Introduction à la biologie des parasites
Immunité anti-parasitaire

(1ère partie)

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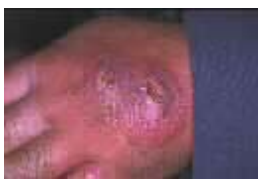
IF2004 IP-d,e,e'
5, 6 et 8 avril 2004

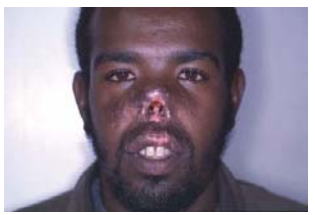
The murine model of infection with *L. major*

Leishmaniose cutanée

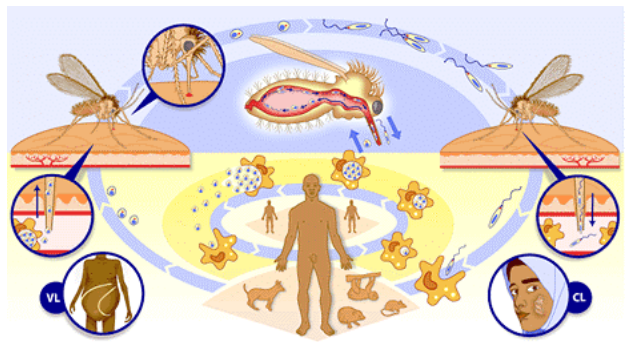


Leishmaniose viscerale

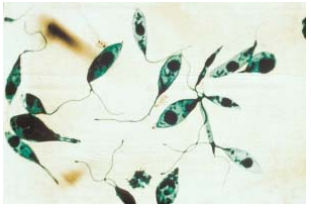
Leishmaniose mucco-cutanée

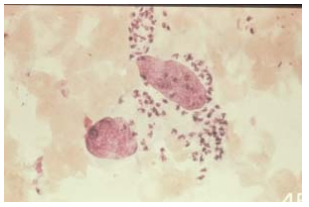


The life cycle of *Leishmania*

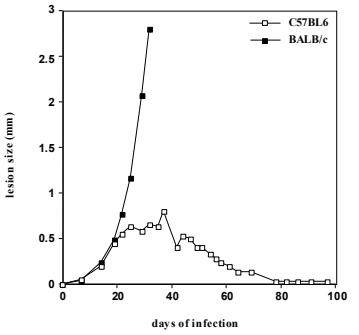


Promastigotes **Amastigotes**

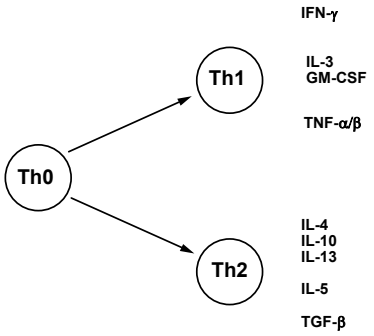




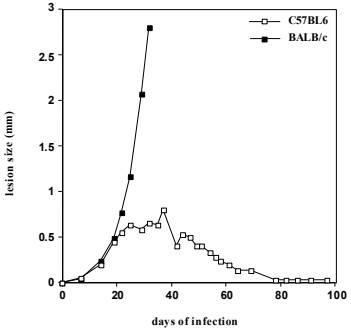
The murine model of infection with *L. major*



Th1/Th2 differentiation



The murine model of infection with *L. major* demonstrates the development of Th1/Th2 in vivo



Susceptibility = Th2

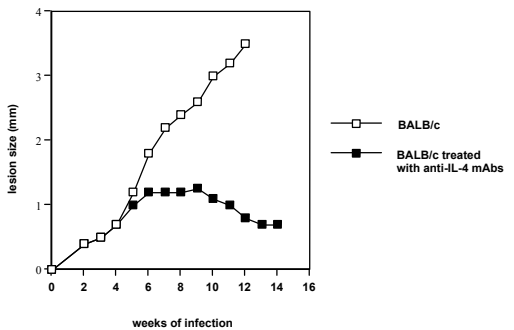
Resistance = Th1

Factors influencing the development of Th1 or Th2 CD4$^+$ T cells from precursors

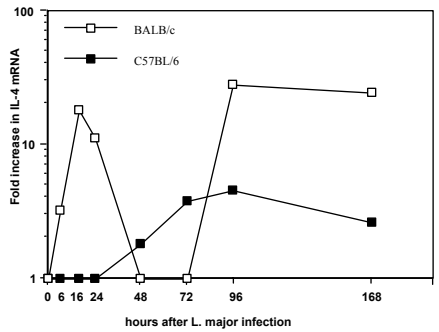
-the type of APCs (Moser and Murphy, Nat Immunol., 2000)
-the nature of co-stimulatory signals (Kuchroo *et al*, Cell, 1995)
-the extend of TCR engagement (Pfeiffer *et al*, J. Exp. Med., 1995)
-the dose of antigen (Hosken *et al*, J. Exp. Med., 1995)
-the route of administration (Guery *et al*, J. Immunol., 1997)
-the number of cell cycles (Bird *et al*, Immunity,1998)
-the TCR affinity (Malherbe *et al*, Immunity, 2000)
- the cytokines themselves

The role of cytokines in the development of polarised TH2 responses

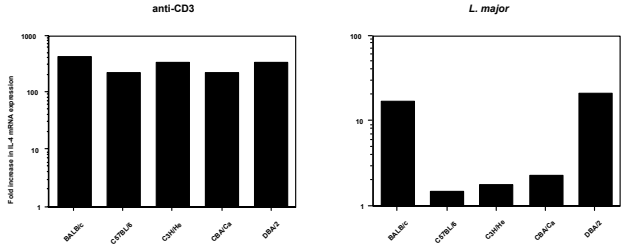
IL-4 is necessary for Th2 maturation during infection with *L. major*



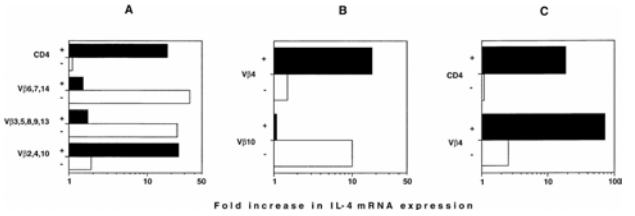
***L. major* rapidly induces increased IL-4 mRNA expression inLN from BALB/c mice**



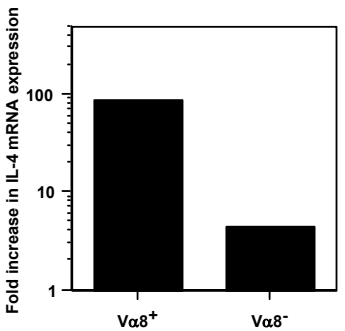
L. major induced early IL-4 mRNA expression only in genetically susceptible mice



Early IL-4 mRNA expression after _L. major_ infection is produced by Vβ4⁺ CD4⁺ T cells



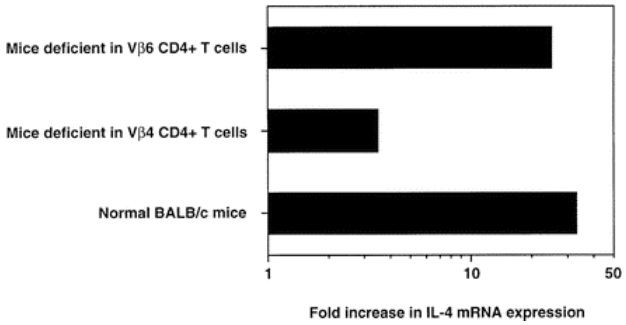
Vα8⁺ CD4⁺ T cells produced early IL-4 mRNA expression after infection with _L. major_



What is the role of the Vβ4 Vα8 CD4⁺ T cells in Th2 differentiation?

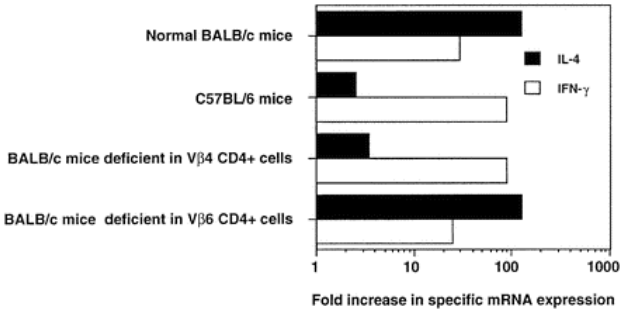
- **MMTV encodes a superantigen that leads**
  - **initially to local stimulation**
  - **subsequently to systemic deletion of CD4⁺ T cells expressing a specific Vβ TCR**
- **MMTV(SIM) = Vβ4⁺ CD4⁺ (Maillard _et al_, 1996)**
- **MMTV (SW) = Vβ6⁺ CD4⁺ (Held _et al_, 1992)**

Early IL-4 mRNA expression in response to *L. major* does not occur in mice rendered deficient in Vβ4⁺ CD4⁺ T cells by exposure to MMTV(SIM)

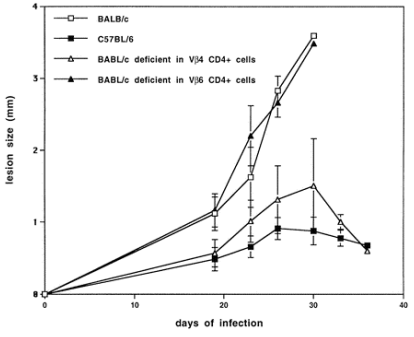


BALB/c rendered deficient in Vβ4⁺ CD4⁺ T cells by exposure to MMTV (SIM) develop Th1 cell differentiation

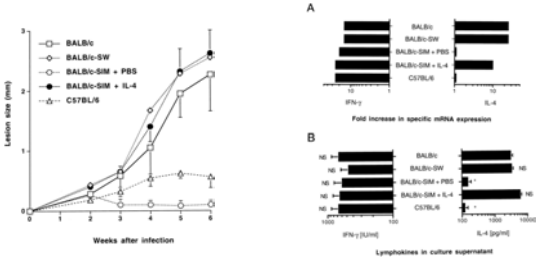
in response to infection with *L. major*



BALB/c mice deficient in Vβ4⁺ CD4⁺ T cells are resistant to infection with *L. major*



Teatment with IL-4 during the first 64 h renders BALB/c mice deficient in Vβ4⁺ CD4⁺ T cells susceptible to infection with *L. major*



Which specifities for the Vβ4 Vα8 CD4$^+$ T cells ?

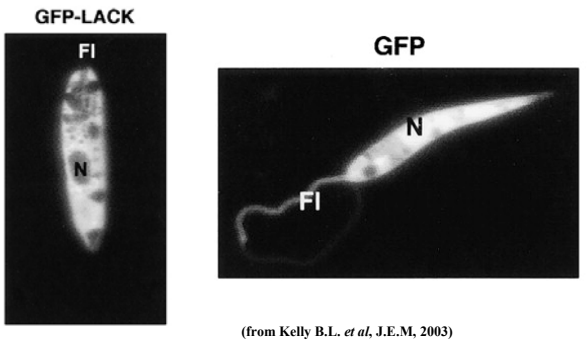
- **Expansion of CD4$^+$ T cells expressing the Vβ4 Vα8 TCR in BALB/c infected with *L. major* (Reiner *et al*, Science, 1993)**
- **These cells recognize LACK (Leishmania Activated C Kinase) (Mougneau *et al*, Science, 1995)**
- **Hybridoma from mice immunized with LACK recognised a single dominant epitope (AA156-173) (R.M. Locksley, personnal communication)**

LACK (Leishmania Activated C Kinase) from *L. major*

- **Homologue to mammalian RACK1 (Receptors for Activated C Kinases)**
- **WD repeat family**
  - **evolutionary conserved**
  - **functions in signal transduction, RNA processing, cell cycle control**
- **Kinetoplastids:**
  - **Trypanosomes : TRACK**
    - **upregulation in parasites undergoing apoptosis and in terminally differentiated bloodstream forms**
  - ***L. infantum***
    - **interactions with proteins involved in DNA replication and RNA synthesis**
  - ***L. major***
    - **tandem duplicate family (2 genes)**
    - ***lack*-null parasites : non viable**
    - **Parasite with one lack gene =attenuation**

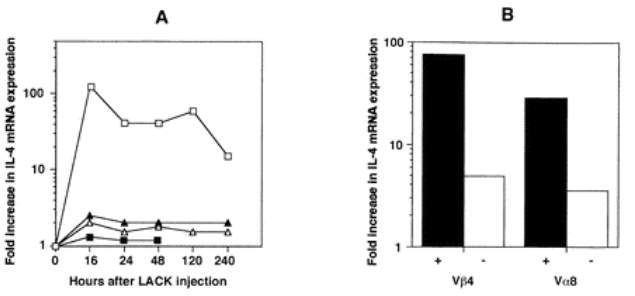
    ⇒ Necessary to parasitation

Localisation of LACK in the parasite



(from Kelly B.L. *et al*, J.E.M, 2003)

LACK from *L. major* induces IL-4 mRNA expression in Vβ4$^+$ Vα8$^+$ CD4$^+$ T cells



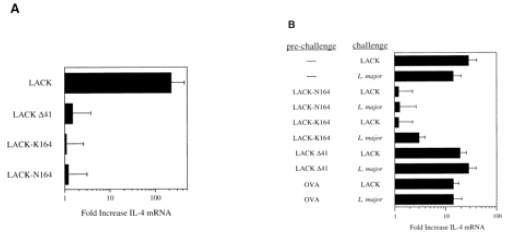
Construction of analogue peptides of the LACK antigenic determinant

- **A single I-Ad restricted epitope localised to AA 156-173**
- **LACK specific hybridoma : CDR3 Vβ negatively charged QE or QD**
- **LACK specific CD4+ T cells in BALB/C : QE motif in Vβ4**
  - ⇒ **Positively charged AA on LACK = critical TCR contact residue=H**
  - ⇒ **Mutated peptides on the Hist position 164**

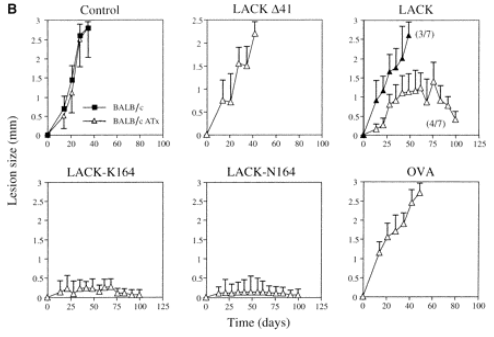
Affinity of LACK Analogue Peptides for I-Ad MHC Class II Molecules

Peptide	Amino acid sequence	I-Ad
		nM
LACK156-173	ICFSPSLEHPIVVSGSWD	63
LACK-K164	ICFSPSLEKPIVVSGSWD	68
LACK-N164	ICFSPSLENPIVVSGSWD	100
OVA323-336	ISQAVHAAHAEINE	150

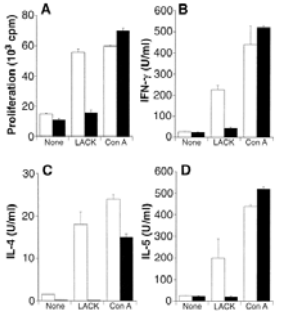
LACK analogue proteins fail to activate IL-4 mRNA in vivo



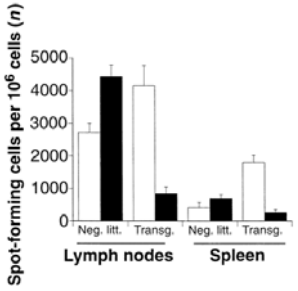
Course of infection in BALB/c mice immunized with altered peptide ligands (APL)



The transgenic expression of LACK in the thymus under MCH class II promoters renders these mice tolerant



Julia *et al.* 1996



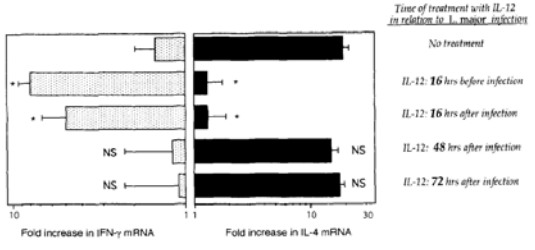
- **IE-LACK mice develop a Th1 response after infection with *L. major* (Julia *et al* 1996)**

Conclusion (1)

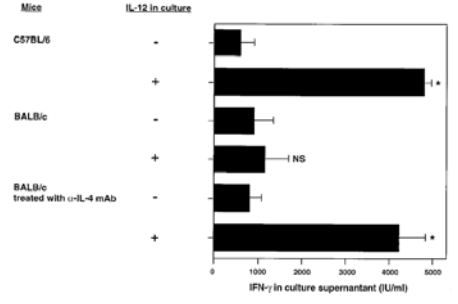
- **Production of IL-4 early after infection is necessary to instruct Th2 cell differentiation in BALB/c mice**
- **The early IL-4 mRNA expression after infection with *L. major* occurs in $CD4^+$ T cells that express the Vβ4 Vα8 TCR receptors**
- **BALB/c rendered deficient in Vβ4 $CD4^+$ T cells by exposure to MMTV SIM are resistant to infection**
- **LACK from *L. major* = same response**

⇒ **IL-4 required for Th2 development and susceptibility to *L. major* infection is produced by a restricted population of Vβ4 Vα8 $CD4^+$ T cells after cognate interaction with a single antigen from the parasite (LACK)**

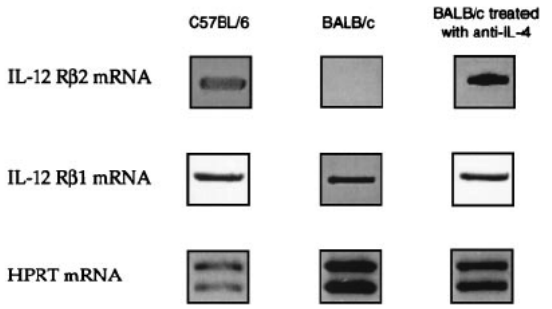
Loss of IL-12 responsiveness 48 hours after infection with *L. major*



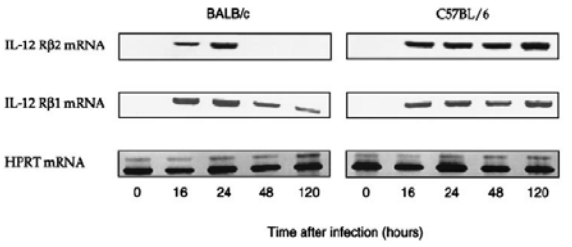
The IL-4 produced early during infection with *L. major* renders $CD4^+$ T cells unresponsive to IL-12



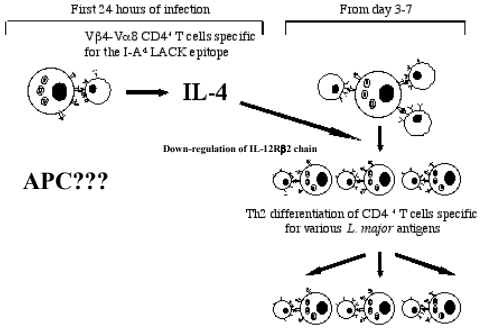
IL-4 renders CD4⁺ T cells unresponsive to IL-12 by down-regulating the IL-12Rβ2 chain mRNA expression



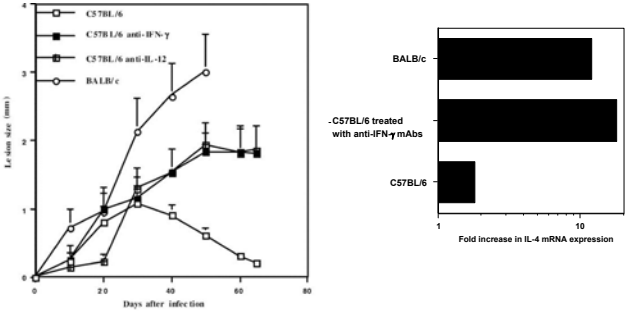
Kinetics of IL-12R mRNA expression following infection with *L. major*



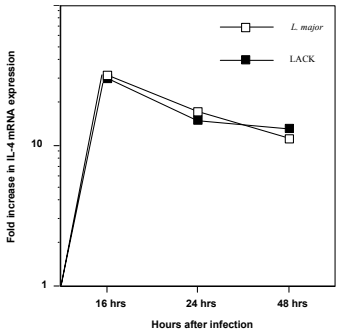
Proposed model



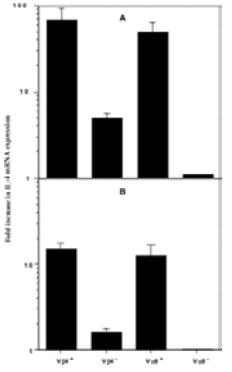
***L. major* induces early IL-4 mRNA expression in resistant mice rendered susceptible by neutralization of either IL-12 or IFN-γ**



Kinetics of IL-4 mRNA expression in draining lymph nodes of C57BL/6 mice treated with α-IFN-γ



The CD4$^+$ T cells from anti-IFN-γ treated mice that express an early IL-4 mRNA in response to *L. major* or LACK are Vβ4$^+$ Vα8$^+$

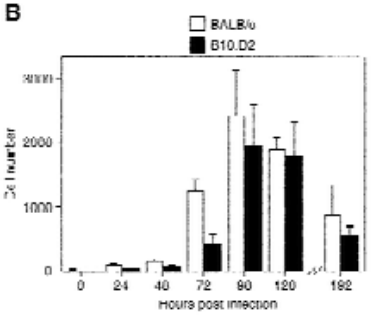


Conclusions (1)

- **Role of the Vβ4 Vα8 CD4$^+$ T cells is to provide IL-4 necessary for Th2 maturation**
- **A single antigen (LACK) drives the early IL-4 response that induce Th2 differentiation and susceptibility to infection**

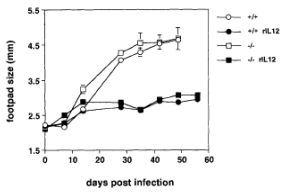
BUT …..

Comparable precursor frequency of IL-4 expressing Vβ4 Vα8 CD4$^+$ T cells in susceptible (BALB/c) and resistant (B10.D2) mice

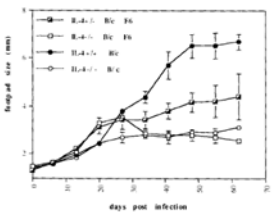


Stetson *et al*, 2002

Conflicting results obtained using IL-4 deficient mice



Kropf *et al*, 1997



Kopf *et al*, 1996

Assessment of the other th2 cytokines?

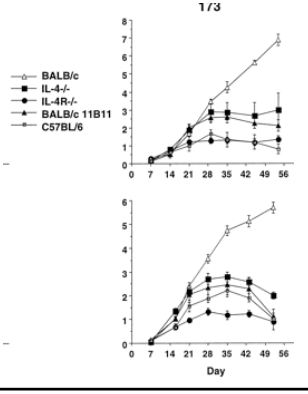
- **IL-13**
- **IL-10**
- **TGF-β**
- **IL-2**

IL-4/IL-13 receptors

- **IL-4 receptors**
  - **Type I = IL-4Rα + γ chain in hematopoeitic cells**
  - **Type II = IL-4Rα + IL-13 Rα1**
- **IL-13 receptors**
  - **Type II identical to IL-4R type I**
  - **IL-13 Rα2 = no signal = decoy receptor?**

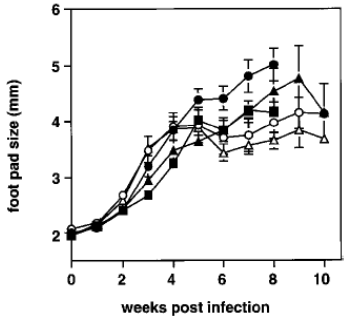
⇒ Previous results suggested the potential role of IL-13 in the susceptibility to infection with *L. major*

Infection of IL-4$^{-/-}$ and IL-4R$^{-/-}$ BALB/c mice with *L. major* NIH173



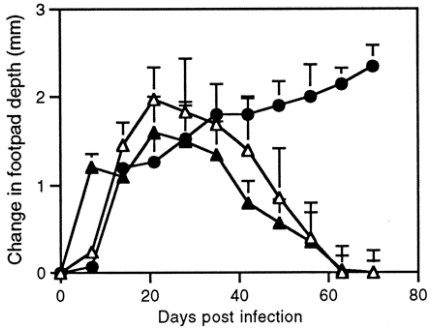
Noben Trauth *et al*, 1999

Treatment of IL-4$^{-/-}$ BALB/C mice with sIL-13Rα2Fc did not change the course of disease after L. major *infection*



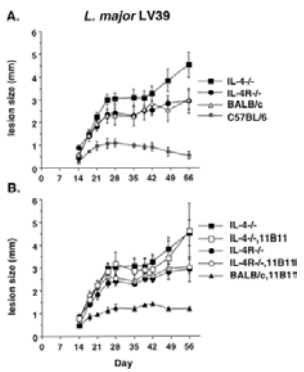
are shown. ■, IL-4$^{+/+}$ BALB/c; ●, IL-4$^{+/+}$ BALB/c + control Ab; ▲, IL-4$^{+/+}$ BALB/c + sIL-13Rα2-Fc; ○, IL-4$^{-/-}$ BALB/c + control Ab; △, IL-4$^{-/-}$ BALB/c + sIL-13Rα2-Fc. **(Kropf *et al*, 1999)**

IL-4 $^{-/-}$ C57BL/6 mice with Tg expression of IL-13 are susceptible

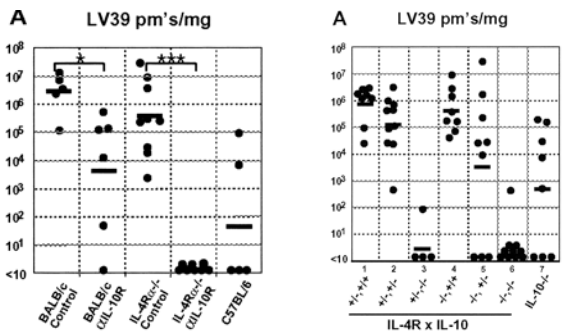


Mattews *et al*, 2000

IL-4$^{-/-}$ BALB/c mice remained susceptible to infection with *L. major* strain LV39

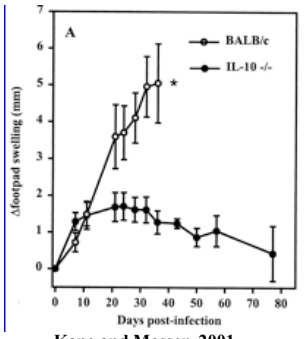


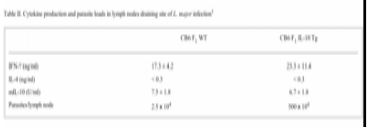
IL-10 could play a role in susceptibility to infection with *L. major*



Noben Trauth *et al*, 2003

Role of IL-10 in promoting disease

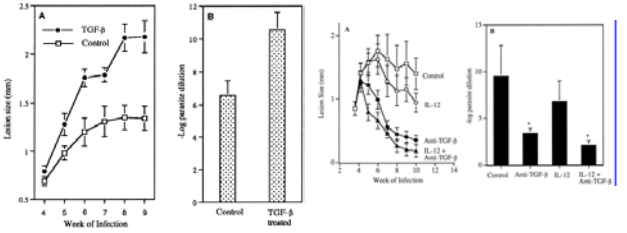




Groux *et al*, 1999

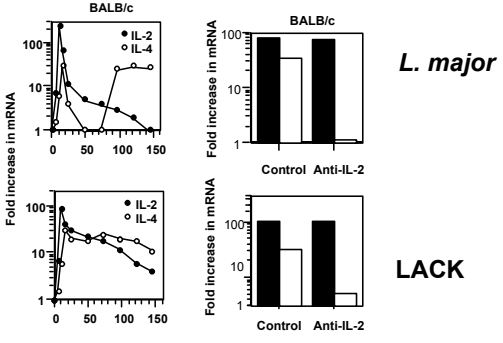
Kane and Mosser, 2001

Administration of TGF-β to resistant mice resulted in progressive disease and neutralisation of TGF-β inhibited progression of lesions

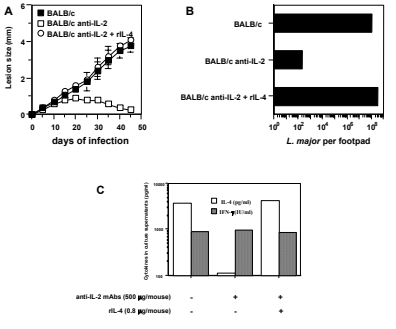


Li *et al*, 1999

IL-2 is produced early after infection in susceptible mice

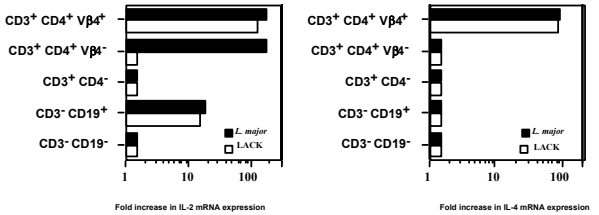


Neutralisation of IL-2 at the onset of infection render susceptible BALB/c mice susceptible to infection with *L. major*



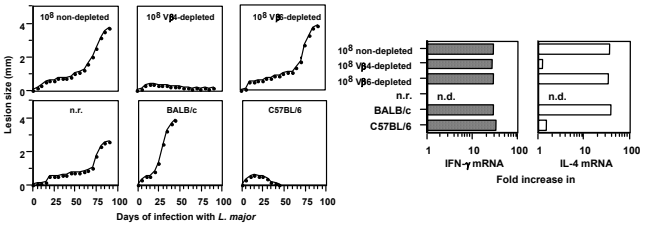
T and B cells are able to express early IL-2 mRNA

after infection with *L. major*

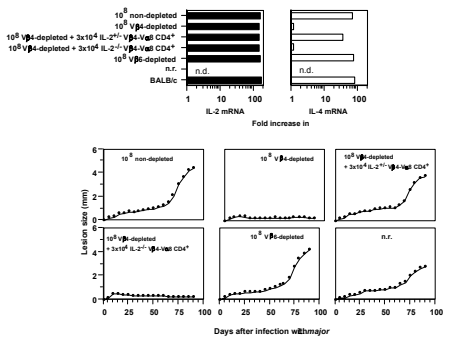


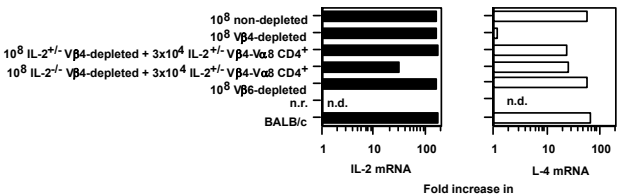
Reconstitution of SCID mice with 10^8 T cells mimics the Th2 differentiation

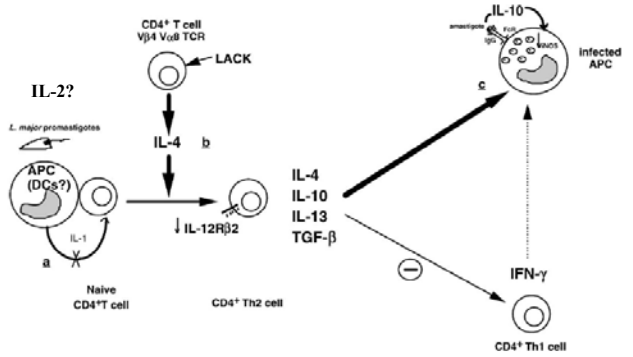
observed in BALB/c mice



Vβ4 Vα8 $CD4^+$ T cells are the source of IL-2 that allows early IL-4 production after infection with *L. major*



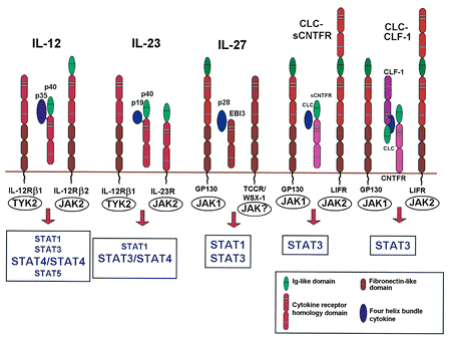




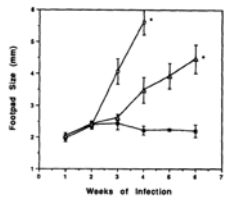
Role of cytokines in the development of a CD4+ Th1 response

- **IL-12**
- **IFN-γ**
- **IL-18, IL-23, IL-27**
- **IL-4**

The IL-12 family of heterodimer cytokines : IL-23 and IL-27



IL-12 is necessary in Th1 cell development



Heinzel *et al* , 1997

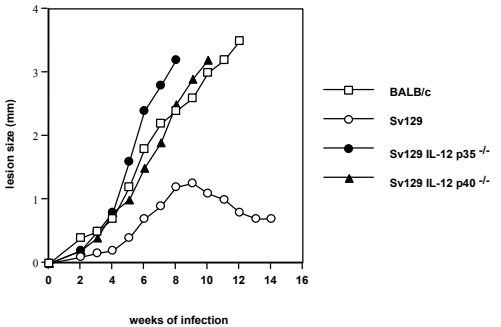
5 weeks post infection:

-4.9x10^4 amastigotes /mg lesion in non treated BALB/c mice

-1.3x10^3 amastigotes /mg lesion in BALB/c mice treated with anti-IL-12 Abs at the onset of infection

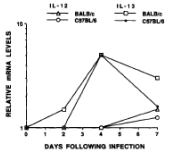
(Sypek *at al*, 1997)

IL-12 is necessary for Th1 development during infection with *L. major*



Mattner *et al*, 1996

But the precis timing of IL-12 production in vivo still unclear ….



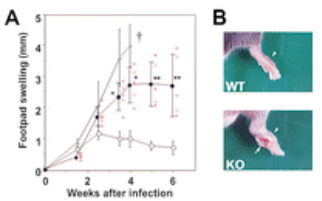
- **IL-12 transcripts not observed before 10 days of infection either in BALB/c or C57BL/6 mice (Reiner *et al*, 1994)**
- **IL-12 production detected in LN in BALB/c mice but not in C57BL/6 mice (Scharton-Kersten *et al*, 1995)**

Role of IL-23 in Th1 cell development

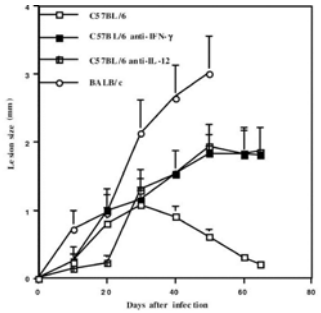
- **IL-23 p19 chain related to IL-12p35 + IL-12 p40**
- **IL-23 induces proliferation of memory T cells , it DOES NOT acts on NAÏVE $CD4^+$ T cells ⇒ not involved in Th1 differentiation but more in the maintance of a optimal IFN-g production**
- **IL-12p35$^{-/-}$**
  production of IL-12 = negative
  production of IL-23 = positive
  but IL-12p35$^{-/-}$ susceptible = IL-23 is NOT a factor implicated in Th1 differentiation

Role of IL-27 in Th1 development

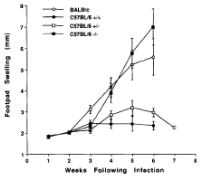
- **IL-27 = EIB3 related to IL-12p40 + p28 related to IL-12 p35**
- **IL-27 in synergy with IL-12 induces proliferation of naive cells but not memory $CD4^+$ T cells**
- **WSX $^{-/-}$ mice (IL-27R$^{-/-}$) mount aTh2 response after *L. major* infection and are susceptible**



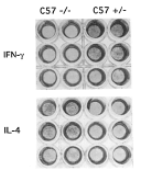
Neutralisation of IFN-γ rendered resistant C57BL/6 mice susceptible to infection with *L. major*



Role of IFN-γ in Th1 cell development

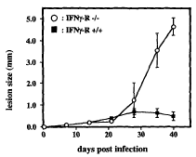


- **IFN-γ deficient C57BL/6 mice develop susceptibility after infection with *L. major***

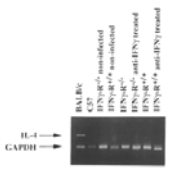


- **IFN-γ deficient C57BL/6 mice develop Th2 response after *L. major* infection**

Wang *et al*, 1995



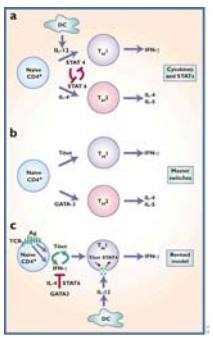
- **Resistant 129/Sv mice deficient for the binding chain of the IFN-γR are susceptible to infection with L. major**



- **But mount a Th1 response …**

Swihart *et al*, 1995

Different models for the effects of IL-12 and IFN-γ in the development of a Th1 reponse

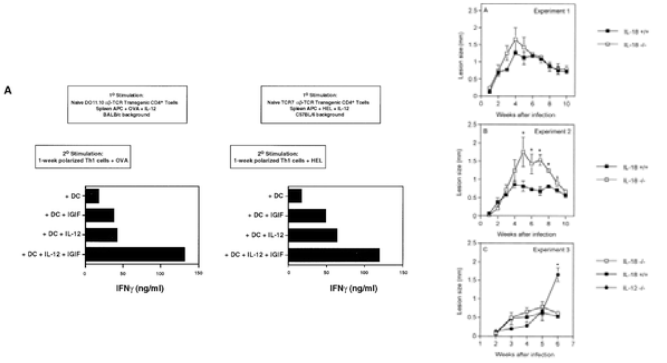


Afakarian *et al*, 2002

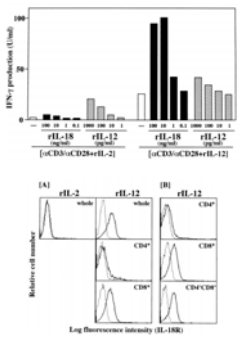
The IL-1 family

Protein name	GenBank® accession number	Refs	Previous names	Splice variant	GenBank® accession number	Refs	Human gene symbol	Mouse gene symbol
(IL-1F1)	NM_000575	–	IL-1α	–	–	–	*IL1A*	*Il1a*
(IL-1F2)	NM_000576	–	IL-1β	–	–	–	*IL1B*	*Il1b*
(IL-1F3)	NM_000577	–	IL-1ra	IL-1F3b	M55646	–	*IL1RN*	*Il1rn*
				IL-1F3c	X84348	–	–	–
(IL-1F4)	NM_000562	–	IL-18, IGIF, IL-1γ	–	–	–	*IL18*	*Il18*
IL-1F5	AF186094	1	IL-1Hy1, FIL1δ, IL-1H3, IL-1RP3, IL-1L3 and IL-1δ	IL-1F5b	AJ242738	4	*IL1F5*	*Il1f5*
IL-1F6	AF201831	2	FIL1ε	–	–	–	*IL1F6*	*Il1f6*
IL-1F7	AF201832	2	FIL1ζ, IL-1H4, IL-1RP1 and IL-1H	IL-1F7b	AF200496	3	*IL1F7*	*Il1f7*
				IL-1F7c	AF251120	5	–	–
IL-1F8	AF201833	2	FIL1η and IL-1H2	IL-1F8b	AF200494	3	*IL1F8*	*Il1f8*
IL-1F9	AF200492	3	IL-1H1, IL-1RP2 and IL-1ε[4]	–	–	–	*IL1F9*	*Il1f9*
IL-1F10	AF334755	6	IL-1Hy2 and FKSG75	IL-1F10b	AY026753	–	*IL1F10*	*Il1f10*

IL-18 acts synergically with IL-12 on IFN-γ production but is not sufficient to instruct Th1 response

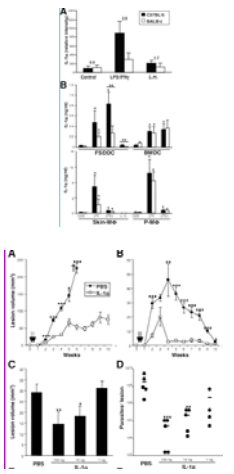


Role of IL-18 in Th1 response

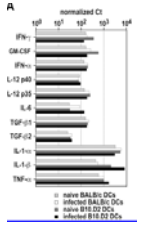


- **IL-18 responsiveness of T cells needs IL-12**
- **Because of up regulation of IL-18R by IL-12**

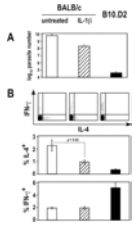
⇒ **IL-18 is a cofactor of Th1 cell development**



- **DCs from BALB/c mice produced less IL-1α in response to LPS/IFN-γ stimulation than those in C57BL/6 mice**
- **IL-1α administration improves disease outcome in susceptible BALB/c and resistant mice C57BL/6**



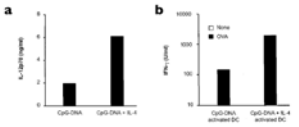
- CD11b$^+$ DCs from B10.D2 expressed more IL-1β than those from BALB/c



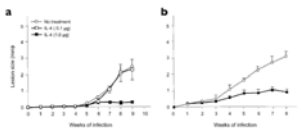
- Treatment of BALB/c mice with IL-1 β reduced parasite load and Th2 polarisation

Filippi *et al*, 2003

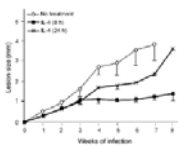
IL-4 can also instructs Th1 response



- IL-4 induced increase amount of IL-12 in DCs
- IL-4 activated DCs promoted Th1 responses



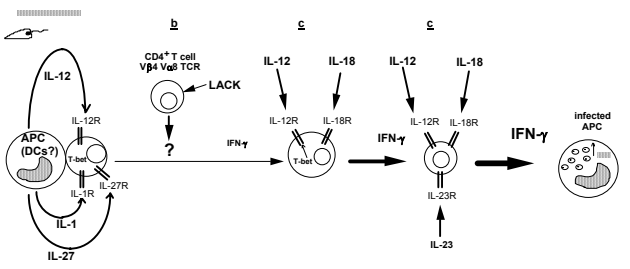
- IL-4 given during the first 8 hrs induces resistance



- Extension of treatment during 24 hrs reversed the IL-4 induced resistance

⇒IL-4 given during the initial period of DCs activation =Th1
⇒IL-4 given during the period of T cell priming =Th2

Th1 cell development

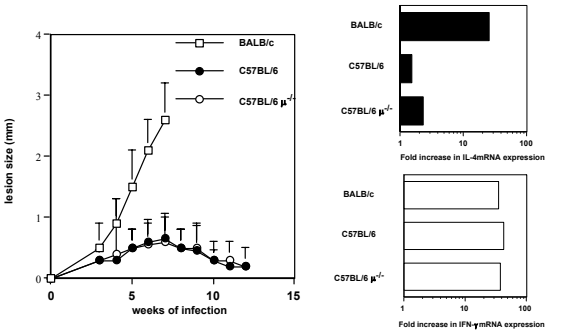


What are the cells able to present LACK to specific CD4$^+$ T cells ?

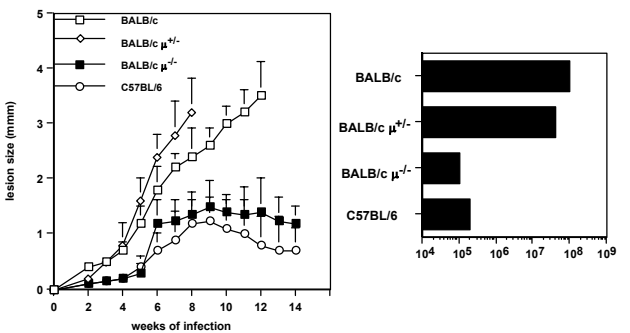
- **B cells have been demonstrated to induce Th2 cell development in vitro system**
- **B cells are required for Th2 induction in murine model of infection with *P. chabaudi chabaudi* (von der Weid *et al*, 1994)**
- **During infection with *L. major***
  - **Treatment with ant-IgM induced resistance in BALB/c mice (Sacks *et al,* 1984)**
  - **Requirement of B cells in Th2 development in reconstituted SCID mice (Hoerauf *et al*, 1996)**

⇒ Are B cells necessary for the Th2 differentiation observed in BALB/c mice by inducing IL-4 mRNA expression in LACK specific CD4$^+$ T cells ?

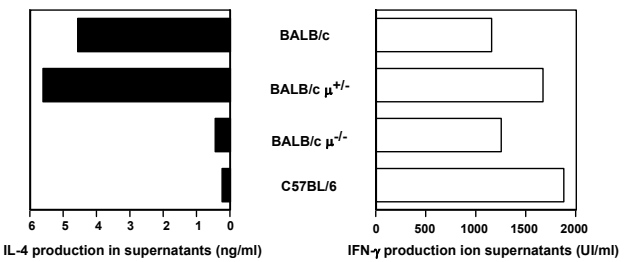
B cell deficient C57BL/6 mice ($\mu^{-/-}$) are resistant to infection with *L. major* and mount a Th1 response



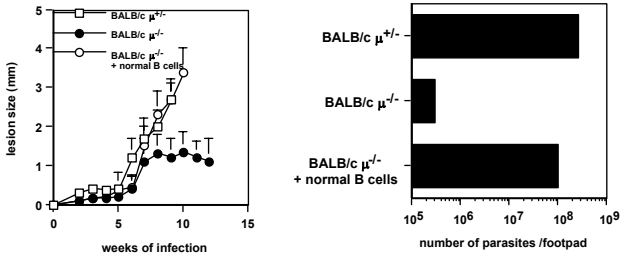
B cell deficient BALB/c mice (μ-/-) are resistant to infection with *L. major*



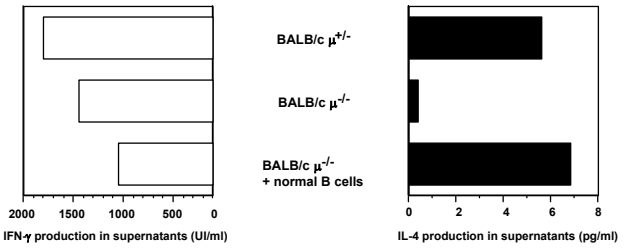
B cell deficient BALB/c mice ($\mu^{-/-}$) mount a Th1 response to infection with *L. major*



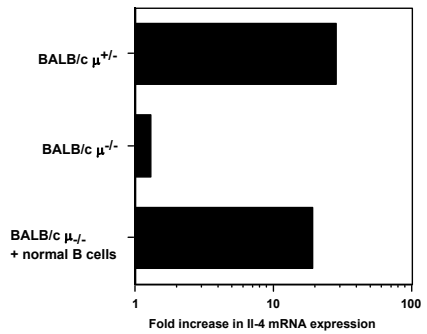
Adoptive transfer of normal B cells restores susceptibility in B cell deficient BALB/c mice infected with *L. major*



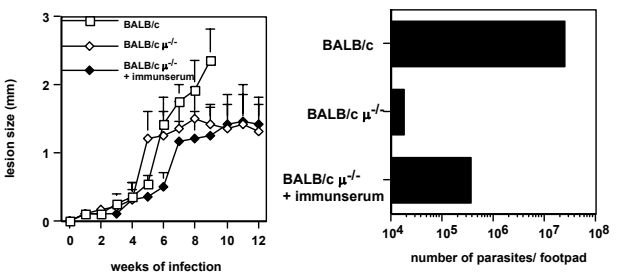
Adoptive transfer of normal B cells induces Th1 response in B cell deficient BALB/c mice infected with *L. major*



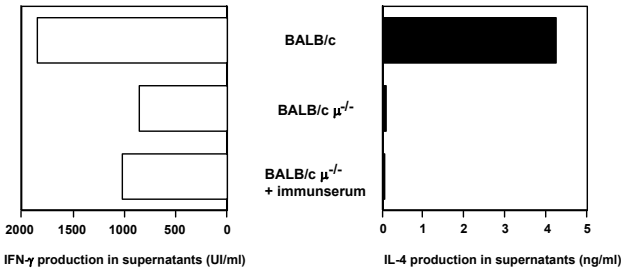
Adoptive transfer of normal B cells in B cell deficient BALB/c mice restores an early IL-4 mRNA expression after infection with *L. major*



Adoptive tranfer of immune serum does not induce susceptibility in B cell deficient BALB/c mice



Adoptive tranfer of immune serum does not induce Th2 cell development in B cell deficient BALB/c mice



- **Results**

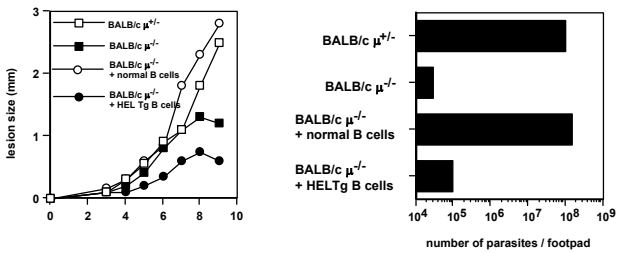
  Normal B cells are necessary to induce early IL-4 mRNA and susceptibility to infection with *L. major*

- **Hypothesis :**

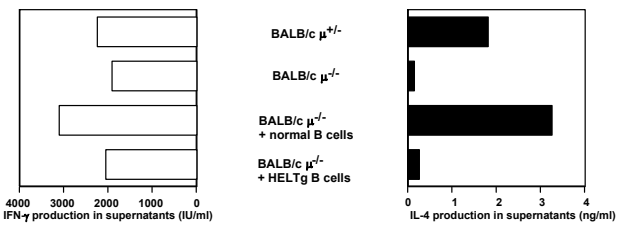
  antigen specific B cells could present LACK in a cognate interaction to Vβ4 Vα8 $CD4^+$ T cells resulting in the production of early IL-4 that instructs Th2 differentiation

  ⇒ If B cells play a role in LACK processing and presentation, B cell deficient BALB/c mice reconstituted with HEL Tg B cells (B cells that express only IgD and IgM specific for HEL)should not be able to induce early IL-4 mRNA expression and susceptibility to infection with *L. major*

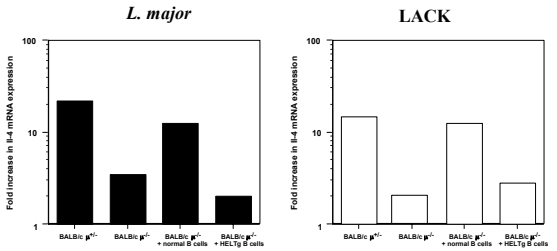
Adoptive transfer of B cells expressing HEL IgM specific does not induce susceptibility in B cell deficient BALB/c mice



Adoptive transfer of B cells expressing HEL IgM specific does not induce Th2 cell development in B cell deficient BALB/c mice



Adoptive transfer of B cells expressing HEL IgM specific in B cell deficient BALB/c mice does not induce an early IL-4 mRNA expression after either *L. major* infection or LACK injection



Conclusion :

Reconstitution of B cell deficient BALB/c mice with HEL Tg B cells is unable to induce early IL-4 mRNA expression and Th2 cell development after infection with *L. major*:

HEL Tg B cells are unable to bind LACK (LACK specific receptor =Ig???)

HEL Tg B cells are unable to internalise LACK

HEL Tg B cells are unable to present LACK to specific $CD4^+$ T cells

If B cells play a role in LACK processing and presentation, B cell deficient BALB/c mice reconstituted with HEL Tg B cells (B cells that express only IgD and IgM specific for HEL)<u>should be able to present LACK-HEL construct to specific cells</u>

⇒ **binding**

internalisation

presentation to LACK specific cells

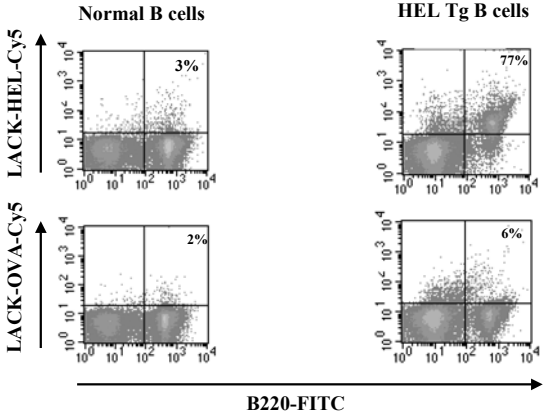
were analysed in vitro using purified $B220^+$ B cells

HEL-LACK construct labelled to fluorochrome (PE ou Cy5)

The different constructs

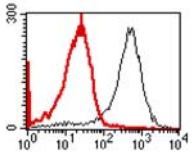
- **LACK was expressed as a 34 KDa his-tagged protein in *E.coli* and purified and NiNTa column**
- **LACK, HEL and Ovalbumin (OVA) used as control were biotinylated with the 22A linker Sulfo-HNS-LC EZ linker**
- **The two biotinylated molecules (LACK and HEL or LACK and OVA) were mixed at a ratio of 2.2:2.2:1 with avidin or fluorescent avidin (PE or Cy5)**

LACK-HEL construct is able to bind to HEL Tg B cells in vitro



LACK -HEL complex is effectively internalised by HEL Tg B cells

A



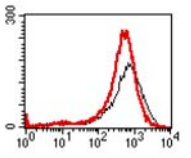
Total splenic cells were incubated with LACK-HEL-PE complexes for 30 min

A at 4° C (A)

B at 37° C (B) for evaluate internalization

Complexes bound to the surface were stripped with 2-mercaptoethanolsulfonic acid

B



Cells stained with FITC -B220 30 min 4° C

before stripping

after stripping

LACK-HEL-PE

LACK-HEL complex is effectively internalised by HEL Tg B cells

Stripping efficiency (SE)

(100 - MFI PE^+ $B220^+$ after stripping 4°C /MFI PE^+ $B220^+$ before stripping 4°C) x100

⇒ 88%

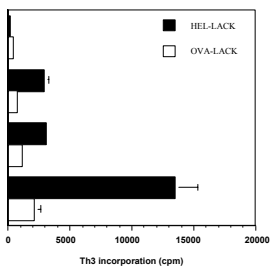
Internalisation efficiency

(MFI PE^+ $B220^+$ after stripping 37°C/ MFI PE^+ $B220^+$ before stripping 37°C) x SE

⇒ 87%

LACK-specific Vβ4⁺ Vα8⁺ CD4⁺ T cells from ABLE mice proliferate in response to presentation of LACK by HEL Tg B cells

APC		
total spleen cells (10^7)	purified B cells (10^6)	$CD4^+$ T cells ($3x10^4$)
BALB/c	-	LACK specific
HEL Tg BALB/c	-	LACK specific
-	BALB/c	LACK specific
-	HEL Tg BALB/c	LACK specific



Conclusion :

The HEL-LACK complex can be bound, internalised, processed and LACK presented to LACK-specific Vβ4 Vα8 $CD4^+$ T cells by B cells in vitro

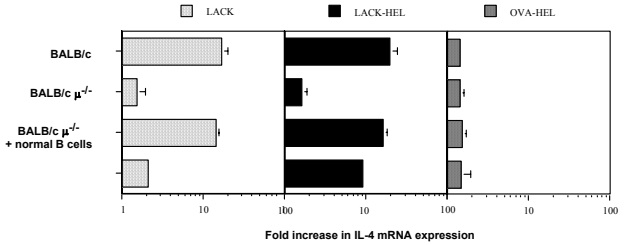
could the LACK part of this complex induce early IL-4 mRNA expression in BALB/c mice?

reconstitution of B cell deficient mice with HEL Tg B cells or normal B cells injection of LACK-HEL construct or the OVA-HEL control construct

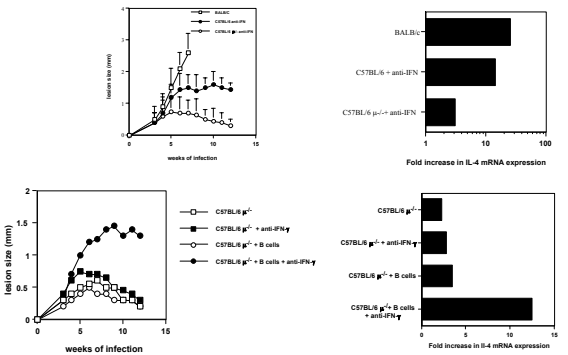
Expected results

	LACK	LACK-HEL	OVA-HEL
BALB/c	+	+	-
BALB/c $\mu^{-/-}$	-	-	-
BALB/c $\mu^{-/-}$ + normal B cells	+	+	-
BALB/C $\mu^{-/-}$ + HEL Tg B cells	-	+ ?	-

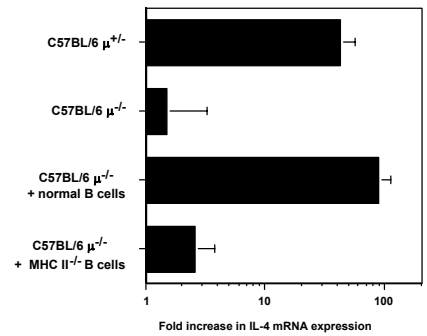
The antigen presenting capacity of B cells is involved in early IL-4 mRNA expression after LACK injection



C57BL/6 μ-/- mice reconstituted with normal B cells and treated with anti-IFN-γ at the onset of infection are susceptible and mount a Th2 response



B cells present LACK to specific CD4+ T cells through MCH Class II molecules In C57BL/6 treated with anti-IFN-γ at the onset of infection

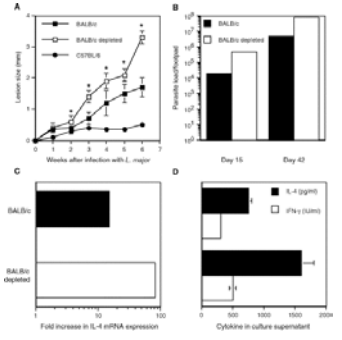


Conclusion (3)

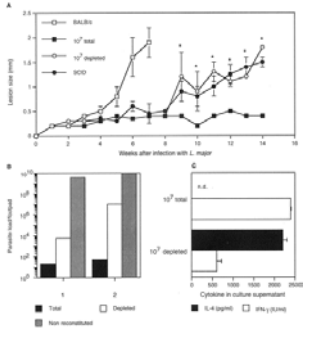
- **In susceptible mice, B cells are able to present LACK to LACK specific Vβ4 Vα8 CD4+ T cells through MCH class II molecules and allow early IL-4 mRNA expression and the subsequent Th2 differentiation and susceptibility to infection with L. major**
- **Specific receptors for LACK on B cells (Ig?)**
- **Other functions of B cells:**
  - **production of different cytokines**
  - ***upregulation of IL-10 mRNA expression in BALB/c $\mu^{-/-}$ mice reconstituted with normal B cells and infected with *L. major***
    - **⇒ role? interaction with other cells : DCs?**

Role des $CD4^+$ $CD25^+$ T cells

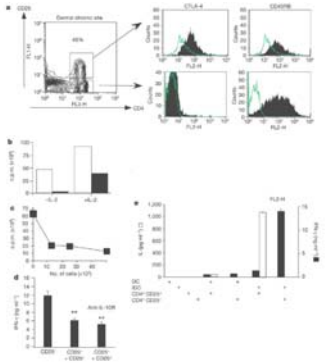
Infection of BALB/c mice depleted of $CD4^+$ $CD25^+$ T cells leads to an exacerbated course of disease



SCID mice reconstituted with 10^7 spleen cells from BALB/c mice depleted of $CD4^+$ $CD25^+$ T cells mount a Th2 cell response and develop progressive disease



$CD4^+$ $CD25^+$ T cells from lesions are suppressive and produced IL-10



Remerciements

WHO-IRTC, Epalinges
Himmelrich H.
Voigt H.
Assefa A.
Gumy A.
Tacchini-Cottier F.
Louis J.
Launois P.

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