Yet, HLA-B molecules are loaded with peptides, showing that the PLC is not required for peptide loading. Finally, HLA-B transport to the cell surface is more rapidly than for HLA-A and HLA-C (Neefjes and Ploegh, 1988; Peh et al., 1998), indicating that the PLC most likely delays the loading process while facilitating high affinity peptide selection by tapasin (Zarling et al., 2003).

MHC-I molecules are even more complex. Within one major HLA-I type, differences in molecular and physiological behavior can be found. For example, specific HLA-variants are highly associated to the development of auto-inflammatory diseases, such as the linkage disequilibrium between HLA-B27.5 and ankylosing spondylitis. The epistatic involvement of an ERAP1 variant implicates that the antigen presentation function of these HLA-B27 molecules is required for the onset or propagation of this disease (Evans et al., 2011; Herberts et al., 2006). Some other alleles, including HLA-A2, have a preference to bind hydrophobic peptides. This leads to increased presentation of signal peptides that do not even require TAP for peptide loading compared to other HLA allotypes (Wei and Cresswell, 1992).

All these fundamental mechanisms behind MHC-I antigen presentation enable immunological control of tumor cell outgrowth, but unfortunately tumor cells respond by negatively controlling MHC-I antigen presentation pathways through specific and more broad manners leading to their immune escape. We will discuss such tumor immune escape mechanisms for conventional components, but also for various recently identified mechanisms of MHC-I regulation.

4. Modulation of MHC-I antigen presentation pathway by tumors

Since MHC-I molecules present a reflection of the intracellular proteome, tumor cells with aberrant proteomes, including tumor-specific antigens are in principle subjected to $CD8^+$ T cell recognition and elimination. Such immune pressure allows for specific outgrowth of tumor cells with defects in MHC-I antigen presentation. MHC-I expression in cancer has been extensively studied (reviewed by (Leone et al., 2013)). The numerous investigations of primary and metastatic tumor lesions demonstrated that MHC-I expression as detected by microarray, RNAseq or immunohistochemistry is regularly affected in many different cancer types, in some cases up to 90 % of the tumors (Cornel et al., 2020; Leone et al., 2013). These analyses further show that the low MHC-I expression is often correlated to poor expression of transcriptional regulators, PLC components, β2 m and other regulators of the pathway, such as the immunoproteasome subunits LMP2 and LMP7 (Ayshamgul et al., 2011; Cathro et al., 2010; Leone et al., 2013; Ogino et al., 2003). Reduction of LMP2 and LMP7 expression may alter the HLA associated peptide repertoire, possibly preventing the presentation of immunogenic tumor-specific peptides (Favole et al., 2012). Finally, several tumors limit antigen presentation in ways that have not yet been extensively explored, including preventing the processing and presentation of DRiPs or through glycosphingolipid-mediated shielding of cell surface MHC-I (Jongsma et al., 2021; Pont et al., 2019). The outcome of downregulation of any of the above mentioned factors is always similar, functional MHC-I mediated antigen presentation is disturbed, rendering tumor cells poor targets for the immune system. Two different types of tumor-induced defects affecting MHC-I antigen presentation can be distinguished: i) irreversible defects (or hard mutations) and ii) reversible defects (or soft mutations) (Garrido et al., 2010).

4.1. Irreversible MHC-I pathway defects in tumors

Genetic defects in tumors are currently irreversible. The different types of genetic alterations that have been reported in tumors to affect MHC-I antigen presentation mainly include point mutations, base pair insertions or deletions (indels) and larger deletions, which is referred to as loss of heterozygosity (LOH) in cases of full gene deletions (Clancy, 2008). Point mutations and indels can have various transcriptional or translational consequences, such as induction of alternative splicing or frameshifted open reading frames resulting in truncated and/or dysfunctional proteins.

4.1.1. Truly irreversible mutations

The MHC-I heavy chain and β2 m light chain are obviously essential for antigen presentation. Therefore genetic mutations and deletions in the MHC-I genes on chromosome 6 and β2 m on chromosome 15 have irreversible effects on antigen presentation (Fig. 1B and C). There are various ways to genetically manipulate MHC-I expression. To give some examples, a splice site mutation in a MHC-I allele caused the deletion of the MHC-I α1-domain (Wang et al., 1999) and indel mutations in the first exons of the β2 m gene led to a frameshifted open reading frame often containing a premature stop codon (Benitez et al., 1998; Gattoni-Celli et al., 1992; Hicklin et al., 1998; Perez et al., 1999; Zaretsky et al., 2016). Point mutations in the MHC-I exon 2 or 3 (encoding for anchor residues in the peptide binding groove) generated a full length protein at the cost of peptide presentation, while mutations in exon 4 altered binding of CD8, which is an important coreceptor for T cell activation (Shukla et al., 2015).

Because of the relative random nature of genetic mutations, in many cases single chromosomes are affected, which may not be sufficient for tumor immune escape. LOH also allows functional protein expression from the remaining chromosome. Nevertheless, β2 M LOH results in a marked reduction of β2 M and consequently MHC-I expression (Maleno et al., 2011; Sade-Feldman et al., 2017). Since the other β2 M gene is usually mutated this then results in a complete absence of functional β2 M and full elimination of MHC-I antigen presentation (Bernal et al., 2012; del Campo et al., 2014). In the case of the polymorphic MHC-I heavy chain, mutations or LOH can delete one or more unique HLA-I alleles from a tumor, which directly reduces the diversity of tumor-specific antigens presented (Garrido and Algarra, 2001; Shukla et al., 2015).

4.1.2. Irreversible mutations with immunological opportunities

Genetic mutations were also detected in other components of the MHC-I antigen presentation, including the PLC members tapasin, ERp57, TAP and calreticulin (Cerami et al., 2012) (Fig. 1D). Examples include frameshift deletions and point mutations in the TAP1 gene resulting in a truncated protein or affecting the functionality of its ATP-binding domain resulting in poor peptide transport (Chen et al., 1996; Seliger et al., 2001). Frameshift mutations in the calreticulin gene led to a protein with a C-terminus lacking its KDEL sequence, which is essential for its ER localization (Arshad and Cresswell, 2018). The absence of calreticulin in the PLC leads to suboptimal peptide loading of MHC-I and consequently inefficient antigen presentation (Howe et al., 2009).

In contrast to the lack of T cell recognition of tumor cells genetically depleted of MHC-I heavy and light chains, mutations in other genes may maintain or even generate opportunities for T cell mediated tumor control when different antigenic peptides are presented. Genetic defects in members of the PLC modulate but do not completely abolish MHC expression because i) expression of various HLA-I alleles is independent of several PLC members as mentioned before, ii) even PLC-dependent HLA-I alleles are usually surface expressed albeit at a low level (de Waard et al., 2021b; Rizvi et al., 2014). Moreover, the PLC components modulate the peptides presented by MHC-I. Defective TAP transport for example leads to the presentation of an altered peptide repertoire containing more TAP-independent peptides, so called T cell epitopes associated with impaired peptide processing (TEIPP) (Doorduijn et al., 2016; Marijt et al., 2018; van Hall et al., 2006). This is not always advantageous to tumor evasion. Although these TEIPPs are usually non-mutated self-peptides, some of them may be selectively presented by TAP-deficient tumor cells and should then be considered neo-epitopes that can be recognized by the immune system. Thus genetic defects in PLC components even provide opportunities for immunotherapeutic targeting of tumor-specific antigens presented by the remaining MHC-I molecules, although careful evaluation of off-target reactivity against healthy cells with natural low PLC expression is required (de Waard et al., 2021a).

4.1.3. Circumventable irreversible mutations

Finally, MHC-I regulatory factors that are not directly influencing peptide loading are also often mutated in cancer. These include the genes encoding the enhanceosome (e.g. NLRC5) or other components involved in the expression of MHC-I or PLC genes (e.g. IRF2) (Kriegsman et al., 2019; Yoshihama et al., 2016) (Fig. 1A). For example, mutations were found in the NLRC5 gene and JAK1/2 (IFN pathway component) leading to protein loss-of-function in tumors (Shin et al., 2017; Yoshihama et al., 2016). It is important to evaluate how irreversible these mutations really are in relation to MHC-I antigen presentation, since the therapeutic induction of other, similar or parallel pathways may compensate for some lost functions. For example, the MHC-I diminishing effects caused by the irreversible loss of IRF2 can be overcome *in vitro* by activating IFN signaling pathways to induce IRF1 in cancer cells (Kriegsman et al., 2019). There are plenty of such opportunities in the field to develop targeted treatments with the goal to make irreversible mutations reversible, some of which are described below.

4.2. Reversible MHC-I pathway defects in tumors

Next to structural irreversible mutations, tumor cells can also contain many reversible defects affecting MHC-I antigen presentation. The negative effect of a large group of reversible defects on antigen presentation can, as the name suggests, potentially be restored by a treatment (cytokines or specific inhibitors) since they are often driven by altered expression levels of MHC-I regulators. We will discriminate here between tumor-driven interference in transcriptional, post-transcriptional and post-translational processes. Here, we define the transcriptional regulatory defects as i) disturbed promotor activation ii) epigenetic dysregulation and iii) oncogene activation. Each of these can affect the expression of MHC-I heavy chain, β2 m and other proteins controlling the different steps of the antigen processing and presentation. Some of this latter group of proteins are encoded by genes located in the MHC-I locus on chromosome 6 and their expression is often correlated with the expression of MHC-I heavy chains, as reported for LMP2, LMP7, TAP subunits and tapasin (Ozcan et al., 2018; Yoshihama et al., 2016).

4.2.1. Disturbed MHC-I promotor activation

As mentioned above, MHC-I heavy chain expression is regulated by a transcriptional complex called the enhanceosome (including NLRC5), NFκB signaling and IFN signaling (Jongsma et al., 2019). These transcriptional regulators are controlled by complex pathways and many positive and negative regulators have been identified over the years. For example, the nuclear cochaperone SUGT was recently identified as a positive regulator of NLRC5 (Dersh et al., 2021), and N4BP1 as well as TNIP1 were identified to negatively regulate NF-κB signaling (Spel et al., 2018) (Fig. 1A). Furthermore the peptidyl-prolyl isomerase, PIN1, and the transcription factor DUX4 are both thought to inhibit MHC-I transcription by interfering in the IFN signaling pathway and found upregulated in cancer (Chen et al., 2018; Chew et al., 2019) (Fig. 1A). Although inhibitors or cytokines regulating these regulators have as far as we know not yet been identified, they provide potential targets to therapeutically increase MHC-I expression levels.

NF-κB and IFN signaling pathways are often upregulated under inflammatory conditions leading to an increase in MHC-I expression. However, recent evidence indicates that individual components of these pathways also regulate basal MHC-I expression. Some IRFs are constitutively expressed in cell lines (Wu et al., 2016) suggesting that IRFs (binding the ISRE elements) can control MHC-I expression also under non-inflammatory conditions. The expression of IRF2, in contrast to IRF1 is constitutive and quite stable in the absence of IFN stimulation (Oshima et al., 2004; Ren et al., 2015; Watanabe et al., 1991). IRF2 activates MHC-I, TAP2 and ERAP1 expression, thereby positively affecting MHC-I antigen presentation under non-inflammatory conditions (Kriegsman, Rock, 2019, J Immunol). Loss of IRF2 in cancer cells

leads to immune evasion (Kriegsman et al., 2019), emphasizing the importance of factors regulating basal MHC-I expression in tumors.

4.2.2. Epigenetic dysregulation

In cancer cells, MHC-I expression is often silenced by epigenetic modifications at the MHC-I locus, including chromosome remodeling, histone modifications and DNA methylation. Such epigenetic dysregulation affects gene expression by modifying the chromatin structure. Because these modifications leave the DNA sequence intact, they are in principle reversible. Chromatin remodeling of the TAP1 promotor can be induced by the histone acetyltransferase CBP, which relaxes the DNA structure of the TAP1 promotor to allow transcription (Setiadi et al., 2007). Not surprisingly, CBP recruitment was decreased in some tumor cells (Setiadi et al., 2007). CBP acts by acetylating Histone H3, a modification that can be removed by Histone deacetylases (HDACs) in order to reduce gene expression (Fig. 1A). The fact that HDACs can be inhibited by small molecules fueled their evaluation to improve antigen presentation. Indeed, chemical HDAC inhibition induced Histone H3 acetylation, leading to enhanced MHC-I surface expression and antigen presentation in multiple tumors (Khan et al., 2008; Mora-Garcia Mde et al., 2006; Ritter et al., 2017; Sun et al., 2019; Yang et al., 2020). Another epigenetic modification affecting gene transcription is the addition of a methyl group to DNA by methyltransferases (DNMTs). Hypermethylation of the MHC-I locus and the NLRC5 promotor region inhibits transcriptional activity and attenuates MHC-I antigen presentation in various cancer types (Nie et al., 2001; Ye et al., 2010; Yoshihama et al., 2016) (Fig. 1A). DNA hypermethylation can be reversed by IFN-γ stimulation or by DNMT inhibitors, as shown in breast cancer and melanoma cell lines (Fonsatti et al., 2007; Luo et al., 2018; Serrano et al., 2001; Vlkova et al., 2014). Hypermethylation of the MHC-I locus and the resulting attenuated antigen presentation were also induced by Polycomb repressive complex 2 (PRC2) activation (Burr et al., 2019; Dersh et al., 2021) (Fig. 1A). Gain of function mutations in the PRC2 encoding gene and its activator EZH2 are frequently observed in cancer and can be corrected by chemical inhibitors. Surprisingly also loss-of-function mutants of PRC2 were identified, which correlated with poor survival (Laugesen et al., 2016). These data suggest a broader transcriptional impact of PRC2 involving other cancer-related factors than MHC-I.

4.2.3. Oncogenic pathways

Oncogenes encode for proteins in pathways important for critical functions like cell survival and proliferation. Uncontrolled activation of these oncogenic pathways has the potential to cause malignant outgrowth of cells. An example of an oncogene is NMYC, a transcription factor overexpressed in some neuroblastomas. Since NMYC suppresses NF-κB signaling in these cells, its overexpression downregulates MHC-I expression (van 't Veer et al., 1993). Other examples of oncogenic pathways affecting MHC-I expression are the RAS/MAPK and PI3K/AKT pathways, activated by EGF and Her2 receptor binding, and Wnt signaling. Activation of these pathways in several types of cancer downregulates MHC-I transcription usually by inhibiting IFN or NF-κB signaling (Fig. 1A) (Brea et al., 2016; Chandrasekaran et al., 2019; Herrmann et al., 2004; Lohmann et al., 1996; Lulli et al., 2017; Maruyama et al., 2010; Mimura et al., 2013; Seliger et al., 1998; Vertuani et al., 2009; Yang et al., 2020). Downstream of PI3K/AKT is the mTOR kinase that senses starvation and controls many processes including translation, leading to the production of radiation-specific peptides. Ionizing radiation activates mTOR which also upregulates MHC-I expression at the cell surface. This finding was the basis for radio-immunotherapy where the specificity in space (radiotherapy) is combined with specificity of the target (through immunotherapy) (Reits et al., 2006). Also the expression of other antigen presentation pathway components is affected by oncogene expression. RAS oncogene expression or KI-RAS mutations downregulate the antigen presentation components LMP2, TAP1 and tapasin in colorectal carcinomas, which can be often restored by cytokine treatment indicating that these defects are caused by dysregulation rather than genetic mutations in these genes (Atkins et al., 2004). Alternative ways by which oncogenes disturb antigen presentation have also been reported. For example, an activating mutation in the Ras-pathway protein BRAF induces internalization of MHC-I molecules from the cell surface towards endolysosomal compartments reducing MHC-I surface expression, which could be restored by MAPK inhibitor treatment (Bradley et al., 2015).

4.2.4. Post-transcriptional modulations

Translation of mRNA encoding for MHC-I pathway components can be modulated by small (~20 nucleotides) single stranded non-coding RNAs called microRNAs (miRNAs). miRNAs bind the 5′UTR, 3′UTR or coding sequence of the targeted mRNA affecting its translation and sometimes inducing its degradation (Bartel, 2004). Therefore it is not surprising that several cancers types exhibit altered expression of miRNAs modifying MHC-I expression and antigen presentation (Fig. 1A). Within the last two years, several more MHC-I modulatory miRNAs have been added to the list as composed by Friedrich et al. (Friedrich et al., 2019). For example miR-19 was identified to negatively modulate the expression of MHC-I genes in human cancer cells (Li et al., 2020) while miR-200a-5p, miR-26b-5p and miR-21-3p target the 3'UTR of TAP1 thereby downregulating the TAP1 protein as shown in melanoma (Lazaridou et al., 2020a, b). Decreased levels of TAP1 as a result of high levels of miR-200a-5p in melanoma patients was associated to shorter overall survival and miR-26b-5p overexpression led to decreased T cell recognition. Both observations support the idea that tumors can alter miRNA expression to evade immune detection by decreasing MHC-I antigen presentation (Lazaridou et al., 2020a, b). Effects of miRNAs were often reverted using miRNA inhibitors, providing new opportunities to enhance current immunotherapies.

Post-transcriptional modification of antigen presentation is also regulated by RNA-binding proteins, such as HNRNPR and the RNA-binding E3 ligases MEX-3B and MEX-3C. All bind the 3'UTR region of MHC-I mRNA. HNRNPR enhances MHC-I mRNA stability (Reches et al., 2016), while MEX-3B and MEX3C destabilize the mRNA leading to its degradation and decreased MHC-I expression (Cano et al., 2012; Friedrich et al., 2019; Huang et al., 2018) (Fig. 1A). Importantly, MEX-3B expression by melanoma confers immune resistance during anti-PD-1 immunotherapy (Huang et al., 2018). Mechanistically, MEX-3C binds the 3'UTR of HLA-A2 mRNA via its RNA-binding KH domain, transports the mRNA towards the cytosol where it associates with de-adenylation complex CCR4-NOT. There MEX-3C ubiquitinates the catalytic subunit CNOT7 regulating its activity leading to removal of the mRNAs stabilizing poly(A) tail followed by degradation in a ubiquitin dependent manner (Cano et al., 2015). The deubiquitinating enzyme USP7 antagonizes this HLA-A2 mRNA degradation (Cano et al., 2012).

4.2.5. Post-translational modulations

Human MHC-I heavy chains are modified by an *N*-glycan at residue Asn86 (Bjorkman et al., 1987), critical for the assembly, peptide loading and cell surface expression of MHC-I and especially HLA-B alleles (Neefjes and Ploegh, 1988; Wearsch et al., 2011; Zhang et al., 2011). Murine MHC-I heavy chains even contain 2 N-linked glycans positioned at the two ends of the peptide binding groove. MHC-I *N*-linked glycans can be modulated by RAS oncogene activation, leading to increased *N*-glycan branching with more sialic acids (Bolscher et al., 1988) (Fig. 1E). These changes in the *N*-glycan may negatively affect immune recognition since shortening glycans or removing sialic acids with glycosidase inhibitors improved T cell responses (Boog et al., 1989; Neefjes et al., 1990), although effects on other surface molecules were not excluded.

At the plasma membrane MHC-I molecules can diffuse laterally (Edidin, 2010; Gromme et al., 1999), which provides the option to interact transiently with other cell surface molecules. This diffusion -perhaps- also facilitates clustering during interactions with a TCR at the immunological synapse or to locate in superclusters with other proteins,

as suggested by biophysical experiments (Edidin, 2010). Recently, MHC-I molecules were shown to interact with molecules that are largely ignored in the fields of immunology and antigen presentation, but abundantly present at the plasma membrane, the glycosphingolipids (GSLs) (Jongsma et al., 2021; Zhang et al., 2019). GSLs are hydrophobic ceramide units containing highly variable hydrophilic sugar structures (Hakomori, 1981). They are generally enriched in membrane microdomains, including lipid rafts, and affect cell surface receptor function (Coskun et al., 2011; Kabayama et al., 2007; Tagami et al., 2002) and protein-protein interactions (Kawakami et al., 2002; Todeschini et al., 2007). Receptor-ligand interactions shape the immune system, therefore it is not surprising that GSLs play important roles in innate and adaptive immunity (Nakayama et al., 2018; Zhang et al., 2019). Still, the many potential roles that GSLs can have in modulating anti-tumor immunity is underexplored because GSLs are difficult to study with the currently available toolset. Yet, we recently identified that high levels of the subtype neolacto-series GSLs (nsGSLs) interferes with the accessibility of MHC-I molecules for T cells and immune cell receptors like LIR-1 and KIR2DL2 (Jongsma et al., 2021). These nsGSL expression levels are generated by the enzyme B3GNT5, which is post-translationally regulated by the Signal Peptide Peptidase Like 3 (SPPL3) protease located in the ER and Golgi (Jongsma et al., 2021) (Fig. 1F). Overexpression of the core synthesis enzyme for GSL production, UGCG, and consequently elevated levels of a diverse repertoire of GSLs, including nsGSLs, have been observed in several tumor types including glioma, AML and adenocarcinomas (Furukawa et al., 2015; Hakomori, 1984; Jennemann et al., 2017; Wang et al., 2012; Wikstrand et al., 1991). Since these nsGSLs affect antigen presentation, they can support tumor cells to evade the immune system, at least when tumor cells produce more of these nsGSLs. Indeed, inhibition of GSL-synthesis by pharmacological inhibition of UGCG can delay tumor growth (Inokuchi et al., 1987; Jennemann et al., 2017; Radin, 1999). Not only GSLs can shield MHC-I molecules, also the cytokeratin CK8 has been shown to mask MHC-I molecules at domains involved in $CD8^+$ T cell activation (Wu et al., 2013) (Fig. 1F). Overexpression of cytokeratins has been observed in malignant tissues (Moll et al., 1982).

Cell surface accumulation of MHC-I molecules at the cell surface is controlled by MARCH9 (ubiquitously expressed) and its close homologue MARCH4 (mainly expressed in brain and placenta). Since the early 2000s, it is known that these MARCH proteins target MHC-I into the endosomal pathway for degradation in an ubiquitin dependent manner (Bartee et al., 2004; De Angelis Rigotti et al., 2017; Eyster et al., 2011; Hoer et al., 2007). Several tumors express MARCH proteins which may support immune evasion by lowering the cell surface expression of MHC-I proteins (Wang et al., 2008) (Fig. 1G). It is still unclear how MARCH activity is controlled and where in the pathway ubiquitination of MHC-I takes place. Next to its role in MHC-I endosomal targeting and degradation, MARCH9 is required at the trans-Golgi network to ubiquitinate and sort MHC-I into syntaxin 6 (STX6) positive endosomes for secretion (De Angelis Rigotti et al., 2017) (Fig. 1G). Furthermore, the de-ubiquitinating enzyme UCH-L1 promotes MHC-I recycling (Reinicke et al., 2019). Strikingly, MHC-I endocytosis can also have a positive effect on antigen presentation, namely when it is not degraded but sorted for recycling back towards the cell surface. The acidic environment of the endosomes promotes the release of the bound peptide and can load the molecule with a new peptide generated in the endocytic pathway where after the MHC-I molecule can be recycled to the cell surface to present its new peptide (Gromme et al., 1999). However tumor cells may eliminate this recycling option by decreasing the endosomal pH below pH 4.5 leading to full and definite dissociation of the MHC-I complex (Fig. 1G). Endosomal pH is controlled by the vacuolar H+-ATPase, which on its turn is regulated by signaling involving proteins such as STAT3 and mTORC2 (Liu et al., 2018). The dysregulation of these factors in tumors may result in acidification of endosomes and attenuation of the MHC-I recycling pathway.

5. Concluding remarks

The MHC-I antigen presentation pathway is one of the best studied pathways in biology (Fig. 1). Still, our understanding is not saturated as new players of this pathway have been identified in unbiased genome-wide knockout studies (Dersh et al., 2021; Jongsma et al., 2021). Successful antigen presentation by MHC-I requires both specific and general processes involved in transcriptional and translational control, protein synthesis and degradation. In fact, there is hardly any cell biological process not involved in MHC-I antigen presentation. The recent introduction of novel factors opens new areas for understanding and manipulation of tumor-specific immune responses. It is important to note that evaluation of tumor immune escape mechanisms usually ignores the potential differential effects on HLA allotypes or immunodominant antigens presented by (primary) tumor cells, while these are known to be crucial determinants of the anti-tumor immune response (Chowell et al., 2018; Schreiber et al., 2002). Tumors do not care which component of the pathway they manipulate as long as MHC-I expression is reduced or eliminated allowing the cells to escape from an immune response. Each of the many components required for successful MHC-I antigen presentation is a potential therapeutic target as long as this is compatible with cell survival. While we are approaching saturation of the components involved in MHC-I antigen presentation, this still presents with great surprises and the introduction in the field of immunology of molecules that are long ignored, such as glycolipids.

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References

Ackerman, A.L., Cresswell, P., 2003. Regulation of MHC class I transport in human dendritic cells and the dendritic-like cell line KG-1. J. Immunol. 170, 4178–4188.
Anton, L.C., Yewdell, J.W., 2014. Translating DRiPs: MHC class I immunosurveillance of pathogens and tumors. J. Leukoc. Biol. 95, 551–562.
Arshad, N., Cresswell, P., 2018. Tumor-associated calreticulin variants functionally compromise the peptide loading complex and impair its recruitment of MHC-I. J. Biol. Chem. 293, 9555–9569.
Atkins, D., Breuckmann, A., Schmahl, G.E., Binner, P., Ferrone, S., Krummenauer, F., Storkel, S., Seliger, B., 2004. MHC class I antigen processing pathway defects, ras mutations and disease stage in colorectal carcinoma. Int. J. Cancer 109, 265–273.
Axelrod, M.L., Cook, R.S., Johnson, D.B., Balko, J.M., 2019. Biological consequences of MHC-II expression by tumor cells in cancer. Clin. Cancer Res. 25, 2392–2402.
Ayshamgul, H., Ma, H., Ilyar, S., Zhang, L.W., Abulizi, A., 2011. Association of defective HLA-I expression with antigen processing machinery and their association with clinicopathological characteristics in Kazak patients with esophageal cancer. Chin. Med. J. (Engl) 124, 341–346.
Bartee, E., Mansouri, M., Hovey Nerenberg, B.T., Gouveia, K., Fruh, K., 2004. Downregulation of major histocompatibility complex class I by human ubiquitin ligases related to viral immune evasion proteins. J. Virol. 78, 1109–1120.
Bartel, D.P., 2004. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116, 281–297.
Batlle, E., Massague, J., 2019. Transforming growth factor-beta signaling in immunity and cancer. Immunity 50, 924–940.
Benitez, R., Godelaine, D., Lopez-Nevot, M.A., Brasseur, F., Jimenez, P., Marchand, M., Oliva, M.R., van Baren, N., Cabrera, T., Andry, G., et al., 1998. Mutations of the beta2-microglobulin gene result in a lack of HLA class I molecules on melanoma cells of two patients immunized with MAGE peptides. Tissue Antigens 52, 520–529.
Bernal, M., Ruiz-Cabello, F., Concha, A., Paschen, A., Garrido, F., 2012. Implication of the beta2-microglobulin gene in the generation of tumor escape phenotypes. Cancer Immunol. Immunother. 61, 1359–1371.
Bjorkman, P.J., Saper, M.A., Samraoui, B., Bennett, W.S., Strominger, J.L., Wiley, D.C., 1987. Structure of the human class I histocompatibility antigen, HLA-A2. Nature 329, 506–512.
Bolscher, J.G., van der Bijl, M.M., Neefjes, J.J., Hall, A., Smets, L.A., Ploegh, H.L., 1988. Ras (proto)oncogene induces N-linked carbohydrate modification: temporal relationship with induction of invasive potential. EMBO J. 7, 3361–3368.
Boog, C.J., Neefjes, J.J., Boes, J., Ploegh, H.L., Melief, C.J., 1989. Specific immune responses restored by alteration in carbohydrate chains of surface molecules on antigen-presenting cells. Eur. J. Immunol. 19, 537–542.

Bradley, S.D., Chen, Z., Melendez, B., Talukder, A., Khalili, J.S., Rodriguez-Cruz, T., Liu, S., Whittington, M., Deng, W., Li, F., et al., 2015. BRAFV600E Co-opts a conserved MHC class I internalization pathway to diminish antigen presentation and CD8+ T-cell recognition of melanoma. Cancer Immunol. Res. 3, 602–609.
Brea, E.J., Oh, C.Y., Manchado, E., Budhu, S., Gejman, R.S., Mo, G., Mondello, P., Han, J. E., Jarvis, C.A., Ulmert, D., et al., 2016. Kinase regulation of human MHC class I molecule expression on cancer cells. Cancer Immunol. Res. 4, 936–947.
Burr, M.L., Sparbier, C.E., Chan, K.L., Chan, Y.C., Kersbergen, A., Lam, E.Y.N., Azidis-Yates, E., Vassiliadis, D., Bell, C.C., Gilan, O., et al., 2019. An evolutionarily conserved function of polycomb silences the MHC class I antigen presentation pathway and enables immune evasion in cancer. Cancer Cell 36, 385-401 e388.
Cali, B., Molon, B., Viola, A., 2017. Tuning cancer fate: the unremitting role of host immunity. Open Biol. 7.
Cano, F., Bye, H., Duncan, L.M., Buchet-Poyau, K., Billaud, M., Wills, M.R., Lehner, P.J., 2012. The RNA-binding E3 ubiquitin ligase MEX-3C links ubiquitination with MHC-I mRNA degradation. EMBO J. 31, 3596–3606.
Cano, F., Rapiteanu, R., Sebastiaan Winkler, G., Lehner, P.J., 2015. A non-proteolytic role for ubiquitin in deadenylation of MHC-I mRNA by the RNA-binding E3-ligase MEX-3C. Nat. Commun. 6, 8670.
Cathro, H.P., Smolkin, M.E., Theodorescu, D., Jo, V.Y., Ferrone, S., Frierson Jr., H.F., 2010. Relationship between HLA class I antigen processing machinery component expression and the clinicopathologic characteristics of bladder carcinomas. Cancer Immunol. Immunother. 59, 465–472.
Cerami, E., Gao, J., Dogrusoz, U., Gross, B.E., Sumer, S.O., Aksoy, B.A., Jacobsen, A., Byrne, C.J., Heuer, M.L., Larsson, E., et al., 2012. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2, 401–404.
Chandrasekaran, S., Sasaki, M., Scharer, C.D., Kissick, H.T., Patterson, D.G., Magliocca, K.R., Seykora, J.T., Sapkota, B., Gutman, D.A., Cooper, L.A., et al., 2019. Phosphoinositide 3-kinase signaling can modulate MHC class I and II expression. Mol. Cancer Res. 17, 2395–2409.
Chen, H.L., Gabrilovich, D., Tampe, R., Girgis, K.R., Nadaf, S., Carbone, D.P., 1996. A functionally defective allele of TAP1 results in loss of MHC class I antigen presentation in a human lung cancer. Nat. Genet. 13, 210–213.
Chen, Y., Wu, Y.R., Yang, H.Y., Li, X.Z., Jie, M.M., Hu, C.J., Wu, Y.Y., Yang, S.M., Yang, Y.B., 2018. Prolyl isomerase Pin1: a promoter of cancer and a target for therapy. Cell Death Dis. 9, 883.
Chew, G.L., Campbell, A.E., De Neef, E., Sutliff, N.A., Shadle, S.C., Tapscott, S.J., Bradley, R.K., 2019. DUX4 suppresses MHC class I to promote cancer immune evasion and resistance to checkpoint blockade. Dev. Cell 50, 658-671 e657.
Chowell, D., Morris, L.G.T., Grigg, C.M., Weber, J.K., Samstein, R.M., Makarov, V., Kuo, F., Kendall, S.M., Requena, D., Riaz, N., et al., 2018. Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy. Science 359, 582–587.
Christopher, M.J., Petti, A.A., Rettig, M.P., Miller, C.A., Chendamarai, E., Duncavage, E. J., Klco, J.M., Helton, N.M., O'Laughlin, M., Fronick, C.C., et al., 2018. Immune escape of relapsed AML cells after allogeneic transplantation. N. Engl. J. Med. 379, 2330–2341.
Clancy, S., 2008. Genetic mutation. Nature Education.
Cornel, A.M., Mimpen, I.L., Nierkens, S., 2020. MHC class I downregulation in cancer: underlying mechanisms and potential targets for cancer immunotherapy. Cancers (Basel) 12.
Coskun, U., Grzybek, M., Drechsel, D., Simons, K., 2011. Regulation of human EGF receptor by lipids. Proc. Natl. Acad. Sci. U. S. A. 108, 9044–9048.
Cresswell, P., Bangia, N., Dick, T., Diedrich, G., 1999. The nature of the MHC class I peptide loading complex. Immunol. Rev. 172, 21–28.
De Angelis Rigotti, F., De Gassart, A., Pforr, C., Cano, F., N'Guessan, P., Combes, A., Camossetto, V., Lehner, P.J., Pierre, P., Gatti, E., 2017. MARCH9-mediated ubiquitination regulates MHC I export from the TGN. Immunol. Cell Biol. 95, 753–764.
de Waard, A.A., Verkerk, T., Hoefakker, K., van der Steen, D.M., Jongsma, M.L.M., Melamed Kadosh, D., Bliss, S., de Ru, A.H., Admon, A., van Veelen, P.A., et al., 2021a. Healthy cells functionally present TAP-independent SSR1 peptides: implications for selection of clinically relevant antigens. iScience 24, 102051.
de Waard, A.A., Verkerk, T., Jongsma, M.L.M., Hoefakker, K., Sethumadhavan, S., Gerke, C., Bliss, S., Kong, X., Janssen, G.M.C., de Ru, A.H., et al., 2021b. PAKC: A novel panel of HLA class I antigen presentation machinery knockout cells from the same genetic origin. Eur. J. Immunol. 51, 734–737.
del Campo, A.B., Kyte, J.A., Carretero, J., Zinchencko, S., Mendez, R., Gonzalez-Aseguinolaza, G., Ruiz-Cabello, F., Aamdal, S., Gaudernack, G., Garrido, F., et al., 2014. Immune escape of cancer cells with beta2-microglobulin loss over the course of metastatic melanoma. Int. J. Cancer 134, 102–113.
Dersh, D., Phelan, J.D., Gumina, M.E., Wang, B., Arbuckle, J.H., Holly, J., Kishton, R.J., Markowitz, T.E., Seedhom, M.O., Fridlyand, N., et al., 2021. Genome-wide screens identify lineage- and tumor-specific genes modulating MHC-I- and MHC-II-restricted immunosurveillance of human lymphomas. Immunity 54, 116–131 e110.
Doorduijn, E.M., Sluijter, M., Querido, B.J., Oliveira, C.C., Achour, A., Ossendorp, F., van der Burg, S.H., van Hall, T., 2016. TAP-independent self-peptides enhance T cell recognition of immune-escaped tumors. J. Clin. Invest. 126, 784–794.
Edidin, M., 2010. Class I MHC molecules as probes of membrane patchiness: from biophysical measurements to modulation of immune responses. Immunol. Res. 47, 265–272.
Evans, D.M., Spencer, C.C., Pointon, J.J., Su, Z., Harvey, D., Kochan, G., Oppermann, U., Dilthey, A., Pirinen, M., Stone, M.A., et al., 2011. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility. Nat. Genet. 43, 761–767.
Eyster, C.A., Cole, N.B., Petersen, S., Viswanathan, K., Fruh, K., Donaldson, J.G., 2011. MARCH ubiquitin ligases alter the itinerary of clathrin-independent cargo from recycling to degradation. Mol. Biol. Cell 22, 3218–3230.
Falk, K., Rotzschke, O., Stevanovic, S., Jung, G., Rammensee, H.G., 1991. Allele-specific motifs revealed by sequencing of self-peptides eluted from MHC molecules. Nature 351, 290–296.
Favole, A., Cascio, P., Cerruti, F., Sereno, A., Tursi, M., Tomatis, A., Della Beffa, C., Ferrone, S., Bollo, E., 2012. MHC class I-related antigen-processing machinery component defects in feline mammary carcinoma. Transl. Oncol. 5, 48–55.
Ferrington, D.A., Gregerson, D.S., 2012. Immunoproteasomes: structure, function, and antigen presentation. Prog. Mol. Biol. Transl. Sci. 109, 75–112.
Fonsatti, E., Nicolay, H.J., Sigalotti, L., Calabro, L., Pezzani, L., Colizzi, F., Altomonte, M., Guidoboni, M., Marincola, F.M., Maio, M., 2007. Functional up-regulation of human leukocyte antigen class I antigens expression by 5-aza-2'-deoxycytidine in cutaneous melanoma: immunotherapeutic implications. Clin. Cancer Res. 13, 3333–3338.
Friedrich, M., Jasinski-Bergner, S., Lazaridou, M.F., Subbarayan, K., Massa, C., Tretbar, S., Mueller, A., Handke, D., Biehl, K., Bukur, J., et al., 2019. Tumor-induced escape mechanisms and their association with resistance to checkpoint inhibitor therapy. Cancer Immunol. Immunother. 68, 1689–1700.
Furukawa, J., Tsuda, M., Okada, K., Kimura, T., Piao, J., Tanaka, S., Shinohara, Y., 2015. Comprehensive glycomics of a multistep human brain tumor model reveals specific glycosylation patterns related to malignancy. PLoS One 10, e0128300.
Garrido, F., Algarra, I., 2001. MHC antigens and tumor escape from immune surveillance. Adv. Cancer Res. 83, 117–158.
Garrido, F., Cabrera, T., Aptsiauri, N., 2010. "Hard" and "soft" lesions underlying the HLA class I alterations in cancer cells: implications for immunotherapy. Int. J. Cancer 127, 249–256.
Garrido, F., Romero, I., Aptsiauri, N., Garcia-Lora, A.M., 2016. Generation of MHC class I diversity in primary tumors and selection of the malignant phenotype. Int. J. Cancer 138, 271–280.
Garstka, M.A., Fish, A., Celie, P.H., Joosten, R.P., Janssen, G.M., Berlin, I., Hoppes, R., Stadnik, M., Janssen, L., Ovaa, H., et al., 2015. The first step of peptide selection in antigen presentation by MHC class I molecules. Proc. Natl. Acad. Sci. U. S. A. 112, 1505–1510.
Gattoni-Celli, S., Kirsch, K., Timpane, R., Isselbacher, K.J., 1992. Beta 2-microglobulin gene is mutated in a human colon cancer cell line (HCT) deficient in the expression of HLA class I antigens on the cell surface. Cancer Res. 52, 1201–1204.
Gavioli, R., De Campos-Lima, P.O., Kurilla, M.G., Kieff, E., Klein, G., Masucci, M.G., 1992. Recognition of the Epstein-Barr virus-encoded nuclear antigens EBNA-4 and EBNA-6 by HLA-A11-restricted cytotoxic T lymphocytes: implications for down-regulation of HLA-A11 in Burkitt lymphoma. Proc. Natl. Acad. Sci. U. S. A. 89, 5862–5866.
Gettinger, S., Choi, J., Hastings, K., Truini, A., Datar, I., Sowell, R., Wurtz, A., Dong, W., Cai, G., Melnick, M.A., et al., 2017. Impaired HLA class I antigen processing and presentation as a mechanism of acquired resistance to immune checkpoint inhibitors in lung cancer. Cancer Discov. 7, 1420–1435.
Gromme, M., Uytdehaag, F.G., Janssen, H., Calafat, J., van Binnendijk, R.S., Kenter, M.J., Tulp, A., Verwoerd, D., Neefjes, J., 1999. Recycling MHC class I molecules and endosomal peptide loading. Proc. Natl. Acad. Sci. U. S. A. 96, 10326–10331.
Hakomori, S., 1981. Glycosphingolipids in cellular interaction, differentiation, and oncogenesis. Annu. Rev. Biochem. 50, 733–764.
Hakomori, S., 1984. Tumor-associated carbohydrate antigens. Annu. Rev. Immunol. 2, 103–126.
Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144, 646–674.
Herberts, C.A., Neijssen, J.J., de Haan, J., Janssen, L., Drijfhout, J.W., Reits, E.A., Neefjes, J.J., 2006. Cutting edge: HLA-B27 acquires many N-terminal dibasic peptides: coupling cytosolic peptide stability to antigen presentation. J. Immunol. 176, 2697–2701.
Herrmann, F., Lehr, H.A., Drexler, I., Sutter, G., Hengstler, J., Wollscheid, U., Seliger, B., 2004. HER-2/neu-mediated regulation of components of the MHC class I antigen-processing pathway. Cancer Res. 64, 215–220.
Hicklin, D.J., Wang, Z., Arienti, F., Rivoltini, L., Parmiani, G., Ferrone, S., 1998. beta2-Microglobulin mutations, HLA class I antigen loss, and tumor progression in melanoma. J. Clin. Invest. 101, 2720–2729.
Hoer, S., Smith, L., Lehner, P.J., 2007. MARCH-IX mediates ubiquitination and downregulation of ICAM-1. FEBS Lett. 581, 45–51.
Howe, C., Garstka, M., Al-Balushi, M., Ghanem, E., Antoniou, A.N., Fritzsche, S., Jankevicius, G., Kontouli, N., Schneeweiss, C., Williams, A., et al., 2009. Calreticulin-dependent recycling in the early secretory pathway mediates optimal peptide loading of MHC class I molecules. EMBO J. 28, 3730–3744.
Huang, L., Malu, S., McKenzie, J.A., Andrews, M.C., Talukder, A.H., Tieu, T., Karpinets, T., Haymaker, C., Forget, M.A., Williams, L.J., et al., 2018. The RNA-binding protein MEX3B mediates resistance to cancer immunotherapy by downregulating HLA-A expression. Clin. Cancer Res. 24, 3366–3376.
Inokuchi, J., Mason, I., Radin, N.S., 1987. Antitumor activity via inhibition of glycosphingolipid biosynthesis. Cancer Lett. 38, 23–30.
Jennemann, R., Federico, G., Mathow, D., Rabionet, M., Rampoldi, F., Popovic, Z.V., Volz, M., Hielscher, T., Sandhoff, R., Grone, H.J., 2017. Inhibition of hepatocellular carcinoma growth by blockade of glycosphingolipid synthesis. Oncotarget 8, 109201–109216.
Jongsma, M.L.M., Guarda, G., Spaapen, R.M., 2019. The regulatory network behind MHC class I expression. Mol. Immunol. 113, 16–21.
Jongsma, M.L.M., de Waard, A.A., Raaben, M., Zhang, T., Cabukusta, B., Platzer, R., Blomen, V.A., Xagara, A., Verkerk, T., Bliss, S., et al., 2021. The SPPL3-defined

glycosphingolipid repertoire orchestrates HLA class I-mediated immune responses. Immunity 54, 132–150 e139.
Kabayama, K., Sato, T., Saito, K., Loberto, N., Prinetti, A., Sonnino, S., Kinjo, M., Igarashi, Y., Inokuchi, J., 2007. Dissociation of the insulin receptor and caveolin-1 complex by ganglioside GM3 in the state of insulin resistance. Proc. Natl. Acad. Sci. U. S. A. 104, 13678–13683.
Kawakami, Y., Kawakami, K., Steelant, W.F., Ono, M., Baek, R.C., Handa, K., Withers, D. A., Hakomori, S., 2002. Tetraspanin CD9 is a "proteolipid," and its interaction with alpha 3 integrin in microdomain is promoted by GM3 ganglioside, leading to inhibition of laminin-5-dependent cell motility. J. Biol. Chem. 277, 34349–34358.
Khan, A.N., Gregorie, C.J., Tomasi, T.B., 2008. Histone deacetylase inhibitors induce TAP, LMP, Tapasin genes and MHC class I antigen presentation by melanoma cells. Cancer Immunol. Immunother. 57, 647–654.
Kriegsman, B.A., Vangala, P., Chen, B.J., Meraner, P., Brass, A.L., Garber, M., Rock, K.L., 2019. Frequent loss of IRF2 in cancers leads to immune evasion through decreased MHC class I antigen presentation and increased PD-L1 expression. J. Immunol. 203, 1999–2010.
Laugesen, A., Hojfeldt, J.W., Helin, K., 2016. Role of the polycomb repressive complex 2 (PRC2) in transcriptional regulation and cancer. Cold Spring Harb. Perspect. Med. 6.
Lazaridou, M.F., Gonschorek, E., Massa, C., Friedrich, M., Handke, D., Mueller, A., Jasinski-Bergner, S., Dummer, R., Koelblinger, P., Seliger, B., 2020a. Identification of miR-200a-5p targeting the peptide transporter TAP1 and its association with the clinical outcome of melanoma patients. Oncoimmunology 9, 1774323.
Lazaridou, M.F., Massa, C., Handke, D., Mueller, A., Friedrich, M., Subbarayan, K., Tretbar, S., Dummer, R., Koelblinger, P., Seliger, B., 2020b. Identification of microRNAs targeting the transporter associated with antigen processing TAP1 in melanoma. J. Clin. Med. 9.
Leone, P., Shin, E.C., Perosa, F., Vacca, A., Dammacco, F., Racanelli, V., 2013. MHC class I antigen processing and presenting machinery: organization, function, and defects in tumor cells. J. Natl. Cancer Inst. 105, 1172–1187.
Li, J., Lin, T.Y., Chen, L., Liu, Y., Dian, M.J., Hao, W.C., Lin, X.L., Li, X.Y., Li, Y.L., Lian, M., et al., 2020. miR-19 regulates the expression of interferon-induced genes and MHC class I genes in human cancer cells. Int. J. Med. Sci. 17, 953–964.
Linnemann, C., van Buuren, M.M., Bies, L., Verdegaal, E.M., Schotte, R., Calis, J.J., Behjati, S., Velds, A., Hilkmann, H., Atmioui, D.E., et al., 2015. High-throughput epitope discovery reveals frequent recognition of neo-antigens by CD4+ T cells in human melanoma. Nat. Med. 21, 81–85.
Liu, B., Palmfeldt, J., Lin, L., Colaco, A., Clemmensen, K.K.B., Huang, J., Xu, F., Liu, X., Maeda, K., Luo, Y., et al., 2018. STAT3 associates with vacuolar H(+)-ATPase and regulates cytosolic and lysosomal pH. Cell Res. 28, 996–1012.
Lohmann, S., Wollscheid, U., Huber, C., Seliger, B., 1996. Multiple levels of MHC class I down-regulation by ras oncogenes. Scand. J. Immunol. 43, 537–544.
Lulli, D., Carbone, M.L., Pastore, S., 2017. The MEK inhibitors trametinib and cobimetinib induce a type I interferon response in human keratinocytes. Int. J. Mol. Sci. 18.
Luo, N., Nixon, M.J., Gonzalez-Ericsson, P.I., Sanchez, V., Opalenik, S.R., Li, H., Zahnow, C.A., Nickels, M.L., Liu, F., Tantawy, M.N., et al., 2018. DNA methyltransferase inhibition upregulates MHC-I to potentiate cytotoxic T lymphocyte responses in breast cancer. Nat. Commun. 9, 248.
Maleno, I., Aptsiauri, N., Cabrera, T., Gallego, A., Paschen, A., Lopez-Nevot, M.A., Garrido, F., 2011. Frequent loss of heterozygosity in the beta2-microglobulin region of chromosome 15 in primary human tumors. Immunogenetics 63, 65–71.
Marijt, K.A., Blijleven, L., Verdegaal, E.M.E., Kester, M.G., Kowalewski, D.J., Rammensee, H.G., Stevanovic, S., Heemskerk, M.H.M., van der Burg, S.H., van Hall, T., 2018. Identification of non-mutated neoantigens presented by TAP-deficient tumors. J. Exp. Med. 215, 2325–2337.
Martin, M.P., Carrington, M., 2013. Immunogenetics of HIV disease. Immunol. Rev. 254, 245–264.
Marty Pyke, R., Thompson, W.K., Salem, R.M., Font-Burgada, J., Zanetti, M., Carter, H., 2018. Evolutionary pressure against MHC class II binding cancer mutations. Cell 175, 416-428 e413.
Maruyama, T., Mimura, K., Sato, E., Watanabe, M., Mizukami, Y., Kawaguchi, Y., Ando, T., Kinouchi, H., Fujii, H., Kono, K., 2010. Inverse correlation of HER2 with MHC class I expression on oesophageal squamous cell carcinoma. Br. J. Cancer 103, 552–559.
Michalek, M.T., Grant, E.P., Gramm, C., Goldberg, A.L., Rock, K.L., 1993. A role for the ubiquitin-dependent proteolytic pathway in MHC class I-restricted antigen presentation. Nature 363, 552–554.
Mimura, K., Shiraishi, K., Mueller, A., Izawa, S., Kua, L.F., So, J., Yong, W.P., Fujii, H., Seliger, B., Kiessling, R., et al., 2013. The MAPK pathway is a predominant regulator of HLA-A expression in esophageal and gastric cancer. J. Immunol. 191, 6261–6272.
Moll, R., Franke, W.W., Schiller, D.L., Geiger, B., Krepler, R., 1982. The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. Cell 31, 11–24.
Momburg, F., Roelse, J., Howard, J.C., Butcher, G.W., Hammerling, G.J., Neefjes, J.J., 1994. Selectivity of MHC-encoded peptide transporters from human, mouse and rat. Nature 367, 648–651.
Mora-Garcia Mde, L., Duenas-Gonzalez, A., Hernandez-Montes, J., De la Cruz-Hernandez, E., Perez-Cardenas, E., Weiss-Steider, B., Santiago-Osorio, E., Ortiz-Navarrete, V.F., Rosales, V.H., Cantu, D., et al., 2006. Up-regulation of HLA class-I antigen expression and antigen-specific CTL response in cervical cancer cells by the demethylating agent hydralazine and the histone deacetylase inhibitor valproic acid. J. Transl. Med. 4, 55.
Nakayama, H., Nagafuku, M., Suzuki, A., Iwabuchi, K., Inokuchi, J.I., 2018. The regulatory roles of glycosphingolipid-enriched lipid rafts in immune systems. FEBS Lett. 592, 3921–3942.
Neefjes, J.J., Ploegh, H.L., 1988. Allele and locus-specific differences in cell surface expression and the association of HLA class I heavy chain with beta 2-microglobulin: differential effects of inhibition of glycosylation on class I subunit association. Eur. J. Immunol. 18, 801–810.
Neefjes, J.J., De Bruijn, M.L., Boog, C.J., Nieland, J.D., Boes, J., Melief, C.J., Ploegh, H.L., 1990. N-linked glycan modification on antigen-presenting cells restores an allospecific cytotoxic T cell response. J. Exp. Med. 171, 583–588.
Neefjes, J.J., Hammerling, G.J., Momburg, F., 1993. Folding and assembly of major histocompatibility complex class I heterodimers in the endoplasmic reticulum of intact cells precedes the binding of peptide. J. Exp. Med. 178, 1971–1980.
Neefjes, J., Jongsma, M.L., Paul, P., Bakke, O., 2011. Towards a systems understanding of MHC class I and MHC class II antigen presentation. Nat. Rev. Immunol. 11, 823–836.
Neisig, A., Wubbolts, R., Zang, X., Melief, C., Neefjes, J., 1996. Allele-specific differences in the interaction of MHC class I molecules with transporters associated with antigen processing. J. Immunol. 156, 3196–3206.
Nie, Y., Yang, G., Song, Y., Zhao, X., So, C., Liao, J., Wang, L.D., Yang, C.S., 2001. DNA hypermethylation is a mechanism for loss of expression of the HLA class I genes in human esophageal squamous cell carcinomas. Carcinogenesis 22, 1615–1623.
Ogino, T., Bandoh, N., Hayashi, T., Miyokawa, N., Harabuchi, Y., Ferrone, S., 2003. Association of tapasin and HLA class I antigen down-regulation in primary maxillary sinus squamous cell carcinoma lesions with reduced survival of patients. Clin. Cancer Res. 9, 4043–4051.
Oshima, S., Nakamura, T., Namiki, S., Okada, E., Tsuchiya, K., Okamoto, R., Yamazaki, M., Yokota, T., Aida, M., Yamaguchi, Y., et al., 2004. Interferon regulatory factor 1 (IRF-1) and IRF-2 distinctively up-regulate gene expression and production of interleukin-7 in human intestinal epithelial cells. Mol. Cell. Biol. 24, 6298–6310.
Ozcan, M., Janikovits, J., von Knebel Doeberitz, M., Kloor, M., 2018. Complex pattern of immune evasion in MSI colorectal cancer. Oncoimmunology 7, e1445453.
Parcej, D., Tampe, R., 2010. ABC proteins in antigen translocation and viral inhibition. Nat. Chem. Biol. 6, 572–580.
Peh, C.A., Burrows, S.R., Barnden, M., Khanna, R., Cresswell, P., Moss, D.J., McCluskey, J., 1998. HLA-B27-restricted antigen presentation in the absence of tapasin reveals polymorphism in mechanisms of HLA class I peptide loading. Immunity 8, 531–542.
Perez, B., Benitez, R., Fernandez, M.A., Oliva, M.R., Soto, J.L., Serrano, S., Lopez Nevot, M.A., Garrido, F., 1999. A new beta 2 microglobulin mutation found in a melanoma tumor cell line. Tissue Antigens 53, 569–572.
Pont, M.J., Oostvogels, R., van Bergen, C.A.M., van der Meijden, E.D., Honders, M.W., Bliss, S., Jongsma, M.L.M., Lokhorst, H.M., Falkenburg, J.H.F., Mutis, T., et al., 2019. T cells specific for an unconventional natural antigen fail to recognize leukemic cells. Cancer Immunol. Res. 7, 797–804.
Radin, N.S., 1999. Chemotherapy by slowing glucosphingolipid synthesis. Biochem. Pharmacol. 57, 589–595.
Reches, A., Nachmani, D., Berhani, O., Duev-Cohen, A., Shreibman, D., Ophir, Y., Seliger, B., Mandelboim, O., 2016. HNRNPR regulates the expression of classical and nonclassical MHC class I proteins. J. Immunol. 196, 4967–4976.
Reinicke, A.T., Raczkowski, F., Muhlig, M., Schmucker, P., Lischke, T., Reichelt, J., Schneider, E., Zielinski, S., Sachs, M., Jurack, E., et al., 2019. Deubiquitinating enzyme UCH-L1 promotes dendritic cell antigen cross-presentation by favoring recycling of MHC class I molecules. J. Immunol. 203, 1730–1742.
Reits, E., Griekspoor, A., Neijssen, J., Groothuis, T., Jalink, K., van Veelen, P., Janssen, H., Calafat, J., Drijfhout, J.W., Neefjes, J., 2003. Peptide diffusion, protection, and degradation in nuclear and cytoplasmic compartments before antigen presentation by MHC class I. Immunity 18, 97–108.
Reits, E.A., Hodge, J.W., Herberts, C.A., Groothuis, T.A., Chakraborty, M., Wansley, E.K., Camphausen, K., Luiten, R.M., de Ru, A.H., Neijssen, J., et al., 2006. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. J. Exp. Med. 203, 1259–1271.
Ren, G., Cui, K., Zhang, Z., Zhao, K., 2015. Division of labor between IRF1 and IRF2 in regulating different stages of transcriptional activation in cellular antiviral activities. Cell Biosci. 5, 17.
Restifo, N.P., Marincola, F.M., Kawakami, Y., Taubenberger, J., Yannelli, J.R., Rosenberg, S.A., 1996. Loss of functional beta 2-microglobulin in metastatic melanomas from five patients receiving immunotherapy. J. Natl. Cancer Inst. 88, 100–108.
Ritter, C., Fan, K., Paschen, A., Reker Hardrup, S., Ferrone, S., Nghiem, P., Ugurel, S., Schrama, D., Becker, J.C., 2017. Epigenetic priming restores the HLA class-I antigen processing machinery expression in Merkel cell carcinoma. Sci. Rep. 7, 2290.
Rizvi, S.M., Salam, N., Geng, J., Qi, Y., Bream, J.H., Duggal, P., Hussain, S.K., Martinson, J., Wolinsky, S.M., Carrington, M., et al., 2014. Distinct assembly profiles of HLA-B molecules. J. Immunol. 192, 4967–4976.
Robinson, J., Barker, D.J., Georgiou, X., Cooper, M.A., Flicek, P., Marsh, S.G.E., 2020. IPD-IMGT/HLA database. Nucleic Acids Res. 48, D948–D955.
Rock, K.L., Gramm, C., Rothstein, L., Clark, K., Stein, R., Dick, L., Hwang, D., Goldberg, A.L., 1994. Inhibitors of the proteasome block the degradation of most cell proteins and the generation of peptides presented on MHC class I molecules. Cell 78, 761–771.
Roelse, J., Gromme, M., Momburg, F., Hammerling, G., Neefjes, J., 1994. Trimming of TAP-translocated peptides in the endoplasmic reticulum and in the cytosol during recycling. J. Exp. Med. 180, 1591–1597.
Sade-Feldman, M., Jiao, Y.J., Chen, J.H., Rooney, M.S., Barzily-Rokni, M., Eliane, J.P., Bjorgaard, S.L., Hammond, M.R., Vitzthum, H., Blackmon, S.M., et al., 2017. Resistance to checkpoint blockade therapy through inactivation of antigen presentation. Nat. Commun. 8, 1136.

Saric, T., Chang, S.C., Hattori, A., York, I.A., Markant, S., Rock, K.L., Tsujimoto, M., Goldberg, A.L., 2002. An IFN-gamma-induced aminopeptidase in the ER, ERAP1, trims precursors to MHC class I-presented peptides. Nat. Immunol. 3, 1169–1176.
Saveanu, L., Carroll, O., Lindo, V., Del Val, M., Lopez, D., Lepelletier, Y., Greer, F., Schomburg, L., Fruci, D., Niedermann, G., et al., 2005. Concerted peptide trimming by human ERAP1 and ERAP2 aminopeptidase complexes in the endoplasmic reticulum. Nat. Immunol. 6, 689–697.
Saverino, D., Fabbi, M., Ghiotto, F., Merlo, A., Bruno, S., Zarcone, D., Tenca, C., Tiso, M., Santoro, G., Anastasi, G., et al., 2000. The CD85/LIR-1/ILT2 inhibitory receptor is expressed by all human T lymphocytes and down-regulates their functions. J. Immunol. 165, 3742–3755.
Schreiber, H., Wu, T.H., Nachman, J., Kast, W.M., 2002. Immunodominance and tumor escape. Semin. Cancer Biol. 12, 25–31.
Seliger, B., 2019. Basis of PD1/PD-L1 therapies. J. Clin. Med. 8.
Seliger, B., Harders, C., Lohmann, S., Momburg, F., Urlinger, S., Tampe, R., Huber, C., 1998. Down-regulation of the MHC class I antigen-processing machinery after oncogenic transformation of murine fibroblasts. Eur. J. Immunol. 28, 122–133.
Seliger, B., Ritz, U., Abele, R., Bock, M., Tampe, R., Sutter, G., Drexler, I., Huber, C., Ferrone, S., 2001. Immune escape of melanoma: first evidence of structural alterations in two distinct components of the MHC class I antigen processing pathway. Cancer Res. 61, 8647–8650.
Serrano, A., Tanzarella, S., Lionello, I., Mendez, R., Traversari, C., Ruiz-Cabello, F., Garrido, F., 2001. Rexpression of HLA class I antigens and restoration of antigen-specific CTL response in melanoma cells following 5-aza-2'-deoxycytidine treatment. Int. J. Cancer 94, 243–251.
Serwold, T., Gonzalez, F., Kim, J., Jacob, R., Shastri, N., 2002. ERAAP customizes peptides for MHC class I molecules in the endoplasmic reticulum. Nature 419, 480–483.
Setiadi, A.F., David, M.D., Seipp, R.P., Hartikainen, J.A., Gopaul, R., Jefferies, W.A., 2007. Epigenetic control of the immune escape mechanisms in malignant carcinomas. Mol. Cell. Biol. 27, 7886–7894.
Shin, D.S., Zaretsky, J.M., Escuin-Ordinas, H., Garcia-Diaz, A., Hu-Lieskovan, S., Kalbasi, A., Grasso, C.S., Hugo, W., Sandoval, S., Torrejon, D.Y., et al., 2017. Primary resistance to PD-1 blockade mediated by JAK1/2 mutations. Cancer Discov. 7, 188–201.
Shukla, S.A., Rooney, M.S., Rajasagi, M., Tiao, G., Dixon, P.M., Lawrence, M.S., Stevens, J., Lane, W.J., Dellagatta, J.L., Steelman, S., et al., 2015. Comprehensive analysis of cancer-associated somatic mutations in class I HLA genes. Nat. Biotechnol. 33, 1152–1158.
So, T., Takenoyama, M., Mizukami, M., Ichiki, Y., Sugaya, M., Hanagiri, T., Sugio, K., Yasumoto, K., 2005. Haplotype loss of HLA class I antigen as an escape mechanism from immune attack in lung cancer. Cancer Res. 65, 5945–5952.
Spel, L., Nieuwenhuis, J., Haarsma, R., Stickel, E., Bleijerveld, O.B., Altelaar, M., Boelens, J.J., Brummelkamp, T.R., Nierkens, S., Boes, M., 2018. Nedd4-binding protein 1 and TNFAIP3-Interacting protein 1 control MHC-1 display in neuroblastoma. Cancer Res. 78, 6621–6631.
Sun, T., Li, Y., Yang, W., Wu, H., Li, X., Huang, Y., Zhou, Y., Du, Z., 2019. Histone deacetylase inhibition up-regulates MHC class I to facilitate cytotoxic T lymphocyte-mediated tumor cell killing in glioma cells. J. Cancer 10, 5638–5645.
Tagami, S., Inokuchi Ji, J., Kabayama, K., Yoshimura, H., Kitamura, F., Uemura, S., Ogawa, C., Ishii, A., Saito, M., Ohtsuka, Y., et al., 2002. Ganglioside GM3 participates in the pathological conditions of insulin resistance. J. Biol. Chem. 277, 3085–3092.
Todeschini, A.R., Dos Santos, J.N., Handa, K., Hakomori, S.I., 2007. Ganglioside GM2-tetraspanin CD82 complex inhibits met and its cross-talk with integrins, providing a basis for control of cell motility through glycosynapse. J. Biol. Chem. 282, 8123–8133.
Toffalori, C., Zito, L., Gambacorta, V., Riba, M., Oliveira, G., Bucci, G., Barcella, M., Spinelli, O., Greco, R., Crucitti, L., et al., 2019. Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation. Nat. Med. 25, 603–611.
Tran, E., Ahmadzadeh, M., Lu, Y.C., Gros, A., Turcotte, S., Robbins, P.F., Gartner, J.J., Zheng, Z., Li, Y.F., Ray, S., et al., 2015. Immunogenicity of somatic mutations in human gastrointestinal cancers. Science 350, 1387–1390.
Trowsdale, J., 2005. HLA genomics in the third millennium. Curr. Opin. Immunol. 17, 498–504.
Valiante, N.M., Uhrberg, M., Shilling, H.G., Lienert-Weidenbach, K., Arnett, K.L., D'Andrea, A., Phillips, J.H., Lanier, L.L., Parham, P., 1997. Functionally and structurally distinct NK cell receptor repertoires in the peripheral blood of two human donors. Immunity 7, 739–751.
van' t Veer, L.J., Beijersbergen, R.L., Bernards, R., 1993. N-myc suppresses major histocompatibility complex class I gene expression through down-regulation of the p50 subunit of NF-kappa B. EMBO J. 12, 195–200.
van Hall, T., Wolpert, E.Z., van Veelen, P., Laban, S., van der Veer, M., Roseboom, M., Bres, S., Grufman, P., de Ru, A., Meiring, H., et al., 2006. Selective cytotoxic T-lymphocyte targeting of tumor immune escape variants. Nat. Med. 12, 417–424.
Vertuani, S., Triulzi, C., Roos, A.K., Charo, J., Norell, H., Lemonnier, F., Pisa, P., Seliger, B., Kiessling, R., 2009. HER-2/neu mediated down-regulation of MHC class I antigen processing prevents CTL-mediated tumor recognition upon DNA vaccination in HLA-A2 transgenic mice. Cancer Immunol. Immunother. 58, 653–664.
Vlkova, V., Stepanek, I., Hruskova, V., Senigl, F., Mayerova, V., Sramek, M., Simova, J., Bieblova, J., Indrova, M., Hejhal, T., et al., 2014. Epigenetic regulations in the IFNgamma signalling pathway: IFNgamma-mediated MHC class I upregulation on tumour cells is associated with DNA demethylation of antigen-presenting machinery genes. Oncotarget 5, 6923–6935.
Wang, Z., Marincola, F.M., Rivoltini, L., Parmiani, G., Ferrone, S., 1999. Selective histocompatibility leukocyte antigen (HLA)-A2 loss caused by aberrant pre-mRNA splicing in 624MEL28 melanoma cells. J. Exp. Med. 190, 205–215.
Wang, X., Herr, R.A., Hansen, T., 2008. Viral and cellular MARCH ubiquitin ligases and cancer. Semin. Cancer Biol. 18, 441–450.
Wang, Z., Wen, L., Ma, X., Chen, Z., Yu, Y., Zhu, J., Wang, Y., Liu, Z., Liu, H., Wu, D., et al., 2012. High expression of lactotriaosylceramide, a differentiation-associated glycosphingolipid, in the bone marrow of acute myeloid leukemia patients. Glycobiology 22, 930–938.
Watanabe, N., Sakakibara, J., Hovanessian, A.G., Taniguchi, T., Fujita, T., 1991. Activation of IFN-beta element by IRF-1 requires a posttranslational event in addition to IRF-1 synthesis. Nucleic Acids Res. 19, 4421–4428.
Wearsch, P.A., Cresswell, P., 2007. Selective loading of high-affinity peptides onto major histocompatibility complex class I molecules by the tapasin-ERp57 heterodimer. Nat. Immunol. 8, 873–881.
Wearsch, P.A., Peaper, D.R., Cresswell, P., 2011. Essential glycan-dependent interactions optimize MHC class I peptide loading. Proc. Natl. Acad. Sci. U. S. A. 108, 4950–4955.
Wei, M.L., Cresswell, P., 1992. HLA-A2 molecules in an antigen-processing mutant cell contain signal sequence-derived peptides. Nature 356, 443–446.
Wikstrand, C.J., He, X.M., Fuller, G.N., Bigner, S.H., Fredman, P., Svennerholm, L., Bigner, D.D., 1991. Occurrence of lacto series gangliosides 3'-isoLM1 and 3',6'-isoLD1 in human gliomas in vitro and in vivo. J. Neuropathol. Exp. Neurol. 50, 756–769.
Wu, M.S., Li, C.H., Ruppert, J.G., Chang, C.C., 2013. Cytokeratin 8-MHC class I interactions: a potential novel immune escape phenotype by a lymph node metastatic carcinoma cell line. Biochem. Biophys. Res. Commun. 441, 618–623.
Wu, C., Jin, X., Tsueng, G., Afrasiabi, C., Su, A.I., 2016. BioGPS: building your own mash-up of gene annotations and expression profiles. Nucleic Acids Res. 44, D313–316.
Yang, W., Li, Y., Gao, R., Xiu, Z., Sun, T., 2020. MHC class I dysfunction of glioma stem cells escapes from CTL-mediated immune response via activation of Wnt/beta-catenin signaling pathway. Oncogene 39, 1098–1111.
Ye, Q., Shen, Y., Wang, X., Yang, J., Miao, F., Shen, C., Zhang, J., 2010. Hypermethylation of HLA class I gene is associated with HLA class I down-regulation in human gastric cancer. Tissue Antigens 75, 30–39.
Yewdell, J.W., Anton, L.C., Bennink, J.R., 1996. Defective ribosomal products (DRiPs): a major source of antigenic peptides for MHC class I molecules? J. Immunol. 157, 1823–1826.
Yoshihama, S., Roszik, J., Downs, I., Meissner, T.B., Vijayan, S., Chapuy, B., Sidiq, T., Shipp, M.A., Lizee, G.A., Kobayashi, K.S., 2016. NLRC5/MHC class I transactivator is a target for immune evasion in cancer. Proc. Natl. Acad. Sci. U. S. A. 113, 5999–6004.
Yossef, R., Tran, E., Deniger, D.C., Gros, A., Pasetto, A., Parkhurst, M.R., Gartner, J.J., Prickett, T.D., Cafri, G., Robbins, P.F., et al., 2018. Enhanced detection of neoantigen-reactive T cells targeting unique and shared oncogenes for personalized cancer immunotherapy. JCI Insight 3.
Zaretsky, J.M., Garcia-Diaz, A., Shin, D.S., Escuin-Ordinas, H., Hugo, W., Hu-Lieskovan, S., Torrejon, D.Y., Abril-Rodriguez, G., Sandoval, S., Barthly, L., et al., 2016. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N. Engl. J. Med. 375, 819–829.
Zarling, A.L., Luckey, C.J., Marto, J.A., White, F.M., Brame, C.J., Evans, A.M., Lehner, P. J., Cresswell, P., Shabanowitz, J., Hunt, D.F., et al., 2003. Tapasin is a facilitator, not an editor, of class I MHC peptide binding. J. Immunol. 171, 5287–5295.
Zhang, W., Wearsch, P.A., Zhu, Y., Leonhardt, R.M., Cresswell, P., 2011. A role for UDP-glucose glycoprotein glucosyltransferase in expression and quality control of MHC class I molecules. Proc. Natl. Acad. Sci. U. S. A. 108, 4956–4961.
Zhang, T., de Waard, A.A., Wuhrer, M., Spaapen, R.M., 2019. The role of glycosphingolipids in immune cell functions. Front. Immunol. 10, 90.