Cancer Immunology, Immunotherapy (2019) 68:1689–1700
https://doi.org/10.1007/s00262-019-02373-1

FOCUSSED RESEARCH REVIEW

Tumor-induced escape mechanisms and their association with resistance to checkpoint inhibitor therapy

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Received: 7 February 2019 / Accepted: 28 July 2019 / Published online: 3 August 2019

Abstract
Immunotherapy aims to activate the immune system to fight cancer in a very specific and targeted manner. Despite the success of different immunotherapeutic strategies, in particular antibodies directed against checkpoints as well as adoptive T-cell therapy, the response of patients is limited in different types of cancers. This attributes to escape of the tumor from immune surveillance and development of acquired resistances during therapy. In this review, the different evasion and resistance mechanisms that limit the efficacy of immunotherapies targeting tumor-associated antigens presented by major histocompatibility complex molecules on the surface of the malignant cells are summarized. Overcoming these escape mechanisms is a great challenge, but might lead to a better clinical outcome of patients and is therefore currently a major focus of research.

Keywords Tumor · Immune escape · MHC · Immunotherapy · Resistance · TIMO XIV

Abbreviations

DAC	5-Aza-2′-desoxycytidine
3′ UTR	3′ Untranslated region
ACT	Adoptive cell therapy
APM	Antigen processing and presentation machinery
BGN	Biglycan
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T-lymphocyte associated protein-4
DCN	Decorin
ER	Endoplasmic reticulum
ERAP	Endoplasmic reticulum aminopeptidase
EBV	Epstein–Barr virus
GAS	Gamma activated site
HC	Heavy chain
HNRNPR	Heterogeneous nuclear ribonucleoprotein R
HCMV	Human cytomegalovirus
iCP	Immune checkpoint
iCPI	Immune checkpoint inhibitor
im-miRNAs	Immune modulatory miRNAs
ILT	Inhibitory receptor Ig-like transcript
IFN	Interferon
IRF	Interferon regulated factor
ISRE	Interferon-sensitive response element
LOH	Loss of heterozygosity
Luc	Luciferase
MHC	Major histocompatibility complex
β_2-m	β_2-Microglobulin
miRNA	MicroRNA
MSI	Microsatellite instability
Mex	Muscle excess
MDSC	Myeloid-derived suppressor cells

This paper is a Focussed Research Review based on a presentation given at the Fourteenth Workshop & Symposium "Tumor Immunology meets Oncology" (TIMO XIV), held in Halle (Saale), Germany, 24th–26th May 2018. It is part of a series of Focussed Research Reviews and meeting report in Cancer Immunology, Immunotherapy.

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NLRC5	NOD-like receptor family and acid domain-containing protein 5
OS	Overall survival
Treg	Regulatory T cell(s)
RBP	RNA-binding proteins
RNAseq	RNA sequencing
STAT	Signal transducer and activator of transcription
SNP	Single nucleotide polymorphism
SLRP	Small leucine-rich proteoglycan
TPN	Tapasin
TCGA	The Cancer Genome Atlas
TGF-β	Transforming growth factor β
TAP	Transporter associated with antigen processing
TAF	Tumor-associated fibroblast(s)
TAM	Tumor-associated macrophages
TAN	Tumor-associated neutrophil(s)
TMB	Tumor mutational burden
TME	Tumor microenvironment

Introduction

During the last decade, different immune escape strategies of tumors have been characterized (summarized in Fig. 1), which include changes in soluble and physical factors of the tumor microenvironment (TME), in the expression of immune modulatory molecules of tumor cells as well as in the cellular composition and activity of tumor infiltrating and peripheral immune cells. While in tumor patients, the frequency and functionality of immune effector cells are often downregulated in the peripheral blood and also in the tumor infiltrate, immune suppressive cells, such as regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAM), tumor-associated neutrophils (TAN) and tumor-associated fibroblasts (TAF), are often upregulated in their frequency. In addition to the cellular composition, soluble and other factors of the TME including immune suppressive cytokines, metabolites, hypoxia and a lowered pH are involved in the immune escape. Moreover, tumor cells often downregulate major histocompatibility complex (MHC) class I surface

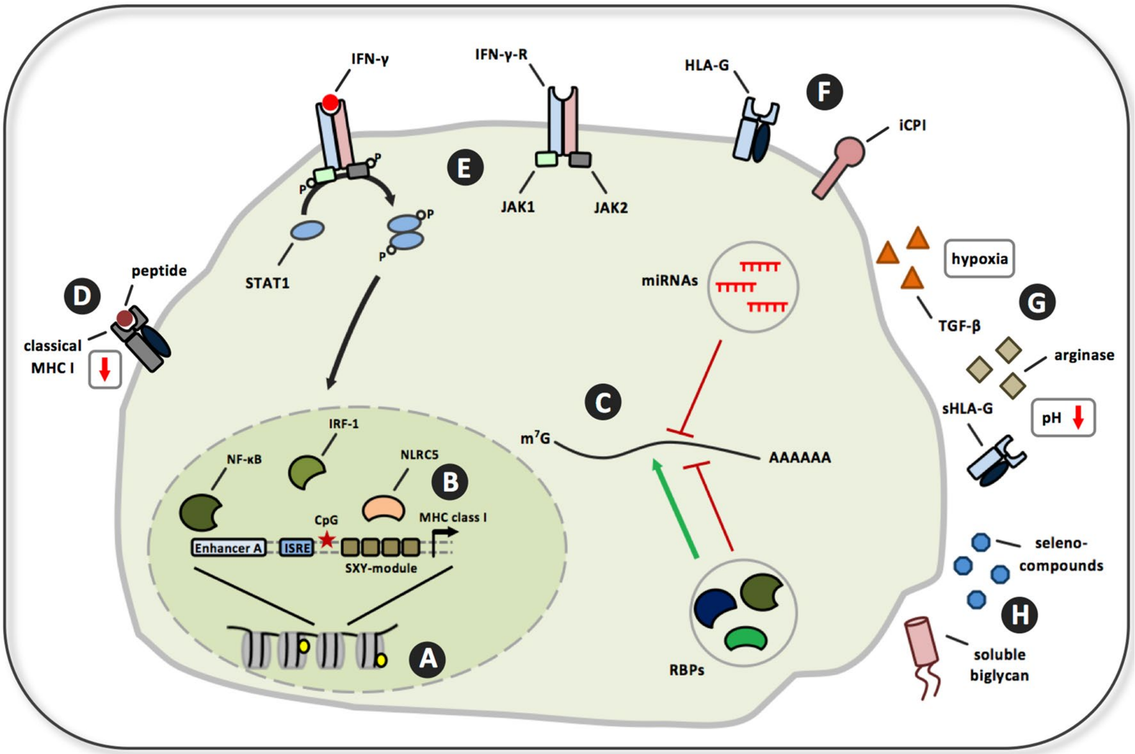

Fig. 1 Tumor escape mechanisms. Different immune escape strategies of tumors discussed in the review are depicted. The figure shows mechanisms based on **a** epigenetic modifications (e.g., histone acetylation, DNA methylation); **b** regulation at the transcriptional level (e.g., for MHC class I, selected transcription factors and promoter motifs are shown); **c** post-transcriptional regulation by miRNAs or RBPs; **d** reduced classical MHC class I surface expression; **e** impaired IFN-γ signaling pathway; **f** expression of immune inhibitory molecules and/or **g** establishment of an immunosuppressive TME. **h** Novel factors identified in the regulation of MHC class I surface expression

antigens as well as components of the antigen processing and presentation machinery (APM) and of the interferon (IFN) pathway. In contrast, the expression of non-classical MHC antigens, immune checkpoints (iCPs), components of oncogenic signaling and cellular metabolism pathways are frequently increased in cancer cells. These changes result in a reduced immune surveillance of tumors associated with tumor progression, poor patient prognosis and survival.

Characteristics of the MHC class I antigen processing and presentation pathway

The so far best characterized escape mechanisms of tumors are abnormalities of the MHC class I APM components, which consist of four major steps [1]: the peptide generation from intracellular proteins—including tumor antigens—is mainly mediated by the multi-catalytic proteasome complex that yield a peptide with a correct C-terminus, whereas the N-terminus can be generated via further trimming, by cytosolic as well as endoplasmic reticulum (ER)-resident aminopeptidases (ERAP) [2, 3]. Cytosolic peptides with a length of 8-12 amino acids are then transported in an ATP-dependent manner, via the transporter associated with antigen processing (TAP) 1 and 2 subunits into the ER, where they bind to MHC class I molecules. The MHC class I heavy chain (HC) and β_2-microglobulin (β_2-m) assemble in the ER, which is assisted by various chaperones, such as calnexin, calreticulin and ERP57. The chaperone tapasin (TPN) facilitates the peptide loading onto MHC class I molecules by interaction with TAP. The trimeric complex of peptide/MHC class I HC/β_2-m complex is then transported via the trans Golgi to the cell surface and there exposed to CD8$^+$ cytotoxic T lymphocytes (CTL) [4, 5].

Deficiencies of classical MHC class I surface expression and their clinical relevance

Defects in the expression of MHC class I APM components could occur at each step of this pathway thereby affecting MHC class I surface expression. However, their frequency highly varies ranging between 15 and 80%. A tumor-dependent downregulation of MHC class I APM components has been suggested, which was more pronounced in metastasis when compared to primary lesions [1]. This had clinical relevance, since it could be correlated with a poor prognosis, a reduced overall survival (OS) of patients and impaired T-cell responses. In silico analyses of samples from The Cancer Genome Atlas (TCGA) as well as RNA sequencing (RNA-seq) data obtained from biopsies demonstrated an altered immune landscape in tumors. High levels of T-cell infiltration were associated with high expression levels of HLA class I APM components induced by the IFN-γ, which is produced by activated T cells within the tumor [6–8].

The non-classical HLA-G as an important mediator of immune escape

Within the group of non-classical MHC class I antigens, HLA-G is the most widely investigated one, since it is normally expressed in a highly restricted way and de novo induced in many tumors of distinct origin [9]. The frequency of HLA-G expression in tumor types is controversially discussed: While the basal expression of HLA-G appears not a frequent event in some solid tumors and hematopoietic malignancies [10–12] and cannot be upregulated by IFN-γ treatment or during transformation [13–15], other studies demonstrated high levels of HLA-G expression in tumors of distinct origin. For example, HLA-G protein expression was detected in 67% of patients with hepatocellular carcinoma [16] and in up to 75% of lung cancer cases [17] using Western blot analysis or immunohistochemistry, respectively. In both cases, the HLA-G expression was associated with a reduced patients' outcome. Thus, it exhibits a highly variable expression among tumor types with a marked inter- and intra-tumorigenic heterogeneity [18, 19]. HLA-G has the ability to inhibit immune cell activation by binding to inhibitory receptors, e.g., the Ig-like transcripts (ILT)-2, ILT-4 and KIR2DL4 suggesting that HLA-G expression is a potential tumor-driven immune escape mechanism [20] and might represent a novel target for immunotherapy [19].

HLA-G in tumor cells is localized on the cell surface; it can be secreted by generation of alternatively spliced isoforms and by shedding and/or incorporated into exosomes. Immune suppression is mediated by binding to inhibitory receptors expressed on NK cells, T and B lymphocytes as well as on antigen-presenting cells. The secreted HLA-G isoform (sHLA-G) plays a crucial role in the establishment of a cancer-promoting TME. In this context, sHLA-G was shown to impair cytotoxic activity of NK and T cells by binding the CD8 co-receptor thereby inducing cell apoptosis [21], whereas the mechanism, by which it modulates the expression of chemokine receptors ultimately affecting chemotaxis and cytokine secretion has not yet been characterized. In addition, HLA-G was shown to antagonize activating signals delivered to NK cells by, e.g., MICA, thus favoring tumor progression [22]. Furthermore, sHLA-G inhibits the fibroblast growth factor 2-induced capillary-like tubule formation hampering angiogenesis in vivo [23]. The important role of HLA-G [24, 25] is further supported by the fact that HLA-G levels are highly variable among tumors and even distinct sections of the same tumor show great heterogeneity, which is linked to the patients' outcome [9]. Since HLA-G, in contrast to any other known iCP molecule, is able to inhibit all essential effector cells of anti-tumor responses and is frequently expressed in many tumors, its therapeutic potential as iCPI has been investigated. Using a murine model system, Agaugué et al. demonstrated that the progression of HLA-G-expressing human tumor cells in an immunocompetent host was associated with an impaired innate and adaptive immunity and that a blockade of HLA-G by a specific antibody was able to restore the anti-tumor immunity against HLA-G-expressing tumor cells [26]. Subsequent studies in mice showed that also sHLA-G is sufficient to induce immune evasion of immunogenic tumors in vivo and demonstrates a high potential for HLA-G as a novel target for immunotherapies [27].

Underlying mechanisms of impaired expression of MHC class I molecules and APM components

Malignant transformation and increased oncogenic signaling have been shown to be associated with MHC class I abnormalities in many different tumor entities [28]. Recently, the frequency of defective HLA class I APM component expression and the associated frequency in different types of cancer have been comprehensively reviewed by Cai et al. [29]. A better knowledge of the underlying mechanisms leading to the reduced expression of MHC class I APM components is urgently needed to re-establish the immune-mediated tumor control by reverting the T-cell-based immune escape [30]. Structural alterations, e.g., homozygous deletions, microsatellite instability (MSI), mutations and loss of heterozygosity (LOH) only seldom occur in HLA class I APM components with the exception of HLA class I HC and/or β_2-m in melanoma, colorectal and lung cancer [31–36]. This is also reflected by the analysis of the mutational landscape in metastatic cancers demonstrating genetic abnormalities only for HLA-A (1.2%), calreticulin (0.7%) and β_2-m (14%), while no alterations of the other HLA genes and APM components were observed [31, 37].

In contrast, deregulation of MHC class I components at the epigenetic, transcriptional as well as post-transcriptional level have been often described and will be addressed below [38–40].

Epigenetic regulation of MHC class I molecules and APM components

While genetic abnormalities appear to be very rare, epigenetic control mechanisms regulating MHC class I as well as APM component expression have been frequently detected. DNA methylation, the best characterized epigenetic process, plays an essential role in modulating the expression of MHC class I and APM components [41]. Treatment with the demethylating agent 5-aza-2′-desoxycytidine (DAC) resulted in an upregulation of HLA class I molecules and APM components (e.g., HLA-A/-B/-C/-G, TAP-1/-2, LMP-2/-7) in numerous independent studies [42–45]. This modification could occur either directly on CpG islands, which are present at a variable frequency in the promoter region of some of the mentioned genes (see Table 1) or indirect via demethylation of putative transcription factors, binding to the promoters of the MHC class I APM components. Although a direct methylation of CpG sites in the promoter of APM components is not frequently detected, the importance of DNA methylation is underlined by the link of a single nucleotide polymorphism disrupting a CpG site (TpG) in the promoter sequence of HLA-A24 with an increased HLA expression [46]. Furthermore, DNA methyltransferases (DNMTs), in particular DNMT1 are responsible for the observed upregulation of HLA class I and APM molecules [47].

An additional mechanism affecting MHC class I and APM component expression levels in vitro and in vivo consists of the covalent post-translational modifications of histones. Indeed, histone deacetylase inhibitors (HDACs) including trichostatin A and valproic acid induced the expression of classical MHC class I antigens, various proteasomal subunits (LMP-2/-7), TAP1/TAP2 and TPN in melanoma [48, 49]. In particular, an increased acetylation of the histone H3 in the promoter region correlates with higher expression of APM genes [50]. Next to histone acetylation, the removal of the methylation repression mark on histone H3 (H3K27me3) was demonstrated to be crucial for

Table 1 Analyses of the promoter sequences (~1500 bp 5′ of start ATG) for IFN-γ responsive elements and CpG regions (according to [138]) of APM components and HLA molecules

Gene symbol	GAS sites	ISRE sites	CpG islands
β_2-m	3	1	0
CALR	1	0	1
CANX	2	0	1
ERAAP	3	0	1
ERP57	1	0	2
HLA-A	3	0	0
HLA-B	3	0	0
HLA-C	2	0	0
HLA-E	4	0	0
HLA-G	3	0	0
LMP2	2	1	1
LMP7	7	0	0
LMP10	2	0	0
TAP1	1	1	2
TAP2	1	0	0
TPN	4	0	1

the induction of MHC class I antigens [50]. Noteworthy, IFN-γ appears to act as an epigenetic modifier by mediating DNA demethylation in combination with increased histone H3 acetylation to upregulate the expression of MHC class I and APM components [42]. Another section of this review will discuss the importance of the IFN signaling on MHC class I regulation (see: role of the interferon pathway for impaired MHC class I expression).

The epigenetic mechanisms controlling components of the classical MHC class I APM pathway also affect the expression of HLA-G. Treatment of distinct HLA-G negative tumor cells with DAC restored HLA-G transcription due to direct demethylation of the HLA-G promoter [51]. Furthermore, an altered methylation pattern of HLA-G specific miRNAs is involved in regulating HLA-G expression. In addition, histone acetylation modifications have also been implicated in the epigenetic control of HLA-G [52].

Transcriptional regulation of MHC class I molecules and APM components

The constitutive and cytokine-regulated expression of MHC class I genes and APM components have been well defined and are controlled by specific regulatory elements as well as genetic regions, which are shared between their promoters and have been summarized by van den Elsen [53, 54]. While the core promoter elements contribute to the general transcriptional control of basal, tissue-specific and cytokine-regulated gene expression [55], its initiation is a dynamic, cell and microenvironment dependent process. Important *cis*-regulatory elements are the enhancer A [56], the IFN-stimulated regulatory element (ISRE) [57], the gamma-activated site (GAS) and the SXY module [58], which are bound by NF-κB, and the interferon regulatory factor (IRF)1.

These conserved regulatory elements play an important role in the inducible and constitutive expression of MHC class I genes [59] and are also involved in the transcriptional activation of components of the MHC class I APM pathway [53, 58–60]. Furthermore, different factors like PML and E2F1 have been suggested to control the transcription of different major MHC class I molecules and APM components including TPN [61, 62]. MHC class I genes and the major APM components could be regulated by IFN-γ, IFN-α, TNF-α and IL-10, which might further explain the differential MHC class I APM expression pattern in distinct tissues [63–69]. IFN-driven activation of the signal transducer and activator of transcription (STAT1 or 2) and IFN regulatory factor (IRF)9 [67, 68, 70] induce the expression of proteases responsible for antigen processing, such as the immunoproteasome, ERAP1 and chaperones of the peptide loading complex (PLC), like TPN [66, 68, 71, 72].

In 2010, the IFN-inducible nuclear protein NOD-like receptor family and acid domain-containing protein 5 (NLRC5) was identified as the key regulator of MHC class I transcription by cooperating with the transcription factor RFX under steady-state conditions [73]. Interestingly, NLRC5 is also required for the induction of the expression of β_2-m, TAP, and LMPs, which are essential for MHC class I antigen presentation. These data suggested that NLRC5 orchestrates the concerted expression of critical components in the MHC class I pathway [73].

Due to a number of imperfect gene duplications [74], the sequence and structure of MHC class I promoter regions are highly similar and represent the basis to their relatively uniform regulation. However, the tolerogenic HLA-G molecule is an exception, since its physiologic expression is restricted to fetal trophoblast cells, cornea, testis, and thymic epithelium suggesting an alternative transcriptional control. Interestingly, HLA-G regulation is characterized by a number of unusual features, which guarantee a restricted expression. While encoding similar regulatory elements in its 5′ DNA region, HLA-G is not regulated by the upstream ISRE, NF-κB sites or the SXY regulatory module [75], its promoter is trans-activated by the cyclic-AMP response element-binding protein (CREB)-1 [76]. In contrast, the transcriptional repressor of HLA-G the Ras-responsive binding protein-1 remodels the chromatin of the HLA-G locus by its interaction with subunits of the CtBP complex in cells lacking HLA-G expression [77].

Post-transcriptional gene regulation of MHC class I molecules and APM components

Though the knowledge about the regulation of MHC class I molecules has increased during the past years, the understanding about the post-transcriptional control is still quite limited. However, key players of the post-transcriptional gene regulation, particularly RNA-binding proteins (RBP) and microRNAs (miRNA), have been recently identified and their altered expression has been shown to contribute to the immune escape of tumor cells [78]. As already described above, functional and stabilized MHC class I surface molecules require the intracellular loading of peptides usually derived from proteolytic degradation [1]. This multistep process is executed by numerous APM components and their deregulation has significant effects on the MHC class I surface expression [79] and subsequently on the recognition of the tumor cells by $CD8^+$ CTL.

A number of immune modulatory miRNAs (im-miRNAs; see also Table 2) was identified using distinct experimental strategies including in silico prediction, miRNA arrays, small RNA-seq, RNA affinity approaches and luciferase (luc) reporter assays. Among them, members of the miR-148/-152

Table 2 Post-transcriptional regulators of HLA molecules and APM components

Target mRNA	miRNA/RBP	References
CALR	miR-455	[139]
	miR-27a	[140]
	miR-1275	[141]
ERAAP	miR-US4-1 (CMV)	[91]
ERP57	miR-148a	[142]
HLA class Ia	HNRNPR	[94]
HLA-A	miR-148a	[143]
	miR-181a	[144]
	Mex3b	[92]
	Mex3c	[93]
	Syncrip	[145]
HLA-B	miR-148a	[143]
HLA-C	miR-148a	[143]
	miR-9	[88]
	miR-148a	[80]
HLA-E	miR-376a(e) [ADAR1 edited miR-376a]	[146]
HLA-G	HNRNPR	[147]
	miR-148/-152	[81]
	miR-152	[82]
	miR-133	[86]
	miR-548q	[83]
	miR-628-5p	[83]
LMP7	miR-451a	[148]
TAP1	miR-346	[89]
TAP2	miR-BHRF1–3 (EBV)	[90]
	miR-125a-5p	[143]
	miR-1270	[149]

family were shown to post-transcriptionally regulate HLA-C as well as the non-classical HLA-G [80–85]. Nucleotide variations within the 3′ untranslated region (3′UTR) of HLA-C regulate miR-148a binding and directly correlate to surface expression. In addition, the existence of the miR-148a-binding site is closely linked to the −35 single nucleotide polymorphism (SNP), known to link the control of HIV and HLA-C surface expression [80]. Binding of miR-148/-152 to the 3′UTR of HLA-G downregulates its mRNA expression level and its translation. This was accompanied by an altered immune cell infiltration in solid tumors and a reduced anti-tumoral immune response by inhibiting the interaction between HLA-G and ILT2/4 on immune effector cells [86]. Furthermore, our own unpublished data also point to a direct interaction of miR-148/-152 with the HLA-A transcript increasing the number of immune modulatory targets (e.g., B7-H1 [87]) for this miRNA family.

Next to MHC class I molecules, a number of im-miRNAs regulating APM component expression have recently been identified. The mimic-based overexpression of the tumor suppressive miR-9 in nasopharyngeal carcinoma upregulated many well-known IFN-induced genes, like TAP1, β_2-m, proteasome subunits (e.g., LMP7, LMP10), classical (e.g., HLA-B, HLA-C) and non-classical HLA class I molecules (e.g., HLA-F) [88], but the underlying mechanisms of this deregulation are still unknown. In addition, overexpression of the ER stress-induced miR-346 in Calu-3 and HeLa cells resulted in reduced TAP1 mRNA levels, which correlated with decreased expression of MHC class I surface antigens [89].

However, it is noteworthy that only a limited number of miRs binding and affecting the function of MHC class I APM in tumors has been identified. More information is available for pathogens utilizing miRNAs to evade immune recognition. In this context, the Epstein–Barr virus (EBV)-derived miR-BHRF1–3 has been reported to directly target TAP2 and indirectly reduce HLA class I surface expression, which results in the inhibition of recognition and killing of infected B cells by EBV-specific CD8$^+$ T cells [90]. Additionally, the human cytomegalovirus (HCMV)-encoded miRs are able to control the expression of immune modulatory molecules. For example, the HCMV-encoded miR-US4-1 targets ERAP1 thereby affecting the CD8$^+$ T cell responses [91].

The interaction of RBPs with their target mRNA can post-transcriptionally influence the biogenesis, stability, function, transport and cellular localization of the mRNA. Regarding RBPs, the association of HLA-A with members of muscle excess (Mex)-3 RNA-binding family is probably best analyzed. Huang et al. described a strong correlation of Mex3B with the resistance to cancer immunotherapy in melanoma. This is mediated by the binding of Mex3B to the 3′UTR of HLA-A that in turn leads to the destabilization of the mRNA and thus to a decreased HLA-A surface expression in tumor cells [92]. Another member of this RBP family, namely Mex3C, is responsible for the post-transcriptional and, importantly, allotype-specific regulation of MHC class I antigens. Binding of Mex3C to the 3′UTR of HLA-A2 mRNA induces its RING-dependent degradation and links ubiquitination with mRNA degradation [93].

Recently, we identified the first positive post-transcriptional regulator for MHC class I antigens. The heterogeneous nuclear ribonucleoprotein R (HNRNPR) binds to the 3′UTR of classical and non-classical MHC class I molecules and positively correlates with the expression of all HLA subtypes. Consequently, the knockdown of HNRNPR reduces the expression of specific HLA-C subtypes and therefore increases NK cell-mediated lysis [94]. However, the specific binding site of HNRNPR or putative interaction partner(s) is currently unknown.

So far, there is no proven interaction of RBPs with the mRNAs of APM components illustrating the need to further investigate the post-transcriptional regulation of APM components. Table 2 lists the so far known interactions of miRNAs and RBPs with MHC class I molecules and APM components in tumors.

Role of the interferon pathway for impaired MHC class I expression

Interferons (IFNs) are pleiotropic cytokines, which exhibit anti-viral and, importantly, immune modulatory properties. While type I and type III IFNs have mainly been involved in the host–pathogen interaction, type II IFN plays a key role in host immune responses and in tumor immune surveillance by stimulating anti-tumor immunity and promoting tumor cell recognition and elimination [95–97]. Upon binding to the IFN-γ receptor (IFN-γ-R), which is composed of the IFN-γ-R1 and IFN-γ-R2 chains, both subunits oligomerize and activate the Janus-activated kinase (JAK)1 and JAK2. This leads to the phosphorylation of STAT1 [98], which homodimerizes and forms a complex γ-factor [99]. Upon translocation of this complex to the nucleus and binding to GAS located at the promoters, the transcription of the primary IFN response genes, such as IRF1, is increased followed by its binding to ISRE and enhanced transcription of secondary IFN response genes, which are in particular responsible for the different immune modulatory functions of IFN-γ [100, 101]. It is noteworthy that the suppressor of cytokine signaling proteins negatively interferes with the IFN-γ pathway by inhibiting the phosphorylation of JAKs and STAT1 [102].

The IFN-γ signaling pathway coordinates different biological responses involved in host defense and immune surveillance and has been recently summarized by Castro et al. [103]. One major effect of IFN-γ is the upregulation of the MHC molecules and components of the MHC class I and class II pathway, TAP1/2, TPN, ERAP 1/2, the invariant chain, CIITA and the expression and activity of proteasome subunits. Thus, IFN-γ initiates an immunogenicity program in target cells [104, 105], which ensures their recognition by immune effector cells.

However, some tumor cells and murine tumor models are insensitive to IFN-γ treatment, which is frequently due to mutations in the IFN-γ pathway [96]. Furthermore, IFN-γ-R-deficient tumor cells have been shown to grow aggressively in immune competent as well as in IFN-γ-R-deficient mice. In contrast, transfection of the IFN-γ-R subunits into tumor cells led to an increased immunogenicity and a reduced tumor growth. Approximately, 30% of human tumor cells exhibit reduced IFN-γ sensitivity as a result of an impaired expression in the different components of the IFN-γ signaling pathways, like the IFN-γ-R or JAKs. Furthermore, JAK1/2 deficiencies found in melanoma and chronic myeloid leukemia cells protect tumor cells from anti-tumor IFN-γ activity, which results in resistance to T-cell responses. In addition, a JAK2 deletion detected in melanoma cells caused IFN-γ resistance, and reduced basal MHC class I expression, which could be restored by JAK2 overexpression [106]. These results suggest that the IFN-γ pathway is often impaired in tumor cells and plays a key role in constitutive as well as IFN-γ-induced MHC class I expression thereby altering tumor immunogenicity [107].

Novel factors involved in MHC class I deficiencies

In addition, other factors of the TME appear to be involved in modulating MHC class I antigens. These include, for example, family members of the small leucine-rich proteoglycans (SLRP), which are constituents of the extracellular matrix (ECM) and contain one or more glycosaminoglycan chains. However, so far their anti-tumor activity has been not well characterized [108]. We were able to show that the SLRP family member biglycan (BGN) is strongly downregulated upon oncogenic transformation [109, 110] and that restoration of BGN expression in these oncogenic transformants leads to an upregulation of MHC class I expression due to induction of various APM components [111]. Similar results were obtained by adding recombinant BGN to tumor cell lines. This was accompanied by an enhanced expression of another SLRP family member, namely decorin (DCN). In contrast, inhibition of BGN expression by shRNA reduced MHC class I surface expression.

BGN expression decreased the levels of the transforming growth factor (TGF)-β and its receptor (TGF-β-R), while the TGF-β inhibitor SB431542 enhanced BGN expression in HER-2 transfectants. In vivo BGN transfectants had a reduced capability to form tumors that were also of smaller size. Interestingly, BGN-positive tumors exhibit an increased T cell infiltration. These results were not only confirmed in murine oncogenic transformed cells, but also in oncogenic transformants of human melanoma cells [111]. Thus, oncogenic transformation modulates the proteoglycan signature leading to a downregulation of BGN as well as DCN expression and subsequently to the activation of the TGF-β pathway. These data were further validated by in silico analyses of TCGA data demonstrating a direct association of BGN expression with patients' survival suggesting a prognostic relevance [112].

Selenium, a fundamental element in the human diet, has been shown to be involved in the intracellular redox balance and has been suggested to have anti-carcinogenic effects in different tumor types [113–115]. Selenocompounds function either as anti-oxidants or by altering the expression levels of genes involved in cancer development. Selenium metabolites could affect three hallmarks of cancer, in particular apoptosis, angiogenesis as well as immune responses. This is in line with an enhanced MHC class I surface expression due to a transcriptional increase of major components of the APM and IFN signaling pathways [116]. Furthermore, the antioxidative response system could be linked to MHC class I antigen processing [117]. Thus, selenium might affect the malignant phenotype by reverting the MHC class I-mediated immune escape and partially mimicking the IFN-γ signaling suggesting that selenocompounds might be also used in combination with immunotherapies.

Resistance to immune checkpoint inhibitor therapy—association with MHC class I abnormalities

Tumor immunotherapy strategies, such as adoptive cell transfer (ACT) and more recently immune checkpoints inhibitors (iCPI), have entered the cancer treatment and improved the outcome of cancer patients [118–121]. However, the number of patients/cancer types that profit from such approaches is still limited and further reduced by the development of resistances to these therapies resulting in tumor relapse [122]. Thus, despite the clinical successes have highlighted the potential of these approaches, a more complete understanding of the immune regulation is critical for the development of new therapeutic strategies [123]. To improve patients' stratification with respect to therapy selection, responding and non-responding patients are being characterized using different molecular, immunologic and biologic approaches to identify biomarkers that predict responsiveness to therapy as well as to characterize the mechanisms of either primary or acquired resistance therapy (summarized in Fig. 2).

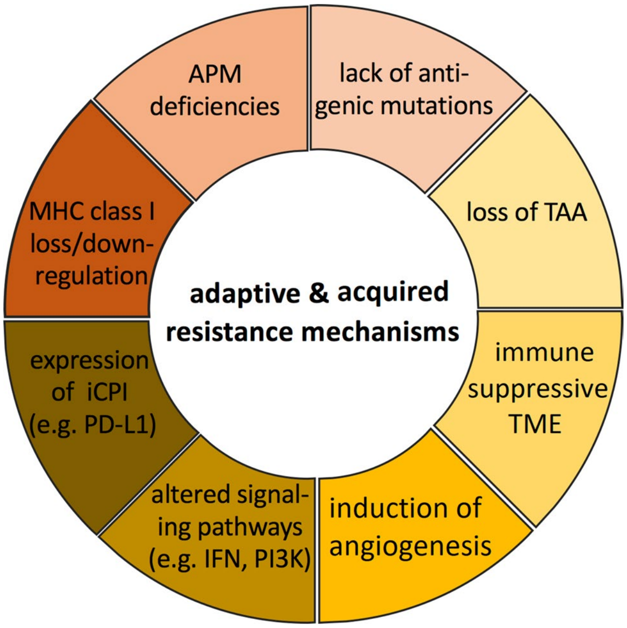

Fig. 2 Resistance mechanisms to cancer immunotherapy. The schematic diagram summarizes the main mechanisms involved in adaptive and acquired resistance to different immunotherapies including iCPI

The expression of MHC class I surface antigens by tumor cells is a potential determinant of the therapeutic success of many immunotherapy approaches [124]. A recent report suggested that a low tumor mutational burden (TMB) and genetic loss of a single HLA allele is associated with iCPI resistance supporting the concept that T cells recognizing very few epitopes may mediate an anti-tumoral response [125]. Different studies have linked responsiveness to immunotherapy with TMB [126] or the presence of defects in the mismatch repair system [127] that leads to MSI. These mechanisms can increase the immunogenicity of the tumor, but can be also responsible for resistance to therapy. In colorectal carcinoma, an enhanced frequency of β_2-m mutations has been only found in the MSI samples [128], while a LOH of β_2-m was detected in metastatic melanoma patients developing resistance to CTLA-4 or PD1 therapy [129]. Similarly, neoantigens characterizing tumors with high TMB can be lost under therapeutic pressure, which results in resistance due to selection of cellular subsets that lack their expression, but also by additional mutational events leading to the loss of the chromosome with the neo-antigen [130].

To characterize the "pattern" of resistance, many laboratories have undergone deep sequencing evaluation of tumor samples detecting mutations in important immunologic pathways. In line with the finding that a transcriptional profile related to IFN-γ genes is predictive for response to PD1 therapy [131], mutations that abrogate this signaling pathway have been identified in resistance [132, 133]. In addition, mutations in the type I IFN pathway have been linked to therapy resistance with anti-CTLA4 [134]. Furthermore, recent work demonstrated that mutations in β_2-m, JAK1 and JAK2 in melanoma cells were associated with resistance to immune checkpoint blockade and could also serve as negative response predictors [132]. However, the mutation frequencies in these molecules were low ranging between 1.8 and 2.6%, but were associated with the TMB.

Next to genetic (i.e., irreversible) alterations, changes in the antigen presentation capabilities of tumors were also detected at the transcriptional level. Analysis of two different patients who developed resistance to ACT and/or PD1 therapy revealed a selective transcriptional downregulation of a specific HLA allele, against which an immune response was directed [135]. This could be potentially reversed by drug therapy. Recently, it has been suggested that in patients with altered antigen processing capabilities due to mutations in APM components, a new antigen repertoire of the so-called "T cell epitope associated with impaired peptide processing" [136] will be presented and could be targeted by therapy.

In addition to "hiding" from recognition, the tumor can resist therapy also by actively suppressing it, for example, by upregulating other checkpoints as has been demonstrated for, e.g., Tim-3 in lung cancer patients treated with anti-PD1 therapy [137]. Thus, targeting alternate immune checkpoints upregulated in the context of PD1 therapy may extend the benefit of these blockades in responsive tumors.

Conclusions

Despite their recent success, immunotherapies fail to control malignancies in a significant number of patients. This might be due to changes in the composition of the TME as well as due to cancer cell autonomous characteristics. This could be explained by either rare structural abnormalities or deregulated expression of components of the MHC class I pathway (Fig. 1). However, little information regarding the molecular mechanisms responsible for MHC class I loss in tumors as well as in metastatic lesions of patients undergoing immunotherapy is available. Therefore, a better knowledge of these tumor intrinsic and extrinsic factors is urgently required and will provide the rationale for novel (immuno)therapies and/or combinations with other treatments, which might lead to increased therapeutic efficacy.

Acknowledgements We would like to thank Maria Heise for excellent secretarial help in preparing the manuscript.

Author contributions Barbara Seliger planned the manuscript. All the authors contributed in writing parts of the manuscript. Michael Friedrich, Simon Jasinski-Bergner, Barbara Seliger discussed the contents, while Michael Friedrich created the figures.

Funding This work was funded by the German Research Foundation (DFG; SE 581/22-1 and RTG, 1591/2-B4), the German Israeli Foundation for Scientific Research and Development (GIF; I-37-414.11-2016), and the Mildred Scheel Foundation.

Compliance with ethical standards

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

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