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Transcriptional regulation of the MHC class II antigen presentation pathway

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The genes encoding the major components of the antigen processing and presentation pathway (MHC class II, invariant chain and HLA-DM) are regulated in a coordinate and concerted fashion by a conserved group of transcription factors. The identification and characterization of these transcription factors over the past few years has provided insight into how these important genes and the process of antigen presentation are regulated. Regulation of the antigen processing genes includes mechanisms involving the epigenetic modification of DNA sequences and chromatin, and the control of nuclear import of transcription factors.

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Abbreviations

APC	antigen-presenting cell
BLS	bare lymphocyte syndrome
CIITA	class II transactivator
CARD	caspase recruitment domain
CLIP	class II associated invariant chain peptide
CREB	cyclic AMP response element binding protein
DC	dendritic cell
GBD	GTP-binding domain
HLA	human leukocyte antigen
Ii	invariant chain
IRF	interferon regulatory factor
pAPC	professional APC
RFX	regulatory factor X
STAT	signal transducer and activator of transcription

Introduction

The MHC class II antigen processing and presentation pathway plays a central role in regulating the activation and specificity of $CD4^{+}$ T cell responses, which in turn regulate many components of the adaptive immune response. This pathway provides a mechanism for sampling and displaying peptides generated from proteins targeted to the endosomal compartments of professional antigen-presenting cells (pAPCs). General features of this pathway are common to all pAPC, which include dendritic cells (DCs), macrophages, B lymphocytes and thymic epithelial cells. MHC class II $\alpha\beta$ heterodimers initially assemble in the endoplasmic reticulum with invariant chain (Ii), which acts as a chaperone to stabilize the heterodimer, prevents premature peptide loading and targets class II molecules to late endosomal compartments. Ii is partially released through a series of proteolytic cleavage events, leaving a residual peptide (class II associated invariant chain peptide; CLIP) occupying the peptide-binding groove of the MHC molecule. The release of CLIP and its replacement with antigenic peptides is catalyzed by HLA-DM, which is independently targeted to late endosomal compartments. The resulting MHC class II–peptide complex is then transported to the cell surface where it awaits interactions with antigen-specific T cells. The expression of MHC class II, Ii and HLA-DM genes is coordinately regulated at the level of transcription by a conserved set of factors and defined *cis*-acting elements.

Expression of the antigen processing genes

The antigen processing machinery is selectively expressed in a tissue-specific manner and it is modulated both during APC development and following stimulation by cytokines and microbial products. For example, processing and presentation functions are highly regulated and temporally segregated in DCs [1–3]. Acting as surveillance cells in peripheral sites, immature DCs are capable of efficient antigen uptake, but their antigen presentation function is relatively weak. Inflammatory agents induce maturation of DCs and stimulate their migration into the T cell areas of secondary lymphoid organs. Maturation is characterized by downregulation of endocytic activity and increased cell surface expression of MHC class II and co-stimulatory molecules. Moreover, there is a striking reorganization of MHC class II molecules, which move from a predominantly intracellular localization in lysosomes to the plasma membrane. During maturation, stored antigen is processed to generate MHC–peptide complexes, which are subsequently displayed for extended time periods on the surface of mature DCs after their arrival in secondary lymphoid organs. Upregulation of cell-surface MHC class II expression is accompanied by the downregulation of MHC class II biosynthesis. This provides a mechanism to limit the initiation of immune response to antigens internalized by DCs immediately preceding or following exposure to inflammatory or microbial stimuli.

MHC class II, Ii and HLA-DM proteins are expressed very early in the development of B cells, including at the pro-B stage [4]. Expression is upregulated at later stages

of development and is followed by silencing of expression as B cells differentiate into plasma cells [5,6]. Expression of the antigen processing machinery can also be induced in non-bone-marrow-derived cells by exposure of the cells to IFN-γ. All of these events involve regulation at the transcriptional level.

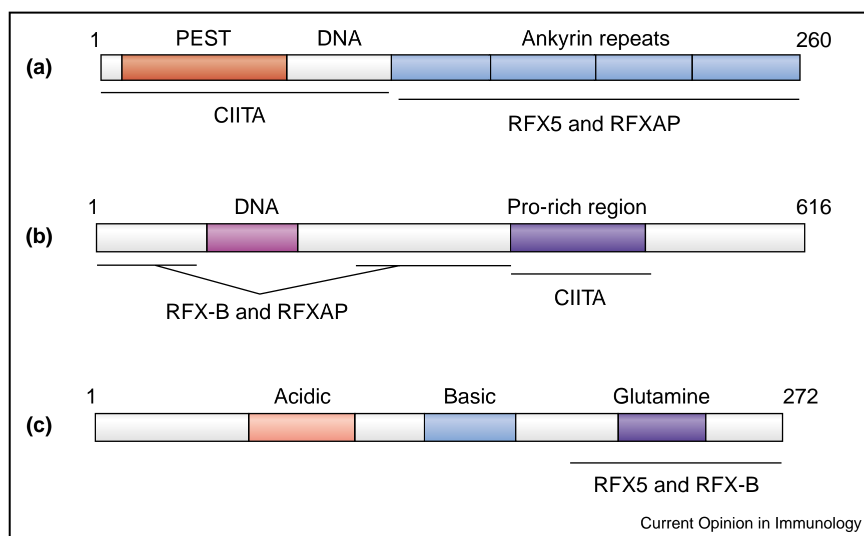
Common *cis*- and *trans*-acting factors control the antigen processing genes

Located ~100–200 bp 5′ to the start site of transcription, each of the antigen processing and presentation genes (MHC class II, Ii and HLA-DM) contain a common set of *cis*-acting elements. This conserved region, which consists of the W/S, X1, X2 and Y boxes, is sufficient for transcriptional activation to all known developmental and induced expression cues. The Y box is ubiquitous in the genome and binds the heterotrimeric transcription factor NF-Y, which is composed of NF-YA, NF-YB and NF-YC. NF-YB and NF-YC contain histone fold domains that are thought to bend the DNA at promoters, a process that may facilitate the efficient assembly of multiple transcription factors and provide easy access for RNA polymerase. The X2 box was found to bind to the cyclic AMP response element binding protein CREB [6]. CREB is involved in numerous regulatory pathways involving neuronal and immunological development and regulation. In addition to a potential novel role in MHC class II gene regulation, CREB is important for the stability and assembly of the X1 box factor, regulatory factor X (RFX), at WXY promoters.

Clues to the factors that interact with the X1 element were derived from the discovery and analysis of patients exhibiting the bare lymphocyte syndrome (BLS), in which MHC class II expression is absent (reviewed in [7]). BLS is caused by mutations in specific *trans*-acting factors, for which four complementation groups are defined (termed BLS groups A, B, C and D). BLS groups B, C and D are deficient for the DNA-binding factor RFX, which binds to the X1 box. RFX is a heterotrimer, with a different subunit affected in each of the three BLS groups. BLS groups B, C and D are deficient in RFX-B (RFXANK), RFX5 and RFXAP, respectively [8–12]. As illustrated in Figure 1, the three subunits have domains that are required for subunit assembly, for which the ankyrin repeats of RFX-B are essential [13–15]. One important feature of the RFX-deficient BLS groups is that the promoters of MHC class II genes are unoccupied in cell lines derived from these individuals [16]. This highlights the importance of RFX and suggests that RFX is essential for assembly of all of the factors at WXY promoters. *In vitro* evidence showing that RFX, CREB and NF-Y form a stable cooperative complex on X–Y DNA supports the idea that these factors form a scaffold for the recruitment of additional factors, such as the class II transactivator (CIITA; see below) and RNA polymerase.

BLS group A patients are wild type for RFX, CREB and NF-Y. Moreover, these factors assemble on MHC promoters *in vivo*, yet the genes are not expressed. The factor deficient in this complementation group is responsible for activating transcription and was termed the CIITA [17]. CIITA does not bind DNA directly, but instead assembles at WXY promoters through direct interactions with the RFX–CREB–NF-Y complex [18••,19]. When bound,

Figure 1



The structure and functional regions of the RFX subunits. **(a)** RFX-B contains a proline, glutamic acid, serine, threonine-rich domain (PEST)-like sequence, a potential DNA-binding region and four ankyrin repeats. **(b)** RFX5 contains a well-defined DNA-binding domain that is similar to other RFX family members, as well as a proline-rich (Pro-rich) region. **(c)** RFXAP contains acidic, basic and glutamine-rich regions. The regions responsible for interactions with other RFX subunits and CIITA are indicated.

CIITA activates transcription through a potent acidic activation domain located in its amino terminus. Through this domain, and other sequences, CIITA interacts with components of the basal transcription machinery. CIITA also interacts with at least three coactivators, including CREB binding protein (CBP), p300 and p300/CBP associated factor (PCAF) [20–22,23••]. These interactions probably facilitate the opening of chromatin, as CIITA binding to the WXY promoter results in the acetylation of histones H3 and H4 [18••]. CIITA has been also shown to interact with the elongation factor pTEFb [24]. These interactions may facilitate the escape of RNA polymerase from the transcription initiation complex.

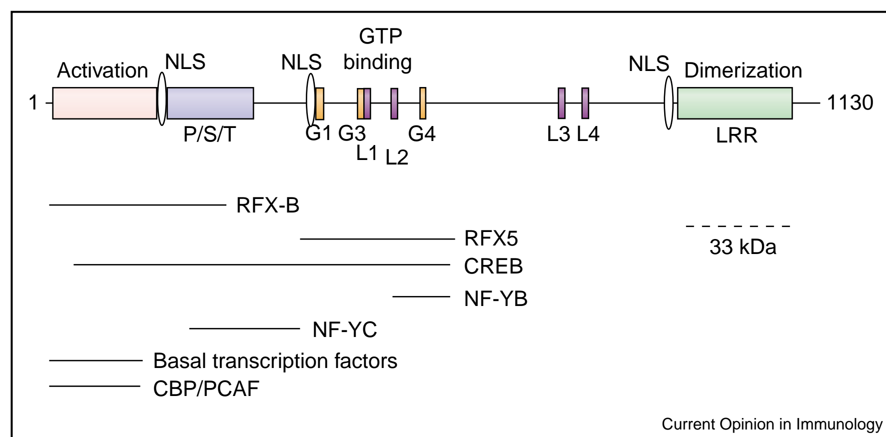
Although the story sounds rather complete, many aspects of RFX, CREB and CIITA function remain to be delineated. Each of the subunits of RFX is phosphorylated, yet the sites and roles of these modifications are unknown. Is it possible that such post-translational modifications control nuclear import/export of RFX, the ability to efficiently bind CIITA, or assembly of the transcription factor complex *in vivo*? The delineation of the role of cAMP in modulating MHC class II expression has been interesting. In some cell systems, agents such as prostaglandin E_2 or other biological conditions that increase cellular cAMP levels result in downregulation of IFN-γ induced MHC class II gene expression. One report shows that CIITA nuclear localization is involved [25•]. Another contributing mechanism in this response could involve CREB, which is directly phosphorylated in the cAMP pathway, an event that leads to the binding of the CBP and p300 coactivators. It is not known if CREB phosphorylation alters the ability of CBP to interact properly at the class II promoter. Additionally, a potentially novel BLS complementation group (E) was described in which the MHC class II genes transcribed in the centromeric direction are not expressed [26]. The factor responsible for this fascinating phenotype is unknown.

CIITA — structure and function

Structurally, CIITA can be divided into four general domains (Figure 2). As stated above, the amino-terminal region functions as a transcriptional activator. This region has been shown to interact with many other proteins and it also has the ability to acetylate histones [27]. Just downstream of the activation domain is a proline–serine–threonine-rich region with regulatory potential, which was found to be important when mutated in some systems. Further downstream is a Walker-type GTP-binding domain (GBD), which binds but does not hydrolyze GTP *in vitro* [28], suggesting that GTP binding may regulate CIITA's conformation. Indeed, mutation of this sequence disrupts CIITA's activity and results in the accumulation of the protein in the cytoplasm. Close to its carboxy-terminal end, CIITA has at least four leucine-rich repeats (LRR; [29,30,31•]). The LRR regions, originally described for RNase inhibitor, form a horseshoe-like structure that functions in protein–protein interactions [32]. Mutation of these sequences disrupts CIITA activity and results in the accumulation of CIITA in the cytoplasm [29]. LRRs and GBD have been found together in several other proteins, such as nucleotide-binding oligomerization domain (NOD) 1, but the functional significance of these combined motifs remains to be investigated [33•].

The LRR and GBD domains of CIITA are also involved in the ability of CIITA to form homomeric complexes

Figure 2



The structure and functional regions of CIITA. CIITA contains an acidic activation domain (pink), three nuclear localization domains (NLS), a proline, serine, threonine-rich (P/S/T) region (blue), the G1, G3 and G4 homology domains that define a Walker-type GTP-binding domain (orange boxes), four LXXL sites that may be involved in protein–protein interactions (L1–L4, purple boxes), and a LRR region (green). The straight lines underneath the schematic indicate regions of CIITA that were found to interact with the RFX, CREB and NF-Y subunits, as well as with basal transcription factors and the coactivators CBP and PCAF. The dotted line indicates a potential interaction with an unknown 33 kDa protein reported by Hake *et al.* [30].

[31•,33•]. Although there is growing evidence that self-associated CIITA may be the functional form, this remains to be firmly established. The concept of CIITA self-association begs two questions. The first question is why does CIITA self-associate? The answer may have been suggested over 13 years ago by the functional identification of inverse WXY box regions 5′ to the mouse class II genes [34]. In a transgenic mouse model, loss of the upstream YXW region resulted in the selective loss of MHC class II transgene expression. Thus, it is possible that both WXY regions function in concert through interactions with oligomeric CIITA. A scan of the MHC class II region in humans results in the identification of numerous XY box regions (U Nagarajan, J Gomez, JM Boss, unpublished data) that could potentially participate as proposed. A second question relates to CIITA self-association — is this event is regulated? As noted above, CIITA has multiple serine and threonine residues which, following phosphorylation, could regulate CIITA's structure and ultimately its activity.

Regulation of CIITA

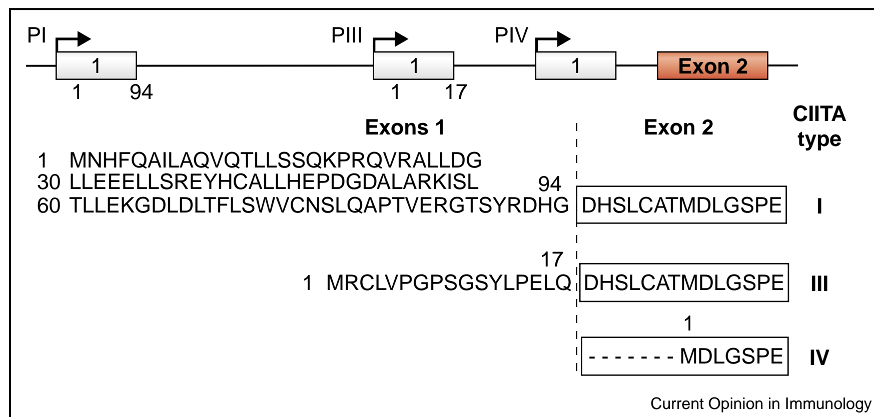
CIITA is expressed from three promoters (PI, PIII, and PIV) that not only provide tissue-specific control but also encode a unique first exon that is spliced into a common exon 2, resulting in distinct amino-terminal sequences for the expressed CIITA proteins (Figure 3; [35]). PIV is induced by non-bone-marrow-derived cells in response to IFN-γ [36••]. PIV's exon 1 does not encode a start codon and therefore CIITA initiates at the first methionine within exon 2. PIII is induced predominantly by B lymphocytes and encodes a novel 17 amino acid amino-terminal segment. PI is induced by macrophages and dendritic cells, and encodes a unique 90 amino acid sequence that shares homology to the caspase recruitment domain (CARD) found on proteins involved in apoptotic signaling cascades [37•]. Although the role of this domain in CIITA is not known, CARDs are often involved in protein–protein interactions. The PI isoform was found to have a greater activation potential than the other forms of CIITA [37•]. It is tempting to speculate that each CIITA isoform provides unique abilities to regulate antigen presentation in specific tissues.

Expression of PIV CIITA requires two IFN-γ inducible factors: signal transducer and activator of transcription (STAT) 1 and interferon regulatory factor (IRF)-1 [38]. STAT1, which is constitutively expressed, is directly activated by IFN-γ induced phosphorylation. IRF-1 expression also requires STAT1. The PIV promoter shows two distinct stages of assembly [39•]. Within 30 minutes of IFN-γ signaling, STAT1 binds and the local chromatin structure undergoes moderate histone acetylation. However, CIITA is not transcribed until enough IRF-1 is synthesized and the PIV IRF-1 site becomes occupied. This process takes between 90 and 240 minutes to occur.

PIII-mediated CIITA expression is constitutive in B cells and follows the developmental stage of B lymphocytes. As B cells progress into the terminally differentiated plasma cell, they lose MHC class II expression. This loss of class II expression directly correlates with the loss of CIITA expression at PIII. It has been suggested that the B lymphocyte inhibitory maturation protein (BLIMP1) directly represses CIITA PIII [5]. It is intriguing that the B cell differentiation factor Pax5 has been implicated in CIITA expression. Although it is not yet known how Pax5 regulates CIITA, Pax5 is also inhibited by the expression of BLIMP1 [40]. Thus, there appears to be a regulatory circuit involving positive and negative regulators of CIITA during B cell development.

Little is known about the regulatory control of CIITA in DCs; MHC class II is highly expressed in DCs. As

Figure 3



CIITA is transcribed from multiple promoters. A schematic drawing of the three murine CIITA promoters is shown. Each promoter transcribes its own first exon sequence, which is spliced into the common exon 2. The resulting amino termini of the promoter-specific CIITA isotypes are shown in amino acid one letter code. The boxed region indicates the amino acids contributed by exon 2.

suggested above, the maturation of DCs after exposure to inflammatory signals results in a rapid repression of CIITA transcription and MHC class II expression. This mechanism appears to be mediated through a global epigenetic mechanism involving histone deacetylation [41••]. Multiple sequence motifs that were active in DCs at PI were also identified [41••]. The factors that bind to these sites remain to be identified. Curiously, knockout of the PIV CIITA promoter, which results in the loss of MHC class II induction by IFN-γ in non-bone-marrow-derived cells, does not alter the ability of macrophages to induce MHC class II following IFN-γ treatment [36••]. The results of this analysis suggest that macrophages can respond to IFN-γ through their PI promoters. The mechanisms by which macrophages upregulate MHC class II and CIITA is clearly important because upregulation of MHC class II is required for their antigen presentation function.

Epigenetic control of MHC class II genes and CIITA

In addition to direct protein binding to DNA, MHC class II genes are regulated by epigenetic mechanisms that serve to restrict expression. Two major examples in which such mechanisms have been observed involve the development of fetal trophoblasts and the formation of some solid tumors [42,43•,44]. In the case of fetal trophoblasts, their inability to induce MHC class II molecules may play a role in preventing the inappropriate expression of paternal antigens. By contrast, the inability of tumors to express MHC class II in response to IFN-γ is probably an immunosurveillance escape mechanism. In both cases, the ability of CIITA to be induced by IFN-γ is lost and treatment of cells with the methylation inhibitor 5′deoxyazacytidine results in the re-expression of CIITA and MHC class II transcription. Such experiments indicate that cytosine methylation is responsible for the loss of expression. In both cases, cytosine methylation of PIV is the target. Fine mapping of the methylated residues points to a global methylation of the region in fetal trophoblast-like cell lines [39•]. Cytosine methylation leads to the deacetylation of local histones and the closing of the chromatin structure. The result is that transcription factors no longer have access to the region. Although several *de novo* DNA methyltransferases have been identified, the one(s) responsible for CIITA methylation are not known.

Concluding remarks

The MHC class II antigen presentation pathway is largely regulated at the level of transcription, through mechanisms involving the interplay between a host of specific and general transcription factors, post-translational modifications, and local changes in chromatin structure. This complex genetic system provides a means of fine-tuning antigen presentation function, controlling the cell types that can participate and providing a mechanism to respond to external cues that regulate the activation and differentiation state of APCs. The precise mechanisms controlling the above regulatory events are still not fully understood. Additionally, the ability of microbes to alter these pathways and regulatory events provides an escape from immune detection for which treatments and immune-based therapies could ultimately be applied. Future work in this field will no doubt focus on the different regulatory mechanisms with the goal of applying this knowledge to the treatment of autoimmune disease, cancer and the development of vaccines.

Update

A recent computer-based search of the genome databases identified numerous mammalian genes that contained structural features similar to CIITA, including CARD, nucleotide-binding and LRR domains. The functional roles of these genes is not known, but their discovery offers not only the ability to determine the evolutionary divergence of ancestral CIITA molecules but also the ability to determine if and how any of these novel genes function in immune responses [45•].

Post-translational phosphorylation of CIITA within the proline, serine, threonine-rich (P/S/T) region was found to be associated with increases in the levels of nuclear CIITA, with the ability of CIITA to oligomerize, and with increased levels of MHC class II expression in immature APCs. These data support the model that CIITA functions in an oligomeric state, which can be controlled by phosphorylation [46].

A mutation in the DNA-binding domain of RFX5, which reduces the affinity of RFX for certain X box regions was recently found to be the genetic cause of the BLS group E [47••].

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