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Review

Transcriptional Control of MHC Genes and T Cell Development in MHC Class II Deficiency

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Abstract. MHC class II deficiency has proven to be an excellent model to study transcription regulation of MHC genes and T cell development. Cell lines established from MHC class II deficient patients have been of great value for the identification of proteins necessary for MHC expression and their study has resulted in the identification of a common regulatory pathway for MHC class II and class I genes. The lack of MHC class II expression was found to have a profound effect on the development of the $CD4^+$ T cell lineage, in particular on the composition of the T cell receptor repertoire, revealing aberrant thymic selection processes in these patients. Here, we will discuss several aspects of the transcriptional regulation of MHC genes and the impact of deficient MHC class II expression on T cell development.

Key words: bare lymphocyte syndrome; MHC class II deficiency; MHC gene regulation; T-cell development.

HLA class I and II molecules, encoded by the major histocompatibility complex (MHC) in man, play a central role in the host's defense mechanisms against foreign pathogens by virtue of their ability to present antigenic peptides to T lymphocytes. Expression of the genes encoding MHC class I and class II molecules is regulated in a tight fashion during development and in fully differentiated cells. In contrast to MHC class I molecules, which are expressed on almost all nucleated cells, MHC class II molecules are primarily expressed by specialized antigen-presenting cells of the immune system, such as macrophages, dendritic cells, thymic epithelial cells and B lymphocytes. Both MHC class I and class II molecules can be induced by immune-regulators, of which interferon γ (IFN-γ) is the most potent. The differences in the expression patterns of MHC class I and class II genes have suggested that these genes are regulated differently at the transcription level. However, it has recently been demonstrated that the transcription of MHC class I as well as of MHC class II genes is controlled by a common regulatory pathway.

Much of our understanding of the transcriptional control of MHC gene expression has been derived from studies with cells obtained from patients with an MHC class II deficiency. MHC class II deficiency, also referred to as bare lymphocyte syndrome (BLS), is a lethal combined immunodeficiency disease inherited in an autosomal recessive fashion. Interestingly, in most patients the lack of MHC class II expression is accompanied by strongly reduced levels of MHC class I expression[49]. BLS patients have severely impaired humoral and cellular immune responses resulting in extreme susceptibility to severe and recurrent infections, mainly

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of the respiratory and gastrointestinal tracts[23]. Currently, allogeneic bone marrow transplantation is considered the treatment of choice for this otherwise lethal immunodeficiency. However, the success rate of engraftment and immunological recovery in these patients is not yet comparable to that of other immunodeficiency conditions[22]. The underlying genetic defect in these BLS patients involves genes that play a role in the transcriptional regulation of MHC genes[4, 30]. At least 4 complementation groups (A–D) are defined in BLS and their defective genes have been isolated and characterized[1]. The products of these genes were found to play a critical role in the transcriptional control of the MHC class II and of the invariant chain (Ii) and HLA-DM genes[6, 21]. The products of the Ii and HLA-DM genes serve as accessory molecules in peptide presentation of MHC class II molecules. Interestingly, as we have shown, the products of the genes which are defective in BLS were found to play a role in the transactivation of MHC class I and β2-microglobulin (β2m), but not of the TAP and LMP genes, the products of which play a key role in antigen degradation and peptide assembly of MHC class I molecules[13, 14, 32].

Despite the absence of MHC class II expression, $CD4^+$ T cells can easily be identified among peripheral blood mononuclear cells, albeit, in most cases, in reduced number[23, 25]. These observations suggest the existence of an MHC class II independent pathway for $CD4^+$ T-cell development in these BLS patients. However, these $CD4^+$ T cells were found to display aberrant phenotypes with respect to T cell receptor (TCR) V-gene skewing patterns and amino acid composition of the complementarity determining region (CDR) 3[17, 50].

Regulation of MHC Class II and Class I Gene Transcription

MHC class II molecules are expressed as heterodimers on the cell surface. Three isotypes can be recognized (HLA-DR, -DQ and -DP), each encoded by a distinct A and B gene. Transcription of MHC class II genes is controlled by a number of transcription factors which interact with a set of conserved cis-acting regulatory elements within the promoter region of all MHC class II genes. These regulatory sequences include the S, X (comprising the X1 and X2 halves) and Y-box elements, and are important for both the constitutive and the IFN-γ induced expression of these genes[4, 30]. The S-X-Y elements act in concert and can therefore be viewed as a regulatory module (Fig. 1). The promoters of HLA-DMA, DMB and the Ii genes, the products of which play an important role in the assembly and transport of MHC class II molecules to the cell surface, also contain the conserved S-X-Y regulatory module[4, 30].

A number of DNA-binding proteins bind to this module and include the RFX complex, which binds to the X1-box; X2BP, which is related to members of the ATF/CREB family of transcription factors and binds to the X2-box, and NF-Y which binds the Y-box[4, 30]. Studies with cell lines from BLS patients revealed the critical role of the RFX complex in the transactivation of MHC class II genes. BLS patients who belonged to complementation groups B–D displayed defects in the individual subunits of the RFX complex: RFXANK[33] (also referred to as RFX-B[36]), RFX5[44] and RFXAP[9] (complementation group B–D, respectively). Binding of RFX, X2BP and NF-Y to their cognate DNA sequences in the promoter of MHC class II genes is not sufficient for transactivation, but requires the activity of the MHC class II transactivator (CIITA)[45]. CIITA is defective in BLS patients belonging to complementation group A[3, 45]. CIITA does not bind to DNA itself, but acts as a coactivator[42, 52] via protein/protein interactions with the RFX5 subunit of the RFX complex bound to the S-X-Y module[43]. As a result of these interactions, CIITA connects the MHC-specific transcription complex with the TBP-associated factors $TAF_{II}32$ and TFIIB of the basal transcription initiation apparatus[11, 31].

Expression of the RFX components is ubiquitous and does not parallel MHC class II expression. This is in contrast to CIITA, which is expressed constitutively in professional APCs of the immune system, whereas it can be induced by IFN-γ in other cell types resulting in MHC class II antigen expression[7, 8, 46]. Transcription of the CIITA gene was found to be controled by multiple promoters[35]. In humans, 4 promoters have been defined which direct CIITA gene transcription in various cell types. Two of these promoters direct the specific constitutive expression in dendritic cells (promoter I) and B cells (promoter III)[26, 35]. The IFN-γ sensitive CIITA promoter (promoter IV) harbors DNA binding sites for IRF-1 and Stat 1, which mediate the IFN-γ induced transcription of CIITA[34, 39]. More recently, a DNA element upstream from promoter III has been described which confers IFN-γ sensitivity of this promoter and, to a lesser extent, also of promoter IV[38].

A series of conserved DNA sequences in the MHC class I gene promoter play a crucial role in the constitutive and cytokine-induced regulation of transcription[48]. They include the enhancer A (enhA), the IFN-stimulated response element (ISRE), site α and enhancer B (enhB) (Fig. 1). The proteins bound to the enhancer A

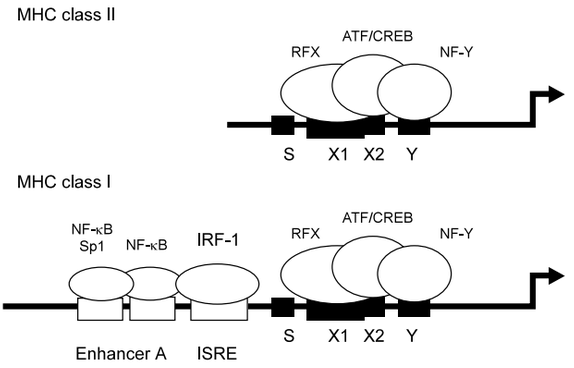

Fig. 1. Schematic representation of the common regulatory module and the MHC class I-specific regulatory elements in the promoter of MHC class II and class I genes.

(NF-κB) and to the ISRE (IRF-1) act synergistically[18] and, therefore, these elements can also be viewed as a regulatory module. Recently it has become clear that the MHC class I and class II promoters share the S-X-Y regulatory module. Site α and the enhancer B in the MHC class I promoter were found to be the homologue of the X2-box and the Y-box respectively in the MHC class II promoter. Furthermore, S and X1 box elements could also easily be discerned in the MHC class I promoter[49]. The S-X-Y regulatory module is highly conserved in evolution, since it is also found in the MHC class I and II promoters of the chicken[24], chimpanzee, gorilla, and orangutan[47].

A similar analysis of the putative S-X-Y regulatory module in the promoters of genes involved in MHC class I cell surface expression revealed the presence of the evolutionarily conserved S-X-Y module in the promoter of the β2m gene[14, 37, 49]. The S-X-Y module was not found in the promoters of the TAP and LMP [49]. This explains the observed lack of CIITA-mediated activation of these genes[13, 32].

We have recently demonstrated that the RFX complex plays a role in the constitutive and CIITA-mediated transactivation of MHC class I and β2m genes[14]. In fibroblast cell lines from BLS patients with a defect in RFX subunits, the reduced levels of constitutive MHC class I and β2m transcripts could be restored upon stable transfection of RFX5 and RFXAP in these cells derived from groups C and D, respectively[14]. Furthermore, we have shown that the RFX subunits RFX5 and RFXAP could directly induce the MHC class I and β2m promoter in RFX-deficient cell lines of complementation groups C and D, respectively, and that this activity required an intact X1-box[14]. Likewise, the CIITA-mediated transactivation of the MHC class I and β2m promoter required the presence of a functional RFX complex. Together, these observations revealed that RFX plays a role in the constitutive and CIITA--mediated transactivation of MHC class I and β2m genes.

There are several lines of evidence to suggest a mutual interdependency of the transcription factors RFX, X2BP (ATF/CREB) and NF-Y in the formation of a highly stable quaternary multiprotein/X-Y DNA complex[10, 28]. Although individual binding of RFX or X2BP to some of the MHC class II promoters has been shown to be absent or poor[15, 28, 40], the RFX/X2BP/NF-Y complex is formed on all class II isotypes and functionally related genes X-Y DNAs, thus allowing the class II isotypes to be regulated in a coordinate fashion[10, 27, 28]. Inversely, the lack of expression of all MHC class II genes in BLS-derived cell lines defective for one of the RFX subunits might be explained by the lack of formation of stable RFX/X2BP/NF-Y complexes. *In vivo* DNA footprint data, which show that the promoters of the various class II isotypes and functionally related genes in RFX deficient cells exhibit a "bare" phenotype with unoccupied X1, X2 and Y-box elements, are in line with this latter hypothesis[5, 19, 20].

T-Cell Development in MHC Class II Deficiency

Gene products of the MHC control the acquisition of the mature T cell repertoire through positive and negative selection processes by thymic epithelial and dendritic cells of the cortex and medulla, respectively[2, 12, 29, 51]. During these selection events, interactions between the TCR and MHC class I or class II molecules play an important role in the development of the $CD8^+$ and $CD4^+$ single positive T cells, respectively. Ultimately, these selection processes result in the generation of a pool of T cells with TCRs which have the appropriate affinity towards MHC/self-peptide complexes (i.e. non-autoreactive) and which are able to recognize and respond to MHC/foreign-peptide complexes. In particular, MHC class II molecules play a central role in mounting an immune response by virtue of their ability to present antigen mainly to $CD4^+$ helper T cells. The lack of MHC class II expression in BLS patients may present special problems with respect to T cell development during thymic differentiation and, subsequently, upon antigen challenge.

In a first step to investigate the impact of deficient MHC class II expression on the shaping of peripheral T cell immune repertoire, we have studied the expression patterns of the CD4 and CD8 antigens amongst PBMC of BLS patients. In the periphery of BLS patients, CD4-positive T cells could be detected within

Table 1. Ratio of peripheral $CD4^+/CD8^+$T lymphocytes in BLS

Patient	Defect	Age	Ratio $CD4^+/CD8^+$
ATU	CIITA	6 months	0.12
EBA	RFX-B	7 months	2.5
EVF	RFX5	6 years	0.6
SSI	RFX5	6 months	0.3
OSE	RFX5	2 years	0.3
MBI	RFXAP	6 months	0.9

Table 2. Co-expression of CD45RO on $CD4^+$ T cells

Patient	%	Age matched control (%)
ATU	36	3–18
EBA	43	3–18
EVF	81	23–45
SSI	70	3–18
OSE	67	23–45
MBI	48	3–18

the peripheral T cell compartment albeit, in almost all cases investigated, at reduced numbers (Table 1). Noteworthy is that these peripheral $CD4^+CD8^-$ T lymphocytes expressed enhanced levels of CD45RO which might be a reflection of *in vivo* activation of these $CD4^+CD8^-$ T cells (Table 2).

Since the generation of the T cell repertoire is influenced by the interaction of the TCR with peptide/MHC class II-complexes, we have investigated the impact of the MHC class II deficiency of TCR V-gene usage by $CD4^+$ and $CD8^+$ T lymphocytes. No restrictions were found in the usage of TCR V-genes incorporated in the TCR α and β chains of the $CD4^+$ and $CD8^+$ T cell sub-populations within the peripheral T cell compartment[41, 50]. These observations indicate that, even in the absence of traditional MHC class II antigen expression, T cell repertoire development with respect to the TCR V-gene usage within the $CD4^+$ T cell subset is not impaired by the absence of MHC class II molecule expression.

We have demonstrated that in healthy individuals incorporation of TCR V-genes in TCR α and β chains is not randomly distributed among the $CD4^+$ and $CD8^+$ T cell subsets, but that the expression of a number of the TCR AV- or BV-genes was skewed either to the $CD4^+$ or to the $CD8^+$ T cell subset[16]. These specific skewing patterns are found in Caucasian individuals and is independent of the immunological state and the HLA haplotype. A similar analysis in BLS patients revealed inversed $CD4^+$ skewing patterns[17, 50]. In contrast, normal skewing pattern of TCR AV- and BV-genes towards the $CD8^+$ T cell subset were observed in these BLS patients [17, 50]. These alternations in the skewing patterns of TCR V-genes towards the $CD4^+$ T cell subset might reflect the lack of MHC class II-mediated positive selection operating on the single CD4 positive subset of T lymphocytes expressing these particular TCR V-genes.

More recently, we have observed that the absence of MHC class II molecule expression in BLS patients has an effect on the net charge and hydropathic index of the TCR complementarity determining region (CDR) 3 within the $CD4^+$ T cell subset[17]. This was the direct result of an altered amino acid composition of the TCR CDR3 in $CD4^+$ T lymphocytes in BLS when compared with healthy controls. Since the TCR CDR3 region predominantly interacts with the MHC bound peptide, the altered CDR3 amino acid composition might have functional implications with regard to affinity and avidity of the TCR-peptide/MHC interactions. Such altered profiles are likely to be a direct reflection of the lack of MHC class II-mediated selection processes in these BLS patients.

Concluding Remarks

Cell material obtained from BLS patients has been instrumental in the description of a common regulatory pathway for MHC class I and class II gene transactivation. Central in this pathway is the S-X-Y regulatory module that exists in the promoters of the MHC class I and class II genes and, interestingly, also in the promoters of a number of accessory genes involved in antigen processing and presentation, i.e. β2m, and invariant chain, and HLA-DM, respectively. The MHC class II transactivator exerts its activity through the multiprotein complex which consists of the RFX complex, X2BP (ATF/CREB) and NF-Y bound to this regulatory module. The formation of this multiprotein complex is critically dependent on the involvement of all components. Absence of complex formation, as is found in BLS patients with a defect in RFX, results in lack of CIITA-mediated transactivation of MHC class I and class II genes.

Despite the absence of MHC class II expression, $CD4^+$ T cell development can occur, albeit less efficiently, which results in a sharp diminution of the number of peripheral $CD4^+$ T cells in BLS patients. Noteworthy is that the enhanced expression of CD45RO on these $CD4^+$ T cells reveals that they can be activated *in vivo.* Furthermore, the MHC class II-deficient environment does not have a major impact on the overall usage of the TCR V-gene segments in the $CD4^+$ and the $CD8^+$ T cell subsets. However, these BLS $CD4^+$ T cells dis-

played reverse skewing patterns of TCR V-genes and modified CDR3 amino acid profiles.

On the basis of the results in this human disease model it could be argued that $CD4^+$ T cell development in BLS is mediated by alternative thymic ligands such as MHC class I molecules. On the other hand, acquisition of $CD4^+$ phenotype might occur at low frequencies in an apparent random fashion during development without any selection.

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