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FOCUSSED RESEARCH REVIEW

Novel insights into the molecular mechanisms of HLA class I abnormalities

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Abstract Alterations in the MHC class I surface antigens represent one mechanism of tumor cells to escape from natural or immunotherapy-induced antitumor immune responses. In order to restore MHC class I expression, knowledge about the underlying molecular mechanisms of MHC class I defects in different tumor types is required. In most cases, abnormalities of MHC class I expression are reversible by cytokines suggesting a deregulation rather than structural abnormalities of members of the antigen-processing and presentation machinery (APM). The impaired expression of APM components could be controlled at the epigenetic, transcriptional and/or posttranscriptional level. Furthermore, a direct link between altered transcription factor binding, interferon signal transduction and MHC class I APM component expression has been shown, which might be further associated with cell cycle progression. This information will not only give novel insights into the (patho) physiology of the antigen-processing and presenting pathway, but will help in the future to design effective T cell-based immunotherapies.

Keywords MHC class I antigens · Antigen processing · Tumors · Gene regulation · Signal transduction

Abbreviations

APC	Antigen-presenting cells
APM	Antigen-processing machinery
β_2-m	β_2-microglobuline
CTL	Cytotoxic T lymphocytes
DC	Dendritic cells
EGF	Epidermal growth factor
ER	Endoplasmic reticulum
HC	Heavy chains
IFN	Interferon
JAK	Janus kinase
luc	Luciferase
MDSC	Myeloid-derived suppressor cells
RCC	Renal cell carcinoma
STAT	Signal transducers and activators of transcription
TA	Tumor antigen
TAP	Transporter associated with antigen processing
TCR	T cell receptor
TFBS	Transcription factor binding sites
TNF	Tumor necrosis factor
Treg	Regulatory T cells

Tumors represent heterogeneous diseases with a variable clinical cause, but a high frequency of recurrences. Although a number of ongoing clinical trials provide promise for the implementation of immunotherapies for the treatment of cancer patients and a number of different immunotherapeutic strategies alone or in combination with irradiation or chemotherapy have been explored, the general efficacies of these therapies are not as potent as expected. This might be due to changes in the tumor host interaction, which is mediated by professional antigen-presenting cells (APC), such as B cells and dendritic cells (DC), effector cells like T,

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NK and NKT cells, tumor stroma and endothelium as well as immune suppressive cells including regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC). The tumor microenvironment may provide protection of tumors against potent T cell responses by increasing for example the frequency of Treg and MDSC [1, 2].

In general, there exists interplay between immune and tumor cells, which profoundly influences each other. An association between host immune responses and prognosis has been described in a variety of tumor types, which is also influenced by the tumor microenvironment, consisting of a heterogeneous mix of cellular and non-cellular components. The immune cells are able to recognize tumor cells, thereby leading to their apoptosis and tumor rejection. This activity is mainly mediated by T cells, NK cells as well as macrophages. During disease progression, host immune responses have been biased against antitumor immune responses. Tumors could not be recognized by immune cells resulting in tumor cell proliferation and in the induction of an immune suppressive microenvironment, which negatively interferes with the systemic and local adaptive immune responses. Lastly, this could lead to the induction of immune escape variants.

Different immune escape strategies of tumors

There exist different strategies how tumors evade the immune system. These include defects in the elucidation or maintenance of an effective antitumor responses such as insufficient antigen processing by DC, poor recruitment of or impaired activation of effector cells, the secretion of immune suppressive factors, like cytokines, prostaglandine and growth factors, the expression of molecules of negative regulatory pathways, such as B7-H1, B7-H3 and B7-H4 and the non-classical HLA-G antigen, increased frequency of Treg and MDSC, altered metabolite expression, modulation of the pH as well as downregulation or lack of the expression of classical HLA class I molecules and signal transduction molecules (Fig. 1). Although there exists evidence for improved responses at earlier disease stages, not only activated effector $CD8^+$ T cells, but also tumor antigen (TA)-specific T cells could be induced. For the antitumoral T cell responses, the interaction of the T cell receptors with their specific HLA class I complex is required. Therefore, the HLA class I antigen-processing machinery (APM) plays a crucial role in mediating immune responses by the generation and expression of the trimeric HLA class I, β_2-microglobuline (β_2-m) and peptide complex. The APM pathway consists of four major steps. The first step involves the peptide generation and peptide trimming, which is mainly mediated by the proteasome and cytosolic peptidases. Endogeneously synthesized proteins are ubiquitinated and

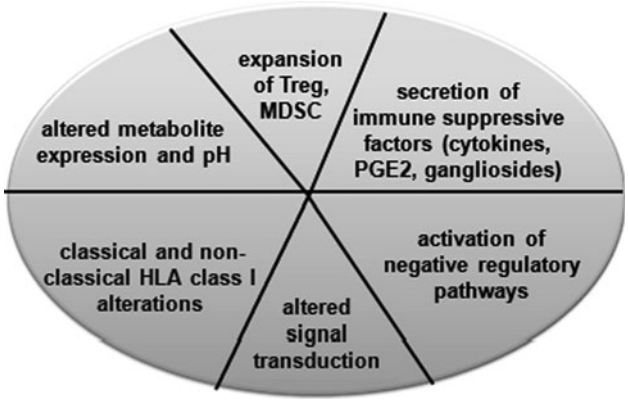

Fig. 1 Different immune escape mechanisms of tumors. Tumors exert different strategies to escape immune cell surveillance. In addition, the frequency and function of immune cells are altered by the tumor microenvironment, which also results in an impaired anti tumor immune response

then degraded by the multi-catalytic proteasome complex consisting of the constitutive and interferon (IFN)-γ-inducible subunits, the low molecular weight proteins (LMP)2, -7 and -10. The proteasome yields peptides with a correct C-terminus and an extended N-terminus, which is further trimmed by cytosolic peptidases. Then, the peptides are transported in an ATP- and sequence-dependent manner from the cytosol into the endoplasmic reticulum (ER). In the ER the MHC class I molecules are assembled, which is assisted by various chaperones, such as calnexin, calreticulin and in particular tapasin, which facilitates peptide loading onto MHC class I molecules [3]. This trimeric complex is then transported via the trans-Golgi to the cell surface and there exposed to $CD8^+$ cytotoxic T lymphocytes (CTL).

Alterations in MHC class I antigens and APM components in tumors

It has been shown by many different groups including ours that MHC class I abnormalities could occur at a relatively high frequency in many solid and hematopoietic tumors [4–6]. A total MHC class I antigen loss, MHC class I downregulation, a selective loss or downregulation of MHC class I allospecificities have been described, which are further associated with disease progression and reduced patients' survival (Table 1) [7–9]. This is often accompanied by an impaired expression of a single or various APM component(s) [10–12]. For example, an altered expression of LMP2, LMP7, TAP1 and β_2-m was found in renal cell carcinoma (RCC), prostate cancers and melanoma when compared to adjacent normal tissues [13–15]. The loss of these APM components was associated with a disease progression and/or an early disease recurrence of patients

Table 1 HLA class I abnormalities in human tumors

Highly variable frequency in many tumors
Total HLA class I antigen loss (9–52%)
HLA class I downregulation (3–20%)
Selective loss or downregulation of HLA class I allospecificities (15–50%)
Association with disease progression
Tissue and/or tumor subtype specificity
Differentiation/cell cycle dependence

[16]. In addition, MHC class I APM component expression appears to be tissue- and tumor subtype-specific regulated and differentially expressed during differentiation process and cell cycle progression.

Molecular mechanisms of APM downregulation

In order to understand the molecular mechanisms of MHC class I loss or downregulation, structural alterations and control mechanisms involved in the deregulation of diverse APM components were determined (Fig. 2) [7–9]. Structural abnormalities of APM components represent a relatively rare event and appear to be tumor specific, for example mutations, deletion and/or loss of heterozygosity of β_2-m and the HLA class I heavy chains (HC) have been mainly described in colorectal carcinoma and melanoma, but not in RCC [17–24]. Mutations in TAP have only been found in two melanoma cell lines, in non-small lung carcinoma and leiomyosarcomas, whereas mutations in tapasin and LMPs were detected in neuroblastoma

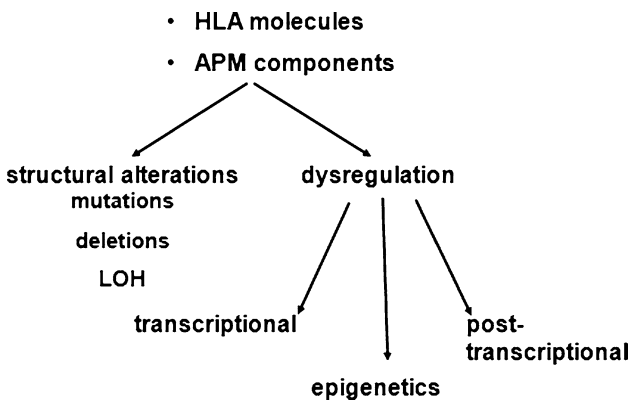

Fig. 2 Molecular mechanisms of MHC class I APM downregulation. The loss or downregulated expression of APM components could occur at the distinct levels of the MHC class I APM pathway and involves transcriptional, posttranscriptional and epigenetic processes resulting in a deregulated expression, whereas structural alterations like mutations, deletions and LOH are rare events

(B. S. unpublished data) [13, 25, 26]. The defective APM component expression could be restored by gene transfer resulting in increased MHC class I surface antigen levels, enhanced antitumoral responses and survival [27, 28]. Thus, the major molecular mechanisms of impaired MHC class I APM component expression appear to be caused by their de-regulation as already demonstrated for virus-transformed cells [29–33]. In addition, cytokine-mediated upregulation of MHC class I APM components further strengthened their deregulation [13, 34, 35]. This could occur either at the epigenetic expression, transcriptional and/or posttranscriptional level. Methylation and histone modifications of APM components appear to be a rare event with a frequency comparable to that of mutations and have been only described for TAP1, β_2-m and HLA class I HC [36–39]. In contrast, transcriptional and/or posttranscriptional control of all major APM components was detected in tumors of distinct histology. Although in most cases APM-specific mRNA and protein were coordinately downregulated, some tumor cells expressed high levels of TAP, LMP, tapasin and ERAP mRNA, but lacked respective protein expression [13, 14]. Interestingly, a posttranscriptional downregulation of TAP2 in cells with TAP1 loss due to a mutation in TAP1 leading to an earlier stop codon was reported [13]. It was speculated that the mutation-mediated lack of TAP1 expression directly destabilises TAP2 protein. In order to prove this hypothesis, cells were left untreated or treated with different proteasome inhibitors like epoxomycin and MG-132. An increased ubiquitination and degradation of TAP2 in the absence of the proteasome inhibitors were found. These data were further confirmed using shRNA plasmids for TAP1 demonstrating a concordant TAP2 downregulation by TAP1 silencing resulting in reduced TAP function and downregulated MHC class I surface expression.

In order to determine the transcriptional activity of MHC class I APM components, the various APM promoters were cloned into a luciferase (luc) expression vector and the APM promoter activity was determined upon transient transfection of the APM-luc constructs into different human tumor cells. In parallel, the mRNA and protein expression of the distinct components was analyzed. Using this approach, a transcriptional as well as posttranscriptional regulation in particular of the LMP subunits, TAP1/2 and tapasin, was observed in melanoma cells. So far, it is not solved, which transcription factors negatively or positively interfere with the APM component expression in tumors. Detailed analysis of the transcription factor binding sites (TFBS) using APM promoter constructs in which the TFBS were altered by site directed mutagenesis will give information about the factors involved in the tumor-mediated suppression of APM components.

Novel insights into MHC class I APM component regulation

By performing cDNA arrays of TAP1$^+$ transfectants and TAP1$^-$ counterparts, an altered expression pattern of genes involved in the IFN signal transduction pathway as well as in the cellular metabolism was detected (B. S. unpublished data). Therefore, a link between the IFN signaling and/or metabolism with proper APM component expression was postulated. So far, there exists no information whether the altered energy metabolism affects APM components, which might be an interesting topic to investigate. In order to test the association of IFN signaling with APM components, human melanoma cell lines were screened for the loss of the IFN-γ inducibility of MHC surface antigens [40]. Indeed, some melanoma cells lack IFN-γ inducibility of MHC molecules. To characterize the mechanisms of IFN resistance, the expression and function of diverse IFN-γ signal transduction pathway components was analyzed. Upon IFN-γ-binding to its specific receptors, a number of proteins were induced including the janus kinase (JAK)1, JAK2 and the signal transducer and activation (STAT)1. A loss of IFN-γ, but not of IFN-α and tumor necrosis factor (TNF)-α inducibility of MHC class I antigens, was found in melanoma cells, suggesting that the lack of IFN-γ inducibility of MHC class I molecules was not due to defects in APM component expression. The IFN-γ resistance in these melanoma cells was caused by a deletion of the JAK2 gene on chromosome 9, whereas upstream and downstream genes were still present and expressed. The loss of JAK2 not only resulted in the lack of JAK2 mRNA and protein expression, but was also directly associated with a downregulation of constitutive APM component expression as determined for TAP1, TAP2, tapasin as well as β_2-m [35]. JAK2 overexpression into the JAK2-deficient melanoma cells upregulated MHC class I surface expression as well as basal APM component expression and also restored their IFN-γ inducibility. Vice versa treatment of cells with JAK2 inhibitors as well as with JAK2-specific shRNA resulted in a downregulation or loss of HLA class I antigens as well as APM component expression.

In vitro models of oncogenic transformation as suitable tools for analyzing the mechanisms of deficient APM component expression

In order to characterize the molecular mechanisms of transcriptional regulation of APM components and MHC class I abnormalities, oncogene-transformed cells served as models. Downregulation of MHC class I surface antigens was found upon mos-, myc- and ras- as well as HER-2/neu-mediated transformation of murine and/or human cells, which is accompanied by an impaired APM component expression [41–45]. However, MHC class I surface expression could be restored by IFN-γ treatment in these cases. The mechanisms of this oncogene-mediated downregulation could be due to a dysregulation mediated by specific factors and/or repressors modulating the APM component expression. HER-2/neu belongs to the epidermal growth factor (EGF) receptor family (HER-1, -2, -3, -4), has receptor tyrosine kinase activity and represents the preferred dimer partner of the different HERs. So far, no soluble ligands for HER-2/neu have been identified. HER-2/neu is physiologically expressed in epithelial cells, whereas gene amplification and/or overexpression of HER-2/neu occurs in solid tumors, such as breast, lung and colon carcinoma and is often associated with disease progression, poor patients' outcome and impaired cell recognition [46]. The HER-2/neu-mediated transformation of murine fibroblasts not only caused an enhanced proliferation, development of foci, anchorage-independent cell growth and tumor formation, but also suppressed MHC class I surface antigens, which is mediated by a transcriptional downregulation of various APM components [43]. Furthermore, an inverse correlation of HER-2/neu and MHC class I APM component expression was found upon analysis of HER-2/neu$^+$ versus HER-2/neu$^-$ mammary carcinoma lesions. These data were confirmed by shRNA-mediated downregulation of HER-2/neu in human tumor cells, resulting in an increased APM component and MHC class I surface expression [47].

So far, transcriptional regulators of the APM have been not well characterized. The role of PML controlling APM expression is controversially discussed [48], although a concordant regulation of PML and HLA class I antigens was described in prostate cancer [49]. Analysis of the activity of wild-type and mutant APM promoters in HER-2/neu$^-$ and HER-2/neu$^+$ cells revealed a downregulation of the activity of the various APM promoters in the presence of HER-2/neu. Regarding the tapasin promoter activity, a mutation of the p300 and E2F1 restored the HER-2/neu-mediated suppression of tapasin promoter activity to levels excluding that of HER-2/neu$^-$ cells. Thus, both transcription factors appear to be important for the HER-2/neu-mediated tapasin downregulation [50]. These data were further confirmed by a siRNA approach inhibiting E2F1, which was accompanied by an upregulation of tapasin expression and consequently also MHC class I surface antigen expression [50]. E2F1 is a member of the large E2F family of highly redundant transcription factors and is often overexpressed in human tumors of distinct histologies. This is further associated with an aberrant cell cycle progression since E2F1 targets genes involved in cell cycle regulation. Our recent data postulated a link between cell cycle control and MHC class I surface expression. However, in order to

support and confirm that an altered cell cycle progression might play an important role in tumor-associated down-regulation of MHC class I APM component expression, combined analyses of cell cycle phases with MHC class I APM molecules should be performed.

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Conflict of interest The authors declare that they have no conflict of interest.

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