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Review

The role of classical and non-classical HLA class I antigens in human tumors

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ABSTRACT

In human tumors alterations in the surface expression and/or function of the major histocompatibility complex (MHC) class I antigens are frequently found and equip neoplastic cells with mechanisms to escape immune control. The aberrant expression of HLA class I molecules can be caused by structural alterations or dysregulations of genes encoding the classical HLA class I antigens and/or components of the HLA class I antigen processing machinery (APM). The dysregulation of APM components could occur at the epigenetic, transcriptional or post-transcriptional level. In some malignancies these abnormalities are significantly associated with a higher tumor staging, grading, disease progression and a reduced survival of patients as well as a failure to $CD8^+$ T cell-based immunotherapies. In addition to HLA class I abnormalities, expression of the non-classical HLA-G antigen is often induced in tumors, which could be mediated by various microenvironmental factors. Interestingly, soluble HLA-G serum and plasma levels have been useful markers for the prediction of some malignancies. The biological consequence of HLA-G expression or sHLA-G is an escape from T and NK cell-mediated recognition. Thus, alterations of non-classical and classical HLA class I antigens and components of the antigen processing pathway provide tumor cells with different mechanisms to inactivate immune responses resulting in tumor growth and evasion from host immune surveillance.

1. Introduction

T cell-based immunotherapy has recently rekindled interest due to convincing data in murine models demonstrating a control of tumor growth [1–5]. In addition, the identification of tumor-associated antigens (TAAs) in different malignancies provide well-defined tools for immunizing patients with neoplasias and for monitoring HLA class I-restricted, TAA-specific T cell responses in vaccinated patients [6–10]. However, the success of these treatment modalities is limited and only in a minority of immunized patients a clinical response was observed without any correlation between T cell response and clinical response [11–15]. These disappointing results have stimulated the interest to define the mechanisms, by which tumor cells escape from immune surveillance. Indeed it has been shown that distinct genetic and phenotypic alterations of tumor cells allow their escape from immune control, which represents a critical step in the progression of human and murine cancers. At the initiation of malignancies tumors express TAA in the context of HLA molecules that could be recognized by the adaptive immune system, while during progression tumors have developed different strategies to evade TAA-specific immune surveillance [13,16–19]. This could be due to alterations in the expression of classical and non-classical MHC class I surface antigens caused by an immune selection process, in which tumor cells with normal HLA class I and lack of HLA-G expression are eliminated. This selection process is dependent on the origin of the tumor as well as on the intensity of immune response of the tumor-bearing host and is followed by an immune escape step resulting in tolerance of tumor cells to immune recognition [13,20,21].

2. Features of the HLA class I antigen processing machinery

A proper constitutive HLA class I surface antigen expression is necessary for the presentation of self/non-self antigens to $CD8^+$ cytotoxic T lymphocytes (CTL) [16,18,22–24]. This is mediated by different molecular processes and involves a number of distinct molecules. The majority of antigenic peptides are generated upon ubiquitination of mainly intracellular proteins followed by

Abbreviations: APM, antigen processing machinery; β_2-m, β_2-microglobulin; CALR, calreticulin; CANX, calnexin; CTL, cytotoxic T lymphocyte; DAC, 5-aza-2′-deoxycytidine; ER, endoplasmic reticulum; ERAP, ER aminopeptidase associated with antigen processing; HC, heavy chain; HCMV, human cytomegalovirus; HDAC, histone deacetylase; HLA, human leukocyte antigen; IFN, interferon; JAK, janus kinase; LMP, low molecular weight protein; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; TAA, tumor-associated antigens; TAP, transporter associated with antigen processing; TPN, tapasin; TF, transcription factor; TFBS, transcription factor binding site; TSA, trichostatin A.

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their degradation via the multicatalytic proteasome complex yielding precursor peptides with a HLA class I compatible correct C-terminus, but an extended N-terminus [25–28]. The activity of the ubiquitin-proteasome pathway could be modified by interferon (IFN)-γ generating the immunoproteasome that contains novel active subunits of the proteasome activator (PA) 28 and the IFN-γ-inducible proteasomal β-subunits, the low molecular weight proteins (LMP)2, LMP7 and MECL1, which can replace their constitutive homologues Y, X, and Z during proteasome assembly [29–31]. The IFN-γ-induced subunits alter the catalytic activity against peptide substrates thereby yielding a different repertoire of HLA class I-presented peptides when compared to that of the constitutive proteasome [32]. These peptides could be further trimmed by different cytoplasmic peptidases, like the bleomycin hydrolase, the leucine aminopeptidase and the tripeptidyl peptidase II. The peptides are then translocated via the heterodimeric transporter associated with antigen processing (TAP)1/TAP2 subunits from the cytosol into the lumen of the endoplasmic reticulum (ER). In the ER the peptides could be further processed by the ER-resident aminopeptidase (ERAP)1 and ERAP2 and loaded onto the newly synthesized β_2-microglobulin (β_2-m)-associated HLA class I heavy chain (HC) with the assistance of the transient interaction with the chaperones calnexin, calreticulin (CALR) and tapasin (TPN). Upon peptide loading the trimeric HLA class I/β_2-m/peptide complex travels via the trans-Golgi to the cell surface for presentation to $CD8^+$ CTL.

Under physiological conditions HLA class I APM components are constitutively expressed in all adult nucleated cells and tissues with the exception of immune priviledged tissues/organs. Furthermore, their expression could be regulated by different cytokines. While, e.g. IFNs are potent enhancers of the majority of these molecules, IL-10 is inhibiting their constitutive expression. This cytokine-mediated regulation of HLA class I APM expression was accompanied by an altered HLA class I surface expression [33].

3. Deficient HLA class I expression in tumors and their clinical relevance

Downregulation or complete loss of HLA class I gene expression has been reported in a variety of human solid and hematopoietic malignancies (Table 1). Immunohistochemical analyses of a large series of tumor lesions have shown defects in HLA class I expression in solid tumors like melanoma, colorectal, bladder, head and neck, breast, lung, kidney, prostate and cervical carcinoma [21,34–36]. The complete lack or downregulation of the HLA class I molecules, selective loss of HLA loci and HLA class I allospecificities ranged between a 3.4% and 60% depending on the tumor (sub)type analyzed. In addition, loss of heterozygosity at the HLA loci is a frequent event in some tumor entities like colorectal carcinoma and melanoma, but not in others, like renal cell carcinoma (RCC) and could therefore contribute to the downregulation of HLA class I antigens in selected tumor types. In this context, it is noteworthy that downregulation of HLA class I components, e.g. HLA-A, was also found in peripheral mononuclear cells of colorectal carcinoma patients. The deficient HLA class I surface expression could be of clinical relevance, since in some tumor types it was associated with tumor grading, staging as well as disease progression and a reduced patients' survival [12,37–40] suggesting that HLA class I abnormalities are unfavorable prognostic predictors of some malignancies. This is in line with the observation that the repression of melanoma metastasis after immune therapy is associated with the activation of antigen presentation and IFN-regulated genes.

4. Underlying mechanisms of altered APM component expression

The molecular mechanisms leading to defects in the HLA class I antigen presentation pathway have been well characterized upon viral infections. The human cytomegalovirus (HCMV) represent one suitable model for viral interference with the HLA class I antigen presentation pathway. For example HCMV encodes at least 4 proteins that impair the antigen processing pathway at different steps from proteasomal degradation to peptide transport, formation of the trimeric HLA class I HC/β_2-m/peptide complex to its transport to the cell surface. Furthermore, many other viruses also interfere with the HLA class I APM [41]. Although only limited information exists about inhibitors of this pathway in human tumors, HLA class I abnormalities have been linked to alterations, which could occur at each step of this process (Fig. 1) [11,14,42–44]. Despite some progress has been made during the recent years in characterizing the molecular mechanisms and functional relevance of impaired HLA class I APM component expression, which will be summarized in the following sections, many fundamental questions still remain unanswered.

4.1. Structural alterations

Inactivating mutations in the human HLA class I HC and β_2-m genes represent important mechanisms, by which tumor cells can escape T cell recognition and lysis. Such mutations have been mainly described in melanoma and in microsatellite instable, but not in microsatellite stable colorectal and gastric cancers [36,45–47]. Thus, microsatellite stable and instable colorectal cancers exert fundamental differences regarding the inactivation of genes involved in the formation of the HLA class I surface complex suggesting a selective pressure for proper antigen presentation [45,46]. In contrast, mutations of other APM components, like TAP1, TAP2, TPN and the proteasomal subunits only rarely occur. So far, structural alterations in these molecules have mainly been found in melanoma, lung and cervical cancer, but e.g. not in RCC [48]. In cervical cancer these abnormalities were also associated with human papilloma virus type 16 and 18 infection [49–52].

4.2. Epigenetic modifications

Epigenetic modifications, like altered histone acetylation or aberrant DNA methylation, represent tumorigenic events that are functionally linked to genetic changes [53–55]. Reexpression of genes altered by epigenetic modifications can be achieved by inhibitors of the histone deacetylation (HDAC) process, e.g. trichostatin A (TSA) and sodium butyrate (NaB) as well as by inhibitors of the DNA methyltransferases, such as 5-aza-2′-deoxycytidine (DAC) or 5-aza-cytidine (5-aza-C). The anti-tumor therapeutic potential of these components have been analyzed in clinical studies and in general target epigenetically silenced tumor suppressor genes [56–58]. Furthermore, the expression of immune active costimulatory/coinhibitory molecules, cytokines and TAA could be directly or indirectly under epigenetic control. Thus, the reversal of the immune escape phenotype of tumor cells could also represent one possible activity, by which epigenetic drugs can inhibit tumor growth. In addition, an impaired HLA class I surface expression mediated by hypermethylation of HLA class I HC and/or β_2-m has been described in some tumors of distinct origin, while DAC resulted in the reexpression of these HLA class I antigens and subsequent restoration of the antigen-specific immune responses after demethylation [59]. Despite epigenetic silencing of the HLA class I promoters have been found in various cancers, an altered methylation status of the promoter DNA of different APM components in particular of the TAP1 and TAP2 subunits, LMP2, LMP7 as well as