Cooperative Binding between Factors RFX and X2bp to the X and X2 Boxes of MHC Class II Promoters*

(Received for publication, March 16, 1994, and in revised form, April 27, 1994)

Walter Reith, Michel Kobr, Patrick Emery, Bénédicte Durand, Claire-Anne Siegrist, and Bernard Macháč

From the Jeanet Laboratory of Molecular Genetics, Department of Genetics and Microbiology, University of Geneva Medical School, Centre Medical Universitaire, 9 Avenue de Champel, 1211 Geneva 4, Switzerland

Transcription of major histocompatibility complex (MHC) class II genes is controlled primarily by the promoter, which contains several conserved cis-acting elements, including the X, X2, and Y boxes. We show here that RFX, the X box-binding protein that is deficient in certain MHC class II regulatory mutants, binds cooperatively with an X2 box-binding protein (X2bp) to form an RFX-X2bp-DNA complex in which the interaction of the two factors with their target sites is strongly stabilized. A functional role of this RFX-X2bp complex is consistent with mutational analysis of the X and X2 boxes of the DRA and DRB1 class II promoters. Together with previous results demonstrating cooperative binding between RFX and the Y box-binding protein NF-Y, our results indicate that RFX plays a central role in promoting cooperative binding interactions required for stable occupation of the MHC class II promoter. This may explain why the highly specific defect in binding of RFX observed in certain MHC class II regulatory mutants is associated in vivo with a bare promoter in which all of the cis-acting elements, including the X, X2, and Y boxes, are unoccupied.

Transcriptional control regions of eukaryotic genes generally consist of arrays of several different cis-acting DNA sequences that are bound by their cognate sequence-specific transcription factors, which function in concert to activate or repress transcription (1–3). Much remains to be learned about the protein-DNA and protein-protein interactions underlying the molecular mechanisms by which transcription factors cooperate to achieve their desired effect on transcription. MHC class II genes represent a good model system to study such interactions under a diverse set of conditions, including cell type-specific activation, repression, and modulation by a variety of stimuli for a review, see Ref. 4).

In man, MHC class II genes encode the α and β chains of the HLA-DR, -DQ, and -DP class II molecules, which present processed exogenous antigens to CD4+ T lymphocytes, thereby eliciting an immune response. Precise regulation of MHC class II gene expression is crucial for the control of the immune response, as demonstrated by the fact that inappropriate or unusually high expression is associated with autoimmune disease and a lack of expression leads to severe immunodeficiency.

RFX class II genes are expressed constitutively in only a limited number of cells, including B lymphocytes, macrophages, dendritic cells, thymic epithelium, and activated T lymphocytes. Their expression can be modulated or induced by a variety of stimuli, of which the most potent is interferon-γ (7–9). Finally, in mature plasma cells they are maintained repressed (10, 11).

In transient transfection experiments the 150-base pair promoter region of MHC class II genes is sufficient to reproduce normal cell-specific and inducible transcription (for reviews, see Refs. 4 and 12–14). All MHC class II promoters contain conserved cis-acting sequence motifs referred to as the W (also called Z, H, or S), X, X2, and Y boxes (4, 12–14). The Y box is the target of NF-Y (or YEBP), a heterodimeric CCAAT-binding transcription factor, which has been shown to be essential for class II promoter activity in vitro transcription systems (15–17).

Proteins binding to the X box include a novel family of DNA-binding proteins called RFX1–RFX4 (18–20) and a distinct nuclear protein called RFX (21, 22). While the role of the cloned X box-binding proteins (RFX1–RFX4) in MHC class II gene transcription is not clear, there is strong evidence that RFX is crucial for MHC class II promoter function. Indeed, RFX binding activity is deficient in several B cell lines derived from patients suffering from MHC class II-deficient immunodeficiency (also called the bare lymphocyte syndrome or BLS), a disease known to be due to a regulatory defect leading to a complete lack of MHC class II gene expression (6, 21–23).

The X2 box is a relatively degenerate sequence element, which, depending on the MHC class II promoter examined, is related to either a CRE or a TRE (4, 12–14), and can hence be recognized in vitro by members of the Jun/Fos and CREB/ATF families (24–28).

The MHC class II promoter appears to function as a single unit in which spacing between the individual cis-acting elements is crucial (29, 30) and in which the W, X, X2, and Y boxes all contribute to both cell-specific and interferon-γ-induced expression (4, 12–14). This suggests that proteins binding to these sequences interact cooperatively to activate the MHC class II promoter. We have confirmed this recently by showing that both cell-specific and interferon-γ-induced expression requires cooperative binding between RFX and NF-Y (31). Several lines of evidence suggested that RFX was also likely to bind cooperatively with proteins binding to the X2 box. First, the X and X2 boxes are always immediately adjacent to each other. Second, the X2 box is quite degenerate and in several MHC class II promoters, such as in the DRB1 and DRB3 genes, consists of essentially only one TRE or CRE half-site, a se-
Cooperative Binding between RFX and X2bp

sequence to which Jun/Fos and CREB/ATF proteins would not be expected to bind efficiently on their own and might require stabilization by a protein such as RFX binding to an adjacent site. Finally, the strongest indication comes from the analysis of X2-binding proteins with their respective target sites is stabilized. The amounts of nuclear extract. All binding mixtures contained 100 ng of a methylated pBR322 oligonucleotide (19, 20). This oligonucleotide eliminates complexes due to binding of the cloned RFX1-RFX4 proteins (19, 20) and CRE oligonucleotides were prepared and provided by J. M. Boss (Atlanta). The Py oligonucleotide is a high affinity binding site for RFX but contains no sites for X2bp. The TRE and CRE oligonucleotides were prepared and provided by M. Yaniv (Pasteur Institute, Paris, France) (34). The wild type DRB1-CAT reporter construct containing nucleotides –176 to +19 of the DRB1 promoter has been described (35). The DRB1Xm and DRB1X2m mutations in the promoter construct containing nucleotides -176 to +19 of the DRB1 promoter will be described in detail elsewhere.2 Briefly, a crude B lymphocyte nuclear extract from a lymphocytic leukemia patient. The protocol for purification of RFX will be described in detail elsewhere.2

RESULTS

RFX Forms Two Distinct Complexes with the X/X2 Box Region—In EMSA experiments performed with a DRA X/X2 oligonucleotide and nuclear extracts from MHC class II-positive B cells, two major complexes are observed (Fig. 2A). The lower complex is due to binding of RFX (21, 22). This lower complex is favored at low protein concentrations and when binding reactions are carried out at 15–20 °C (Fig. 2A). Like RFX (lower complex), the upper complex does not form in nuclear extracts from RFX-negative regulatory mutants such as Robert and SJO (Fig. 2A), suggesting that it also contains RFX. To determine whether this is indeed the case, an SJ0 extract was complemented with an affinity-purified fraction of RFX. This RFX fraction has been purified to near homogeneity,2 and in EMSA experiments only the band characteristic of RFX (lower complex), even when essentially all of the probe is bound (Fig. 2A). Both complexes are restored in the complemented SJO extract, thus confirming that the upper complex also contains RFX (Fig. 2A). Further evidence for this is provided by the finding that both complexes are eliminated by competitor oligonucleotides (X/X2 and Py) specific for RFX (Fig. 2B).

RFX Binds Together with a Protein Binding to the X2 Box—The lower RFX complex corresponds to binding of RFX alone, because it comigrates with affinity-purified RFX (Fig. 2A) and exhibits methylation interference contact points that are identical to those previously characterized for RFX (Fig. 1) (21, 22, 36). The upper complex also contains the major contact points of RFX, but in addition exhibits two additional contact points (Fig. 1) that are characteristic of X2 box-binding proteins (36), suggesting that it contains RFX together with a second protein (X2bp) bound to the X2 box. The target site of X2bp was confirmed by competition experiments (Fig. 2B) and binding experiments using DRA X/X2 oligonucleotides containing point mutations in the X2 box (Fig. 3A). The upper complex was not formed in the presence of an excess of unlabeled X2 oligonucleotide, while addition of oligonucleotides flanking the X/X2 region (Y and W) had no effect (Fig. 2B). Moreover, mutations falling within the X2 box, but not outside the X2 box, specifically inhibited formation of the upper band (Fig. 3A).

X2bp Is a TRE/CRE-binding Protein—To determine whether X2bp could belong to the Jun/Fos or CREB/ATF families, of which several members are known to be able to bind to the X2 box (24–28), we performed competition experiments with various TRE and CRE oligonucleotides. Formation of the RFX-X2bp complex is specifically inhibited by several of these oligonucleotides (Fig. 3B), suggesting that X2bp is indeed a member of the above mentioned transcription factor families. The two CRE oligonucleotides show the most efficient competition (oligonucleotides 4 and 5 in Fig. 3B), while a perfect TRE

2 Durand, B., Kohr, M., Reith, W., and Mach, B. (1994) Mol. Cell. Biol., in press.
Cooperative Binding between RFX and X2bp

Sequences of the DRA and DRB1 promoters, as well as mutations introduced into the X box (DRB1Xm or X2 box (DRB1X2m) or DRB1, are indicated below a schematic representation of the MHC class II promoter containing the W, X, X2 and Y cis-acting sequences. Methylation interference contact points derived for RFX on DRA, RFX.X2bp on DM, and RFX-X2bp on DRBl are indicated by arrowheads. Solid arrowheads indicate G residues at which methylation inhibits binding, and the open arrowhead indicates a G residue at which methylation enhances binding. Large arrowheads, strong inhibition; small arrowheads, weak inhibition.

The comparison of the half-lives of these complexes shows that stability of the RFX-DNA interaction is enhanced at least 100-fold by the presence of X2bp (Fig. 4).

The methylation interference experiments suggest that stabilization of RFX by X2bp results in a change in the interaction of RFX with the X box (Fig. 1). Two weak inhibitions observed for the lower complex (RFX) at the 5' end of the X box are consistently missing for the upper complex (RFX-X2bp). This change in the interaction of RFX with the X box is likely to be due to the stabilizing effect of X2bp, which might be expected to render the RFX-X2bp complex less sensitive to methylated G residues that already exhibit only a weak inhibition on binding of RFX on its own.

Enhanced Stability of the RFX-X2BP Complex Allows Its Formation on the Low Affinity X and X2 Boxes of the DRB1 Promoter—The X and X2 boxes of the DRB1 promoter are both only very low affinity target sites for RFX and X2bp, respectively. RFX binds very poorly to the DRB1 X box (35), such that little or no specific complex is detected using a DRB1 oligonucleotide containing only a functional X box (Fig. 5A). Similarly, no X2-binding complexes are observed with a DRB1 oligonucleotide containing only a functional X2 box (Fig. 5A). Nevertheless, the RFX-X2bp complex forms readily on the wild type DRB1 promoter fragment containing intact X and X2 boxes (Fig. 5A). This RFX-X2BP complex is in all respects identical to the one formed on the DRA promoter. First, it is eliminated by an excess of the DRA X2 box competitor oligonucleotide (Fig. 5A). Second, it has very similar methylation interference contact points within the X and X2 boxes (Fig. 1). Third, it does not form in extracts from RFX-deficient regulatory mutants (35). Finally, it has the same relative affinities for the different TRE and CRE oligonucleotides tested in Fig. 3B (data not shown). The interaction between RFX and X2bp thus stabilizes their binding sufficiently to allow them to bind together efficiently to the DRB1 promoter.

Functional Relevance of the RFX-X2bp Complex—It has been shown previously that many of the DRA X box mutations that inhibit binding of RFX also compromise DRA promoter function (40, 41). Mutations of the DRA X2 box also lead to a reduction in promoter activity (41). Interestingly, DRA X2 box point mu-
Cooperative Binding between RFX and X2bp

A, EMSA experiments were performed using DRA x/x2 probes containing point mutations in the X/X2 region. Mutations introduced into the DRA X/X2 region are indicated above the lanes. Only the region of the gel containing the upper (U, RFX.X2bp) and lower (L, RFX) complexes is shown. The relative amounts of the upper complex formed on the mutated and wild type (wt) probes was quantified and is indicated below each lane.

B, EMSA experiment performed with the DRA X/X2 probe in the presence of a 50- and 250-fold molar excess of competitor oligonucleotides containing the TRE or CRE sites of 1) the DRA X2 box, 2) the c-fos enhancer, 3) the collagenase gene, 4) the cjun gene, and 5) the somatostatin gene. Sequences of these sites are given below the gel.

Fig. 3. RFX binds together with a protein binding to the X2 box. A, EMSA experiments were performed using DRA X/X2 probes containing point mutations in the X/X2 region. Mutations introduced into the DRA X/X2 region are indicated above the lanes. Only the region of the gel containing the upper (U, RFX.X2bp) and lower (L, RFX) complexes is shown. The relative amounts of the upper complex formed on the mutated and wild type (wt) probes was quantified and is indicated below each lane. B, EMSA experiment performed with the DRA X/X2 probe to allow complex formation, supplemented with a 1000-fold molar excess of unlabeled X/X2 competitor oligonucleotide, and then continued for 0, 2.5, 5, 15, 60, or 120 min prior to gel electrophoresis. The gels shown were quantified by PhosphorImager analysis, and the results are shown below; the percentage of RFX-DNA and RFX-X2bp-DNA complexes remaining after addition of the competitor DNA is plotted as a function of time.

Fig. 4. Binding of RFX is stabilized by X2bp. Binding reactions optimized for RFX or RFX-X2bp were first incubated with the DRA X/X2 probe to allow complex formation, supplemented with a 1000-fold molar excess of unlabeled X/X2 competitor oligonucleotide, and then continued for 0, 2.5, 5, 15, 60, or 120 min prior to gel electrophoresis. The gels shown were quantified by PhosphorImager analysis, and the results are shown below; the percentage of RFX-DNA and RFX-X2bp-DNA complexes remaining after addition of the competitor DNA is plotted as a function of time.

Fig. 5. Formation and functional analysis of the RFX-X2bp complex on the DRB1 promoter. A, EMSA was performed using a Dextra nuclear extract and the wild type (wt) or mutated DRB1 probes (Xm and Xm) shown in Fig. 1. Binding reactions were done in the absence (-X) or presence (+X) of a 250-fold molar excess of the DRA X2 competitor oligonucleotide. Positions of free probe and probe bound by RFX.X2bp (U, upper complex) are indicated. Expected position of probe bound by RFX alone (L, lower complex) is also shown. B, wild type (wt) and mutated (Xm and Xm2) DRB1-CAT reporter plasmids were tested for expression in the B cell line Raji. Results are expressed relative to the CAT activity of the wild type plasmid. The mean of three independent experiments is shown.

The respective roles of the X and X2 boxes of the DRB1 gene have not been studied previously, although the entire X/X2 region is clearly crucial for DRB1 promoter activity (35). The DRB1 X box is a poor target site for RFX (Fig. 5A). Moreover, the DRB1 X2 box is only a poorly conserved CRE (Fig. 1) which does not even have one perfect half-site (GTCA), and by itself does not appear to be bound by X2-binding proteins (Fig. 5A). Yet even these poor X and X2 sites should be functionally important if the RFX-X2bp complex formed on the DRB1 X/X2 region is relevant for promoter function. We therefore constructed two mutated DRB1 promoter-CAT reporter gene constructs. One, DRB1Xm, contains clustered point mutations that completely disrupt the X box but leave the X2 box intact. The second, DRB1X2m, contains X2 box mutations that eliminate all homology to TRE or CRE sequences. To eliminate all potential TGA half-sites, two additional point mutations were introduced into the 3' end of the X box (Fig. 1), but these mutations are known from a previous study on the DRA gene to have no effect on binding of RFX (40) and do not eliminate weak binding of RFX to the DRB1 X box (data not shown). Disruption
Cooperative Binding between RFX and X2bp

of the X box (DRBlXm) results in an activity that is only 4% of wild type (Fig. 5B). Mutation of the X2 box (DRBlX2m) leads to an activity that is only 40% of wild type (Fig. 5B). Thus, both the X and X2 boxes contribute to activity of the DRBl promoter, although taken individually they constitute only low affinity sites for RFX and X2bp, respectively.

The effect of the X2 box mutation is, as expected, less strong than that of the X box mutation. Residual activity of the DRBlX2m promoter can be explained by the fact that disruption of the X2 box does not affect formation of second functionally relevant complex (RFX-NF-Y) on the DRA (31) and DRBl (data not shown) promoters. Mutation of the X box (DRBlXm), on the other hand, completely eliminates promoter activity because it disrupts both the RFX-X2bp (Fig. 5) and RFX-NF-Y (31) complexes.

**DISCUSSION**

It is becoming increasingly clear that protein-protein interactions play a key role in determining the transcriptional activity of eukaryotic genes. Despite detailed analysis of the individual promoter elements and the proteins that bind to them (4, 12–14), few studies have addressed the question of protein-protein interactions that allow MHC class II promoter-binding proteins to cooperate in activating transcription. In other systems, cooperation between transcription factors has been shown to occur indirectly at the level of transcription activation by synergistic interactions with the basal transcription machinery (3, 42–44) or directly at the level of DNA binding (45–47). Activity of MHC class II promoters appears to depend to a large extent on cooperative binding interactions in which the X box-binding protein RFX is a central player. In a previous study, we have shown that RFX binds cooperatively with the Y box-binding transcription factor NF-Y to form a strongly stabilized RFX-NF-Y-DNA complex that is crucial for promoter activity (31). We show here that RFX also binds cooperatively with X2bp, an X2 box-binding protein, to form an RFX-X2bp-DNA complex in which the interaction of both proteins with their target sites is strongly stabilized. Formation of the RFX-NF-Y and RFX-X2bp complexes is not mutually exclusive because the trimeric RFX-X2bp-NF-Y complex can form efficiently on promoter fragments containing both X, X2, and Y boxes (data not shown). The stabilizing RFX-X2bp interaction is evident on both the DRBl promoter and on the promoter of the DRBl gene. In addition, a complex now known to represent RFX X2bp has previously also been shown to bind to the DRB3 promoter (35). The RFX-X2bp complex thus forms on at least three different coregulated MHC class II promoters. Moreover, the efficiency of RFX X2bp complex formation, DRA > DRBl > DRB3, correlates with the relative strengths of these promoters (35).

An interaction between proteins binding to the X and X2 boxes has been postulated on the basis of mutational analysis of the X and X2 boxes of the DRA promoter (41). The cooperative binding between RFX and X2bp described here provides direct biochemical evidence for this model. Further evidence for a functional role of the RFX-X2bp complex comes from analysis of the DRBl promoter. Although taken individually the X and X2 boxes of the DRBl promoter are only very low affinity sites for RFX and X2bp, they are nevertheless crucial for promoter activity. These results are fully consistent with the observation that a cooperative interaction between RFX and X2bp is required to recruit these proteins to the DRBl X-X2 region. This situation is reminiscent of the composite response element of the proliferin gene, at which the glucocorticoid receptor interacts with members of the AP1 family (48, 49). It is becoming more and more evident that such composite cis-acting elements, which integrate diverse regulatory signals by permitting interactions between different DNA-binding proteins, play an important role in the transcriptional control of eukaryotic genes (2, 50).

The results presented here and in a recent report by Reith et al. (31) demonstrate that the analysis of cis-acting elements by the introduction of point mutations must be interpreted and evaluated with caution. Indeed, single point mutations may disrupt binding of individual proteins on their own without affecting significantly the recruitment of these same proteins to the mutated elements by cooperative binding interactions. Three observations emphasize this point. 1) A mutation of the X box that completely eliminates binding of RFX on its own has no effect on formation of the RFX-NF-Y complex, and hence does not adversely affect promoter activity (mutant M2 in Reith et al., 1994 (31)). 2) With respect to the DRA promoter, the DRBl X-X2 region contains several nucleotide differences that abolish binding of both RFX and X2bp on their own, yet the RFX-X2bp complex forms efficiently (Fig. 5) such that DRBl promoter activity is only 2-fold lower than that of the DRA promoter (35). 3) The C residue immediately preceding the GTCA sequence of the consensus CREB/ATF binding site has been shown to be essential both for the function of this site and binding of CREB/ATF proteins (51, 52). However, mutation of the corresponding C residue in the X2 box (position -94) only partially inhibits formation of the RFX-X2bp complex (Fig. 3A) and promoter activity (41). Stabilization by RFX thus appears to allow X2bp to bind to function even at very unusual CRE sites. Clearly, meaningful conclusions concerning the role of the individual MHC class II promoter-binding proteins can only be extrapolated from the effects of promoter mutations if cooperative binding interactions are taken into account.

Several different proteins have been shown to be able to bind in vitro to the X2 boxes of certain MHC class II genes. These include members of the Jun/Fos and CREB/ATF families such as c-Jun, c-Fos, hXBPI, and mXBPI (24–28). We have as yet not been able to identify which, if any, of the above mentioned proteins are present in the X2bp complex detected here. Antibodies specific for CREB, c-Jun, c-Fos, and hXBPI have proved unable to affect formation of the RFX-X2bp complex (data not shown). It is, however, not clear whether this indicates that RFX does not contain these proteins or whether the epitopes recognized by these antibodies are masked in the RFX-X2bp complex. Nevertheless, the data presented here should help identification of the proteins functioning at the MHC class II X2 box. The functionally relevant X2-binding protein(s) must exhibit the characteristic ability to bind cooperatively with RFX at the coregulated DRA, DRBl, and DRB3 promoters. This criterion is clearly more stringent and functionally relevant than those based solely on specificity for the X2 box of a given MHC class II promoter. The latter approach can be misleading because the X2 box is extremely variable in sequence, such that in the absence of stabilization by RFX the X2 box of different MHC class II genes may be bound preferentially by different proteins (24–28, 36).

The study of MHC class II gene regulation has been greatly facilitated by the availability of regulatory mutants (BLS cells) deficient in expression of MHC class II genes. These mutants have been classified into at least three complementation groups (53–55). In vitro binding studies have shown that two of these complementation groups are characterized by the RFX binding activity (21, 22, 56–58). This binding defect is specific for RFX and does not affect X2-binding proteins or NF-Y (21, 22, 56, 57). Surprisingly, footprint experiments have demonstrated that in these mutants, the entire promoter, including the X2 and Y boxes as well as the X box, is unoccupied in vivo (32, 33). The finding that RFX stabilizes binding of both X2bp and NF-Y to the X2 and Y boxes, respectively, may provide an explanation for this apparent discrepancy between the
in vitro and in vivo binding studies. In vitro, formation of the higher order RFX-X2bp, RFX-NF-Y, and RFX-X2bp-NF-Y complexes is strictly dependent on RFX, since they can only form in extracts from RFX-deficient BLS cells if these extracts are complemented with purified RFX (Fig. 2 and data not shown). This suggests that the bare promoter phenotype observed in BLS cells in vivo is due to the fact that such higher order complexes can not form and occupy the promoter in the absence of cooperative binding with RFX. Stabilizing interactions with RFX may be required to allow access of X2bp and NF-Y to their target sites in the context of chromatin.

Acknowledgments—We are grateful to J. M. Boss for providing the mutated DRA oligonucleotides, to M. Yaniv for the gift of the TRE and CRE oligonucleotides, and to E. Barras for excellent technical assistance.

REFERENCES

1. Dynan, W. S. (1989) Cell 58, 1–4
2. Lucas, P. C., and Granner, D. K. (1992) Annu. Rev. Biochem. 61, 1131–1173
3. Herschlag, D., and Johnson, F. B. (1993) Genes & Dev. 7, 173–179
4. Gilmcher, L. H., and Karr, C. J. (1992) Annu. Rev. Immunol. 10, 13–49
5. Rotaruzzo, G. F., Todd, I., Mirzaian, R., Belfiore, A., and Pujol-Borrell, R. (1986) Immunol. Rev. 94, 137–169
6. Griscelli, C., Lisowski-Grospierrre, B., and Mach, B. (1989) Immunodeficiency 1, 135–153
7. Amaldi, I., Reith, W., Berte, C., and Mach, B. (1989) J. Immunol. 142, 999–1004
8. Blanar, M. A., Beutger, E. C., and Flavell, R. A. (1998) Proc. Natl. Acad. Sci. U. S. A. 85, 4672–4676
9. Collins, T., Korman, A. J., Wake, C. T., Boss, J. M., Kappes, D. J., Fiers, W., Autil, K. A., Gimbrone, M. A. J., Strominger, J. L., and Pober, J. S. (1984) Proc. Natl. Acad. Sci. U. S. A. 81, 4917–4921
10. Dellabona, P., Latron, F., Maffei, A., Scarppellino, L., and Accolla, R. S. (1989) J. Immunol. 142, 2902–2910
11. Latron, F., Jotterand-Bellomo, M., Maffei, A., Scarppellino, L., Bernard, M., Strominger, J. L., and Accolla, R. S. (1988) Proc. Natl. Acad. Sci. U. S. A. 85, 2229–2233
12. Benoist, C., and Mathis, D. (1990) Annu. Rev. Immunol. 8, 681–715
13. Kara, C. J., and Gilmcher, L. H. (1991) Curr. Opin. Immunol. 3, 16–21
14. Ting, J. P. Y., and Baldwin, A. S. (1995) Curr. Biol. 5, 5–16
15. Hooft van Huijsgen, R., Li, X.-Y., Knapp, A., Pasquali, J.-L., Benoist, C., and Mathis, M. (1990) EMBO J. 9, 3119–3127
16. Mantovani, R., Pessara, U., Treche, F., Li, X.-Y., Knapp, A.-M., Pasquali, J.-L., Benoist, C., and Mathis, M. (1992) EMBO J. 11, 3315–3322
17. Zelenik-Le, N. J., Azizkhan, J. C., and Ting, J. P. Y. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 1873–1877
18. Reith, W., Herrero Sanchez, C., Kohr, M., Silacci, P., Berte, C., Barras, E., Fei, S., and Mach, B. (1990) Genes & Dev. 4, 1528–1540
19. Siegrist, C. A., Durand, B., Enerley, P., David, R., Hearing, P., Mach, B., and Reith, W. (1993) Mol. Cell. Biol. 13, 6575–6584
20. Reith, W., Ucla, C., Barras, E., Gaud, A., Durand, B., Herrero Sanchez, C., Kohr, M., and Mach, B. (1994) Mol. Cell. Biol. 14, 1230–1244
21. Reith, W., Satola, S., Sanchez, C. H., Amaldi, I., Lisowski-Grospierre, B., Griscelli, C., Hadam, M. R., and Mach, B. (1988) Cell 53, 897–906
22. Herrero Sanchez, C., Reith, W., Silacci, P., and Mach, B. (1992) Mol. Cell. Biol. 12, 4076–4083
23. De Préal, C., Lisowski-Grospierrre, B., Loche, M., Griscelli, C., and Mach, B. (1996) J. Biol. Chem. 271, 18293–18298
24. Liu, H.-C., Boothby, M. R., and Gilmcher, L. H. (1988) Science 242, 69–71
25. Liu, H.-C., Boothby, M., Finn, P. W., Davidson, R., Nabavi, N., Zelenik-Le, N. J., Ting, J. P. Y., and Gilmcher, L. H. (1990) Science 247, 1581–1584
26. Ono, S. J., Liu, H.-C., Davidson, R., Strominger, J. L., and Gilmcher, L. H. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 4300–4304
27. Ono, S. J., Bazil, V., Levi, B.-Z., Oztos, K., and Strominger, J. L. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 4304–4308
28. Anderson, S., and Peterlin, B. M. (1980) J. Immunol. 125, 3456–3462
29. Vilen, B. J., Caygwell, J. P., and Ting, J. P. Y. (1991) Mol. Cell. Biol. 11, 3456–3465
30. Vilen, B. J., Penta, J. F., and Ting, J. P. Y. (1992) J. Biol. Chem. 267, 23728–23734
31. Reith, W., Siegrist, C. A., Durand, B., Barras, E., and Mach, B. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 354–358
32. Kara, C. J., and Gilmcher, L. H. (1991) Science 252, 709–712
33. Kara, C. J., and Gilmcher, L. H. (1995) Immunogenetics 37, 227–230
34. Hirai, S.-J., and Yaniv, M. (1989) Nucl. Acids Res. 17, 151–154
35. Emery, F., Mach, B., and Reith, W. (1995) Hum. Immunol. 38, 137–147
36. Kohr, M., Reith, W., Herrero Sanchez, C., and Mach, B. (1990) Mol. Cell. Biol. 10, 965–971
37. Shapiro, D. J., Sharp, P. A., Wahl, W. H., and Keller, M. J. (1986) DNA 4, 47–55
38. Hesthorn, P., Zervas, P., Raducha, M., Harris, H., and Kadesch, T. (1988) Proc. Natl. Acad. Sci. U. S. A. 85, 6342–6346
39. Gorman, C. M., Moffit, L. F., and Howard, B. H. (1982) Mol. Cell. Biol. 2, 1044–1051
40. Hasegawa, S. L., Sloan, J. H., Reith, W., Mach, B., and Boss, J. (1991) Nucleic Acids Res. 19, 1283–1294
41. Sloan, J. H., Hasegawa, S. L., and Boss, J. M. (1992) J. Immunol. 148, 2591–2599
42. Carew, M., Lin, Y.-S., Green, M. R., and Ptaschnie, M. (1990) Nature 345, 361–364
43. Lin, Y.-S., Carew, M. F., Ptaschnie, M., and Green, M. R. (1988) Cell 54, 659–664
44. Lin, Y.-S., Carew, M. F., Ptaschnie, M., and Green, M. R. (1990) Nature 359, 359–361