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The *IL-4* and *IL-5* Genes Are Closely Linked and Are Part of a Cytokine Gene Cluster on Mouse Chromosome 11

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Abstract—*The murine* IL-4 *and* IL-5 *genes encode hemopoietic growth factors involved in the stimulation, proliferation, and differentiation of cells of the T lymphocyte, B lymphocyte, and granulocyte lineages. We have mapped the Il-4 and Il-5 loci representing the structural genes for* IL-4 *and* IL-5, *respectively, to mouse chromosome 11 using Chinese hamster* × *mouse and rat* × *mouse somatic cell hybrids. Physical linkage studies of the* IL-4 *and* IL-5 *genes by pulsed field gel electrophoresis have shown that they are closely linked, being 110–180 kb apart. Since the Il-5 locus maps to the interface of bands A5 and B1 in the same location as the genes for* IL-3 *and GM-CSF, this places these three cytokine genes, as well as the* IL-4 *gene, within a region of about 5000–10,000 kb. The present physical linkage studies indicate that the* IL-4 *and* IL-5 *genes are a minimum of 600 kb apart from the closely linked* IL-3 *and* GM-CSF *genes. The gene clustering, together with similarities in gene structure, regulation, and biological function, raises the possibility that the four genes may be part of a distantly related cytokine gene family.*

INTRODUCTION

Interleukin 4 (IL-4, B-cell stimulating factor 1) and interleukin 5 (IL-5, eosinophil differentiation factor, T-cell replacing factor, B-cell growth factor II, IgA enhancing factor) belong to a family of secreted glycoproteins involved in the regulation of hemopoiesis and the immune system. They are expressed after mitogenic or antigenic stimulation of T lymphocytes (1, 2). Murine IL-4 stimulates the growth of B cells, T cells, mast cells, and granulocytes. It causes the induction of class II major histocompatibility (MHC) antigens and Fc receptors on resting B cells (3, 4). It has also been shown to enhance production of IgE and IgG_1 isotypes by activated B cells (5–8). Murine IL-5 supports the proliferation and Ig secretion of activated B cells, the proliferation of eosinophil precursors, and the activation of mature eosinophils (9–11). It also preferentially enhances IgA production (2). Of interest to the present study are two other cytokines, interleukin 3 (IL-3) and granulocyte/macrophage colony stimulating factor (GM-CSF), which are multilineage hemopoietic regulators that have overlapping biological effects on hemopoietic progenitor cells. GM-CSF stimulates progenitor cells to form mainly granulocyte, macrophage, or mixed granulocyte/macrophage colonies, as well as some eosinophil containing colonies, whereas IL-3 also stimulates the formation of erythroid cells, megakaryocytes, and mast cells and supports the self-renewal of pluripotent stem cells (12).

The murine genes for IL-4, IL-5, IL-3,

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and GM-CSF have been cloned and sequenced (13–18). They are all single-copy genes and do not belong to a classical type of gene family since there is little nucleotide sequence homology between these genes, and little significant amino acid homology in their predicted protein sequences. There is, however, some homology close to the C terminus of all four proteins (19) and there are similarities in their gene structure (see below and Table 1). They are all expressed by helper T lymphocytes after mitogenic or antigenic stimulation. GM-CSF is also expressed in macrophages (20–22) and endothelial cells (23–25). Expression of IL-3 and IL-5 in cells other than helper T lymphocytes has not yet been demonstrated. IL-4 may also be expressed in mast cells (26).

The gene structure of IL-4, IL-5, IL-3, and GM-CSF is similar in that: the exons are interrupted between codons; all genes have four exons except the *IL-3* gene which has five, where exons three plus four could correspond to exon three in the other genes (Table 1); the sizes of exons are similar; and in all cases there is a small second exon between 11 and 16 amino acids in length.

Previous studies using mouse × Chinese hamster hybrids have shown that the murine *IL-3* and *GM-CSF* genes are located on chromosome 11 (27, 28) and physical mapping studies have shown that the two genes are within 230 kb of each other (28). More recently we have shown by molecular cloning that these two genes are actually 14 kb apart and in the same orientation (Lee and Young, submitted).

In this paper we show that the murine *IL-4* and *IL-5* genes are also located on mouse chromosome 11 and that they are closely linked, being 110–180 kb apart. In studies reported elsewhere, we have mapped the *IL-5* gene and the *IL-3* gene by in situ hybridization to the interface of bands A5 and B1 on mouse chromosome 11 (Webb et al., submitted). Taken together, this physical and cytogenetic mapping indicates a cluster of four cytokine genes, *IL-4*, *IL-5*, *IL-3*, and *GM-CSF* at the interface of bands A5 and B1 on mouse chromosome 11, and suggests that these genes may have evolved following ancient gene duplication events.

Table 1. Exon Sizes in Amino Acids of Murine *IL-5*, *IL-4*, *IL-3*, and *GM-CSF* Genes

	Exon				
Gene	1	2	3	4	5
IL-5	47	11	43	32	
IL-4	44	16	51	29	
GM-CSF	50	14	42	35	
IL-3	55	14	32	14	51

MATERIALS AND METHODS

DNA Hybridization Probes. The murine IL-5 probe was a 260-bp cDNA fragment described previously (16). A 600-bp HaeII–AccI murine IL-5 cDNA fragment was also used. The murine IL-3 probe was a 588-bp EcoRI fragment derived from pILM21 (16). The murine GM-CSF probe was a 700-bp HindIII–EcoR1 fragment derived from plasmid pGM38 (29). The murine IL-4 probe was a 373-bp RsaI fragment (30), reisolated as an EcoRI–BamHI fragment after recloning into the SmaI site of pGEM-1 (Promega). A similar subclone in pGEM-3 was obtained from C.J. Watson and W.E. Paul (26). The ^{32}P-labeled probes were synthesized by the random primer method (15, 31).

Somatic Cell Hybrid Analysis. The Chinese hamster × mouse somatic cell hybrids were prepared and characterized by methods described previously (32, 33). A rat × mouse microcell hybrid containing only mouse chromosome 11 was kindly provided by Dr R.E.K. Fournier (Hutchinson Cancer Center, Seattle, Washington) (34). DNA was prepared, digested with restriction enzymes, electrophoresed on 1% agarose gels, and blotted to nitrocellulose by standard methods (35).

Preparation of High-Molecular-Weight DNA. DNA was prepared from the spleens of BALB/c mice. Single-cell suspensions were prepared by sieving the spleens through a fine wire mesh into phosphate-buffered saline and then mixing the suspension repeatedly with a Pasteur pipet. The cells were then embedded in agarose beads and DNA prepared as described by Jackson and Cook (36), using the modifications of Overhauser and Radic (37). DNA restriction enzyme digests were done as described by Overhauser and Radic (37).

Field Inversion Gel Electrophoresis. Field inversion gel electrophoresis was done as described by Carle et al. (38), using a voltage gradient of 7.5 V/cm, buffer temperature of 12°C, a forward to reverse ratio of 3:1, with the period ramped from 6 sec at the start to 90 sec at the end of the run. Electrophoresis times varied between 34 and 40 h. These conditions resolved DNA fragments between 90 kb and 600 kb, and there was a linear relationship between the distance migrated and the molecular weight. To resolve DNA fragments between 5 and 200 kb, the conditions were as above except that the period was ramped from 0.5 sec at the start to 20 sec at the end of the run. Yeast chromosome standards were prepared as described by Schwartz and Cantor (39), using yeast strain YP148 (40). The sizes of the yeast chromosomes were cross-checked using lambda oligomers of EMBL3A prepared according to Herrmann et al. (41). Blotting onto nitrocellulose and hybridization was done according to standard procedures (35). Hybridization and washing was done at moderate stringency, 5 × SSC, 65°C, for hybridization and 1 × SSC, 65°C, for washing. Increasing the stringency of washing to 0.2 × SSC, 65°C, did not specifically reduce the signal of any of the hybridizing bands, although the overall signal was reduced.

RESULTS

Analysis of Somatic Cell Hybrids. The *Il-4* and *Il-5* loci representing the structural genes for IL-4 and IL-5, respectively, were initially mapped using somatic cell hybrids. Since NFS/N and BALB/c mice were used for construction of the mouse × hamster hybrids, we initially examined NFS/N and BALB/c mouse DNA, and hamster DNA by Southern blotting following digestion with HincII, SacI, and EcoRI/HindIII. These enzymes were chosen because the BALB/c *IL-5* gene sequence (16) predicts the presence of conveniently sized hybridizing fragments of 1.8, 4.5, and 4.3 kb, respectively. These fragments were observed using the murine IL-5 probe and appeared of identical size in BALB/c and NFS/N mouse DNA. With hamster DNA, these enzymes also yielded single bands of ~16, 2.6, and 4.5 kb, respectively. The panel of 15 mouse × hamster hybrids was then examined after HincII digestion of the DNA, since this enzyme should allow ready discrimination of the mouse (1.8 kb) and hamster (~16 kb) alleles. The 16-kb hamster band was observed in each of the 15 mouse × hamster hybrids examined, and the 1.8-kb fragment was observed in BALB/c DNA run as a control (not shown). However, the 1.8-kb mouse fragment was not observed in any of the mouse × hamster cell lines, even after prolonged overexposure of the autoradiograms (not shown). The only mouse chromosome not present in any of these hybrids is chromosome 11, so these results suggest that the *IL-5* gene is located on this chromosome.

In order to confirm this assignment, DNA from a rat × mouse hybrid in which chromosome 11 is the only mouse chromosome present was examined, together with rat and mouse DNA. Using the restriction enzymes mentioned above, the sizes of the bands observed with rat DNA were quite different from the mouse bands. The rat × mouse hybrid contained both the rat and the mouse IL-5 bands, with the mouse bands being weaker than the rat bands (Fig. 1a). The results from all of the hybrids are summarized in Table 2, and show that the *IL-5* gene

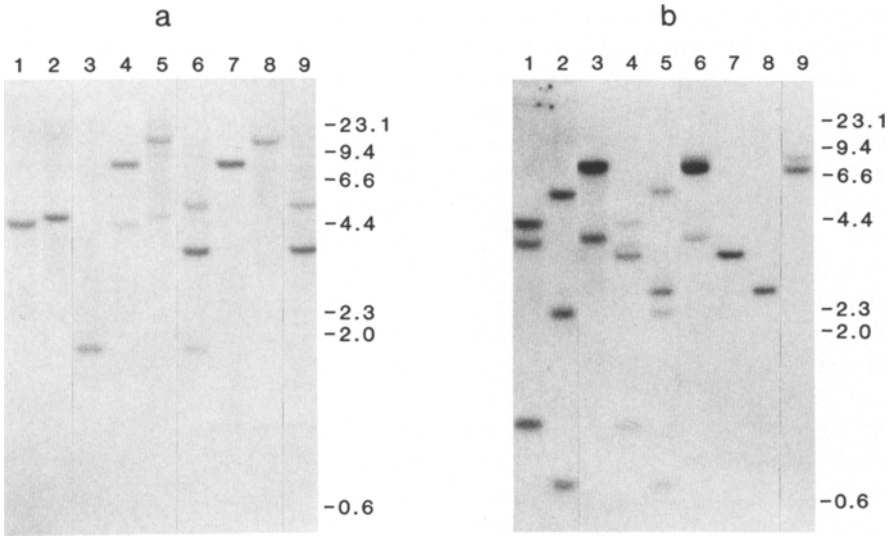

Fig. 1. Southern blot analysis of genomic DNA from a rat–mouse hybrid cell line containing mouse chromosome 11. (a) Mouse IL-5 cDNA probe. (b) Mouse IL-4 cDNA probe. Lanes 1–3, BALB/c DNA; lanes 4–6, HM91 (rat–mouse hybrid) DNA; lanes 7–9, HM92 (rat) DNA. All lanes were loaded with 5 μg of genomic DNA cut with EcoRI plus HindIII (lanes 1, 4, 7), SacI (lanes 2, 5, 8), or HincII (lanes 3, 6, 9). The sizes of markers are indicated in kilobase pairs.

Table 2. Correlation of Presence of *IL-5* and *IL-4* Genes and Mouse Chromosomes in Somatic Cell Hybrids[a]

Mouse chromosome	No. of hybrid clones with *IL-5* or *IL-4* gene/chromosome retention				*t*	Discordant (%)
	+/+	−/−	+/−	−/+		
1	0	5	1	9	15	66.7
2	0	6	1	9	16	62.5
3	0	5	1	4	10	50.0
4	0	7	1	8	16	56.2
5	0	13	1	1	15	13.3
6	0	4	1	11	16	75.0
7	0	2	1	13	16	87.5
8	0	7	1	7	15	53.3
9	0	8	1	7	16	50.0
10	0	12	1	3	16	25.0
11	1	11	0	0	12	0.0
12	0	1	1	9	11	90.9
13	0	5	1	9	15	66.7
14	0	10	1	4	15	33.3
15	0	0	1	10	11	100.0
16	0	8	1	3	12	33.3
17	0	4	1	11	16	75.0
18	0	6	1	6	13	53.8
19	0	8	1	6	15	46.7
20	0	5	1	9	15	66.7

[a]DNA (5 μg) from 15 Chinese hamster–mouse hybrids and one rat–mouse hybrid was analyzed for the presence of the mouse *IL-5* or *IL-4* genes by Southern blotting and hybridization to ^{32}P-labeled random-primer probes. The total number of hybrids (*t*) tested for concordance between the presence of the *IL-5* or *IL-4* gene and chromosome retention varies because not all hybrids were characterized for the presence of every mouse chromosome.

is on mouse chromosome 11, since the gene is readily detected in a hybrid cell line containing mouse chromosome 11, but cannot be detected in a panel of hybrid cell lines containing all of the remaining mouse chromosomes.

The blots described above were stripped of mouse IL-5 probe and rehybridized to a mouse IL-4 cDNA probe. It was found that the mouse and hamster *IL-4* genes could be readily distinguished following HincII digestion of genomic DNA (not shown). It was then found that the mouse *IL-4* gene, like the *IL-5* gene, was absent from the panel of mouse–hamster hybrids (not shown) but was present in the rat × mouse hybrid containing mouse chromosome 11 (Fig. 1b). These results are summarized in Table 2 and show that the mouse *IL-4* gene is also located on chromosome 11.

The identity of bands in the hybrids was assigned on the basis of similarity in size to the authentic mouse, rat, or hamster bands under conditions of moderate wash stringency (1–2 × SSC, 65°C). This assignment was further confirmed by examining the variation in intensity of the bands under different conditions of wash stringency. At high stringency (0.1 × SSC, 65°C), the bands assigned as rat or hamster were greatly diminished in intensity, as expected for these heterologous hybridizations, whereas the mouse bands retained good signal strength (not shown).

Pulsed Field Gel Analysis. DNA fragments between 30 and 1500 kb were generated using restriction enzymes that cut mammalian DNA infrequently. The digests were then separated using field inversion gel electrophoresis, the DNA transferred onto nitrocellulose and sequentially hybridized with probes for the *IL-4, IL-5, IL-3,* and *GM-CSF* genes. Common hybridizing bands were sought to provide evidence that the genes could reside on the same DNA fragment.

Nine different enzyme digests were successively screened with the gene probes for *IL-4, IL-5, IL-3,* and *GM-CSF* (Fig. 2). Autoradiograms obtained using the *IL-3* and *GM-CSF* gene probes had six bands in common, confirming the very close linkage of these genes, as has been shown previously (28, Lee and Young, submitted). When the *IL-4* and *IL-5* gene probes were used, three common bands were demonstrated. However, comparison of autoradiograms obtained using *IL-4* or *IL-5* gene probes with those obtained using *IL-3* and *GM-CSF* gene probes failed to show any common bands.

Since the *IL-4* and *IL-5* genes hybridized to three bands of the same fragment size, it seemed likely that these two genes were quite close together, although not as close as the *IL-3* and *GM-CSF* genes (Lee and Young, submitted). To confirm the *IL-5* and *IL-4* gene linkage and to compile a map of the region, a series of double-restriction enzyme digests and digests using additional restriction enzymes were carried out and screened. Double-enzyme digests confirmed that the *IL-4* and *IL-5* genes were on the same fragments as the initial results indicated (Fig. 3, lanes 4, 5, 7; and Table 3). Table 3 lists the fragment sizes that were used to map the *IL-4, IL-5* gene region. In some cases the DNA was not digested to completion, resulting in partial digests that could be used to construct the map. A notable example is with the NarI digests. This enzyme is known to have site preferences, apart from its recognition sequence. We found that with short incubation times (3–4 h), only the 382-kb band was visible with the gene probes for *IL-4* and *IL-5,* whereas the use of longer incubation times (up to 24 h), or an increase in the enzyme concentration, resulted in two hybridizing bands for each gene probe. The *IL-5* gene probe gave a strong band at 382 kb and a weak band at 160 kb and the *IL-4* gene probe a strong band at 382 kb and a weak band at 220 kb.

The subchromosomal restriction map covering the *IL-4* and *IL-5* genes shows them to be a minimum of 110 kb apart and a maximum of 180 kb apart (Fig. 4).

The pulsed-field results do not demonstrate linkage between the *IL-3/GM-CSF* and

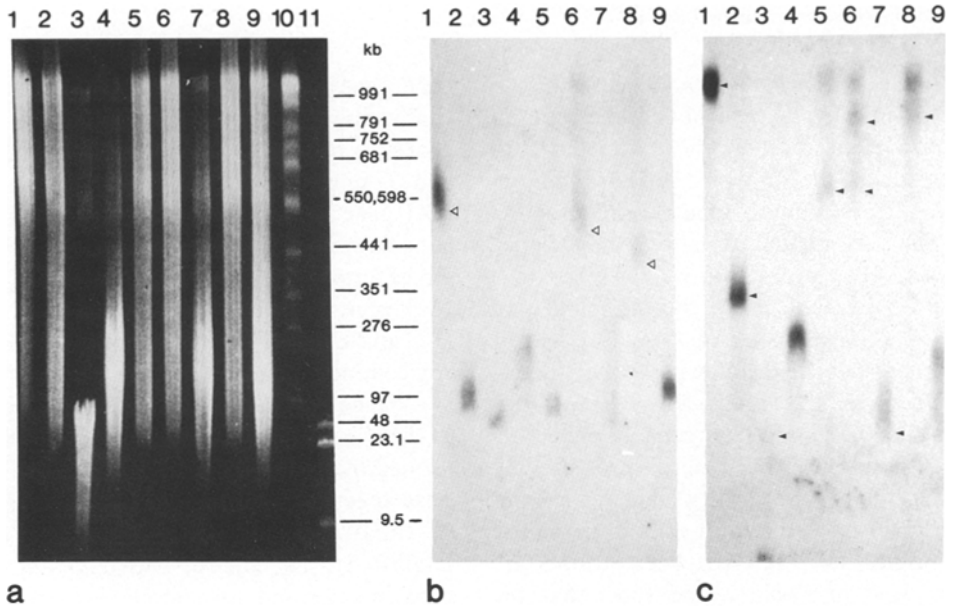

Fig. 2. Field inversion gel analysis of the *IL-4, IL-5, IL-3,* and *GM-CSF* genes. (a) Gel stained with ethidium bromide. (b) Autoradiograph obtained after transfer to nitrocellulose and hybridization with an IL-5 cDNA probe. The bands also hybridizing with the IL-4 cDNA probe are marked with an open arrow. (c) Autoradiograph obtained after rehybridizing nitrocellulose filter used in (b) with a GM-CSF cDNA probe. The bands also hybridizing with the IL-3 cDNA probe are marked with a closed arrow. Lanes 1–9, BALB/c spleen DNA digested with NotI, BssHII, KpnI, SfiI, SacII, SalI, XhoI, NarI, and SmaI, respectively. Lane 10, yeast chromosomes (*Saccharomyces cerevisiae,* strain YP148). Lane 11, λ DNA plus λ DNA digested with HindIII.

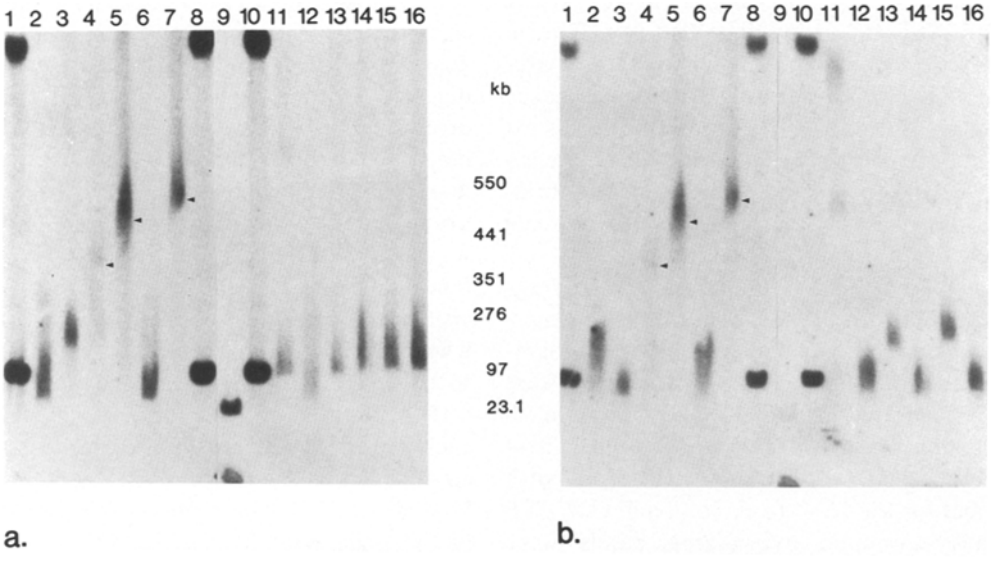

Fig. 3. Field inversion gel analysis of the *IL-4* and *IL-5* genes. (a) and (b) are autoradiographs obtained after transfer to nitrocellulose and hybridization with *IL-4* and *IL-5* gene probes, respectively. Common hybridizing bands are marked with an arrow. Lanes 1, 8, 10, yeast chromosome standards; lane 9, λ DNA plus λ DNA digested with HindIII and end-labeled with [α-^{32}P]dATP. Lanes 2–7, 11–16, BALB/c DNA digested with (2) SfiI, (3) BssHII, (4) NarI/SalI (5) SalI/NotI, (6) SfiI/NarI, (7) NotI, (11) MluI, (12) MluI/SfiI, (13) MluI/NotI, (14) MluI/BssHII, (15) MluI/SalI, (16) MluI/NarI. Yeast strain YP148 has been modified by insertion of a plasmid into chromosome 14 (reference 40), resulting in two chromosomes of approximately 1188 kb and 97 kb. The presence of fragments of plasmids in these chromosomes causes the two hybridizing bands seen in lanes 1, 8, and 10.

Table 3. Pulsed Field Gel Fragments Hybridizing with *IL-5* and *IL-4* Genes[a]

Restriction digest	Probe used	
	IL-5	IL-4
MluI	1000, 512	95
MluI/NotI	190	95
MluI/NarI	70	95
MluI/SalI	190	95
MluI/BssHII	68	95
MluI/SfiI	70	30, 16
NotI	520	520
NotI/NarI	382	382
NotI/SalI	466	466
NotI/SfiI	175	150
SalI	466	466
SalI/NarI	382	382
SalI/SfiI	175	48
SalI/BssHII	80	190
NarI	382, 160	382, 220
NarI/SfiI	175	150, 48
NarI/BssHII	80	190, 110
BssHII	80	190
SfiI	175	150, 48

[a]DNA was digested with the enzymes indicated. Where two enzymes were used the digests were carried out in the order shown. Fragment sizes are given in kb. Figures underlined indicate common fragment sizes for both genes.

the *IL-4/IL-5* genes. An estimate of the minimum distance between the *IL-4* and *IL-5* genes and the *IL-3* and *GM-CSF* genes was made using the subchromosomal map of the region around the *IL-3* and *GM-CSF* genes from Barlow et al. (28) which agreed well with our own data (Lee and Young, unpublished), and the subchromosomal map of the region around the *IL-4* and *IL-5* genes (Fig. 4). The distance between the two pairs of genes was estimated to be a minimum of 600 kb but may be as great as 5000–10,000 kb since the upper limit is defined by in situ hybridization.

DISCUSSION

We have studied the chromosomal organization of the murine genes for IL-4 and IL-5, which had not previously been mapped. We have shown that the genes for IL-4 and IL-5 are both on mouse chromosome 11, and they are closely linked, being 110–180 kb apart. In a study reported elsewhere (Webb et al., submitted), we have shown that the *IL-5* and *IL-3* genes are both located at the interface of bands A5 and B1 on chromosome 11. However, the similarity of results obtained by in situ hybridization does not exclude a wide separation at the level of kilobase pairs. Analysis of the physical linkage between the *IL-4/IL-5* genes and the *IL-3/GM-CSF* genes (which are 14 kb apart) showed that they were a minimum of 600 kb apart.

Although the *IL-5* and *IL-4* genes could not be physically linked to the *IL-3* and *GM-CSF* genes in the present study, it may be possible using alternative techniques that give better resolution of larger fragments. In this study we used field inversion gel electrophoresis to analyze physical distances. This method can resolve fragments up to 700 kb (38, 42),

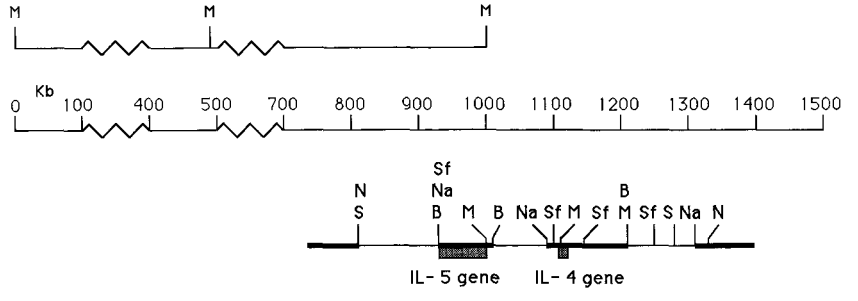

Fig. 4. Subchromosomal map of the *IL-5* and *IL-4* gene region. The orientation of the *IL-5* gene relative to the *IL-4* gene is not known. M, MluI; N, NotI; Na, NarI; S, SalI; Sf, SfiI; B, BssHII. Sites for MluI extending beyond the *IL-5* gene are indicated above the main map. The thin line indicates regions of the map where all of the restriction sites cannot be precisely mapped.

but beyond 700 kb the resolving power diminishes rapidly. Pulsed-field gel electrophoresis methods, such as contour-clamped homogenous electric field (CHEF) (40), transverse alternating electrophoresis (TAFE) (43, 44), and orthogonal field gel electrophoresis (OFAGE) (39, 45), have the capacity to resolve DNA fragments up to 10,000 kb (44, 45), and these methods may enable future determination of the physical distance between these two linkage groups, *IL-4/IL-5* and *IL-3/GM-CSF*.

The close linkage of the *IL-4, IL-5, IL-3,* and *GM-CSF* genes is of interest with respect to the possibility that they may have evolved by ancient gene duplication. The genes for IL-3 and GM-CSF are only 14 kb apart, have a similar gene structure, and overlapping biological activities, making a plausible case that they may have arisen by an ancient gene duplication. The *IL-4* and *IL-5* genes are not as close, being 110–180 kb apart and therefore the evidence for the *IL-4* and *IL-5* genes arising from an ancient gene duplication is not as strong. However, the *IL-4* and *IL-5* genes have a similar exon structure to that of the *IL-3* and *GM-CSF* genes (Table 1) and are coordinately expressed in some classes of helper T lymphocytes along with IL-3 and GM-CSF (1, 2). These cytokines also overlap in some of their biological activities.

At present it is uncertain how many lymphokines there are, nor is it clear how they are related. The clustering of these four cytokine genes raises the possibility that they could be part of a larger family of cytokine genes, including some as yet uncharacterized, that had a common evolutionary origin and that have subsequently diverged rapidly. Cross-species sequence analysis indicates that several of the clustered genes are evolving rapidly, particularly the *IL-3* gene. The amino acid sequence homologies between mice and humans are 29%, 50%, 50%, and 67% for *IL-3, GM-CSF, IL-4,* and *IL-5,* respectively; whereas the cDNA nucleotide sequence homologies are 45%, 70%, 70%, and 77% (10, 11, 16, 29, 30, 47–53). Rapid divergence following ancient gene duplication could explain why there is little significant nucleotide sequence homology detectable between the four genes studied in the present work. The γ-interferon (*γIFN*) and interleukin 2 (*IL-2*) genes also share many of the characteristics of the other genes mentioned (54), particularly the *IL-2* gene, but are located on different chromosomes, at least in humans. The *γIFN* gene is on human chromosome 12 (55) and the *IL-2* gene on human chromosome 4 (56). They may also be members of this gene family. The murine *γIFN* gene is on chromosome 10 (57). The chromosome location of the murine *IL-2* gene has not yet been reported.

The clustering of the *IL-3, IL-4, IL-5,* and *GM-CSF* genes may be important in the regulation of their expression. *cis*-Acting gene proximal regulatory elements are essential for normal gene regulation, including tissue-specific expression and developmental regulation. These regulatory elements have been identified by short- and long-term transfection studies. Transgenic animal studies show that chromosomal configuration is important and may be essential for the proper utilization of these *cis*-acting regulatory elements. Transgenic animal studies have shown that expression of a thymidine kinase promoter/*lac* Z gene construct is dictated entirely by chromosomal position (58). It is also clear that the sites responsible for the proper chromosomal configuration can be large distances away from the gene. For example, in the β-globin gene locus, sites up to 70 kb 5′ and 3′ of the genes have been shown to be necessary to mimic the endogenous expression of the gene (59, 60). The mechanism(s) whereby chromosome configuration influences expression is unknown, but it may influence expression by regulating the flow of *trans*-acting regulatory molecules into a chromosomal domain.

An analogous cluster of cytokine genes also appears to exist on the long arm of human chromosome 5 at 5q23-31. The human *IL-3, GM-CSF, IL-5,* and *IL-4* genes have been

localized to 5q23-31 by in situ hybridization (61–63, van Leeuwen et al., submitted), and recently the *IL-3* and *GM-CSF* genes have been shown to be only 9 kb apart (64). This region, the distal end of the long arm of chromosome 5, is also of interest with respect to chromosomal deletions and inversions associated with hemopoietic disorders. Deletion of the 5q region is associated with hemopoietic disorders of a type secondary to toxic environmental agents and to cancer therapeutic agents. These disorders include secondary acute nonlymphocytic leukemia and refractory macrocytic anemia (65). Inversions in the 5q region have been associated with lymphoid and myeloid malignancies (66). In recent studies we have demonstrated that the human *IL-4* and *IL-5* genes show a similar linkage to that demonstrated in the present work (van Leeuwen et al., submitted). The conservation of the close linkage of the *IL-3/GM-CSF* genes and the *IL-4/IL-5* genes in both the mouse and human genomes implies that it may have some significance in the regulation of the expression of these genes.

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