Introduction

Malignant tumors, as a genetic disease, are caused by structural alterations of the genome which can give rise to the expression of tumor-associated antigens (TAA) in the form of either structurally altered molecules or of overexpressed normal molecules. TAA may be recognized by the host’s immune system and may induce a T-cell-mediated immune response. Consequently, out-growing cancers develop different strategies to evade potential destruction by the host’s immune system. In particular, immune evasion mechanisms affecting the expression and/or function of human leukocyte antigens (HLA) are of special interest to tumor immunologists, since these molecules play a crucial role in the interaction of malignant cells with immune cells. As summarized in Table 1, the two types of classical HLA antigens, HLA class I and II antigens, share certain similarities, but also substantial differences.

Analyses of tumor cell lines and of large numbers of surgically removed tumor lesions of distinct histology have demonstrated defects in HLA class I surface expression in most of the tumors tested. This was associated with a downregulation or loss of components of the HLA class I antigen-processing machinery (APM) as summarized in Table 1 in solid and hematopoietic tumors; however, the frequency of these defects strongly varied among the different types of cancer. Multiple molecular mechanisms have been shown to underlie these abnormalities, which cause defective synthesis and/or expression of HLA class I antigen/tumor antigen (TA)-derived peptide complexes. The latter mediate the interactions of tumor cells with antigen-specific cytotoxic T lymphocytes (CTL). The functional significance of these defects is indicated by their negative impact on the CTL-mediated elimination of tumor cells. An impaired interaction of immune cells with HLA class I antigen-deficient cancer cells also accounts for the association between defective HLA class I APM component expression in tumors and poor clinical course identified in various types of malignancies. Alterations of HLA class I APM and their significance in malignant tumors have been recently reviewed by various groups and we refer the interested reader to these reviews. In contrast, HLA class II antigens expressed by malignant cells of solid tumors have been characterized only to a limited

## Abbreviations:
- APC: antigen presenting cell
- APM: antigen-processing machinery
- CIITA: class II transactivator
- CLIP: class II associated invariant chain peptide
- CRC: colorectal carcinoma
- CREB: cAMP-responsive element binding protein
- CTL: cytotoxic T lymphocyte
- DAC: 5'-aza-2'-deoxycytidine
- DC: dendritic cells
- ER: endoplasmic reticulum
- GILT: gamma interferon inducible lysosomal thiolreductase
- HLA: human leukocyte antigen
- HNSCC: head and neck squamous cell carcinoma
- HPV: human papilloma virus
- IFN: interferon
- Ii: invariant chain
- MHC: major histocompatibility complex
- MIC: microsatellite instability
- MSI: microsatellite instability
- PADRE: pan-HLA-DR reactive epitope
- RB: retinoblastoma
- RFX: regulatory factor X
- TAA: tumor-associated antigen
- TCR: T-cell receptor
- TSA: trichostatin A
- USF: USF-1, upstream regulatory factor
The increased availability of mAbs recognizing HLA class II APM components during the last few years has greatly facilitated the export of HLA class II molecules from the ER and is responsible for directing the HLA class II complexes into specialized endosomal/lysosomal antigen loading compartments, termed MHC class II containing compartment (MIIC). Here, the li is proteolytically degraded by cathepsin into the 14 amino acid long class II-associated invariant chain peptide (CLIP) occupying the HLA class II peptide-binding groove.16

Exogeneous engulfed proteins delivered into the endosomal/lysosomal network are also exposed to distinct endosomal/lysosomal aspartyl and cysteine proteases including cathepsin S,16 peptidases and reductases, such as the gamma-interferon inducible lysosomal thiol reductase GILT, yielding peptide ligands for HLA class II molecules.17,18 In the MIIC, the exchange of CLIP for such antigenic high-affinity peptides is facilitated by low pH, endosomal proteases and the assistance of the non-classical MHC class II molecule HLA-DM. The latter serves as a peptide editor.19 Following peptide loading, the HLA class II/peptide complex is then transported via the trans-Golgi to the cell surface and there presented to cognate CD4+ T cells. The CD4+ T cells have a helper function or display an effector function with HLA class II bearing tumor cells. The function of HLA class II proteins has been associated with the regulation of immune responses by presenting antigenic peptides to CD4+ T cells and by controlling B-cell differentiation into antibody-producing blasts. Efficient and long-lasting TAA-specific immunity requires both CD8+ CTL and CD4+ T lymphocytes during priming and effector phases of TAA-specific immune responses.20,21 However, not only exogeneous, but also endogeneous peptides can be loaded onto HLA class II molecules;22 this process is mediated by an li-independent, but proteasome- and peptide transporter-dependent presentation pathway.23

**Table 1.** Comparison of the major characteristics of the HLA class I and II APM pathway.

| Steps of APM                          | HLA class I APM | HLA class II APM |
|--------------------------------------|----------------|-----------------|
| Antigen presentation                 | HLA-A, -B, -C  | HLA-DR, -DQ, DP |
| Stabilization and loading            | Tapasin        | HLA-DM          |
| Peptide generation                   | Proteasome     | Lyosomal enzymes|
| Transactivation                      | No             | Yes, CIITA      |
| Assembly and stabilization           | β2-m           | Invariant chain |
| Peptide loading                      | ER             | MCI             |
| compartment                           | CD8+ T cells   | CD4+ T cells    |
| Presentation to                       | IFNγ           | IFNγ            |
| Regulation by cytokines              | Loss            | Loss            |
| Expression by tumor cells            | Downregulation | Down- or upregulation |

**Organization of the HLA class II antigen-processing machinery**

The expression levels of HLA class II antigens are tightly regulated to ensure an immune response directed against pathogens as well as malignant or virally transformed cells.24 The promoters of HLA class II and related genes share a set of conserved sequence elements, the W/S, X1, X2 and Y boxes, which interact with transcription factors (TF) including members of the regulatory factor X (RFX) family, the nuclear factor Y and the cAMP-responsive element binding protein CREB.25,26 All these TF and co-factors bind to cis regulatory elements of the HLA class II promoters to form a highly stable multimeric complex known as MHC enhanceosome. Due to their ubiquitous expression, the enhanceosome components fail to account for the cell type specificity and/or IFNγ inducibility of HLA class II antigen expression.27 In contrast, the HLA class II transactivator CIITA, the master key transcriptional activator interacting with the DNA-binding proteins of the HLA class II promoters, exhibits a cell type-specific, cytokine-inducible and differentiation-specific expression pattern. This is controlled by the alternative usage of the four distinct CIITA promoters (CIITA-P I, II, III and IV. CIITA-PIV is involved in the IFNγ-

**HLA class II antigen expression in normal cells**

It has been assumed for a long time that under physiological conditions the constitutive expression of the gene products of HLA class II loci is primarily restricted to professional antigen presenting cells (APCs) and to thymic epithelial cells in man and in other animal species.13 With the availability of HLA class II antigen-specific monoclonal antibodies (mAb), the expression of these antigens could be studied in a variety of normal tissues, revealing that HLA class II antigens have a broader distribution in normal tissues than originally postulated14-13: A weak to moderate expression of HLA class II antigens has been shown in skin, breast, lung and kidney tissues (www.proteinatlas.org), indicating that in addition to APC, other tissues are able to constitutively express HLA class II antigens.
mediated induction of HLA class II surface expression. In addition, to promote the binding of TF to CIITA-PIV, IFN also includes the acetylation of histones leading to an accessibility of CIITA-PIV. Furthermore, a variety of signal transduction pathways, such as PKA, upregulates CIITA expression, which, in turn, enhances HLA class II antigen cell surface expression.

Expression of HLA class II antigens in malignant tumors

Malignant transformation of cells is not only associated with changes in HLA class I, but also in HLA class II antigen expression. The frequency of these changes varies among the different types of hematopoietic and solid tumors depending on their origin and/or molecular phenotype: for example, more than 80% of ductal breast carcinoma lesions analyzed lack HLA class II antigen expression. In contrast, about 50% of papillary thyroid carcinoma and 60% of primary melanoma express HLA class II antigens, suggesting a gain of HLA class II antigen expression in these tumor types. In addition, a heterogeneous intra-tumoral HLA class II antigen expression pattern was detected in HLA class II antigen-positive tumor lesions. While there is concordant information in the literature about the frequency of HLA class II antigen expression in some tumor types, in others the information is conflicting. For example, the frequency of HLA class II positivity in colorectal carcinoma (CRC) reported in the literature varied between 21 and 55% depending on the study. These different results may reflect differences in the methodology and antibodies used, in the characteristics of the patients’ population included in the studies and in the molecular pathogenesis of the disease. In this context, it is noteworthy that HLA class II antigen expression in CRC is closely related to the high-level microsatellite instability (MSI-H) phenotype, underlining that a precise molecular classification is required to obtain reliable information about the frequency of HLA class II antigen expression in defined tumor subtypes. This conclusion is further supported by the observation in head and neck cancers, where HLA class II antigen expression is related to human papillomavirus infection of the lesions.

Altered constitutive and IFNγ inducible HLA class II antigen expression in cancer cells

So far, five distinct HLA class II phenotypes have been described in human tumors, which are characterized by (i) a strong cytokine-independent homogeneous overexpression, (ii) total lack of expression, (iii) downregulation, (iv) altered IFNγ inducibility of basal HLA class II surface antigens in terms of level and kinetics quantity and time and (v) lack of IFNγ inducibility. In addition, a novel, cytokine-independent mechanism of HLA class II antigen upregulation has recently been
detected in Schwann cells, which express high levels of HLA class II antigens upon inactivation of the tumor suppressor gene neurofibromin.\(^{41}\) The molecular mechanisms mediating the selective lack or downregulation of constitutive as well as IFN\(\gamma\)-mediated upregulation of HLA class II antigens by malignant cells have been characterized to a limited extent. They appear to be mainly mediated by structural abnormalities, by epigenetic, transcriptional and post-transcriptional regulation of HLA class II molecules and/or APM components (Table 2)\(^{42}\) and by genomic instability.\(^{33}\) Furthermore, the function of genes encoding IFN\(\gamma\) as well as components of the IFN\(\gamma\) signal pathway, which regulate HLA class II antigen expression, may be impaired by multiple mechanisms. They include either gene-inactivating mutations, silencing through promoter methylation, transcriptional downregulation or post-translational alterations, such as an altered phosphorylation pattern.\(^{42-45}\) In the following section, we will focus on structural alterations and de-regulation of HLA class II antigen expression since they are the best characterized abnormalities affecting HLA class II antigen expression in tumors.

### Structural alterations of HLA class II APM components in malignant cells

Sequence abnormalities, such as mutations or rearrangements in CIITA, RFX5, RFXAP and/or HLA class II alleles leading to impaired constitutive or IFN\(\gamma\)-inducible HLA class II expression have been described in particular in diffuse large B-cell lymphoma, CRC and melanoma.\(^{46,47}\) These structural alterations appear to occur at a low frequency, although this might be underestimated due to the heterogeneity of clinical samples. Mutations in the HLA class II-regulatory gene RFX5 were found at frequency of about 30% of HLA class II antigen-negative microsatellite-unstable (MSI-H) CRC (28.9%), while CIITA mutations were only found in about 5% of these lesions.\(^{33}\)

Also in tumor types distinct from CRC, structural alterations of HLA class II antigen-regulatory genes have been detected. In melanoma A to G substitutions in the 5' flanking region of the CIITA-PIII were found, which were associated with higher levels of constitutive HLA-DR expression.\(^{48}\) Recently, CIITA has been described as a recurrent gene fusion partner in B-cell lymphoma and Hodgkin’s disease.\(^{46}\) The presence of the CIITA rearrangement was associated with HLA class II antigen downregulation and significantly correlated with a shorter disease-specific survival, which is compatible with a reduced immunogenicity of the affected tumor cells.\(^{46}\)

### Deregulation of HLA class II APM components in malignant cells

Impaired HLA class II antigen cell surface expression may be also caused by the deregulation of APM components at each step of this pathway. Suppression of CIITA transcription mediated by the overexpression of HASH-1, c-Myc and N-Myc, which competitively bind to the E-box in the CIITA-PIV has been reported in neuroblastoma, in small cell lung carcinoma (SCLC) and in B-cell tumors.\(^{49,50}\) In contrast, RET/PTC expression is correlated with increased CIITA expression associated with an increased HLA class II antigen expression.\(^{51}\) The lack of STAT1\(\alpha\) and the retinoblastoma tumor suppressor gene affects CIITA expression and consequently leads to an impaired constitutive and IFN\(\gamma\)-inducible HLA class II antigen expression as demonstrated in breast carcinoma and NSCLC cells.\(^{50,52}\) Furthermore, a low frequency of mutations or downregulated expression of the interferon regulatory factor (IRF)-2 have been found in tumors, which is associated with impaired CIITA expression and IFN\(\gamma\) response.\(^{53}\) These data demonstrate an important role of the IFN\(\gamma\) signal pathway for both the basal and IFN\(\gamma\)-inducible HLA class II expression.

In addition, an epigenetic control of different HLA class II APM components including HLA-DR and CIITA due to alterations in their chromatin accessibility and DNA methylation status has been described; these abnormalities lead to a lack of HLA class II antigen expression.\(^{42,54}\) These abnormalities could be reverted by treatment of tumor cells with pharmacologic substances like 5-aza-2-deoxycytidine (DAC) and trichostatin A (TSA), which induce DNA demethylation and block histone deacetylation, respectively.\(^{55}\) The hypermethylation of the CIITA promoter, in particular of CIITA-PIV was found at a high frequency in gastric cancers, HNSCC and ocular melanoma, but not in CRC suggesting tumor type-specific CIITA methylation.\(^{33,55,56}\) Pro-moters of the HLA class II antigen-encoding genes could also be directly silenced by methylation. In RFX5-negative B-lymphoma cells, the HLA-DO, HLA-DR and HLA-DQ promoters are methylated.\(^{57}\) Furthermore,

### Table 2. Molecular mechanisms causing HLA class II abnormalities in malignant tumors.

| Molecular mechanism                        | Tumor type                                      |
|-------------------------------------------|------------------------------------------------|
| Mutations in CIITA and RFX5               | Colorectal cancer (MSI-H subtype)\(^{31,47}\)    |
| CIITA promoter polymorphism A to G substitution | Melanoma\(^{59}\)                                      |
| Transcriptional downregulation of the CIITA promoter due to HASH-1, L-myc and c-myc overexpression | SCLC, neuroblastoma\(^{50}\) B cell tumors\(^{65}\) |
| Hypermethylation of CIITA                 | Teratocarcinoma\(^{108}\) Embryonal carcinoma\(^{108}\) Lymphoblastic leukemia\(^{98,109}\) Ocular melanoma\(^{109}\) Head and neck squamous cell carcinoma\(^{102}\) B-cell lymphoma\(^{95,96}\) Squamous cell carcinoma\(^{58}\) Leukemia\(^{96,109}\) Head and neck squamous cell carcinoma, ocular melanoma\(^{101,102}\) Thymoma\(^{105}\) Thymoma\(^{105}\) Melanoma, large B cell lymphoma\(^{66}\) B-cell lymphoma\(^{49}\) Esophageal squamous cell carcinoma\(^{52}\) Acute myeloid leukemia\(^{107}\) Head and neck squamous cell carcinoma\(^{104}\) B-cell lymphoma\(^{103}\) B-cell lymphoma\(^{46}\) |
| Histone acetylation of CIITA               |                                               |
| Post-transcriptional regulation of HLA class II antigens |                                               |
| Absence of AIRE                            |                                               |
| STAT1 defects associated with impaired IFN\(\gamma\)-induction |                                               |
| Low expression of GILT                      |                                               |
| Decreased expression of HLA-DM             |                                               |
| Hypermethylation of HLA class II gene promoters |                                               |
| Low CLIP expression                        |                                               |
| Lack of HLA-DM                             |                                               |
| CLIP occupation                            |                                               |
| CIITA gene fusion                          |                                               |
modification of histone deacetylation could be also associated with CIITA silencing in some tumor types, like squamous cell carcinoma and hematopoietic tumors. The clinical relevance of the epigenetic control of HLA class II antigen expression was shown for esophageal squamous cell carcinoma and adrenocortical tumors promoting their recurrence and progression.

Impaired HLA class II-restricted TAA presentation due to abnormalities in the processing pathway could limit CD4+ T-cell help for the induction of CD8+ T-cell responses. Intracellular synthesis and occupancy of HLA class II antigen with CLIP as well as low to basal levels of GILT negatively interfere with the activation of CD4+ T cells reactive against acute myeloid leukemia (AML) and lymphoma cells. This caused immune tolerance or unresponsiveness to leukemia antigens and lead to a significantly shortened disease-free survival of patients with AML or diffuse large B-cell lymphoma. In contrast, some CLIP+ tumor cells were able to process i-independent endogenous antigens generated by the proteasome for HLA class II-restricted presentation thereby activating TAA-specific CD4+ T cells.

Furthermore, it has recently been suggested that the different HLA class II phenotypes in tumors can be controlled at the post-transcriptional level, in particular by microRNAs (miRs). Bioinformatic analyses have identified a number of miRs binding to the 3'-untranslated region (3'-UTR) of CIITA. As an example, miR-150 was shown to abrogate CIITA expression in macrophages upon infection with pathogenic mycobacteria. However, a miR-mediated altered expression of HLA class II pathway components in tumors has not yet been identified. Furthermore, HLA class II molecules could be regulated by the interaction with ubiquitin ligases leading to their intracellular sequestration and degradation.

Clinical significance of HLA class II antigens in cancer

A functional role of HLA class II antigens on the tumor cell surface is suggested by the observation that HLA class II antigen expression is related to prognosis in several types of cancers. However, the available information about the prognostic significance of HLA class II antigen expression in cancers is conflicting (Table 3). While constitutive HLA class II antigen expression was reported to be associated with a favorable prognosis in some tumor types, e.g., CRC and larynx squamous cell carcinoma, it was associated with higher metastatic dissemination, increased tumor stage and reduced patients’ survival in other malignancies, such as melanoma and cervical carcinoma. Conflicting is the information about the clinical relevance of HLA class II antigen expression in osteosarcoma; however, the number of tumors analyzed is too small to draw conclusions.

In addition, even within defined cancer types, the prognostic value of HLA class II antigens is conflicting depending on the studies. Immunohistochemically detectable HLA class II antigen expression was associated with a better prognostic outcome of CRC patients in some studies, but not associated with tumor grade, stage and survival in other studies. A positive prognostic effect of HLA class II antigen expression in CRC may reflect the increased T-cell infiltration which is one of the strongest favorable prognostic biomarkers in CRC. Consequently, high levels of IFNγ might induce HLA class II antigen expression in densely T-cell-infiltrated tumors, which has a good prognosis.

Immune selection of HLA class II-deficient tumors

The role of immune selection in the generation of tumors with defects in HLA class I antigen expression has been extensively investigated. In vitro experiments, studies in animal models and clinical investigations have convincingly shown that the selective pressure imposed by HLA class I antigen-restricted, TAA-specific T cells on a tumor cell population can facilitate the outgrowth of tumor cells, which are not recognized by cognate CTL due to defective synthesis and/or expression of HLA class I antigen-TAA-derived peptide complexes. The latter mediate the interactions of tumor cells with host’s immune system. In contrast, limited information is available about the impact of immune selection on HLA class II antigen expression by tumor cells. We are aware of only one example suggesting that immune selection facilitates the outgrowth of HLA class II antigen-negative tumor cells: MSI-H CRCs are characterized by a pronounced antitumor immune response, which is triggered by a high amount of mutation-induced neoantigens. In MSI-H CRCs, pronounced CD4+ T-cell infiltration was associated with HLA class II antigen loss induced by RFX5 or CIITA mutations. The association between CD4+ T-cell infiltration and lack of HLA class II antigen expression by tumor cells may reflect the role of immune selection in the generation of tumors without detectable HLA class II antigen expression. The selective pressure imposed by CD4+ cells on the tumor cell population may lead to the elimination of MSI-H CRC cells expressing HLA class II antigens by cognate CD4+ T cells and may facilitate the outgrowth of tumor cells, which have lost the ability to express HLA class II antigens. This possibility is supported by the detection of mutations in HLA class II-regulatory genes in the tumor cells, which do not express HLA class II antigens. If our interpretation is correct, our results imply that human TAA recognized by cognate CD4+ T cells are effective in inducing a TAA-specific immune response and in mediating tumor rejection through an antigen-specific CD4+ T-cell response. This hypothesis is supported by recent studies in mouse models reporting that the presence of MHC class II molecules on the tumor cell surface can mediate efficient elimination of tumor cells through direct recognition by CD4+ T cells.

Beyond conventional recognition of HLA class II molecules by CD4+ T cells, the expression of HLA class II antigens may have consequences for tumor/immune cell interactions and

### Table 3. Clinical relevance of HLA class II expression.

| Tumor type                  | HLA class II level | Prognosis    | Citation |
|-----------------------------|--------------------|--------------|----------|
| CRC                         | High               | Favorable    | 72-74,80 |
| Larynx squamous cell carcinoma | High              | Favorable    | 71       |
| Oropharyngeal squamous carcinoma | High              | Favorable    | 40       |
| Melanoma                    | High               | Poor         | 76, 77   |
| Cervical cancer             | High               | Poor         | 75       |
| Osteosarcoma                | High               | Controversial| 78, 79   |
| Pediatric adrenocortical tumors | Low               | Poor         | 63       |
tumor cell survival. For example, the interaction between LAG3, a surface molecule expressed on exhausted lymphocytes, and HLA class II antigens can enhance survival and apoptosis resistance of melanoma cells.87

Concluding remarks and perspectives

Although there exist major differences in the HLA class I and II APM pathways, interactions between both pathways have been identified, which allow the cross-presentation of antigens as a key feature for the induction of TAA- and viral antigen-specific CD8+ T cell responses.88 However, the mechanisms underlying antigen cross-presentation have not yet been defined, but an escape of internalized proteins from the endosomes via an unknown transporter is currently being discussed. Other possibilities involve the TAP-mediated transport of cytosolic peptides back to the phagosome or endosome89,90 and the escort of the unknown transporter is currently being discussed. Other possibilities involve the TAP-mediated transport of cytosolic peptides back to the phagosome or endosome91,92 and the escort of the HLA class I antigens by the li to the endosomal compartment.91,92

The role of HLA class II antigen expression by tumors and its clinical relevance remains controversial and appears to depend on the tumor type including its genetic determinants. There is increasing evidence that HLA class II antigens on tumor cells shape the TAA-specific antitumoral immune response suggesting that HLA class II antigens may represent a novel therapeutic target.93 Thus, there are still many open questions, which have to be addressed in order to fully characterize the function of HLA class I and class II antigens in tumors.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by a grant from the German Cancer Aid 110703 (BS).

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