



REVIEW

Cytokine gene polymorphism in human disease: on-line databases

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The pathologies of many infectious, autoimmune and malignant diseases are influenced by the profiles of cytokine production in pro-inflammatory (TH1) and anti-inflammatory (TH2) T cells. Interindividual differences in cytokine profiles appear to be due, at least in part, to allelic polymorphism within regulatory regions of cytokine gene. Many studies have examined the relationship between cytokine gene polymorphism, cytokine gene expression in vitro, and the susceptibility to and clinical severity of diseases. A review of the findings of these studies is presented. An on-line version featuring appropriate updates is accessible from the World Wide Web site, <http://www.pam.bris.ac.uk/services/GAI/cytokine4.htm>.

Keywords: cytokines; gene polymorphism; gene expression

Introduction: cytokines, the cytokine network and the Th1–Th2 paradigm

Cytokines are humoral immunomodulatory proteins or glycoproteins which control or modulate the activities of target cells, generally those within the haematopoietic system. They act on target cells by binding to specific cytokine receptor ligands, initiating signal transduction and second messenger pathways within the target cell.^{1–5} This can result in gene activation, leading to mitotic division, growth and differentiation, migration, or apoptosis.

Cytokines are produced by a wide range of cell types and have been broadly classified as monokines (produced by cells of the monocyte lineage) or lymphokines (produced by lymphocytes), though this is arguably an over-simplistic classification: other classifications are based on functional or structural groupings.^{6,7} Cytokines act in a highly complex coordinated network in which they induce or repress their own synthesis as well as that of other cytokines and cytokine receptors. In addition, many cytokines appear to be pleiotropic, with the cor-

ollary that the cytokine network is highly flexible, since there is considerable overlap and redundancy between the function of individual cytokines.^{8–12} This feature continues to complicate efforts to analyse both the function of individual cytokines and the influence of cytokine gene polymorphism on gene expression and disease.

Cytokine production by the cells of the immune system may occur through antigen-specific and non-antigen specific stimuli. For example, monocytes when exposed to bacterial cell wall products, such as lipopolysaccharide, produce IL-12 and other cytokines which have multiple functions including influencing the expression of cytokines by other cells. Antigen-specific responses are generated by B and T cells through immunoglobulin and T cell receptors respectively. B cell activation may result in the production of IL-6 and other cytokines. T cells are central players in linking non-antigen specific, B cell and T cell responses together. Two classes of T cells are recognized: α , β and γ , δ T cells, defined by their T cell receptor (TCR) chain usage. The majority of circulating α , β T cells carry either CD4 or CD8 molecules, which bind to MHC class II or MHC class I molecules, respectively. The ligand of γ , δ T cells is not clearly known, and these cells typically carry neither CD4 nor CD8 molecules, hence the name 'double negative' T cells. Functionally, CD8⁺ T cells, are typically cytotoxic T cells and can kill target cells presenting processed foreign peptide via HLA class I molecules; some CD8⁺ T cells secrete cytokines such as

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IFN γ . CD4 $^{+}$ T cells are typically helper T cells, although rare subsets have cytotoxic function. Several TH subsets of CD4 $^{+}$ T cells have been identified. In the mouse these subsets are well defined and include Type 1 (TH1), which promote cell-mediated effector responses; and Type 2 CD4 $^{+}$ helper T cells (TH2), which promote B cell-mediated humoral responses. Cytokines produced by TH1 cells include interleukin-2 (IL-2), interferon gamma (IFN γ) and tumour necrosis factor beta (TNF β), and constitute a pro-inflammatory cytokine profile; those produced by TH2 cells include IL-4, IL-5, IL-6, and IL-10, ie, a predominantly anti-inflammatory cytokine profile. Both TH1 and TH2 cells produce IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF).^{13–20} Recently a TH3 subset (characterized by TGF β) has been defined. In humans, the distinction between TH1, TH2 and TH3 is less well defined, and a subset of TH0 cells, which produce some cytokines typical of TH1 and TH2 profiles can be identified. The clinical outcome of many infectious, autoimmune, or malignant diseases appears to be influenced by the overall balance of production (profiles) of pro-inflammatory and anti-inflammatory cytokines.^{21–31} Hence, much interest has focused upon the regulation of genes expressing these cytokines. In particular, a significant number of studies have addressed whether genetic polymorphism within these genes might influence the levels of expression, and therefore the overall immune response. A review of the findings of these studies is presented here.

Cytokine gene polymorphism: influence on protein structure, expression and disease

Cytokine gene polymorphism

Non-conservative mutation within the coding region of genes can result in loss, abrogation, or change of function in the expressed protein as a result of change in protein structure. Cytokine and cytokine receptor genes are generally highly conserved in terms of exon sequences,^{32,33} although examples of amino acid sequence variation have been found for IL-4 receptor, LT α (TNF β), TGF β and GM-CSF receptor β in healthy individuals; and in the IL-2 receptor γ gene for persons with severe combined immunodeficiency (Tables 1 and 3). Although conservative (silent) mutations do not affect amino acid sequence, they may influence protein expression in a variety of other ways: for example, they can alter mRNA splicing, mRNA stability, and levels of gene transcription. Polymorphisms within the 5'- and 3'-regulatory sequences or introns of genes may have a significant effect on transcription, since they may alter the structure of transcription factor binding sites within gene promoters or the structure of enhancers and silencers within introns or at more remote regulatory sites. Finally, they may alter binding sites within the nuclear matrix for architectural transcription factors which modulate promoter geometry.³⁴ Many of the reported polymorphisms within cytokine genes occur within known or putative regulatory regions^{32,33} (Table 1).

The rationale for studying cytokine gene polymorphisms in human disease can be broadly summarised as follows:

Table 1 List of human cytokine gene polymorphisms

Gene	Polymorphism	Reference
IL-1 α	Intron 6, 46 bp VNTR	40
	-889	41
	+4345 T \rightarrow G	41
	Dinucleotide repeat (TTA) repeat	42,43
IL-1 β	-511 G \rightarrow A (AvaI)	44
	-35 T \rightarrow C (AluI)	45
	nt5810 A \rightarrow T (BsoFI)	46
	+3953 (nt5887) C \rightarrow T (TaqI)	46
IL-1Ra	+2016 T \rightarrow C	47
	Intron 2 86 bp VNTR	41
	nt8006 T \rightarrow C (MspI)	48
	nt8061 C \rightarrow T (MwoI)	46
IL-1RI	nt9589 A \rightarrow T (SspI)	46
	nt11100 T \rightarrow C (MspAII)	46
	2 PstI RFLPs	49
	IL-2	50
IL-2	-330	50
	+166	50
	Dinucleotide repeat	51
	TaqI RFLP	52
IL-2R α	Dinucleotide repeat	53
	BglII RFLP	54
	-211 C \rightarrow A	55
	-16 C \rightarrow T	55
IL-2R β	+5 C \rightarrow T	55
	+131 C \rightarrow T	55
	Enhancer nt232	55
	Enhancer nt236	55
IL-3	Enhancer nt283	55
	-590 C \rightarrow T (BsmFI)	56
	Intron 3, (GT) repeat	57
	Intron 2, 70 bp VNTR	57
IL-4	nt148 A \rightarrow G	58
	nt426 C \rightarrow T	58
	nt747 C \rightarrow G	58
	nt864 T \rightarrow C	58
IL-4R	nt1124 A \rightarrow C	58
	nt1167 G \rightarrow T	58
	nt1216 T \rightarrow C	58
	nt1218 C \rightarrow T	58
IL-5R α	nt1224 T \rightarrow C	58
	nt1232 C \rightarrow T	58
	nt1902 G \rightarrow A (R576Q)	59
	nt2281 T \rightarrow C	58
IL-6	Dinucleotide repeat	51
	-80 G \rightarrow A (MaeIII)	60,61
	-174 G \rightarrow C (NlaIII)	62–64
	3' (AT)-rich minisatellite	65,66
IL-6R	MspI RFLP	67
	BglII RFLP	67,68
	XbaI RFLP	69
	nt565 G \rightarrow A (FokI)	64
IL-8	5' (AT)-tract (5 alleles)	64
	(CA)n repeat	70
	(CA)n repeat	71
	HindIII RFLP	72
IL-9	Dinucleotide repeat	73
	-1082 G \rightarrow A	74,75
	-819 C \rightarrow T	75,76
	-592 C \rightarrow A	75,76
IL-10	5' proximal (CA) repeat (IL10.G)	77
	5' distal (CA) repeat (IL10.R)	78
	5' dinucleotide repeat	79
	TNF α	80
IL-11	-1031	80
	-862 (*-863)	*80 81
	-856 (*-857)	*80 81
	-574	81
TNF α	-376 G \rightarrow A	82

Continued

Table 1 *Continued*

Gene	Polymorphism	Reference
	-308 G→A	83
	(TNF1=G; TNF2=A)	84
	-238 G→A	85
	-163 G→A	82
	+70 G→A	82
	TNFa, b, c, d, e microsatellites	86,87
LTα (TNFβ)	Intron 1, <i>NcoI</i> RFLP (Thr26Asn)	88
	(TNFB*1=Asn26; TNFB*2=Thr26)	89
	<i>AspHI</i> RFLP	90
TNF-RI	nt36 A→G (<i>MspA1</i> I)	91
	-383 A→C (<i>BglIII</i>)	92
TNF-RII	3'-UTR SSCP '5/6'	93
	3'-UTR SSCP '7/8'	93
IFNα	For review see	94
IFNα	Dinucleotide repeat	95
IFNαR	<i>HindIII</i> RFLP	96
IFNβ	3' <i>MspI</i> RFLP	97
IFNγ	Intron 1, (CA) repeat	98,99
IFNγRI	<i>TaqI</i> RFLP	100
TGFα	<i>TaqI</i> RFLP	101
TGFβ1	nt869 (Leu10Pro)	102,103
	nt915 (Arg25Pro)	102,103
	nt72 unspecified	103
	-988	102
	-800	102,103
	-509	102,103
	nt713-8delC	104
	nt788 C→T	104
TGFβ2	4 RFLPs, SSPCs	105
GM-CSF-Rα	nt199 C→G	106
	nt824 C→T	106
	nt640 A→G	106
	nt428 A→G	106
	nt1148 G→A	106
GM-CSF-Rβ	nt301 C→T (Cys91)	107
	nt773 G→C (Glu249Glu)	107
	nt962 G→A (Asp312Asn)	107
	nt1306 C→T (Ser426)	107,108
	nt1835 C→A	108
	nt1968 G→T	108
	nt1972 G→A	108
	nt1982 G→A	108
	nt2427 G→A	108

- To enhance the understanding of the aetiology and pathology of human disease.
- To identify potential markers of susceptibility, severity, and clinical outcome.
- To identify potential markers for responders vs non-responders in therapeutic trials.
- To identify targets for therapeutic intervention.
- To identify novel strategies to prevent disease or to improve existing preventions such as vaccines.

The influence of cytokine gene polymorphisms on gene expression and disease has been addressed at two levels of research: studies using *in vitro* gene expression, and those involving *in vivo* disease association. Only a few studies have thus far integrated both of these approaches.

***In vitro* gene expression studies**

Up-regulated and/or down-regulated expression and production of cytokine mRNA and cytokines, or of their receptors, is a feature in most immune responses in human diseases. However, this response may differ significantly among individuals. *In vitro* gene expression

Table 2 *In vitro* expression studies

Gene	Polymorphism and allele (or haplotype)	Expression	Reference
IL-10	R 3	Decreased	109
IL-10	R 3, G 7	Decreased	109
IL-10	R 2, G 14	Increased	109
IL-10	-1082 G, -819 C, -592 C	Increased	75
IL-10	-1082 A, -819 C, -592 C	Decreased	75
IL-10	-1082 A, -819 T, -592 A	Decreased	75
IL-1α	Intron 6, 46 bp VNTR	Related to VNTR allele	40,110
IL-1β	+3953 (nt5887) T	Increased	47
IL-1Ra	Intron 2 86 bp VNTR, allele 2	Increased	48,111,112
IL-6	-174 G	Increased	64
IFNγ	Intron 1 (CA)n repeat, allele 2	Increased	113
TGFβ1	nt915 (Arg25)	Increased	114
TNFα	a	No effect on LTα (TNFβ) secretion	115
TNFα	a2	Decreased	116
TNFα	c	No effect on LTα (TNFβ) secretion	115
TNFα	d3	Increased	117
TNFα	-1031	Increased	80
TNFα	-862 (*-863)	Increased	80
TNFα	-862 (*-863)	No effect	81
TNFα	-856 (*-857)	Increased	80
TNFα	-856 (*-857)	No effect	81
TNFα	-574	No effect	81
TNFα	-238 A	Increased	118
TNFα	-238 G→A	No effect	81,119-121
TNFα	-308	No effect	81,117, 120,122
TNFα	-308A (TNF2)	Increased	84,123
TNFα	-376 G→A	No effect	120,121
TNFα	+70 G→A	No effect	81
LTα (TNFβ)	Intron 1, <i>NcoI</i> RFLP	No effect on LTα(TNFβ) secretion	115
LTα (TNFβ)	Intron 1, <i>NcoI</i> RFLP: TNFB*1 (Asn26)	Increased	88
LTα (TNFβ)	Intron 1, <i>NcoI</i> RFLP: TNFB*2 (Thr26)	Decreased	88
LTα (TNFβ) + TNFα	Intron 1, <i>NcoI</i> RFLP: TNFB*2 (Thr26), TNFa2	Increased	115
LTα (TNFβ) + TNFα	Intron 1, <i>NcoI</i> RFLP: TNFB*1 (Asn26), TNFa6	Decreased	115

studies attempt to determine a genetic basis for interindividual differences in the immune response. This is achieved by examining the relationship between individual polymorphic alleles or haplotypes of cytokine genes and the expression of the transcript or cytokine *in vitro*. The main approaches used to date include measuring the levels of cytokine or cytokine receptor mRNA, or of cytokine or receptor protein, expressed as a result of *in vitro* stimulation of cells in culture with a mitogen; and isolation of individual alleles of gene promoters by cloning adjacent to a reporter gene in an expression vector, followed by transfection of an appropriate cell line and measurement of reporter protein expression. The majority of studies to date have followed the first approach. It is becoming increasingly apparent that the results of expression stud-

Table 3 *In vivo* disease association studies

<i>Cytokine and polymorphism</i>	<i>Disease</i>	<i>Association</i>	<i>References</i>
EPO-R nt5964 C→G	Primary familial and congenital polycythaemia	yes	124
FGF1-α (GT)n 5'-UTR	Early-onset pauciarticular juvenile chronic arthritis	no	125
FGF1-α (GT)n 5'-UTR	Multiple sclerosis	no	126
GM-CSF-Rβ nt1306 C→T (Ser426)	Acute myeloid leukaemia	no	107
GM-CSF-Rβ nt301 C→T (Cys91)	Acute myeloid leukaemia	no	107
GM-CSF-Rβ nt773 G→C (Glu249Glu)	Acute myeloid leukaemia	no	107
GM-CSF-Rβ nt962 G→A (Asp312Asn)	Acute myeloid leukaemia	no	107
IFNα (CA)n intron 1	Early-onset pauciarticular juvenile chronic arthritis	no	125
IFNγ (CA)n intron 1	Grave's disease	yes (increased frequency of allele 5; decreased frequency of allele 2)	127
IFNγ (CA)n intron 1	Insulin-dependent diabetes mellitus	yes	128
IFNγ (CA)n intron 1	Insulin-dependent diabetes mellitus	no	129
IFNγ (CA)n intron 1	Lung allograft fibrosis	yes	130
IFNγ (CA)n intron 1	Multiple sclerosis	no	126, 131
IFNγ (CA)n intron 1 and IL-10 -1082 G→A	Renal transplant rejection	yes	132
IFNγ-R Val14Met	Systemic lupus erythematosus	yes	133
IL-10 (<i>IL10.G</i>)	Inflammatory bowel disease and ulcerative colitis	no	134
IL-10 (<i>IL10.G</i>)	Multiple sclerosis	yes	135
IL-10 (<i>IL10.G</i>)	Systemic lupus erythematosus	no	132
IL-10 (<i>IL10.G12-G15</i>)	UVB-induced immunosuppression	yes	136
IL-10 (<i>IL10.R</i>)	Graft-versus-host disease in allogeneic bone marrow transplantation	no	137
IL-10 (<i>IL10.R</i>)	Rheumatoid arthritis	yes	138
IL-10 -592	Systemic lupus erythematosus	no	139
IL-10 +571 C→A	Primary biliary cirrhosis	no	140
IL-10 -1082	Asthma (elevated IgE)	yes	141
IL-10 -1082	Asthma severity	yes	142
IL-10 -1082	Rheumatoid arthritis	no	143
IL-10 -1082, -819, -592 haplotype	Rheumatoid arthritis and Felty's syndrome	yes	144
IL-10 -1082A, -819C, -592C haplotype	Rheumatoid arthritis (IgA RF+ve, IgG RF-ve)	yes	145
IL-10 -1082A, -819T, -592A haplotype	Systemic lupus erythematosus nephritis (Chinese)	yes	146
IL-10 -1082G, -819C, -592C haplotype	Systemic lupus erythematosus	yes (Ro+)	147
IL-1Ra nt8061 C→T (<i>Mwol</i>)	Ulcerative colitis	yes	148
IL-1Ra VNTR	Acute myeloid leukaemia (secondary)	no	149
IL-1Ra VNTR	Alcoholic hepatic fibrosis (Japanese)	yes	150
IL-1Ra VNTR	Alopecia areata	yes (severity)	151,152
IL-1Ra VNTR	Bone loss (early postmenopausal)	yes	153
IL-1Ra VNTR	EBV seronegativity	weak	154
IL-1Ra VNTR	Grave's disease	yes	155
IL-1Ra VNTR	Grave's disease and Grave's ophthalmopathy	no	156,157
IL-1Ra VNTR	Henoch-Schonlein nephritis	yes	158
IL-1Ra VNTR	Insulin-dependent diabetes mellitus	yes	159
IL-1Ra VNTR	Insulin-dependent diabetes mellitus, Non-insulin-dependent diabetes mellitus nephropathy	yes	160
IL-1Ra VNTR	Inflammatory bowel disease	no	161,162
IL-1Ra VNTR	Inflammatory bowel disease	yes	163-165
IL-1Ra VNTR	Lichen sclerosis	yes	166
IL-1Ra VNTR	Malaria (<i>P. falciparum</i>): severity	no	167
IL-1Ra VNTR	Multiple sclerosis	yes	168,169
IL-1Ra VNTR	Multiple sclerosis	no	126,131,170,171
IL-1Ra VNTR	Myasthenia gravis	no	172
IL-1Ra VNTR	Rheumatoid arthritis	no	173

Continued

Table 3 Continued

Cytokine and polymorphism	Disease	Association	References
IL-1Ra VNTR	Single vessel coronary disease	yes	174
IL-1Ra VNTR	Sjögren's syndrome	yes	173
IL-1Ra VNTR	Systemic lupus erythematosus	yes	175,176
IL-1Ra VNTR	Systemic lupus erythematosus	no	177
	Ulcerative colitis	no	178
IL-1Ra VNTR & IL-1β +3953 exon 5	Myasthenia gravis	yes	172
IL-1RI	Insulin-dependent diabetes mellitus	yes	159,179
IL-1RI RFLP-A	Insulin-dependent diabetes mellitus	yes	49
IL-1α (CA)n intron 5	Early-onset pauciarticular juvenile chronic arthritis	no	125
IL-1α (CA)n intron 5	Multiple sclerosis	no	126
IL-1α (CA)n intron 5	Rheumatoid arthritis	no	180
IL-1α -889	Juvenile rheumatoid arthritis	yes	181
IL-1α intron 6	Rheumatoid arthritis	no	182
IL-1β	Periodontitis	yes	41,183
IL-1β + IL-1Ra	Inflammatory bowel disease	yes	184,185
IL-1β +3953 exon 5	Insulin-dependent diabetes mellitus	no	186
IL-1β +3953 exon 5	Insulin-dependent diabetes mellitus (with nephropathy)	yes	187
IL-1β +3953 exon 5	Insulin-dependent diabetes mellitus (DR3-/DR4-)	yes	47
IL-1β +3953 exon 5	Inflammatory bowel disease	no	162
IL-1β +3953 exon 5	Low-grade squamous intraepithelial lesions	yes	188
IL-1β +3953 exon 5	Multiple sclerosis	no	131
IL-1β +3953 exon 5	Myasthenia gravis	yes	172
IL-1β +3953 exon 5	Periodontitis	yes	189
IL-1β +3953 exon 5	Ulcerative colitis	no	178
IL-1β +3953 exon 5	Ulcerative colitis	yes	148
IL-1β -511 G→A (Aval)	EBV seronegativity	yes	154
IL-1β -511 G→A (Aval), IL-1α -889, IL-1Ra VNTR	Schizophrenia	yes	190
IL-2 (CA)n 3'-flanking region	Early-onset pauciarticular juvenile chronic arthritis	no	125
IL-2 (CA)n 3'-flanking region	Inflammatory bowel disease	no	135
IL-2 (CA)n 3'-flanking region	Multiple sclerosis	no	126,132
IL-2 (CA)n 3'-flanking region	Rheumatoid arthritis	no	180
IL-2 (CA)n 3'-flanking region	Ulcerative colitis	weak	135
IL-2Rβ (GT)n 5'-UTR	Multiple sclerosis	no	126
IL-2Rβ dinucleotide repeat	Schizophrenia	no	191,192
IL-2Rγ	Severe combined immunodeficiency disease*	yes	193-200
IL-4 -590 C→T (BsmFI)	Asthma and atopy	weak	56
IL-4 -590 C→T (BsmFI)	Asthma and atopy (Japanese)	yes	201,202
IL-4 Intron 2, 70 bp VNTR	Multiple sclerosis	yes	203
IL-4 Intron 2, 70 bp VNTR	Myasthenia gravis	no	204
IL-4 Intron 3, (GT) repeat	Multiple sclerosis	no	132
IL-4 Intron 3, (GT) repeat	Myasthenia gravis	no	204
IL-4Rα nt148 A→G (150 V)	Atopic disease	yes	205,206
IL-4Rα nt1902 G→A (R576Q)	Atopic disease	yes	59
IL-5Rα (GA)n 3'-UTR	Early-onset pauciarticular juvenile chronic arthritis	no	125
IL-5Rα (GA)n 3'-UTR	Multiple sclerosis	no	126
IL-5Rα (GA)n 3'-UTR	Rheumatoid arthritis	no	180
IL-6 -174 C→G	Systemic-onset juvenile chronic arthritis	yes	64
IL-6 3' (AT)-rich minisatellite	Bone loss (bone mineral density)	yes	66
IL-6 3' (AT)-rich minisatellite	Systemic lupus erythematosus	yes	69
IL-6 BgIII	Rheumatoid arthritis	no	68
IL-6 MspI & BglII	Rheumatoid arthritis, pauciarticular juvenile rheumatoid arthritis, systemic lupus erythematosus	no	207
IRF-1 (GT)n intron 7	Multiple sclerosis	no	126
TGFα TaqI RFLP	Cleft lip	no	208
TGFβ1 nt509 C→T	Asthma (elevated IgE)	yes	142
TGFβ1 nt509 C→T	Coronary artery disease and hypertension	no	209
TGFβ1 nt713-8delC	Diabetic nephropathy	no	210
TGFβ1 nt713-8delC	Insulin-dependent diabetes mellitus	no	210
TGFβ1 nt713-8delC	Osteoporosis	yes	104
TGFβ1 nt788 C→T (T2631)	Coronary artery disease and hypertension	no	209

Continued

Table 3 *Continued*

<i>Cytokine and polymorphism</i>	<i>Disease</i>	<i>Association</i>	<i>References</i>
TGFβ1 nt788 C→T (T2631)	Diabetic nephropathy	yes	210
TGFβ1 nt788 C→T (T2631)	Insulin-dependent diabetes mellitus	no	210
TGFβ1 nt800 G→A	Coronary artery disease and hypertension	no	209
TGFβ1 nt869 (Leu10Pro)	Coronary artery disease and hypertension	no	209
TGFβ1 nt869 (Leu10Pro)	Postmenopausal osteoporosis (Japanese)	yes	211
TGFβ1 nt915 (Arg25Pro)	Coronary artery disease and hypertension	no	209
TGFβ1 nt915 (Arg25Pro)	Fibrotic lung disease and lung allograft fibrosis	yes	103,114
TGFβ1 nt915 (Arg25Pro)	Hypertension	yes	212
TNFα, TNFβ	Multiple sclerosis	yes, via LD with HLA?	213
TNFα, TNFβ, TNFγ, TNFδ	Pharyngeal cancer	no	214
TNFα1b5, a2b1, a2b3, a7b4, a6 b5	Insulin-dependent diabetes mellitus	via LD with HLA?	215,216
TNFα2	<i>Campylobacter jejuni</i> -related Guillain-Barre syndrome	yes	217
TNFα2	Celiac disease	yes	179
TNFα2	Colorectal cancer	yes	218
TNFα2	Multiple sclerosis	yes, via LD with HLA?	126
TNFα2	Myasthenia gravis	yes	219
TNFα2	Rheumatoid arthritis	yes	180
TNFα2, a6	Insulin-dependent diabetes mellitus	yes	115
TNFα2, b3	Celiac disease	via LD with HLA-DQ2+ haplotypes	220
TNFα6	Early-onset pauciarticular juvenile chronic arthritis	yes	125
TNFα6, b5, c1, d3, e3	Rheumatoid arthritis	yes	221
TNFα9	Renal transplant rejection	yes	222
TNFβ3	Laryngeal cancer	yes	214
TNFβ3, d4, d5	Clozapine-induced agranulocytosis	yes	223
TNFγ2	Ulcerative colitis (progression)	yes	178
TNFγ1	Rheumatoid arthritis	yes	221
TNFγ2	HIV disease progression	yes	224
TNFγ3	Cardiac transplant rejection	yes	117
TNFγ3	Graft-versus-host disease in allogeneic bone marrow transplantation	yes	139
TNFγ4	Renal transplant rejection	yes	222
TNF-RI (p55) C52F	TNF receptor-associated periodic syndromes	yes	225
TNF-RII 3'-UTR SSCP '7/8'	Grave's disease	no	226
TNF-RII 3'-UTR SSCP '7/8'	Insulin-dependent diabetes mellitus	no	226
TNFα -163	Non-insulin-dependent diabetes mellitus	no	227
TNFα -238	Alcoholic steatohepatitis	yes	118
TNFα -238	Chronic hepatitis B	yes	228
TNFα -238	Chronic active hepatitis C	yes	229
TNFα -238	Early-onset pauciarticular juvenile chronic arthritis	no	125
TNFα -238	Early-onset psoriasis	no	230
TNFα -238	Insulin resistance (decreased)	yes	231
TNFα -238	Multiple sclerosis	no	126
TNFα -238	Multiple sclerosis	yes	120
TNFα -238	Non-insulin-dependent diabetes mellitus	no	227
TNFα -238	Periodontitis (adult)	no	123
TNFα -238	Rheumatoid arthritis	yes (erosion)	82
TNFα -238	Rheumatoid arthritis	yes (joint destruction)	121
TNFα -238	Rheumatoid arthritis	no	232
TNFα -238	Scarring trachoma (Chlamydial)	no	233
TNFα -238, -244, -308	Chaga's disease	no	234
TNFα -238, -308	Ankylosing spondylitis	no	235
TNFα -238, -308	Pneumoconiosis	yes (TNFα -308)	236
TNFα -238, -308	Meningococcal disease	no	237
TNFα -238, -308	Systemic lupus erythematosus (Whites and Black S. African)	no, via LD with HLA?	238
TNFα -238, TNFα	Systemic lupus erythematosus (Italians)	no	239
TNFα -308	Actinic prurigo	no	240
TNFα -308	Alcoholic steatohepatitis	no	118

Continued

Table 3 Continued

Cytokine and polymorphism	Disease	Association	References
TNF α -308	Ankylosing spondylitis	no	241
TNF α -308	Cardiac transplant rejection	no	117
TNF α -308	Celiac disease	via LD with HLA?	242
TNF α -308	Cerebral malaria	yes	243
TNF α -308	Chronic hepatitis B	no	228
TNF α -308	Chronic active hepatitis C	no	229
TNF α -308	Chronic lymphocytic leukaemia	yes	244
TNF α -308	Chronic lymphocytic leukaemia	no	245
TNF α -308	Coronary heart disease	no	246
TNF α -308	Dermatitis herpetiformis	via LD with HLA?	247
TNF α -308	Early-onset pauciarticular juvenile chronic arthritis	no	125
TNF α -308	Graft-versus-host disease in allogeneic bone marrow transplantation	no	248
TNF α -308	HIV-encephalitis	no	249
TNF α -308	Hodgkin's disease	no	245
TNF α -308	Insulin-dependent diabetes mellitus	no, via LD with HLA?	83,122,250
TNF α -308	Inflammatory bowel disease	trend	165
TNF α -308	Insulin resistance	no	231
TNF α -308	Leprosy	yes (lepromatous)	251
TNF α -308	Leprosy	no (tuberculoid)	251
TNF α -308	Lichen sclerosis	no	252
TNF α -308	Multiple sclerosis	no	120,126,253,254
TNF α -308	Nephropathia epidemica	yes	255
TNF α -308	Non-insulin-dependent diabetes mellitus	no	227
TNF α -308	Obesity	yes	246
TNF α -308	Periodontitis (adult)	no	123
TNF α -308	Primary sclerosing cholangitis	yes	256
TNF α -308	Rheumatoid arthritis	yes (nodular disease)	232
TNF α -308	Rheumatoid arthritis, systemic lupus erythematosus	yes, via LD with HLA?	257,258
TNF α -308	Scarring trachoma	yes	233
TNF α -308	Severe malarial and other infections	yes	259
TNF α -308	Severe sepsis	no	260
TNF α -308	Systemic lupus erythematosus and nephritis (Koreans)	yes, via LD with	261,262
TNF α -308	Systemic lupus erythematosus (African-Americans)	yes	263
TNF α -308	Systemic lupus erythematosus (Chinese)	no, via LD with HLA?	264
TNF α -308	UVB-induced immunosuppression	no	138
TNF α -308	Venous thromboembolism	no	265
TNF α -308 and IL-10 -1082 G→A	Cardiac transplant rejection	yes	266
TNF α -308 and IL-10 -1082 G→A	Renal transplant rejection	yes, TNF α -308 alone	267,268
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Asthma	yes	269
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Asthma and atopy (Italians)	yes (LT α , (TNF β) <i>NcoI</i> only)	270
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Asthma (childhood)	yes	271
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Colorectal cancer	yes (β <i>NcoI</i> only)	272
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Congestive heart failure	no	273
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Dermatitis herpetiformis	yes	274
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Hairy cell leukaemia	no	275
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Multiple sclerosis	yes (development)	276
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Non-Hodgkin's lymphoma (outcome)	yes	277
TNF α -308 and LT α (TNF β) <i>NcoI</i>	Mucocutaneous leishmaniasis	yes	278
TNF α -376 G→A	Non-insulin-dependent diabetes mellitus	no	227
TNF α -376 G→A	Multiple sclerosis	no	120
TNF α +488A	Common variable immunodeficiency	yes	279
LT α (TNF β) <i>NcoI</i>	Ankylosing spondylitis	no	280
LT α (TNF β) <i>NcoI</i>	Ankylosing spondylitis	yes	235
LT α (TNF β) <i>NcoI</i>	Autoimmune thyroiditis	no	281
LT α (TNF β) <i>NcoI</i>	Chronic lymphocytic leukaemia	yes (advanced stage)	244
LT α (TNF β) <i>NcoI</i>	Gastric cancer	yes (survival)	282
LT α (TNF β) <i>NcoI</i>	Grave's disease	via LD with HLA?	283

Continued

Table 3 *Continued*

Cytokine and polymorphism	Disease	Association	References
LT α (TNF β) <i>NcoI</i>	Hashimoto's disease	no	284
LT α (TNF β) <i>NcoI</i>	Hyperinsulinaemia in coronary artery disease	yes	285
LT α (TNF β) <i>NcoI</i>	Insulin-dependent diabetes mellitus	via LD with HLA?	115,286-295
LT α (TNF β) <i>NcoI</i>	Idiopathic membranous nephropathy	via LD with HLA?	296
LT α (TNF β) <i>NcoI</i>	Inflammatory bowel disease	no	297
LT α (TNF β) <i>NcoI</i>	Lung cancer	yes (survival)	298,299
LT α (TNF β) <i>NcoI</i>	Multiple sclerosis and optic neuritis	no	253,300
LT α (TNF β) <i>NcoI</i>	Myasthenia gravis	yes	301
LT α (TNF β) <i>NcoI</i>	Non-insulin-dependent diabetes mellitus (hypertriglyceridaemia)	yes	302
LT α (TNF β) <i>NcoI</i>	Primary biliary cirrhosis	via LD with HLA?	303
LT α (TNF β) <i>NcoI</i>	Primary biliary cirrhosis	no	304
LT α (TNF β) <i>NcoI</i>	Rheumatoid arthritis	no	232
LT α (TNF β) <i>NcoI</i>	Rheumatoid arthritis, pauciarticular juvenile rheumatoid arthritis, systemic lupus erythematosus, Sjögren's	via LD with HLA?	305,309
LT α (TNF β) <i>NcoI</i>	Severe sepsis	yes	260
LT α (TNF β) <i>NcoI</i>	Spontaneous abortion	no	310
LT α (TNF β) <i>NcoI</i> & <i>EcoRI</i>	Behcet's disease	yes (<i>NcoI</i>)	311
LT α (TNF β) <i>NcoI</i> , TNF α , <i>b</i> , <i>c</i>	Multiple sclerosis	no	309,312

*For other SCID-IL-2R γ associations, information is available from the World Wide Web site:
<http://www.nhgri.nih.gov/DIR/LGT/SCID/IL2RGbase.html>

ies may be critically influenced by several factors such as the cell lineage used in the assay and the therapeutic preconditioning or treatment of subjects prior to harvesting cells for the assay. Therefore, the reader should refer to publications of individual studies in which apparent contradictions between results are evident. A review of the results of the principal studies is shown in Table 2.

***In vivo* disease association studies**

These studies attempt to identify immunogenetic markers for a given disease. Association is sought between specific cytokine gene polymorphisms and clinical outcome by direct comparison of individual cytokine genotypes and the clinical features of the disease (eg, susceptibility, duration and severity). The *a priori* involvement of dysregulation of a specific cytokine or receptor in the disease is usually, though not always, the rationale for selecting a cytokine or cytokine receptor gene for analysis. Such data may be generated using population-based or family studies in humans or using animal models, and may be from analysis of secreted, cell surface or intracellular protein, or of cytokine mRNA. Using these and other clues, many studies have identified statistically significant associations between cytokine alleles and disease. However, in many of these studies the *in vitro* expression studies have not been attempted, or are the subject of controversy, or by consensus have not indicated a convincing functional rationale for the association.

The genetic analysis of cytokines in human disease has traditionally focused on case-control association studies, in which the frequencies of marker alleles in groups of patients and healthy controls are compared, and the difference is subjected to statistical analysis. The association is often expressed as the relative risk (or odds ratio) that an individual will develop the disorder if he or she carries the particular allele or marker, compared to an individual who does not carry the allele or marker. These studies have met with only modest success in identifying disease-causing cytokine genes, in part because of the dif-

ficulty in selecting from among the many candidate possibilities, and the likely modest effect of any single disease susceptibility gene. The difficulty in identifying a perfectly matched control group creates an additional limitation, increasing the possibility that a potentially positive association is biologically irrelevant because of population admixture. Furthermore, even when cases and controls are adequately matched, most study designs involve relatively small sample sizes which lack the statistical power to detect small or moderate gene effects. Other approaches to identifying associations between complex traits and cytokine or cytokine receptor gene polymorphism use a variety of family-based study designs. These include whole genome scanning using linkage analysis (LOD scores) and affected sib-pair (ASP) methods. With identification of specific chromosomal regions, more precise localisation required the development of linkage disequilibrium mapping³⁵ and transmission disequilibrium testing^{36,37} with the establishment of ancestral haplotypes among disease-associated chromosomes.³⁸

Allelic association methods based on increased transmission of marker alleles will need to be employed for the mapping of complex disease susceptibility genes. However, because the extent of association of single marker alleles with disease is a function of the relative frequency of the allele on disease-associated chromosomes vs non disease-predisposing chromosomes, the most associated marker allele in a region will not necessarily be closest to the disease locus. Although this area is controversial, the extended transmission/disequilibrium test (TDT)³⁷ may be best approach.³⁹

While combined analysis of data from several studies can be pooled to increase confidence in the strength of observed associations, biases in reporting positive or weak associations as opposed to lack of reporting negative associations also influences interpretation of published observations.

One of the sometimes overlooked aspects of such dis-

ease association studies is that the cytokine network is highly complex, containing interactive cascades of gene activation and suppression. One consequence of mutual TH1–TH2 antagonism may be the predominance of one or the other subset, which might directly influence the clinical outcome of disease. Therefore, genetic polymorphisms in cytokine genes and their receptors which regulate expression should not in all cases be studied strictly in isolation. This is because individual associations may be non-informative, whereas specific combinations of cytokine genotypes might predispose to disease susceptibility or outcome. Only a very few studies to date have attempted to analyse the combined contribution of more than one cytokine gene polymorphism to disease.

A review of the results of the principal disease association studies is shown in Table 3, both statistically significant (scored as 'yes') and statistically non-significant (scored as 'no'). The statistical significance is recorded as interpreted by the originating authors: for details of the statistical tests and corrections used, the reader should refer to the papers cited. For certain combinations of polymorphisms and diseases, contradictory results have been published. In these cases, the discordancy may be attributable to differences in ethnicity of populations, patient and/or control cohort selection *or* size, disease classification or status, or methods of statistical analysis. Both *in vitro* expression studies and *in vivo* disease association studies involving TNF α and LT α (TNF β) polymorphisms are often complicated by their linkage disequilibrium (LD) with HLA genes and haplotypes within the major histocompatibility complex. This has created difficulties in dissecting the independent role of TNF in expression and disease (see Table 2 and 3 for examples).

On-line databases

Tables 1, 2 and 3 and associated citations are reproduced in electronic form on the World Wide Web. They are searchable using the appropriate 'find' command of Web browsers. It is the intention of the authors to issue regular updates of these tables as part of an ongoing feature of this Journal. Notification and details of the revisions to the tables will be published as appropriate.

The Web site URL for Tables 1, 2 and 3 and associated citations is:

<http://www.pam.bris.ac.uk/services/GAI/cytokine4.htm>

Cytokine reviews database

In addition to these databases, we have issued a searchable reference database containing 1000 cytokine review citations, from 1990 to the present. This database is provided in two formats:

- Endnote™ version 3 (filename CYTOREVIEWS.ENL)
- Tagged MEDLARS format (.TAG) file (filename CYTOREVIEWS.TAG)

The files contain both *general* and *disease-specific* reviews relating to cytokines and cytokine receptors. The Endnote version may be searched using any criteria available within the Endnote™ application, eg, by author or keyword. The tagged MEDLARS version may be imported directly into other reference manager programs. Both files may be downloaded directly from the Web site shown above.

Related World Wide Web sites

Human cytokine gene nucleotide sequence alignments:
<http://www.pam.bris.ac.uk/services/cytokine2.htm>

PubMed search engine, primed to search for cytokine gene polymorphisms:
<http://www.gla.ac.uk/Acad/FacMed/Surgery/ggtemp/gghome/ggformat.html>

On-line Mendelian Inheritance in Man (OMIM) Web site:
<http://www3.ncbi.nlm.nih.gov/Omim/searchomim.html>

But a note of caution...

In addition, other elements which can influence the expression of cytokine (and other?) genes should not be forgotten. For example, the rigour with which Fishman *et al*⁶⁴ approached the measurement of IL-6 production in their control subjects, demonstrates the importance of the natural metabolic variation which occurs daily. This supported earlier studies, for example that of Petrovsky and Harrison,³¹³ who showed that the LPs induction of IL-10 and IFN-gamma varied throughout the day, observing that the IFN-gamma/IL-10 ratio peaked early in the morning and concluding that both cortisol and melatonin could regulate diurnal immune variation. Although much has been made of the requirement for caution when interpreting genetic data from the TNF cluster without due consideration of the MHC and linkage disequilibrium, MHC effects on cytokines off chromosome 6 have not been so well documented. The evidence is beginning to emerge, however. A study in 1997³¹⁴ demonstrated that secreted levels of IFN-gamma varied markedly with class-II alleles, in an MLR. DR1, DR2 and DR6 were associated with high IFN-gamma secretion while DR3, DR4 and DR7 were associated with lower IFN-gamma production. Similar conclusions were drawn for those DQ alleles in linkage disequilibrium with the DR alleles noted above. This pattern was reversed for TNF secretion (ie, DR3 was high TNF and so on), mirroring earlier work by Pociot *et al*¹⁵ who demonstrated a DR-based hierarchy of TNF secretion which was of greater magnitude than the TNF-allele results for which they are more usually remembered. Similar data are available for other aspects of the immune system, for example antibody production.³¹⁵

In this regard, DR3 has received the greatest attention. T cell activation varies in DR3-positive individuals, perhaps because of diminished CD69 expression,³¹⁶ as do cytokines themselves³¹⁷ particularly in regard to auto-immune DR3 positive subjects.³¹⁸ Apoptosis may differ because these individuals have diminished expression of CD95 (FAS³¹⁹) and indeed lower total lymphocyte counts have been described in association with B8-DR3.³²⁰ Little insight to the mechanism of these various effects by the class-II on immune function was available until recently, when it was demonstrated that different class-II molecules varied in the efficiency with which they transduce signals from CD4 across the cell membrane, and that this variation is carried with the intracellular portion of the class-II molecule.³²¹ As if this were not confusing enough, the age of the donors themselves has been shown to affect T cell activation^{322,323} through various mechanisms. In conclusion, the genetic effect seen to be acting on cytokine production, and implicating them as disease-associated loci in their own right, are complicated by the MHC and age.

How well we as a research community deal with these complications will determine how efficiently the influence of cytokine immunogenetics on disease is elucidated.

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