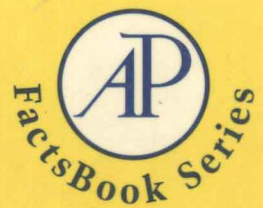
THE CYTOKINE *FactsBook*

Robin Callard
Andy Gearing



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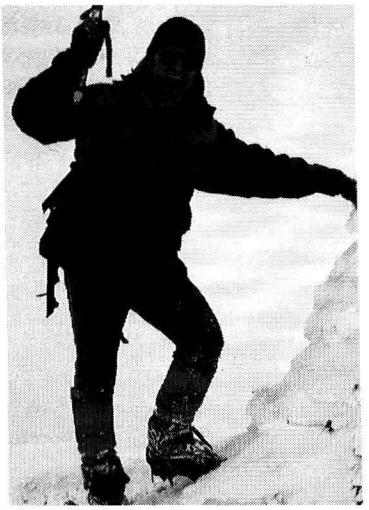
Preface

The FactsBook series had its inception during a conversation between the authors and Susan King at Academic Press four years ago. The first of the series, The Leucocyte Antigen FactsBook, was published in 1993 and fully vindicates Susan's vision and hard work to get the series started. We hope that the present volume meets the same high standard set by the first FactsBook. There are many people who have helped with advice and information during the writing of this book. In particular, we would like to mention Luke O'Neill for advice on signal transduction, Julian Symons and Gordon Duff for information on IL-1, Mark Mercola for unpublished sequence data on murine PDGF, Tadimitsu Kishimoto for information on murine gp130, and Ken Grabstein for advance information on the latest cytokine IL-15. Robin Thorpe, Antony Meager and Tony Mire-Sluis helped frequently when we could not obtain some vital piece of information. Richard Armitage and David Gearing also supplied us with unpublished information on cytokine receptors. We are especially grateful to Neil Barclay for allowing us to use his carefully prepared diagrams of cytokine receptors which appeared in The Leucocyte Antigen FactsBook, and the many reviewers who were kind enough to comment on early drafts of the various chapters. We also wish to thank Susan King, and subsequently Tessa Picknett, Leona Daw and Claire Gilman for their hard work and patience in getting the manuscript into press.

One of us (R.E.C.) also wishes to acknowledge funding from Action Research, the Leukaemia Research Fund, the Medical Research Council, and the Wellcome Trust.

The other (A.J.H.G.) wishes to thank Kate Owen for cheery help, British Biotech for employment, Academic Press for very nearly understanding I had a day job (sorry Tessa!) and finally Frances, Jamie and Catherine.

There will undoubtedly be some omissions and errors in this volume although we hope they will be infrequent. We would greatly appreciate being informed of any inaccuracies by writing to the Editor, Cytokine FactsBook, Academic Press, 24-28 Oval Road, London NW1 7DX, UK, so that these can be rectified in future editions.



Left: *Robin Callard*, Right: *Andy Gearing*

Abbreviations

CCP-SF	Complement control protein superfamily
CKR-SF	Cytokine receptor superfamily
CSF	Colony stimulating factor
DAG	1,2-Diacylglycerol
EBV	Epstein–Barr virus
FNIII	Fibronectin type III domain
GAG	Glycosaminoglycan
GAP	GTPase activating protein
GF	Growth factor
GPI	Glycosyl-phosphatidylinositol
IFN	Interferon
IFNR-SF	Interferon receptor superfamily (also CKR-SF type II)
Ig-SF	Immunoglobulin superfamily
IL	Interleukin
IP_3	Inositol 1,4,5-trisphosphate
LAK	Lymphokine-activated killer
LPS	Lipopolysaccharide
LRR	Leucine-rich region
LTR	Long terminal repeat
M_r	Molecular ratio
NGFR-SF	Nerve growth factor receptor superfamily
NK	Natural killer
ORF	Open reading frame
PGE_2	Prostaglandin E_2
PHA	Phytohaemagglutinin
PI	Phosphatidylinositol
PIP_2	Phosphatidylinositol bisphosphate
PKC	Protein kinase C
PLC	Phospholipase C
PLD	Phospholipase D
PTK	Protein tyrosine kinase
PTKR-SF	Protein tyrosine kinase receptor superfamily
SF	Superfamily
STSR-SF	Seven transmembrane spanning receptor superfamily
TCR	T Cell receptor
4PS	I L-4 induced phosphotyrosine substrate

Abbreviations for all the cytokines are not included here as the abbreviation and full name appears at the beginning of each entry

Contents

Preface ____ VII
Abbreviations ____ VIII

Section I THE INTRODUCTORY CHAPTERS

Chapter 1
Introduction ____ 2

Chapter 2
Organization of the Data ____ 7

Chapter 3
The Cytokine Network ____ 12

Chapter 4
Cytokine Receptor Superfamilies ____ 18

Section II THE CYTOKINES AND THEIR RECEPTORS

Interleukins

IL-1 ____ 31
IL-2 ____ 39
IL-3 ____ 46
IL-4 ____ 53
IL-5 ____ 59
IL-6 ____ 64
IL-7 ____ 70
IL-8 ____ 75
IL-9 ____ 79
IL-10 ____ 83
IL-11 ____ 87
IL-12 ____ 89
IL-13 ____ 92
IL-14 ____ 95
IL-15 ____ 97

Other Cytokines (in alphabetical order)

BDNF ____ 99
CNTF ____ 104
EGF ____ 109
Epo ____ 114
FGF ____ 119
G-CSF ____ 134
GM-CSF ____ 139
I-309/TCA-3 ____ 144
γIP-10 ____ 146
IFNα ____ 148
IFNβ ____ 155
IFNγ ____ 157
LIF ____ 163
LT (TNFβ) ____ 168
MCP-1, 2 and 3 ____ 171
M-CSF ____ 174
MIF ____ 179
MIP-1α ____ 181
MIP-1β ____ 185
MIP-2 ____ 188
NGF ____ 191
NT-3 ____ 199
NT-4 ____ 204
OSM ____ 207
PBP ____ 210
PBSF ____ 212
PDGF ____ 214
PF-4 ____ 223
RANTES ____ 226
SCF ____ 228
TGFα ____ 233
TGFβ ____ 235
TNFα ____ 241
Tpo ____ 247
VEGF ____ 252

Appendix: Cytokine standards ____ 258
General Bibliography ____ 259
Index ____ 261

Section I

THE INTRODUCTORY CHAPTERS

1 Introduction

AIMS OF THE BOOK

The main aim of this book is to provide a compendium of human and murine cytokines and their receptors. The information provided is confined largely to physicochemical properties, and includes amino acid sequences. The biological properties are not treated in detail but are described briefly. There are also introductory chapters on the nature of cytokines and cytokine families, the cytokine network, and cytokine receptor superfamilies.

WHAT IS A CYTOKINE?

Cytokines are soluble proteins or glycoproteins produced by leucocytes, and in many cases other cell types, which act as chemical communicators between cells, but not as effector molecules in their own right. Most are secreted, but some can be expressed on the cell membrane, and others are held in reservoirs in the extracellular matrix. Cytokines bind to specific receptors on the surface of target cells which are coupled to intracellular signal transduction and second messenger pathways. Most cytokines are growth and/or differentiation factors and they generally act on cells within the haematopoietic system.

Most of the molecules covered in this book fall easily within this definition of cytokines, but some do not. Erythropoietin (Epo) is not produced by leucocytes, but does act on haematopoietic precursors to generate red blood cells, and its receptor belongs to the cytokine receptor superfamily. Nerve growth factor (NGF), neurotrophin-3 (NT-3), and brain derived neurotrophic factor (BDNF) are all members of the same family of cytokines which are produced and act predominantly in the nervous system, but NGF also affects B cells, and its low affinity receptor is related to the tumour necrosis factor receptor (TNFR). Not all soluble peptide mediators are considered to be cytokines (e.g. insulin) and these exceptions have not been included. In the end, the decision whether to include a molecule as a cytokine or not must be somewhat arbitrary. If there are any omissions which offend, please let the Editor know and we will try to include them in the next edition. Information in this book is provided only for human and murine (or in some cases rat) cytokines which have been cloned, and for which there is a reasonable body of biological information. Where the receptors have been cloned, they are also included.

CYTOKINE FAMILIES

It should become clear from reading the entries in this book that cytokine nomenclature owes little to any systematic relationships between molecules. This is a reflection of the different historical approaches to naming new cytokines which were based either on cell of origin or initial defining bioassay. These systems have created anomalies such as tumour necrosis factor, originally defined as causing necrosis of solid tumours, but which is now thought to be primarily an immunomodulatory and pro-inflammatory cytokine, and which has proven ineffective as an anti-cancer agent in several clinical trials [1]. The interleukin nomenclature, which merely assigns a sequential number to new factors, is a rational system, but it has not been universally applied to new factors. This has created new anomalies such as IL-8 which is clearly a member of the chemokine cytokine family [2]. All of the molecules in this family share at least 25% amino acid

homology, have similar structures and bind to seven transmembrane spanning receptors of the rhodopsin superfamily, but none of the other chemokines have been given interleukin numbers. The chemokines are further subdivided into the CXC or α-chemokines located on human chromosome 4, and the CC or β-chemokines located on chromosome 17. The CXC chemokines are neutrophil chemoattractants whereas the CC chemokines are predominantly monocyte chemoattractants. Other attempts to impose order on the cytokine field by grouping cytokines as lymphokines (lymphocyte-derived) or monokines (monocyte-derived) have usually proved misleading when sensitive detection systems are used [3].

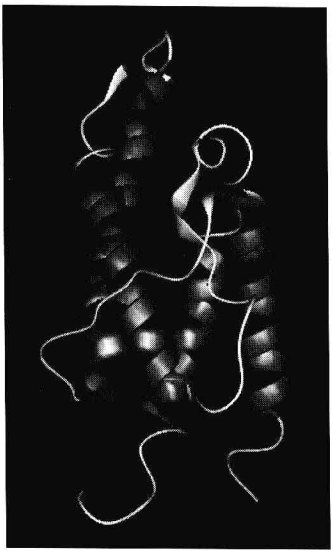
With the availability of large quantities of recombinant cytokines, X-ray and NMR studies have generated accurate structures for many molecules, and these have been used to model the structures of related cytokines (see individual entries, and refs 4–6). Further homologies derived from studying gene organization, chromosomal location and receptor usage have allowed most cytokines to be placed into one of at least six different families [7,8]. Table 1.1 describes one scheme for these families, and Figure 1.1 shows solid models of representative members of each family. It seems unlikely that cytokine nomenclature will reflect these emerging family relations in the near future. However, information from these studies should at least help to establish general principles of the properties of the groups.

Table 1.1 *Structural families of cytokines*

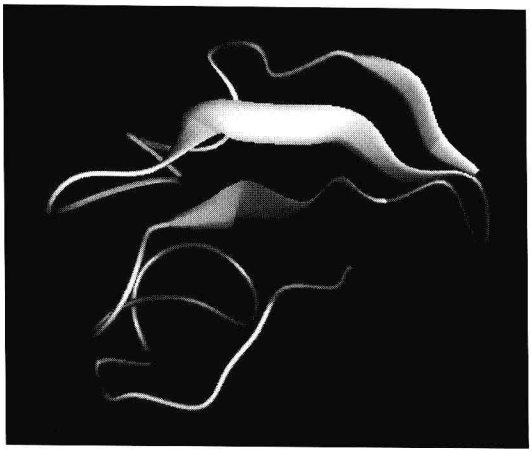
Family	Members	Receptor type
Haematopoietins (4 α-helical bundles)	IL-2, IL-3, **IL-4**, IL-5, IL-6, IL-7, IL-9, IL-13, G-CSF, GM-CSF, CNTF, OSM, LIF, Epo	Cytokine receptor class I
	IL-10, IFNα, IFNβ, IFNγ	Cytokine receptor class II
	M-CSF	Tyrosine kinase
EGF (β-sheet)	**EGF**, TGFα	Tyrosine kinase
β-Trefoil	FGFα, FGFβ	Split tyrosine kinase
	IL-1α, **IL-1**β, IL-1Rα	IL-1 receptor
TNF (jelly roll motif)	**TNF**α, TNFβ, LTβ	NGF receptor
Cysteine knot	NGF	NGF receptor
	TGFβ1, **TGFβ2**, TGFβ3	Serine/threonine kinase
	PDGF, VEGF	Tyrosine kinase
Chemokines- (triple-stranded, anti parallel β-sheet in Greek key motif)	**IL-8**, MIP-1α, MIP-1β, MIP-2, PF-4, PBP, I-309/TCA-3, MCP-1, MCP-2, MCP-3, γIP-10	Rhodopsin superfamily

Cytokines in bold are illustrated in figure 1.

IL-4



EGF



IL-1β

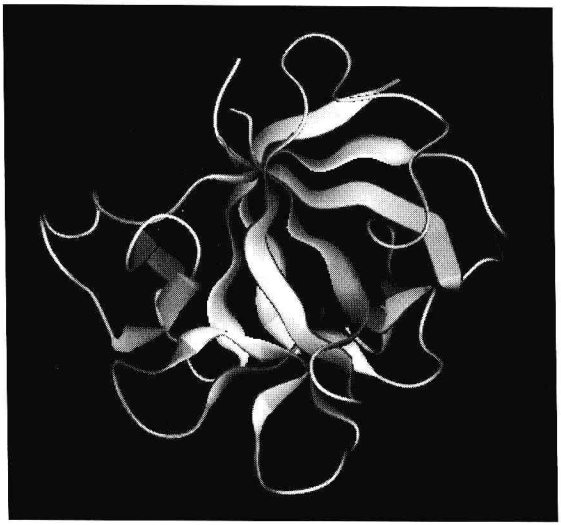
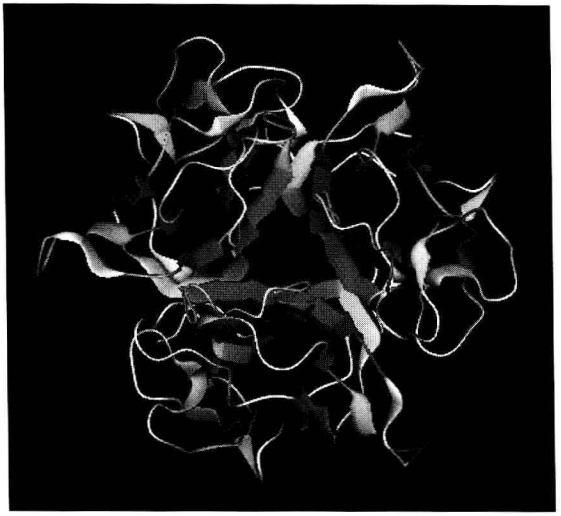
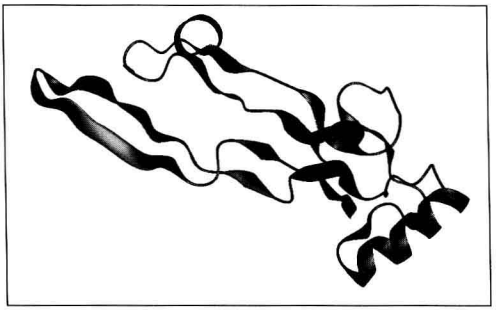


Figure 1.1. *Solid models not to scale of representative cytokines. These solid models of IL-4 (1BBN.PDB), EGF (1EGF.PDB), IL-1β (1I1B.PDB), TNFα trimer (1TNF.PDB), TGFβ 2 (2TGF.PDB) and IL-8 dimer (1IL8.PDB) were prepared with information from the Brookhaven database using the "Quanta" modelling package by Ed Hodgkin.*

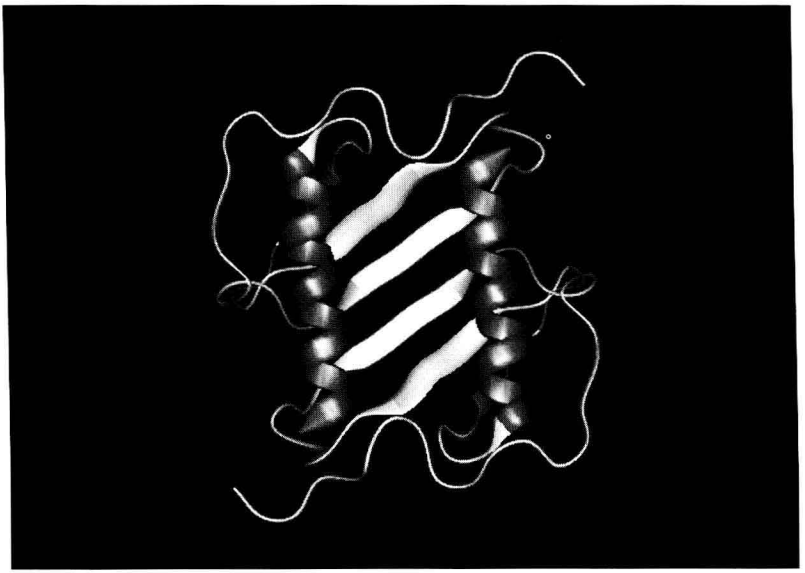
TNFα trimer



TGFβ2



IL-8



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8 Bazan, J.F. (1990) Immunol. Today 11, 350–354.

2 Organization of the data

Each cytokine entry includes information under the following headings:

Other names

Most cytokines have more than one name. We have used the interleukin nomenclature whenever this has been assigned unequivocally. All other cytokines are entered under their most commonly accepted name. Alternative names are also listed.

THE MOLECULE

At the beginning of each entry is a brief description of the molecule and its main biological properties.

Crossreactivity

The degree of amino acid sequence homology between human and mouse cytokines is given when known together with cross species reactivity. In some cases, comparisons with other species are also given.

Sources

A list of cell types known to produce each cytokine is included.

Bioassays

Bioassays for each cytokine are described in brief. For the most part, these have been taken from methods used by the National Institute for Biological Standards, South Mimms, UK as described in refs 1 and 2.

Physicochemical properties of the cytokines

This table includes basic physicochemical information on human and mouse cytokines. The number of amino acids and predicted molecular weight for the mature proteins are calculated after removal of the signal peptide and propeptides where relevant. In some cases the cleavage point of the signal peptide has been determined by sequencing and in others from computer prediction. Potential N-linked glycosylation sites are identified by the consensus sequence Asn–X–Ser/Thr except when X is Pro or for the sequence Asn–X–Ser/Thr–Pro which is not usually glycosylated. The number of potential sites in the table is for the extracellular portion of the molecule only.

3-D structure

Information on the tertiary structure of each cytokine is taken from original papers or from Macromolecular Structures 1991–1993 published by Current Biology [3]. It includes data derived from X-ray or NMR structures, or predictions based on molecular models.

Gene structure and chromosomal localization

The chromosomal localization for the human cytokines is taken from original papers and/or the Human Gene Mapping (HGM 11) [4]. Mouse mapping data are taken from ref. 5. The exon–intron gene structure is drawn to scale from original papers with the number of amino acids shown for each exon.

Amino acid sequences

Human and mouse amino acid sequences are given for each cytokine and receptor where known. In some cases, the murine sequence is not available and the rat sequence is given instead. The sequences for most entries were taken directly from databases accessed through the VAX SEQNET computer at the Daresbury Laboratories using the Wisconsin GCG suite of programs. Where possible, amino acid sequences were obtained from the Swissprot database. Alternatively, cDNA nucleic acid sequences were obtained from EMBL and/or Genbank and translated. In each case, the accession number is listed with the sequence. Swissprot accession numbers begin with P. Recent submissions to EMBL and Genbank are assigned the same accession number, sometimes referred to as the Genembl accession number.

In all sequences, the single-letter amino acid code is used (Table 2.1). The numbering starts with the N-terminal amino acid after removal of the signal peptide. If the N-terminus has not been unequivocally assigned, the signal sequence is predicted according to consensus rules [6] and numbered to –1. Propeptides removed during post-translational modifications are shown in italics. The transmembrane portions of the sequences for cytokine receptors are underlined. The CNTF receptor is the only cytokine receptor so far which has been shown to have a GPI anchor and the proposed cleaved sequence is also shown in italics. Potential N-linked glycosylation sites marked by N in bold type are predicted by the presence of sequences Asn–X–Ser or Asn–X–Thr with the exceptions Asn–Pro–Ser/Thr which are not normally glycosylated and Asn–X–Ser/Thr–Pro which are often not glycosylated [7–9]. O-Linked glycosylation occurs at Ser or Thr residues. Although there is no clear-cut sequence motif that invariably indicates O-linked glycosylation, it usually occurs where there is a preponderance of Ser, Thr and Pro. When a high level of O-linked glycosylation on the receptors is expected, it is indicated on the receptor diagrams. Sequence motifs of particular interest are annotated under the sequence.

THE RECEPTORS

A brief description of the cytokine receptors with comments on important features is given in this section. A diagram of the receptor using the scheme described by Barclay et al. [10] is given for each receptor. In each case, the drawings are of the human receptors, and include protein domains, the mode of membrane attachment and degree of glycosylation. Orientation in the membrane is shown by labelling the intracellular terminus. The symbols used to represent the various domains, glycosylation and membrane attachment are taken directly from The Leucocyte Antigen FactsBook and are given in Figure 2.1.

The criteria used for defining cytokine receptor superfamilies are given in

Table 2.1 *Single-letter amino acid codes*

	Amino acid	Code	
Small hydrophilic	**Serine**	**Ser**	**S**
	Threonine	**Thr**	**T**
	Proline	**Pro**	**P**
	Alanine	**Ala**	**A**
	Glycine	**Gly**	**G**
Acid, acid amide	**Asparagine**	**Asn**	**N**
Hydrophillic	**Aspartic**	**Asp**	**D**
	Glutamine	**Gln**	**Q**
	Glutamic	**Glu**	**E**
Basic	**Histidine**	**His**	**H**
	Arginine	**Arg**	**R**
	Lysine	**Lys**	**K**
Small hydrophobic	**Methionine**	**Met**	**M**
	Isoleucine	**Ile**	**I**
	Leucine	**Leu**	**L**
	Valine	**Val**	**V**
Aromatic	**Phenylalanine**	**Phe**	**F**
	Tyrosine	**Tyr**	**Y**
	Tryptophan	**Trp**	**W**
Sulphydryl	**Cysteine**	**Cys**	**C**

Chapter 4. In those cases where no superfamily domain structure is known, the extracellular region is shown as a circle containing a question mark. The diameter of the circle is approximately proportional to the size of the extracellular region or domain. If a protein sequence contains a high proportion of Ser, Thr and Pro residues, it is probably heavily O-glycosylated, and is shown as an extended structure to distinguish it from regions likely to have a folded conformation. Only those disulphide bonds in the Ig superfamily (Ig-SF) domains are shown. The majority of cytoplasmic domains do not yet belong to well-defined superfamilies and are represented by wavy lines whose length is proportional to the number of amino acids.

Distribution

The tissue distribution of the receptors has been determined in some cases by ligand (cytokine) binding studies. Otherwise, it is assumed from mRNA expression or biological response.