Interleukin-1 role in human Th-17 cell responses, dendritic cell activation, and epithelial cell transformation

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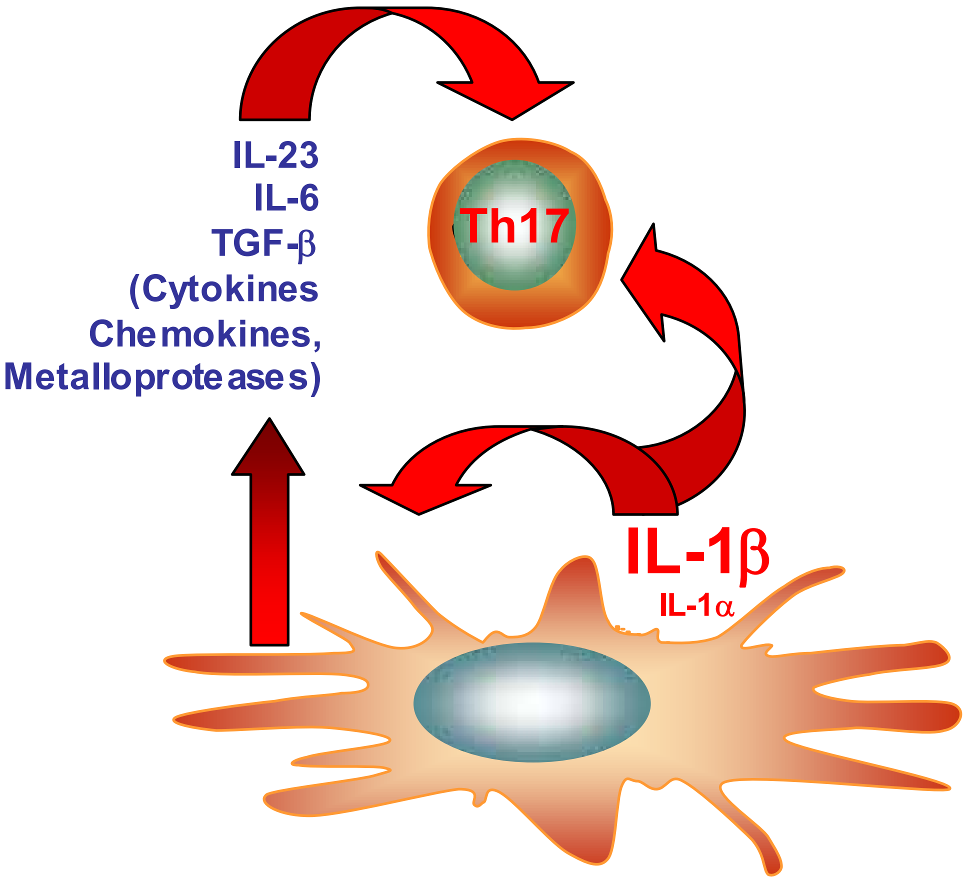
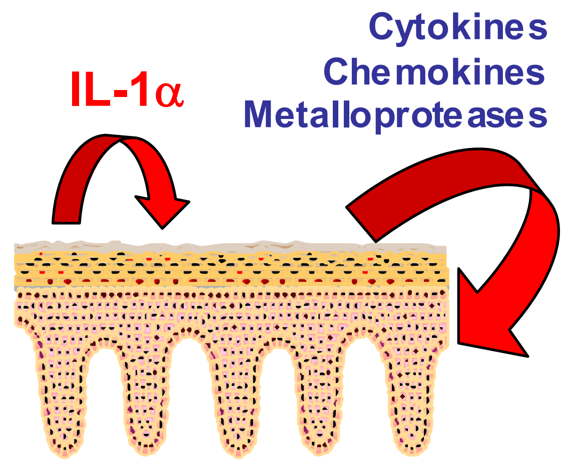
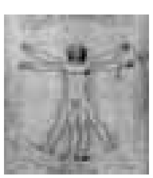
BACK TO THE FUTURE: several new important biological roles of the Interleukin-1 cytokine family emerge from studies of inflammation-dependent carcinogenesis



Human Dendritic Cells Activation by β-Glucan

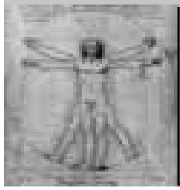


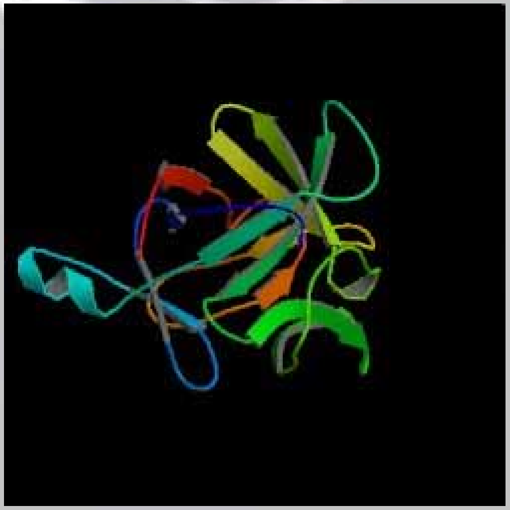
Skin carcinogenesis (DMBA/TPA)



Activation of human Dendritic Cells by ITAM-signaling receptors

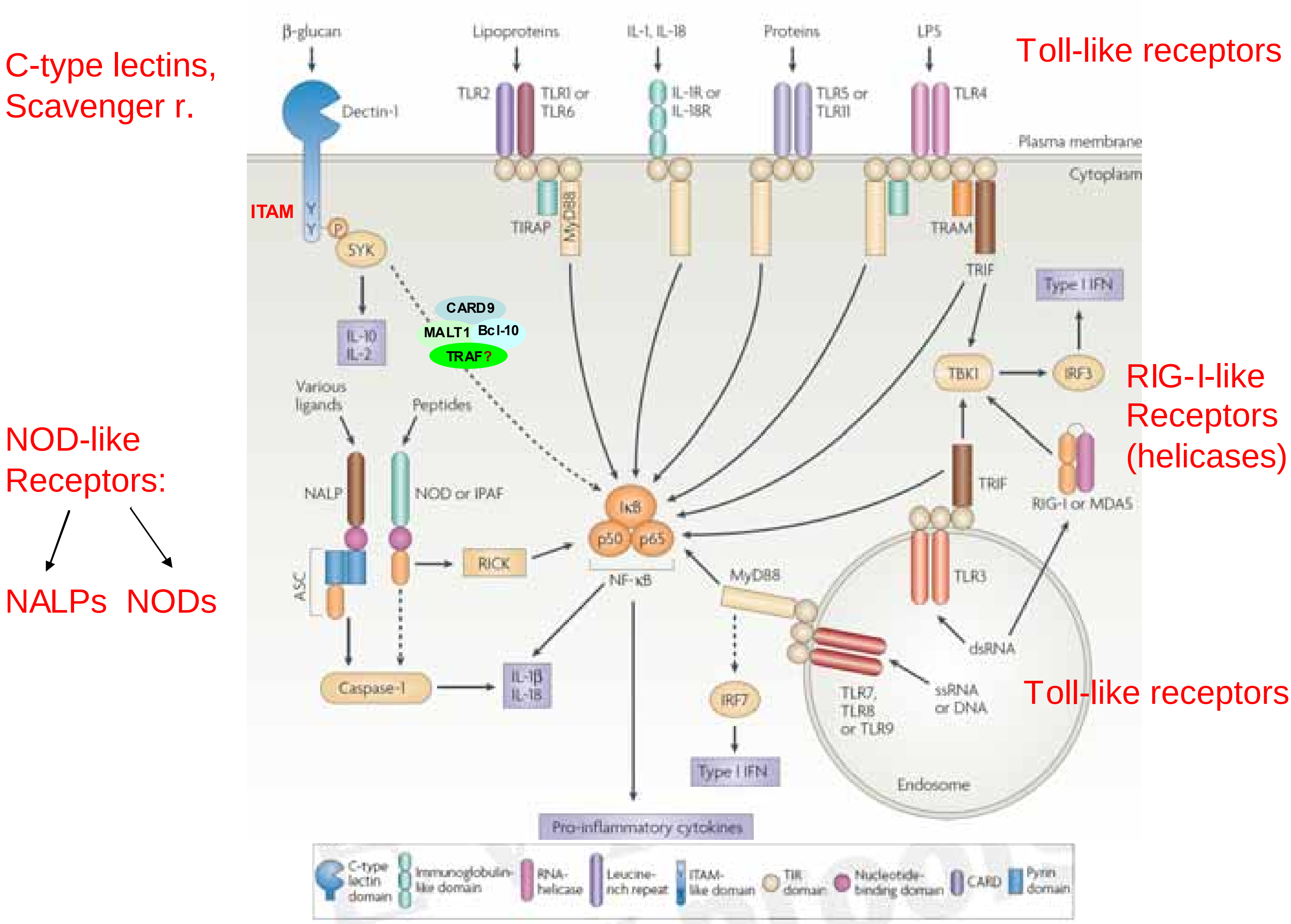
IL-1β

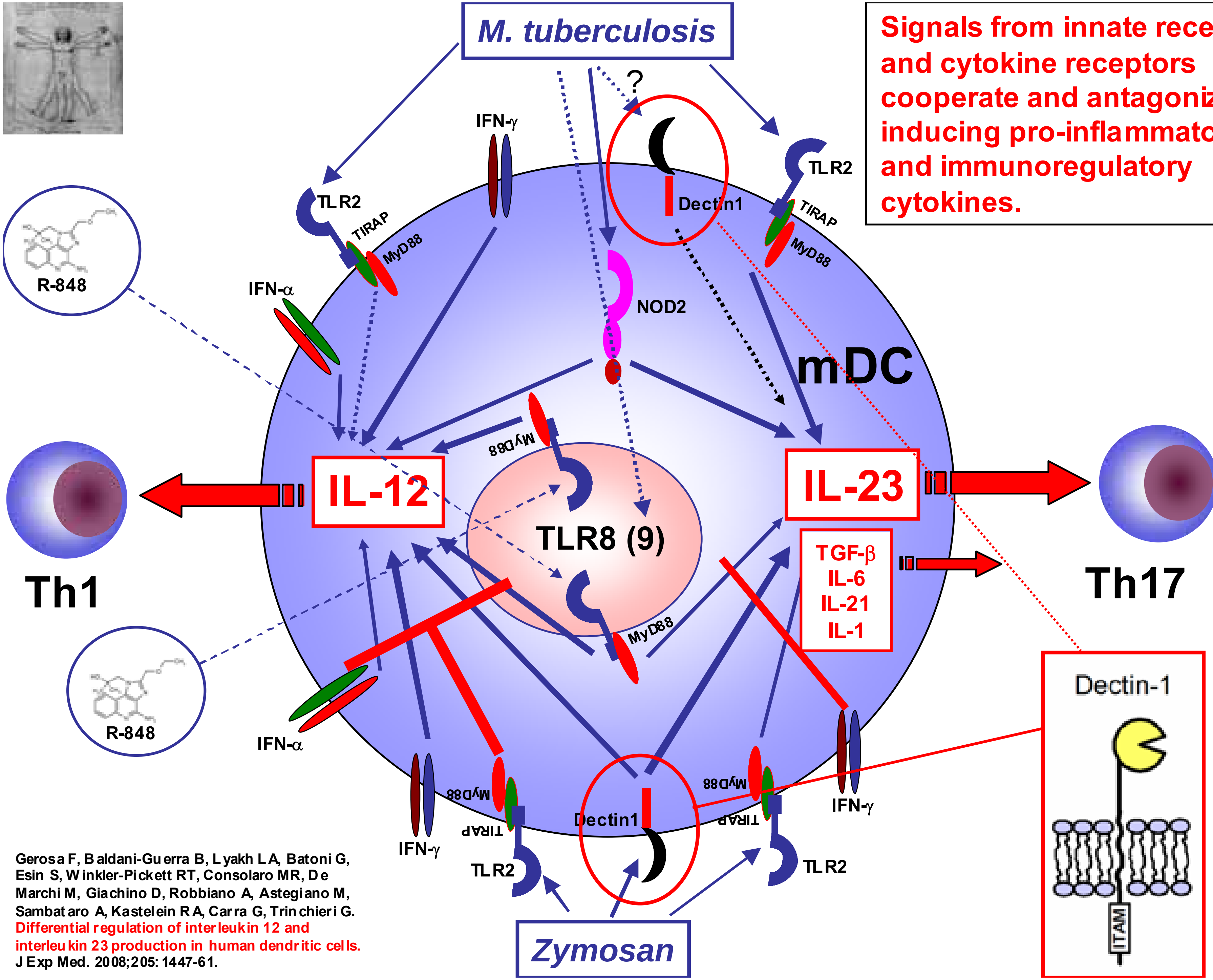




Human Monocyte-derived Dendritic Cells

Pattern Recognition Receptors (PRR)





Signals from innate receptors and cytokine receptors cooperate and antagonize in inducing pro-inflammatory and immunoregulatory cytokines.

Gerosa F, Baldani-Guerra B, Lyakh LA, Batoni G, Esin S, Winkler-Pickett RT, Consolaro MR, De Marchi M, Giachino D, Robbiano A, Astegiano M, Sambataro A, Kastelein RA, Carra G, Trinchieri G. Differential regulation of interleukin 12 and interleukin 23 production in human dendritic cells. J Exp Med. 2008;205:1447-61.

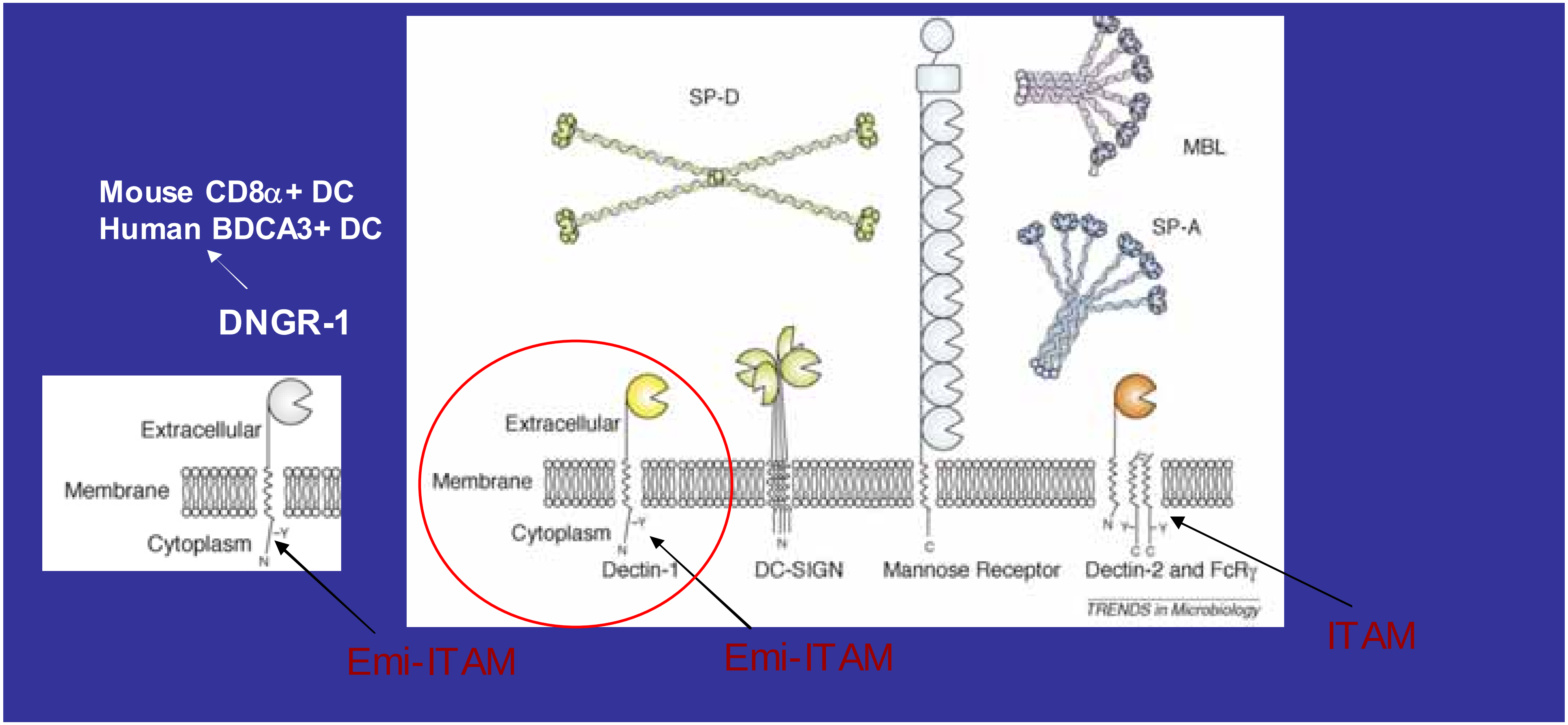
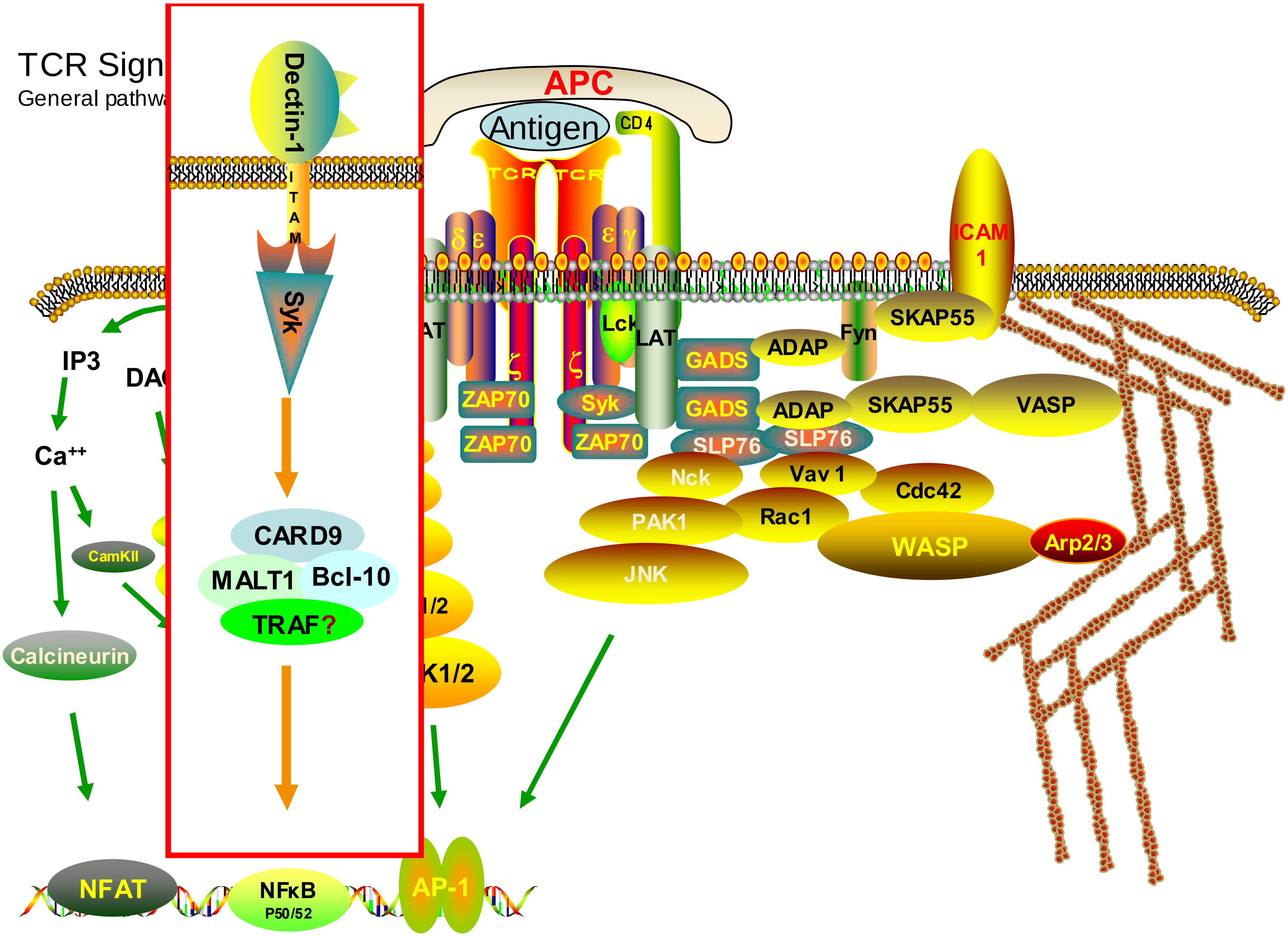
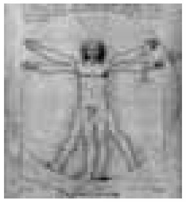


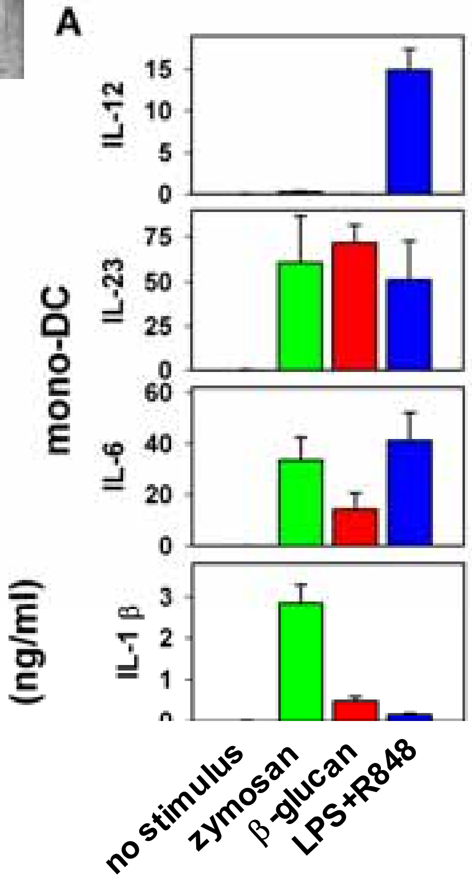
Table 1. Fungal PAMPs and their receptors

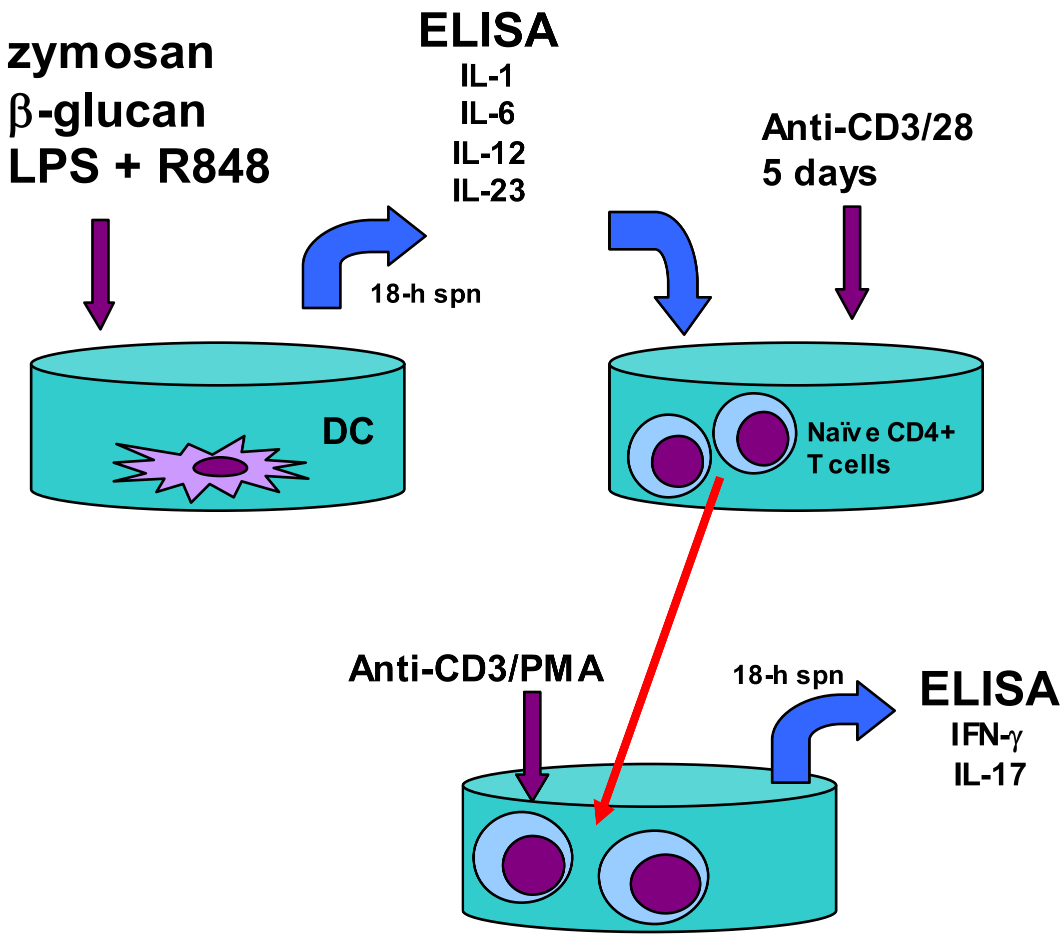
PAMP	PRR(s)
β-1,2 mannosides	Galectin-3
β-glucan	Dectin-1, SP-D, lactosylceramide
Chitin	Unknown
Phospholipomannan	TLR2
Glucuronoxylomannan	CD14, TLR4
Mannan	TLR4; SP-A; SP-D, MR, DC-SIGN, Dectin-2, MBL
Galactomannan	PTX3 (pentraxin-3)
DNA	TLR9



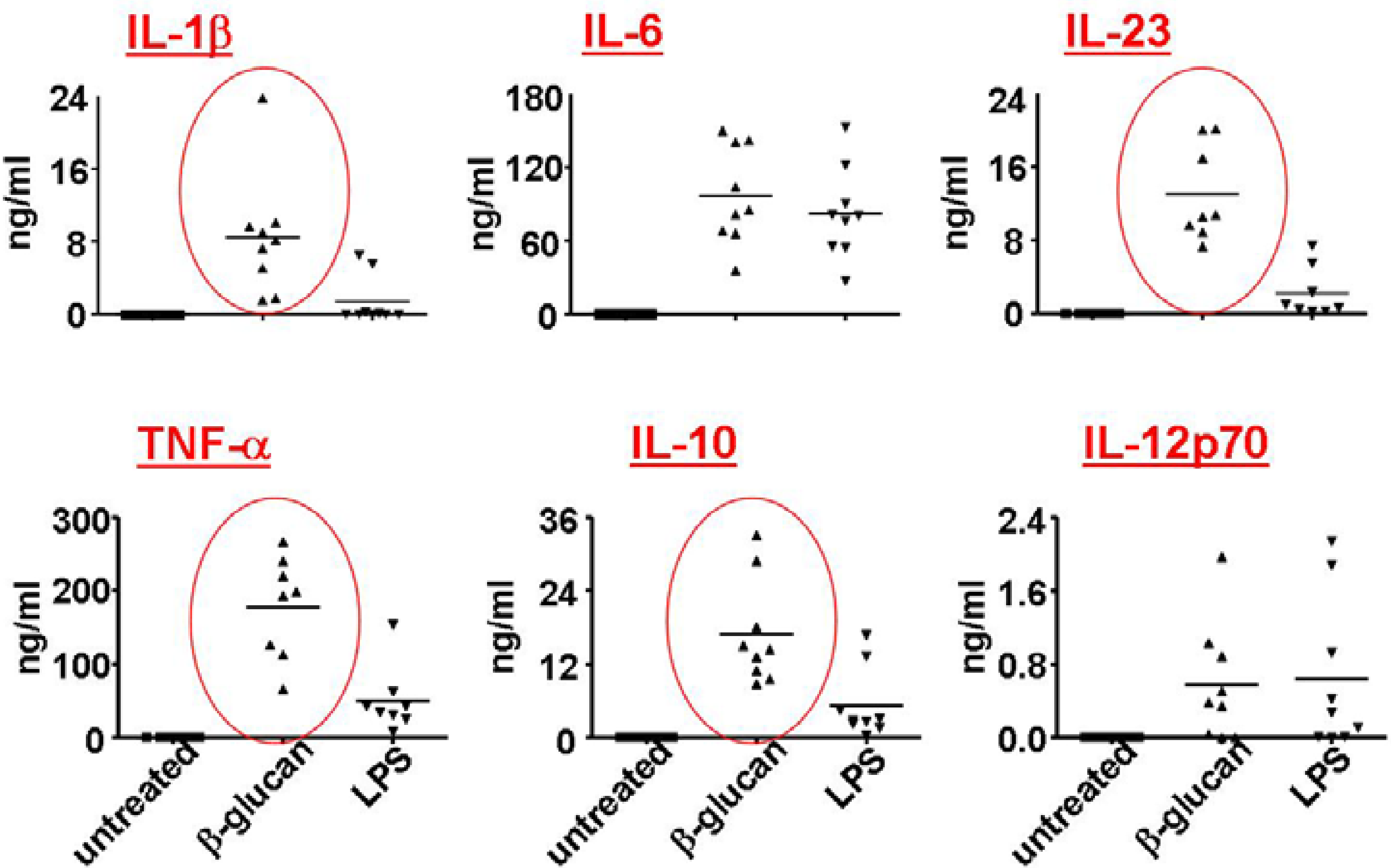
TCR Sign
General pathwa
Dectin-1
ITAM
Syk
CARD9
MALT1
Bcl-10
TRAF?
APC
Antigen
CD4
TCR
TCR
δ ε
ε γ
ζ
ζ
ICAM 1
AT
Lck
LAT
ZAP70
ZAP70
Syk
ZAP70
GADS
GADS
ADAP
ADAP
Fyn
SKAP55
SKAP55
VASP
SLP76
SLP76
Nck
Vav 1
Cdc42
PAK1
Rac1
WASP
Arp2/3
JNK
IP3
DA
Ca++
CamKII
Calcineurin
l/2
K1/2
NFAT
NFκB
P50/52
AP-1

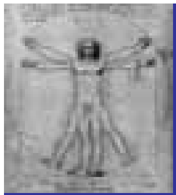



A
mono-DC
(ng/ml)
IL-12
IL-23
IL-6
IL-1 β
15
10
5
0
75
50
25
0
60
40
20
0
3
2
1
no stimulus
zymosan
β-glucan
LPS+R848

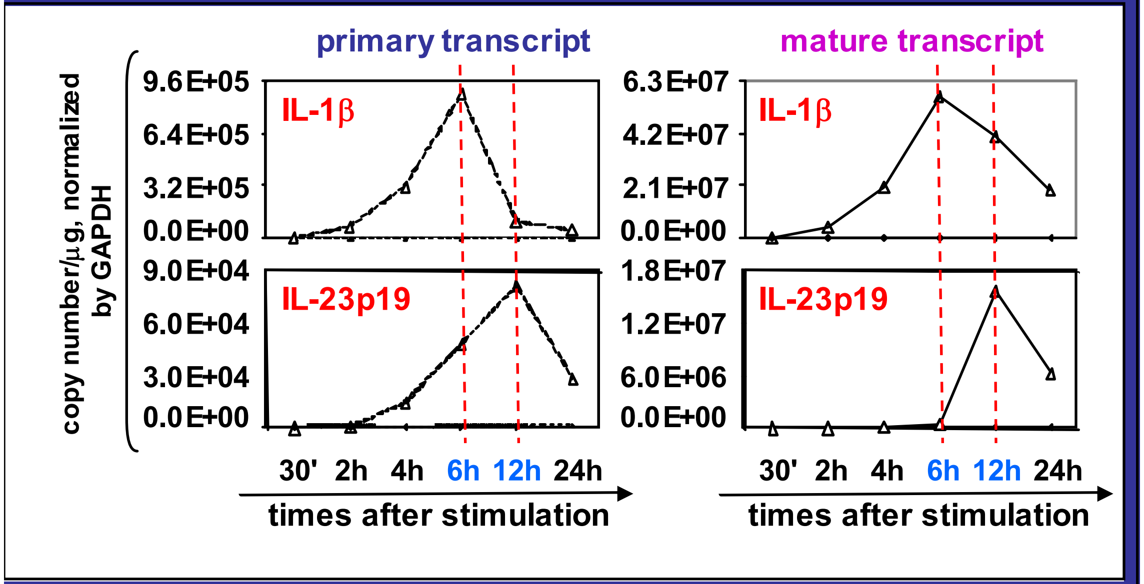

zymosan
β-glucan
LPS + R848
DC
18-h spn
ELISA
IL-1
IL-6
IL-12
IL-23
Anti-CD3/28
5 days
Naïve CD4+
T cells
Anti-CD3/PMA
18-h spn
ELISA
IFN-γ
IL-17

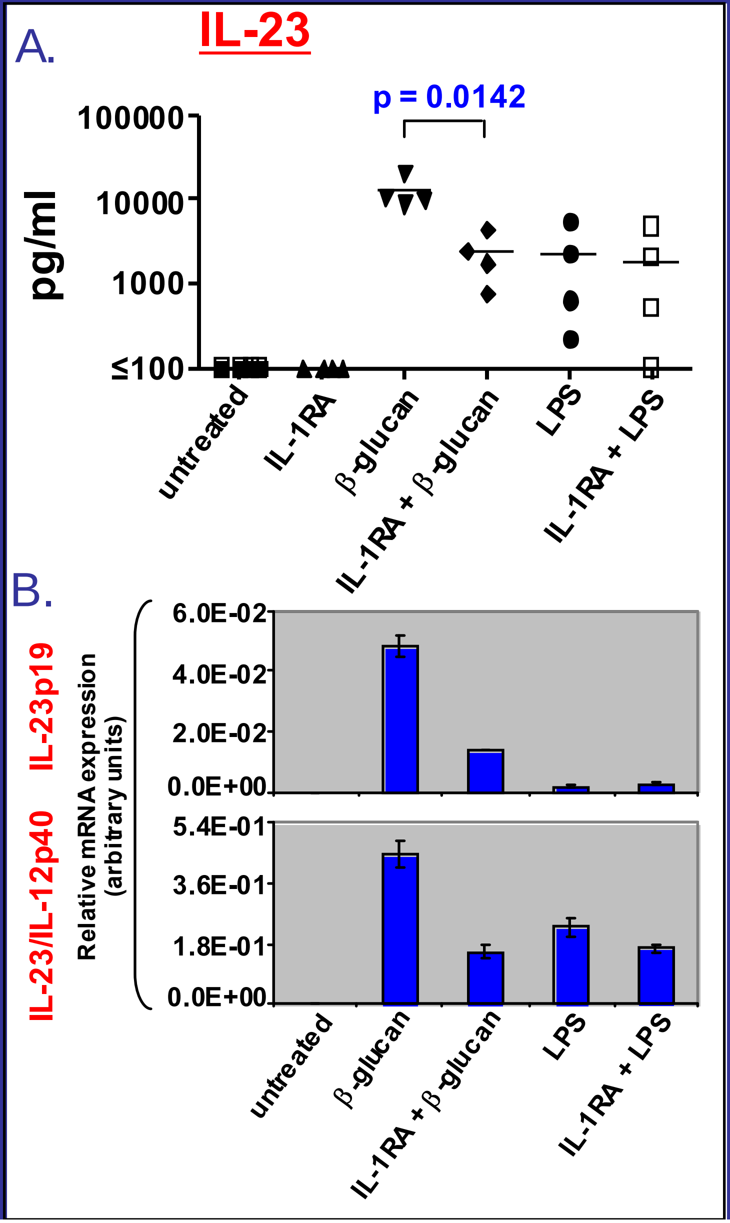
Cytokine profile induced by β-glucan and LPS in human monocyte-derived DCs





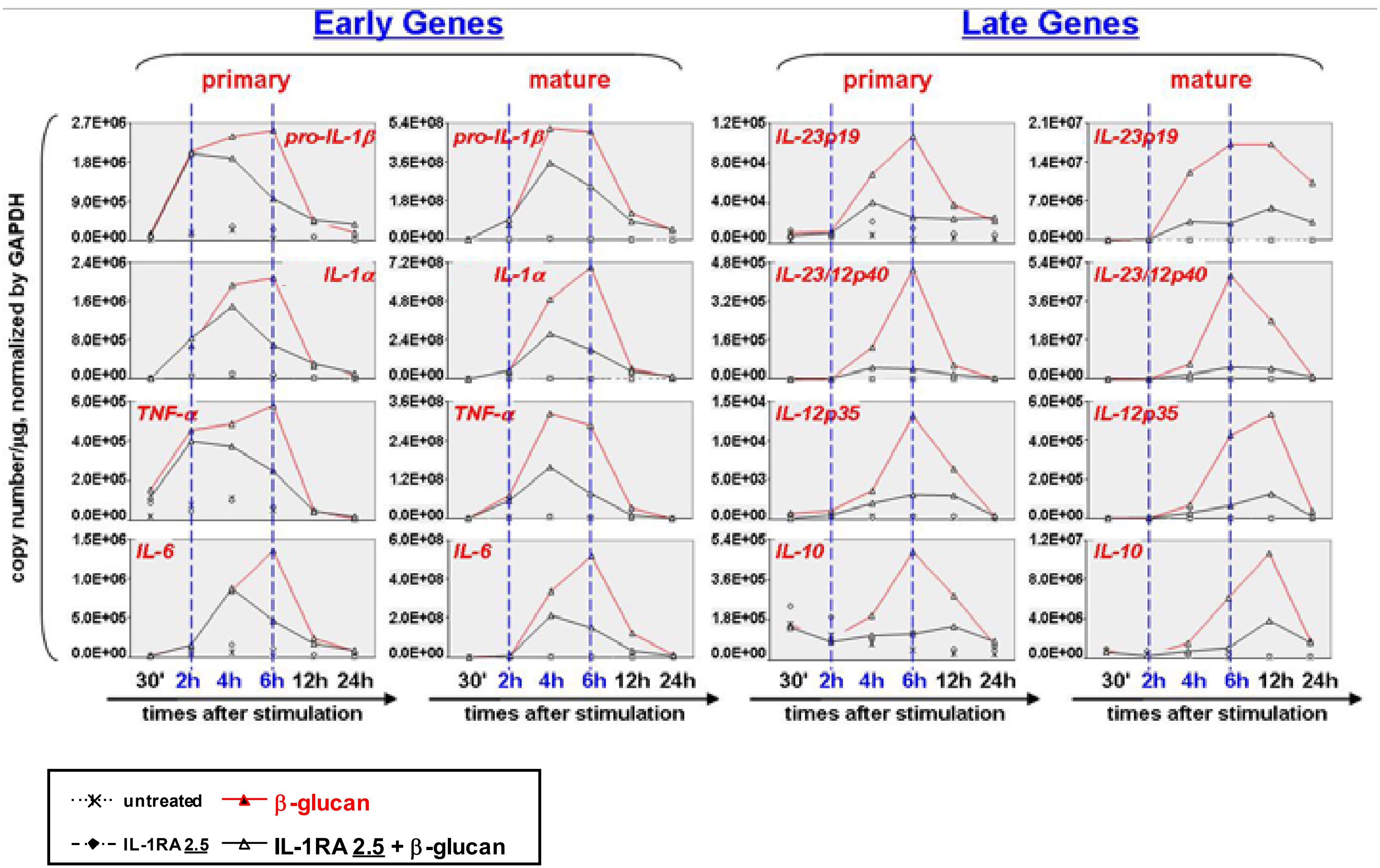
Role of endogenous IL-1 in IL-23 production in human monocyte-derived DCs activated by β-glucan

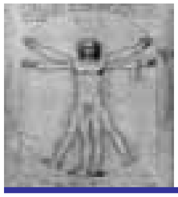




✓ **In the presence of the IL-1RA the ability of β-glucan treatment to induce IL-23 protein production (A) and IL-23 p19 and IL-12 p40 mRNA expression (B) in human mono-DCs is decreased.**

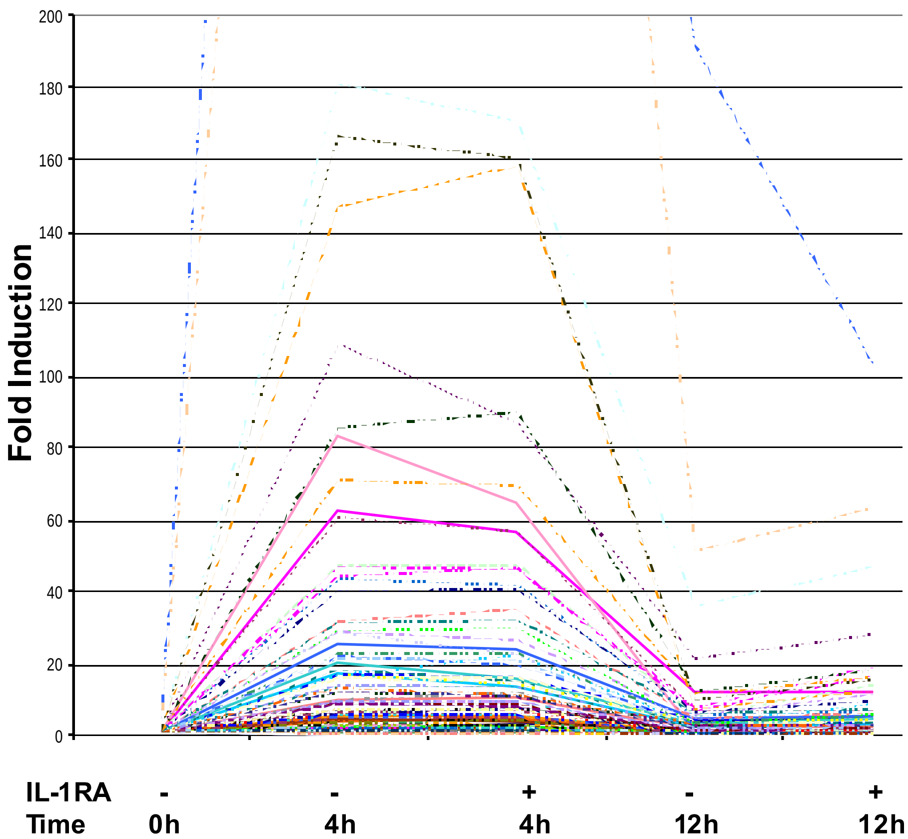
Role of endogeneous IL-1 in the regulation of the late gene expression induced by β-glucan in human mono-DCs



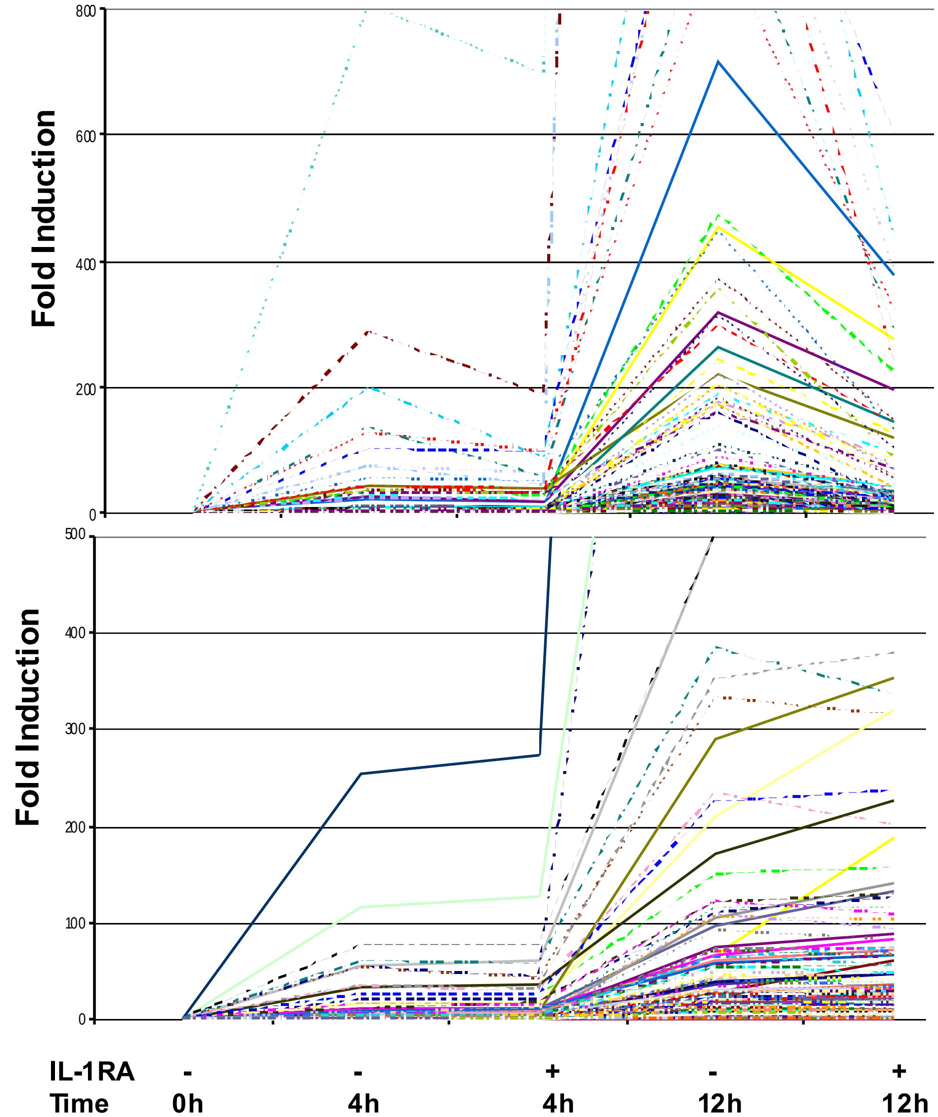


Microarray analysis of the transcripts induced by b-glucan in human mono-DCs in the presence or not of IL-1RA

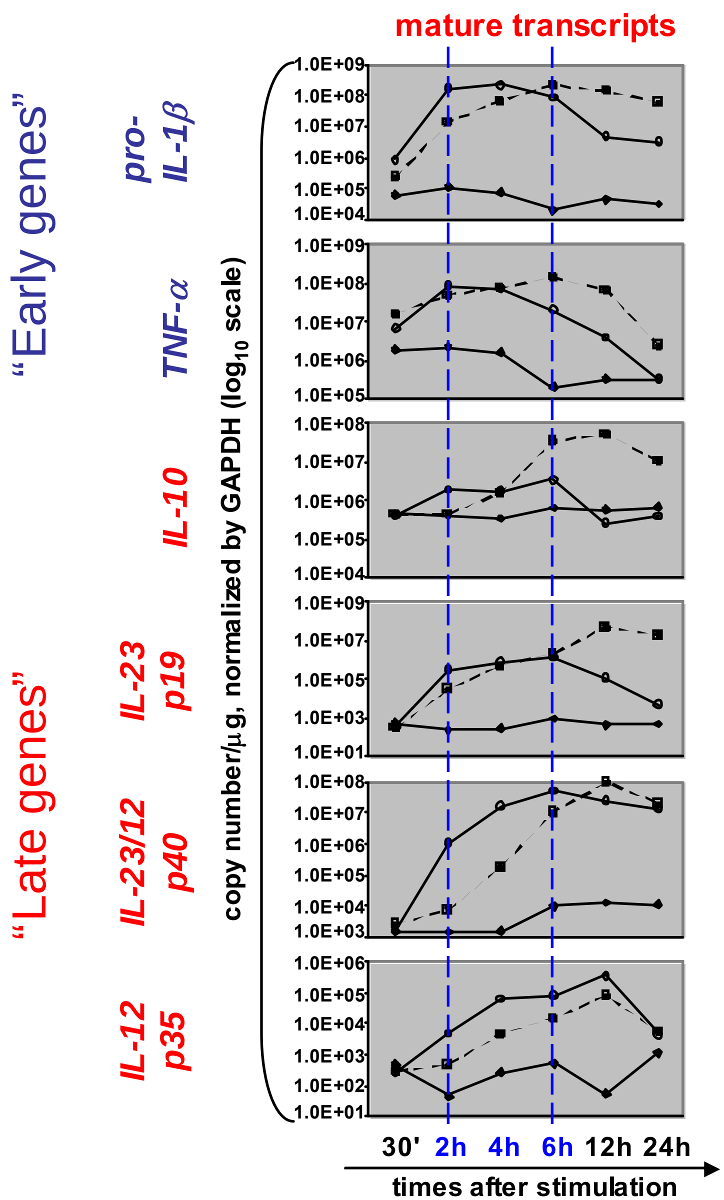
"Early genes"



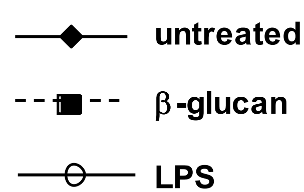
"Late genes"

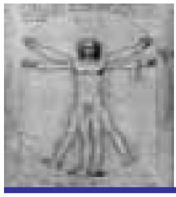


LPS induces “late genes” expression with a faster kinetic than β-glucan in human mono-DCs



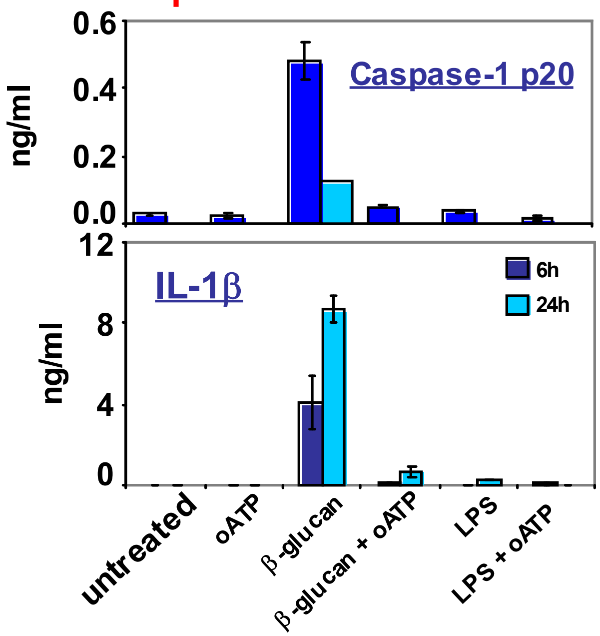
- Both LPS and β-Glucan induce phosphorylation of p38 and ERK1/2 at 30 minutes or earlier.
- LPS induces phosphorylation of IkB-α and NF-κB activation already at 30 minutes whereas β-Glucan induces them only at 4-6 hours.
- IkB-α phosphorylation and degradation by β-glucan but not by LPS is reversed by Interleukin-1RA.



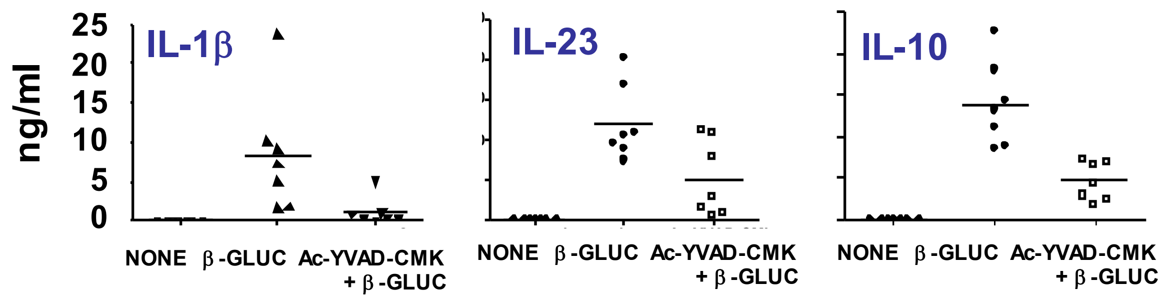


The expression of "Late genes" in human DCs stimulated by β-Glucan is dependent on IL-1β and, to a lesser extent, IL-1α

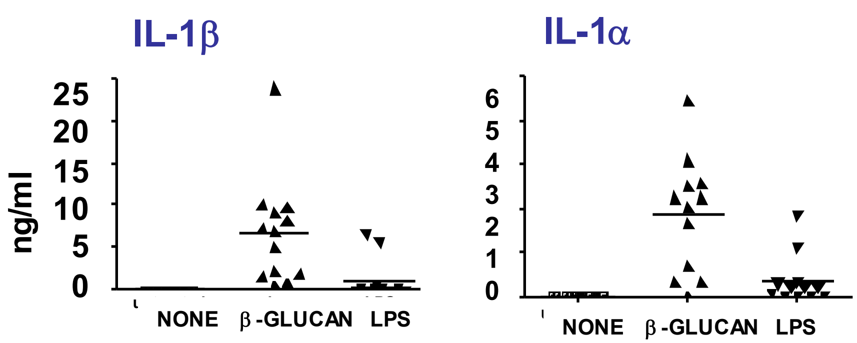
β-glucan but not LPS activates Caspase-1 in mono-DC



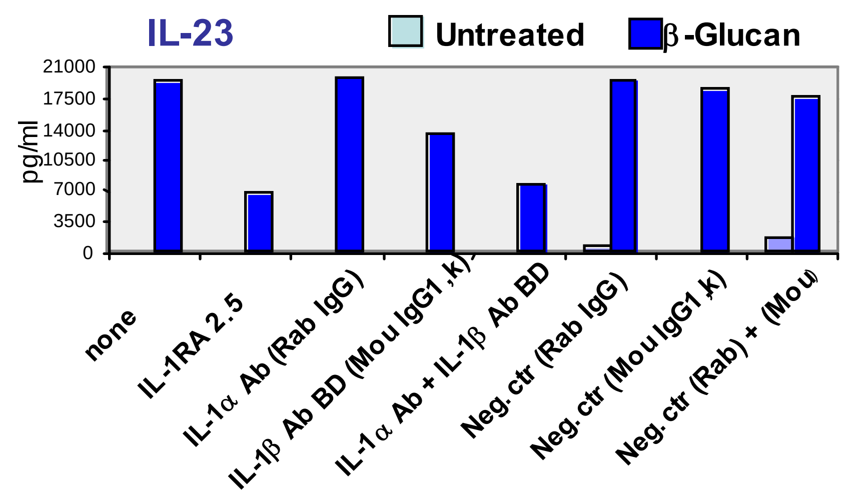
Caspase-1 inhibitors decrease IL-1β and also IL-23 and IL-10 secretion by β-glucan-activated mono-DC

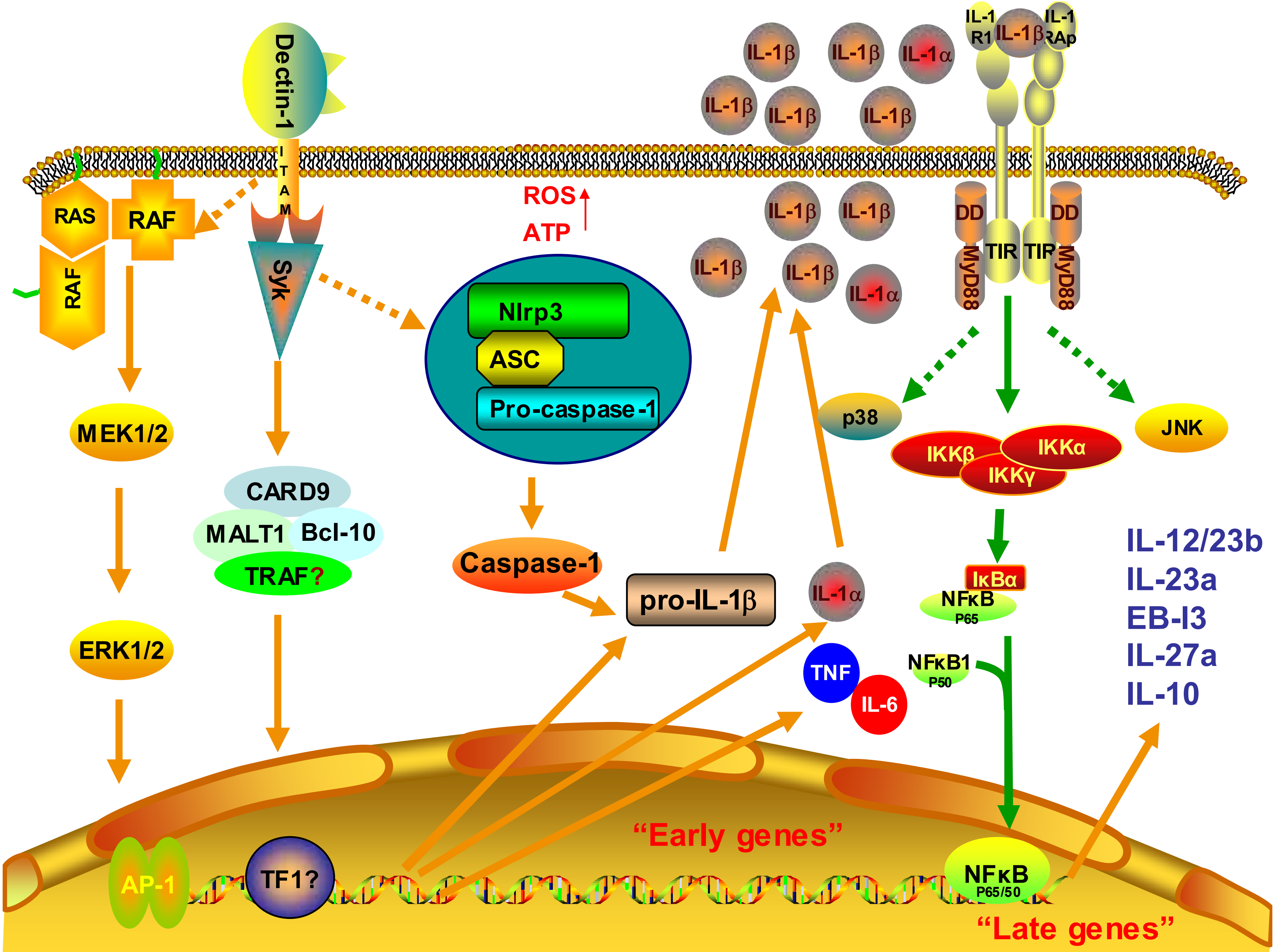


Production of IL-1β and IL-1α by β-glucan-stimulated mono-DC



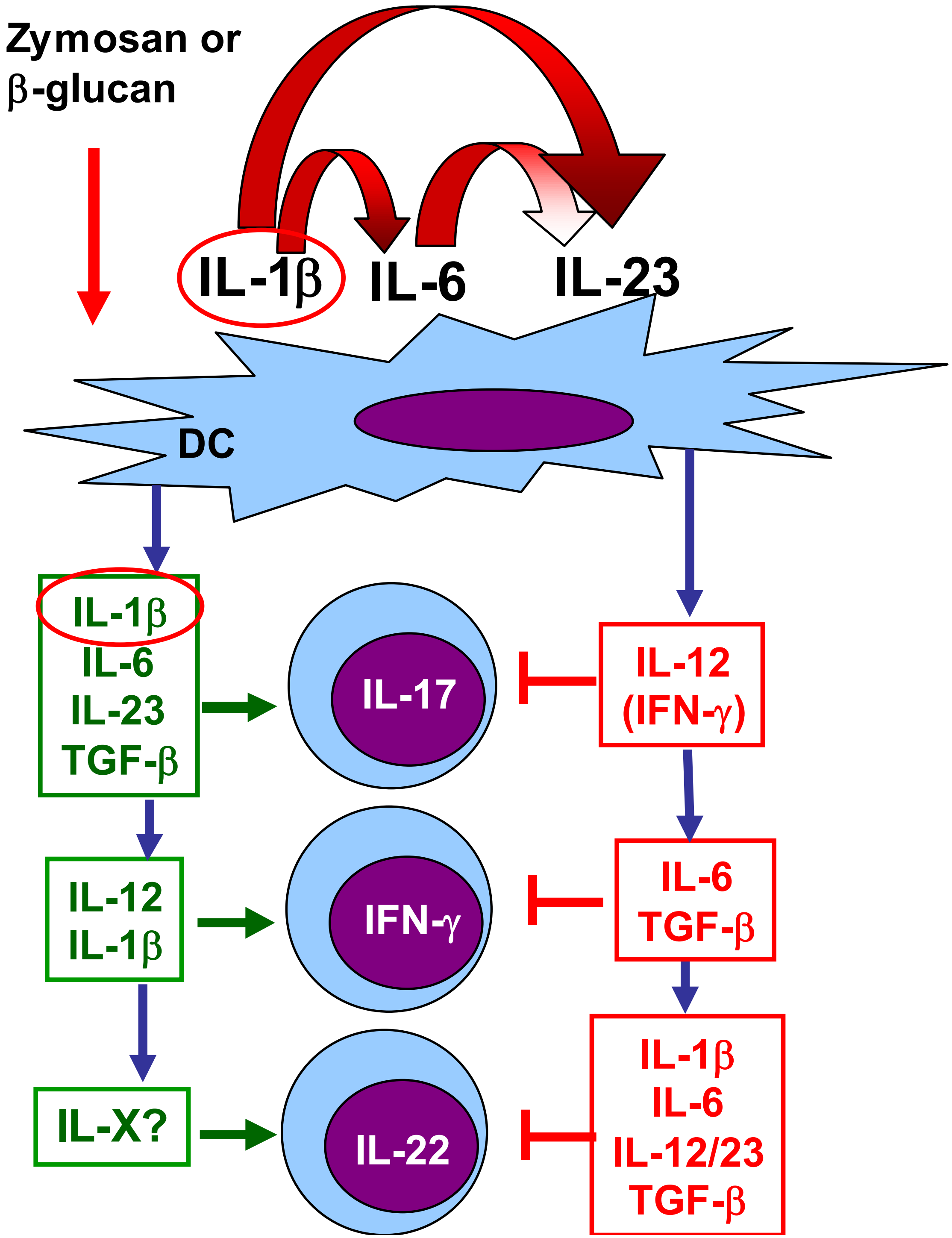
Anti-IL-1β is more effective than anti-IL-1α to inhibit IL-23 production by β-glucan-activated mono-DC

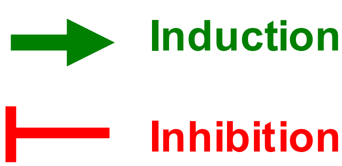




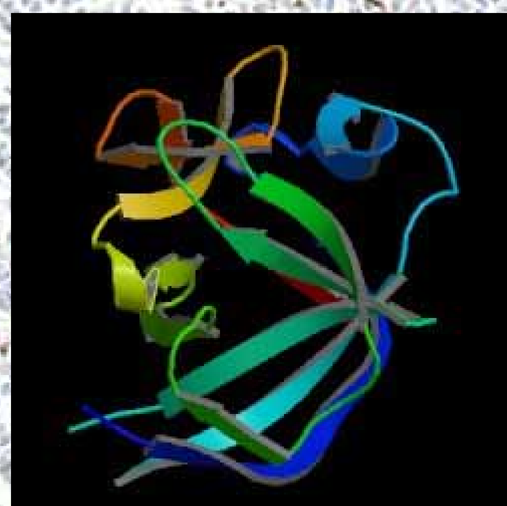
Dectin-1
ITAM
Syk
RAS
RAF
RAF
MEK1/2
ERK1/2
AP-1
CARD9
MALT1
Bcl-10
TRAF?
TF1?
ROS
ATP
Nlrp3
ASC
Pro-caspase-1
Caspase-1
pro-IL-1β
IL-1β
IL-1α
IL-1 R1
IL-1β
IL-1 RAp
DD
DD
TIR
TIR
MyD88
MyD88
p38
JNK
IKKβ
IKKα
IKKγ
IκBα
NFκB P65
NFκB1 P50
TNF
IL-6
IL-12/23b
IL-23a
EB-I3
IL-27a
IL-10
"Early genes"
NFκB P65/50
"Late genes"

IL-1β has a central role in the Th17 response by being involved in an autocrine way to increase production of the Th-17 inducing cytokine IL-6 and IL-23 from DC and by directly acting on the CD4+ T cells in the induction of IL-17 production.





Role of IL-1α in skin carcinogenesis



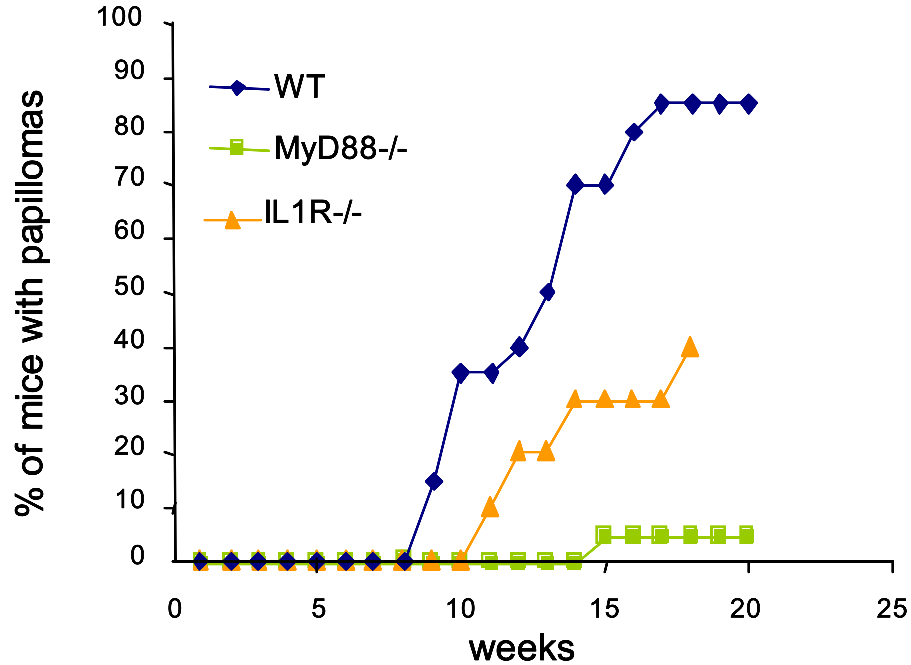
MyD88 is required for DMBA-induced Mouse Skin Tumorigenesis

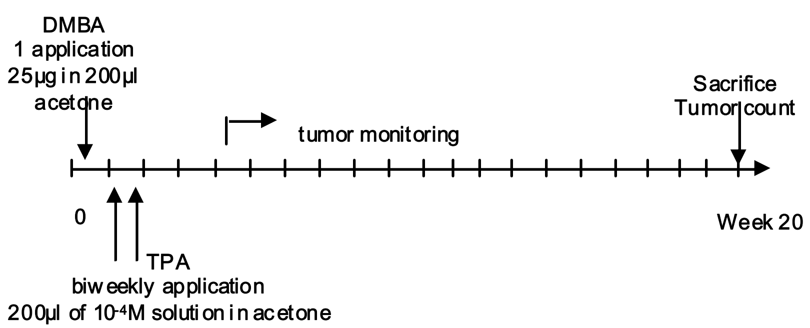
(19) United States
(12) Patent Application Publication (10) Pub. No.: US 2006/0141490 A1
Jun. 29, 2006

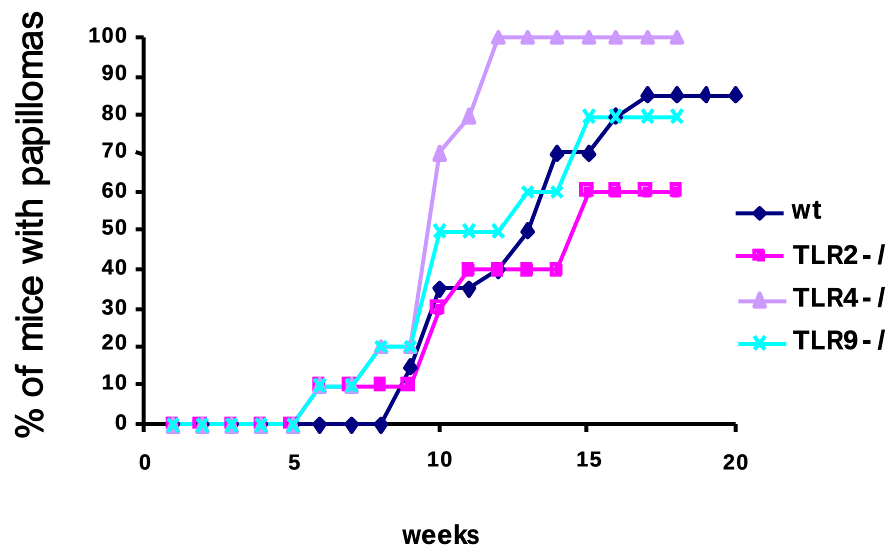
(54) MYD88 AS A THERAPEUTIC TARGET FOR CANCER

(76) Inventors: Isabelle Coste-Invernizzi, Chazay d'Azergues (FR); Toufic Renno, Civrieux d'Azergues (FR)

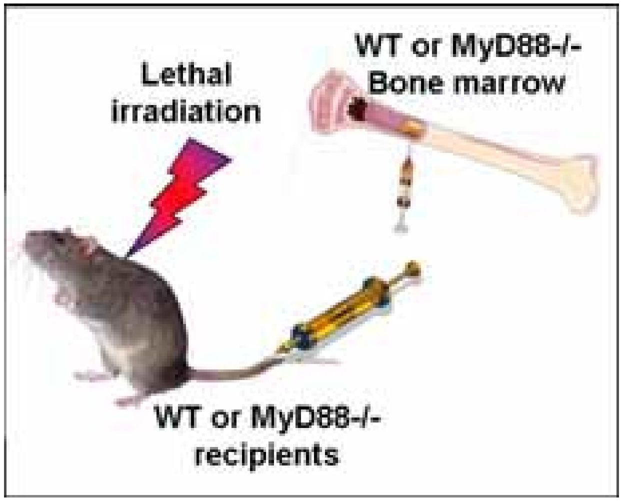
Correspondence Address:
SCHERING-PLOUGH CORPORATION

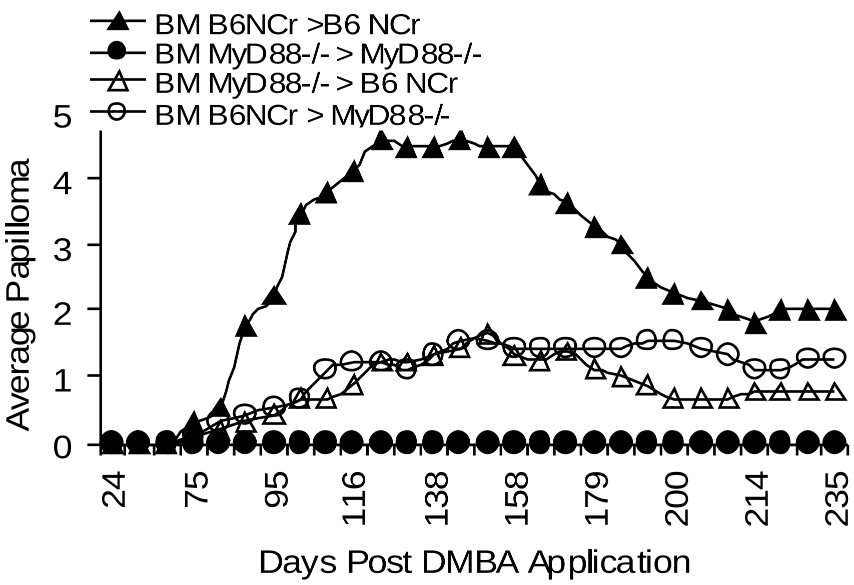


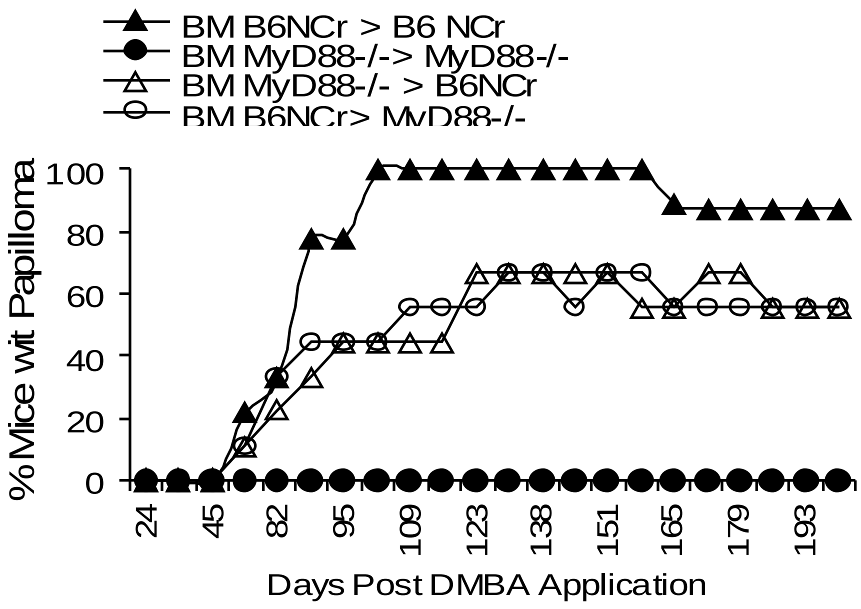




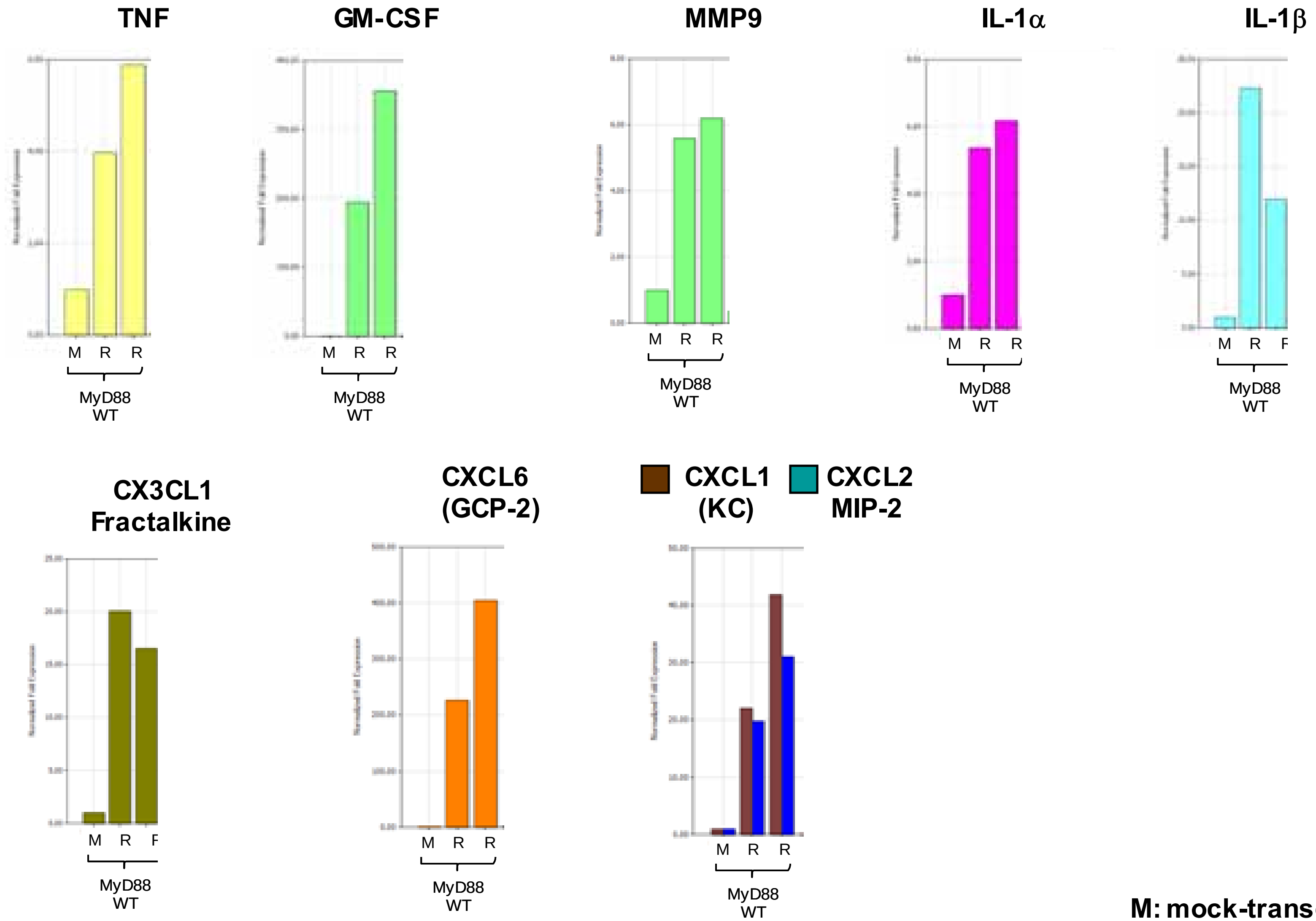
Bone marrow chimera experiments indicate that optimal skin carcinogenesis requires MyD88 expression both in hematopoietic cells and in recipient cells





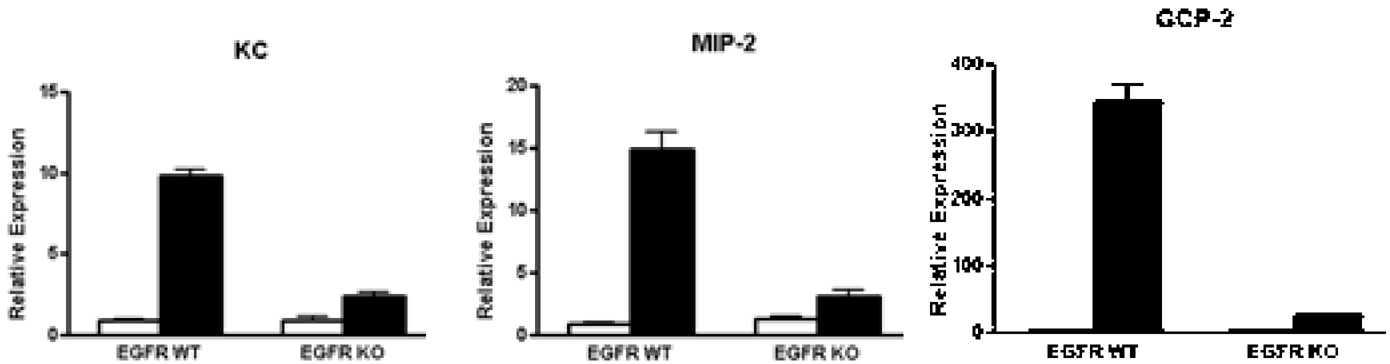


v-ras^{Ha} transformed keratinocytes from wild type mice produce CXCR2 ligands and other cytokines



M: mock-transduced
R: v-ras^{Ha}-transduced

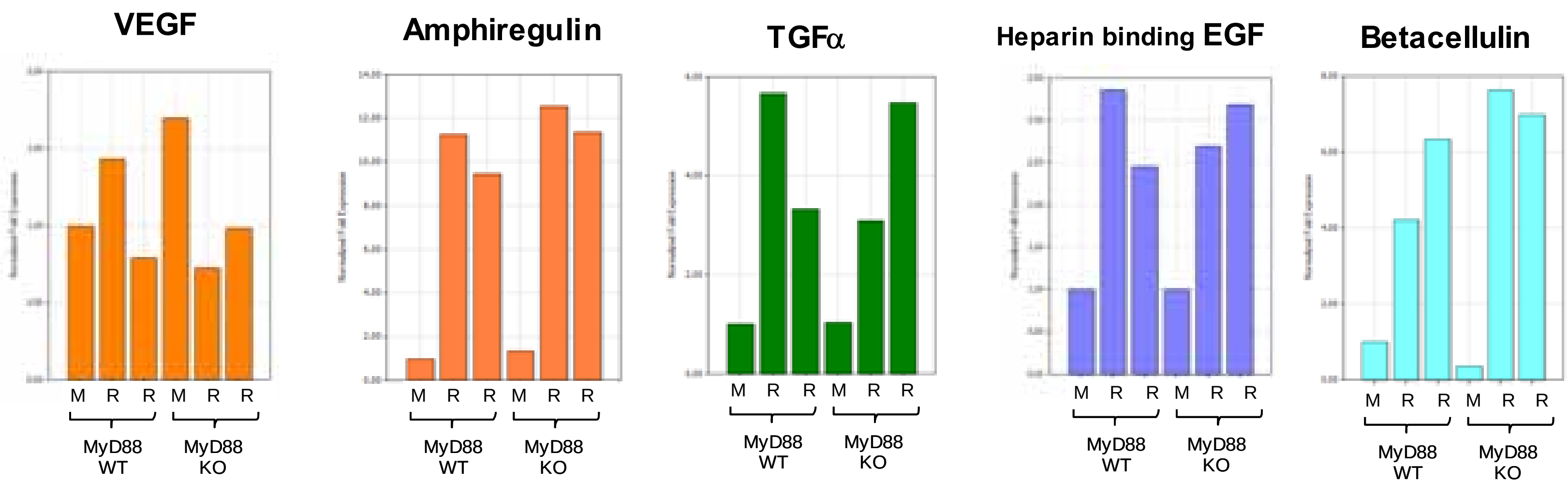
Upregulation of CXCR2 ligands by oncogenic v-ras^{Ha} in primary keratinocytes requires EGFR expression



Real-time PCR analysis

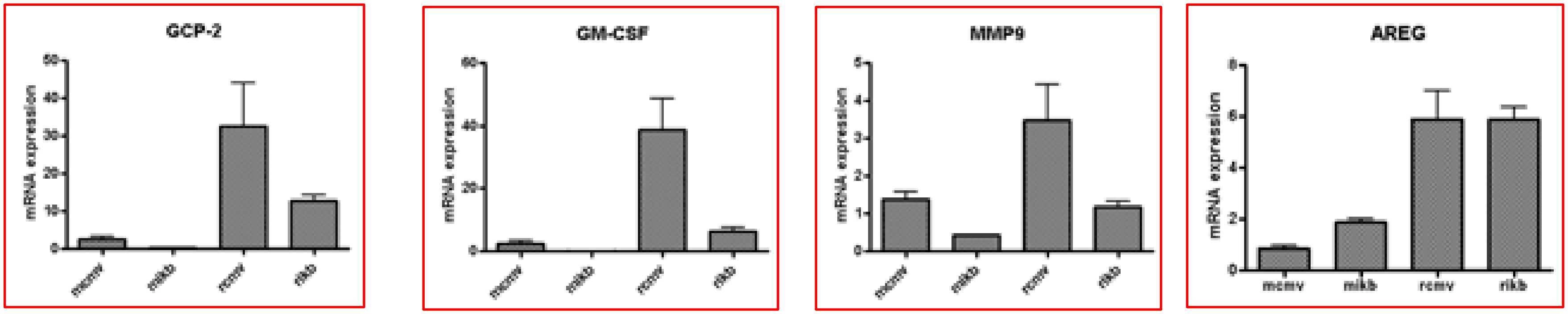
☐ Mock transduced
■ v-ras^{Ha} transduced

v-ras^{Ha} transformed keratinocytes from MyD88-/- mice are able to produce EGFR ligands



M: mock-transduced
R: v-ras^{Ha}-transduced

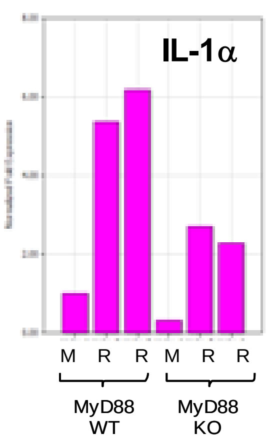
Ras target genes affected by MyD88 deficiency are NF-κB regulated



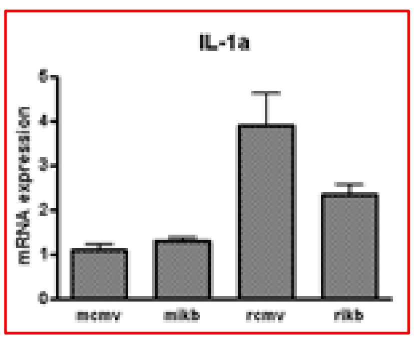
mcmv: mock, control Ad; **mikb**: mock, IκBαSR Ad
rcmv: v-ras, control Ad; **rikb**: v-ras, IκBαSR Ad

Ras induction of IL-1α is EGFR-dependent but only partially MyD88 and NFκB dependent

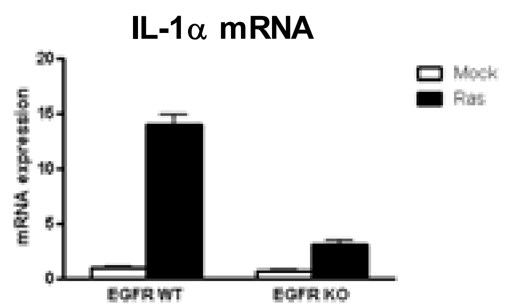
MyD88

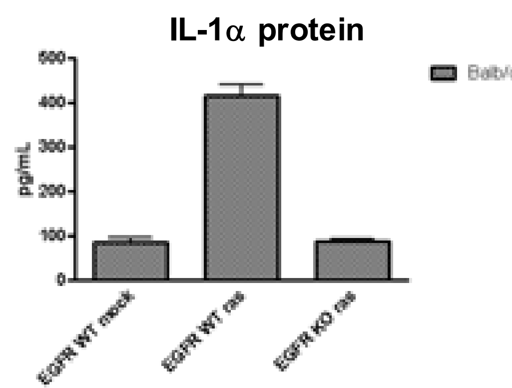


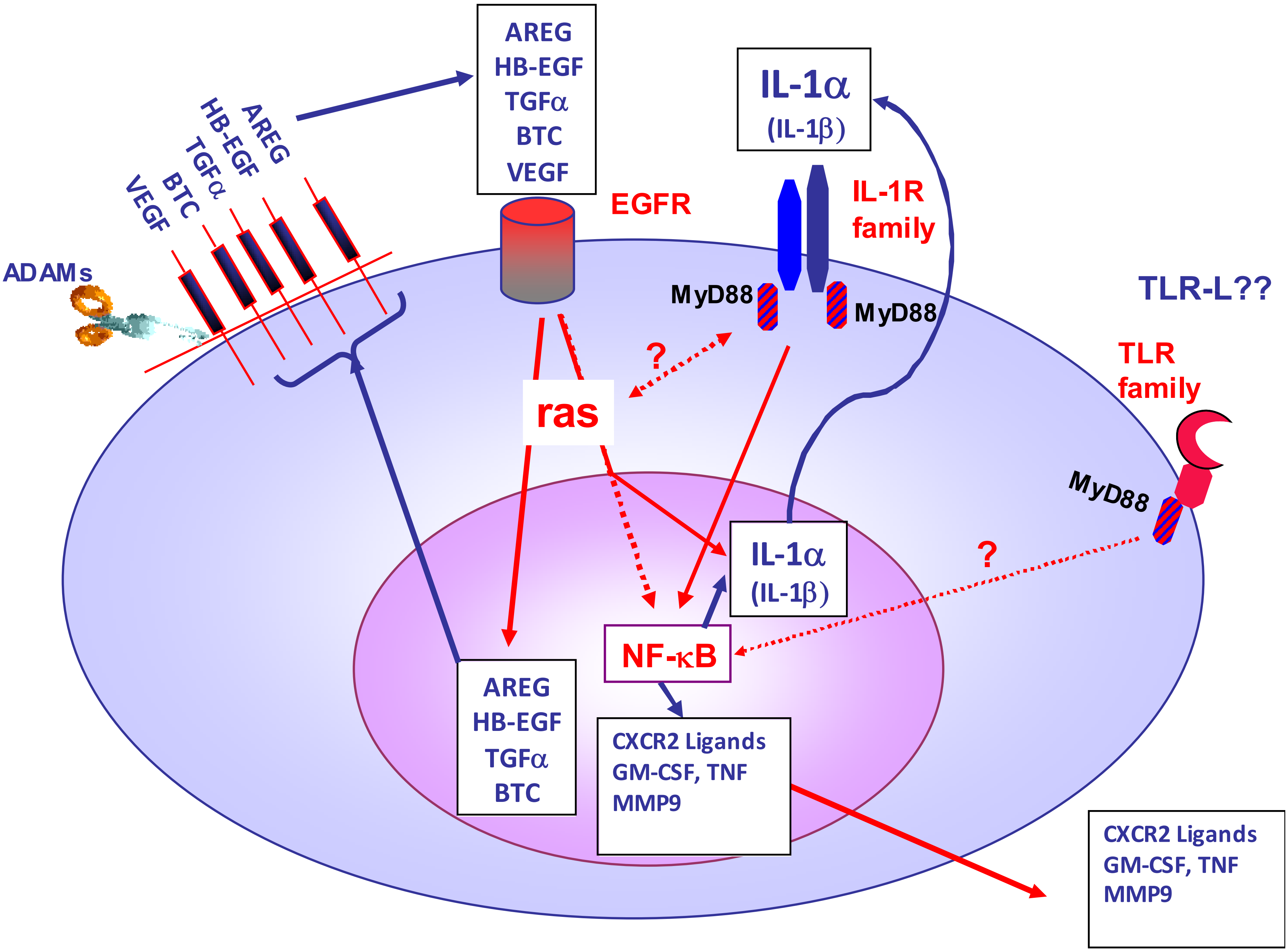
NFκB



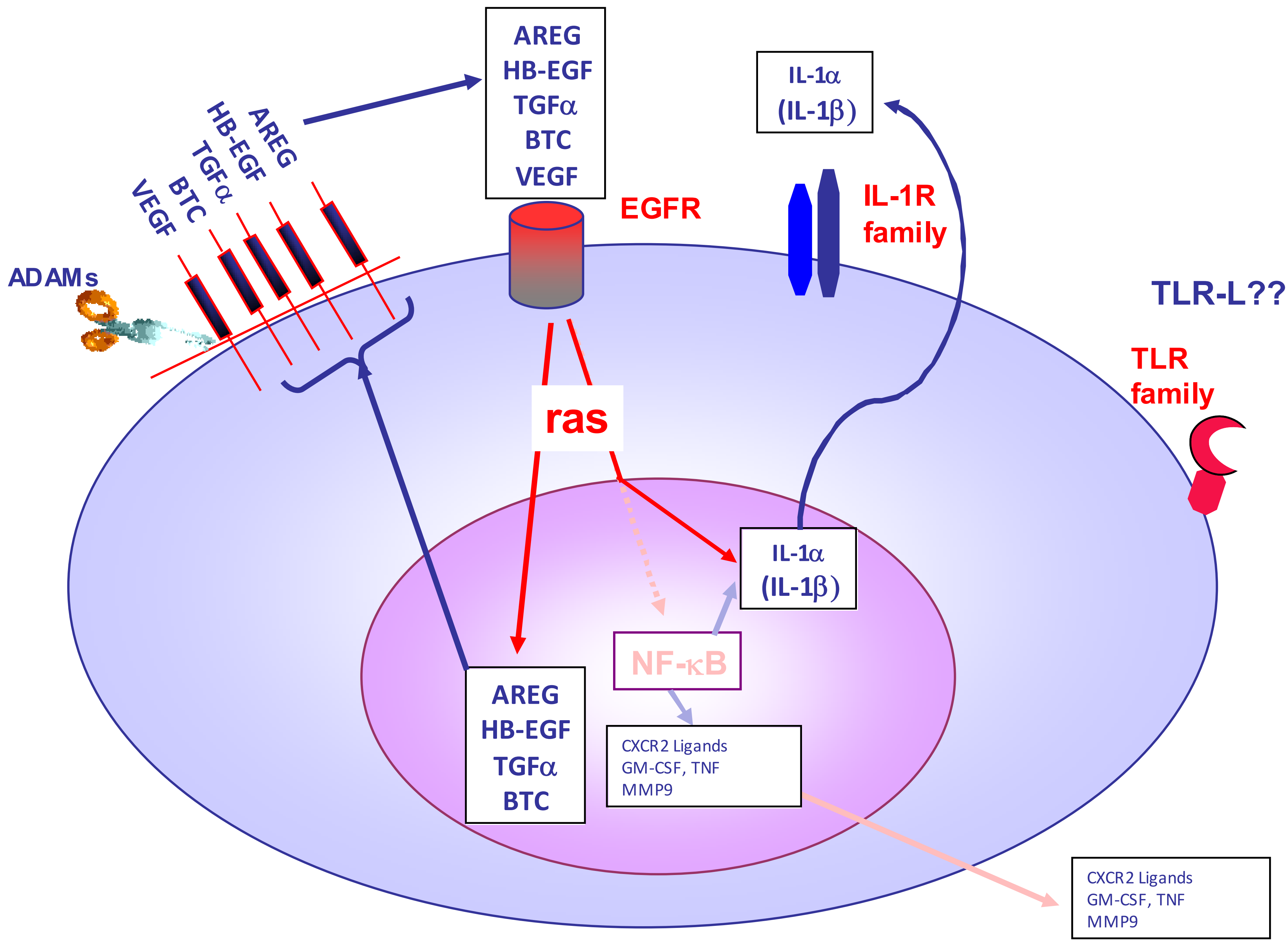
EGFR





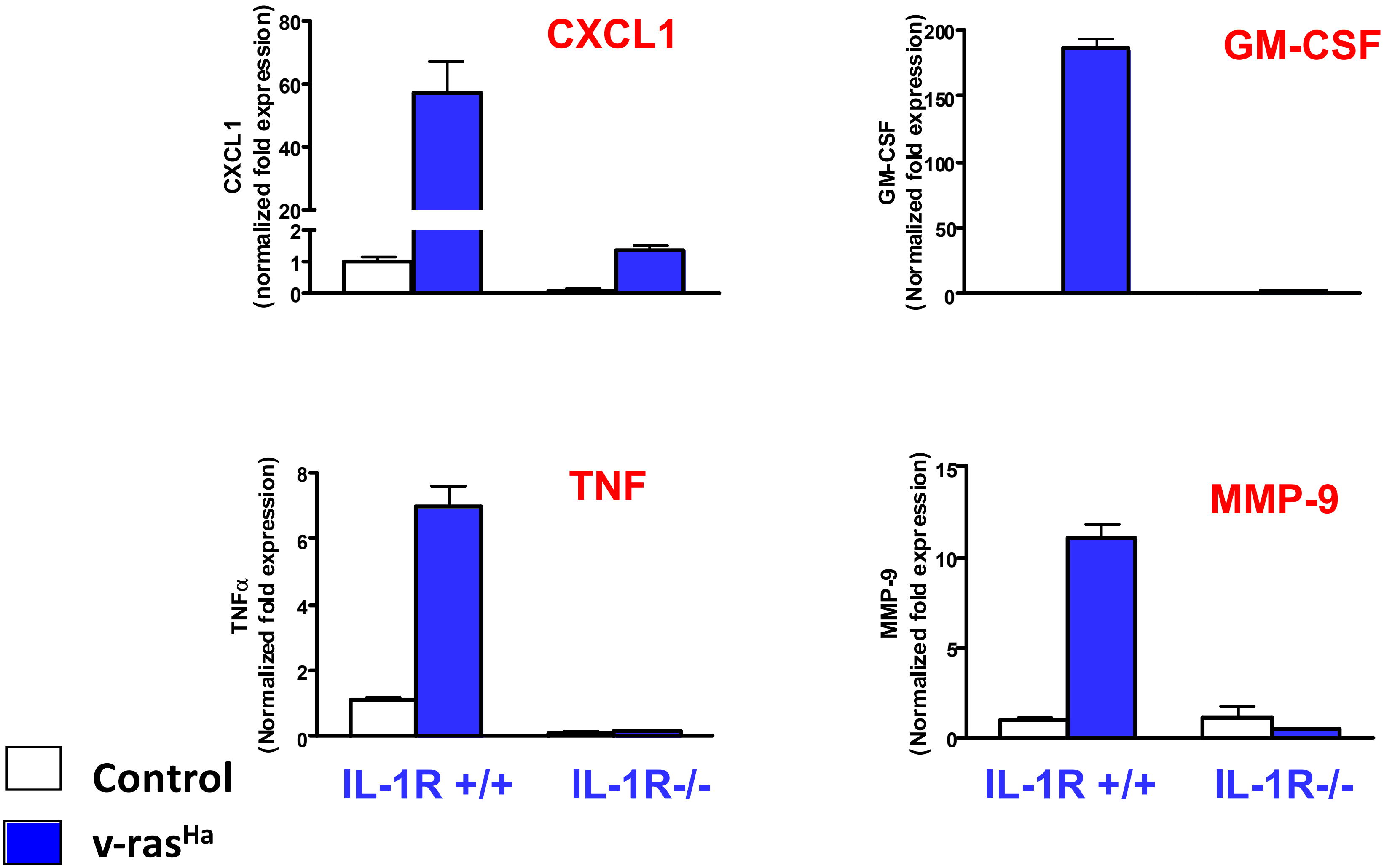


AREG
HB-EGF
TGFα
BTC
VEGF
IL-1α
(IL-1β)
EGFR
IL-1R
family
ADAMs
VEGF
BTC
TGFα
HB-EGF
AREG
MyD88
MyD88
TLR-L??
?
ras
TLR
family
MyD88
IL-1α
(IL-1β)
?
NF-κB
AREG
HB-EGF
TGFα
BTC
CXCR2 Ligands
GM-CSF, TNF
MMP9
CXCR2 Ligands
GM-CSF, TNF
MMP9

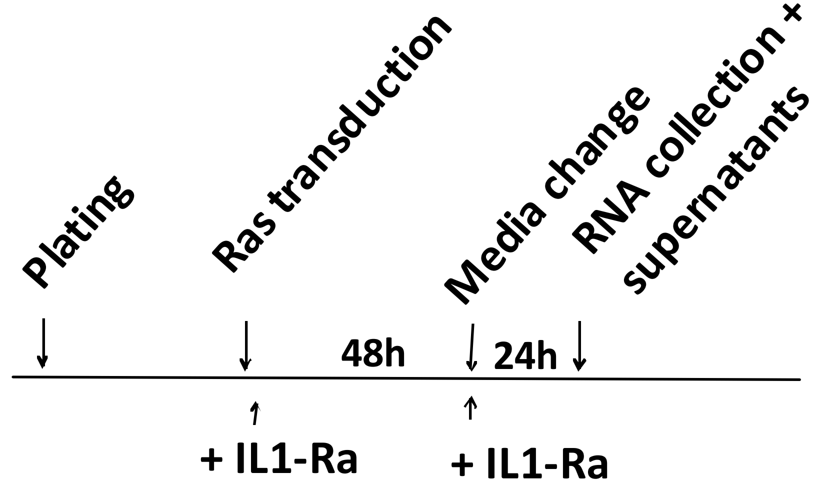


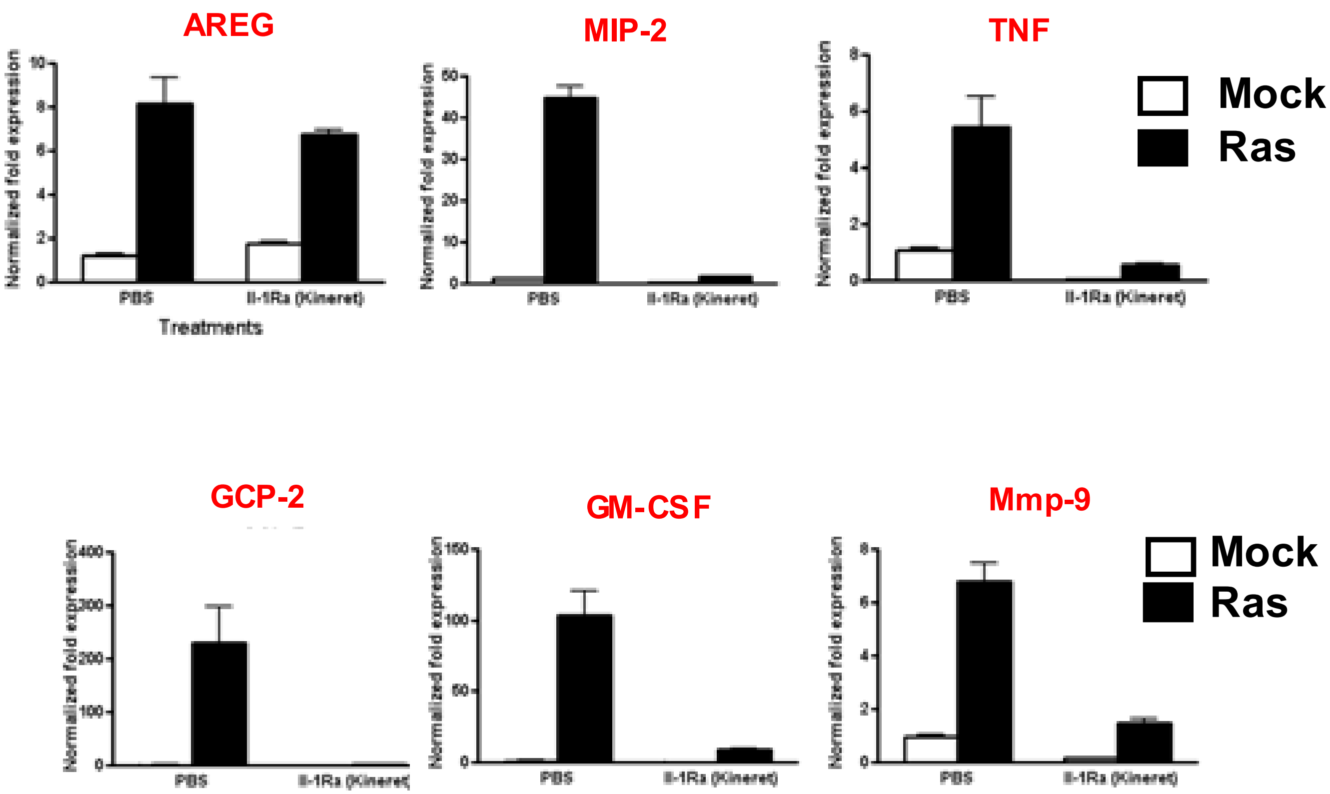
AREG
HB-EGF
TGFα
BTC
VEGF
EGFR
IL-1α
(IL-1β)
IL-1R family
TLR-L??
TLR family
ADAMs
AREG
HB-EGF
TGFα
BTC
VEGF
ras
NF-κB
IL-1α
(IL-1β)
AREG
HB-EGF
TGFα
BTC
CXCR2 Ligands
GM-CSF, TNF
MMP9
CXCR2 Ligands
GM-CSF, TNF
MMP9

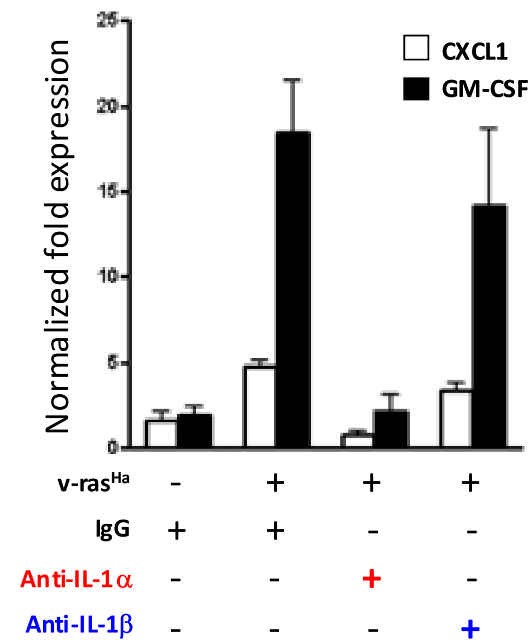
v-ras^{Ha} transformed keratinocytes from IL-1R-/- mice are defective in production of CXCR2 ligands



IL-1RA inhibits the production of pro-inflammatory chemokines and cytokines by v-ras^{Ha} transformed keratinocytes

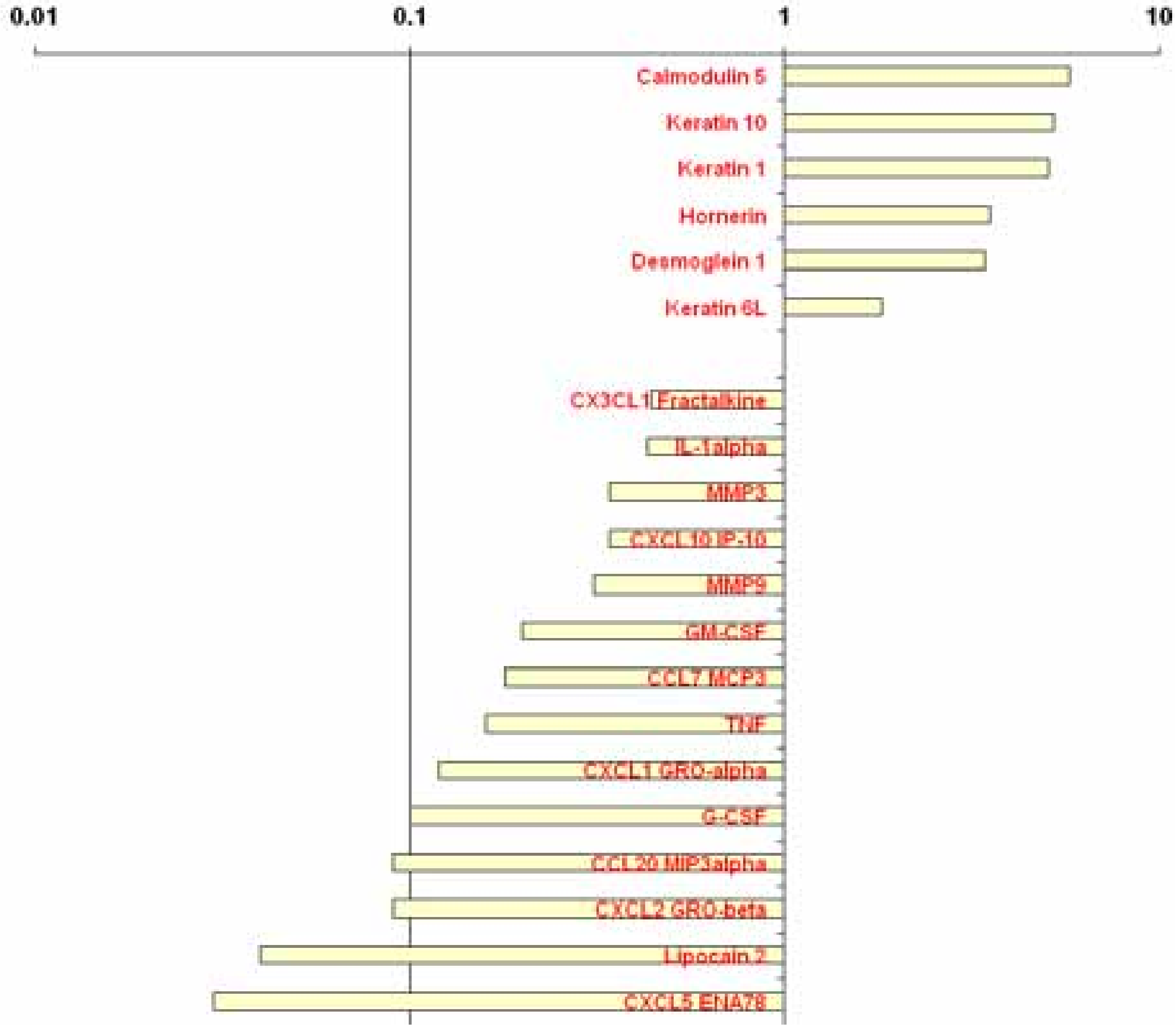




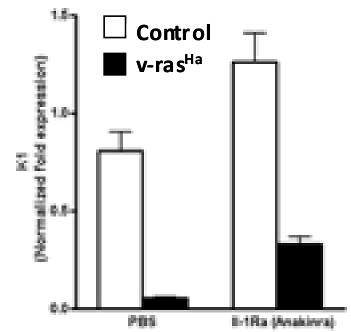


Gene expression (microarray analysis) in v-ras^{ha} transduced mouse keratinocytes treated with IL-1RA

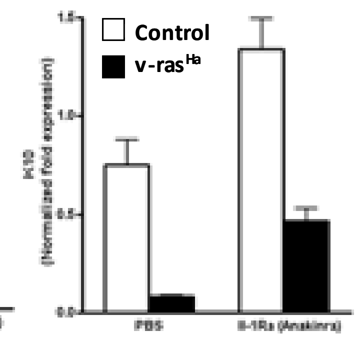
Fold gene expression IL-1RA-treated vs untreated

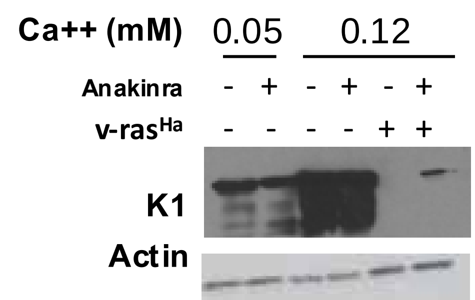


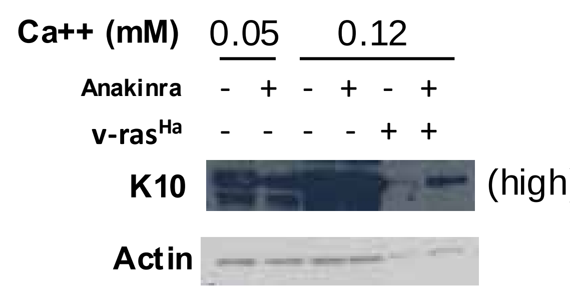
K1



K10

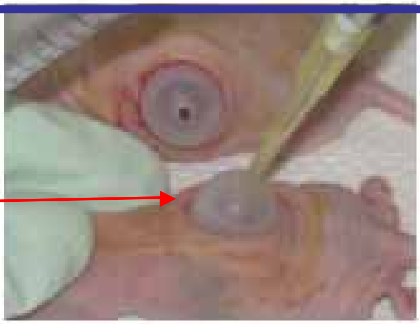


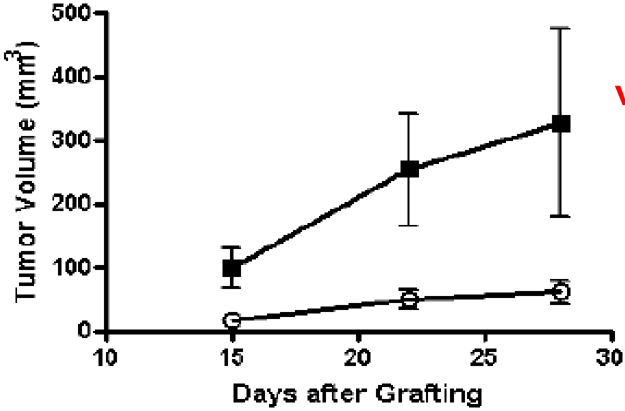




Nude mouse grafting of v-ras^{Ha} transduced keratinocyets

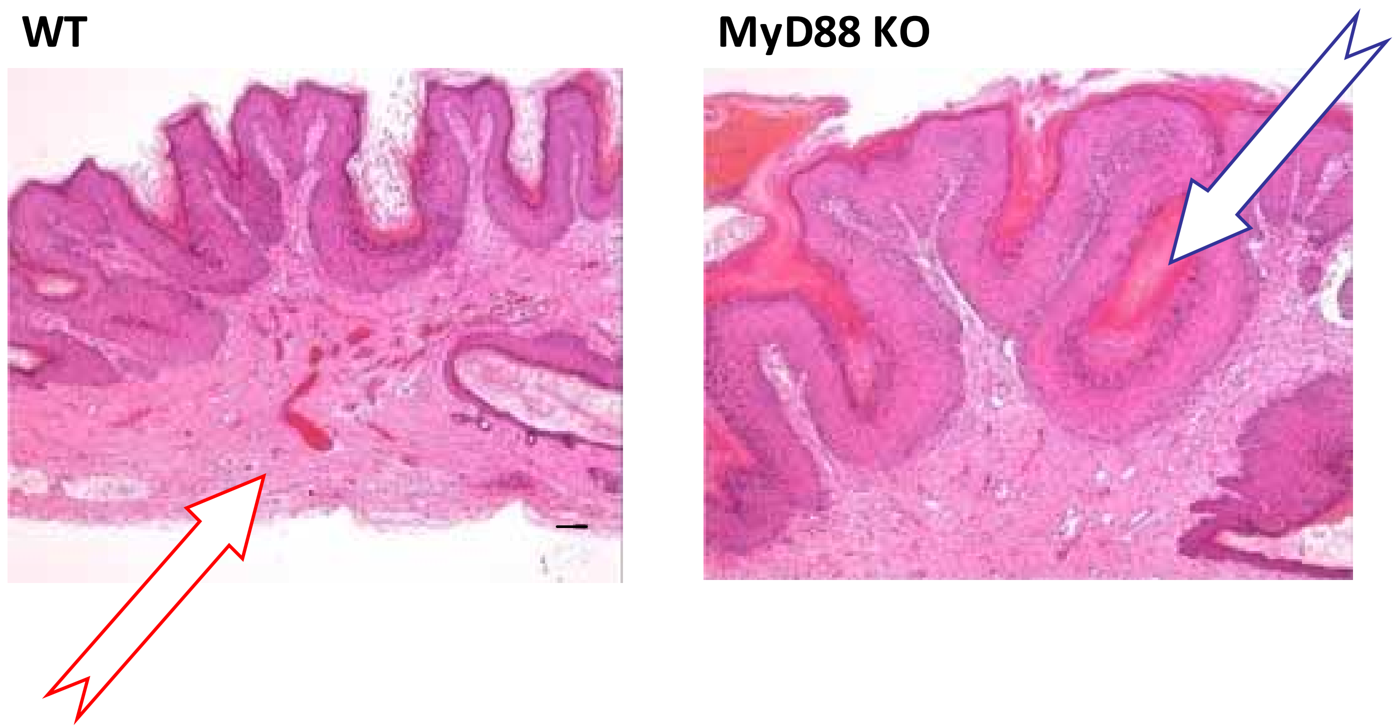
v-ras^{Ha} transduced primary keratinocytes (4 x 10^6)
C57/Bl6
or
MyD88ko
+
primary dermal fibroblasts (SENCAR) (6 x 10^6)

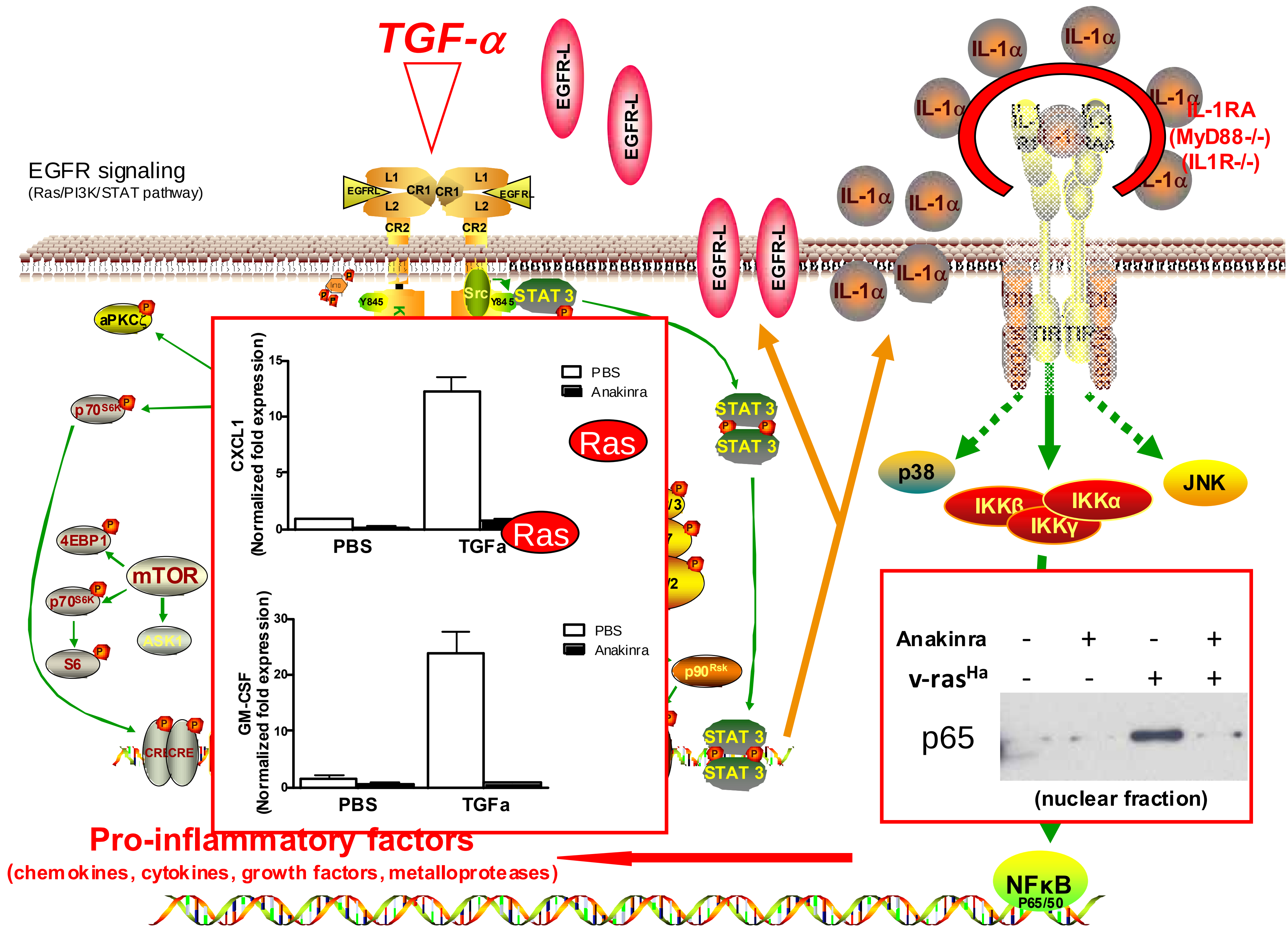


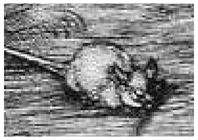


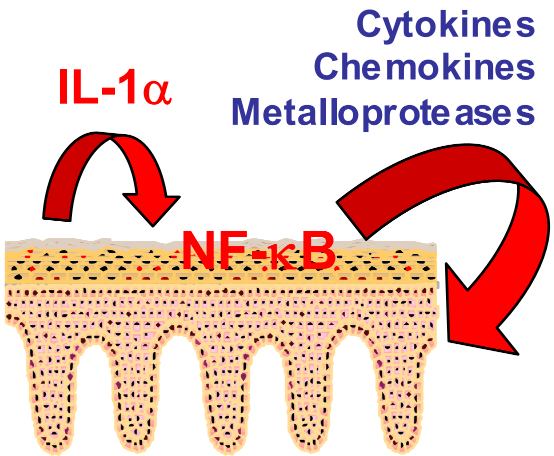
MyD88+/+ MyD88-/-

Nude mouse grafting of v-ras^{Ha} transduced keratinocyets

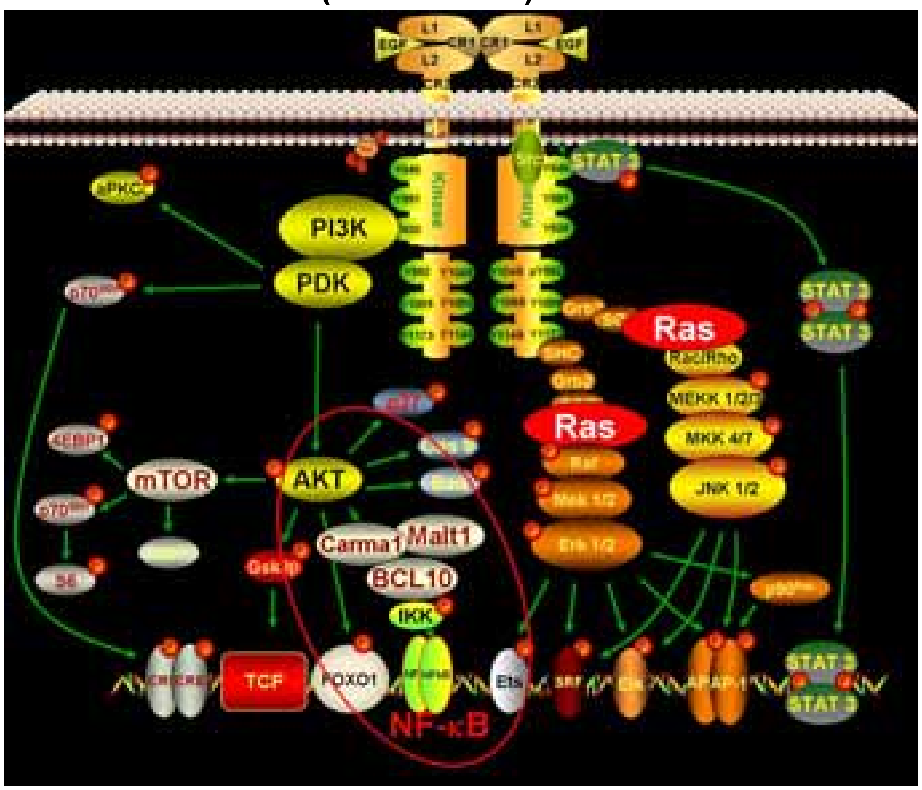


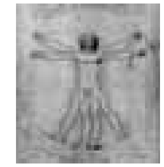

TGF-α
EGFR-L
EGFR signaling
(Ras/PI3K/STAT pathway)
L1
CR1
L2
CR2
EGFRL
Src
STAT 3
Y845
aPKCζ
p70S6K
4EBP1
mTOR
ASK1
S6
CRE
IL-1α
IL-1RA
(MyD88-/-)
(IL1R-/-)
p38
JNK
IKKβ
IKKα
IKKγ
p90Rsk
CXCL1
(Normalized fold expression)
PBS
Anakinra
TGFa
Ras
GM-CSF
v-ras^Ha
p65
(nuclear fraction)
NFκB
P65/50
Pro-inflammatory factors
(chemokines, cytokines, growth factors, metalloproteases)

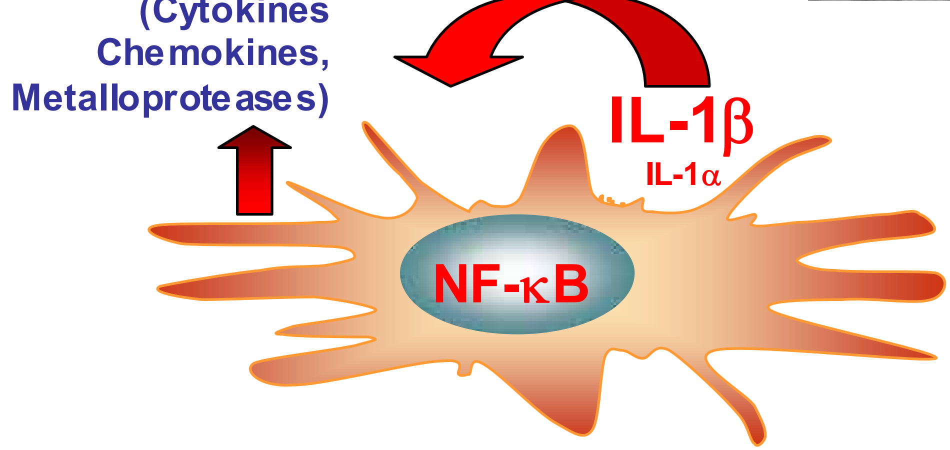


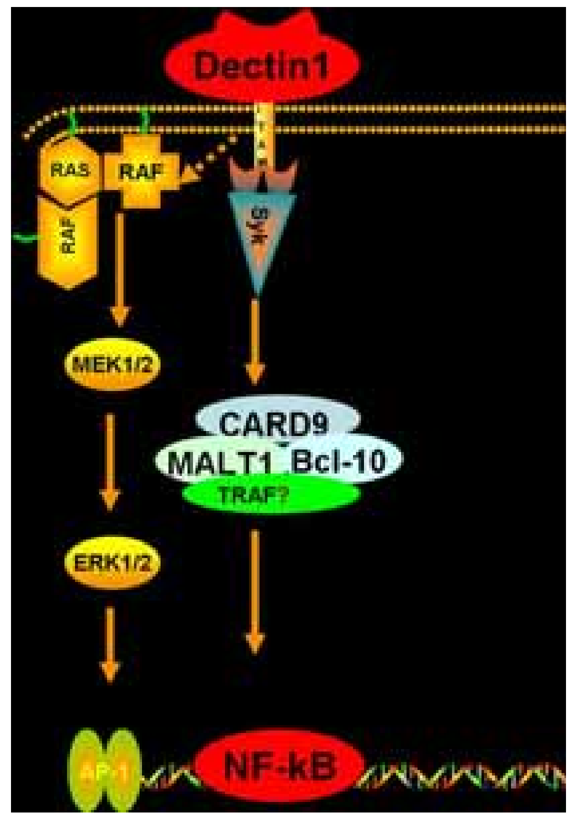


Skin carcinogenesis
(DMBA/TPA)







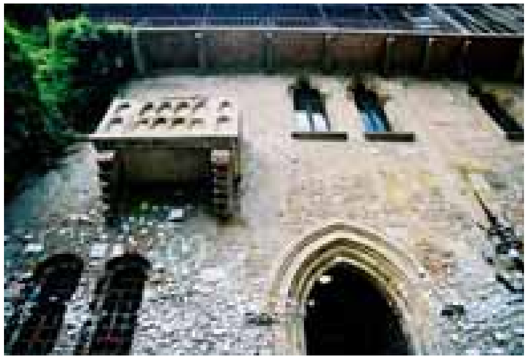


Human
Dendritic
Cells
Activation by
β-Glucan

Uzma Hasan
Vladimir Vlach

Isabelle Coste
Toufic Renno

LIR, Schering-Plough
Research Institute
Dardilly, France



Franca Gerosa
Giuseppe Carra

Verona University
Italy

Rosalba Salcedo
Zsofia Gyulai
Yava Jones
Marco Cardone
Lyudmila Lyakh

Robin Winkler Pickett
Loretta Smith
Ren Meng Dai
Anna T Mason

Cancer and Inflammation
Program,
CCR, NCI, Frederick, MD

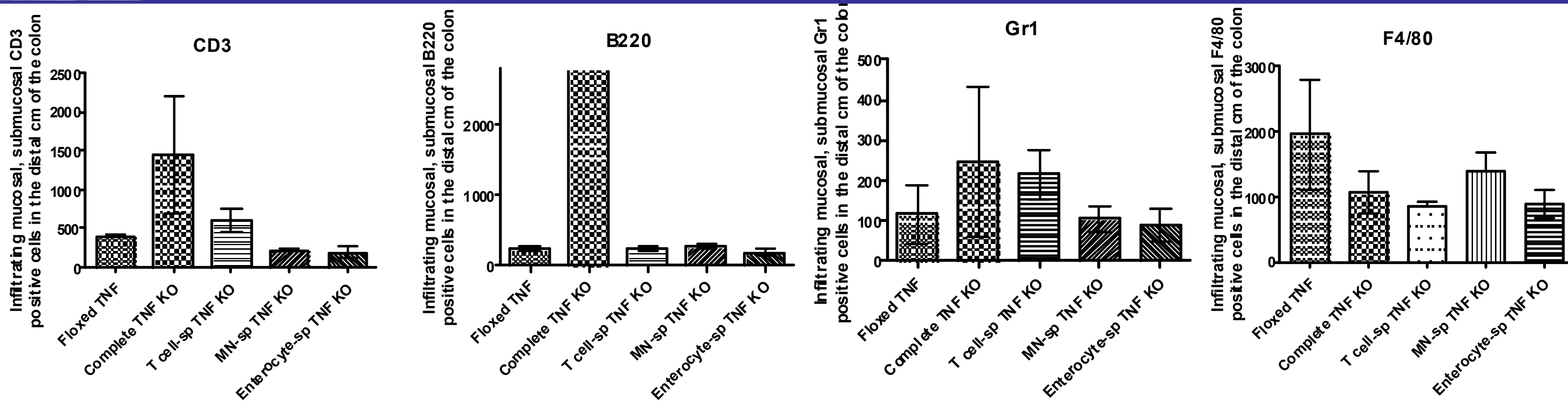
Christophe Cataisson
Stuart Yuspa

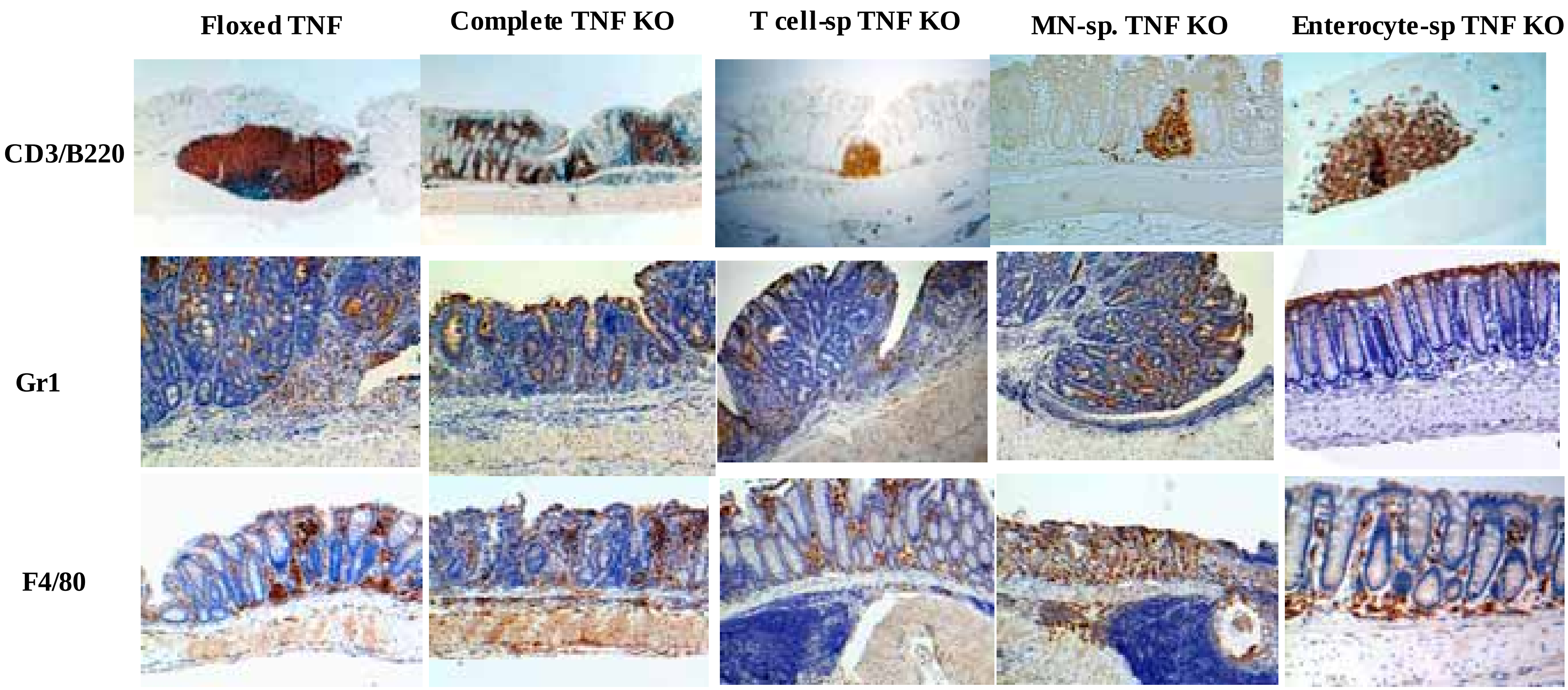
Franco Marincola
Ena Wang

NIH, Bethesda, MD

[redacted]

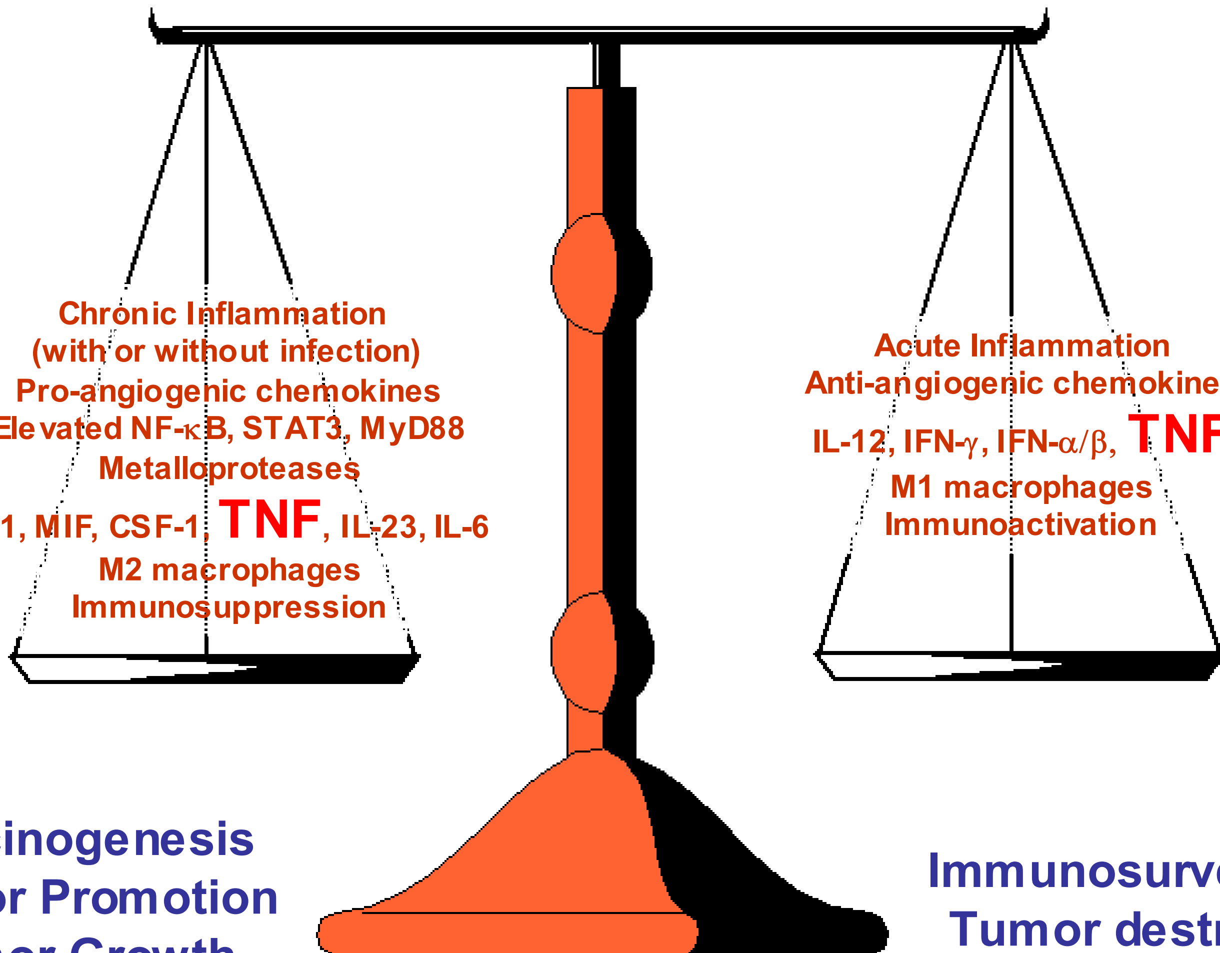
TNF -/- mice have more lymphocytic infiltration and more pronounced inflammation following 4 cycles of DSS





Cancer and Inflammation

Tumor Necrosis Factor can be an anti-tumor or a tumor promoting factor depending on the producer cell type and likely the location and time of production



Carcinogenesis
Tumor Promotion
Tumor Growth
and Dissemination

Immunosurveillance
Tumor destruction
Anti-tumor immunity

Targeting inflammation for preventing cancer initiation and progression

William B. Coley (1862-1936)

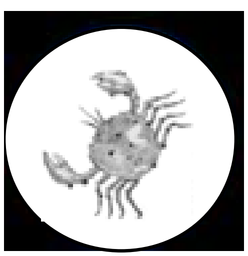
Coley's mixed toxins (mixed bacterial vaccine, MBV):

Heat-killed
Streptococcus pyogenes
and
Bacillus prodigiosus
(Serratia marcescens)

W. B. Coley: "The treatment of malignant tumors by repeated inoculation of erysipelas: With a report of ten original cases". A. J. Med. Sci. 105:487, 1893

W. B. Coley: "The therapeutical value of the mixed toxins of streptococcus of erysipelas and Bacillus prodigiosus in the treatment of inoperable malignant tumors, with a report of 160 cases". A. J. Med. Sci. 112:251, 1896

Infection



Cancer

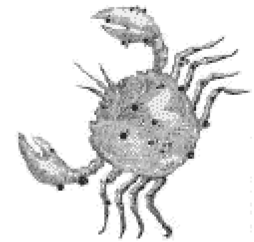
Innate (Natural) Resistance (Inflammation) ⇔ **Adaptive Immunity**

Natural resistance to tumors
Non-specific inflammatory anti-tumor effects ⇔ Tumor-specific Immunity
Immuno-surveillance

Pro-inflammatory cancer therapy
(Coley Toxin, BCG, TLR ligands)

Antigen-specific immunotherapy

Claudius Galenus of Pergamon
ca 130- ca 200

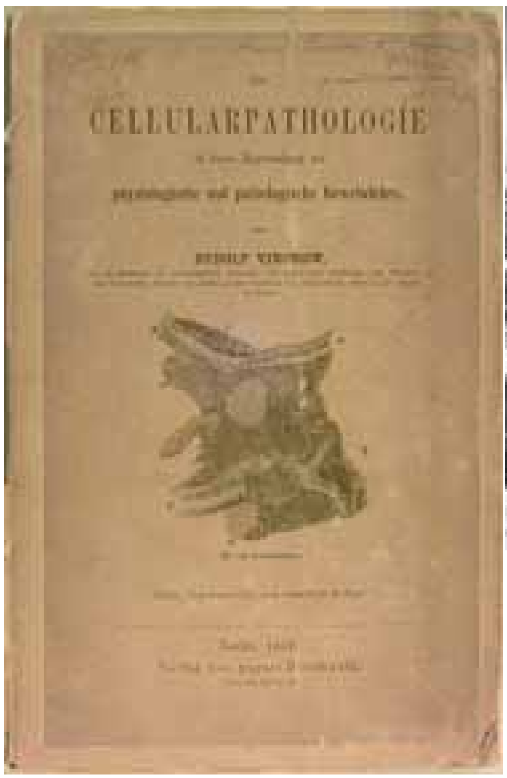


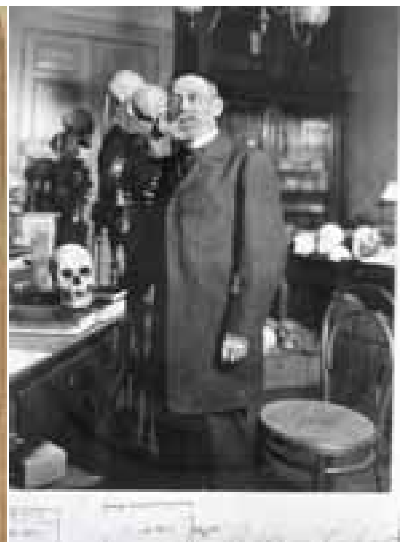
The term cancer was originally applied by Galenus to certain tumors of the breast in which superficial veins appeared much swollen and radiated somewhat like the claws of a crab Later the name was extended to include all malignant and infiltrating growths.

Although the role of inflammation in favoring carcinogenesis has generated much interest in the last 10-15 years, the Greek physician Claudius Galenus already observed almost 2 thousand years ago some similarity among cancer and inflammation.

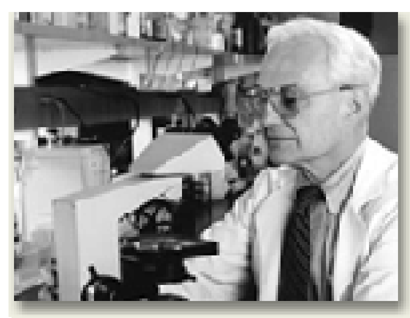
In 1863 Rudolf Virchow noted leucocytes in neoplastic tissues and made a connection between inflammation and cancer. He suggested that the"lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation.

The recent upsurge of studies linking cancer and inflammation were inspired by the observation made two decades ago by Harold Dvorak, M.D., of Harvard University, who observed that inflammation and cancer share some basic developmental mechanisms (angiogenesis) and cells (lymphocytes, macrophages, and mast cells), and that tumors act like "wounds that do not heal."



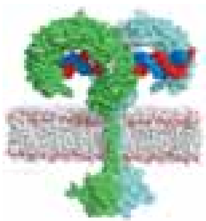


Rudolph Virchow
1821-1902



Dr. Harold Dvorak

Harvard University



Role of Toll-like receptors (TLRs) in cancer

•Toll-like receptors were originally studied prevalently in hematopoietic cells (primarily dendritic cells, phagocytes, and B lymphocytes) but at least some members of this receptor family are widely expressed on other cell types including tumor cells.

•Although they have been described to recognize products of foreign organisms (pathogenic or not) they also participate in the regulation of inflammation by recognizing endogenous ligands (“alarmins”) that are present in inflamed tissues.

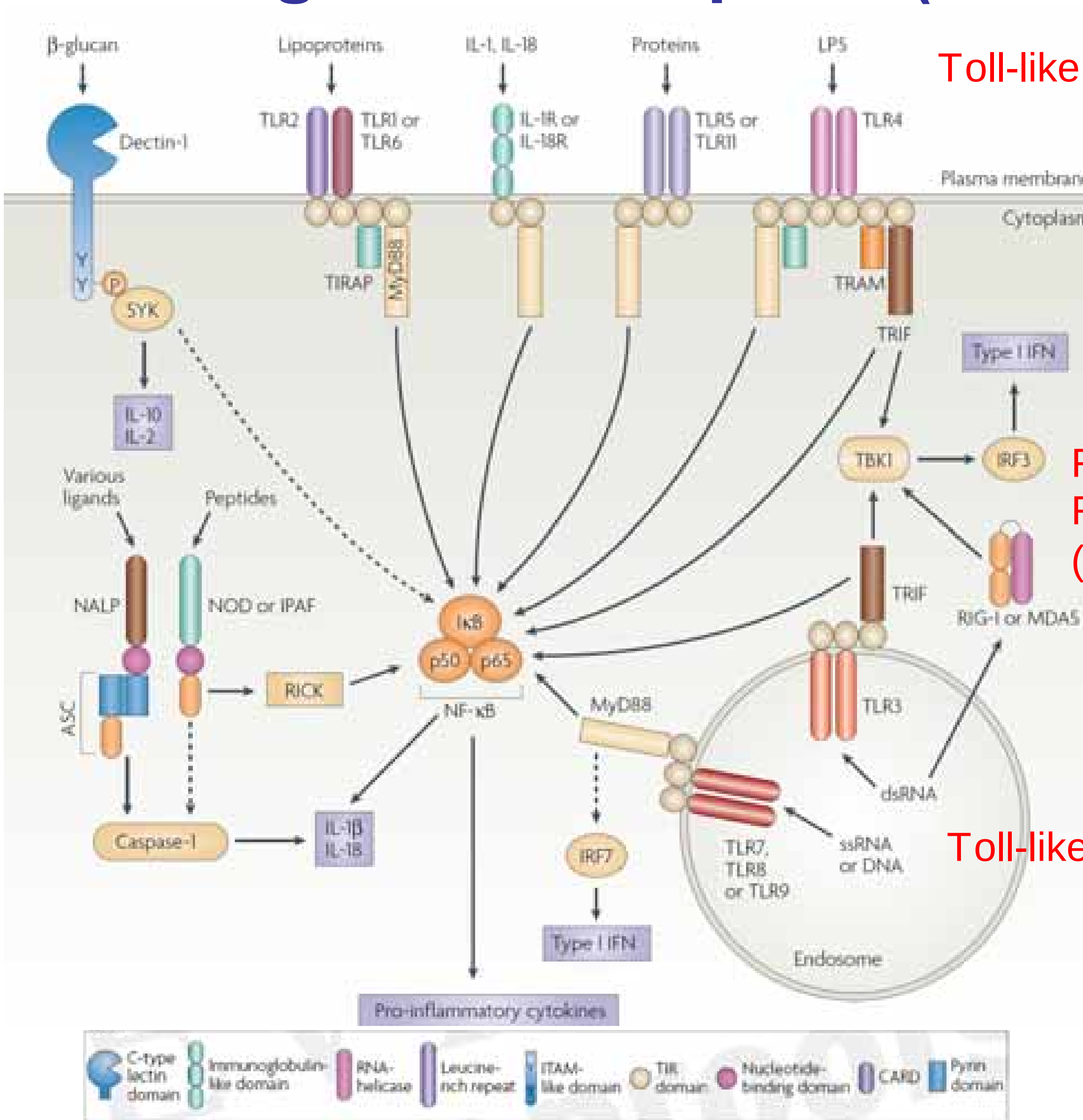
•The cellular response to TLR ligands is not only production of pro-inflammatory mediators but they are also involved in control of tissue homeostasis and regulate cellular differentiation, proliferation, and apoptosis. The balance between MyD88 and TRIF signaling and the production of type I IFN determine proliferation versus apoptosis in tissue and tumor cells and activation versus survival in dendritic cells.

•Epidemiologic/genetic evidence indicates a role of TLRs and signaling molecules (TLR1,2,6,10,3,4, MyD88, IRAK4) in the frequency and progression of human cancer.

Pattern Recognition Receptors (PRR)

C-type lectins, Scavenger r.

Toll-like receptors



RIG-I-like Receptors (helicases)

NOD-like Receptors:

NALPs NODs

Toll-like receptors

Role of MyD88 in inflammation-dependent carcinogenesis: A tale of three Interleukins-1