CYTOKINES AND INFLAMMATION

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- antagonist and soluble receptors
- anti-inflammatory cytokines
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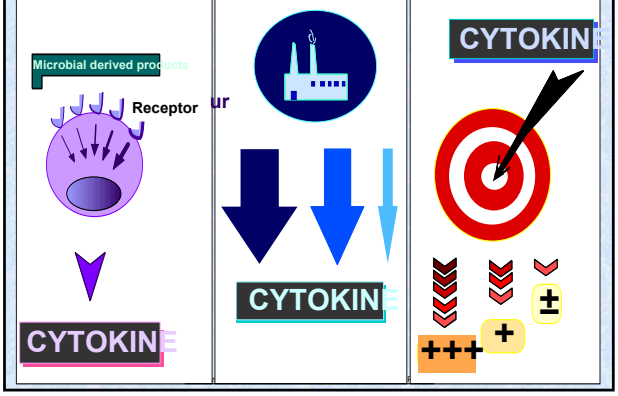
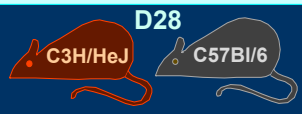
INDIVIDUAL HETEROGENEITY



STRAIN SIFFERENCE IN SUSCEPTIBILITY TO SILICOSIS

Ohtsuka et al. Am.J.Resp.Crit.Care Med. 1995, 152, 2144

One surgical exposure of trachea to silica



lung / body weight ratio	10.9	13.2
protein in BALF (µg/ml)	208	306
Total cells in BAL (x10⁶)	215	416
Fibrosis index	1.3	2.4
TNFα production by BAL cells (pg/ml)	59	1527

GENETICALLY DISTINCT ENDOTHELIAL CELL LINES DERIVED FROM HUMAN UMBILICAL VEIN (n = 35)

Bender et al. P.N.A.S. 1994,91,3994

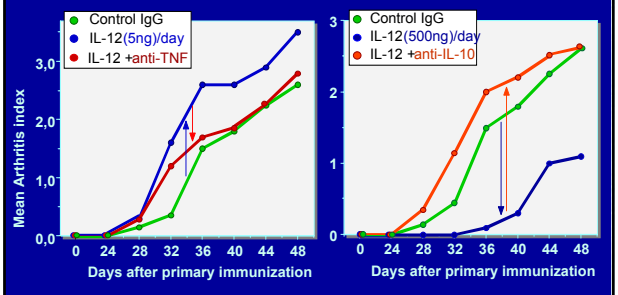
		HIGH RESPONDER	INTERMEDIATE RESPONDER	LOW RESPONDER
IL-1 ACTIVATION	ELAM-1	+++	++	±
	ICAM-1	+++	++	±
	VCAM-1	+++	++	±
	NF-κB	+++	+++	+++
		46%	40%	14%

AMOUNT OF CYTOKINE

PRO- AND ANTI-INFLAMMATORY PROPERTIES OF IL-
IN A MURINE TYPE II COLLAGEN INDUCED ARTHRITIS

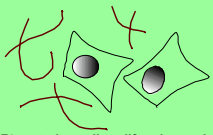
* 100µg acidified type II collagen i.d. in CFA D0
* 100µg acidified type II collagen i.d. in IFA D21

Kasama et al. 1999 Arthr. Rheumat. 42, 100



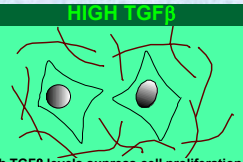
IN ADDITION ONLY HIGH LEVELS OF IL-12 INDUCED CIRCULATING CORTICOSTERONE

NORMAL TGFβ



TGFβ restrains cell proliferation and controls turnover of the extracellular matrix (ECM)

HIGH TGFβ

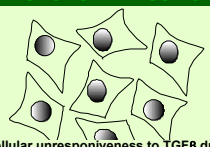


high TGFβ levels supress cell proliferation but stimulates production of pathological amounts of ECM (fibrosis)

LOW TGFβ

low levels of TGFβ predispose to excesive cell proliferation, atherogenesis or underproduction of ECM and impaired wound healing

UNRESPONSIVENESS TO TGFβ

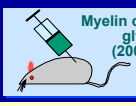


cellular unresponiveness to TGFβ due to mutation or loss of receptors can lead to uncontroled cell growth and malignancy

Border & Noble. Nature Medicine 1995,1,1000

TNF IS A POTENT ANTI-INFLAMMATORY CYTOKINE IN AUTO-IMMUNE-MEDIATED DEMYELINATION

Liu et al. Nature Med. 1998, 4, 78



Myelin oligodendrocyte glycoprotein (200 µg in CFA) → MULTIPLE SCLEROSIS - LIKE DISEASE

	Incidence	Mortality	Duration (days)	clinical score *
C57 BL /6 TNF +/+	63%	0%	7	2.6
C57 BL /6 TNF -/-	83%	17%	13	3.4
129/SV TNF +/+	0	0%	0	0
129/SV TNF -/-	75%	0%	7	2.2

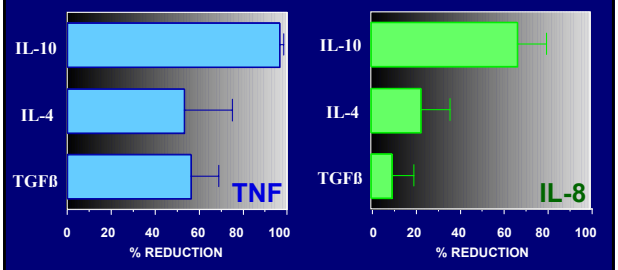
* inflammation lesions and demyelination in brain and spinal cord

Administration of rTNF (8 µg i.v. every 2 days starting at d-2 until day+20) reduces disease severity in +/+ and -/- mice

NATURE OF THE CYTOKINE

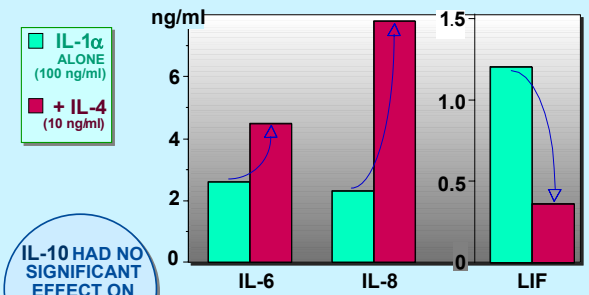
EFFECT OF IL-10, IL-4 & TGFß ON CYTOKINE PRODU

(whole blood assay in the presence of N.m. LPS [2µg/
and anti-inflammatory cytokines [20 ng/ml])



n = 4

REGULATION OF CYTOKINE PRODUCTION BY HUMAN BONE MARROW STROMA CELLS ACTIVATED BY IL-1



IL-10 HAD NO SIGNIFICANT EFFECT ON IL-6, IL-8, & LIF PRODUCTION

Denizot et al. Biochem Biophys. Acta 1999, 1449, 83

PRO-INFLAMMATORY PROPERTIES OF IL-6

Osteoclasts Bone	BONE RESORPTION	*Ishimi et al. 1990, J. Immunol. 145, 329* *Jilka et al. 1992 Science 257, 88*
IL-6 transgenic mice	MUSCLE ATROPHY	*Tsujinaka et al. 1996 JClin. Invest. 97, 244*
	Neurodegenerative disease (tremor, ataxia)	*Campbell et al. 1993 PNAS 90, 10061*
IL-6 i.p. (14 days in rat)	ANAEMIA caused by intestinal blood loss	*Jongen et al. 1996 Clin Exp Immunol. 103, 32*
IL-6 and PMN	Production of PAF	*Biffl et al. 1996 J. Leuk. Biol. 59, 569*
	priming for superoxide secretion	*Kharazmi et al. 1989 Immunol Lett 21,* *Borish et al. 1989 Cell Immunol. 121, 2*
IL-6 + sIL-6R and endothelial cells	MCP-1 production ICAM-1 expression	*Romano et al. 1997 Immunity 6, 315*

IFNγ INHIBITS THE INDUCED EXPRESSION OF E- AND P-SELECTIN ON ENDOTHELIAL CELLS

Melrose et al. J. Immunol. 1998, 161, 2457

IFNγ + TNFα or IL-1β → HUVEC → E-selectin expr.

IFNγ and IL-4 → HUVEC → P-selectin expr.

CAM-1 & VCAM-1expression similar or increased

=> *IFNγ inhibits neutrophil adherence to activated endothelium*

IFNγ INHIBITS THE INDUCE PRODUCTION OF IL-8 BY ENDOTHELIAL CELLS

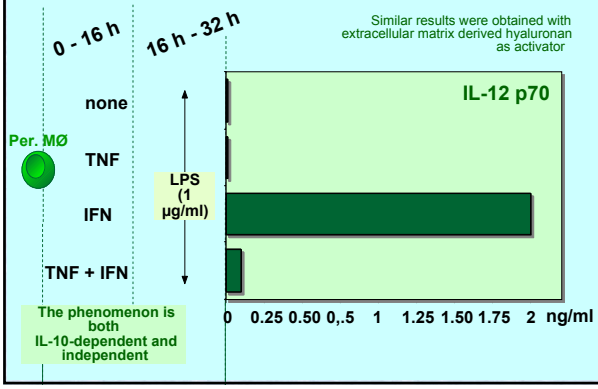
Nyhlen et al. Cytokine 1999, 12, 355

IFNγ and TNFα or IL-1β → HUVEC → IL-8

INHIBITION OF IFNγ INDUCED IL-12 PRODUCTION : A POTENTIAL MECHANISM FOR THE ANTI-INFLAMMATORY ACTIVITIES OF TN

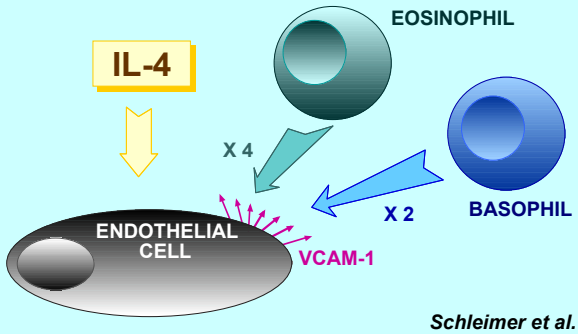
Hodge-dufour et al. PNAS 1998, 95, 13806

Similar results were obtained with extracellular matrix derived hyaluronan as activator

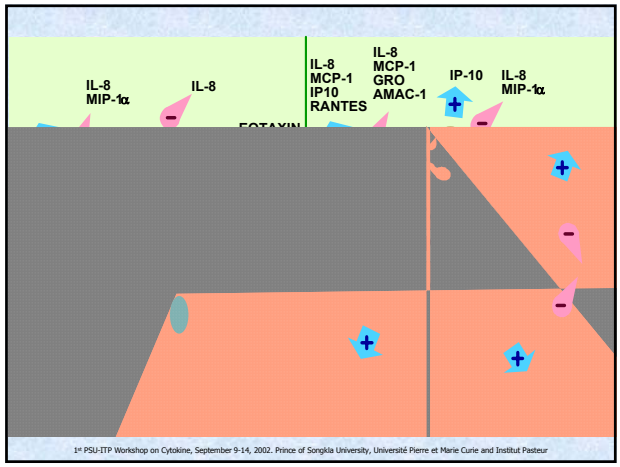


The phenomenon is both IL-10-dependent and independent

IL-4 INDUCES ADHERENCE OF EOSINOPHILS AND BASOPHILS BUT NOT NEUTROPHILS TO ENDOTHELIUM

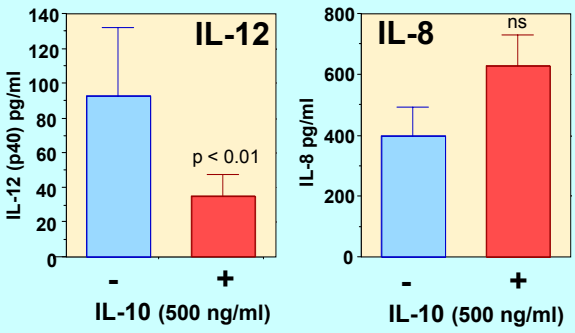


Schleimer et al. J. Immunol. 1992,148,1086



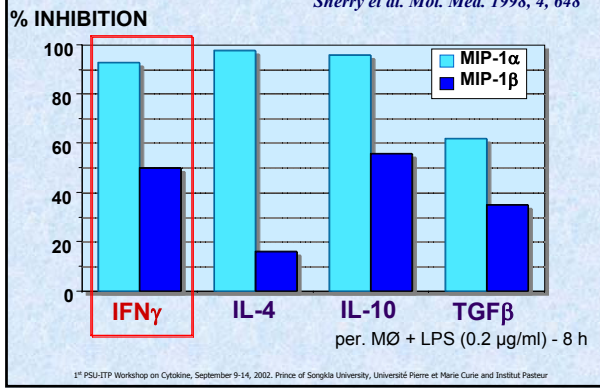
DIFFERENTIAL EFFECTS OF INTERLEUKIN-10 ON THE PRODUCTION OF IL-12 AND IL-8 BY HUMAN DENDRITIC CELL GENERATED FROM PERIPHERAL BLOOD

Buelens et al. Transpl. Proc. 1996, 28, 3255



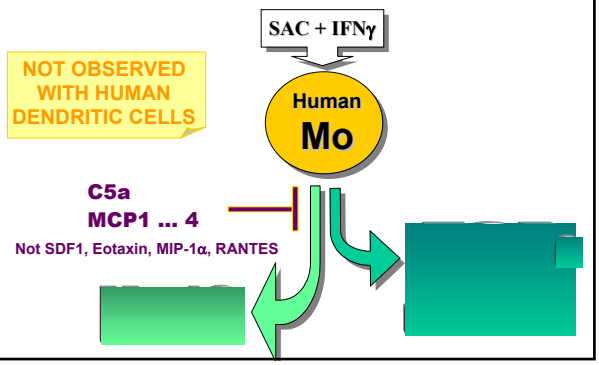
MODULATION OF LPS-INDUCED MIP-1α and MIP-1β BY CYTOKINES

Sherry et al. Mol. Med. 1998, 4, 648



SELECTIVE SUPPRESSION OF IL-12 BY CHEMOATTRACTANTS

Braun et al. J. Immunol. 2000, 164, 3009

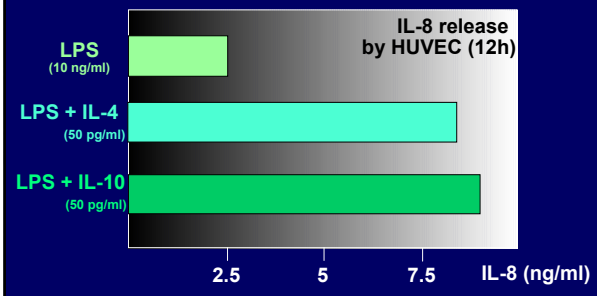


NATURE OF THE TARGET CELL

1st PSU-ITP Workshop on Cytokine, September 9-14, 2002. Prince of Songkla University, Université Pierre et Marie Curie and Institut Pasteur

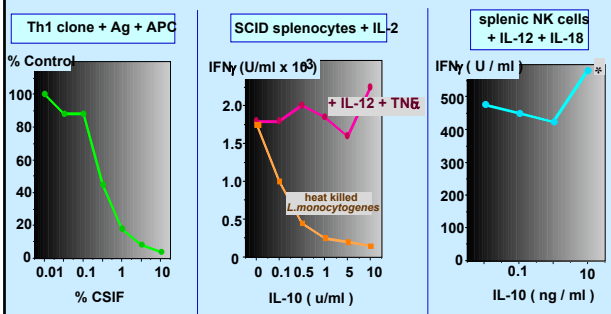
IL-4 & IL-10 INCREASE LPS-INDUCED IL-8 BY ENDOTHELIAL CELLS

De Beaux et al. J. Interferon Cyt. Res. 1995, 15, 441



there was no spontaneous IL-8 release, there was no effect of IL-4 or IL-10 alone, LPS and cytokines had to be added simultaneoulsy

EFFECT OF IL-10 ON INTERFERON-γ PRODUCTION



Fiorentino et al. 1989 J.Exp.Med. 170, 2081

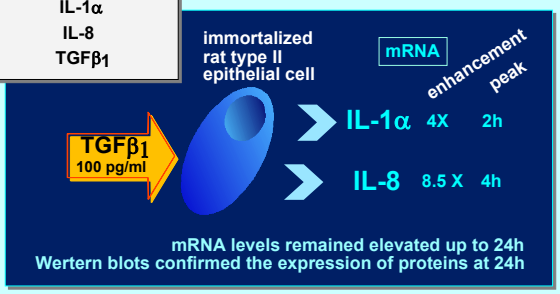
Tripp et al. 1993 P.N.A.S. 90, 3725

Shibata et al. 1998 J.Immunol. 161,4 283

INDUCTION OF IL-1 & IL-8 by TGFβ1 IN RAT LUNG ALVEOLAR EPITHELIAL CELLS

Silica-injured lungs : immunostaining for
IL-1α
IL-8
TGFβ1

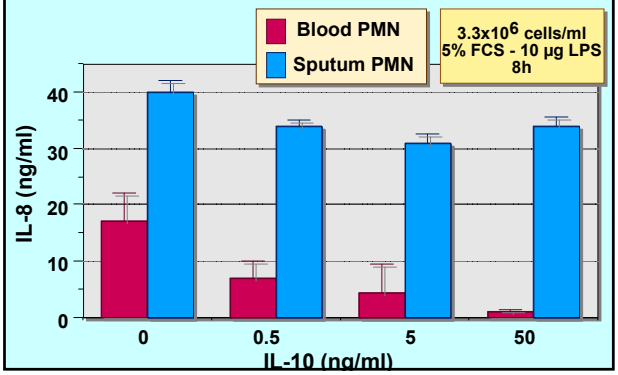
Kumar et al. J.Cell.Physiol. 1996,169,186



mRNA levels remained elevated up to 24h
Wertern blots confirmed the expression of proteins at 24h

MODULATION BY IL-10 OF IL-8 PRODUCTION BY BLOOD AND SPUTUM NEUTROPHILS IN CHRONIC BRONCHIAL SEPSIS

Pang et al. (1997) Am J Respir Crit Care Med 155, 726



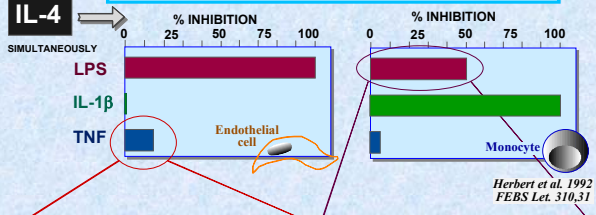
REGULATION OF TNFα and IL-1β SYNTHESIS BY C3a / C3adesArg

Takabayashi et al. J. Immunol. 1996, 156, 3455

	non adherent PBMC		adherent PBMC	
	IL-1β	TNFα	IL-1β	TNFα
C3a / C3adesArg	0	0	0	0
C3a / C3adesArg + LPS	↘↘ 19 - 57% decrease	↘↘ 20 - 71% decrease	↗↗ 119 - 274% increase	↗↗ 75 - 188% increase

INHIBITION OF TISSUE FACTOR EXPRESSION

IL-4 SIMULTANEOUSLY



Herbert et al. 1992 FEBS Let. 310,31

A PRE-TREATMENT OF HUVEC WITH IL-4 FOR 8 TO 16 h IS REQUIRED FOR A SIGINFICANT INHIBITION OF TF

Martin et al. Thromb. Haemost. 1993,70,1037

NO INHIBITION WHEN THE EXPERIMENTS WERE PERFORMED IN WHOLE BLOOD ASSAYS

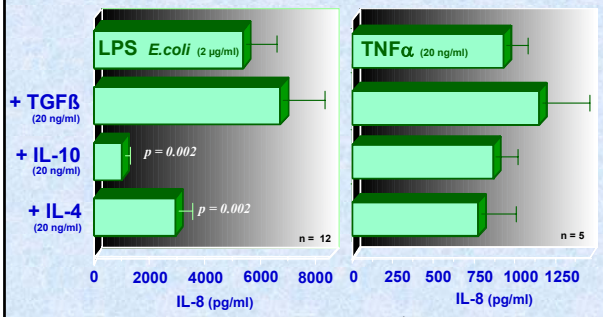
Lindmark et al. Brit. J. Haematol. 1998, 102, 597

NATURE OF THE ACTIVATING SIGNAL

The nature of the activating signal influences the observation

REGULATION BY ANTI-INFLAMMATORY CYTOKINES OF IL-8 PRODUCTION BY ACTIVATED HUMAN PMN

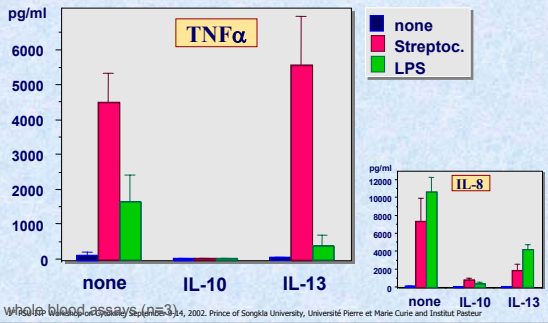
Marie et al. Mediators Inflamm. 1996, 5, 334



The nature of the activating signal influences the observation

IL-13 INHIBITS LPS-INDUCED TNF BUT FAILS TO INHIBIT *Streptococcus pyogenes*-INDUCED TNF

Marie et al. Cytokine 2000, 11, 55



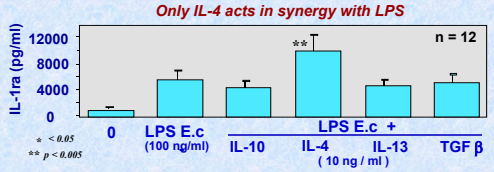
Human whole blood assays (n=3)

The nature of the activating signal influences the observation

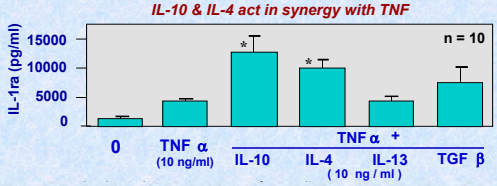
IL-1ra PRODUCTION BY HUMAN NEUTROPHILS

Marie et al. Cytokine 1996, 8, 147

Only IL-4 acts in synergy with LPS



IL-10 & IL-4 act in synergy with TNF



INHIBITORY AND STIMULATORY EFFECTS OF IL-10 ON HUMAN CD8+ T CELLS

Groux et al. J. Immunol. 1998, 160, 3188

PROLIFERATION	CD8+ T cells +	+ IL-10
	Allogenic monocytes *	↘
	cross-linked anti-CD3 MAb	=
	IL-2	↗

* ↘ cytotoxic activity versus allogenic PHA T-cell blasts

MONOCYTES CULTURED IN CYTOKINE-DEFINED ENVIRONMENTS DIFFER FROM FRESHLY ISOLATED MONOCYTES IN THEIR RESPONSES TO IL-4 & IL-10

Hart et al. J. Leuk.Biol. 1995, 57, 909

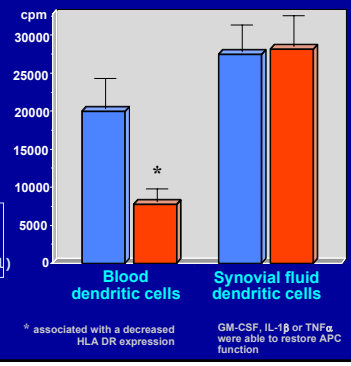
		Freshly isolated monocytes	Cultured-monocytes for 7 days in the presence of			
			0	IL-4	M-CSF	GM-CSF
Effect of IL-4 on LPS-induced	TNFα	↓↓	0	0	0	0
	IL-1β	↓↓	↓↓	↓↓	↓↓	↓↓

IL-10 has a constant inhibitory activity indepently of the culture conditions

IL-10 DOWN-REGULATES THE APC FUNCTION OF HUMAN PERIPHERAL BLOOD DERIVED DENDRITIC CELLS BUT NOT OF RHEUMATOID ARTHRITIS SYNOVIAL FLUID DENDRITIC CELLS

MacDonald et al. J. Immunol. 1999, 163, 5599

^{3}H-Thymidine uptake by allogenic normal blood T cells (10^5) in the presence of dendritic cells ($3x10^3$) pre-incubated or not for 18h with IL-10



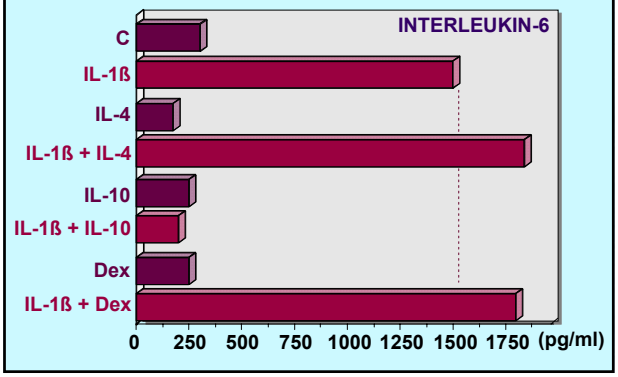
» SF DC do not express IL-10 R on their surface

* associated with a decreased HLA DR expression

GM-CSF, IL-1β or TNFα were able to restore APC function

REGULATION OF ASTROCYTES DERIVED CYTOKINE PRODUCTION

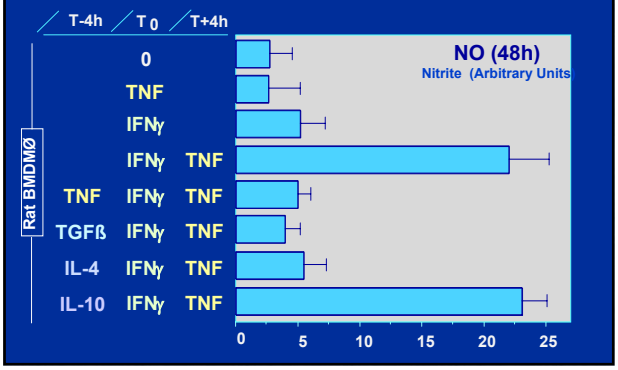
Pousset et al. Glia 1999, 26, 12



TIMIN

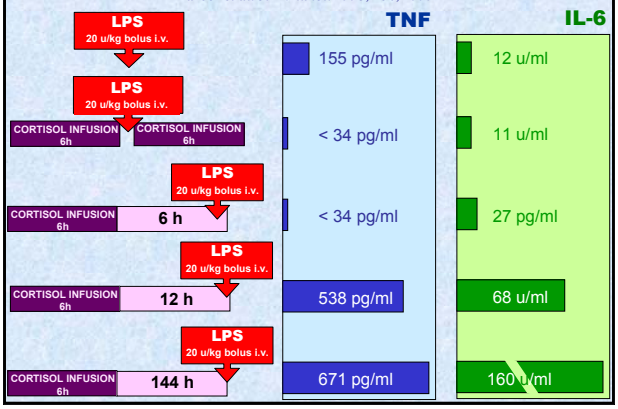
INITIAL CYTOKINE EXPOSURE DETERMINES FUNCTION OF MACROPHAGES AND RENDERS THEM UNRESPONSIVE TO OTHER CYTOKINES

Erwing et al. J. Immunol. 1998, 161, 1983



GLUCOCORTICO-THERAPY AND ENDOTOXIN IN MEN

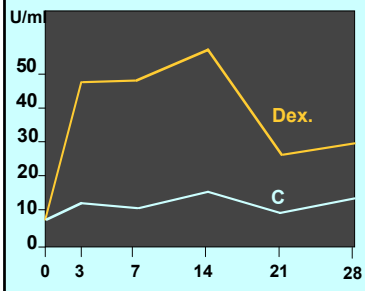
Barber et al. J. Immunol. 1993, 150, 1999



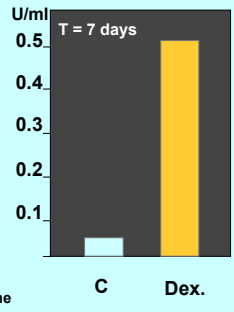
DEXAMETHASONE IN VIVO IN RATS AND TNF RELEASE

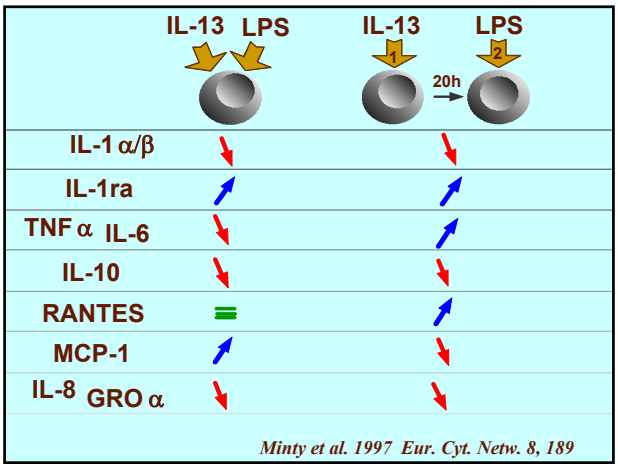
Renz et al. Cell. Immunol. 1992, 144, 249

TNF release from LPS-stimulated alveolar macrophages (20 h)



In vivo TNF upon LPS injection (90 min)

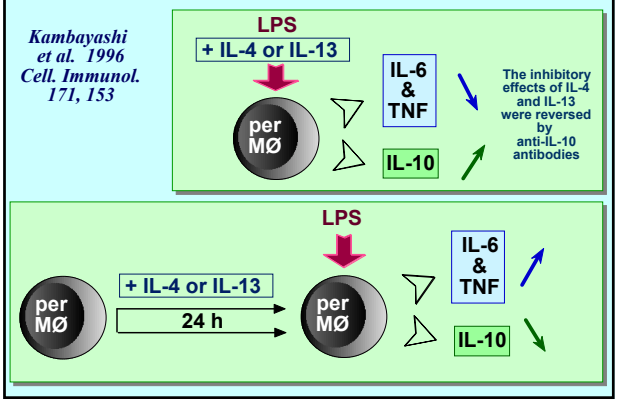




Minty et al. 1997 Eur. Cyt. Netw. 8, 189

IL-4 and IL-13 MODULATE IL-10 RELEASE IN LPS-STIMULATED MURINE PERITONEAL MACROPHAGES

Kambayashi et al. 1996 Cell. Immunol. 171, 153



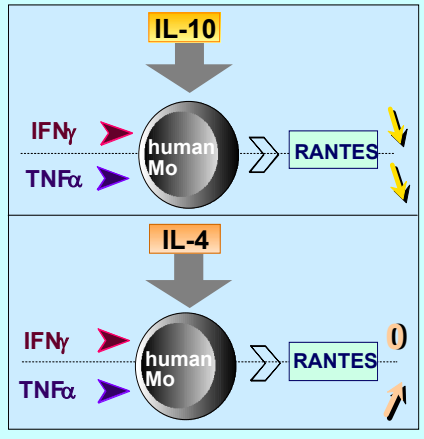
PRETREATMENT OF HUMAN PBMC WITH IL-4 & IL-13 ENHANCE THE PRODUCTION OF TNF AND IL-12

D'Andrea et al. J. Exp. Med. 1995, 181, 537

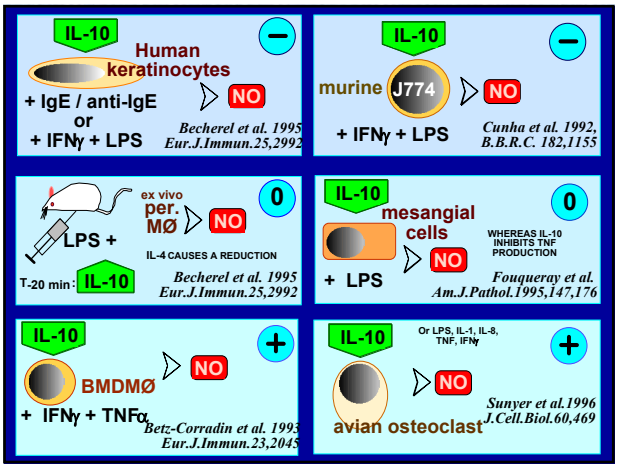
20h pre-treatment	Stimulus	TNFα	IL-12 p40	IL-1β	IL-10
none	S. aureus	1680	15860	19100	103
IL-4		2630	48030	12900	177
IL-13		2640	61200	21800	129
IL-10			1719		
TGFβ			1213		
none	LPS	236	1720	14100	80
IL-4		512	3832	5680	40
IL-13		604	5584	7130	40

CONTRASTING EFFECTS OF IL-4 and IL-10 on RANTES PRODUCTION BY HUMAN MONOCYTES

Marfaing-Koka et al. 1996 Intern. Immunol. 8, 1587



NATURE OF THE EXPERIMENTAL MODEL



INTERLEUKIN-13 AND LUNG INFLAMMATORY RESPONS

IL-13 TRANSGENIC MICE

Zhu et al. J.Clin.Invest. 1999, 103, 779

Inflammatory mononuclear infiltrate and eosinophils around airways and in parenchyma

Airway epithelial hypertrophy

Goblet cell hyperplasia and hyperproduction of mucus

Selective local production of EOTAXIN

cf role of IL-13 in tissue eosinophilia, mucus metaplasia, airway hyperrespoonsiveness in acute aeroallergen MODELS OF ASTHMA

Wills-Karp et al. Science 1998, 282, 2258
Grünig et al. Science 1998, 282, 2260

ANTI-IL-13 ACCENTUATES IMMUNE COMPLEX-INDUCED ACUTE LUNG INFLAMMATIO

Lentsch et al. J. Immunol. 1999, 162, 1071

Rat Model : BSA iv / anti-BSA it

ANTI-IL-13 (intratracheal) :

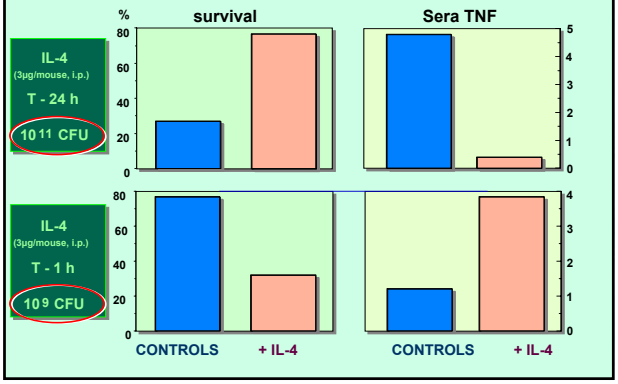
Increased vascular permeability
BAL PMN
BAL TNF
NF-κB activation

Weak increase of CICN & MIP-2

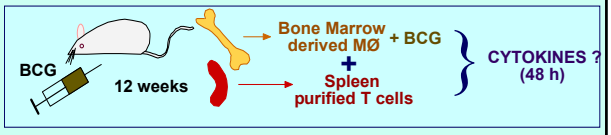
No change of vascular ICAM-1 expr

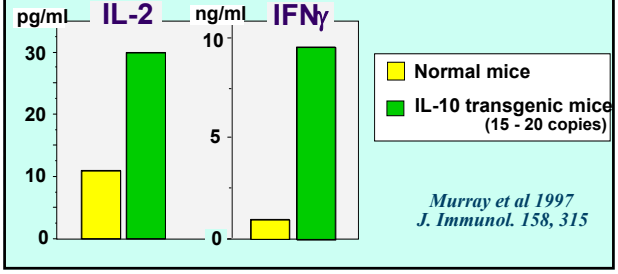
DUAL EFFECT OF IL-4 ON RESISTANCE TO SYSTEMIC *Pseudomonas aeruginosa* INFECTION

Giampietri et al. Cytokine 2000, 12, 417



IL-10 AND MYCOBACTERIAL INFECTION

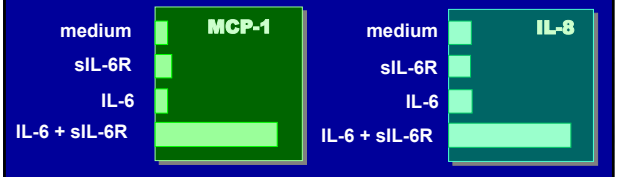




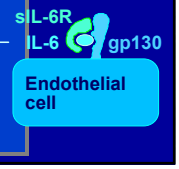
Murray et al 1997
J. Immunol. 158, 315

ENDOTHELIAL CELL ACTIVATION BY IL-6 + sIL-6R

Romano et al. Immunity 1997 6, 315



	STAT-3 DNA binding activity	ICAM-1 Expression	VCAM-1 Expres. E-SELECTIN Expres. PAF release NOS prod.
medium	0	0	0
sIL-6R	0	0	0
IL-6	0	0	0
IL-6 + sIL-6R	√	√	0



IL-10 can effect very different outcor depending on timing, dose and locat of expression.

In some scenarios the expected immuno-suppressive activities are observed, while in others IL-10 enhances immune or inflammatory responses.

K. Moore, R. de Waal Malefyt, R. Coffman & A. O'Garra
Annu. Rev. Immunol. 2001, 19, 683

IN VIVO PRO-INFLAMMATORY AND/OR IMMUNOSTIMULATING ACTIVITY OF IL-10

AUTO-IMMUNITY			
Transgenic expression of IL-10 in pancreatic islet	A cells β cells	ACCELERATEE ONSET & DEVELOPMENT OF AUTOIMMUNE DIABETES	Moritani et al. 1994 Intern Immunol. 6, 1927 Wogensen et la . 1994 J Exp Med 93, 1332
GRAFT			
Allogenic islet cell transplant	+ IL-10-Fcγ2a treatment	ACCELERATED ALLOGRAFT REJECTION	Zheng et al. 1995 J. Immunol 154, 5590
Heart allograft	+ IL-10 treat		Qian et al. 1996 Transpl. 62, 1709
INFLAMMATION			
Endotoxin-induced uveitis	+ IL-10 i.p.	POTENTIATION OF OCCULAR INFLAMMATION	Rosenbaum et al. 1995 J. Immunol. 155, 4090
TUMOR			
Sarcoma, melanoma, colorectal carcinoma	+ IL-10 x 7 days	TUMOR REJECTION	Berman et al. 1996 J. Immunol. 157, 231

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LOCAL RELEASE OF IL-10 BY TRANSFECTED MOUSE ADENOCARCINOMA CELLS EXHIBITS PRO- AND ANTI-INFLAMMATORY ACTIVITY

Tumor growth area (D+4)	Mouse Mammary adenocarcinoma	IL-10 transfecte cells
TNFα	±	±
IL-6	+	±
MCP-1	–	±
iNOS	–	±
ICAM-1	±	±
VCAM-1	–	+
ELAM-1	–	++
Macrophages	26.5	60.4
Granulocytes	6.8	32.1
CD8+ lymphocytes	3.2	23.6
(/ 0.180 mm² field)		

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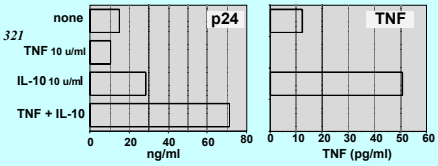
IL-10 ENHANCES HIV REPLICATION AND TNF PRODUCTION BY INFECTED CELLS

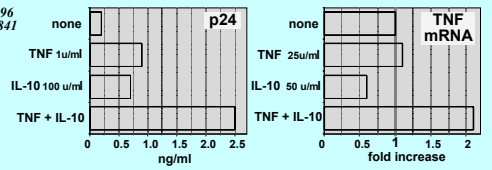
Rabbi et al. 1998
J AIDS Hum Retrovirol 19, 321

latently infected T-cells (ACH-2)



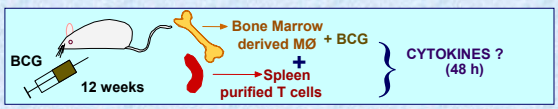
Finnegan et al. 1996
J. Immunol. 156, 841

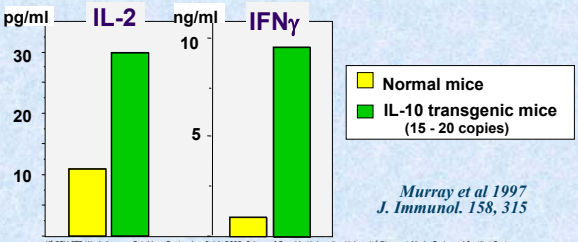
Chronically infected promonocytic cell U1



In combination with TNF, IL-10 stimulated AP-1 and NFB translocation in the nucleus

IL-10 AND MYCOBACTERIAL INFECTION





Murray et al 1997
J. Immunol. 158, 315

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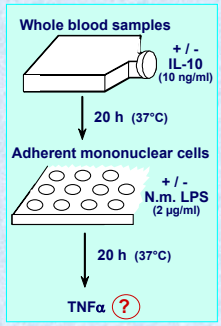
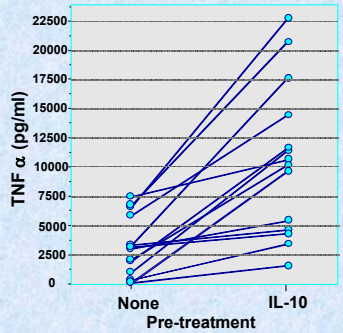
Myth or reality ?

PRIMING EFFECT OF IL-10 IN WHOLE BLOOD

Adib-Conquy et al. Intern. Immunol. 1999, 11, 689





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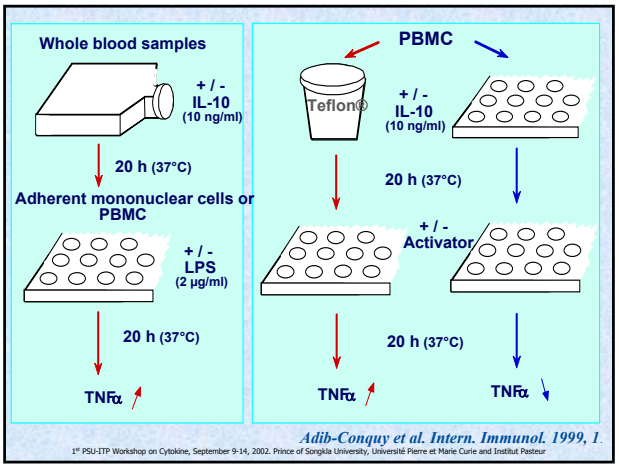
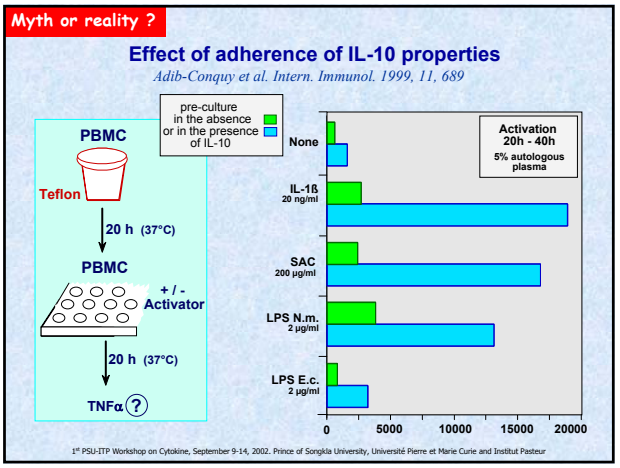

Whole blood samples
+ / -
IL-10
(10 ng/ml)
20 h (37°C)
Adherent mononuclear cells or
PBMC
+ / -
LPS
(2 µg/ml)
20 h (37°C)
TNFα
PBMC
Teflon®
+ / -
IL-10
(10 ng/ml)
20 h (37°C)
+ / -
Activator
20 h (37°C)
TNFα
TNFα
Adib-Conquy et al. Intern. Immunol. 1999, 1.
1st PSU-ITP Workshop on Cytokine, September 9-14, 2002. Prince of Songkla University, Université Pierre et Marie Curie and Institut Pasteur


Myth or reality ?
Effect of adherence of IL-10 properties
Adib-Conquy et al. Intern. Immunol. 1999, 11, 689
pre-culture
in the absence
or in the presence
of IL-10
PBMC
Teflon
20 h (37°C)
PBMC
+ / -
Activator
20 h (37°C)
TNFα ?
Activation
20h - 40h
5% autologous
plasma
None
IL-1ß
20 ng/ml
SAC
200 µg/ml
LPS N.m.
2 µg/ml
LPS E.c.
2 µg/ml
0
5000
10000
15000
20000
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