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REVIEW ARTICLE

The link between MHC class I abnormalities of tumors, oncogenes, tumor suppressor genes, and transcription factors

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Abstract

MHC class I abnormalities, frequently detected in tumors of distinct origins, are often associated with disease progression and/or poor patient survival. The underlying molecular mechanisms of these defects are either mediated by structural alterations of MHC class I antigens and/or components of the antigen processing machinery (APM) or by their deregulation, which could occur at the transcriptional, post-transcriptional, and/or epigenetic level. Recently, it has been identified that signal transduction pathways, oncogenes, and putative tumor suppressor genes play an important role in controlling the expression of MHC class I APM components in tumor cells. In addition, their expression could be modulated by various factors of the tumor microenvironment, like changes in the pH level, in the metabolism, as well as due to hypoxic conditions. The increased knowledge of MHC class I defects could be employed for (i) the selection of patients undergoing immunotherapies and for (ii) the design of novel therapeutic approaches leading to an induction of MHC class I surface expression, which might enhance the anti-tumor immune response.

Keywords

MHC, oncogenes, transcription factors, tumor, tumor suppressor genes

History

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The features and function of the MHC class I antigen processing and presentation

Under physiologic conditions, either lysosomal or ubiquitin-proteasome pathways are used to degrade cellular proteins. While the lysosomal pathway degrades proteins in particular bacteria, bacterial antigens, and parasites taken up by endocytosis and by autophagy, the ubiquitin-proteasome pathway is mainly involved in degradation of intracellular-derived proteins including regulatory proteins, mis-folded, or ubiquitin-conjugated proteins, mutated and viral proteins (Jensen, 2007; York et al., 1999). The peptides generated by the ubiquitin-proteasome pathway and other cytosolic peptidases are presented by MHC class I molecules to $CD8^+$ cytotoxic T-lymphocytes. In this context, it is noteworthy that peptides derived from normal cellular (self) proteins are ignored by $CD8^+$ T-lymphocytes, whereas those generated from mutated proteins/from non-self proteins or other intracellular pathogens could be recognized by $CD8^+$ T-lymphocytes, thereby triggering the adaptive immune response.

The peptide generation process via proteasome pathways is initiated by ubiquitiniation of the targeted proteins, which are then processed by the multi-catalytic proteasome complex consisting of constitutive and the interferon (IFN)-γ-inducible low molecular weight proteins (LMP)-2, LMP7, and LMP10. The peptides generated by the proteasome often have a correct C-terminus, but frequently extended N-termini, thus requiring further trimming in a proteasome-independent process by additional cytosolic proteases, such as the tri-peptidyl peptidase II (TPPII), the thimet oligopeptidase (TOP), as well as other enzymes (Rock et al., 2004). In addition, peptides produced in the cytosol could be further trimmed by endoplasmic reticulum (ER)-resident enzymes in order to fit into the MHC class I binding groove. These include the IFNγ-regulated endoplasmic reticulum aminopeptidases (ERAP)1 and 2. In particular, ERAP1 trims peptides (9–16 amino acids in length), with a preference for peptides with a hydrophobic C-terminus (Saveanu et al., 2005).

Furthermore, peptides generated by both proteasome-dependent and independent pathways are transported from the cytosol into the ER by the heterodimeric transporter associated with antigen processing (TAP) consisting of the TAP1 and TAP2 subunits. The peptide transport mediated by TAP is length- (8–12 residues) and sequence-specific as well as ATP-dependent. Newly-synthesized MHC class I heavy chain (HC) molecules are transported into the ER and stabilized by the chaperone calnexin (CALX), which facilitates its folding and interaction with β_2-microglobulin (β_2-m). This leads to a release of CALX, stabilization of this heterodimer by calreticulin (CALR), and then the loading of peptides. In the ER, the transported peptides are loaded onto the MHC class I HC molecules in the so-called peptide loading complex (PLC) consisting of the chaperones CALX, the ER oxidoreductase ERp57, CALR, and tapasin (TPN). After the peptide-loading the PLC is disassembled, in particular by releasing the ER-resident chaperones and TAP, and the trimeric peptide/MHC class I complexes that are then transported via the trans-Golgi network to the cell surface and presented to $CD8^+$ T-lymphocytes (Jensen, 2007).

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Abbreviations

ATCC, American Tissue Culture Collection
APM, antigen processing machinery
CREB, cAMP response element binding protein
BGN, biglycan
β_2-m, β_2-microglobulin
CALR, calreticulin
CALX, calnexin
ER, endoplasmic reticulum
ERAP, endoplasmic reticulum aminopeptidase
ERK, extracellular-signal regulated kinase
HC, heavy chain
IFN, interferon
JAK, Janus kinase
LMP, low molecular weight protein
LOH, loss of heterozygosity
mAb, monoclonal antibody
MAPK, mitogen-activated protein kinase
MEK, MAP kinase kinase
MHC, major histocompatibility complex
STAT, signal transducer and activator of transcription
TAP, transporter associated with antigen processing
TOP, thimet oligopeptidase
tpn, tapasin
TPPII, tri-peptidyl peptidase II
PLC, peptide loading complex; SNP, single nucleotide polymorphisms
TF, transcription factor.

Alterations in MHC class I antigen-processing machinery components in tumor cells

In tumors of distinct histology, defects in the expression and/or function of components of the antigen processing machinery (APM) have been found (Seliger et al., 2006). Both single or multiple deficiencies of APM components have been reported, but their frequency as well as their nature substantially varied between given tumor types, differentiation status, intra-tumoral heterogeneity, as well as their proliferative capacities (Seliger et al., 2000). The molecular mechanisms underlying these defects have been only partially identified thus far (Seliger, 2008). However, for some APM components it has been demonstrated they can occur at the genetic, epigenetic, as well as regulatory, level (Khan et al., 2008; Nie et al., 2001; Sigalotti et al., 2004).

The down-regulation of constitutive, but also IFN-γinducible subunits has been detected in various solid tumors and hematologic diseases. Single nucleotide polymorphisms (SNP) within the LMP2 and LMP7 promoters have been identified in cervical cancer lesions, while other reports demonstrated promoter methylation in some of the LMP. The loss of the IFNγ-mediated up-regulation of LMP2 in renal cell carcinoma (RCC) cells was associated with a lack of the IFN-regulatory factor (IRF)-1 and signal transducer and activator of transcription 1 (STAT1) binding activities as well as of Janus-associated kinase (JAK)-1, JAK2, and STAT1 phosphorylation (Respa et al., 2011). Furthermore, a lack of IFNγ-mediated up-regulation of LMP2 and LMP10 in melanoma cells was caused by a deletion of the *JAK2* gene on chromosome 9.

Despite the fact that low or reduced levels of TAP1 mRNA and/or protein were observed in many tumors, the reduced expression levels were only rarely associated with structural alterations, suggesting a frequent dysregulation of TAP subunits in human tumors. Indeed, both epigenetic mechanisms, such as methylation of TAP promoters, as well as a post-transcriptional down-regulation of TAP1 and TAP2 have been reported. Intriguingly, TAP1 is stabilizing of TAP2 expression; this is supported by the fact that, in the absence of TAP1, TAP2 was degraded by the proteasome. Furthermore, impaired IFNγ signal transduction capacity could be correlated with reduced TAP expression levels.

Regarding the chaperones, in particular structural abnormalities in TPN were detected in tumors (e.g. neuroblastoma), while only rare frameshift mutations have been described in colo-rectal carcinoma and/or gastric carcinoma for CALX, TPN, CALR, and/or ERp57. With a few exceptions, the expression of CALX, CALR, and Erp57 was not altered in most tumor cells when compared to in corresponding normal tissue. In contrast, TPN expression was often reduced in tumors with distinct origin. Even more interestingly, transcriptional down-regulation of TPN – as demonstrated in HER-2/neu over-expressing tumor cells – was directly associated with the over-expression of the transcription factor (TF) E2F1. TPN expression levels could be modulated via E2F1, which can be linked to altering cell proliferation rates – thereby suggesting that expression of MHC class I APM components might be (at least to some extent) regulated in a cell cycle-dependent manner (Bukur et al., 2010). Moreover, reduced MHC class I molecule expression levels could be due to a general, locus, haplotype, or allele-specific deletions. However, the molecular mechanisms underlying these genetic alterations might vary dependent on the given tumor type (Romero et al., 2005). Interestingly, locus-specific down-regulation or even total loss of MHC class I surface expression levels were found upon oncogenic and viral transformation of murine and human cells. In most cases these defects could be restored by IFNγ treatment, suggesting that structural alterations within the coding region of MHC class I HC genes are generally quite rare events. Nevertheless, loss of heterozygosity (LOH) and mutations within the MHC class I HC have been found in some tumors, in particular in melanoma and colorectal carcinoma, but not yet or at a low frequency in RCC.

In addition, factors involved in the transcriptional/post-transcriptional down-regulation of MHC class I APM components have been identified. These include, for example, the cAMP-binding protein CREB, which is activated upon oncogenic transformation and leads in parallel to a down-regulation of MHC class I surface expression levels. This demonstrates a link between oncogenic activation, CREB function, and deficient APM component expression. These results are in contrast to the role of the glycoprotein biglycan (BGN). BGN expression is down-regulated or lost in tumor cells and oncogene-transformed model cell lines. In contrast, high levels of BGN expression were found in normal non-malignant cells, suggesting that, at least in the model cell line systems analyzed thus far, BGN might indeed exert tumor suppressor activity. This is further strengthened by the fact that restoration of BGN expression in tumor cells resulted in up-regulation of MHC class I surface expression levels. In addition, the relative frequencies of tumor formation observed in $CREB^-$ vs $CREB^+$ or BGN^- vs BGN^+ cell lines are clearly distinct and associated with an altered immune cell repertoire, respectively.

Clinical relevance of APM defects

Impaired expression of APM components is of importance, since they have been demonstrated to be associated with tumor progression and the clinical outcome of tumor patients (Mehta

et al., 2008; Tanaka et al., 2012). In melanoma, reduced TAP expression levels were more frequently found in metastatic than in primary lesions and nevi. Moreover, down-regulation of MHC class I surface expression correlates in primary lesions with thickness, advanced disease stage, as well as with shorter time to progression rates. Correlations between MHC class I APM abnormalities and the clinical outcome of patients have not only been described for melanoma, but also for other malignancies including RCC, prostate, cervical, ovarian, and head and neck squamous cell carcinoma (Atkins et al., 2004; Ferris et al., 2006; Kageshita et al., 1999; Mehta et al., 2008; Meissner et al., 2005; Vitale et al., 1998). In prostate cancer, down-regulation of MHC class I molecules did correlate with higher progression rates and early tumor recurrence, which can be further accompanied with reduced or even loss of TAP1 and ERAP1 expression levels (Norell et al., 2006; Seliger et al., 2010). Thus, the characterization of the molecular mechanisms resulting in the down-regulation of APM components in human and murine tumors, as well as in oncogene-transformed cells of distinct origin, is currently still of great interest.

Conclusions

In summary, during the last years some novel molecular mechanisms underlying defects in the regulation of expression of APM components have been identified, thereby shedding more light into both the mechanisms of tumor initiation as well as of tumor progression. This information might also lead to the development of improved personalized immunotherapy approaches, such as targeting the up-regulation of APM components by different cytokines. In the future, further strategies have to be developed, which have to overcome the modulation of the expression levels of APM components in tumor cells *in vivo*.

Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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