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The Bare Lymphocyte Syndrome: Molecular Clues to the Transcriptional Regulation of Major Histocompatibility Complex Class II Genes

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Major histocompatibility complex (MHC) class II proteins are cell-surface heterodimeric glycoproteins that function in the initiation of acquired immune responses. In antigen-presenting cells, antigenic peptides are loaded onto MHC class II molecules in a process that depends on the class II invariant chain and another accessory protein, human leukocyte antigen (HLA-DM). This process is completed in a specialized, post-Golgi intracellular compartment, the MHC class II compartment (MIIC; Peters et al. 1991), where peptides with the highest affinity for the MHC class II proteins are selected for presentation (Denzin and Cresswell 1995). Subsequently, the MHC-peptide complex is transported to the surface where it can interact with antigen-specific $CD4^+$ T-helper cells, initiating an immune response. MHC class II molecules are expressed in a limited subset of immune cells, including B cells, macrophages, activated T cells, thymic epithelial cells, and dendritic cells. MHC class II genes may also be induced in many other cell types by the cytokine interferon-γ (IFN-γ). Induction by IFN-γ may allow presentation of antigens to the immune system by nonimmune cells.

Because of this intimate involvement in immune responses, aberrant expression of MHC class II genes could potentially lead to or sustain autoimmune disorders, tumor growth, or failure to mount an immune response. Lack of expression of MHC class II genes results in a severe combined immunodeficiency, called bare lymphocyte syndrome (BLS). Patients with BLS are 5% of all cases of severe combined immunodeficiency (Elhasid and Etzioni 1996). Cell lines derived from these patients and a collection of lab-generated cell lines that share the same characteristics as BLS-derived cells have provided unique tools for elucidating the regulation of MHC class II genes. This review will focus on the molecular basis for BLS and on how understanding the genetics of this system has provided the current models of MHC class II gene regulation.

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MHC Class II Genes

MHC class II genes are located on the short arm of chromosome 6. The MHC class II locus encodes separate α and β chains for each of the three isotypes: HLA-DR, HLA-DQ, and HLA-DP. Driving the expression of these isotypes—and the expression of other gene products that are involved in antigen presentation—is a conserved upstream *cis*-acting regulatory region that coordinately regulates their expression.

This regulatory region consists of four major elements: the W, X1, X2, and Y boxes. Maximal expression in B lymphocytes and during IFN-γ induction requires the presence of all these elements (reviewed by Boss 1997). The W box is the least fully characterized of the four elements, but the DNA-binding factor regulatory-factor X (RFX; discussed extensively below) has been suggested to interact with this region. RFX and the X2-box–binding protein (X2BP), recently identified as the cAMP response-element–binding protein (CREB), bind to the X1 and X2 boxes, respectively (Boss 1997; Moreno et al. 1999). The Y box, an inverted CCAAT box, is bound by the heterotrimeric factor nuclear-factor y (NF-Y). These three DNA-binding factors are required, but are not alone sufficient, for MHC class II expression. A fourth factor, the class II transactivator (CIITA), which does not appear to bind DNA (Steimle et al. 1993), is also required. CIITA is proposed to interact with the DNA-bound factors RFX, CREB, and NF-Y at the class II promoter and to use its acidic activation domain to activate transcription.

BLS and MHC Class II Expression

BLS is a rare autosomal recessive disease characterized by severe combined immunodeficiency. More than 40

cases have been diagnosed since its description (Griscelli et al. 1989). Although some patients show very low levels of MHC class II cell-surface expression, most patients do not express MHC class II proteins or mRNA in their cells. Patients can also vary in the levels of expression of MHC class I proteins, which are expressed on virtually all cell types. Patients with BLS usually present in the first year of life with infections in the respiratory system and the gastrointestinal tract. In addition, viral infections are extremely dangerous, and, as a result of intestinal infections, affected children exhibit protracted diarrhea, severe malabsorption, and failure to thrive. The humoral immune response in these patients is severely impaired, varying from panhypogammaglobulinemia to reduction in one or two of the Ig isotypes (Klein et al. 1993). The prognosis for these patients is very poor, and most do not reach puberty (Elhasid and Etzioni 1996). The current treatment for BLS includes regular intravenous immunoglobulin support and prophylactic antibiotics (Klein et al. 1993; Elhasid and Etzioni 1996). The only effective long-term treatment is a bone-marrow transplant. The prognosis for post-transplant BLS patients depends on the age of the patient, with younger patients responding more favorably. Infection as a result of the immune suppression after transplant causes many of the complications associated with recovery (Elhasid and Etzioni 1996).

Haplotyping of family members of patients with BLS shows that the MHC locus segregates independently of the BLS phenotype (de Preval et al. 1985), suggesting, as proposed by Gladstone and Pious (1980), that one or more transacting factors that regulate expression of MHC class II genes are mutated in this syndrome. To determine how many genes are involved in BLS, somatic cell-fusion experiments were performed between the different patient cell lines and in vitro–generated cell lines. Four complementation groups—A, B, C, and D—have been defined (Benichou and Strominger 1991; Seidl et al. 1992), demonstrating that, although patients with BLS share a similar phenotype, the genetic basis of the disease is heterogeneous (table 1).

This complementation analysis provided a powerful system with which to identify the defective genes in two of the complementation groups. Further clues about the different molecular defects in the various complementation groups came from in vitro and in vivo studies of protein-DNA interactions in the MHC class II gene promoters. In a variety of DNA-binding assays, X2BP/CREB and NF-Y binding is seen, both in wild-type cells and in all complementation groups of BLS cells. However, two patterns emerged with regard to RFX binding. RFX activity was present in BLS group A cells but not in cells from groups B–D, suggesting that RFX activity may be encoded in three or more distinct genes. Furthermore, in vivo footprint analysis reveals two patterns that correlate with RFX activity (Kara and Glimcher 1991, 1993), corresponding to the X1-, X2-, and Y-box regions of the MHC class II promoters. Both wild-type and BLS group A cells contain fully occupied promoters, but the other BLS groups show no binding to X1, X2, or Y elements.

Complementation Group A: CIITA Deficiency

Defects in CIITA are common to all cells in complementation group A—the first of the BLS groups to be characterized at the molecular level. *MHC2TA,* the gene that encodes CIITA, maps to 16p13. CIITA was cloned by cDNA complementation in an in vitro–generated cell line (Steimle et al. 1993). The N-terminal portion of the 1,130 amino acid CIITA protein carries a transcriptional-activation domain (Riley et al. 1995; Zhou and Glimcher 1995). The finding that CIITA does not bind to DNA (Steimle et al. 1993) is consistent with the in vivo footprinting results showing a fully occupied promoter region in BLS group A cells and suggests that CIITA interacts with the DNA-bound W-, X-, and Y-box factors. Indeed, CIITA appears to act as a master regulator, because it is developmentally regulated in B cells (Chang et al. 1992) and because it is induced by IFN-γ (Steimle et al. 1994) in nonlymphoid cells prior to their induction of MHC class II genes.

The cloning of *MHC2TA* has allowed for mutation analysis of cells in complementation group A, whether from cultured mutant cell lines or from the two known patients in this group, patient BCH and patient BLS-2. Mutations in the BLS group A–like cell line, RJ2.2.5, comprise a complete loss of one allele (Steimle et al. 1993) and an internal deletion of 1,811 bp in the second allele (Brown et al. 1995). Patient BCH is a compound heterozygote with a G→T transversion that results in a nonsense mutation and a severely truncated protein in one allele (Bontron et al. 1997). The second allele contains a G→A transition in a splice-donor sequence leading to an 84 bp in-frame deletion of an exon. Both mutations completely inactivate the CIITA protein. Patient BLS-2 is homozygous for a G→A transition in a splice-donor sequence that results in a 72 bp in-frame deletion (Steimle et al. 1993). This deletion removes a 5 amino acid nuclear-localization sequence, rendering CIITA unable to translocate to the nucleus (Cressman et al. 1999).

Two CIITA knockout mice have been generated (Chang et al. 1996; Williams et al. 1998). Both mutant mouse strains display a phenotype similar to that of patients with BLS in that they lack MHC class II molecules on their antigen-presenting cells and have a reduced number of peripheral $CD4^+$ T cells. Interestingly, both mutant strains have residual MHC class II expression on a subset of thymic epithelial cells and on a subset

Table 1

Mutations in BLS Genes

BLS Group and Gene (Location)	Cell and Patient Lines	Genotype	Mutation(s)	Result of Mutation	MHC Levels
A:					
CIITA (16p)	BLS-2	H	G→A at s.d.	72 bp in-frame Δ of exon encoding a.a. 940–963 that contains nuclear localization signal	ND
	BCH	CH	G→T; G→A at s.d.	GAA (Glu^{381})→TAA (stop); 84 bp in-frame Δ (a.a 1079–1106)	ND
	RJ2.2.5[a]	CH	1,811-bp Δ in mRNA completely deleted	Frameshift; complete null	ND
B:					
RFX-B or *RFX-ANK* (19p12)	Bequit (Ab), Nacera (Nh), and Ramia (RA)[b]	H	26-bp Δ in s.a. of exon 6	Frameshift	ND
	BLS-1	H	58-bp Δ in s.d. of exon 6	Frameshift	ND
	EBA	H	G→T in exon 5	GAG (Glu^{102})→TAG (stop)	Low
	FZA	H	T→C in exon 8	CTG (Leu^{195})→CCG^{195} (Pro)	Low
C:					
RFX5 (1q21.1-q21.3)	Ro	H	C^{1032} →T^{1032}	CGA (Arg^{294})→TGA (stop)	Low
	SJO	CH	G→A in the s.a. of exon 5; other allele is not defined	Use of a cryptic s.a. at +5 results in 5-bp Δ and frameshift; not expressed	ND
	THF, EVF[c]	H	G→A at + 5 s.d. of exon 2	Use of a cryptic s.d. at −10 results in 10-bp Δ and frameshift	ND
	OSE	H	G→A in the s.a. of exon 4	Use of a cryptic s.a. at −4 results in 4-bp Δ and frameshift	ND
	SSI	H	C^{1122}→T	CAG (Gln^{321})→TAG (stop)	ND
D:					
RFXAP (13q)	ABI, AkO[b]	H	C^{279}→T^{279}	CAG (Gln^{55})→TAG (stop)	Low
	DA, ZM, SS[b]	H	ΔG^{484}	Frameshift	Low
	6.1.6[a]	CH	G insertion at 418 bp; G insertion at 508 bp	Frameshift; frameshift	Low
	ShA, ShG[c]	H	7-bp insertion at 151 as a result of duplication of 144–150 bp	Frameshift	Low

NOTE.—See text for references. Abbrieviations: H = homozygous; CH = compound heterozygous; s.a. = splice acceptor; s.d.= splice donor; Δ = deletion; and ND = not detectable.

[a] Experimentally derived mutant cell lines.

[b] Unrelated patients.

[c] Siblings or cousins.

of dendritic cells. Mice of both groups show a reduction, but not a complete loss, in their expression of the invariant chain and of H-2M (the mouse orthologue of HLA-DM; Chang et al. 1996; Williams et al. 1998). A reduction in global MHC class I expression that is observed in some human patients was not detected in either mouse. Unexpectedly, cells from both CIITA-deficient mouse strains up-regulate MHC class I when treated with IFN-γ. However, the level of IFN-γ–induced MHC class I was definitively lower in the *C2ta*$^{-/-}$ mouse, described by Williams et al. (1998), than in wild-type mice. Thus, although these knockout mice do not provide a perfect model for BLS, they do follow some of the variation that has been documented in patients with BLS. Importantly, these studies suggest CIITA-independent mechanisms of MHC class II regulation that require investigation.

Complementation Group B: RFX-B/ANK Deficiency

Patient-derived cell lines lacking RFX binding to MHC class II promoters are represented in the complementation groups B, C, and D. Co-immunoprecipitation experiments with the RFX5 subunit of RFX identified two associated proteins, with apparent molecular weights of 41 and 33 kDa (Moreno et al. 1997). The co-immunoprecipitation of p41 requires the presence of p33 and vice versa, suggesting that RFX5 and the two associated subunits form a tight complex. The study by Moreno et al. (1997) also predicted that BLS groups B, C, and D would be affected in the genes encoding the three subunits of RFX.

The largest of the four BLS complementation groups is group B, with >24 patients (Fondaneche et al. 1998). The defective gene in this group was cloned by isolating the RFX complex, sequencing the 33-kDa protein, and isolating the cDNA on the basis of the protein sequence. The gene, which maps to 19p12, was termed "*RFX-B*" (Nagarajan et al. 1999) or "*RFX-ANK*" (Masternak et al. 1998), the latter name indicating that the gene protein contains three ankyrin repeats, domains that typically mediate protein-protein interactions. These regions could be involved in RFX-complex formation and/or interaction with other DNA-bound factors, such as X2BP/CREB or NF-Y. BLS group B patients display the greatest diversity of disease alleles. BLS group B–derived cell lines Bequit, Nacera, and Ramia carry a common homozygous deletion of 26 bp that removes the splice-acceptor region of exon 6, resulting in the deletion of exon 6, and a frameshift that results in a truncated protein (Nagarajan et al. 1999; Masternak et al. 1998) (table 1). These three patients are unrelated but come from the same geographical area of North Africa, suggesting a common ancestor for this allele. Patient BLS-1 has a 58-bp deletion in the splice-donor region of exon 6, resulting in a frameshift (Masternak et al. 1998). Patient EBA has a nonsense mutation in exon 5, resulting in a truncated protein (U. Nagarajan and J. Boss, unpublished data). Patient FZA has a homozygous point mutation, changing a conserved leucine in the third ankyrin repeat to a proline in exon 8 (U. Nagarajan and J. Boss, unpublished data). Cell lines from patient EBA and patient FZA can be induced to express low levels of MHC class II genes, which may be due to an alternatively spliced product or to some residual activity of the variant protein.

Complementation Group C: RFX5 Deficiency

Complementation group C mutations are in the gene encoding RFX5, which maps to 1q21. RFX5 was the first of the RFX subunits to be identified genetically. *RFX5* was cloned by complementation of the MHC class II–negative cell line of patient SJO (Steimle et al. 1995). At 66 kDa and 616 aa, RFX5 is the largest of the RFX subunits and is the only subunit to contain a known DNA-binding motif. Patient Ro and patient SSI both carry nonsense mutations, at position 1032 and 1122, respectively (Steimle et al. 1995; Peijnenburg et al. 1999). The remaining patients all carry G→A transitions at splice junctions that result in the use of cryptic splice sites and premature truncations; these splice junctions occur in exon 5 in SJO cells (Steimle et al. 1995), in exon 2 in patient THF and patient EVF cells (Villard et al. 1997*b*), and in exon 4 in patient OSE cells (Peijnenburg et al. 1999).

Clausen et al. (1998) have generated an *Rfx5* knockout mouse and have determined that the phenotype recapitulates many aspects of human BLS. *Rfx5*$^{-/-}$ mice have a severe immunodeficiency because of absence of CD4^{+} T cells and a lack of MHC class II molecules on resting B cells and macrophages. As observed in *C2ta*$^{-/-}$ mice, MHC class II expression is present on dendritic cells, and invariant chain and H2-M were reduced but not absent. In contrast to the *C2ta*$^{-/-}$ mice, however, strong MHC class II expression was detected in thymic medullary epithelial cells and activated B cells. The finding of RFX5-independent MHC class II expression is intriguing and suggests a novel mechanism of MHC class II gene control.

Complementation Group D: RFXAP Deficiency

The gene mutated in complementation group D is *RFXAP,* which maps to 13q14. This gene was cloned by isolation of the RFX complex and sequencing of the 41-kDa protein. With its cloning, the question of

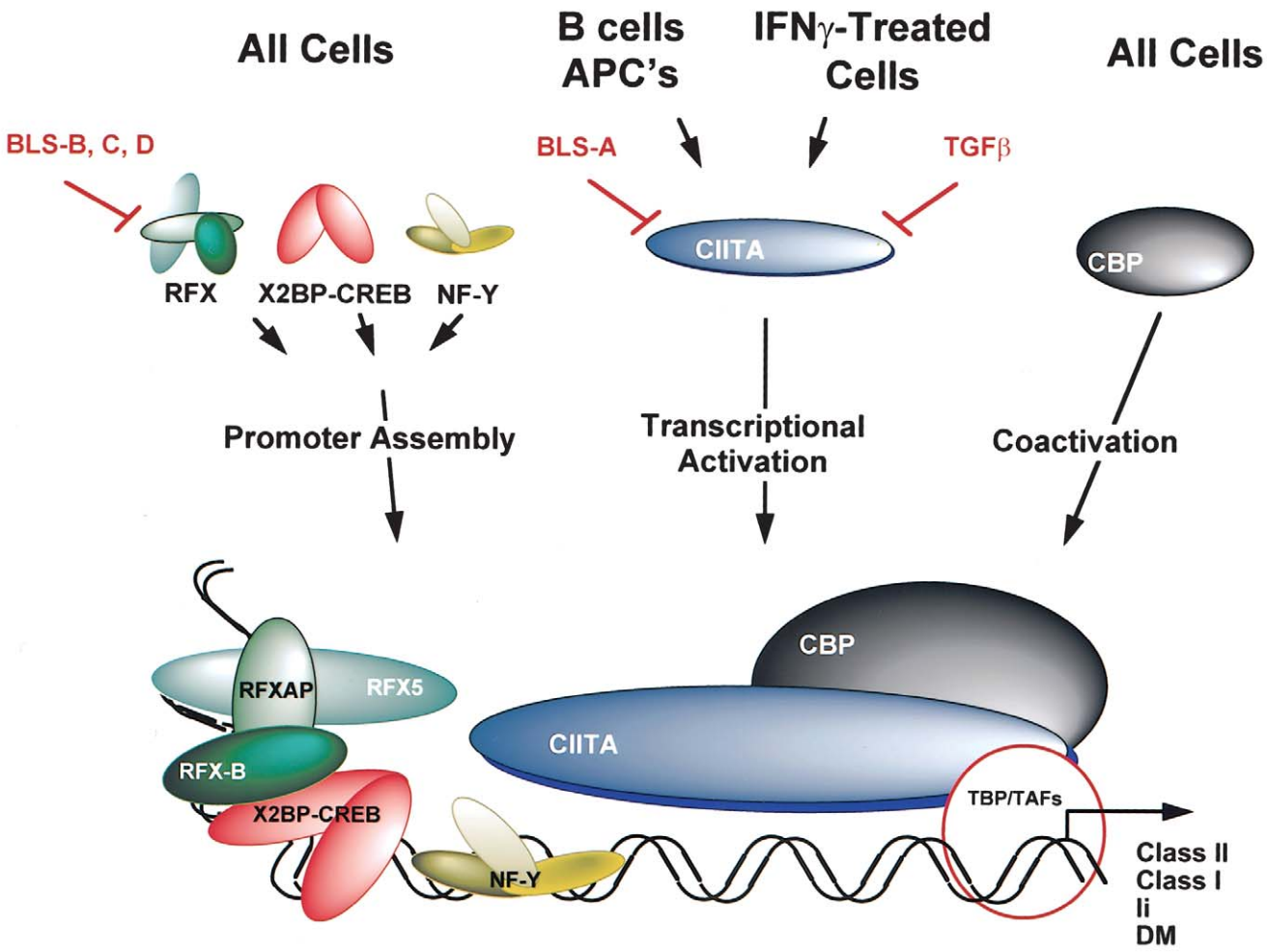

Figure 1 Model of MHC class II gene regulation. Three stages of regulation are represented. The sequence-specific transcription factors that interact with the X1-, X2-, and Y-box elements assemble in all cells. Activation of gene expression occurs in two parts. The first is through the expression of CIITA and its interaction(s) with the DNA-bound factors. CIITA may interact with components of the general-transcription complex, including TATA-binding protein and its associated factors. The second part is provided by general coactivators of transcription (represented by CBP in this model) that augment activator-dependent transcription. Regulation of expression of MHC class II genes can occur at any of these steps, as depicted by the arrows and stops.

whether a fourth complementation group existed was resolved. The question arose from the fact that cell line 6.1.6—the BLS group D experimental cell line most studied (Gladstone and Pious 1978)—as well as the patient cell lines, showed slight MHC class II expression. However, this expression did not lead to fully functional MHC class II proteins, since the patients exhibited BLS symptoms. Patient ABI (Villard et al. 1997*a*) and patient AkO (Fondaneche et al. 1998) carry, in homozygous form, a C→T transition that results in a premature stop codon and truncated protein. Patient ZM, patient SS (Fondaneche et al. 1998), and patient DA (Durand et al. 1997) have a deletion of a G at position 484 that causes a frameshift and premature stop codon. Patient ShA and pateint ShG, who are cousins, have a 7-bp insertion (duplication) at bp 151 that also results in a frameshift and premature stop codon (Fondaneche et al. 1998). Although both RFX-B and RFX5 make sequence-specific contacts with the X1 box, RFXAP binds at many positions (Westerheide and Boss 1999). The role that RFXAP plays in the RFX complex remains to be determined, but its multiple contacts with the X1 box may indicate that it helps to stabilize the binding of the RFX complex to specific DNA sequences.

Model of Class II Regulation

Figure 1 illustrates the current model of MHC class II gene regulation and the role of the BLS proteins. The RFX subunits X2BP/CREB and NF-Y are expressed in a ubiquitous manner, although their levels may vary between cell types. If present in high enough concentrations, these factors form an extremely stable complex on the X- and Y-box–regulatory region, both in vivo and in vitro. This complex is inactive in the absence of CIITA, a factor that is constitutively expressed in B lymphocytes and other antigen-presenting cells, and that is inducible by IFN-γ in most other cell types (Steimle et al. 1994). The N-terminal–activation domain of CIITA most likely interacts with the X- and Y-box factors to activate transcription (Riley et al. 1995; Zhou and Glimcher 1995). CIITA may also stabilize the binding of the RFX-CREB-NF–Y complex to DNA in cells in which the concentration of the latter factors is limiting (Moreno et al. 1997; Wright et al. 1998). Kretsovali et al. (1998) and Fontes et al. (1999) showed that the histone acetyltransferase CREB-binding protein can bind to CIITA, perhaps allowing the assembled class II transcription factor–complex to open chromatin for more efficient transcription and factor binding. Both CIITA and RFX have been found to be involved in the IFN-γ induction of MHC class I genes (Gobin et al. 1997, 1998; Martin et al. 1997), suggesting that the control of antigen presentation is an ancient system that may have existed prior to the divergence of MHC class I and class II genes.

Conclusion

The analysis of BLS has provided genetic proof that the RFX complex and CIITA are integral components of MHC class II expression. The cooperative binding of RFX with X2BP/CREB and NF-Y has substantiated their roles in the assembly and regulation of the class II promoter. Thus, this unfortunate disorder has provided a unique set of tools to unravel an important aspect of the control of the immune response: control of antigen processing and presentation. Future work will no doubt focus on how the regulatory complex assembles, additional components that may be required for activation, possible treatments for patients with BLS, and pharmaceuticals that can control the assembly and activation of these factors for use in immune-based therapies.

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Additional relevant references are included in a Supplemental Reading List, which appears, in the electronic version of this article, immediately after the References.

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