Assistance Publique
Hôpitaux de Marseille
Service de Médecine interne
HOPITAL DE LA CONCEPTION

SYNDROMES HEMOPHAGOCYTAIRES

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DEFINITION

- **Syndrome hémophagocytaire ou Lymphohistiocytose Hémophagocytaire (LH) ou Hémophagocytose Lympho-Histiocytaire (HLH) ou Syndrome d'Activation Macrophagique (SAM)**

- **Entité clinique et biologique**

- **Prolifération anormale de lymphocytes T et de cellules mono/macrophagiques bénins avec activité d'hémophagocytose associée à une hypersécrétion massive de cytokines**

- **Pronostic 30-50% de décès**

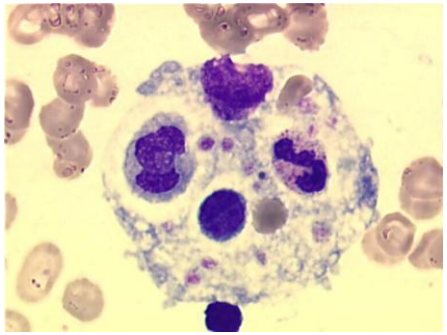
DIFFERENTES FORMES DE SH

- **SH PRIMAIRES**
  - Farquhar and Claireaux 1952
  - Forme « familiale », déficit immunitaire génétique
  - Diagnostic 70-80 % âge <1an
  - Facteur infectieux déclenchant

- **SH SECONDAIRES/REACTIONNELS**
  - Risdall et al. Cancer 1979
  - Enfant et adulte
  - INFECTIONS INTRA-CELLULAIRES (VIRUS HERPES++, Bactéries, Parasites..)
  - HEMOPATHIES LYMPHOIDES
  - MALADIES INFLAMMATOIRES (STILL, LUPUS…)

SH PRIMAIRE
CRITERES DIAGNOSTIQUES

Henter JI et al . Crit Rev Oncol Hematol 2004



- **Fièvre**
- **Splénomégalie**
- **Bicytopénie**
  - **Neutropénie < 1G/L**
  - **Anémie < 90 g/L**
  - **Thrombopénie < 100 G/L**
- **Triglycérides > 3mmol/L**
- **ou fibrinogène < 1,5g /L**
- **Ferritine > 1000 ng/ml**
- **Images d'hémophagocytose**
- **Élévation sIL2R**
- **Diminution ou abolition de la cytotoxicité NK**

5 Items / 8

SH PRIMAIRES

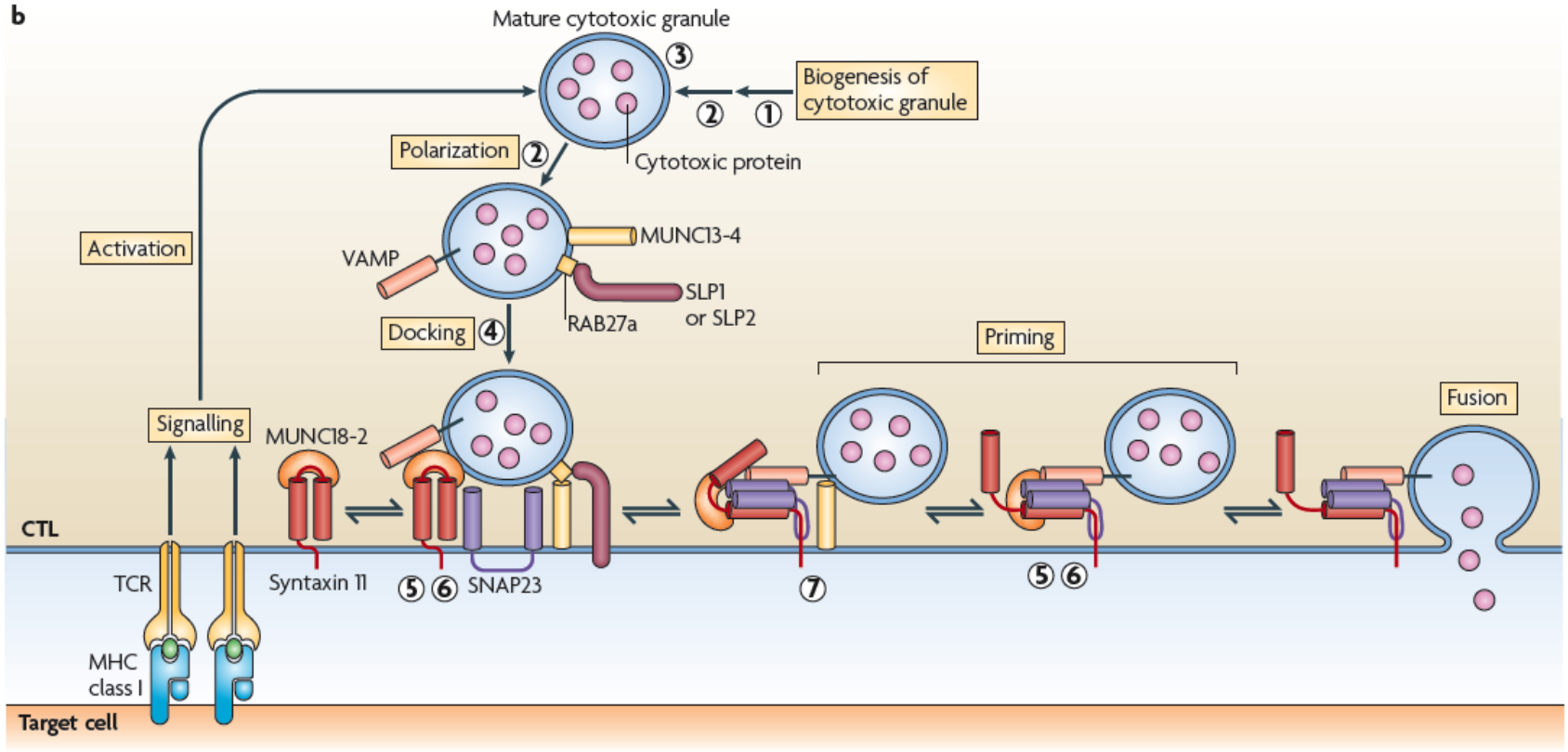
Table 1. Genetic disorders associated with occurrence of HLH and their murine counterparts

	Gene locus	Hemophagocytic syndrome	Cytotoxic activity	Hypopigmentation	Mouse model
Familial hemophagocytic lymphohistiocytosis (FHL): gene					
FHL type 2: perforin	10q21-22	+	−	−	*Pko*
FHL type 3: Munc13-4	17q25	+	−	−	*Jinx*
FHL type 4: syntaxin 11	6q24	+	+/	−	*Stx11-/-
FHL type 5: Munc18-2	19q13	+	+/	−	
Griscelli syndrome type 2					
Rab27a	15q21	+	−	+	*Ashen*
Chediak–Higashi syndrome					
LYST	1q42-43	+	−	+[b]	*Beige*
X-linked lymphoproliferative syndrome					
XLP 1: SH2D1A (SAP)	Xq25	±	±[a]	−	*Sap*
XLP 2: XIAP	Xq25	+	+	−	*Xiap*

[a]Defect in SLAM-mediated toxicity.
[b]Abnormal granule size.

SH PRIMAIRES

Anomalies génétiques de l'exocytose des granules cytotoxiques des Lymphos CD8 et NK



De Saint Basile et al. Nature Review 2010

DIAGNOSTIC BIOLOGIQUE

-Numération Lymphocytaire

-Immuno-phénotypage lymphocytaire

-Expression cytoplasmique de la Perforine (CD8 ou NK)

-Etude de la dégranulation (CD107)

-Etude de la cytotoxicité in vitro

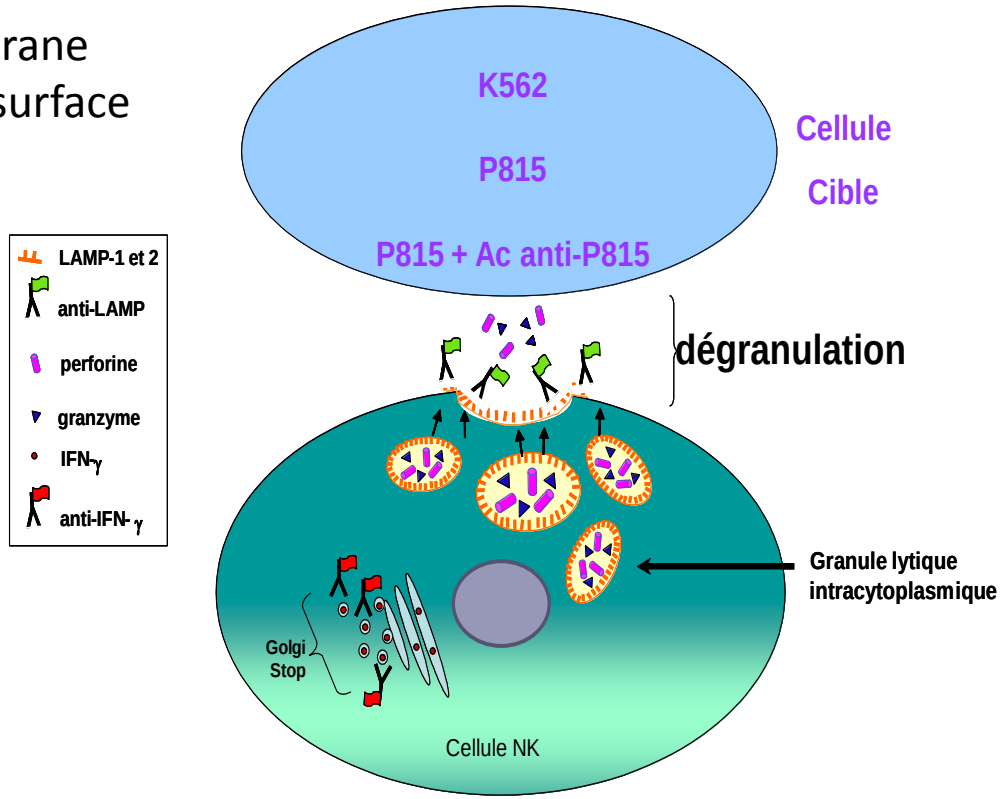
-Etude génétique

Etude de la Dégranulation : Principes

CD107a+b = LAMP a et b:

-Protéine de la membrane des granules cytotoxiques

-Lors de la fusion membrane granule/NK : CD107 en surface des NK

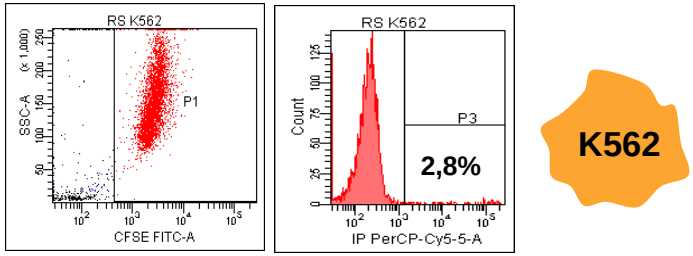


ETUDE DE LA CYTOTOXICITE NK

Protocol

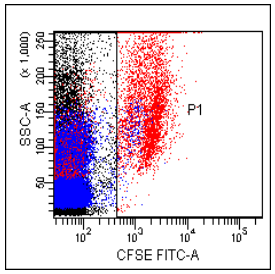
- Target staining with 0,5µM CFSE
- 10^4 targets + effector cells
- 4h at 37°C in U bottom 96-wells plate
- Monitoring of target cell viability using Propidium Iodide staining
- Analysis by flow cytometry

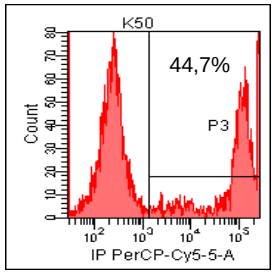
➢**Spontaneous targets cell death after 4h culture in medium**

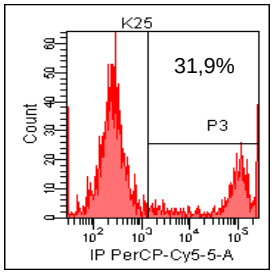


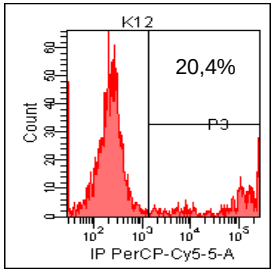
➢**Target cell death after 48h culture with effector cells (E/T ratio)**

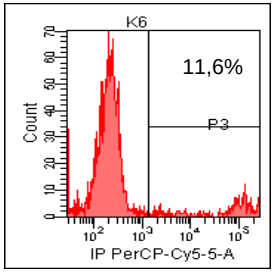
E/T ratio 50 25 12 6 3

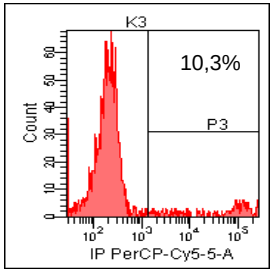












DIAGNOSTIC DES LH PRIMAIRES

- Age de début
- Histoire familiale de LH
- Consanguinité
- Anomalies de pigmentation

- Perforine<10%
- CD107<5%
- Cytotoxicité abaissée

(Attention: XLP: Nmle)

FORMES PRIMAIRES ATYPIQUES

Hypomorphic mutations in *PRF1*, *MUNC13-4*, and *STXBP2* are associated with adult-onset familial HLH

Kejian Zhang,[1] Michael B. Jordan,[2,3] Rebecca A. Marsh,[3] Judith A. Johnson,[1] Diane Kissell,[1] Jarek Meller,[4,5] Joyce Villanueva,[6] Kimberly A. Risma,[7] Qian Wei,[8] Peter S. Klein,[9] and Alexandra H. Filipovich[3,6]

Familial Hemophagocytic Lymphohistiocytosis May Present during Adulthood: Clinical and Genetic Features of a Small Series

Elena Sieni[1,3], Valentina Cetica[1,3], Andrea Piccin[2], Filippo Gherlinzoni[3], Ferdinando Carlo Sasso[4], Marco Rabusin[5], Luciano Attard[6], Alberto Bosi[7], Daniela Pende[8], Lorenzo Moretta[9], Maurizio Aricò[1,*]

Perforin gene mutations in adult-onset hemophagocytic lymphohistiocytosis

Koji Nagafuji, Atsushi Nonami, Takashi Kumano, Yoshikane Kikushige, Goichi Yoshimoto, Katsuto Takenaka, Kazuya Shimoda, Shouichi Ohga, Masaki Yasukawa, Hisanori Horiuchi, Eiichi Ishii, Mine Harada

A proportion of patients with lymphoma may harbor mutations of the perforin gene

Rita Clementi, Franco Locatelli, Loïc Dupré, Alberto Garaventa, Lorenzo Emmi, Marco Bregni, Graziella Cefalo, Antonia Moretta, Cesare Danesino, Margherita Comis, Andrea Pession, Ugo Ramenghi, Rita Maccario, Maurizio Aricò, and Maria Grazia Roncarolo

➢ Mono-allelic mutations affecting F-HLH genes (PERF) in adult HLH? Possible but rare

Reference	ZHANG et al. Blood 2011	SIENI et al PLoS One 2012	WANG et al PLoS One 2014	CETICA et al J Allergy clin immunol 2015
Patients n / age	175 > 18 yo	ITALIAN REGISTRY 11 > 18 yo	CHINESE REGISTRY 252 > 13 yo	ITALIAN REGISTRY 500
Mono allelic mutation	14%		7%	15%
Misssense perforin mutation	50%	50%	50%	
Cytotoxicity screening	↘	↘	↘ (less severe than biallelic)	↘ (less severe)

Perf A91V: 5% european population

SH SECONDAIRES
CRITERES DIAGNOSTIQUES

Imashuku et al. Int J Haematol 1997

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  - **Neutropénie < 1G/L**
  - **Anémie < 90 g/L**
  - **Thrombopénie < 100 G/L**
- **Ferritinémie > 3DS ou 1000 ng/ml**
- **LDH > 3DS**
- **Images d'hémophagocytose**
- **NK ???? (PHRC++)**

REVUE: 775 pts

	Patients (N=775)
Epidemiological features	
Mean age (range)	49·03 years (41–67 years)
Women	275/746 (37%)
Clinical features	
Fever	524/546 (96%)
Splenomegaly	420/609 (69%)
Hepatomegaly	389/580 (67%)
Pulmonary involvement	61/145 (42%)
Peripheral adenopathies	91/277 (33%)
Neurological involvement	41/161 (25%)
Skin lesions	63/250 (25%)
Gastrointestinal involvement	27/149 (18%)
Renal involvement	9/56 (16%)
Encephalopathy	9/102 (9%)
Haematological and coagulation features	
Anaemia	
Haemoglobin <5·6 mmol/L	122/181 (67%)
Haemoglobin <4·3 mmol/L	33/151 (22%)
Thrombocytopenia	
<100 000 cells per mm³	178/227 (78%)
<10 000 cells per mm³	10/168 (6%)
Leukopenia <4000 cells per mm³	198/285 (69%)
Neutropenia	
<1000 cells per mm³	61/144 (42%)
<500 cells per mm³	15/64 (23%)
Coagulopathy	91/153 (59%)
D-dimer >5·4·8 mmol/L	24/49 (49%)
Fibrinogen <4·4 µmol/L	39/81 (48%)
Disseminated intravascular coagulation	40/101 (40%)

(Continues in next column)

	Patients (N=775)
(Continued from previous column)	
Biochemical features	
Ferritin	
>1123·5 pmol/L	178/198 (90%)
>2247 pmol/L	164/230 (71%)
>22 470 pmol/L	40/170 (24%)
Triglycerides	
>1·7 mmol/L	132/192 (69%)
>3·0 mmol/L	42/100 (42%)
Hyponatraemia	
<135 mmol/L	57/73 (78%)
<130 mmol/L	10/17 (59%)
Raised transaminases (ALT and AST)	
>40 IU/L	164/286 (57%)
>100 IU/L	48/115 (42%)
Alkaline phosphatase >290 U/L	66/93 (71%)
Increased lactate dehydrogenase	
>500 IU/L	190/243 (78%)
>1000 IU/L	81/152 (53%)
Increased sIL2R	
>2400 IU/mL	95/120 (79%)
>10 000 IU/mL	45/120 (38%)
Haemophagocytosis	
Positive bone marrow aspirate	257/304 (85%)
Positive bone marrow biopsy	14/22 (64%)

Ramos-Casals Lancet 2014

HS Score

Fardet, A&R 2014

312 pts, 3 experts

Parameter	No. of points (criteria for scoring)
Known underlying immunosuppression*	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
No. of cytopenias†	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/liter)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (gm/liter)	0 (>2.5) or 30 (≤2.5)
Serum glutamic oxaloacetic transaminase (IU/liter)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)

* Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (i.e., glucocorticoids, cyclosporine, azathioprine).

† Defined as a hemoglobin level of ≤9.2 gm/dl and/or a leukocyte count of ≤5,000/mm^3 and/or a platelet count of ≤110,000/mm^3.

HS<129= non

HS<140 <10% de chances

HS score>222= oui

HS>200>90% de chances

SH SECONDAIRES
CRITERES DIAGNOSTIQUES

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- **Ferritinémie > 3DS ou 1000 ng/ml**
- **LDH > 3DS**
- **Images d'hémophagocytose**

ETIOLOGIES DES FORMES DE L'ADULTE

Karras A, Hermine O. Rev Med Int 2002

Étiologies du syndrome d'activation macrophagique (analyse des 8 plus grandes séries)

	Risdall[1]	Reiner[2]	Albert[7]	Tiab[8]	Sailler[5]	Wong[4]	Tsuda[6]	Kaito[9]	Total	Pourcentage
Année	1979	1988	1992	1996	1997	1992	1997	1997		
Nombre de patients	19	23	45	23	99	40	23	34	306	
Enfants/adultes	6/13	0/23		6/17	9/90	3/37	0/23	1/33		
Infection virale	15	10	17	5	12	4	20	4	87	28,4 %
HSV	1	4	3	0	1	0	0	0	9	2,9 %
EBV	1	1	4	1	4	1	7	2	21	6,9 %
CMV	10	7	5	2	5	0	3	0	32	10,5 %
VIH	0	2	3	5	16	1	0	0	27	8,8 %
Autre infection	0	10	10	5	26	10	0	2	63	20,6 %
Bactérie	0	6	7	0	17	10	0	0	40	13,1 %
Mycobactérie	0	0	0	5	2	0	0	0	7	2,3 %
Parasite/champignon	0	4	3	0	7	0	0	2	16	5,2 %
Néoplasie	0	6	18	13	27	18	4	5	91	29,7 %
Lymphome	0	3	9	11	18	16	2	2	61	19,9 %
Autre hémopathie	0	2	9	2	7	1	1	3	25	8,2 %
Cancer solide	0	1	0	0	2	1	1	0	5	1,6 %
Maladie systémique	1	6	3	0	3	4	3	2	22	7,2 %
Sans étiologie	4	2	7	2	16	2	2	20	55	18,0 %
Héréditaire	5	0	10	4	0	0	0	0	19	6,2 %
Pronostic fatal	6	7	28	17	49	18	5	20	150	49 %

Panel 1: List of triggers and associated diseases and processes detailed in 2197 adult haemophagocytic lymphohistiocytosis cases identified through search strategy

Infection (1108)

a) Viruses (762)
- Epstein-Barr virus (330)
- HIV (173)
- Herpes viruses (74)
- Cytomegalovirus (69)
- Viral hepatitis (20)
- Influenza (14)
- Human parvovirus B19 (14)
- Other viruses or not specified (68)

b) Bacteria (206)
- *Mycobacterium tuberculosis* (78)
- *Rickettsia* spp (17)
- *Staphylococcus* spp (15)
- *Escherichia coli* (11)
- Other bacteria or not specified (85)

c) Parasites (53)
- *Leishmania* spp (17)
- *Plasmodium* spp (14)
- *Toxoplasma* spp (10)
- Other parasites (12)

d) Fungi (37)
- *Histoplasma* spp (18)
- Other fungi (19)

e) Infection not specified (50)

Neoplasms (1047)

a) Haematological (981)
- T-cell or natural-killer lymphoma (369)
- B-cell lymphoma (333)
- Leukaemia (67)
- Hodgkin's lymphoma (61)
- Not specified lymphoma (35)
- Castleman's disease (22)
- Other haematological neoplasmsor not specified (94)

b) Solid (32)

c) Not specified neoplasm (34)

Autoimmune diseases (276)

a) Systemic (244)
- Systemic lupus erythematosus (133)
- Adult-onset Still's disease (54)
- Rheumatoid arthritis (18)
- Vasculitis (11)
- Other or not specified (28)

b) Organ-specific (32)
- Inflammatory bowel disease (11)
- Other diseases (21)

Other circumstances or diseases (184)

a) Transplantation (95)
- Kidney (53)
- Haematological (29)
- Other (13)

b) Other circumstances (76)
- Drugs (20)
- Surgery or biopsies (11)
- Vaccination or acute injuries (10)
- Diabetes or chronic liver disease (14)
- Pregnancy (11)
- Haemodialysis (10)

c) Other or not specified (13)

Idiopathic or unknown (81)

Number of reported cases in parentheses.

Ramos-Casals Lancet 2014

ETIOLOGIES DES FORMES DE L'ADULTE

	Positive Patients N = 162 (52.0%)
Hematologic malignancies	92 (56.8%)
Hodgkin lymphoma	17 (10.5%)
Non-Hodgkin lymphoma	57 (35.2%)
T-cell lymphoma	22 (13.6%)
B-cell lymphoma	35 (21.6%)
Castleman disease	17 (10.5%)
Other hematologic malignancies	1 (0.6%)
Infections	40 (24.7%)
Bacteria	9 (5.5%)
Mycobacteria	13 (8%)
Mycobacterium tuberculosis	12 (7.4%)
Atypical mycobacteria	1 (0.6%)
Virus	10 (6.1%)
CMV	6 (3.7%)
EBV	2 (1.2%)
Other	2 (1.2%)
Parasites*	6 (3.7%)
Fungi†	2 (1.2%)
Hematologic malignancies and infection	6 (3.7%)
Systemic disease	5 (3.1%)
SLE	3 (1.8%)
Still's disease	2 (1.2%)
Other	0
Solid cancer	5 (3.1%)
Other/unknown underlying disease	14 (8.6%)

86%

CLINICAL SIGNIFICANCE

- Only 70% of patients with hemophagocytic syndrome had hemophagocytosis features on bone marrow aspiration.
- Approximately half of the patients have a known immunosuppression. All of the causes of immunosuppression identified led to defects in cellular immunity.
- Hematologic malignancies, particularly non-Hodgkin lymphomas, were the main diseases associated with hemophagocytic syndrome.
- Mortality rate within 1 month after diagnosis was 20%. Patients with hematologic malignancies—associated hemophagocytic syndrome have a poorer early outcome than those with underlying infection.

Riviere, Am J Med 2014

SAM ET MALADIES SYSTEMIQUES

PubMed 1990-2012

580 Articles

duplicata

Absence de cas rapporte

117 Articles
421 patients

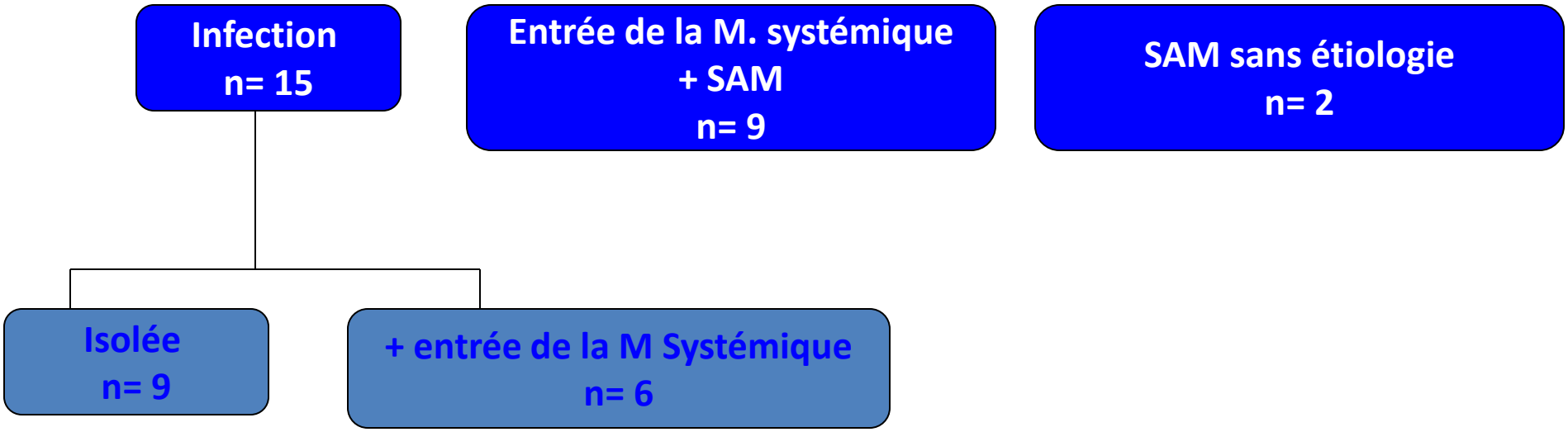
Arthrite juvenile systémique idiopathique n=219
Maladie de Still de l'adulte n =39
Lupus erythémateux disséminé n =94
Kawasaki n=25
Polyarthrite rhumatoïde n=13
Dermatomyosite n= 7
Panartérite noueuse n=6
Sarcoidose n=5
Sjögren n=3
Spondylarthrite ankylosante n=2
Maladie de Wegener n=1
Connectivite mixte n =1

Atteritano et al. Eur Rev Med Pharmacol Sci 2012

SAM ET MALADIES SYSTEMIQUES

Dhote R et al. Arthritis Rheum 2003

- **Etude sur questionnaire, SNFMI.**
- **26 patients**
  - **LED n= 14**
  - **Still n= 4**
  - **PR n= 2**
  - **PAN n= 2**
  - **connectivite mixte, sarcoïdose pulmonaire, Sjogren, sclérodermie n= 1**



SAM ET ARTHRITE CHRONIQUE JUVENILE SYSTEMIQUE/M. de STILL

-Fréquence: 10% ont un vrai SAM; 30% ont un SAM infra-clinique
DONC il existe un lien physiopathologique entre les 2 maladies

-Soit initialement, soit en cours d'évolution MAIS toujours des formes actives

-Soit spontanément, soit après une infection ou lors des modifications thérapeutiques

-Difficultés du diagnostic car les symptômes se recoupent

SAM ET ARTHRITE CHRONIQUE JUVENILE SYSTEMIQUE/M. de STILL
CRITERES DIAGNOSTIQUES (Ravelli et al)

-Baisse du taux de plaquettes

-Hyperferritinémie>>5000

-Hémophagocytose dans la moelle osseuse

-Hépatite biologique

-Baisse du taux des leucocytes

-Fièvre persistante continue>38°C

-Baisse de la VS

-Hypofibrinogénémie

-Hypertriglycéridémie

SAM ET LUPUS

Lambotte O et al. Medicine 2006

- 12 patients, 15 épisodes de SAM
- Exclusion des causes infectieuses

- Diagnostic simultané de LED et SAM n= 8
- SAM, puis diagnostic de LED n= 1
- Diagnostic LED au cours récidive de SAM n= 1
- Diagnostic de Kikushi/SAM, puis LED n= 1
- Diagnostic de LED avant SAM n= 1

- Particularité LED associé au SAM:
  - Atteinte cardiaque; péricardite 33%, myocardite 27%
  - CRP peu élevé, fièvre importante
  - Hépatosplénomégalie (13%-27%) peu fréquente
  - adénomégalie fréquente

- Survie immédiate 100% mais 33% Réanimation

QUE SAIT-ON DE LA PHYSIOPATHOLOGIE?

EXCES DE CYTOKINES INFLAMMATOIRES

- **Fièvre : TNF-α, IL-1, IL-6**
- **Cytopénie : TNF-α, IFN-γ**
- **Hypertriglyceridémie : TNF-α**
- **Cytolyse hépatique: TNF-α, FasL**
- **Hémophagocytose : IFN-γ (?), GM-CSF**

Komp et al. Blood 1989, Henter et al. Blood 1991, Imashuku et al. Blood 1995, Osugi et al. Blood 1997

MODELES ANIMAUX
Déficit de cytotoxicité + Infection virale

➢MODELES « CLASSIQUES »: FORMES PRIMAIRES

- Perf KO + LCMV
- Munc 13-4 KO + LCMV ***Virus peu cytopathique***
- Rab27 KO + LCMV

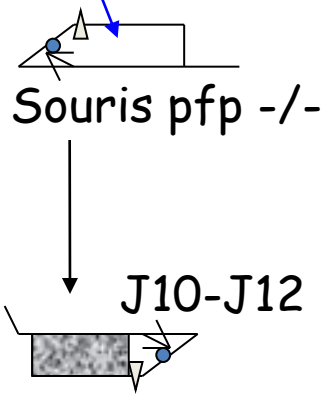
- Perf KO + MCMV ***Virus cytopathique***
- Granz KO + MCMV déplétés en NK

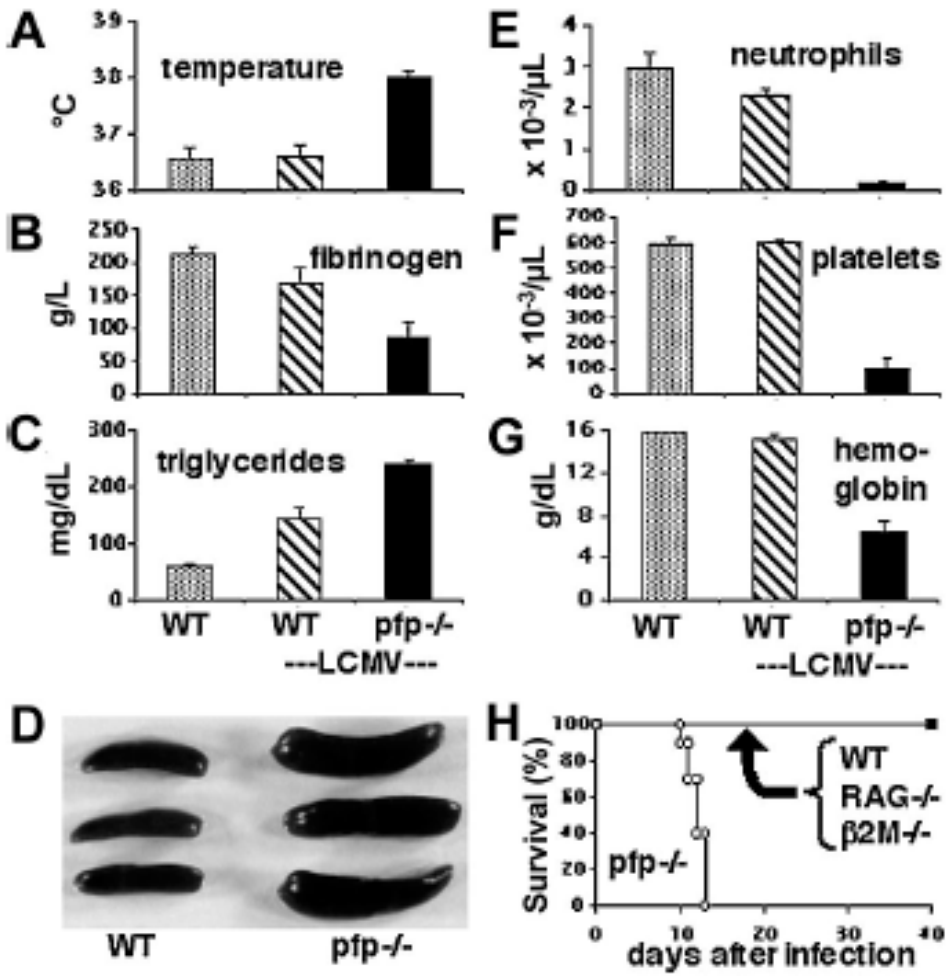
PHYSIOPATHOLOGIE:

JORDAN MB et al. Blood 2004

MODELES ANIMAUX

LCMV
Lymphocyte choriomeningitis virus

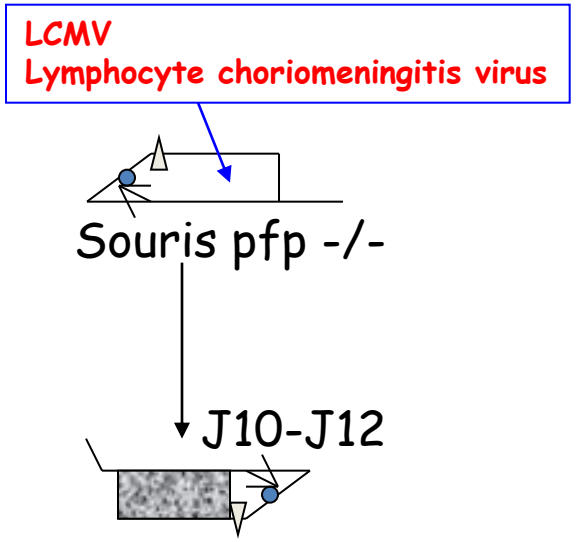




PHYSIOPATHOLOGIE:

JORDAN MB et al. Blood 2004

MODELES ANIMAUX



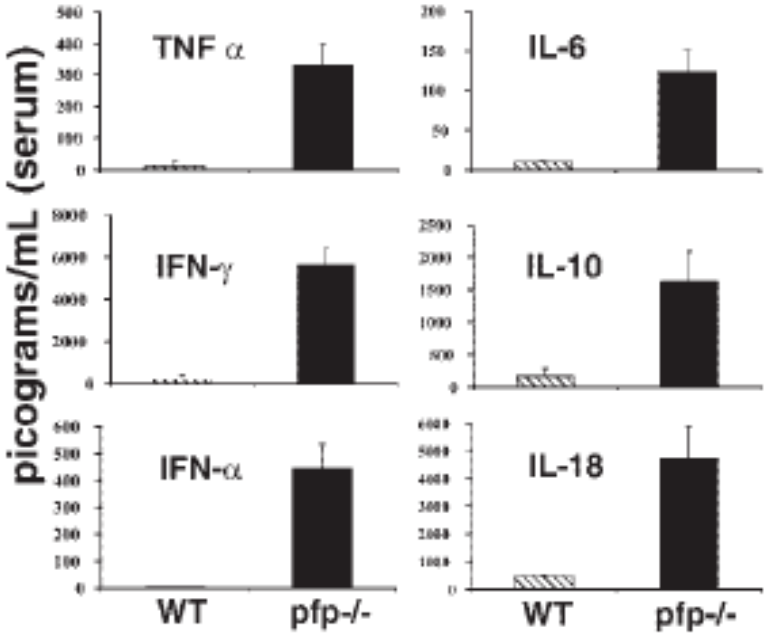


Figure 3. LCMV-infected pfp$^{-/-}$ mice display striking elevations of serum cytokine levels. Serum cytokine levels from either wild-type or pfp$^{-/-}$ mice infected with LCMV are shown. All assays were performed on sera obtained 12 days after infection, except IFNα, which was assayed on sera from mice infected 6 days previously. Data (± standard error) are representative of at least 2 experiments with at least 3 mice in each group.

Jordan MB et al. Blood 2004

LCMV
Lymphocyte choriomeningitis virus

Souris pfp -/-

J6 J6 J6

A.

Ac anti-NK

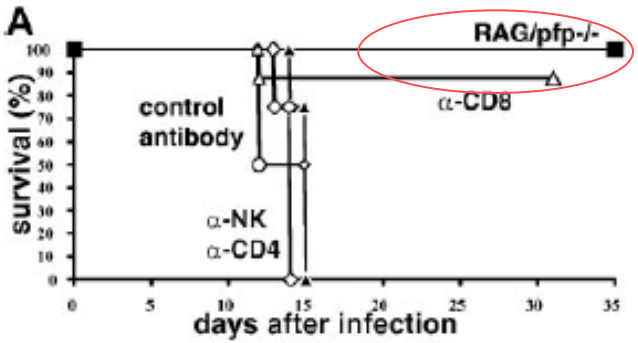
Ac anti-CD4

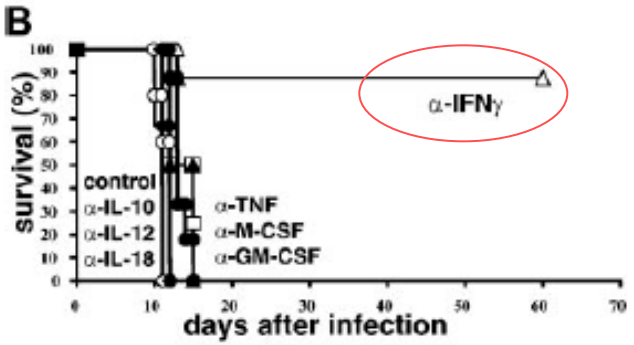
Ac anti-CD8

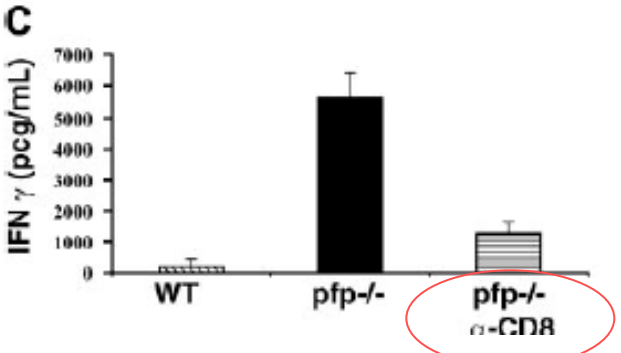
B.

Ac anti:-IL-10 /IL-12/
IL-18, TNF,MCSF,GMCSF

Ac anti-IFNγ



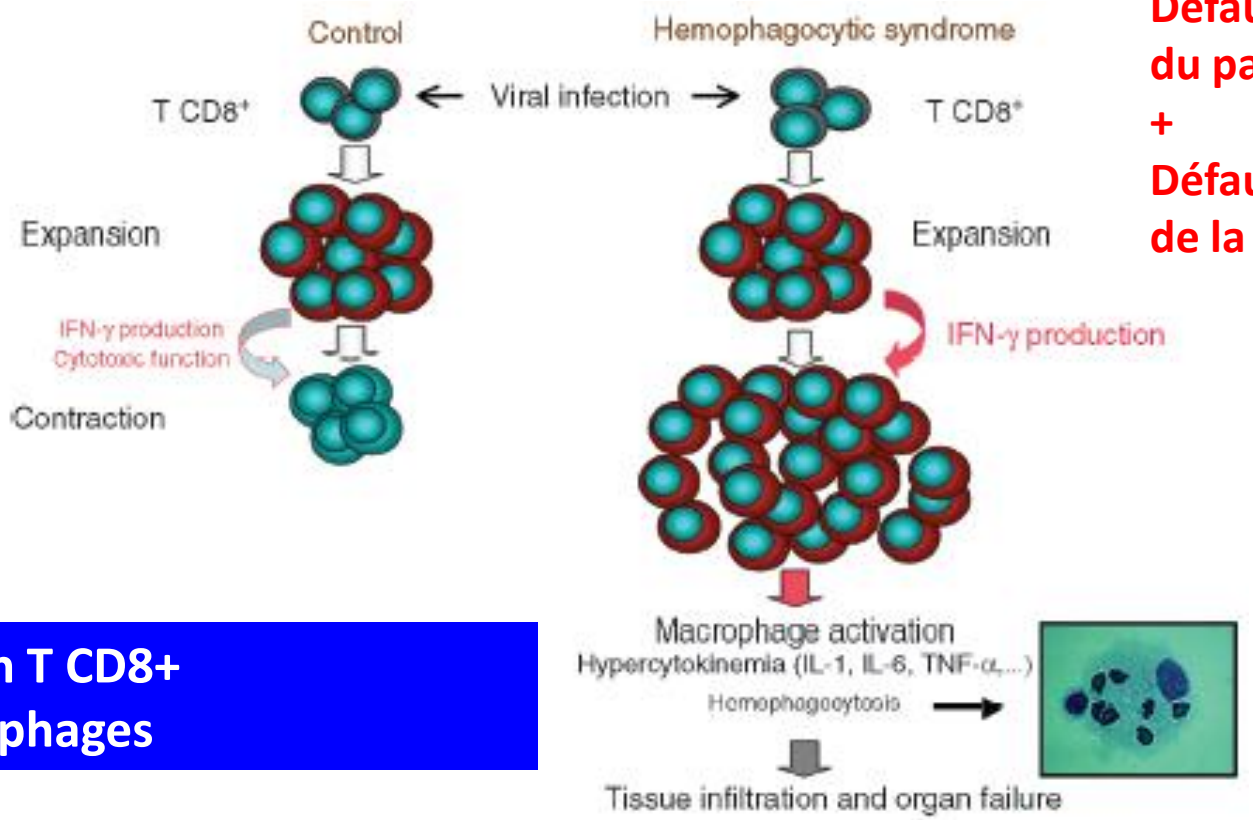




PHYSIOPATHOLOGIE DE LA LH

Antigen-specific CD8+T-cell homeostasis

Ménasché et al. Immunological Reviews 2005

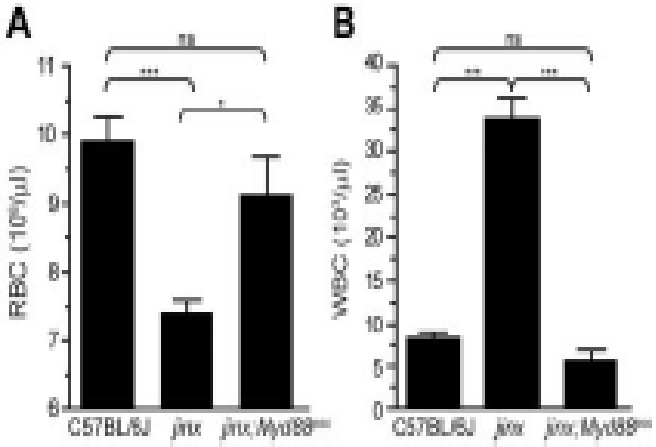


Défaut d'élimination du pathogène
+
Défaut de contrôle de la rép. immunitaire

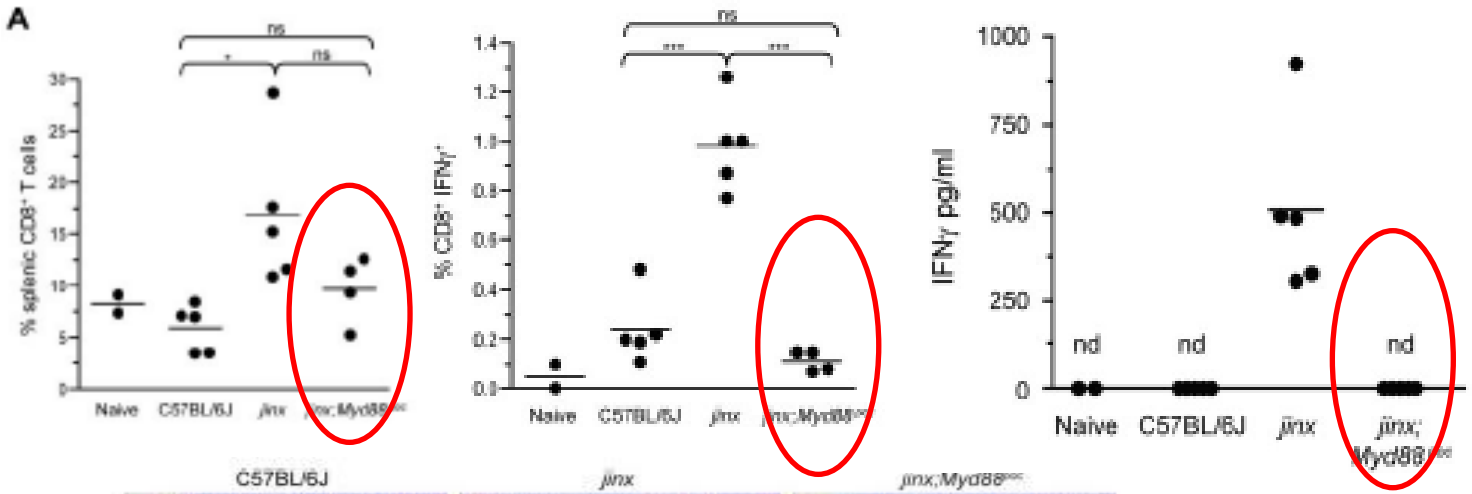
Expansion T CD8+ et macrophages

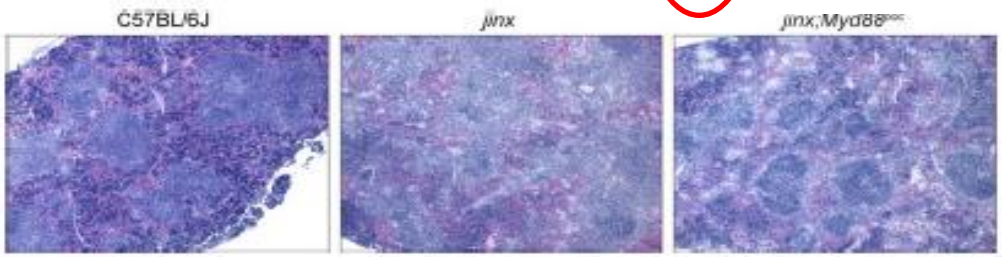
ROLE DE L'ACTIVATION DES TLR

Modèle UNC13D KO + LCMV+ MyD88 KO



Bloquer la voie des TLR diminue les CD8- IFNg et améliore le SAM





Krebs, Blood 2011

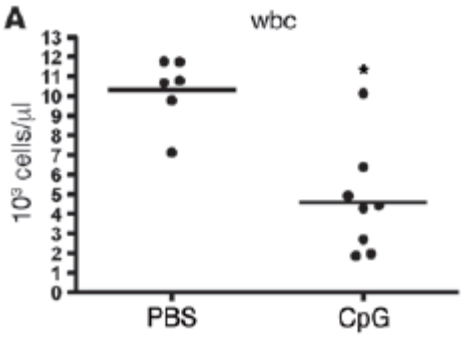
MODELES ANIMAUX
HYPERSTIMULATION INFLAMMATOIRE

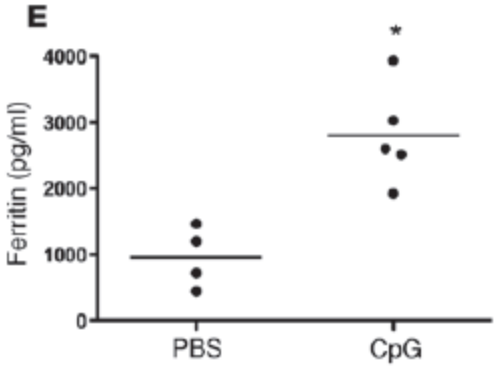
MODELES PLUS RECENTS: Formes secondaires

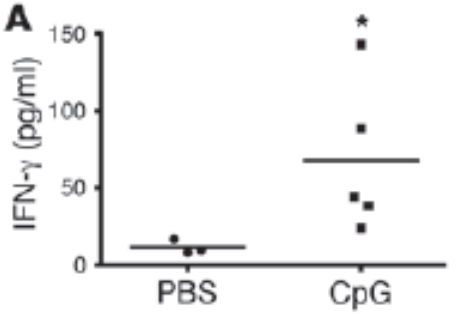
-Stimulation continue de TLR-9 avec CpG

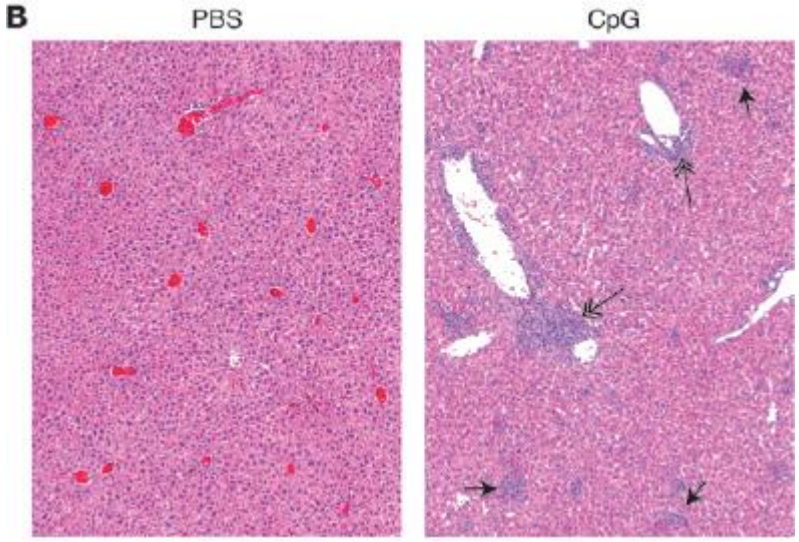
-Transgéniques IL-6 + LPS

ACTIVATION CONTINUE DE TLR-9
(Behrens, J Clin Invest 2011)

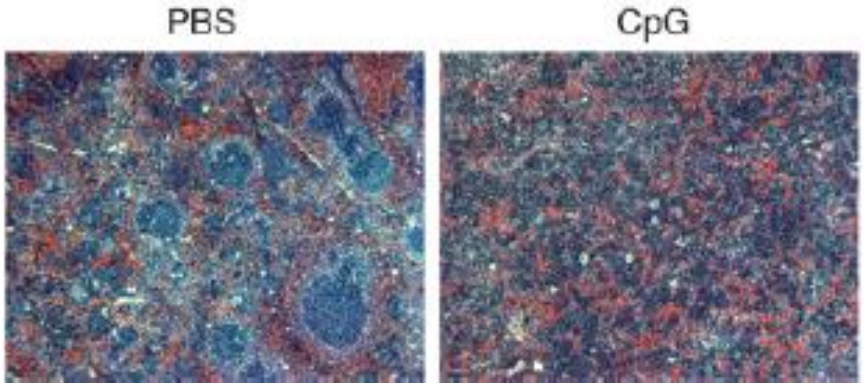






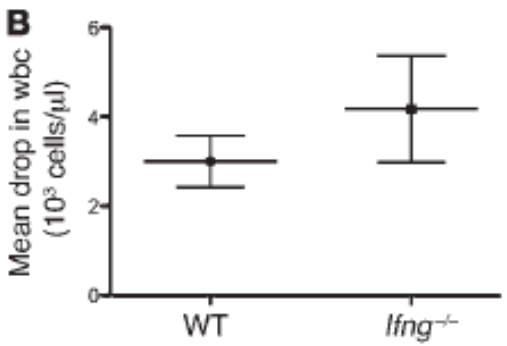


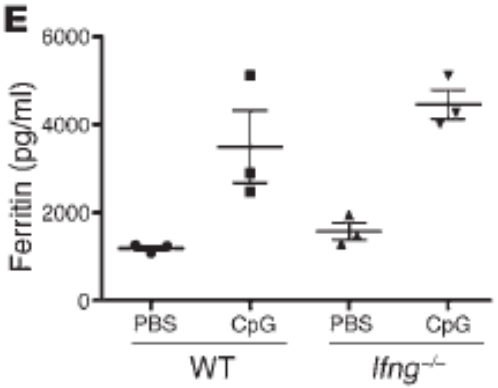
FOIE

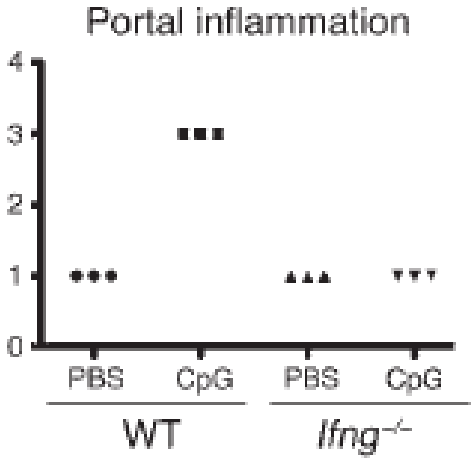


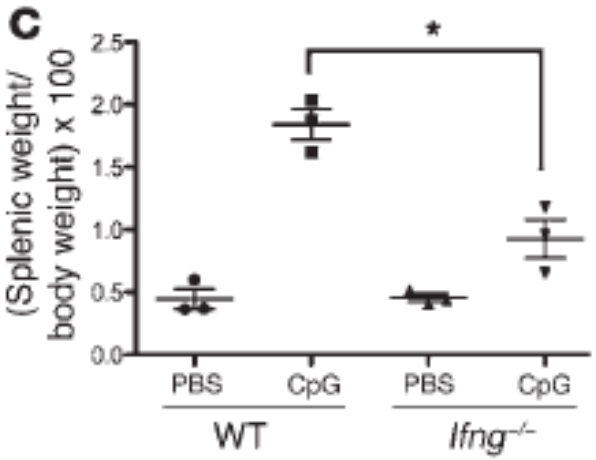
RATE

SAM MAIS SANS HEMOPHAGOCYTOSE++++





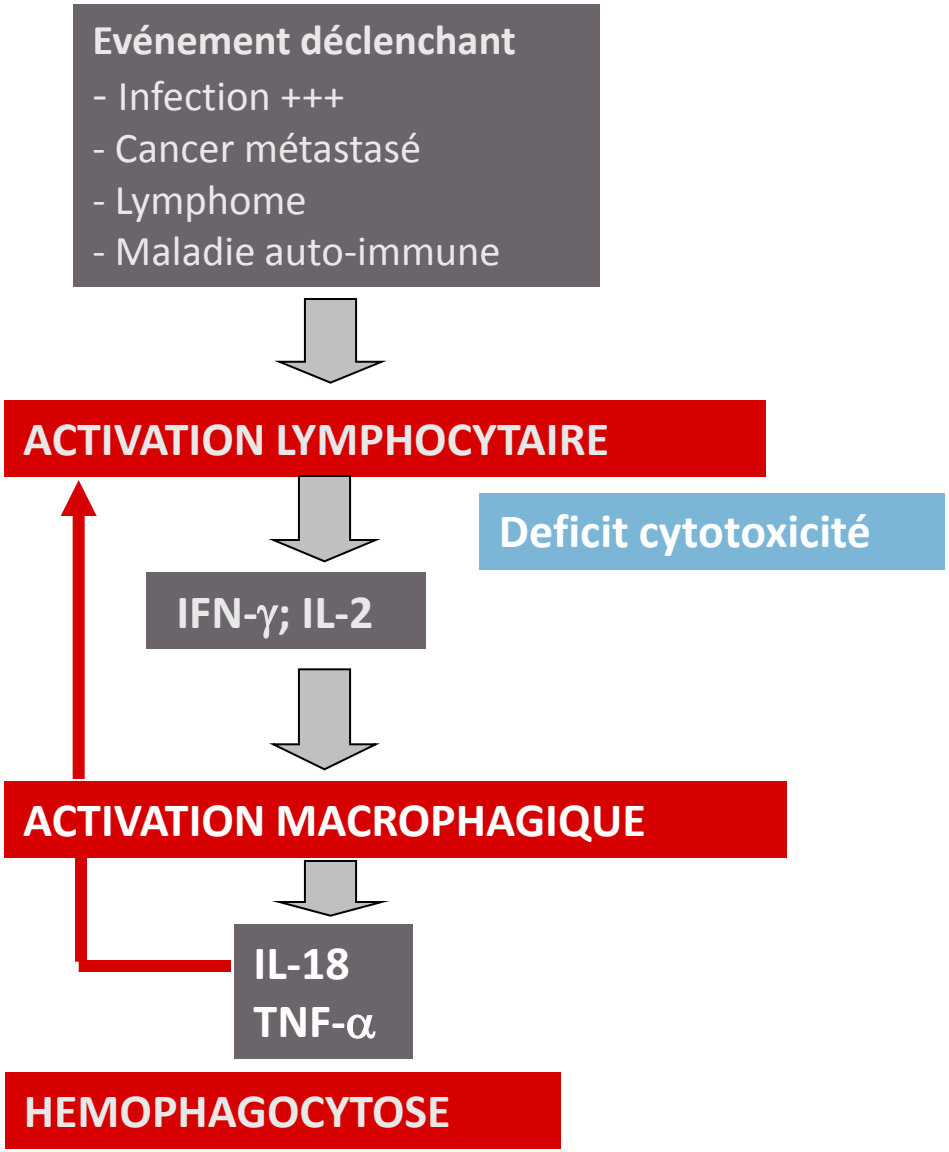




Modèle également dépendant de l'IFN-g qui est donc central dans la physiopathologie

TRAITEMENT

TRAITEMENT LH REACTIONNEL : LES PRINCIPES



Traitement pathologie sous-jacente

- traitement anti-infectieux

ACTIVATION LYMPHOCYTAIRE

- **Corticoïdes**
- **Ciclosporine**
- **Etoposide**

ACTIVATION MACROPHAGIQUE

- **Corticoïdes**
- **Immunoglobulines intraveineuses**

IL-18BPrh ?

SUPPORT TRANSFUSIONNEL

TRAITEMENT : PROTOCOLE HLH-94

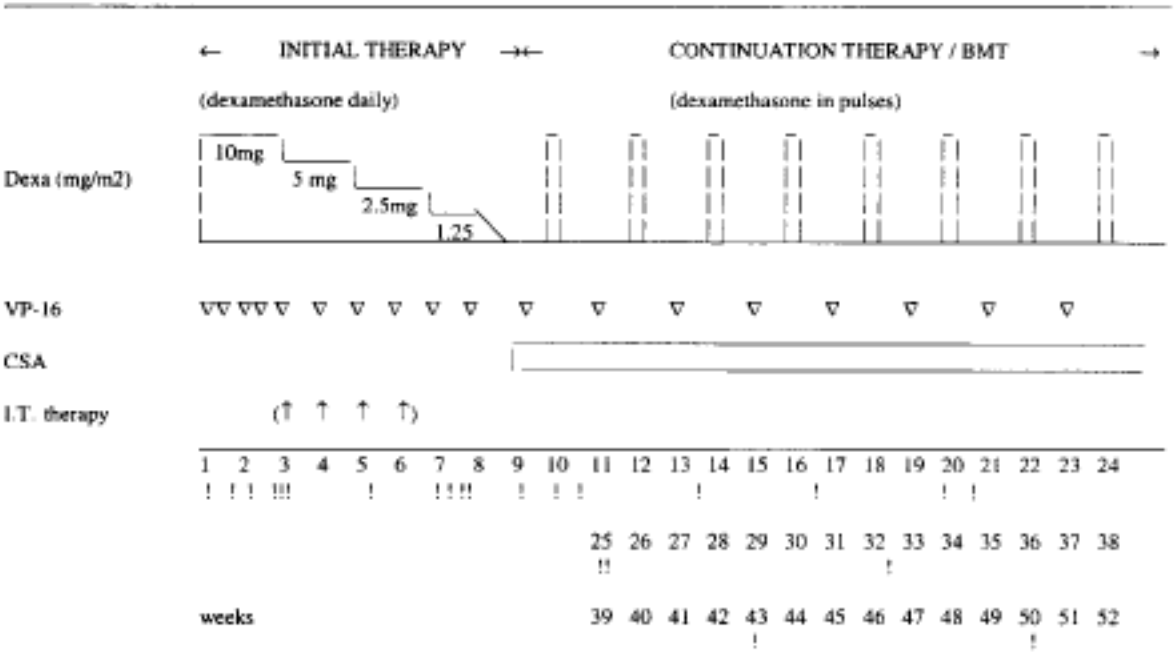


Figure 1. Overview of the treatment protocol HLH-94. Day of death for the 23 patients who died the first year of therapy, except those who underwent BMT, is marked with an exclamation point (!). (BMT – Go to BMT during continuation therapy as soon as an acceptable donor is available, preferably when the disease is nonactive. The patients without either familial or persistent disease were recommended to cease therapy after the initial therapy and restart in case of reactivation. Dexa – dexamethasone daily [pulses are 10 mg/m² for 3 days]; VP-16 – etoposide 150 mg/m² intravenously; CSA – cyclosporin A; I.T. therapy – intrathecal methotrexate [if progressive neurological symptoms or if an abnormal CSF has not improved].)

VP-16: 150mg/m2 2 fois/semaine puis 1 fois/semaine; adaptation fonction rénale
Ciclosporine A à S8:
+/- MTX en intrathecal:

CONCLUSION:

- **QUAND PENSER AU SAM DE L'ADULTE ?**
  - **Cytopénie fébrile**
  - **Contexte, en particulier d'immunodépression**
  - **Examens complémentaires simples**
    - **Ferritine**
    - **Triglycéride**
    - **Myélogramme**

URGENCE THERAPEUTIQUE

50% de décès

1.Traitement anti-infectieux

Corticoïdes

(IgIV)

2.Traitement étiologique

BILAN ETIOLOGIQUE

Myélogramme/BOM

- **Infectieux**
- **Hémopathie, Néoplasie**
- **Maladie systémique**

Plusieurs causes associées

ARBRE GENEALOGIQUE/CONSANGUINITE

FORME GENETIQUE A REVELATION TARDIVE