Targeting the MHC Class II antigen presentation pathway in cancer immunotherapy

Jacques Thibodeau,1,* Marie-Claude Bourgeois-Daigneault,1 and Réjean Lapointe2

1Laboratoire d’Immunologie Moléculaire; Département de Microbiologie et Immunologie; Université de Montréal; Montréal, QC Canada; 2Centre de Recherche du Centre hospitalier de l’Université de Montréal (CRCHUM)—Hôpital Notre-Dame; Université de Montréal and Institut du Cancer de Montréal; Montréal, QC Canada

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The success of immunotherapy relies on the participation of all arms of the immune system and the role of CD4+ T lymphocytes in preventing tumor growth is now well established. Understanding how tumors evade immune responses holds the key to the development of cancer immunotherapies. In this review, we discuss how MHC Class II expression varies in cancer cells and how this influences antitumor immune responses. We also discuss the means that are currently available for harnessing the MHC Class II antigen presentation pathway for the development of efficient vaccines to activate the immune system against cancer.

Tumors and the Immune System

The interplay between immune and tumor cells is complex. Various genetic immunodeficiency syndromes have been linked to an increased incidence of tumors in mice.1 Moreover, many tumors downregulate the expression of MHC molecules, suggesting a role for the immune system in controlling the progression and evolution of cancer.2 Accordingly, solid tumors, stromal cells and neighboring tissues often are infiltrated by a vast array of immune cells.3 Generally, the magnitude of the T-cell infiltrate correlates with good prognosis.

The very recent FDA approval of sipuleucel-T (an autologous antigen-presenting cell-based vaccine) and the development of therapeutic antibodies that modulate T-cell responses announce the future of cancer immunotherapy as promising and bright.4 Understanding how tumors evade immune responses holds the key to the development of cancer immunotherapies. In this review, we discuss how MHC Class II expression varies in cancer cells and how this influences antitumor immune responses. We also discuss the means that are currently available for harnessing the MHC Class II antigen presentation pathway for the development of efficient vaccines to activate the immune system against cancer.

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Role of Adaptive CD4+ T-Cell Responses in Tumor Eradication

MHC Class II molecules are crucial for the activation of CD4+ T cells. Patients affected by the Bare lymphocyte syndrome (BLS) Type II (MHC Class II deficiency) usually die of infections at a young age, making it difficult to assess cancer incidence.7 Still, evidence supporting the role of CD4+ T cells in the antitumor response is compelling, in both mice and humans. Tumor eradication following immunization with cancer cells or specific peptides relies on a functional CD4+ T-cell effector compartment, even for MHC Class II-negative tumors.8 A role for helper T cells in the direct mobilization of effector cytotoxic T lymphocytes (CTLs) to virus-infected tissues has recently been demonstrated. Such interplay may also prove to be critical in some cancers.9

It is well known that CD4+ helper T cells can directly mediate cytotoxicity against tumor cells.10 However, CD4+ helper T-cell activation generates regulatory T cells (Tregs) which may limit the success of immunotherapy in vivo.11 The exact role of pro-inflammatory interleukin (IL)-17-producing (Th17) cells, which have first been identified in the murine tumor microenvironment, remains to be established.12 According to studies performed in IL-17-deficient mice, Th17 cells may either promote or prevent tumor growth.

In recent years, the search for new TAAs has intensified, in part because of their importance as biomarkers in cancer diagnosis.13 Based on these discoveries, multiple therapeutic cancer vaccines designed to stimulate helper T cells have been developed. Despite evidence supporting the role of helper T-cell responses in tumor eradication, clinical studies in which melanoma patients received either Class I- or Class II-restricted peptides have yielded discordant results regarding the impact of Class II epitopes.14 The generation of effective helper T-cell responses requires a deeper understanding of the fine tuning of T-cell receptor
(TCR)-transduced signals. For instance, modulating the functional avidity during antigen presentation might impact the generation of memory CD4⁺ T-cell responses. Given that avidity is an influencing factor in the escape of some CD4⁺ T cells from the induction of central tolerance, self-reactive clones can be enrolled in the fight against cancer by careful vaccination.

Tumor Cells as Antigen-Presenting Cells

At some point in their natural history, most tumors are able to present antigens and act as antigen-presenting cells (APCs). However, the lack of co-stimulatory molecules on tumor cells promote tolerance, thus exerting detrimental effects. Many solid tumors do not express MHC Class II and the involvement of CD4⁺ T cells depends mainly on infiltrating APCs that either pick up available antigens or engulf tumor cells. IL-2 and interferon γ (IFNγ)-producing tumor-infiltrating lymphocytes (TILs) help create an inflammatory, delayed type hypersensitivity (DTH)-type of microenvironment, thereby enabling tumor clearance through bystander killing. A tumor expressing MHC Class II could amplify such an immune response.

Why Do Antitumor T-Cell Responses Often Prove Defective?

Considering the diversity of defense mechanisms that contribute to antitumor immunity, it is surprising that spontaneously arising cancer cells can proliferate to an extent that is lethal to the host. Hence, the mechanisms that facilitate immune evasion are likely to also hinder the efficacy immunotherapy. Such mechanisms include the presence of increased numbers of regulatory T cells (Tregs), reduced adhesion, reduced expression of co-stimulatory molecules, increased expression of FAS ligand (FASL) by tumor cells, the presence of inhibitory factors or regulatory cytokines such as transforming growth factor β (TGFβ) and altered signal transduction pathways in TILs, resulting in T-cell unresponsiveness.

Although IFNγ undoubtedly favors an antitumor inflammation and promotes MHC Class II expression, it also has immunosuppressive effects. In many cells types, expression of indoleamine 2,3-dioxygenase-1 (IDO1) is strongly induced by IFNγ, and less so by Type I IFNs (IFNα and IFNβ). IDO, an intracellular heme-containing enzyme that catalyzes the initial, rate-limiting step in tryptophan degradation along with the kynurenine pathway, plays an important immunoregulatory role by inhibiting T lymphocyte functions and reprogramming Tregs. The importance of IDO1 in human cancers is now well documented.

Subversion of MHC Class II Antigen Presentation in Tumors

Overview of the exogenous antigen presentation pathway. As opposed to MHC Class I, classical MHC Class II molecules (HLA-DR, -DP and -DQ) bind the invariant chain (Ii) and do not associate with peptides in the endoplasmic reticulum (ER) (Fig. 1). The Ii chaperone associates with folding MHC Class II, occupying the peptide-binding groove and preventing aggregation. Ii is then degraded in endosomes, ultimately leaving only a short Class II-associated invariant chain peptide (CLIP) inside the MHC Class II groove.

The peptide-binding groove of most MHC Class II molecules must be freed by the action of the non-classical MHC Class II HLA-DM. In most resting APCs, the function of HLA-DM is negatively regulated by HLA-DO.

Endogenous TAAas can gain access to MHC Class II-loading compartments by multiple distinct means. For example, transmembrane proteins from the plasma membrane can be endocytozed and sent to lysosomes for degradation. Cytoplasmic and nuclear antigens can be engulfed by autophagy and hence they can encounter classical MHC Class II and HLA-DM. The MHC Class II antigen processing pathway can be significantly altered as part of the tumorigenesis process, thereby precluding efficient presentation of T-cell epitopes.

Patterns of MHC Class II expression in tumor cells. During the past 30 years, much research has focused on describing and characterizing the expression pattern of MHC Class II in mouse and human tumor cell lines or primary samples of various origins. Studies have yielded mixed results, mostly due to confounding factors that include tumor type, origin and source. As such, the prognostic value of MHC Class II expression is certainly not universal.

MHC Class II molecules are often expressed in tumors including colorectal and breast carcinomas. However, the correlation between such expression and clinical outcome has yet to be elucidated. Given that the breast epithelium does not typically express MHC Class II molecules, it is believed that the MHC expression phenotype arises in response to hormones or cytokines. In contrast, expression of key components of the MHC Class II pathway is often lost in MHC II⁺ cells. Moreover, differential constitutive or inducible expression of MHC Class II isotypes, mainly DR and DQ, occurs in many tumor types. In this context, many functional studies have addressed the capacity of MHC II⁺ tumor cells to present antigens. For instance, despite high levels of surface MHC Class II, peripheral blood B cells from B-cell chronic lymphocytic leukemia (B-CLL) patients have been shown to be poor stimulators in mixed lymphocyte reactions (MLR) and to have a limited capacity to present a model soluble antigen. Altogether, these results suggest that the impact of MHC Class II on disease outcome is the result of a delicate balance between intrinsic tumor factors and host factors regulating the immune response.

How do tumors of different types, origins and from different patients acquire different phenotypes regarding MHC Class II expression? The answer to this question lies into the transcriptional and post-transcriptional mechanisms regulating the expression of MHC Class II molecules as well as their various chaperones. As a general rule, genes involved in MHC Class II antigen presentation are co-regulated by the Class II transactivator (CIITA) (Fig. 2). CIITA binds to promoter elements involved in both constitutive MHC Class II expression and IFNγ-mediated induction. Some tumors do not upregulate MHC Class II molecules in response to IFNγ. This functional deficit may be due to defects in the CIITA synthesis, either at
Finally, the cell surface exposure of MHC Class II molecules can be regulated, either indirectly, by modifications in the activity of chaperones, or directly, following the interaction with ubiquitin ligases of the membrane-associated RING-CH (MARCH) family. MARCH1 and MARCH8 can add ubiquitin to the cytoplasmic tail of MHC Class II molecules, leading to MHC Class II intracellular sequestration and degradation (Fig. 3). While MARCH8 is expressed rather ubiquitously, MARCH1 is induced by IFNγ.

transcription, mRNA translation or protein stability levels. Very recently, reduced MHC Class II expression, as seen in some lymphomas, has been attributed to fusion transcripts caused by genomic breaks in the CIITA gene. BLIMP1, a transcription regulator expressed in plasma cells, downregulates CIITA transcription. BLIMP1 expression does not always show an inverse correlation with MHC Class II expression as CIITA is upregulated in multiple myeloma cells by IFNγ.

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MHC Class II can be very efficient in activating the immune system, provided that they do not express Ii. It is assumed that, in the absence of Ii, the palette of antigens (including TAAs) capable of binding MHC Class II molecules increases over a wider range of compartments. Ii is expressed by many hematological malignancies and the Ii-specific humanized monoclonal antibody milatuzumab is now used as immunotherapeutic agent.

Patterns of HLA-DM and HLA-DO expression in tumors. The combined action of HLA-DM and HLA-DO affects the level of CLIP at the cell surface. When Ii is normally expressed, CLIP levels are inversely and directly proportional to HLA-DM and HLA-DO levels, respectively. Because CLIP prevents the binding of antigenic peptides, these non-classical chaperones have a profound impact on the immune response. Yet, the importance of HLA-DM is still the object of an intense debate, as it was shown in a mouse model that tumor cells transfected with MHC Class II and HLA-DM, with or without Ii, can be highly immunogenic. Thus, it is likely that HLA-DM plays a critical role only in the context of Ii expression.

HLA-DM is co-regulated with HLA-DR. Interestingly, low CLIP occupancy of MHC Class II molecules has been reported in a number of malignancies. In tumor cells, expression of HLA-DM and HLA-DO levels inversely and directly proportional to HLA-DM and HLA-DO levels, respectively. Because CLIP prevents the binding of antigenic peptides, these non-classical chaperones have a profound impact on the immune response. Yet, the importance of HLA-DM is still the object of an intense debate, as it was shown in a mouse model that tumor cells transfected with MHC Class II and HLA-DM, with or without Ii, can be highly immunogenic. Thus, it is likely that HLA-DM plays a critical role only in the context of Ii expression.

Patterns of Ii expression in tumor cells. In normal and neoplastic cells, the pattern of Ii expression generally correlates with that of MHC Class II molecules, even at the final stage of B cell maturation, when neither molecule is expressed. However, additional analyses revealed numerous instances of discordant expression patterns for these two molecules (see ref. 36 for example). The Ii and MHC Class II genes share common CIITA-dependent regulatory elements. In addition, the human and mouse Ii promoters contain two functional NFκB/Rel-binding sites, which either activate or inhibit expression depending on the cell type.

The level of proteins, the proportion of the various isoforms, and the presence of cleavage products are some of the variables influencing the expression of Ii in various tumor types. In humans, Ii exists in four isoforms that originate from alternative splicing and alternative translation initiation sites. Translated from the most 5' AUG triplet, the Iip35 isoform encodes an RxR (Arg-x-Arg) ER retention motif that is masked upon MHC Class II binding and Ii phosphorylation by protein kinase C (PKC). Intriguingly, high levels of Ii, and especially of Iip35, were found in hairy cell leukemia (HCL) and some B-CLL patients. Such an increase correlated with a high proportion of MHC Class II molecules bound to Iip35, and it was postulated that this tight association might prevent the binding of endogenous tumor antigens.

The impact of Ii on endogenous antigen presentation by MHC Class II molecules has been mainly addressed in the context of tumor vaccines. Tumor cells genetically engineered to express MHC Class II can be very efficient in activating the immune system, provided that they do not express Ii. It is assumed that, in the absence of Ii, the palette of antigens (including TAAs) capable of binding MHC Class II molecules increases over a wider range of compartments. Ii is expressed by many hematological malignancies and the Ii-specific humanized monoclonal antibody milatuzumab is now used as immunotherapeutic agent.

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HLA-DM is co-regulated with HLA-DR. Interestingly, low CLIP occupancy of MHC Class II molecules has been reported in a number of malignancies. In tumor cells, expression of HLA-DM has been associated with a Th1 cytokine profile and shown to predict better survival in breast carcinoma patients. This is in line with the role of HLA-DM in reducing CLIP at the cell surface, thereby avoiding Th2 polarization. Leukemic blasts also lack CLIP at the cell surface, which promotes the activation of specific CD4+ Th1 cells. In addition, some pre-B acute lymphocytic leukemia (ALL) (namely ETV6-AML1) display low amounts of CLIP, perhaps inducing a favorable immune response.

Figure 2. Transcriptional regulation of MHC Class II genes. The binding of interferon γ (IFN-γ) to its receptor at the cell surface leads to the transcriptional activation of the Class II transactivator (CIITA). This transcription factor binds to the promoters of the invariant chain and MHC Class II genes. BLIMP-1 can block the transcription at such promoters by directly inhibiting CIITA upregulation. The expression of the invariant chain can also be modulated by NFκB in response to various pro-inflammatory signals. On the other hand, the binding of interleukin-10 (IL-10) to its receptor at the cell surface triggers the upregulation of CIITA.
Defects in autophagy have been associated with cellular transformation. Because autophagy has been intimately linked to antigen processing by MHC Class II molecules in a variety of systems, autophagy-deficient tumors are likely to exhibit defects in the processing of certain antigens. Endosomal/lysosomal protease regulation can have a tremendous negative impact on the generation of T-cell epitopes and on Ii degradation.

As mentioned above, many murine tumor cell lines do not express or upregulate the MHC Class II antigen presentation machinery in response to IFNγ. In melanoma, the absence of IFNγ-inducible lysosomal thiol reductase (GILT) disrupts T-cell recognition of immunodominant epitopes. Additionally, in head and neck cancer cells, CIITA does not induce cathepsin S, a cysteine protease involved in the late stage of Ii processing. As new alterations are continuously found in tumor cells, the characterization of their effects on adaptive responses in the context of immune evasion will undoubtedly uncover many surprises.

Modulation of MHC Class II accessory molecules in tumors. Presentation of peptides in normal cells depends on efficient synthesis, sorting and processing of antigens as well as on the proper trafficking and maturation of MHC Class II molecules. In tumor cells, intrinsic modifications of a cellular compartment and its components such as lipids and enzymes are likely to influence, directly or indirectly, the processing, loading and presentation of antigens to T cells. Several examples of such potentially clinically-relevant perturbations are given below.

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Counteracting the Subversion of Antigen Presentation

Several methods have been considered to maximize antigen presentation. For instance, tumor cells expressing MHC molecules are being used as vaccines. However, the more common approach is to transfer natural or artificial APCs that have been manipulated in vitro to display defined antigens (loaded under controlled conditions). Other in vivo approaches are being developed to limit
the manipulations of host cells and to avoid cumbersome personalized immunotherapy. In this last section, we will address the needs to discover additional TAAAs, improve cellular vaccines and define alternative methods to effectively stimulate CD4+ T cells.

**Discovery of novel TAAAs and T-cell epitopes.** Tumor-specific antigens (TSAs) may result from gene mutations or from the expression of alternative open reading frames resulting from chromosomal rearrangements. In recent years, TSAs and TAAAs have been discovered at a regular pace. TAAAs are often found in normal tissues. Thus, while breaking tolerance to these antigens through vaccination should result in tumor recognition, it may also lead to autoimmunity. It should be kept in mind that other treatments such as chemotherapy have the potential to modify the proteome of cancer cells and provide new targets for immunotherapy.

The genetic diversity at the MHC I and II loci is another hurdle in the development of effective immunotherapy. The identification of new epitopes recognized in the context of a series of isotypes and alleles should open the door to a more universal use of immunotherapy. Defining immunopeptidomes specific to different cancer-patient combinations should produce valuable information. Mass spectrometry is used to map MHC Class I and II binding antigens. A variety of cell-based approaches has been considered as a means to increase cancer-specific immune responses. These therapeutic protocols are mostly based on the transfer of modified tumor cells, APCs or engineered T cells.

**Tumor vaccines.** The rationale underlying tumor vaccines is that tumor cells, although poorly immunogenic themselves, express a full complement of endogenous TAAAs. To increase T-cell activation, tumor vaccines can be genetically modified with elements of the MHC Class II processing and presentation machinery. Treatment of cells with cytokines that promote the processing of endogenous (even nuclear) antigens through autophagy may increase the variety of T-cell epitopes generated in tumor-cell vaccines. Instead of using whole tumor lysates, synthetic peptides that correspond to carefully selected epitopes may be processed more easily, enabling the definition of novel TSAs that may have originated from processes including alternative splicing.

**Cellular vaccines.** A variety of cell-based approaches has been considered as a means to increase cancer-specific immune responses. These therapeutic protocols are mostly based on the transfer of modified tumor cells, APCs or engineered T cells. The rationale underlying tumor vaccines is that tumor cells, although poorly immunogenic themselves, express a full complement of endogenous TAAAs. To increase T-cell activation, tumor vaccines can be genetically modified with elements of the MHC Class II processing and presentation machinery. Treatment of cells with cytokines that promote the processing of endogenous (even nuclear) antigens through autophagy may increase the variety of T-cell epitopes generated in tumor-cell vaccines.

Interestingly, many groups reported that Ii expression was detrimental to the presentation of endogenous antigens in mouse and human tumor cells. For example, the depletion of Ii by various means has been shown to increase the presentation of some antigens and to improve the efficacy of immunotherapy.

As mentioned above, because many tumors do not express either classical or non-classical MHC Class II, they need to be further manipulated in vitro. IFNγ upregulates the MHC Class II antigen presentation machinery as well as more than 200 additional genes. In the presence of IFNγ, some tumors gain full antigen presentation properties (see above). For tumors that do not respond to IFNγ, genetic engineering can be considered. However, although complete rejection and antitumor memory have been demonstrated in mice immunized with CIITA-expressing tumor cell lines, other studies have cast doubts on the efficiency of such an approach. In addition, the introduction of CIITA has been achieved in cellular vaccines, yet some tumors do not fully respond to this transactivator and some genes have been reported to remain silent. Under such conditions, gene expression profiles should be carefully monitored to ensure that the desired antigen presentation machinery is upregulated.

**Dendritic cell-based vaccines.** One of the most promising therapeutic cancer vaccines is based on dendritic cells (DCs). Different methods have been used to display specific T-cell epitopes on APCs. For instance, tumor cell lysates can be pulsed onto DCs, or recombinant antigens can be coupled to monoclonal antibodies directed against DC surface receptors. In this approach, the choice of the receptor is critical, given that most receptors only allow for presentation on either MHC I or MHC Class II. Moreover, because of their heterogeneity, some DC subsets are more efficient than others at MHC Class I cross-presentation or MHC Class II presentation, which adds a further level of complexity to this approach.

Synthetic peptides that correspond to carefully selected epitopes constitute the most useful antigens. Their formulation has evolved in recent years. For example, multi-epitope Trojan antigen peptide vaccines and peptides with overlapping CD4-specific and CD8-specific epitopes can induce both CTL and helper immune responses. However, even though empty MHC Class II molecules are expressed at the surface of DCs, their loading is rather inefficient. Chemical agents that can break hydrogen bonds linking low affinity peptides to HLA-DR have recently been discovered. Moreover, small molecules that can enhance the catalytic activity of HLA-DM have been identified. Other genetic approaches aimed at delivering antigens to DCs for the induction of a CD4+ T-cell response have been described.

**B cell-based vaccines.** Alternative sources of APCs have also been evaluated in vitro. For instance, B lymphocytes stimulated by the CD40 ligand (CD40L) proliferate in high numbers and display a wider array of MHC Class II epitopes due to lowered HLA-DM/HLA-DO ratios. B cells serve as efficient APCs for the expansion of TAA-specific CD8+ and CD4+ T cells. Interestingly, not only can B cells present MHC Class II epitopes independently of the specificity of their B-cell receptor (BCR), when pulsed exogenously, but they can also promote MHC Class I cross-presentation.

**Surrogate APCs.** To overcome the need for living autologous hematopoietic cells in immunotherapy, alternative ways whereby only basic antigen presentation requirements are expressed on “artificial” supports have been developed. Such alternatives include cellular systems such as fibroblasts and Drosophila cells or acellular artificial APCs that consist of microbeads, liposomes or exosomes.

**Adaptive T-cell therapy: ex vivo-expanded and genetically engineered T cells.** To counteract the production of immunosuppressive cytokines by tumors, autologous T cells normally are activated and expanded ex vivo before adoptive transfer. Clinical remissions have been observed in melanoma patients treated with CD4+ T cells expanded ex vivo in the presence of tumor antigens. The benefit of using CD4+ T cells was recently demonstrated in a MHC Class II-negative ovarian cancer model. Efficiency can be maximized by expressing high affinity TAA-specific recombinant TCRs in recipient human T cells. Such T cell clones can expand, secrete cytokines and lyse target cells.

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Still, the loss of HLA molecules at the surface of tumor cells represents an important barrier for both conventional and engineered MHC-restricted T cells. One way of bypassing the TCR-MHC axis that has been developed relies on chimeric antigen receptors (CARs). The rationale of this approach is that the TAA-specific binding domain of a single-chain (scFv) antibody endows T cells with a defined specificity and the intracellular portion of the chimeric receptor triggers signal transduction upon ligand binding. Using recombinant DNA technology, different types of CARs have been generated with various combinations of specific parts of the TCRCD3 complex, immunoglobulins (usually derived from a mouse B-cell hybridoma) and intracellular domains of co-stimulators such as CD28, 41BB or OX40.83

One hurdle in the development of antibody-based CARs is the need to target TAAs that are displayed at the cell surface. Fortunately, the search for novel specificities in different types of tumors is ongoing, as monoclonal antibodies are used in anticancer therapy and as prognostic tools.84 Recombiant monoclonal antibody-superaugantigen fusion proteins have also been used to activate large fractions of the T-cell repertoire at the tumor site.85

Conclusions

To understand the role of CD4+ T cells in the antitumor response, as well as that played by CD4+ Tregs, studies in humans will need to decipher the pathways leading to the generation of various helper T-cell subsets, and to the presentation of immunogenic (as opposed to tolerogenic) MHC Class II epitopes. Also, we must develop new methods to increase antigen presentation via the in vivo targeting of immunogens. For example, electrodes have been designed for the in vivo DNA delivery by direct electroporation.86 Such an approach may seem extreme, but we will need more ingenious ideas to spark the field of cancer vaccination and, as usual, only imagination will be a limit to innovation.

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