INTERLEUKIN 1:
A MOLECULAR BASIS FOR SICK PEOPLE FEELING BAD

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INTRODUCTION

The acute phase response refers to the characteristic constellation of events induced by infection, inflammation, immunologic reactions, injury and neoplasia. Some of the features of this response include fever, somnolence, anorexia, lassitude, myalgias, leukocytosis, and an elevated erythrocyte sedimentation rate. For many years it was suspected that the acute phase response might be caused by products of tissue damage. For example, Homburger showed in 1945 that pus from sterile chemically-induced abscesses could increase the level of plasma fibrinogen in experimental animals (1). Subsequently, three separate lines of investigation coalesced to provide insight into the nature of the mediator causing the acute phase response. Paul Beeson found that a partially purified extract obtained from rabbit leukocytes (Leukocytic Pyrogen) could induce fever (2). Later experiments described material found in the plasma of animals during experimental fever (Endogenous Pyrogen) that had all the properties of Leukocytic Pyrogen (3,4). Kampschmidt and colleagues studied the effect of extracts of leukocytes on serum iron and zinc levels and published a series of experimental results indicating that changes in acute phase reactants could be accounted for by the action of a Leukocytic Endogenous Mediator (5,6). Although it was initially thought that polymorphonuclear leukocytes produced these endogenous factors, subsequent work clearly indicated that mononuclear phagocytes were their major source (7). At about the same time, Gery and co-workers demonstrated that a factor produced by mononuclear phagocytes, Lymphocyte Activating Factor, had the capacity to enhance responsiveness of T lymphocytes (8,9). This factor, which was found to exert a number of activities on various lymphocyte populations, was given the name Interleukin 1 to delineate it from other cytokines active on lymphoid cells (10). It quickly became apparent that the activities of Endogenous Pyrogen, Leukocytic Endogenous Mediator and Lymphocyte Activating Factor could be accounted for by the same or a very similar molecule (11-13). Over

the past 5 years there has been a rapid expansion in knowledge concerning the role of IL 1 and related molecules in the mediation of various aspects of the acute phase response, culminating in the isolation of the cDNA's encoding the IL 1 genes (14-17) and the identification of IL 1 receptors (18,19). It has become clear that the IL 1 family of molecules exerts a wide range of biologic activities that play a central role not only in host defense against a variety of challenges but also as an important element in the pathogenesis of a number of chronic diseases.

TABLE I

A BRIEF HISTORY OF INTERLEUKIN 1

1948 - Beeson: Granulocyte pyrogen (endogenous pyrogen)

- extracts of leukocytes cause fever (2)

1969 - Kampschmidt: Leukocyte endogenous mediator

- phagocyte product induces the acute phase response (5)

1972 - Gery: Lymphocyte activating factor

- macrophage product enhances T lymphocyte responses (8,9)

1979 - International Lymphokine Workshop: Interleukin 1 (10)

1984,85 - Lomedico, Auron, March, Furutani: Molecular cloning of the cDNA encoding interleukin 1 (14-17)

1985 - Dower: Identification of interleukin 1 receptors (18,19)

TABLE II

ACRONYMS, SYNONYMS AND PSEUDONYMS OF MEMBERS OF THE INTERLEUKIN 1 FAMILY

FACTOR	ACTIVITY	REFERENCES
EP - Endogenous pyrogen	A monocyte/macrophage product that induces fever in vivo.	(20-23)
LEM - Leukocyte endogenous mediator	A monocyte/macrophage product that induces neutrophilia, stimulates the production of acute phase reactants and depresses serum zinc and iron in vivo.	(24)
LAF - Lymphocyte activating factor	A monocyte/macrophage product that augments mitogen induced proliferation of murine thymocytes. This factor also augments antibody production from T cell depleted B lymphocytes.	(8,9)
BAF:	B cell activating factor (25-28)	
MP:	Mitogenic protein (29)	
HP-1:	Helper-peak 1 (30)	
TRF-III:	T cell replacing factor III (31)	
$TRF_{M\phi}$:	T cell replacing factor $_{M\phi}$ (32)	
BDF:	B cell differentiation factor (33)	
MCF - Mononuclear cell factor	A monocyte product that augments the production of PGE_2 and collagenase from synovial fibroblasts.	(34-38)
PIF - Proteolysis inducing factor	A factor (M_r4200) found in plasma of febrile, burned or traumatized patients that stimulates muscle cells to produce prostaglandins leading to proteolysis, release of amino acids and muscle wasting. It is also pyrogenic, causes elevation in acute phase reactants and has thymocyte stimulatory activity.	(39-40)
ETAF- Epidermal cell-derived thymocyte activating factor	A factor produced by keratinocytes with IL-1 activity	(41,42)
Catabolin	A factor produced by porcine synovial cells and monocytes that induces proteoglycan matrix degradation of cartilage.	(43-45)

Table III

INTERLEUKIN 1

1. 14,000 - 17,000 dalton protein (46)
   - sensitive to heating, acid pH
   - pronase sensitive
   - murine IL 1 - trypsin resistant

     human IL 1 - trypsin, chymotrysin sensitive
   - inhibited by the arginine specific inhibitor, phenyl glyoxal (47)

2. Charge heterogeneity:

   pI 5.0

   pI 7.0

3. Not glycosylated (48)

4. Low molecular weight fragments of 2 and 4kD found in urine and plasma are active (49-51)

TABLE IV

ACTIVITIES OF INTERLEUKIN 1

T Lymphocytes

1. Co-mitogenic with lectins (8,9)
2. ↑ Lymphokine production (IL 2, IFNɣ) (52,53)
3. ↑ Activity of cytotoxic T cells (54)
4. ↑ Receptors for IL-2 (55,56)
5. Chemotaxis (57)
6. Radioprotection (58)
7. ↑ Cell cycle progression of activated cells (59)
8. ↑ Membrane viscosity and (?) antigen binding (60)

B Lymphocytes

1. Maturation of pre-B cells (61,62)
2. Cofactor in clonal expansion (63,64)
3. Promote differentiation of antibody forming cells (65,66)
4. Chemotaxis (57)

NK Cells

1. Enhance killing and synergistically enhance killing with IFN-ɣ (67,68)

Macrophages

1. ↑ Production of prostaglandin (69)
2. ↑ Tumoricidal activity (70)

Polymorphonuclear Leukocytes

1. ↑ Release from bone marrow (71)
2. ↑ Margination (72)
3. ↑ Extravasation (73)
4. Chemotaxis (74,75)
5. Activation of glucose metabolism (74)
6. Stimulate NBT reduction (74)
7. Stimulate release of lysosomal enzymes (76,77)
8. Stimulate adherence to endothelial cells (78,79)

Endothelial Cells

1. ↑ Proliferation (80)
2. ↑ Prostacyclin production (81)
3. ↑ Adhesiveness (82,83)
4. ↑ Procoagulant activity (84,85)
5. Induction of new surface antigens (86)

Synovial Cells and Fibroblasts

1. PGE_2 production (34-38))
2. Collagenase production (34-38,87)
3. Proliferation (88,89)
4. Production of β interferon (90)

TABLE IV (Cont)

Chondrocytes

1. ↑ Production of collagenase (91)
   Neutral proteases (92), plasminogen activator (93)
2. ↑ Production of PGE_2 (94)

Central Nervous System

1. Stimulation of hypothalamic PGE_2 production → fever (20)
2. Somnolence (95)
3. Slow wave sleep (96,97)
4. Anorexia (98)
5. Proliferation of glial cells (99)

Hepatocytes

1. ↑ Synthesis of acute phase proteins (24)
2. ↓ Synthesis of albumin and prealbumin (24)

Muscle Cells

1. Proteolysis (PIF) (39,40)

Mesangial Cells

1. Proliferation (100)

Osteoblasts

1. ↑ Proliferation (101)
2. ↑ Alkaline phosphatase production (101)

Osteoclasts

1. ↑ Bone resorption (102)

Epidermal Cells

1. ↑ Synthesis of collagen type IV (103)

Adipocytes

1. ↓ Lipoprotein lipase (104)

Tumor Cells

1. ↑ Cytocidal activity (105,106)

TABLE V

MULTIPLE BIOLOGIC ACTIVITIES ATTRIBUTED TO INTERLEUKIN 1

- Fever*
- Hypoferremia
- Hypozincemia
- Hypercupremia
- Increased
  - Blood neutrophils*
  - Hepatic acute-phase proteins*
  - Bone resorption*
  - Cartilage breakdown
  - Muscle proteolysis
  - Slow-wave sleep
  - Endothelial procoagulant
  - Chondrocyte proteases
  - Synovial collagenase*
  - Endothelial neutrophil adherence
  - Neutrophil degranulation*
  - Neutrophil superoxide
  - Interferon production
- Proliferation of
  - Fibroblasts
  - Glial cells
  - Mesangial cells
  - Synovial fibroblasts
  - EBV B-cell lines
- Chemotaxis of
  - Monocytes
  - Neutrophils*
  - Lymphocytes*
- Stimulation of PGE_2 in
  - Hypothalamus
  - Cortex
  - Skeletal muscle
  - Dermal fibroblast*
  - Synovial fibroblast*
  - Chondrocyte
  - Macrophage/monocyte*
  - Endothelium (PGI_2)
- Decreased
  - Hepatic albumin synthesis*
  - Appetite*
  - Brain binding of opioids
  - Lipoprotein lipase activity*
- Augmentation of
  - T-cell responses*
  - B-cell responses
  - NK activity
  - IL-2 production*
  - Lymphokine production

* Activity confirmed by recombinant materials

Dinarello, J Clin Immunol 5:287, 1985 (21)

TABLE VI

INTERLEUKIN 1 AND THE ACUTE PHASE RESPONSE

I. Increased hepatic senthesis of:

a) serum amyloid A protein (107-114)
b) fibrinogen (115-124)
c) C reactive protein (118,121,125,126)
d) haptoglobin (118-120,123,126-128)
e) ceruloplasmin (118,123)
f) complement factor B (129)

II. Decreased hepatic synthesis of:

a) albumin (128)
b) pre-albumin (128)

III. Decrease in serum

a) iron - sequestration in lactoferrin complexes (126,130-134)
b) zinc - induction of hepatic metallothionein (120,131,132,135)

TABLE VII

INDUCERS OF IL-1 PRODUCTION FROM MONOCYTE/MACROPHAGES

Microorganisms
- Viruses
- Bacteria
- Spirochetes
- Yeasts

Microbial products
- Endotoxins from gram-negative bacteria
- Peptidoglycans from all bacteria
- Exotoxins from pathogenic strains of Staplylococci and Streptococci
- Yeast polysaccharides

Inflammatory agents
- Bile salts
- Etiocholanolone
- C5a
- Silica
- Urate crystals

Plant lectins
- Phytohemagglutinin
- Concanavalin A

Cytokines
- Colony-stimulating factor
- Tumor necrosis factor

Other inducers
- Bleomycin
- PolyI:C
- Muramyl dipeptide

Dinarello, CA. Interleukin I. Rev Inf Dis 6:51, 1984 (20)

TABLE VIII

AGENTS THAT INHIBIT THE ACTIVITY OF INTERLEUKIN-1

Inhibitors of Release from Monocytes and Macrophages

Corticosteroids (136-138)

Prostaglandins E_2 (139)

Chloroquine (140,141)

Ultraviolet light (142)

Inhibitors of Activity

Cyclooxygenase inhibitors (fever, muscle proteolysis) (21)

Urinary inhibitors: 20-30 kDa - urine of febrile people (143)

Uromodulin: 85 kDa - urine of pregnant women, normal and febrile plasma (144)

Products of macrophages (22kDa [145,146]), EBV transformed B cell lines (95kDa [147])

Inhibitors in synovial fluid (148,149)

Inhibitors in serum (150,151)

TABLE IX

CELL SOURCES OF IL-1 AND IL-1 LIKE ACTIVITIES (152)

Cell Type	Stimulants	Ref.
Monocyte, macrophages, and macrophage lines	LPS, particles, PMA MDP,	(153)
	C containing Immune complexes,	(145,154)
	Cytokines (CSF, IFN-γ, TNF)	(155-160)
	Activated T cells	(161-165)
	C5a	(166)
	Cell injury	(167)
Keratinocytes	PMA,MDP,LPS	(41,42,74,75,168-170)
Dendritic cells	LPS	(171)
Langerhans cells	LPS, *Staph. albus*	(172)
Large granular lymphocytes	LPS	(173)
B cell lines	None	(147,174,175)
B lymphoblasts	LPS, anti-IgM	(176)
Endothelial cells	LPS, thrombin	(177)
Mesangial cells	Cell cycle dependent	(178)
Astrocytes	LPS	(179)
Glioma cell lines	Cell cycle dependent	(180,181)
Microglial cells	LPS, *Staph. aureus*, injury	(182)
Neutrophils	Aluminum hydroxide	(183)
Fibroblasts	MDP	(184)
Epithelial cells	PMA, LPS, UV irradiation	(185,186)
Corneal epithelium	-	(187)

Abbreviations: LPS = lipopolysaccharide; PMA = phorbol myristate acetate; MDP = muramyl dipeptide; CSF = colony stimulating factor; IFN-γ = interferonγ; TNF = tumor necrosis factor

TABLE X

DETECTION OF IL-1-LIKE ACTIVITY IN HUMAN TISSUES AND FLUIDS

1. Synovial fluid (148,149)
2. Gingival fluid (188)
3. Plasma
    a) febrile animals (189)
    b) marathon runners (190)
    c) following ovulation (150)
    d) burned, traumatized, febrile or cirrhotic subjects (PIF) (40,40a)
    e) patients with Crohn's disease (191)
4. Urine (192)
5. Stratum corneum from the human heel (193)

TABLE XI

DEFECTIVE INTERLEUKIN 1 PRODUCTION FROM PERIPHERAL BLOOD MONOCYTES IN VIVO

1. Patients with some cancers (194,195)
2. Patients with systemic lupus erythematosus (196)
3. Some neonates (197)
4. Some elderly persons (198)
5. Malnutrition (199,200)

TABLE XII

FUNCTIONAL COMPARISON OF INTERLEUKIN 1 AND TUMOR NECROSIS FACTOR (TNF, CACHECTIN)

Shared Activities

1. Pyrogenic (157)
2. Stimulation of prostaglandin E_2 and collagenase production by synovial cells and dermal fibroblasts (34-38,201)
3. Activation of osteoclasts → bone resorption (101,202)
4. Stimulation of procoagulant activity by vascular endothelial cells (84,85,203)
5. Stimulation of neutrophil adherence to endothelial cells (78,79,82,83,204)
6. Stimulation of neutrophil phagocytosis, respiratory burst and degranulation (74,76,77,205)
7. Inhibition of lipoprotein lipase (104,206)
8. Induction of new surface antigens on endothelial cells (86)

Unique features of TNF

1. Cytolytic activity (206)
2. Induction of IL-1 biosynthesis (157)
3. Shock (206)

Unique features of IL-1

1. Thymocyte stimulatory activity
2. Induction of acute phase reactants

TABLE XIII

CHARACTERISTICS OF MURINE AND HUMAN INTERLEUKIN 1 PRECURSOR COMPLEMENTARY DNA (14-17)

	Murine (pI 5)	Human IL-1∝ (pI 5)	Human IL-2β (pI 7)
Source	P388D1	Human macrophages	Human monocytes
mRNA	2.0 Kb	2.0 - 2.4 Kb	1.6 Kb
Abundance of mRNA (% total polyA + RNA)	0.005%	0.01%	0.1%
Amino acids	270	271	269
Predicted M_r of primary translation product	31,026	30,606	30,747*
Molecular weight of secreted product with biologic activity	17,992 (C terminal 156 amino acids)	17,500 (C terminal 159 amino acids)	17,500 (C terminal 153 amino acids)
N terminal hydrophobic signal sequence	No	No	No
Membrane spanning region	No	No	No
Homology**	←——→ 62%		
	←——————→ 30%		
		←——→ 26%	

* Not biologically active

** Over 50% of the identical positions between IL-1 proteins occur in the M_r 17,500 C terminal biologically active portion of the molecule and a large proportion of these occur in the middle and C terminal regions suggesting that these regions are critical for biologic activity. However, 47% of all common residues occur in the portion of the primary translation product that precedes the active IL-1 segment. This degree of homology is not expected in a non-functional portion of a protein and therefore suggests that the N-terminal portion of the molecule may have some unknown biologic function.

FIGURE 1: Nucleotide Sequence and Predicted Amino Acid Sequence of Human IL-1β Primary Translation Product (16)

```
5' TTCGAGGCACAAGGCACAACAGGCTGCTCTGGGATTCTCTTCAGCCAATCTTCATTGCTCAAGTGTCTGAAGCAGCC    -1

ATG GCA GAA GTA CCT GAG CTC GCC AGT GAA ATG ATG GCT TAT TAC AGT GGC AAT GAG GAT     60
Met Ala Glu Val Pro Glu Leu Ala Ser Glu Met Met Ala Tyr Tyr Ser Gly Asn Glu Asp     20

GAC TTG TTC TTT GAA GCT GAT GGC CCT AAA CAG ATG AAG TGC TCC TTC CAG GAC CTG GAC    120
Asp Leu Phe Phe Glu Ala Asp Gly Pro Lys Gln Met Lys Cys Ser Phe Gln Asp Leu Asp     40

CTC TGC CCT CTG GAT GGC GGC ATC CAG CTA CGA ATC TCC GAC CAC CAC TAC AGC AAG GGC    180
Leu Cys Pro Leu Asp Gly Gly Ile Gln Leu Arg Ile Ser Asp His His Tyr Ser Lys Gly     60

TTC AGG CAG GCC GCG TCA GTT GTT GTG GCC ATG GAC AAG CTG AGG AAG ATG CTG GTT CCC    240
Phe Arg Gln Ala Ala Ser Val Val Val Ala Met Asp Lys Leu Arg Lys Met Leu Val Pro     80

TGC CCA CAG ACC TTC CAG GAG AAT GAC CTG AGC ACC TTC TTT CCC TTC ATC TTT GAA GAA    300
Cys Pro Gln Thr Phe Gln Glu Asn Asp Leu Ser Thr Phe Phe Pro Phe Ile Phe Glu Glu    100

GAA CCT ATC TTC TTT GAC ACA TGG GAT AAC GAG GCT TAT GTG CAC GAT GCA CCT GTA CGA    360
Glu Pro Ile Phe Phe Asp Thr Trp Asp Asn Glu Ala Tyr Val His Asp ALA PRO VAL ARG    120

TCA CTG AAC TGC ACG CTC CGG GAC TCA CAG CAA AAA AGC TTG GTG ATG TCT GGT CCA TAT    420
SER LEU ASN Cys THR LEU ARG ASP SER GLN GLN LYS SER LEU VAL MET SER GLY PRO TYR    140

GAA CTG AAA GCT CTC CAC CTC CAG GGA CAG GAT ATG GAG CAA CAA GTG GTG TTC TCC ATG    480
GLU LEU LYS ALA LEU HIS LEU GLN GLY GLN ASP MET GLU GLN GLN VAL VEL PHE Ser Met    160

TCC TTT GTA CAA GGA GAA GAA AGT AAT GAC AAA ATA CCT GTG GCC TTG GGC CTC AAG GAA    540
SER PHE VAL GLN GLY GLU GLU Ser ASN ASP LYS Ile Pro Val Ala Leu Gly Leu Lys Glu    180

AAG AAT CTG TAC CTG TCC TGC GTG TTG AAA GAT GAT AAG CCC ACT CTA CAG CTG GAG ACT    600
LYS ASN LEU TYR LEU SER Cys Val Leu Lys Asp Asp Lys Pro Thr Leu Gln Leu Glu SER    200

GTA GAT CCC AAA AAT TAC CCA AAG AAG AAG ATG GAA AAG CGA TTT GTC TTC AAC AAG ATA    660
VAL ASP PRO Lys Asn Tyr Pro Lys Lys Lys Met GLU LYS ARG PHE VAL PHE ASN Lys ILE    220

GAA ATC AAT AAC AAG CTG GAA TTT GAG TCT GCC CAG TTC CCC AAC TGG TAC ATC AGC ACC    720
GLU ILE ASN ASN Lys LEU GLU Phe Glu SER ALA GLN PHE PRO ASN TRP TYR ILE Ser Thr    240

TCT CAA GCA GAA AAC ATG CCC GTC TTC CTG GGA GGG ACC AAA GGC GGC CAG GAT ATA ACT    780
Ser Gln Ala Glu Asn Met PRO VAL PHE LEU GLY GLY Thr Lys Gly Gly Gln Asp Ile Thr    260

GAC TTC ACC ATG CAA TTT GTG TCT TCC TAA AGAGAGCTGTACCCAGAGAGTCCTGTGCTGAATGTCGAC    849
Asp Phe Thr Met GLN PHE VAL SER SER End

TCAATCCCTAGGGCTGGCAGAAAGGGAACAGAAAGGTTTTTGAGTACGGCTATAGCCTGGACTTTCCTGTTGTCTACAC    928
CAATGCCCAACTGCCTGCCTTAGGGTAGTGCTAAGAGGATCTCCTGTCCATCAGCCAGGACAGTCAGCTCTCTCCTTTC   1007
AGGGCCAATCCCAGCCCCTTTTGTGAGCCAGGCCTCTCT - 3'          1047
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Amino acids in capitals indicate those residues confirmed by protein sequencing analysis.

FIGURE 2: Nucleotide Sequence and Predicted Amino Acid Sequence of Human IL-1∝ Primary Translation Product (16)

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                                5' -- TGAGGGAGTCATTTCATTGGCGYTTGAGTCAGCAAAGAAGTCAAG      -1

ATG GCC AAA GTT CCA GAC ATG TTT GAA GAC CTG AAG AAC TGT TAC AGT GAA AAT GAA GAA      60
Met Ala Lys Val Pro Asp Met Phe Glu Asp Leu Lys Aan Cys Tyr Ser Glu Asn Glu Glu      20

GAC AGT TCC TCC ATT GAT CAT CTG TCT CTG AAT CAG AAA TCC TTC TAT CAT GTA AGC TAT     120
Asp Ser Ser Ser Ile Asp His Leu Ser Leu Asn Gln Lys Ser Phe Tyr His Val Ser Tyr      40

GGC CCA CTC CAT GAA GGC TGC ATG GAT CAA TCT GTG TCT CTG AGT ATC TCT GAA ACC TCT     180
Gly Pro Leu His Glu Gly Cys Met Asp Gln Ser Val Ser Leu Ser Ile Ser Glu Thr Ser      60

AAA ACA TCC AAG CTT ACC TTC AAG GAG AGC ATG GTG GTA GTA GCA ACC AAC GGG AAG GTT     240
Lys Thr Ser Lys Leu Thr Phe Lys Glu Ser Met Val Val Val Ala Thr Asn Gly Lys Val      80

CTG AAG AAG AGA CGG TTG AGT TTA AGC CAA TCC ATC ACT GAT GAT CAG CTG GAG GCC ATC     300
Leu Lys Lys Arg Arg Leu Ser Leu Ser Gln Ser Ile Thr Asp Asp Asp Leu Glu Ala Ile     100

GCC AAT GAC TCA GAG GAA GAA ATC ATC AAG CCT AGG TCA GCA CCT TTT AGG TTC CTG AGC     360
Ala Asn Asp Ser Glu Glu Glu Ile Ile Lys Pro Arg Ser Ala Pro Phe Ser Phe Leu Ser     120

AAT GTG AAA TAC AAC TTT ATG AGG ATC ATC AAA TAC GAA TTC ATC CTG AAT GAC GCC CTC     420
Asn Val Lys Tyr Asn Phe Met Arg Ile Ile Lys Tyr Glu Phe Ile Leu Asn Asp Ala Leu     140

AAT CAA AGT ATA ATT GGA GCC AAT GAT CAG TAC CTC AGC GCT GCT GCA TTA CAT AAT CTG     480
Asn Gln Ser Ile Ile Arg Ala Asn Asp Gln Tyr Leu Thr Ala Ala Ala Leu Hil Asn Leu     160

GAT GAA GCA GTG AAA TTT GAC ATG GGT GCT TAT AAG TCA TCA AAG GAT GAT GCT AAA ATT     540
Asp Glu Ala Val Lys Phe Asp Met Gly Ala Tyr Lys Ser Ser Lys Asp Asp Ala Lys Ile     180

ACC GTG ATT CTA AGA ATC TCA AAA ACT CAA TTG TAT GTG ACT GCC CAA GAT GAA GAC CAA     600
Thr Val Ile Leu Arg Ile Ser Lys Thr Gln Leu Tyr Val Thr Ala Gin Asp Glu Asp Gln     200

CCA GTG CTG CTG AAG GAG ATG CCT GAG ATA CCC AAA ACC ATC ACA GGT AGT GAG ACC AAC     660
Pro Val Leu Leu Lys Glu Met Pro Glu Ile Pro Lys Thr Ile Thr Gly Ser Glu Thr Asn     220

CTC CTC TTC TTC TGG GAA ACT CAG GGC ACT AAG AAC TAT TTC ACA TCA GTT GCC CAT CCA     720
Leu Leu Phe Phe Trp Glu Thr His Gly Thr Lys Asn Tyr Phe Thr Ser Val Ala His Pro     240

AAC TTG TTT ATT GCC ACA AAG CAA GAC TAC TGG GTG TGC TTG GCA GGG GGG CCA CCC TCT     780
Asn Leu Phe Ile Ala Thr Lys Gln Asp Tyr Trp Val Cys Leu Ala Gly Gly Pro Pro Ser     260

ATC ACT GAC TTT CAG ATA CTG GAA AAC CAG GCG TAG GTCTGGAGTCTCAGTTGTCTCACTTGTGCAG     847
Ile Thr Asp Phe Gln Ile Leu Glu Asn Gln Ala End                                     271

TGTTGACAGTTCATATGTACCATGTACATGAAGAAGCTAAATCCTTTACTGTTAGTCATTTGCTGAGCATGTACTGAGC     926
CTTGTAATTCTAAATGAATGTTTACACTCTTTGTAAGAGTGGAACCAACACTAACATATAATGTTGTTATTTAAAGAAC    1005
ACCCTATATTTTGCATAGTACCAATCATTTTAATTATTATTCTTCATAACAATTTTAGGAGGACCAGAGCTACTGACTA    1084
TGGCTACCAAAAAGACTCTACCCATATTACAGATGGGCAAATTAAGGCATAAGAAAACTAAGAAATATGCACAATAGCA    1163
ATTGAAACAAGAAGCCACAGACCTAGGATTTCATGATTTCATTTCAACTGTTTGCCTTCTGCTTTTAAGTTGCTGATGA    1242
ACTCTTAATCAAATAGCATAAGTTTCTGGGACCTCAGTTTTATCATTTTCAAAATGGAGGGAATAATACCTAAGCCTTC    1321
CTGCCGCAACAGTTTTTTATGCTAATCAGGGAGGTCATTTTGGTAAAATACTTCTCGAAGCCGAGCCTCAAGATGAAGG    1400
CAAAGCACGAAATGTTATTTTTTAATTATTATTTATATATGTATTTATAAATATATTTAAGATAATTATAATATACTAT    1479
ATTTATGGGAACCCCTTCATCCTCTGAGTGTGACCAGGCATCCTCCACAATAGCAGACAGTGTTTTCTGGGATAAGTAA    1558
GTTTGATTTCATTAATACAGGGCATTTTGGTCCAAGTTGTGCTTATCCCATAGCCAGGAAACTCTGCATTCTAGTACTT    1637
GGGAGACCTGTAATCATATAATAAATGTACATTAATTACCTTGAGCCAGTAATTGGTCCGATCTTTGACTCTTTTGCCA    1716
TTAAACTTACCTGGGCATTCTTGTTTCATTCAATTCCACCTGCAATCAAGTCCTACAAGCTAAAATTAGATGAACTCAA    1795
CTTTGACAACCATAGACCACTGTTATCAAAACTTTCTTTTCTGGAATGTAATCAATGTTTCTTCTAGGTTCTAAAAATT    1874
GTGATCAGACCATAATGTTACATTATTATCAACAATAGTGATTGATAGAGTGTTATCAGTCATAACTAAATAAAGCTTG    1953
CAAGAAAAAAAAAAAAAAAAAAAAAA - 3'                                                     1979
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FIGURE 3: Alignment of Human IL-1α, Murine IL-1 and Human IL-1β Amino Acid Sequences (16)

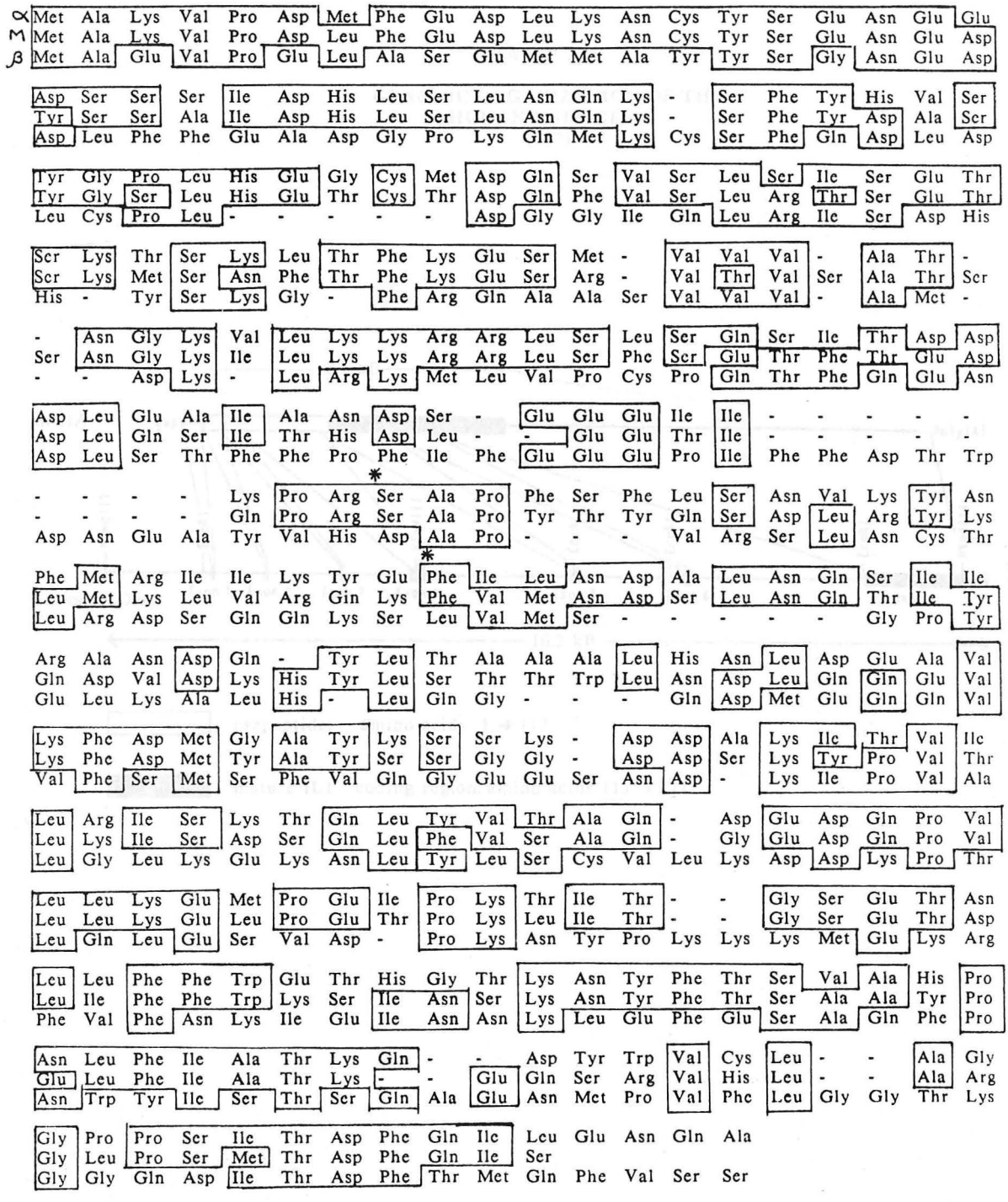

TABLE XIV

GENOMIC ORGANIZATION OF THE HUMAN IL-1∝ GENE (207)

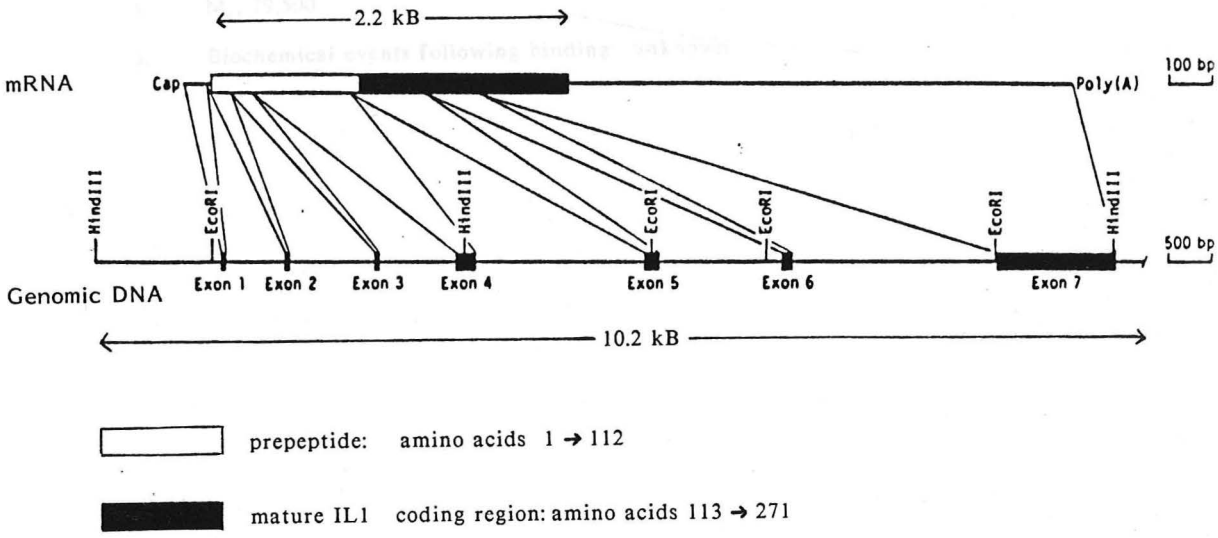

TABLE XV

INTERLEUKIN-1 RECEPTORS (18,19)

1. Widely distributed in low numbers
2. Ka: $2.6 - 3.6 \times 10^9/M$
   - [Preliminary evidence for both high (Kd 8-15 pM) and lower (Kd 1nM) affinity receptors (208)]
3. Bind both IL-1α and IL1β but not other polypeptide hormones
4. M_r, 79,500
5. Biochemical events following binding: unknown

TABLE XVI

CELLULAR DISTRIBUTION OF IL-1 RECEPTORS (18)

Primary cells

Species	Cell Type	Receptor sites per cell
Mouse	Thymocytes	<10
Mouse	PNA+ fraction	<10
Mouse	PNA- fraction	27
Mouse	Spleen cells	<10
Mouse	Lymph node cells	<10
Human	Peripheral blood mononuclear cells	27
Human	T cell line	100
Human	Gingival fibroblasts	$4x10^3$

In vitro cell lines

Species	Cell Type	Designation	
Mouse	T lymphoma	LBRM-33-1A4	550
Mouse	T lymphoma	LBRM-33-5A4	<10
Mouse	T lymphoma	EL-4	185
Mouse	Fibroblast	L929	144
Mouse	Fibroblast	SC-1	1850
Human	T lymphoma	Jurkat-FHCRC	<10
Human	T lymphoma	HSB-2	79
Human	T leukemia	PEER	<10
Human	Monocyte	U937	<10
Human	Myelogenous leukemia	KG-1	<10
Human	Erythroleukemia	K562	<10
Human	Promyelocyte	HL-60	<10
Human	Myeloma	ARH77	330
Human	B lymphoma	BMB	540
Human	Melanoma	A375	465
Human	Hepatoma	SKHEP-2	<10
Rat	Fibroblast	XC	450
Rat	Hepatoma	HEP-2	540
Rat	Epithelial cell	HTC	510
Bovine	Endothelial cell	CPAE	750

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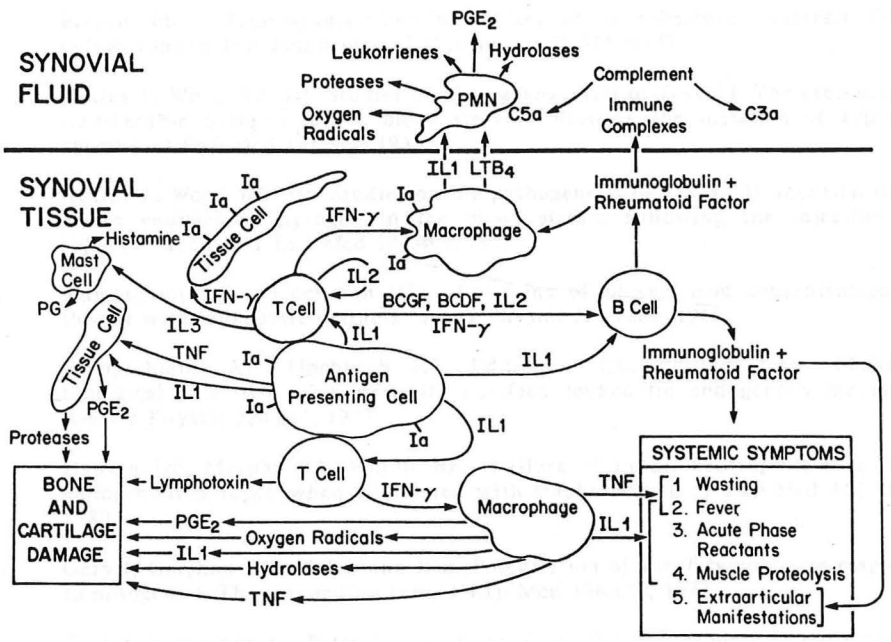
FIGURE 4: The role of interleukin 1 in the pathogenesis of rheumatoid arthritis



Abbreviations: BCDF, B cell differentiation factor; BCGF, B cell growth factor; Ia, class II molecules encoded by genes of the major histocompatibility complex; IFNγ, interferonγ; IL-1, interleukin 1; IL-2, interleukin-2; IL-3, interleukin-3; PGE_2, prostaglandin E_2; TNF, tumor necrosis factor.

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