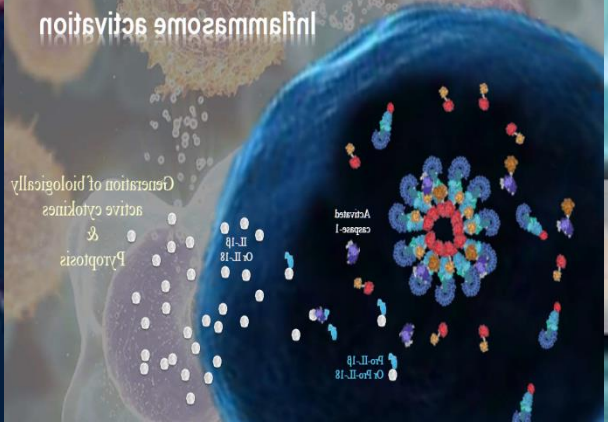
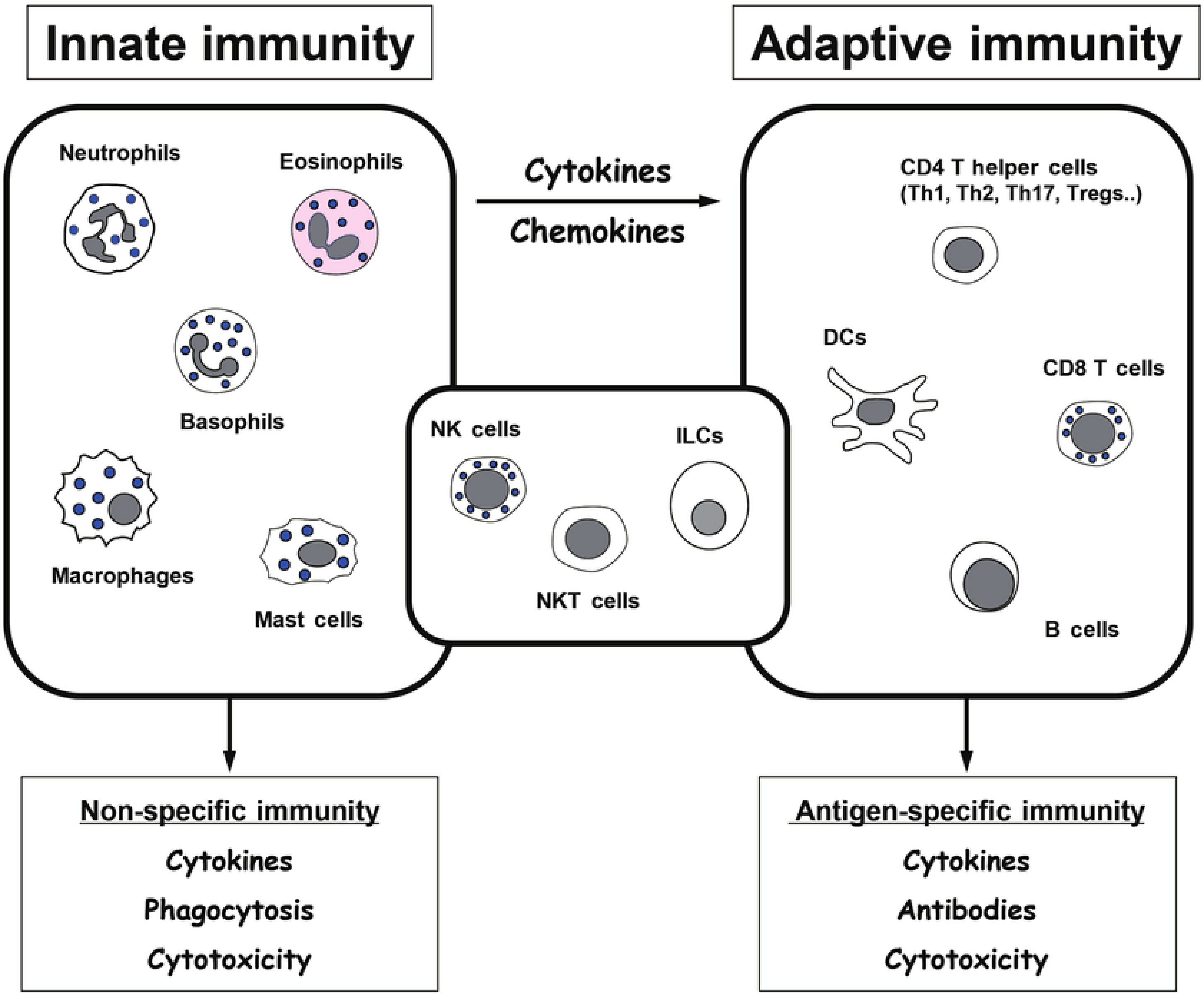


Φλεγμονόσωμα και παθήσεις αναπνευστικού

Ροβίνα Νικολέττα
Επίκουρη καθηγήτρια Πνευμονολογίας - Εντατικής Θεραπείας
ΕΚΠΑ
Α Πανεπιστημιακή Πνευμονολογική Κλινική
ΝΝΘΑ «η Σωτηρία»



Innate immunity
Adaptive immunity
Neutrophils
Eosinophils
Basophils
Macrophages
Mast cells
Cytokines
Chemokines
NK cells
ILCs
NKT cells
CD4 T helper cells
(Th1, Th2, Th17, Tregs..)
DCs
CD8 T cells
B cells
Non-specific immunity
Cytokines
Phagocytosis
Cytotoxicity
Antigen-specific immunity
Cytokines
Antibodies
Cytotoxicity

Innate immunity (Έμφυτη ανοσία)

Η έμφυτη ανοσία αναγνωρίζει τα σημάδια «κινδύνου» εντοπίζοντας μικροβιακά μοτίβα μέσω των υποδοχέων αναγνώρισης προτύπων (pattern-recognition receptors-PRRs)

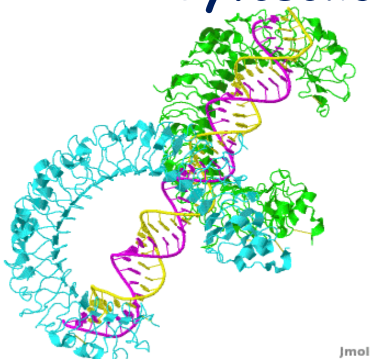
PRRs

- pathogen-associated molecular patterns (PAMPs)
- danger associated molecular patterns (DAMPS)

Οι υποδοχείς PRR εκφράζονται στα κύτταρα άμυνας πρώτης γραμμής (μακροφάγα, μονοκύτταρα, δενδριτικά κύτταρα, ουδετερόφιλα, επιθηλιακά κύτταρα)

Συνδέονται στη μεμβράνη→ Toll like receptors, C-type lectin receptors

Cytosolic → NOD like receptors, RIG like receptors



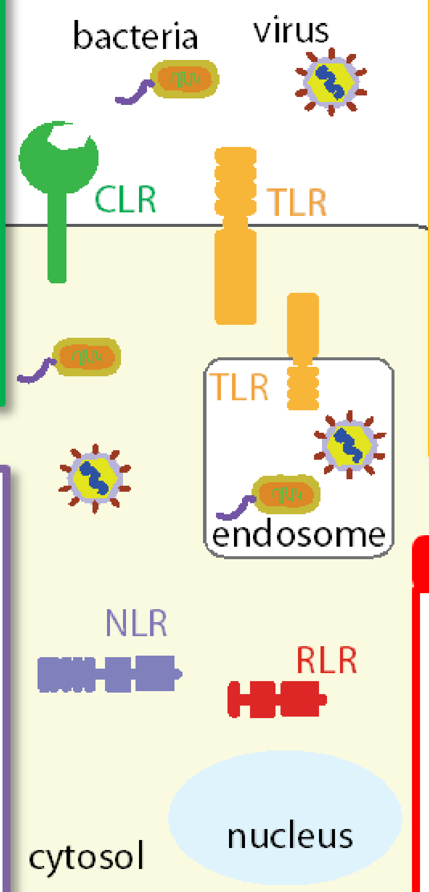
Schroder & Tschopp The inflammasomes Cell 2010

Pattern recognition receptors ligands

CLR

- Transmembrane proteins localized at the **plasma membrane**
- Recognize **glycans** from the wall of fungi and some bacteria
- Activate kinase **syk** and **CARD9/MALT1 /Bcl-10** adapter complex

Example: Dectin-1/CLEC7A recognizes β-1,3-glucans of the cell wall of various fungi species



TLR

- Transmembrane proteins localized either at the **plasma membrane** or in **endosomes**
- Broad range of specificities recognizing **proteins, nucleic acids, glycans** etc…
- Activate **MAP kinase, NFκB** and **IRF** pathways

Example: TLR4 recognizes lipopolysa-ccharide (LPS) , a component of the gram- bacteria cell wall

NLR

- **Cytoplasmic** sensors
- Multiple subfamilies:

NLPRs recognize bacterial, viral, parasitic and fungal PAMPs

AIM2 detects viral and bacterial **DNA**

- Form multiprotein signalling complexes known as **inflammasomes**
- Activates caspase-1-mediated processing and activation of pro-interleukins IL-1β and IL-18

NOD1 and NOD2 recognize bacterial peptidoglycan

RLR

- **Cytoplasmic** sensors of **viral RNA**
- Signal via the mitochondrial adaptor protein **MAVS**
- Trigger antiviral responses including the production of type I interferon

Examples: RIG-I and MDA5

Rossana Zaru, European Bioinformatics Institute EMBL-EBI, UK

British Society for immunology

NLRP3 inflammasome activators

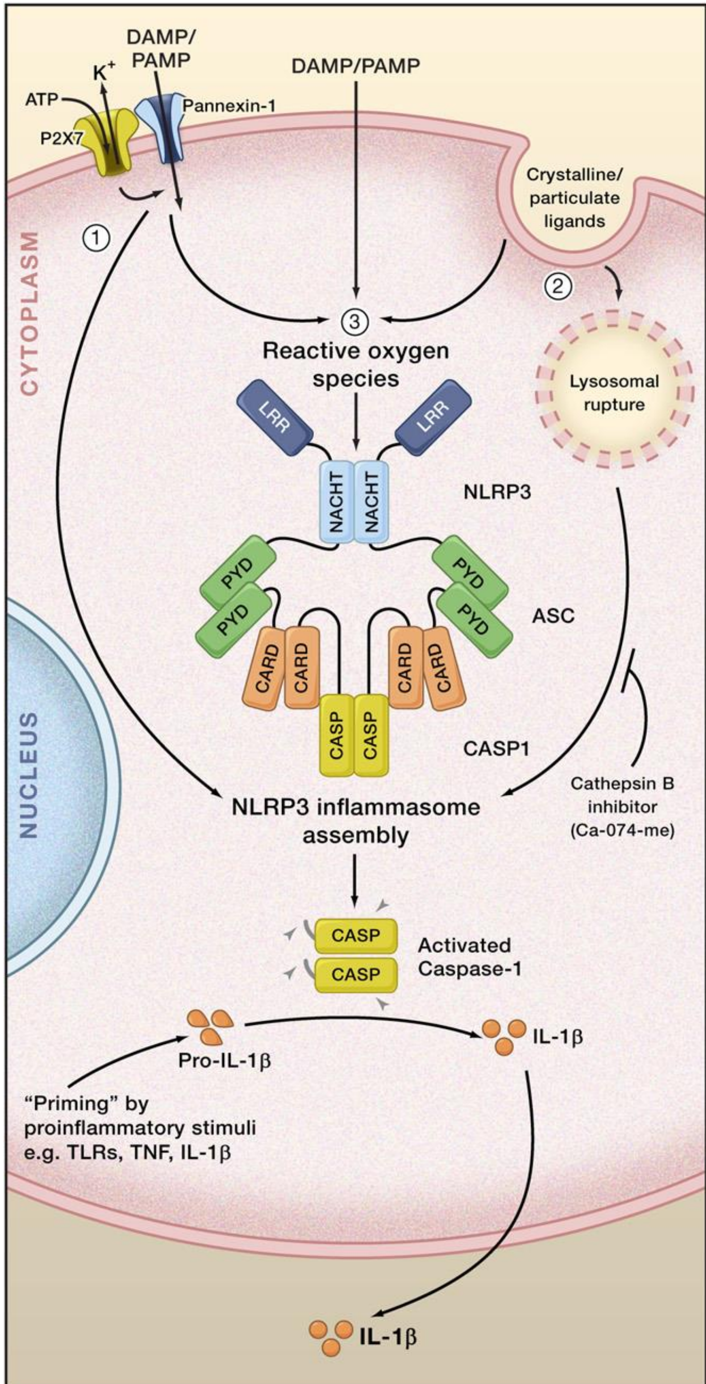
Activator	Source	Examples
DAMP	Self-derived	ATP, cholesterol crystals, monosodium urate crystals, calcium pyrophosphate dihydrate crystals, calcium oxalate crystals, soluble uric acid, neutrophil extracellular traps, cathelicidin, α-synuclein, amyloid-β, serum amyloid A, prion protein, biglycan, hyaluronan, islet amyloid polypeptide, hydroxyapatite, haeme, oxidized mitochondrial DNA, membrane attack complex, cyclic GMP–AMP, lysophosphatidylcholine, ceramides, oxidized phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine and sphingosine
	Foreign-derived	Alum, silica, aluminium hydroxide, nanoparticles, carbon nanotubes, chitosan, palmitate (also self-derived), UVB, imiquimod (R837)/CL097 and resiquimod (R848)
PAMP	Bacterial	Lipopolysaccharide, peptidoglycan, muramyl dipeptide, trehalose-6,6'-dibehenate, c-di-GMP–c-di-AMP, bacterial RNA and RNA–DNA hybrid
		Toxins: nigericin (*Streptomyces hygroscopicus*), gramicidin (*Brevibacillus brevis*), valinomycin (*Streptomyces fulvissimus* and *Streptomyces tsusimaensis*), β-haemolysin (*Streptococcus* sp. 'group B'), α-haemolysin (*Staphylococcus aureus*), M protein (*Streptococcus* sp. 'group A'), leucocidin (*Staphylococcus aureus*), tetanolysin O (*Clostridium tetani*), pneumolysin (*Streptococcus pneumoniae*), listeriolysin O (*Listeria monocytogenes*), aerolysin (*Aeromonas hydrophila*), streptolysin O (*Streptococcus pyogenes*), enterohaemolysin (*Escherichia coli* O157:H7), haemolysin BL (*Bacillus cereus*), adenylate cyclase toxin (*Bordetella pertussis*), M protein (*Streptococcus* sp. 'group A') and maitotoxin (*Marina* spp. dinoflagellates)
	Viral	Double-stranded RNA and single-stranded RNA
	Fungal	β-Glucans, hyphae, mannan and zymosan

Structures of the inflammasomes

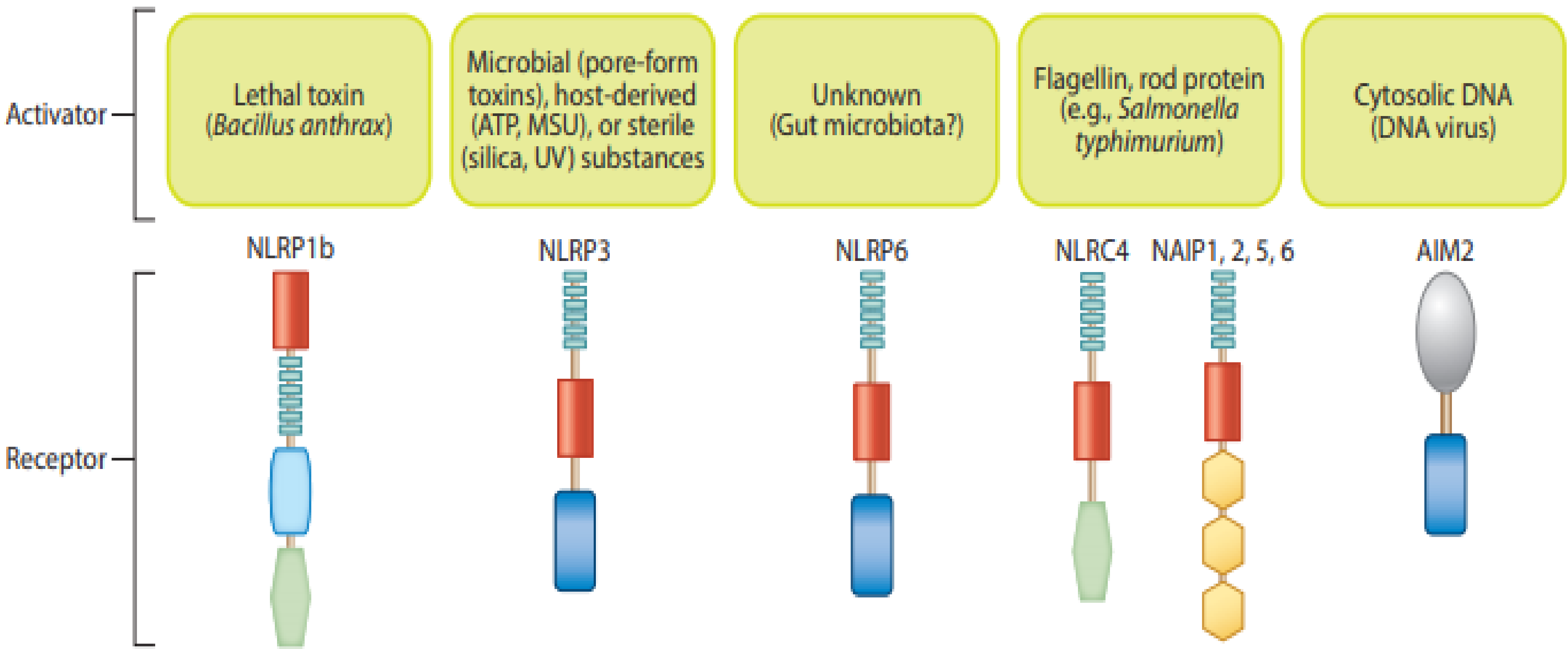
- NLR family
  - *a sensor - central nucleotide-binding* n
    n 5 NPUa6 n 9 p
    p n o P: n p :
    p n 5Y 6
  - *an adaptor molecule known as apoptosis-associated speck-like protein containing caspase activation and recruitment domain (CARD) (ASC),* 5 f 6 n
  - *the effector molecule caspase-1*

  - p n n → Y 5 9 6
  - d -n-pn np p - n -→ Y P
- Y -J- - - p - -n- n -
  - O -p n np

p -3-a p -a - n n -P - = =

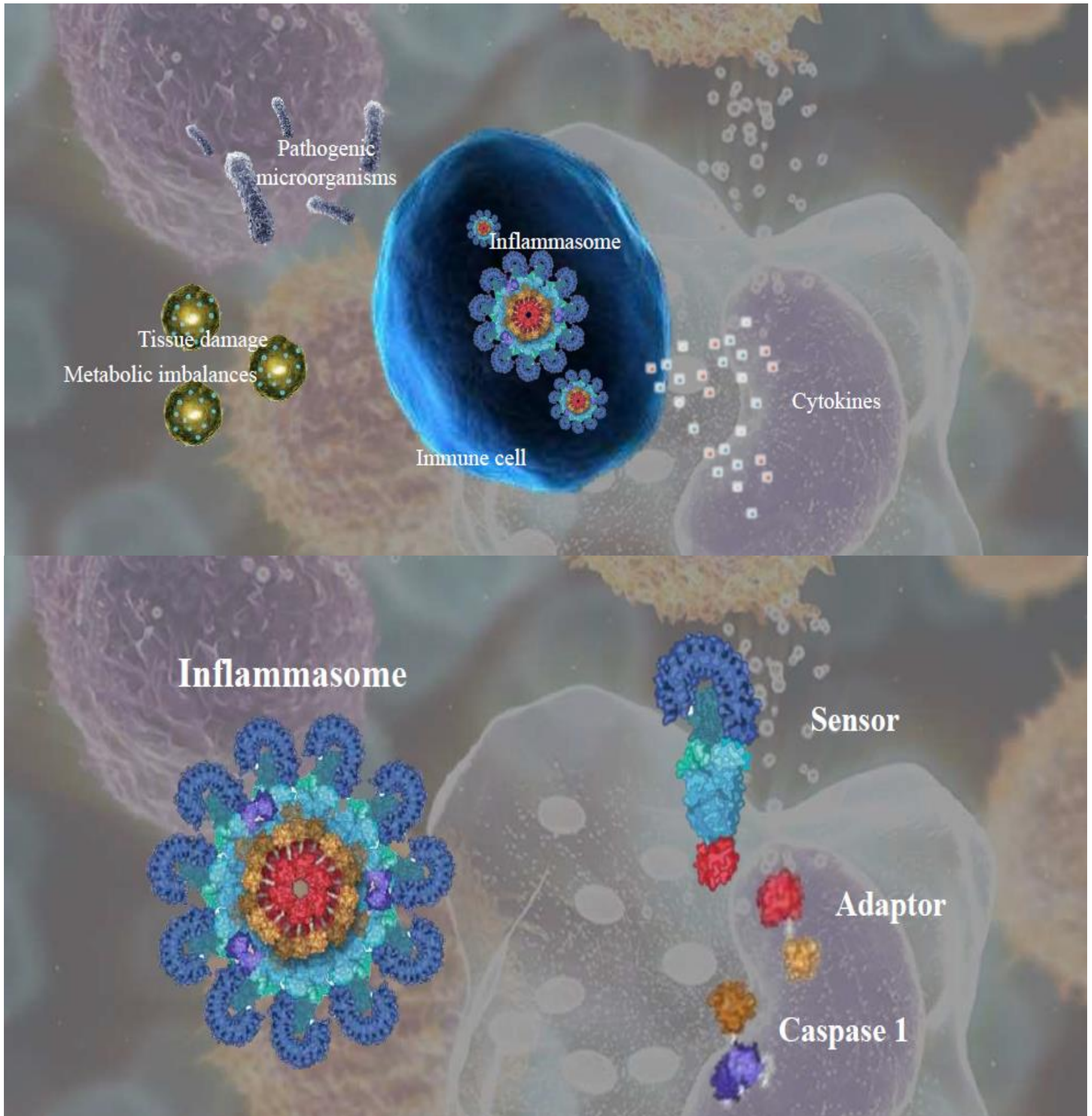


NOD-like receptors and their activators

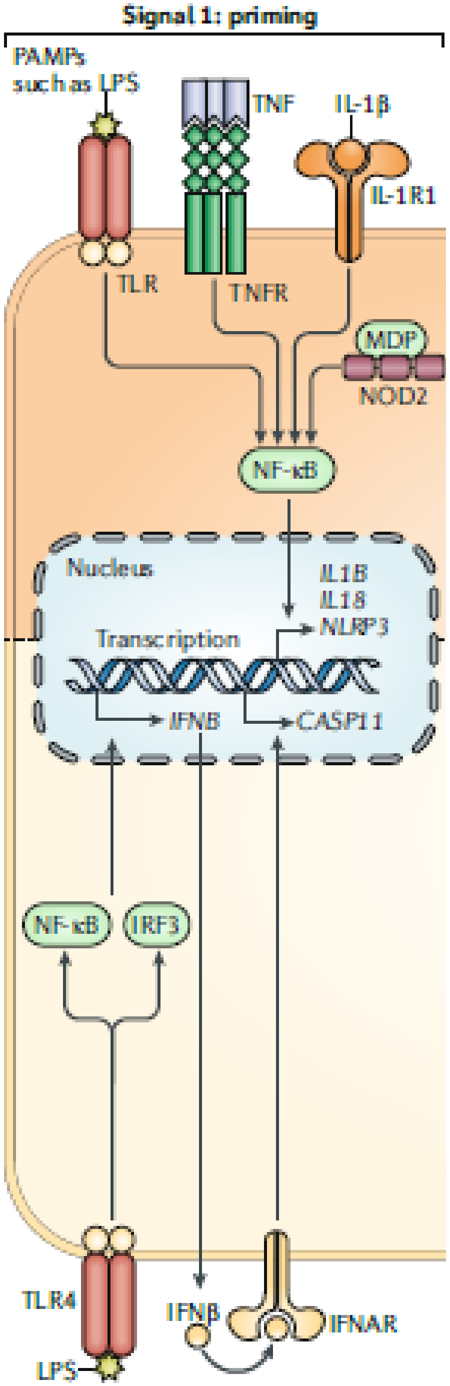


N - - ; = D-S o- =HDF AD : AFA

Οι PRRs ενεργοποιούν έναν καταρράκτη σηματοδότησης που επάγει φλεγμονώδη απάντηση ➡ ενεργοποίηση της επίκτητης ανοσίας

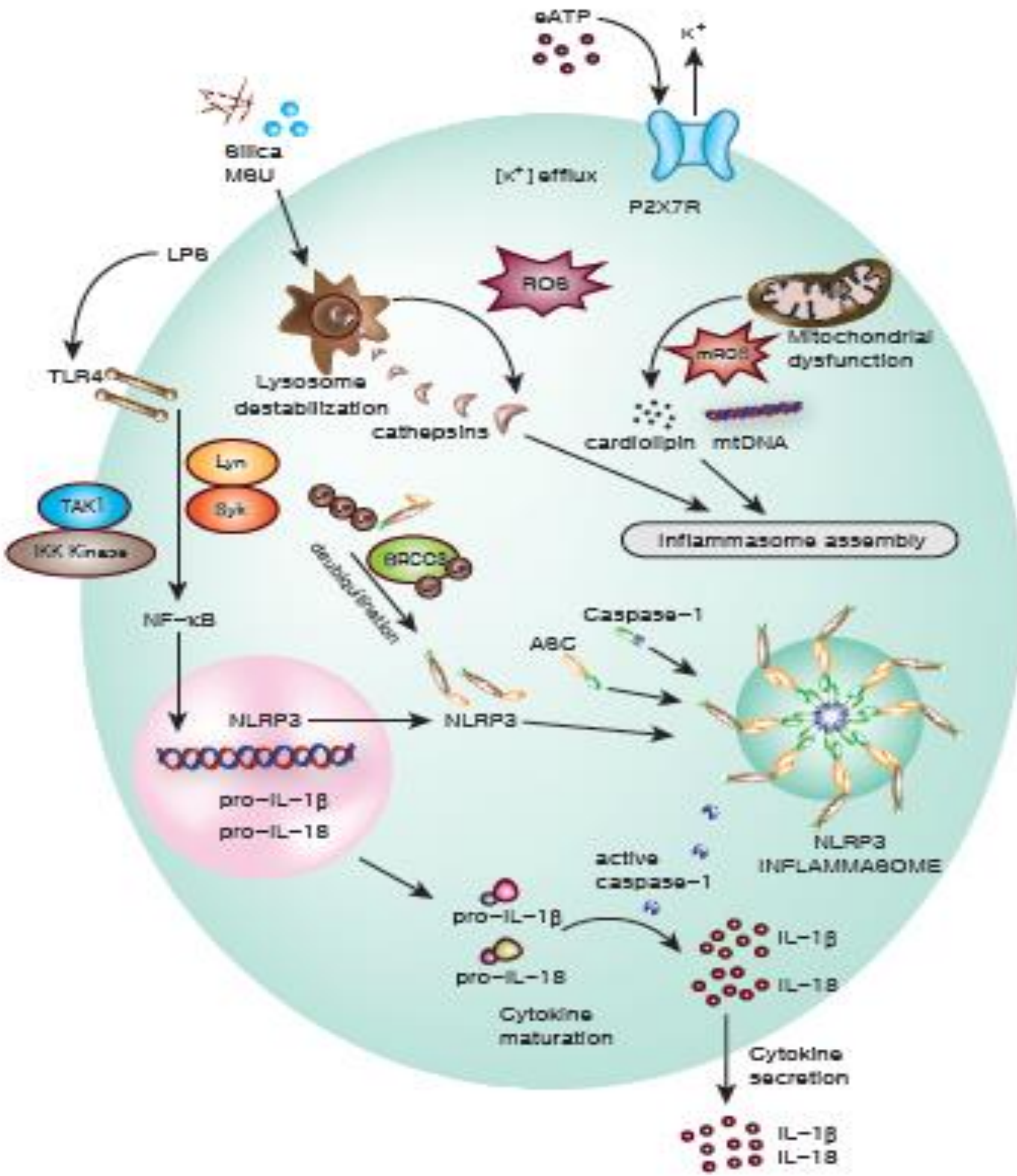


Alarmins



- - -o - -np n - -p - -
n : n p n - p n - n -5 N 69
n - - - n p n - n - -pn pn
n - : pn pn - Y -5 : 9Y : n - - n :
p n - - 6 n n -p ;-

a - Y - n n - - -np n - n - -n- : - np n -



Step 1

n - - pn - -o - n - o -5 ; ;9Y 6 -a - - p -5 ; ;9 aY A6n - n - p ;-a - - - np n - - S: O p - n pn - - p -n -np n - - n p - - n n p 9 p - Y 9 n - - : - - n n : n - p -5; ;9 : Y: -n - : Y: E6-

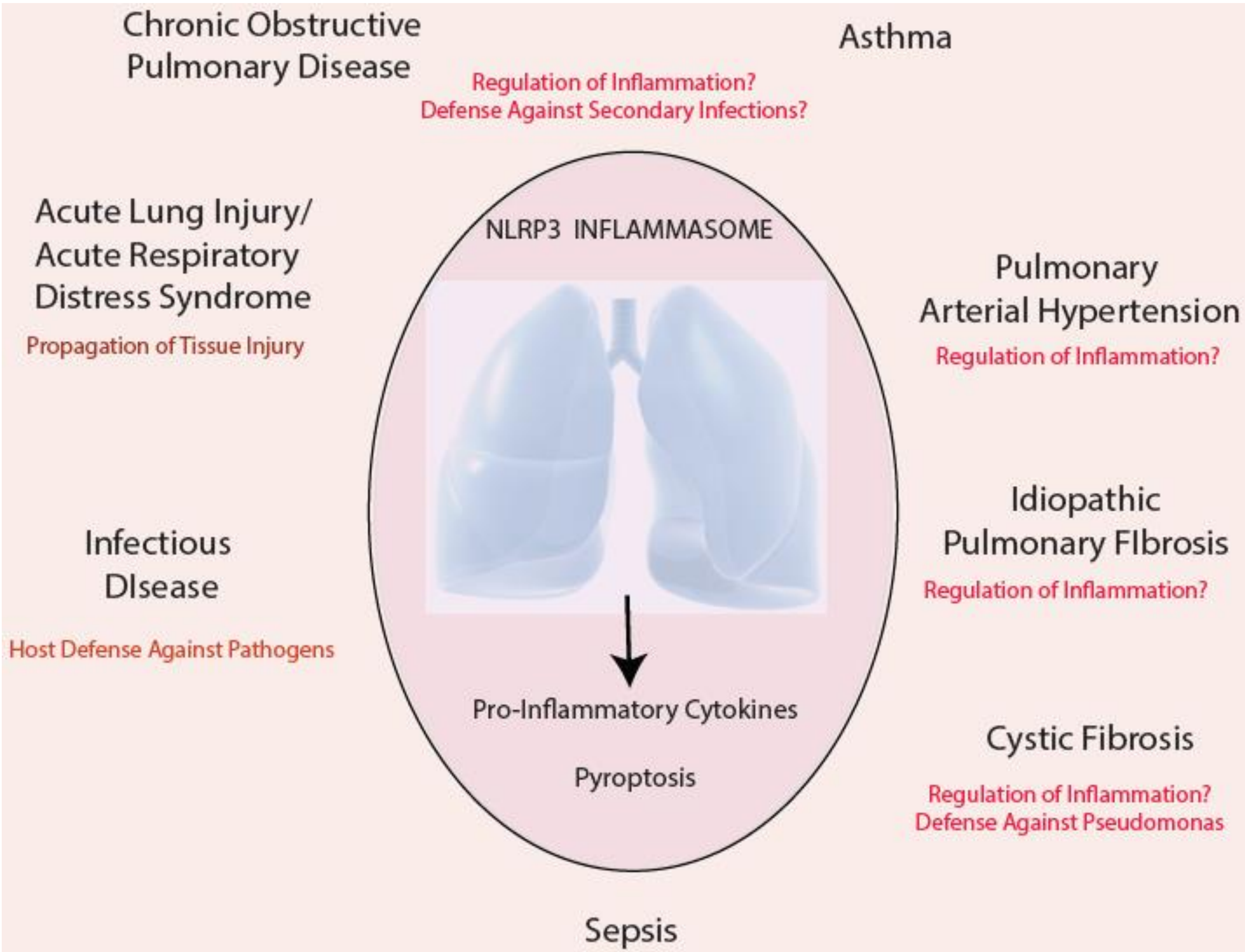
Step 2

N- p - n - - - -n o - - - n n - - n - p -5 ; ;9 Y 9N P9 : pn n : 6-

- a -pn pn - n - - -o - eD- n -o - n -5 ; ;9 Na 69 p - - n - - ;-
- N n -p o - n - n - p - - no n - - -n - -n - n p - -p n - o n - p -n - - n - p n -5 b 69n - - - - p n9 n - - - n - - p n - N - p -n -pn n - N;-
- Np n - - n n :n pn - pn n : - - - -np n - 5p n n 6 - : n n -p - 5 ; ;9 Y: 9 Y: E69 - - - p -

N -W -P - -O ; = C-S olHBA5 6 B : C=

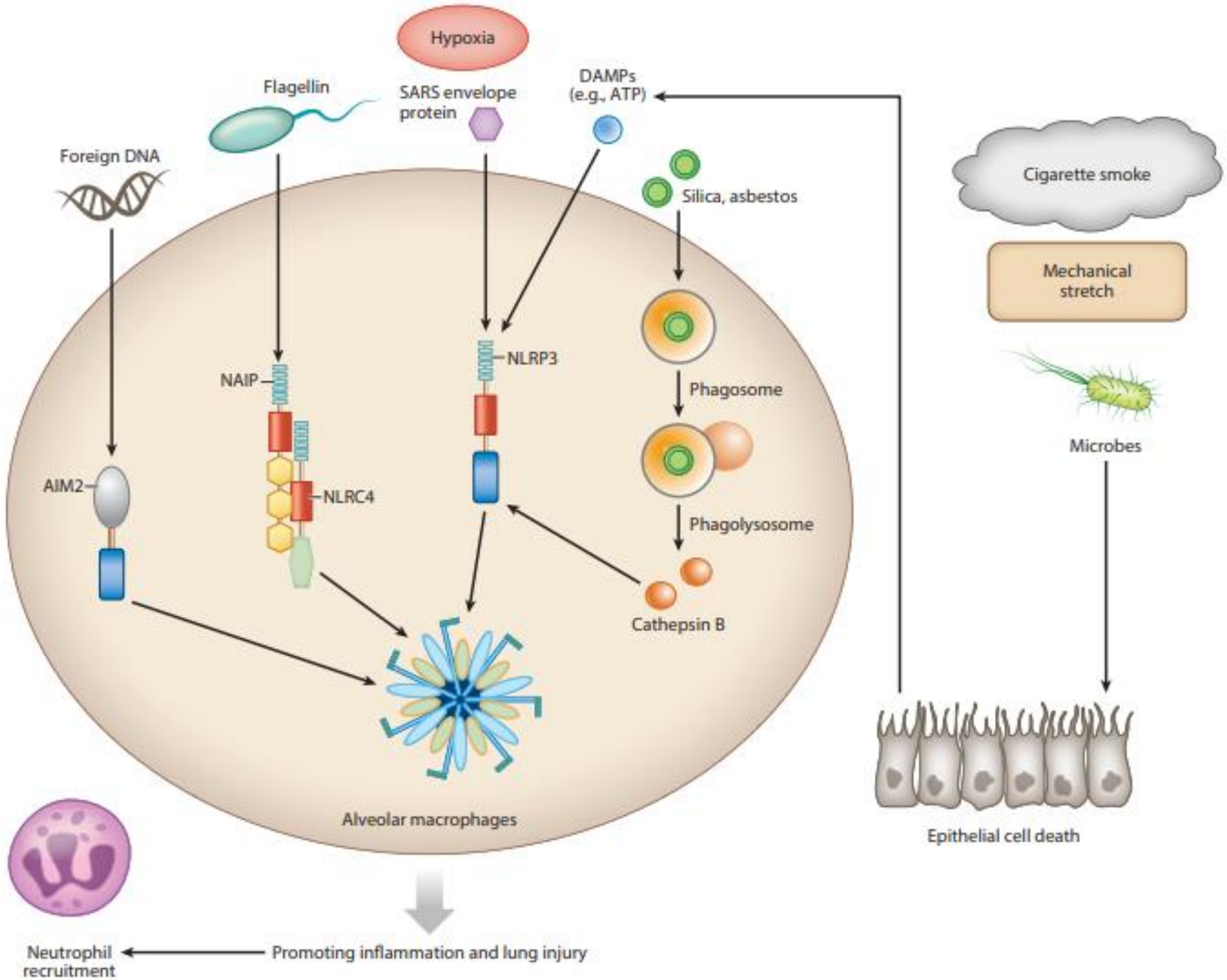
NLRP3 inflammasome in lung disease



N -W -P - -O ; = C-S oHBA5 6 B : C=

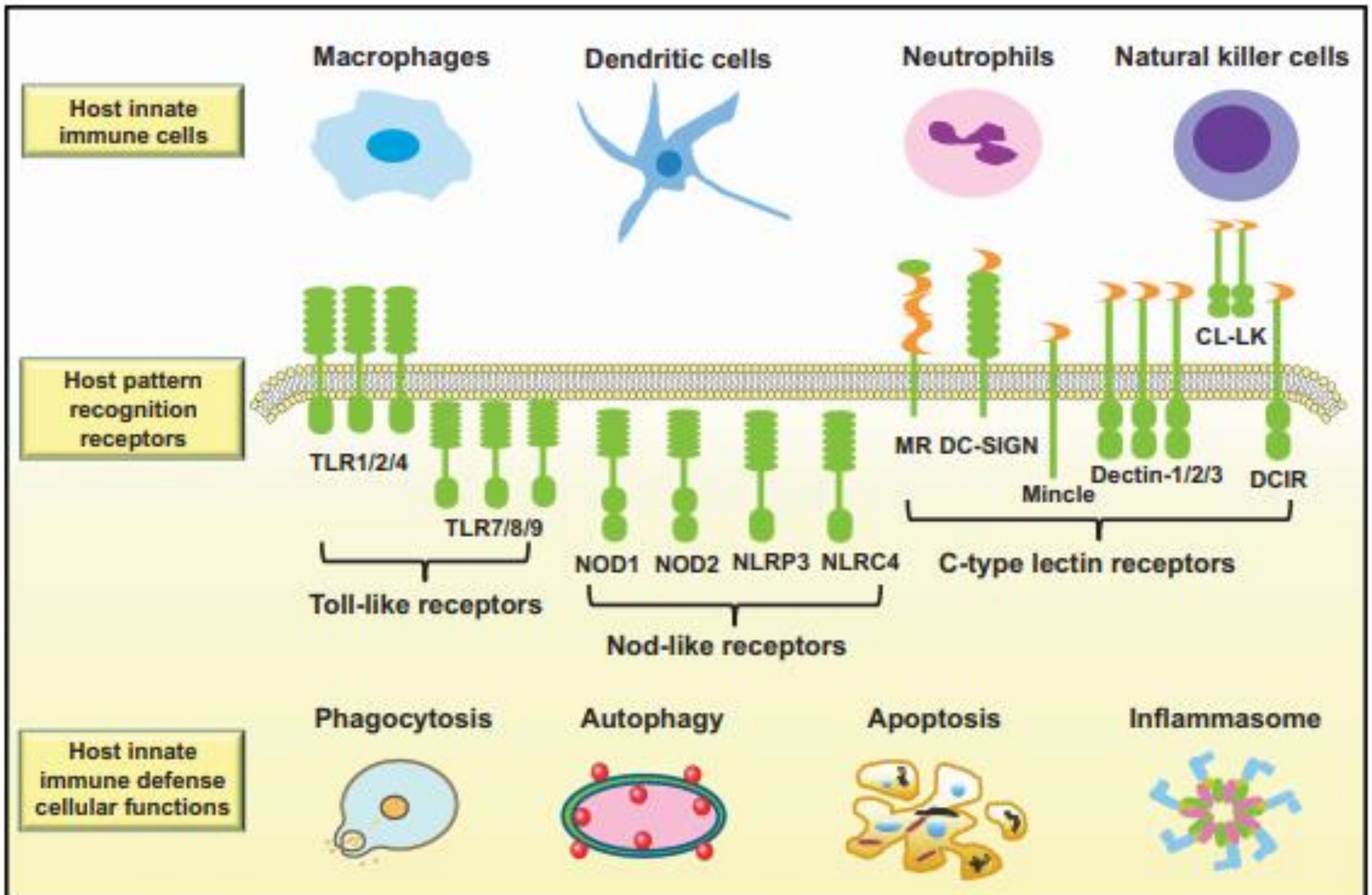
Infectious disease

Environmental triggers of inflammasome activation in a pulmonary macrophage



Innate immunity in tuberculosis: host defense *vs* pathogen evasion

Cui Hua Liu[1,2], Haiying Liu[3] and Baoxue Ge[4]



P - - ; = D- pHA5 6FC :FDB

PULMONARY PERSPECTIVE

Investigating the Role of Nucleotide-Binding Oligomerization Domain–Like Receptors in Bacterial Lung Infection

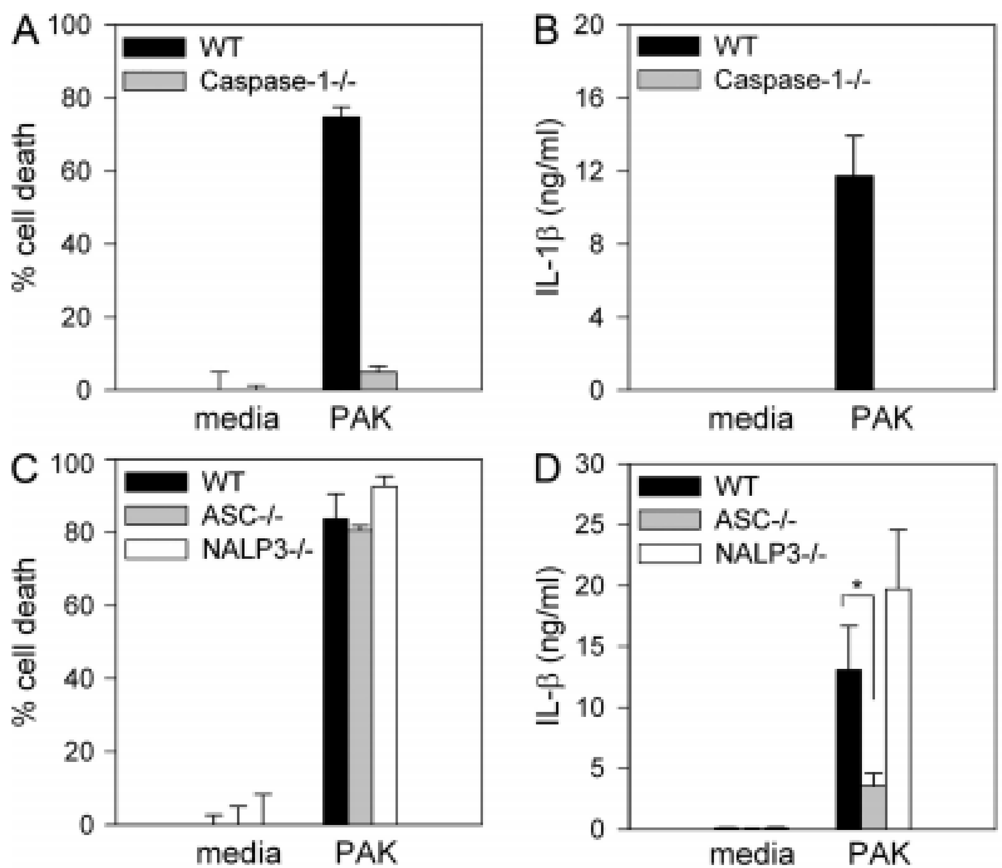
Mary Leissinger[1], Ritwij Kulkarni[1], Rachel L. Zemans[2], Gregory P. Downey[2], and Samithamby Jeyaseelan[1,3]

Bacteria	MAMP	NLR	Phenotype*
Bordetella pertussis	CyaA	Unknown Inflammasome	S*nd* N*nd* BB↑ BD*nd* (IL-R1$^{-/-}$ mice)
Chlamydophila (Chlamydia) pneumoniae	Unknown	Unknown Inflammasome	S↓ N*nd* BB↑ BD*nd* (caspase-1$^{-/-}$ mice)
	PGN	NOD1/NOD2	S↓ N↑ BB↑ BD*nd*
Klebsiella pneumoniae	Unknown	NLRC4	S↓ N↓ BB↑ BD↑
	Unknown	NLRP3	S↓ N↓ BB*nd* BD*nd*
Legionella pneumophila	Flagellin	NLRC4	S*nd* N*ns* BB↑ BD*nd*
	PGN	NOD1/NOD2	S↓ N↓ BB↑ BD*nd*
Mycobacterium tuberculosis	mAGP	NOD2	S*ns* N*ns* BB*ns* BD*nd*
Pseudomonas aeruginosa	Flagellin/ExoUT3SS	NLRC4	S*ns* N*nd* BB↑ BD↑
Staphylococcus aureus	MDP	NOD2	S*ns* N↓ BB*ns* BD*nd*
Streptococcus pneumoniae	Pneumolysin	NLRP3	S↓ N*ns* BB*ns* BD*ns*

N -W -P -Pn - ; = A-W - BHEF5 6 AC :E

Immune recognition of *Pseudomonas aeruginosa* mediated by the IPAF/NLRC4 inflammasome

Fayyaz S. Sutterwala,[1,2] Lilia A. Mijares,[2,4] Li Li,[2,4] Yasunori Ogura,[1]
[redacted]

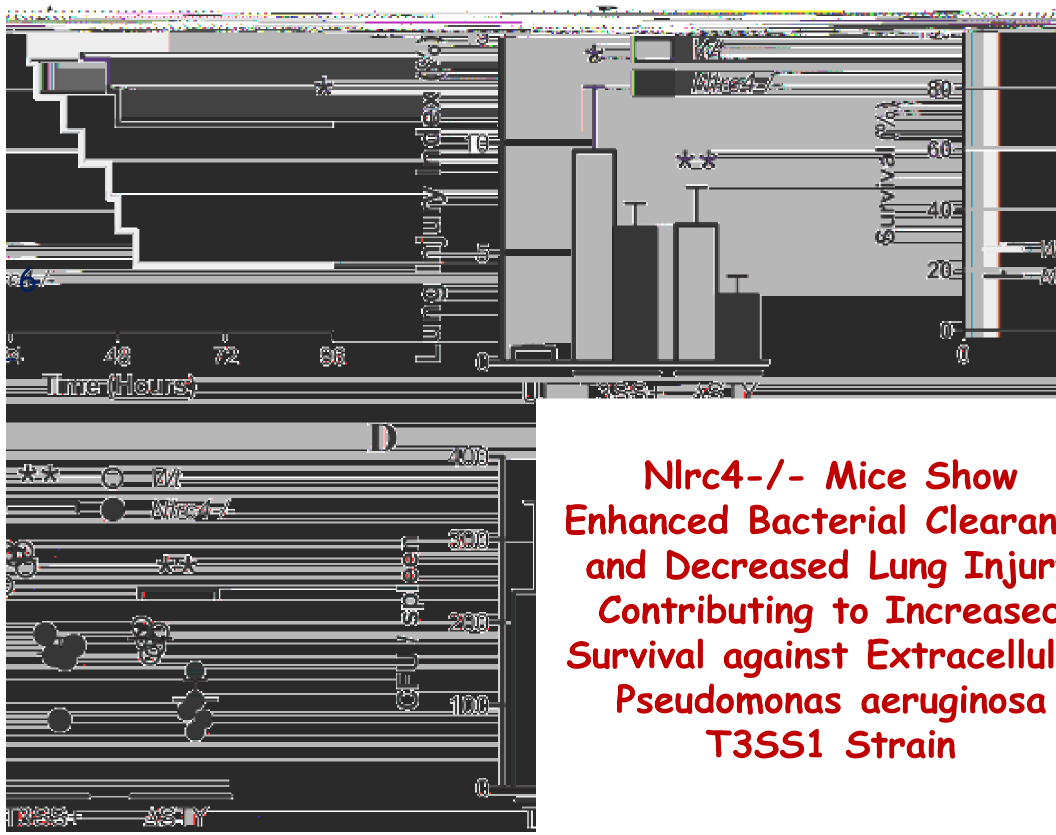


WR - ; ==D- p- AH=A5 6 B:AB

ORIGINAL ARTICLE

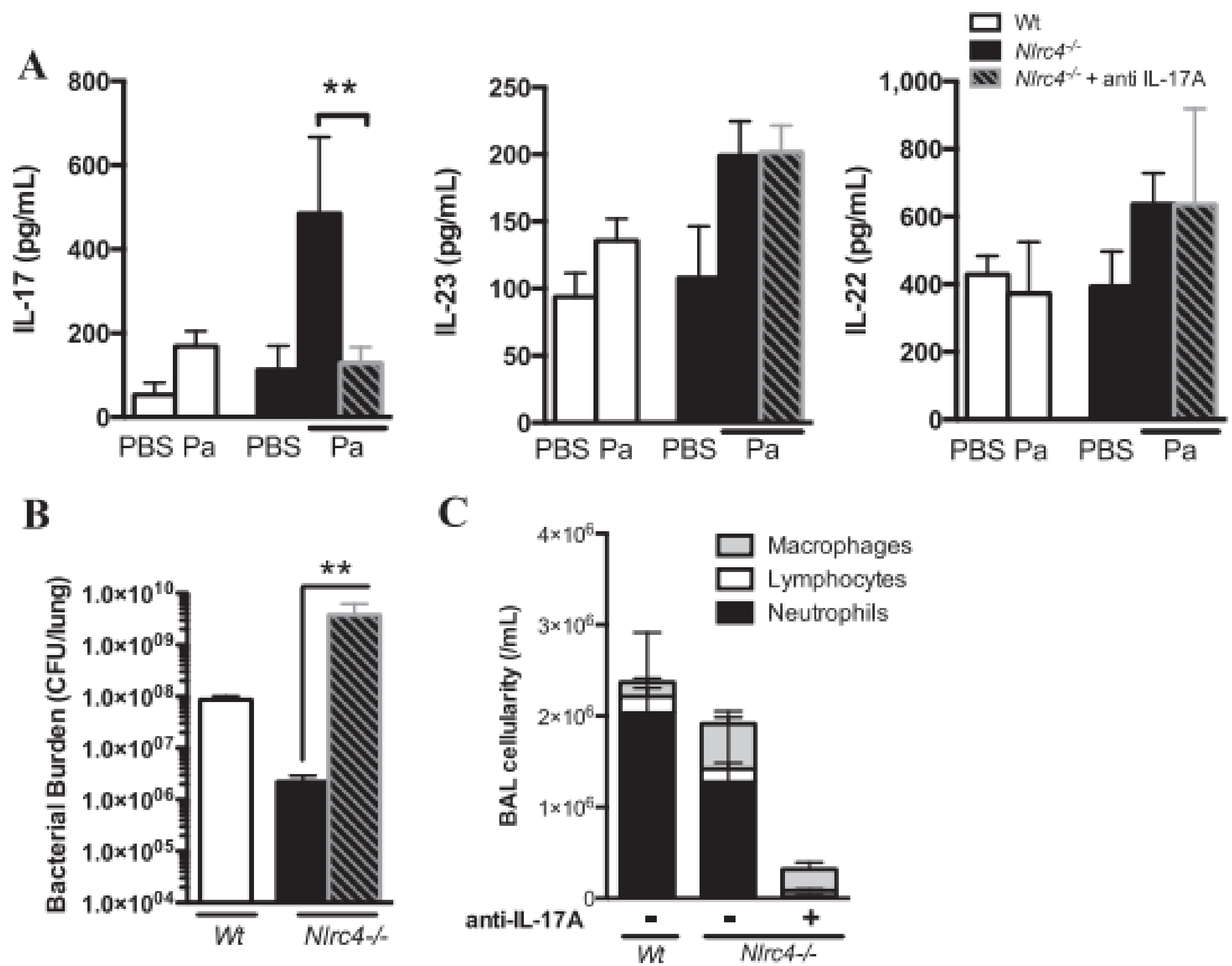
Pseudomonas aeruginosa Type-3 Secretion System Dampens Host Defense by Exploiting the NLRC4-coupled Inflammasome

Maillard, Emmanuel Faure, Jean-Baptiste Mear, Karine Faure, Sylvain Normand, Aurélie Couturier, Teddy Grandjean, Viviane Balloy, Bernhard Ryffel, Rodrigue Dessein, Michel Chignard, Catherine Uyttenhove, Benoit Guery, Philippe Gosset, Mathias Chamaillard, and Eric Kipnis



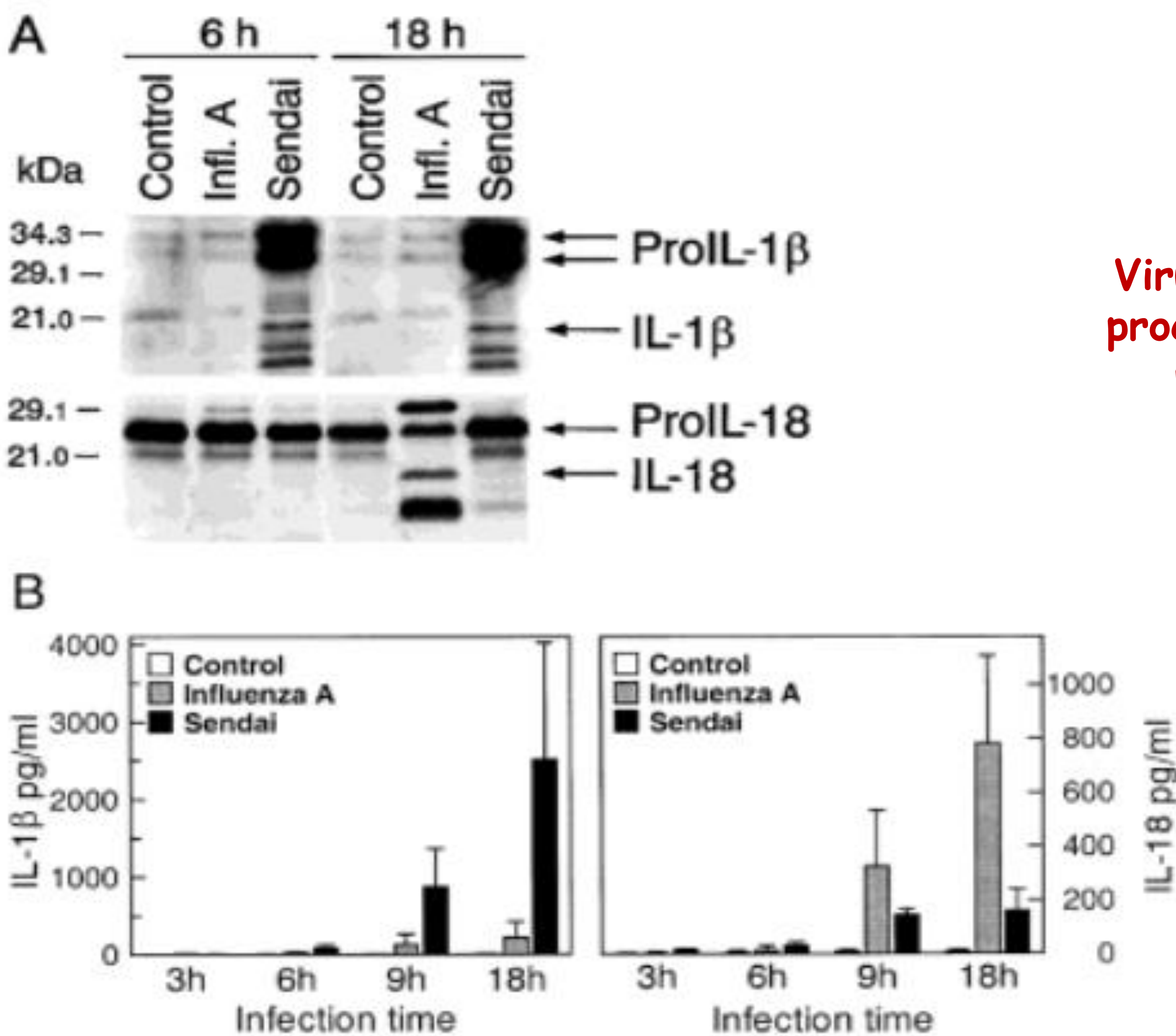
Nlrc4-/- Mice Show Enhanced Bacterial Clearance and Decreased Lung Injury Contributing to Increased Survival against Extracellular Pseudomonas aeruginosa T3SS1 Strain

IL-17-mediated Host Response Is Increased in Nlrc4-/- Mice



Virus infection induces proteolytic processing of IL-18 in human macrophages via caspase-1 and caspase-3 activation

Jaana Pirhonen, Timo Sareneva, Ilkka Julkunen and Sampsa Matikainen

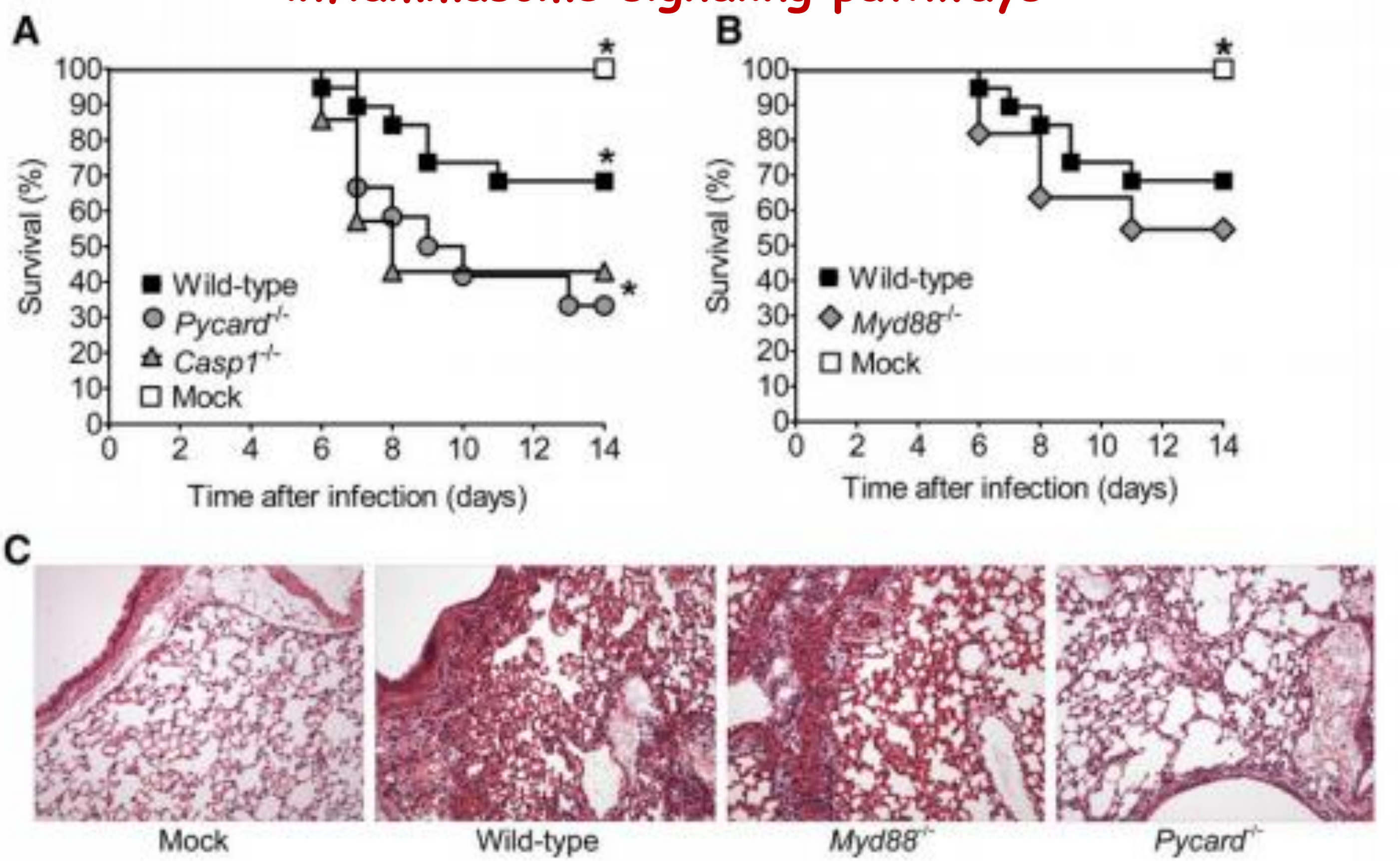


Virus infection induces the processing of pro-IL-1 and pro-IL-18 into their mature forms in macrophages

The NLRP3 Inflammasome Mediates *in vivo* Innate Immunity to Influenza A Virus through Recognition of Viral RNA

Irving C. Allen[1], Margaret A. Scull[2,3], Chris B. Moore[1], Eda K. Holl[2], Erin McElvania-TeKippe[2], Debra J. Taxman[2], Elizabeth H. Guthrie[1], Raymond J. Pickles[2,3], and Jenny P.-Y. Ting[1,2]

Pathogenicity and immune response in mice deficient in inflammasome signaling pathways

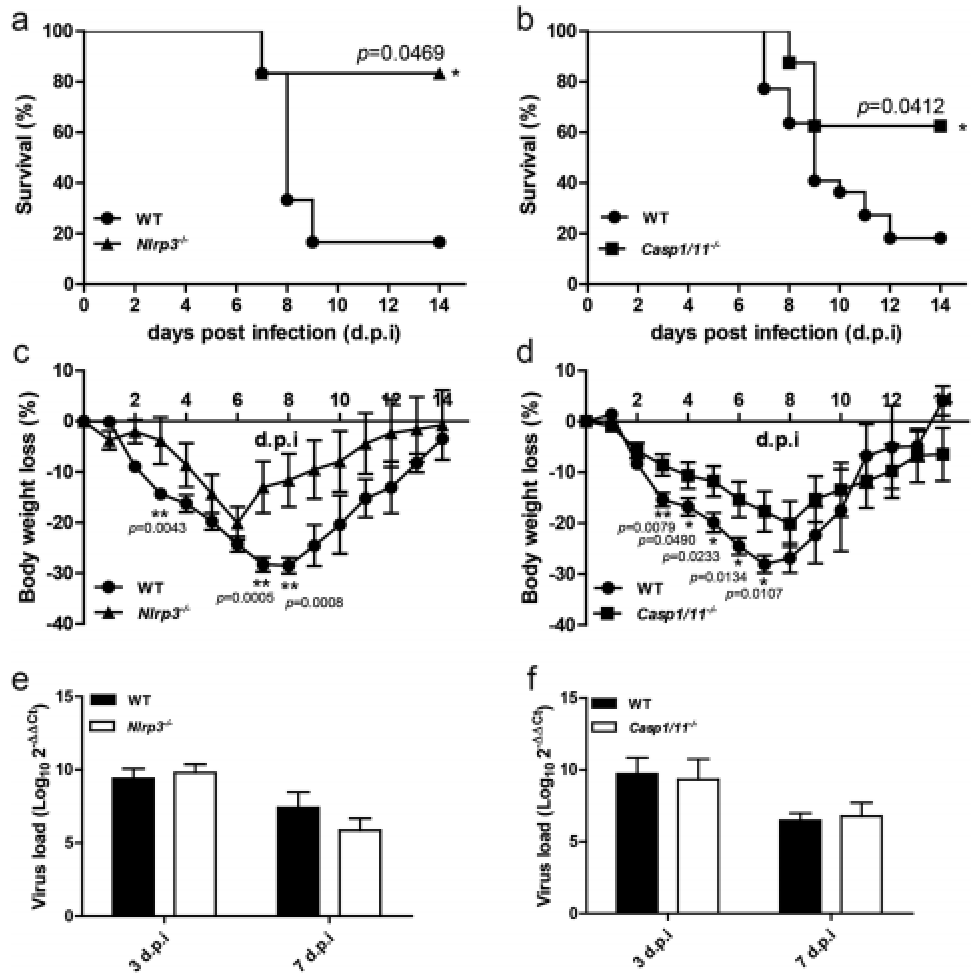


==F-N - DH=5A6BBC: CB

The H7N9 influenza A virus infection results in lethal inflammation in the mammalian host via the NLRP3-caspase-1 inflammasome

Yuqin Yang[3], Xiaonan Ren[1], Yanling Feng[1], Lixiang ... g[1], Zhigang Song[1], Di Tian[1], Yunwen Hu[1,3], Xiaohui

Rongrong Ren[1], Shuxian Wu[2], Jialin Cai[4], Y... Chen[1], Boyin Qin[1], Chunhua Xu[1], Hua Yan... Zhou[1,3] & Guangxun Meng[2]



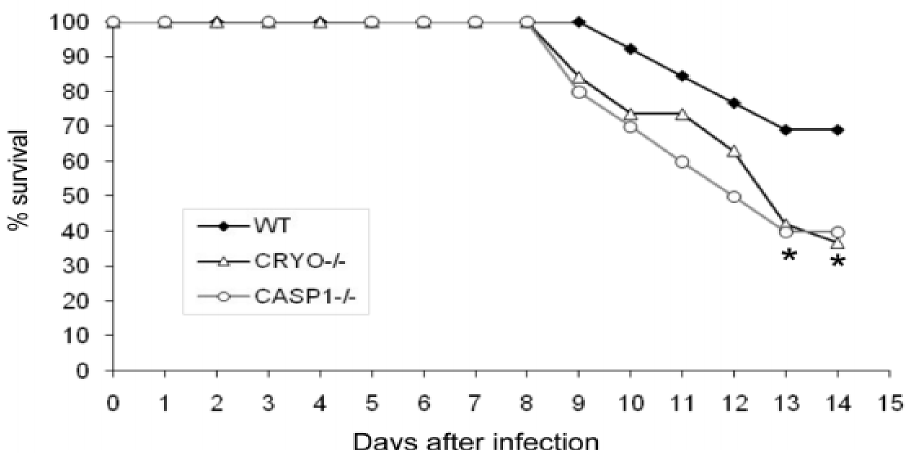
Mice deficient for NLRP3 inflammasome components, including NLRP3, caspase-1, and Apoptosis-associated speck-like protein containing a CARD (ASC), were less susceptible to H7N9 viral challenge than wild type (WT) controls.

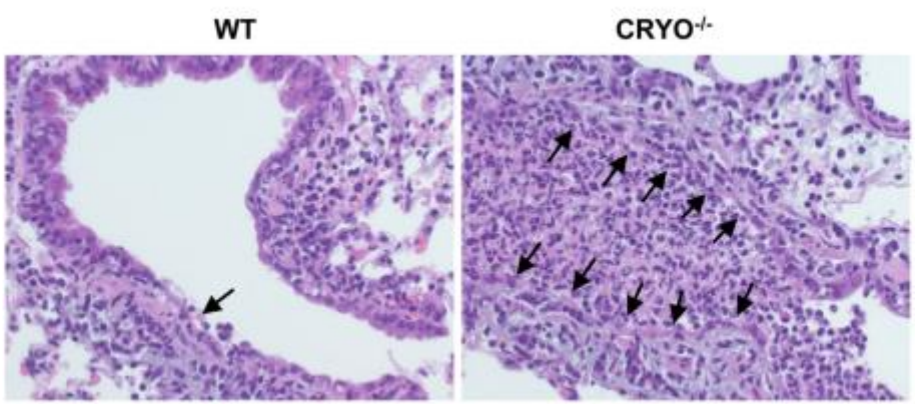
p - ; = D-N -EHD5 6DC B

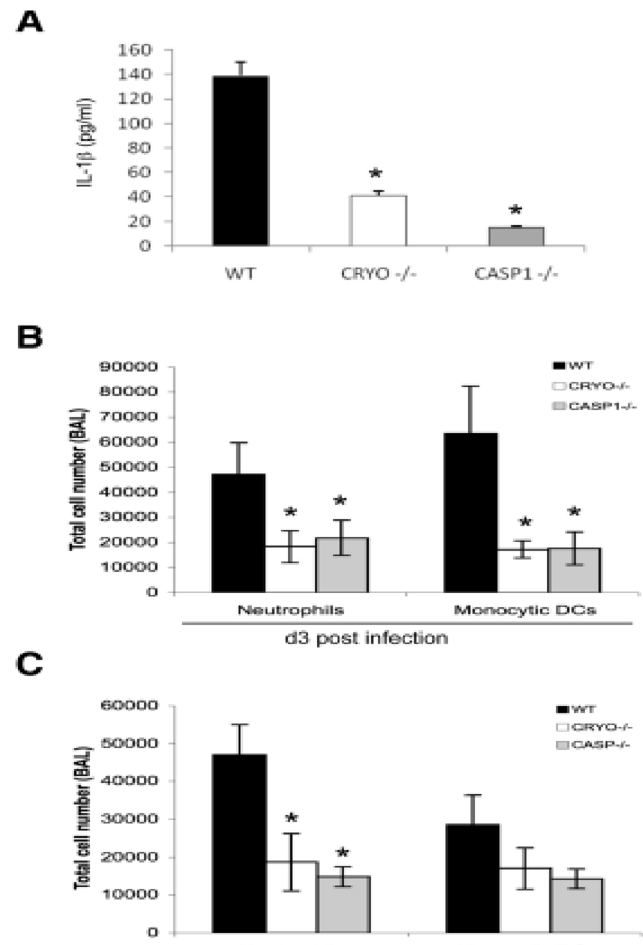
NLRP3 (NALP3/CIAS1/Cryopyrin) mediates key innate and healing responses to influenza A virus via the regulation of caspase-1

Paul G. Thomas[1], Pradyot Dash[1], Jerry R. Aldridge Jr.[2], Ali H. Ellebedy[2], Cory Reynolds[1], Amy J. Funk[3], William J. Martin[3], Mohamed Lamkanfi[5], Richard J. Webby[2], Kelli L. Boyd[4], Peter C. Doherty[1,6] and Thirumala-Devi Kanneganti[1]

Nlrp3(-/-) and Casp1(-/-) mice were more susceptible than wild-type mice after infection with a pathogenic influenza A virus. This enhanced morbidity correlated with decreased neutrophil and monocyte recruitment



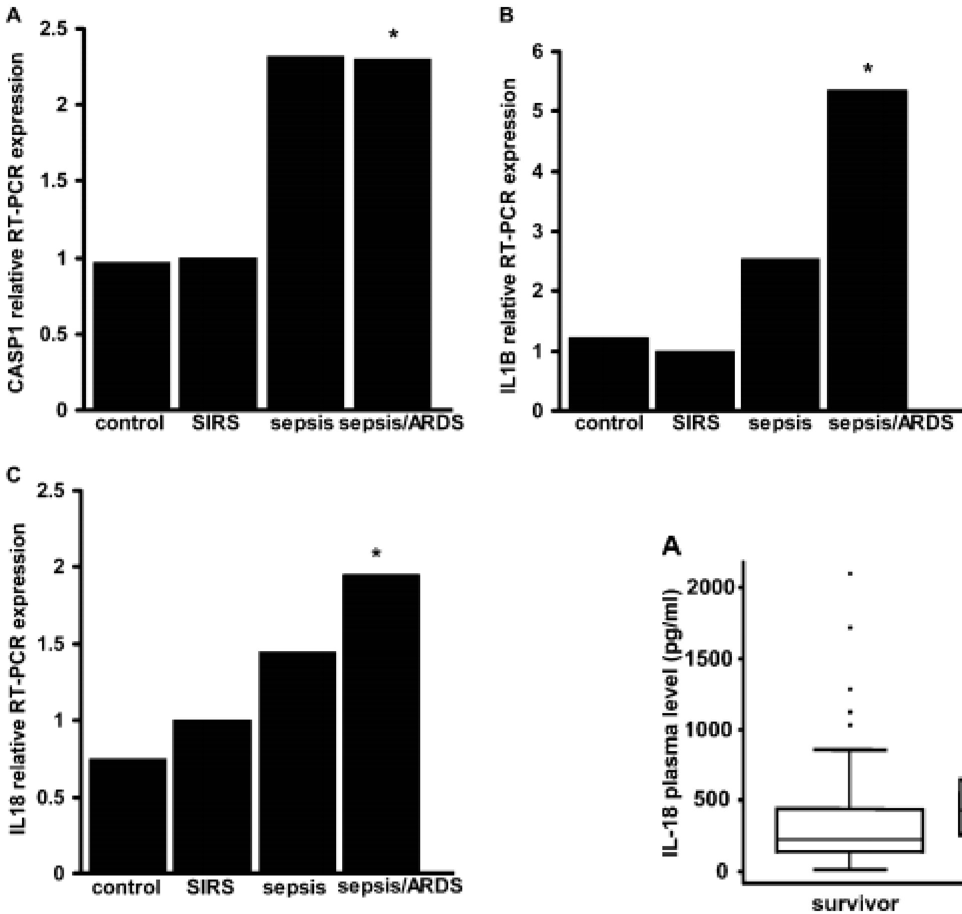


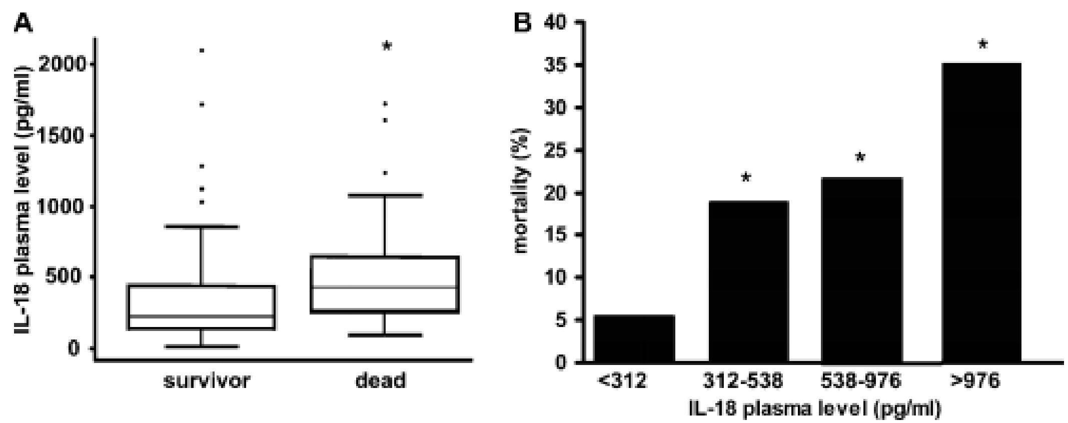


Acute lung injury and ARDS

Inflammasome-regulated Cytokines Are Critical Mediators of Acute Lung Injury

Tamás Dolinay[1], Young Sam Kim[1], Judie Howrylak[1,2], Gary M. Hunninghake[1,2], Chang Hyeok An[1], Laura Fredenburgh[1], Anthony F. Massaro[1], Angela Rogers[1,2], Lee Gazourian[1], Kiichi Nakahira[1], Jeffrey A. Haspel[1], Roberto Landazury[1], Sabitha Eppanapally[3], Jason D. Christie[4], Nuala J. Meyer[4], Lorraine B. Ware[5], David C. Christiani[6,7], Stefan W. Ryter[1], Rebecca M. Baron[1], and Augustine M. K. Choi[1]

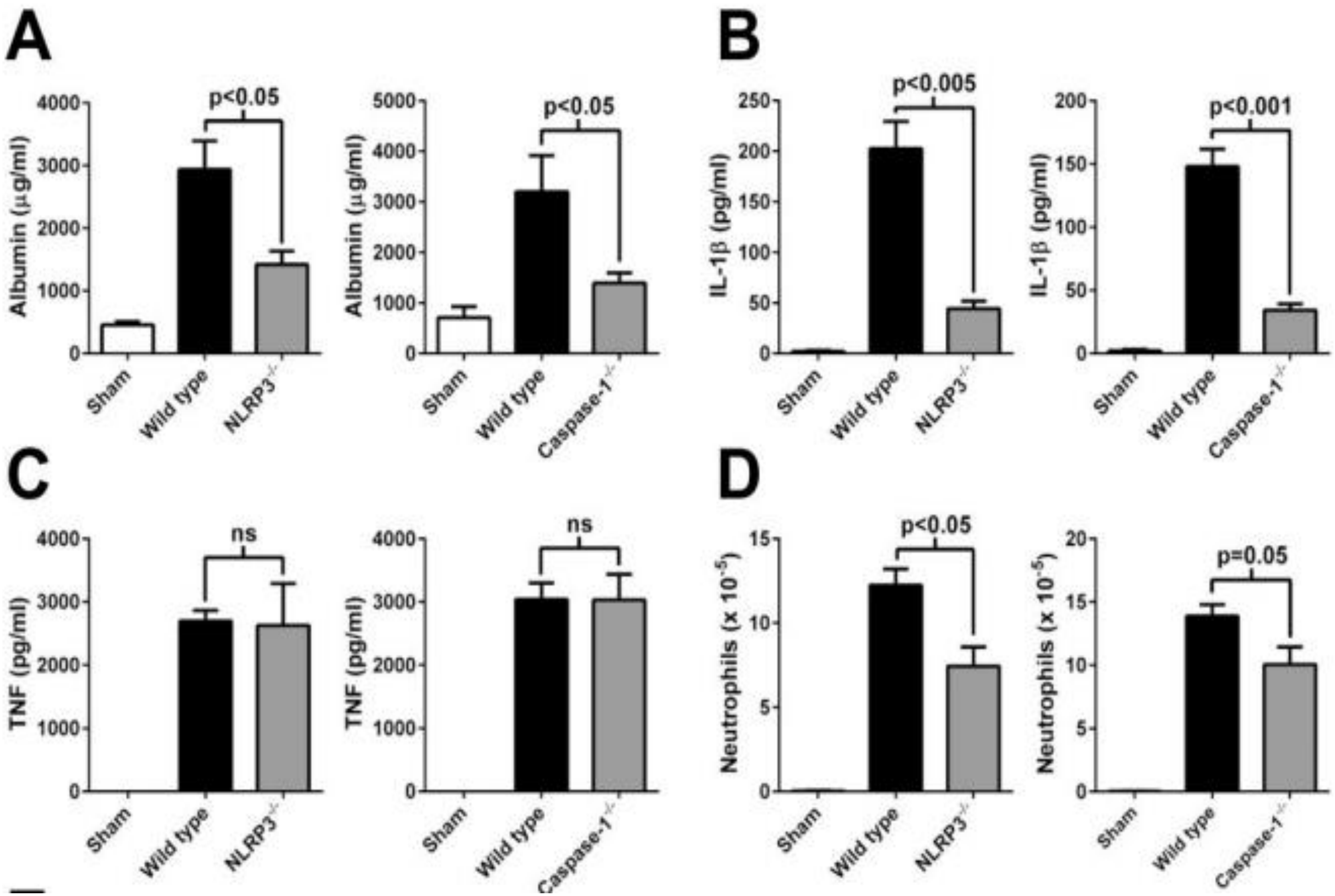




N -W -P -Pn - ; = -W - HEB5 6 B: A

Critical role for the NLRP3 inflammasome during acute lung injury[1]

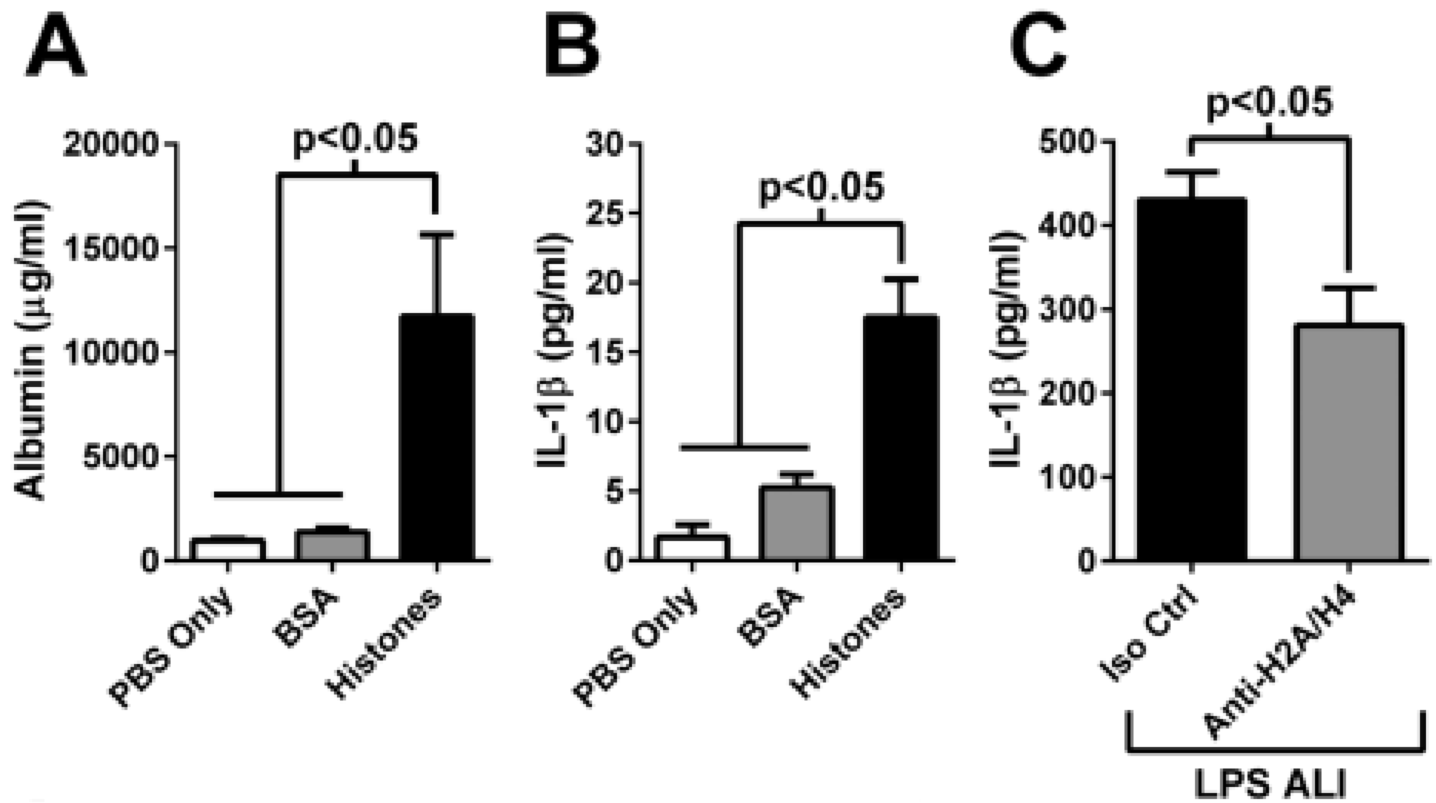
Jamison J. Grailer, **Bethany A. Canning**, **Miriam Kalbitz**, **Mikel D. Haggadone**, **Rasika M. Dhond**, **Anuska V. Andjelkovic**, **Firas S. Zetoune**, and **Peter A. Ward***



W ; = A-W - BHF 5 6BFDA:E ;

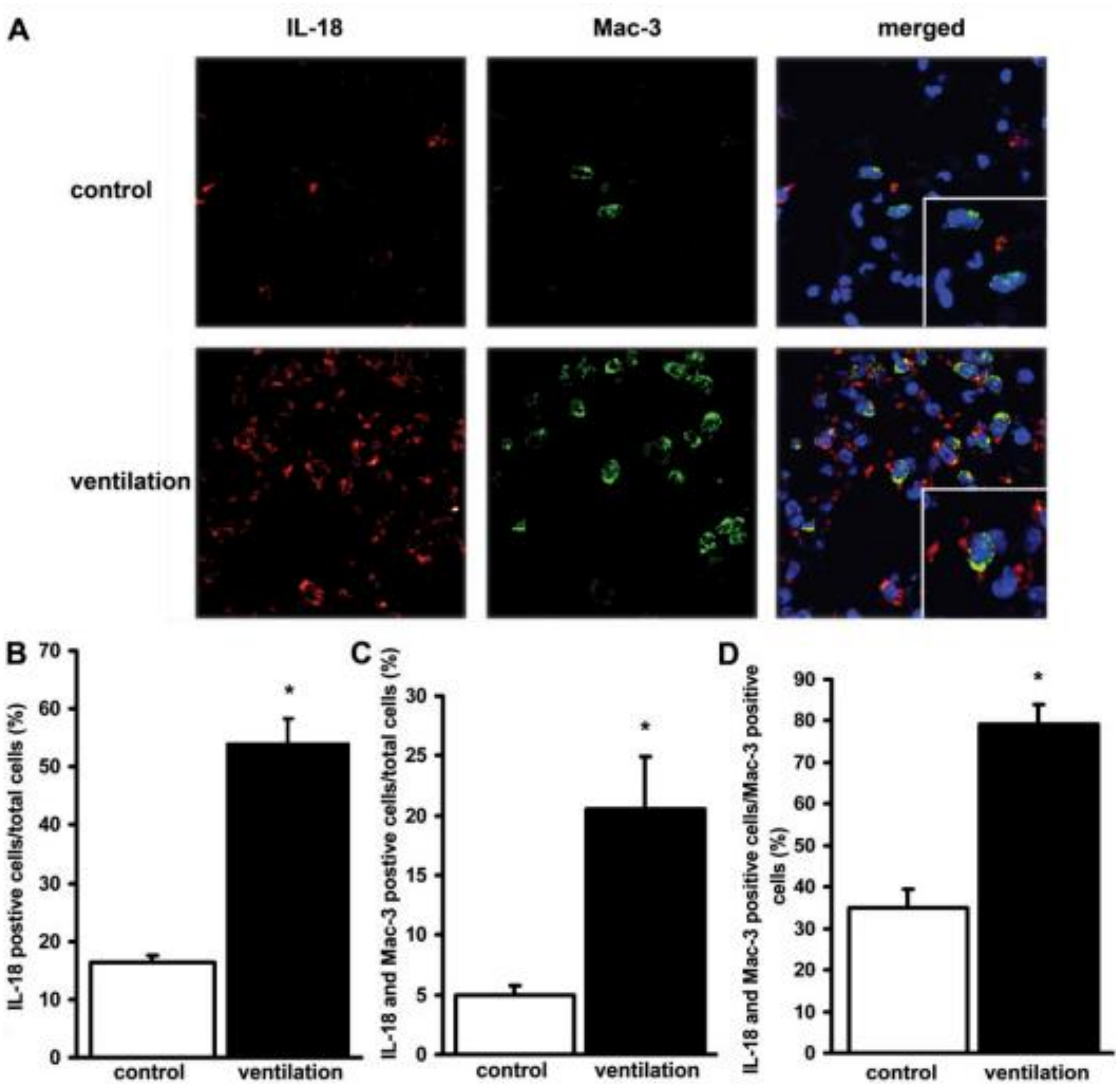
Extracellular histones activate the inflammasome

a - n n- pn -n - np -o - np n - -n -
Y n n 9 - NY ;- p - - - - n -
- n - NY 9 - p - - -p - - - pnp - ;



W ; = A-W - BHF 5 6BFDA:E ;

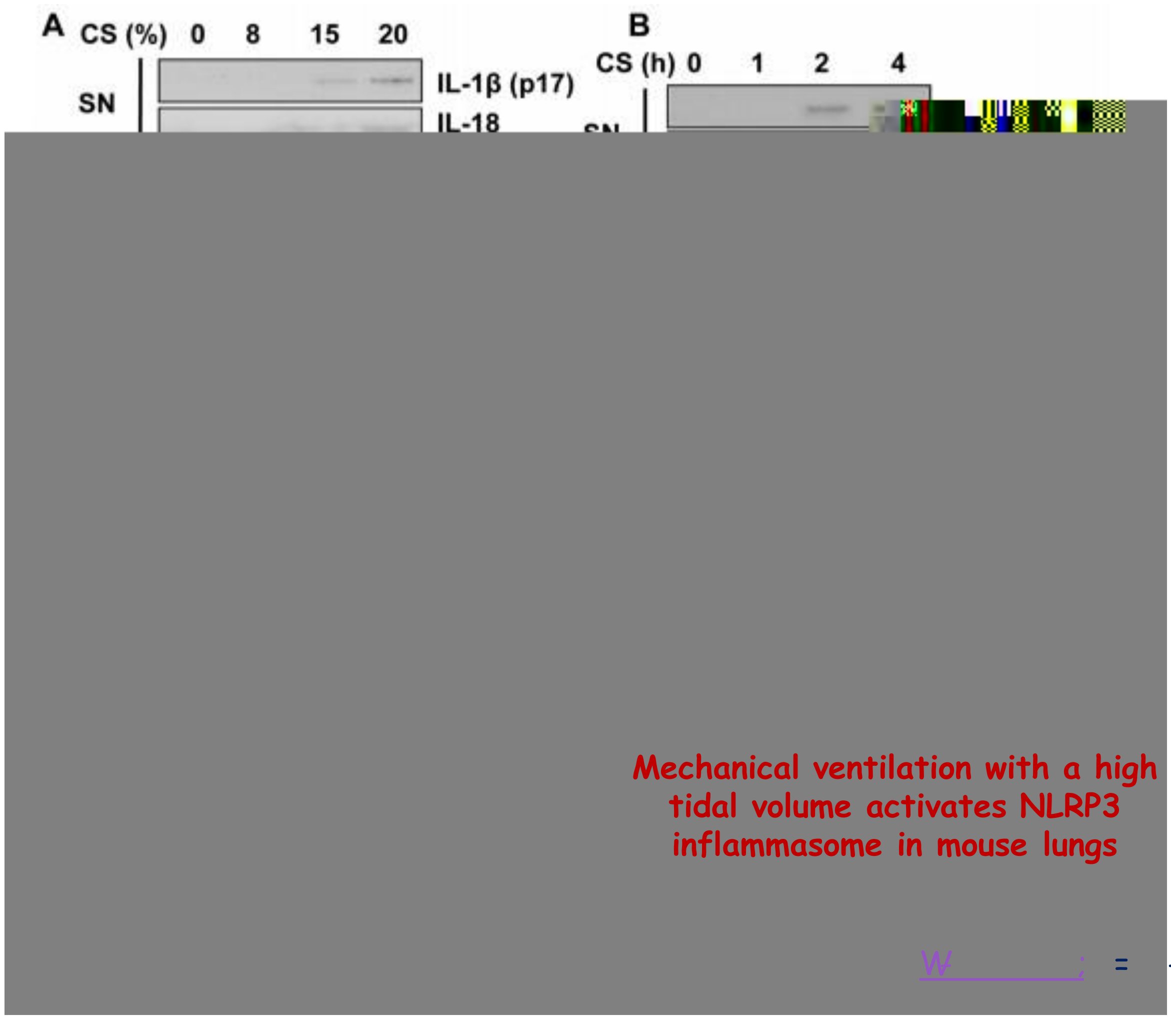
Mechanical ventilation (MV) increases the expression of the cleaved form of IL-18 in alveolar macrophages



N -W -P -Pn - ; = -W - HEB5 6 B: A

Activation of NLRP3 inflammasome in alveolar macrophages contributes to mechanical stretch-induced lung inflammationand injury

Jianbo Wu[*,†,1], Zhibo Yan[‡,§,1], David E. Schwartz[*], Jingui Yu[†], Asrar B. Malik[‡], and Guochang Hu[*,‡]

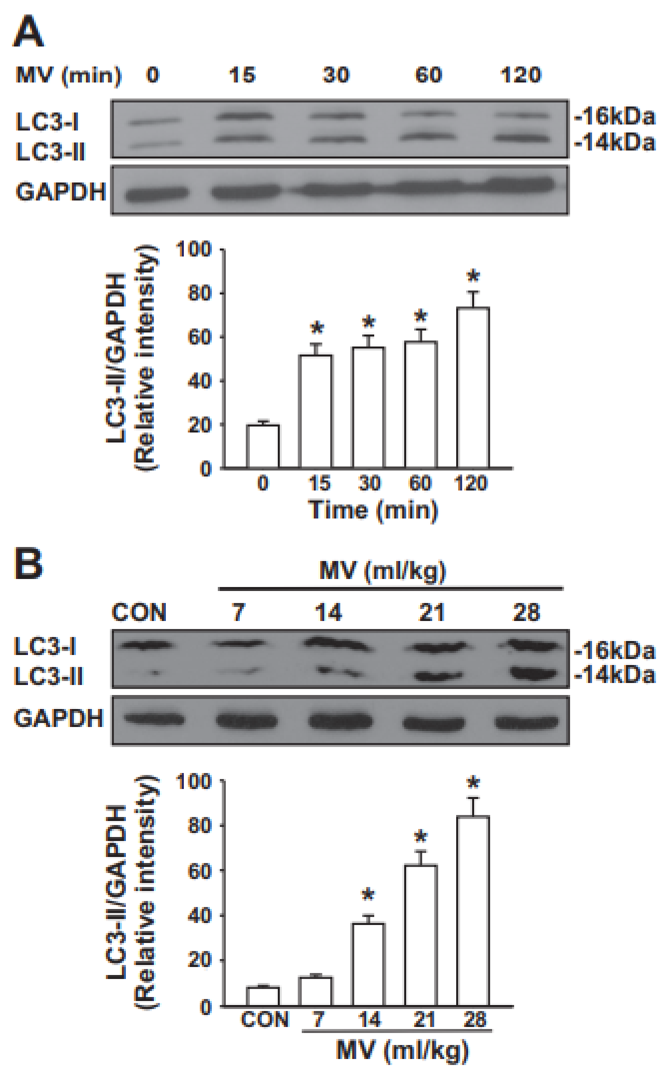


Mechanical ventilation with a high tidal volume activates NLRP3 inflammasome in mouse lungs

W ; = -N - HF=5D6 BF=:F

Autophagy in pulmonary macrophages mediates lung inflammatory injury via NLRP3 inflammasome activation during mechanical ventilation

Yang Zhang,[1,3] Gongjian Liu,[3] Randal O. Dull,[1] David E. Schwartz,[1] and Guochang Hu[1,2]

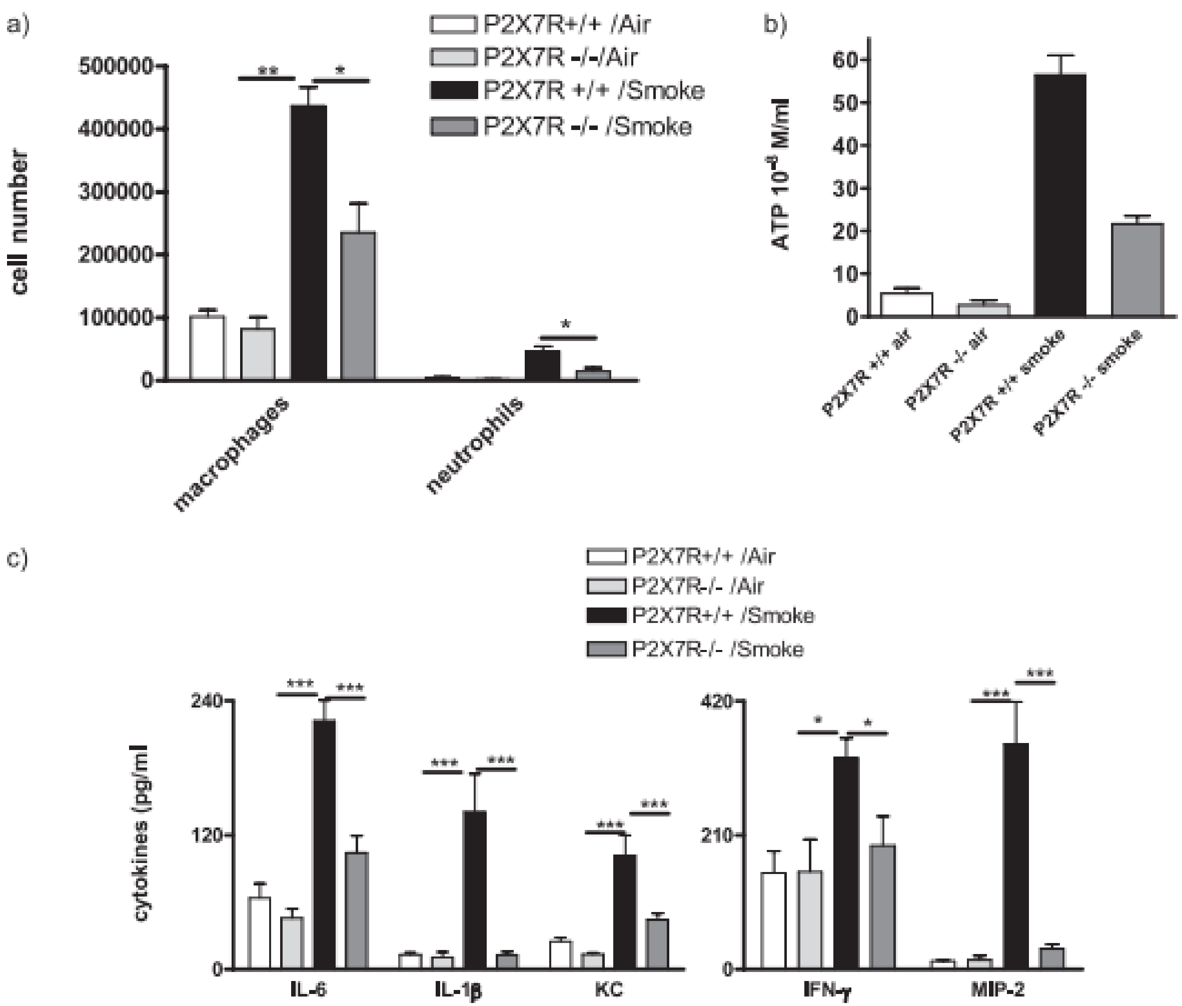


The cytosolic form of microtubule-associated protein 1A/1B-light chain 3 (LC3-I) is conjugated to phosphatidylethanolamine to form LC3-II, which is recruited to autophagosomal membranes, the process of which is essential for the autophagosome formation

COPD

P2X$_7$ Receptor Signaling in the Pathogenesis of Smoke-Induced Lung Inflammation and Emphysema

Monica Lucattelli[2*], Sanja Cicko[1*], Tobias Müller[1*], Marek Lommatzsch[3], Giovanna De Cunto[2], Silvia Cardini[2], William Sundas[2], Melanie Grimm[1], Robert Zeiser[5], Thorsten Dürk[1], Gernot Zissel[1], Stephan Sorichter[1], Davide Ferrari[4], Francesco Di Virgilio[4], J. Christian Virchow[3], Giuseppe Lungarella[2*], and Marco Idzko[1]

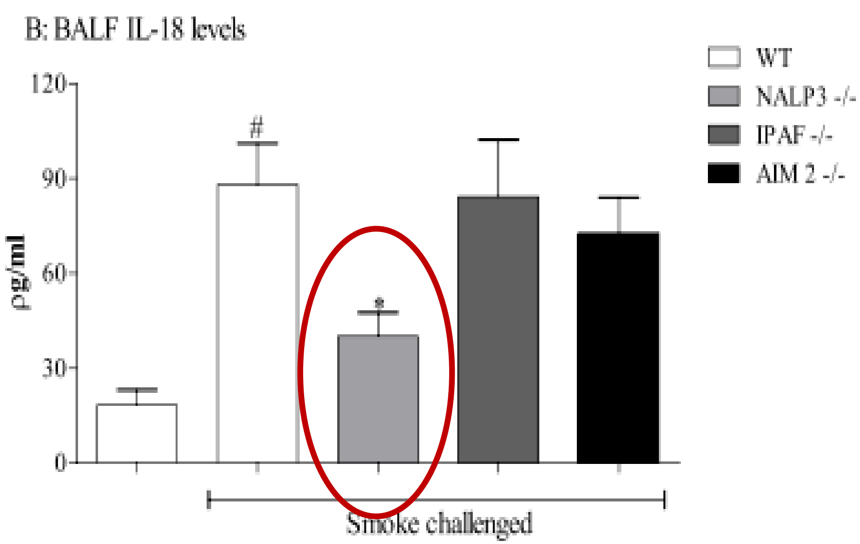


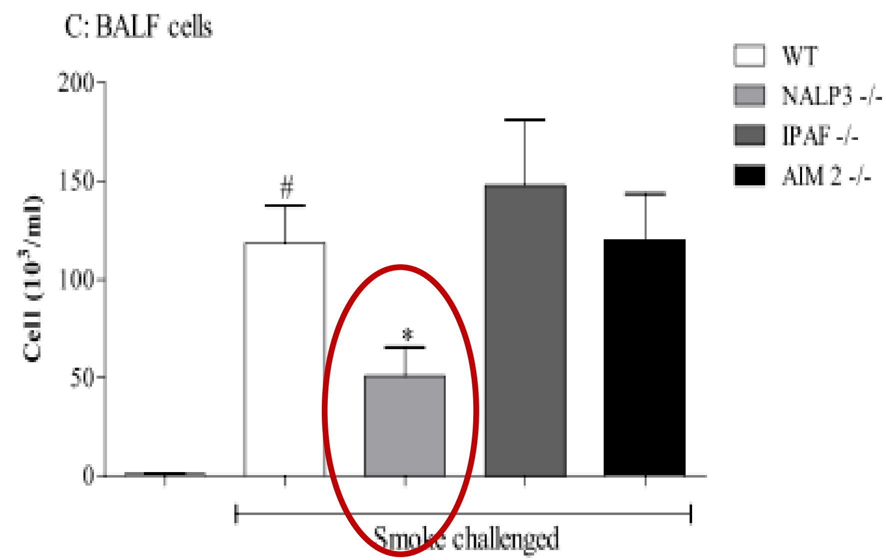
eD : p -n n -n -
n n - p - -
p n - -5P 6 p -
- n n

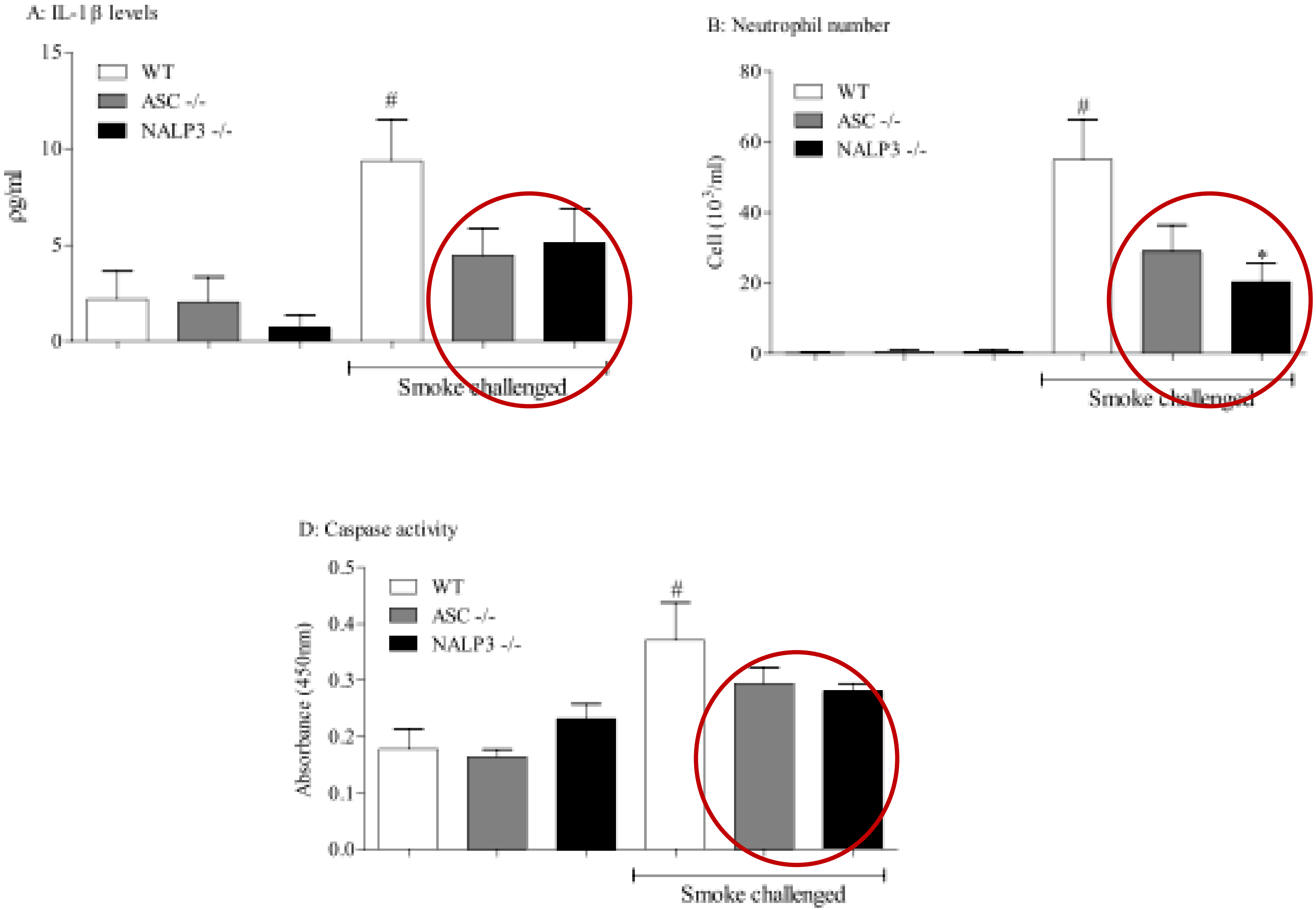
N -W -P - -O ; = - n HAA5 6A :F;

Role of the Inflammasome-Caspase1/11-IL-1/18 Axis in Cigarette Smoke Driven Airway Inflammation: An Insight into the Pathogenesis of COPD

Suffwan Eltom[1], Maria G. Belvisi[1], Christopher S. Stevenson[2¤], Sarah A. Maher[1], Eric Dubuis[1], Kate A. Fitzgerald[3], Mark A. Birrell[1*]





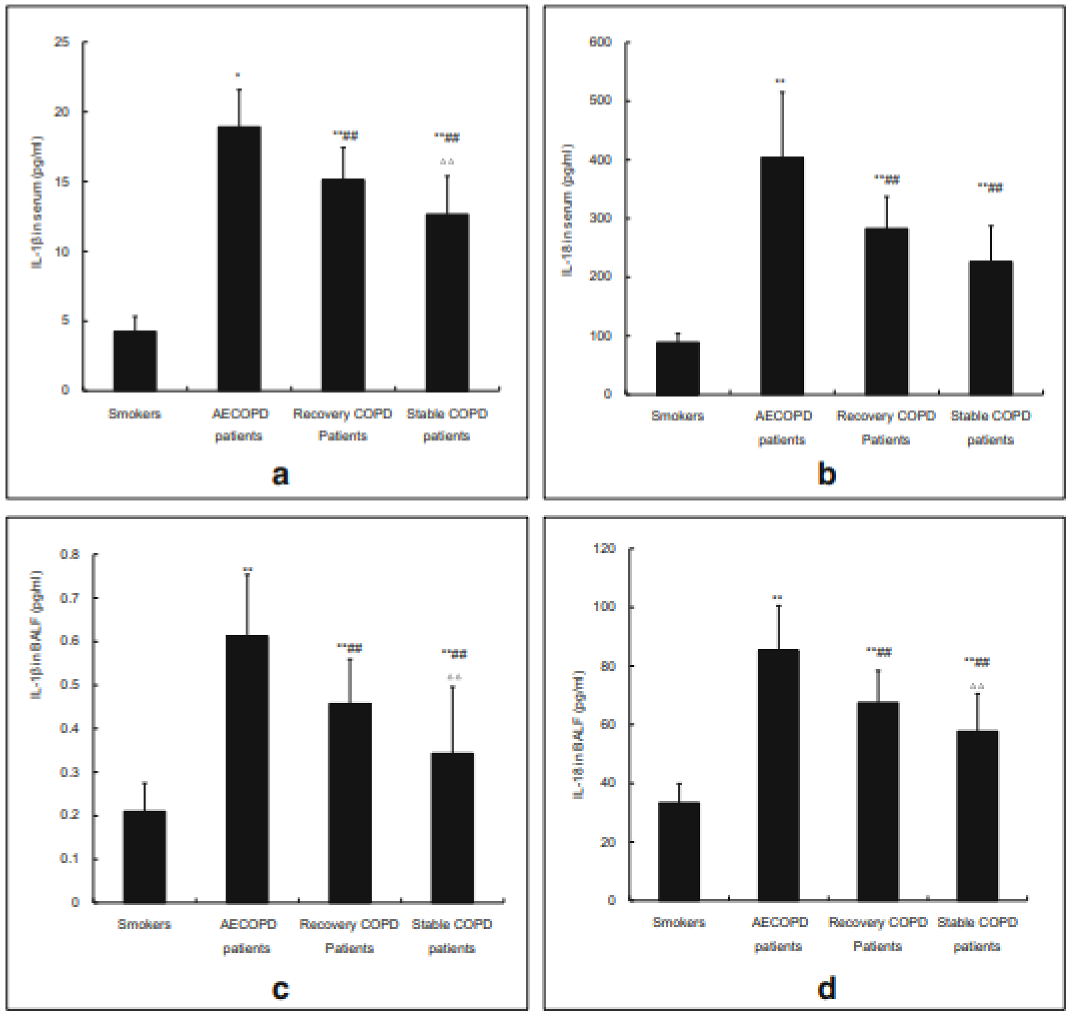

A: IL-1β levels
15
10
5
0
ρg/ml
WT
ASC -/-
NALP3 -/-
#
Smoke challenged
B: Neutrophil number
80
60
40
20
0
Cell (10³/ml)
WT
ASC -/-
NALP3 -/-
#
*
Smoke challenged
D: Caspase activity
0.5
0.4
0.3
0.2
0.1
0.0
Absorbance (450nm)
WT
ASC -/-
NALP3 -/-
#
Smoke challenged

Y - ; = A- - EHF5 6 E F;

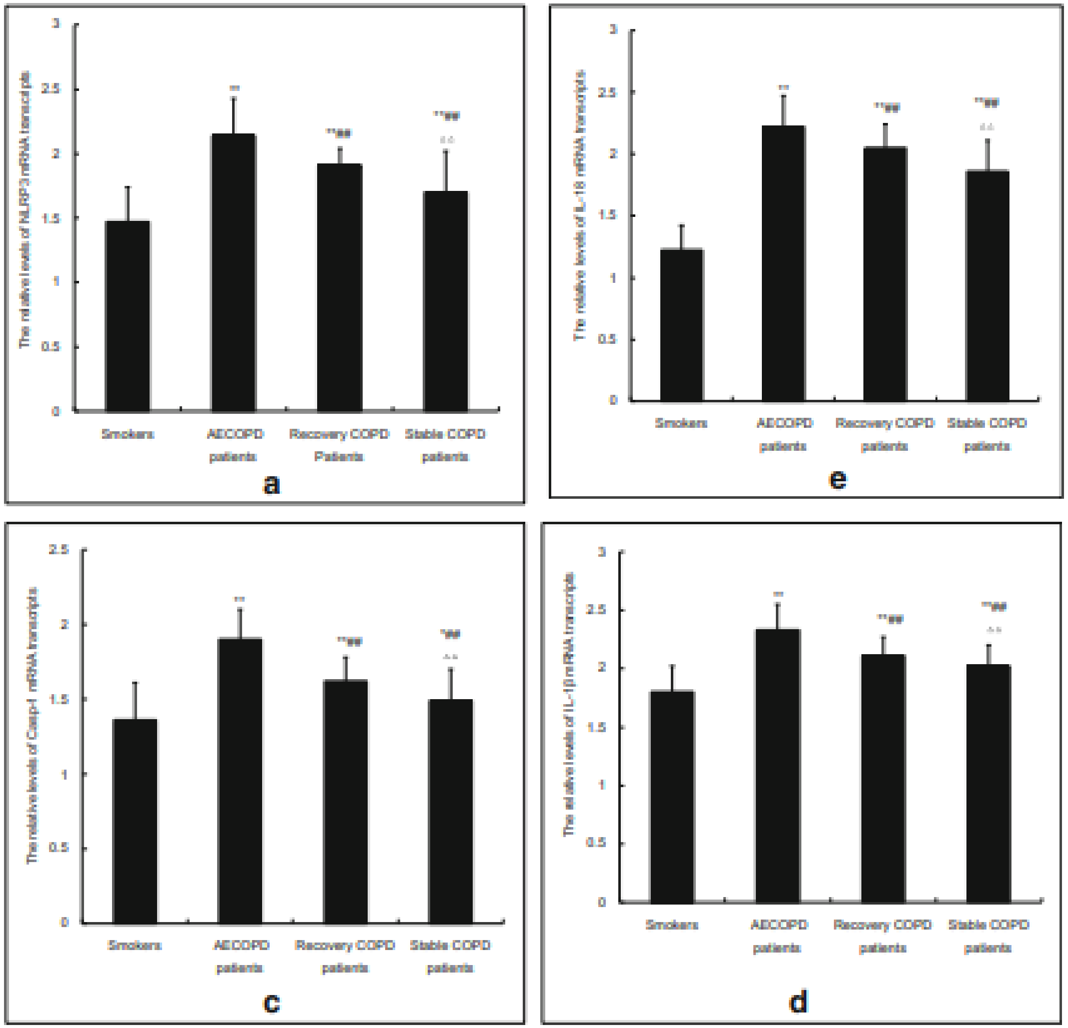
NLRP3 Inflammasome Involves in the Acute Exacerbation of Patients with Chronic Obstructive Pulmonary Disease

ng Weng,[2] and Wanjun Yu[1,3] Huaying Wang,[1] Chun'er Lv,[1] Shi Wang,[1] Huajuan Ying,[1] Yueso

[redacted]



The relative mRNA levels of NLRP3 (a), ASC (b), Casp-1 (c), IL1β (d), and IL-18 (e) to the internal control GAPDH, in bronchial tissues



n n ; = E-N HA 5A6 :

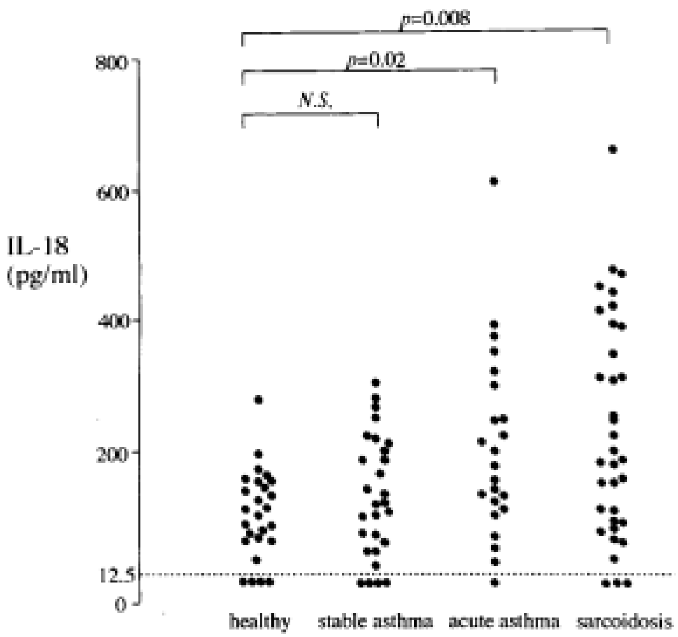
Correlation Analysis of NLRP3, ASC, Casp-1, IL-1β, and IL-18 mRNA levels with the bacteria burden in the airways

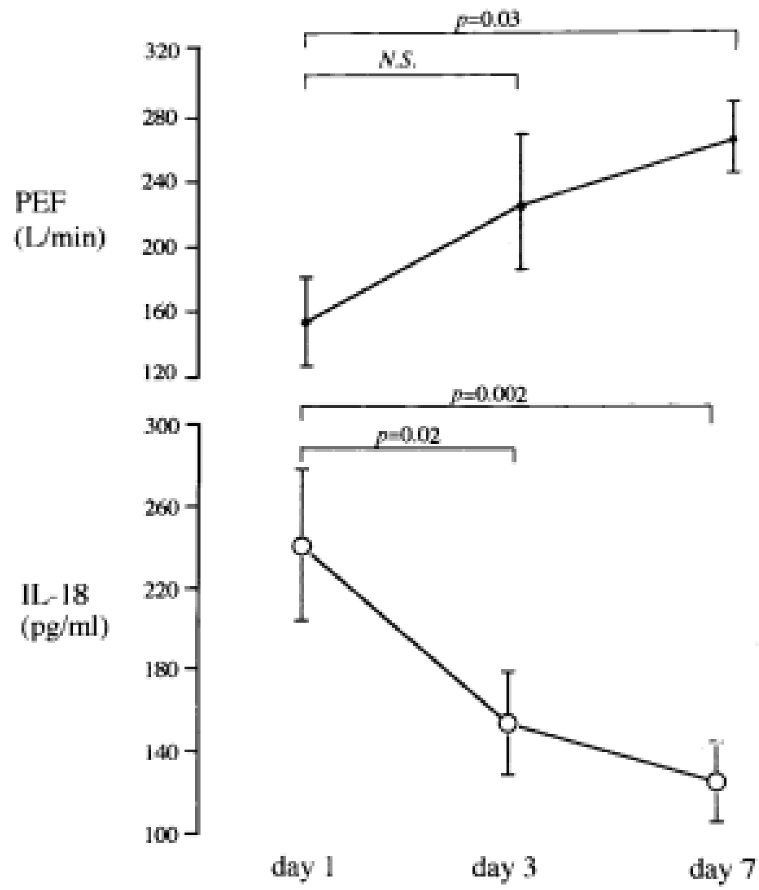
n n ; = E-N HA 5A6 :

Asthma

IL-18 might reflect disease activity in mild and moderate asthma exacerbation

Hiroshi Tanaka, MD,[a] Naomitsu Miyazaki, MD,[a] Kensuke Oashi, MD,[a] Shin Teramoto, MD,[a] Masanori Shiratori, MD,[a] Midori Hashimoto, MD,[a] Mitsuhide Ohmichi, MD,[b] and Shosaku Abe, MD,[a] *Sapporo, Japan*

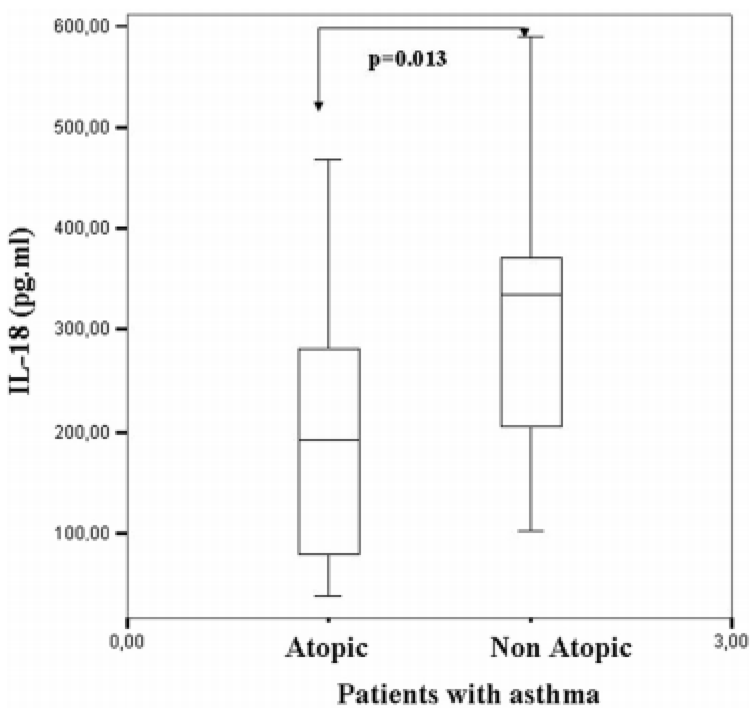


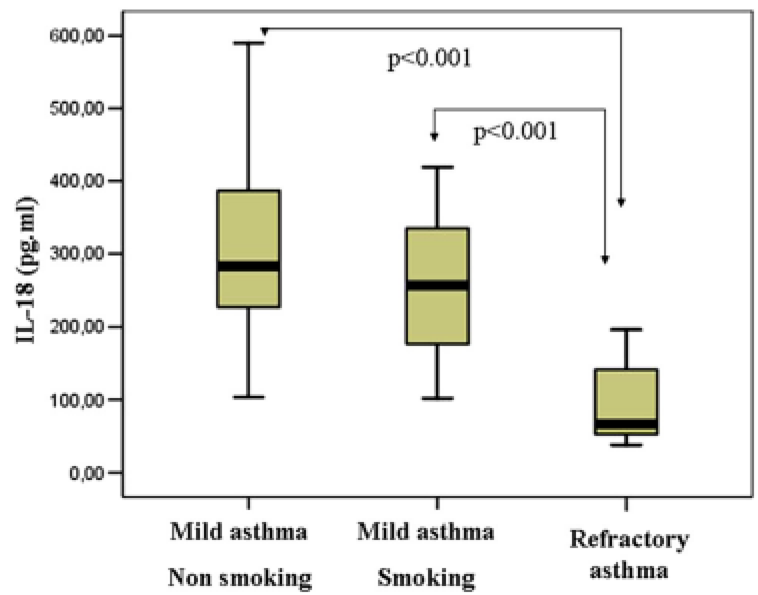


WN -P - ; == -S oH=D5 6 :C

Low interleukin (IL)-18 levels in sputum supernatants of patients with severe refractory asthma

Nikoletta Rovina [a,*], Efrossini Dima [a], Petros Bakakos [a],
Antonia Koutsoukou [a],
Stelios Loukides [b]



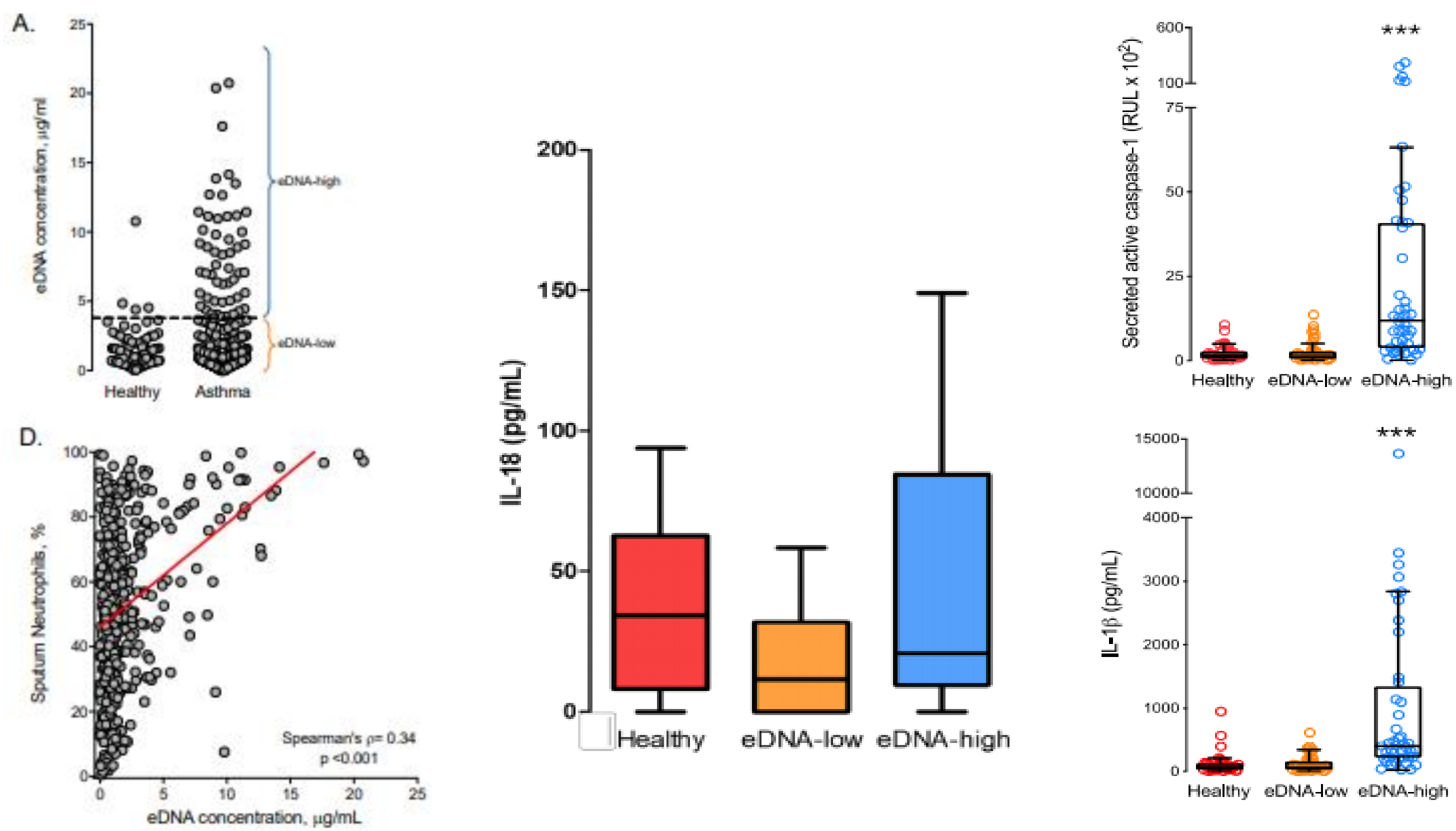


Title: Extracellular DNA, Neutrophil Extracellular Traps, and Inflammasome activation in Severe asthma

Marrah E. Lachowicz-Scroggins Ph.D.[1*], Eleanor M. Dunican M.D.[2*], Annabelle R. Charbit Ph.D.[1], Wilfred Raymond[1], Mark R. Looney M.D.[1], Michael C. Peters M.D.[1], Erin D. Gordon

National Heart, Lung, and Blood Institute Severe Asthma Research Program-3 Investigators

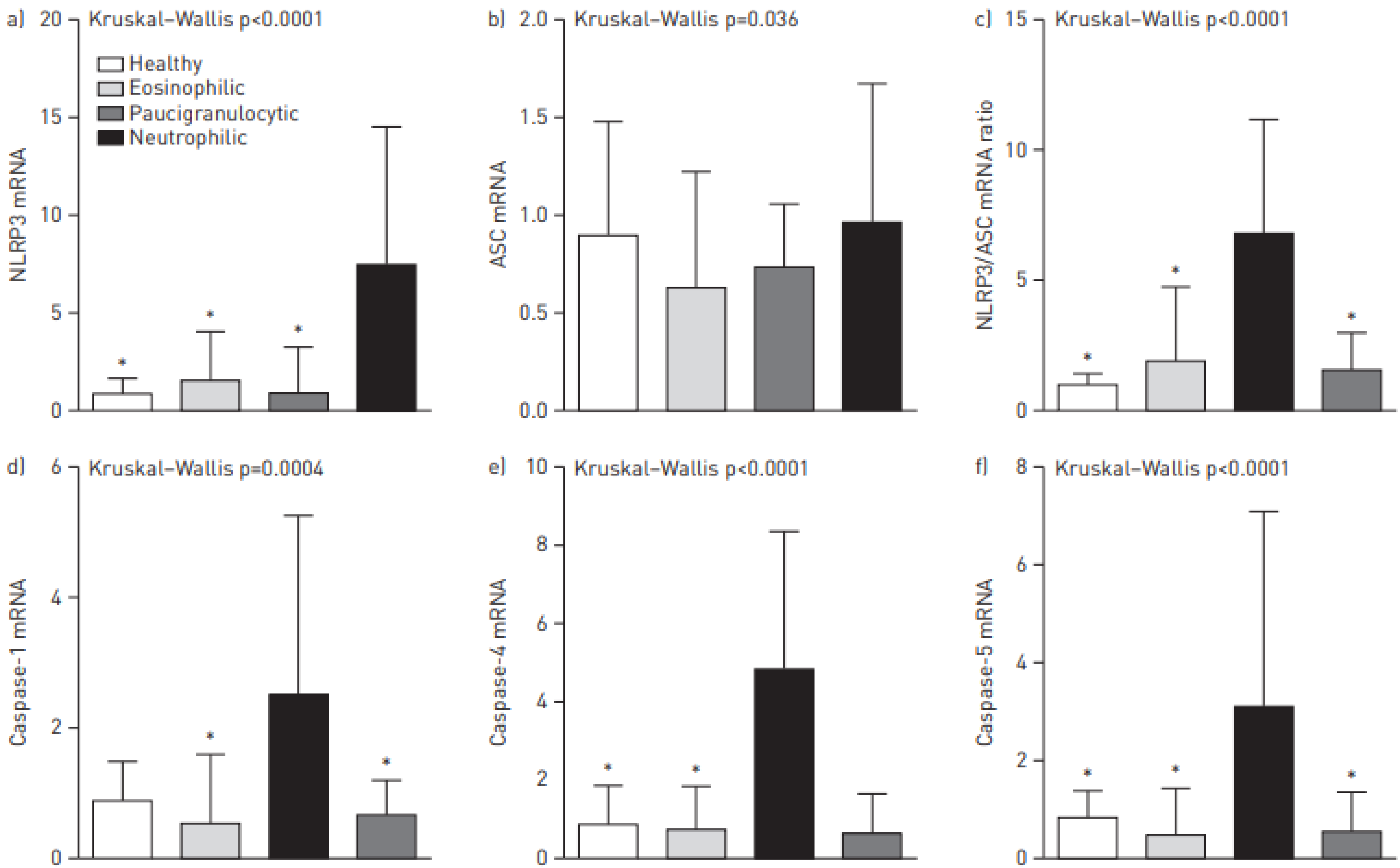
Increased extracellular DNA (eDNA) in sputum from a subset of asthmatics reflects neutrophil activation



N -W -P -Pn - ;- = F- n - HFF5F6 =DC: =EB

Elevated expression of the NLRP3 inflammasome in neutrophilic asthma

Jodie L. Simpson[1,6], Simon Phipps[2,3,6], Katherine J. Baines[1], Kevin M. Oreo[4], Lakshitha Gunawardhana[1] and Peter G. Gibson[1,4,5]

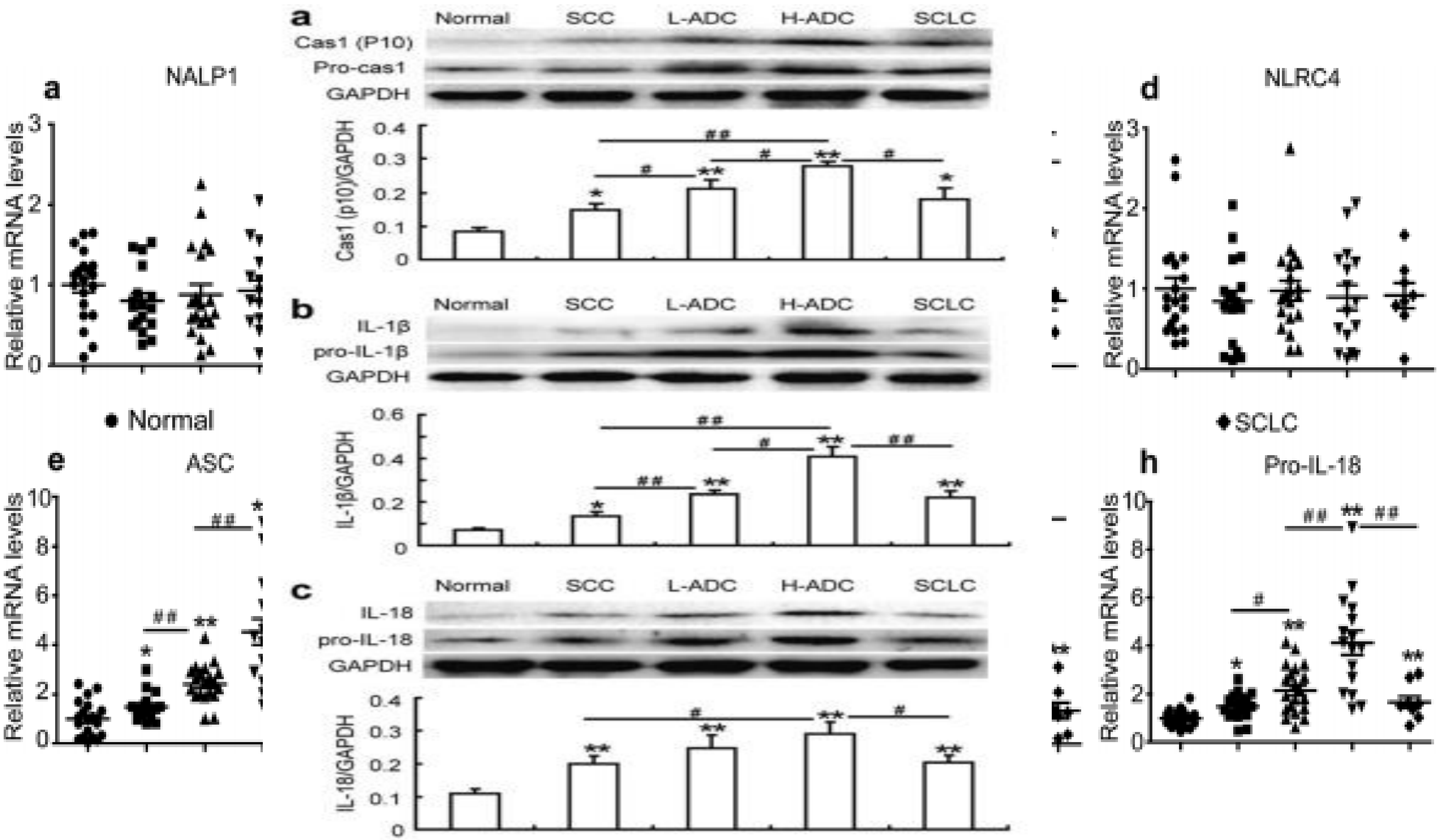


R - -W = A-N HA 5A6 = CD: DC

Lung cancer

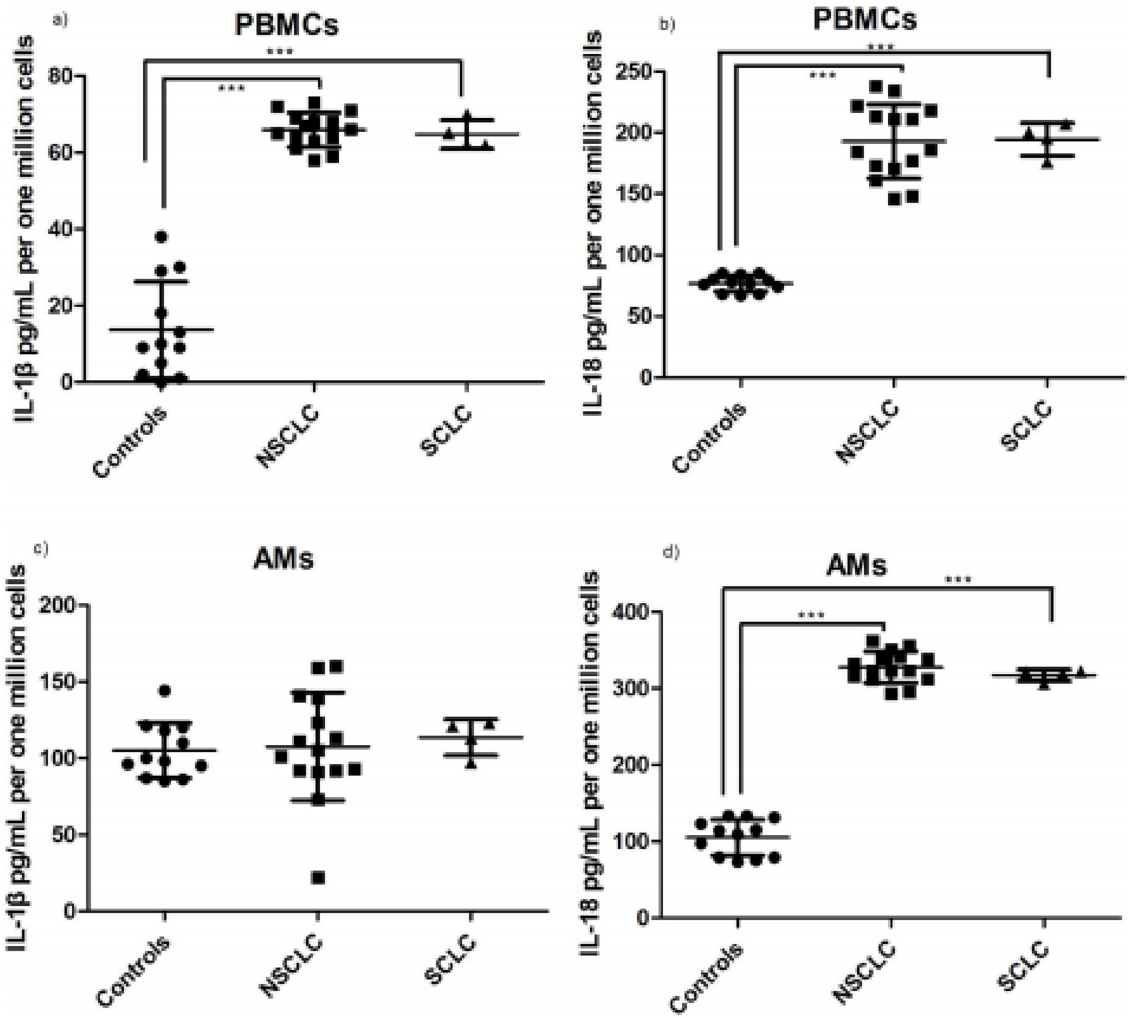
Differential expression of inflammasomes in lung cancer cell lines and tissues

Hui Kong[1] · Yanli Wang[1] · Xiaoning Zeng[1] · Zailiang Wang[1] · Hong Wang[1] · Weiping Xie[1]



NLRP3/Caspase-1 inflammasome activation is decreased in alveolar macrophages in patients with lung cancer

Ismini Lasithiotaki[1], Eliza Tsitoura[1], Katerina D. Samara[1], Athina Trachalaki[1], Irini Charalambous[1], Nikolaos Tzanakis[1,2], Katerina M. Antoniou[1,2]*

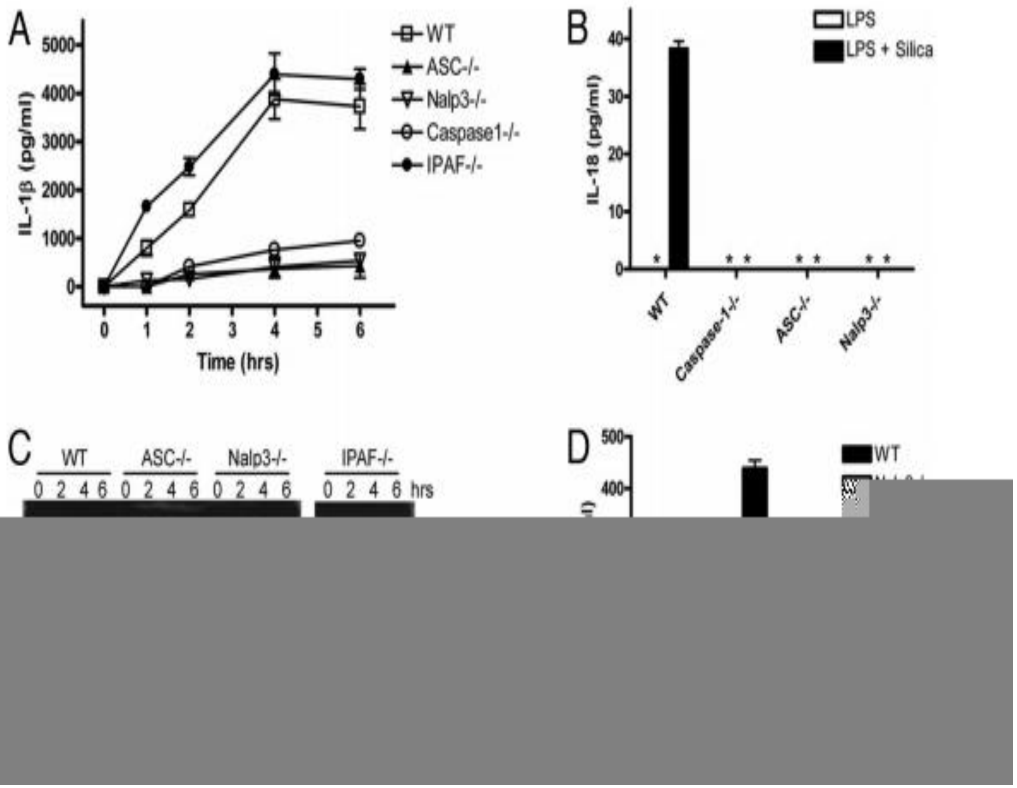


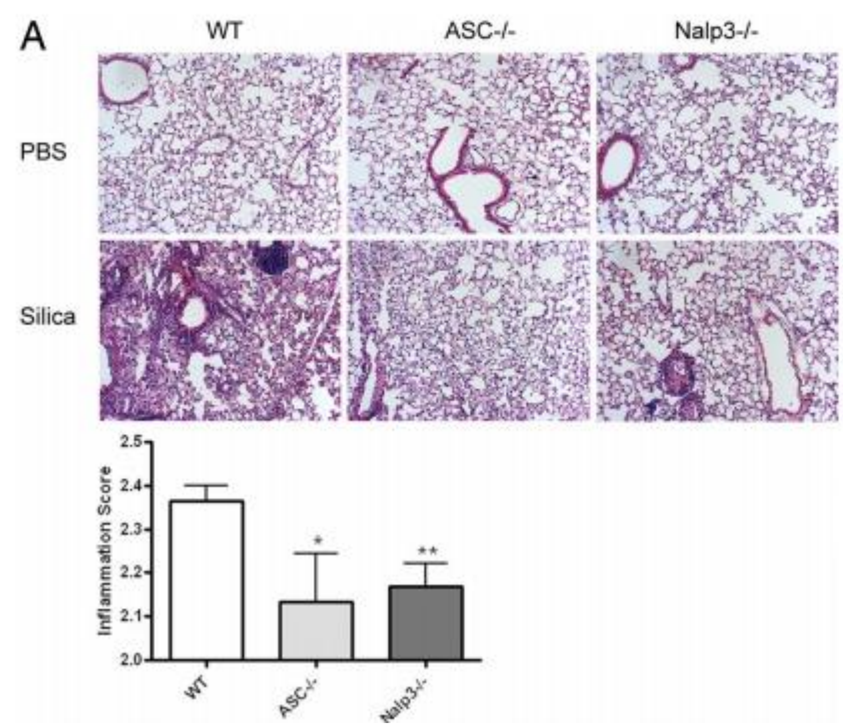
Y - ; = E- p - CH 5=6 = =B A

Pulmonary fibrosis

The Nalp3 inflammasome is essential for the development of silicosis

Suzanne L. Cassel[a], Stephanie C. Eisenbarth[b,c], Shankar S. Iyer[d,e], Jeffrey J. Sadler[d,e], Oscar R. Colegio[c,f], Linda A. Tephly[g], A. Brent Carter[g], Paul B. Rothman[h], Richard A. Flavell[c,i,j,k], and Fayyaz S. Sutterwala[c,d,e,j,l]

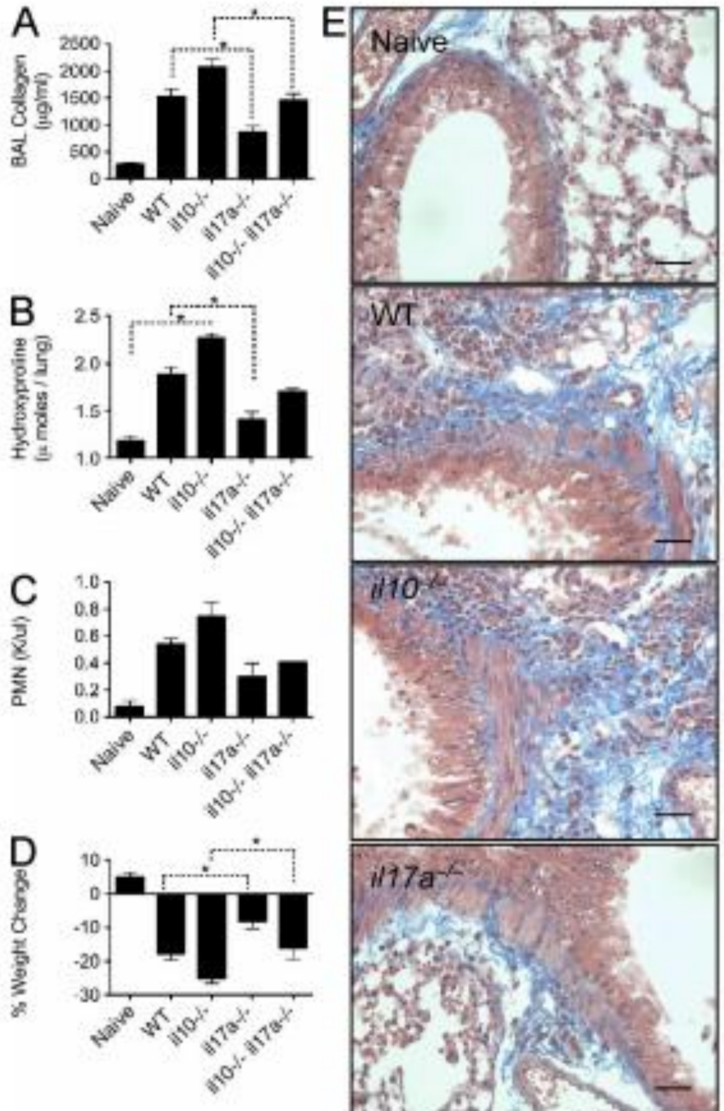




N - ==E-W - H=B5 C6F= B:A=

Bleomycin and IL-1β–mediated pulmonary fibrosis is IL-17A dependent

Mark S. Wilson,[1] Satish K. Madala,[1] Thirumalai R. Ramalingam,[1] Bernadette R. Gochuico,[2] Ivan O. Rosas,[3] Allen W. Cheever,[4] and Thomas A. Wynn[1]

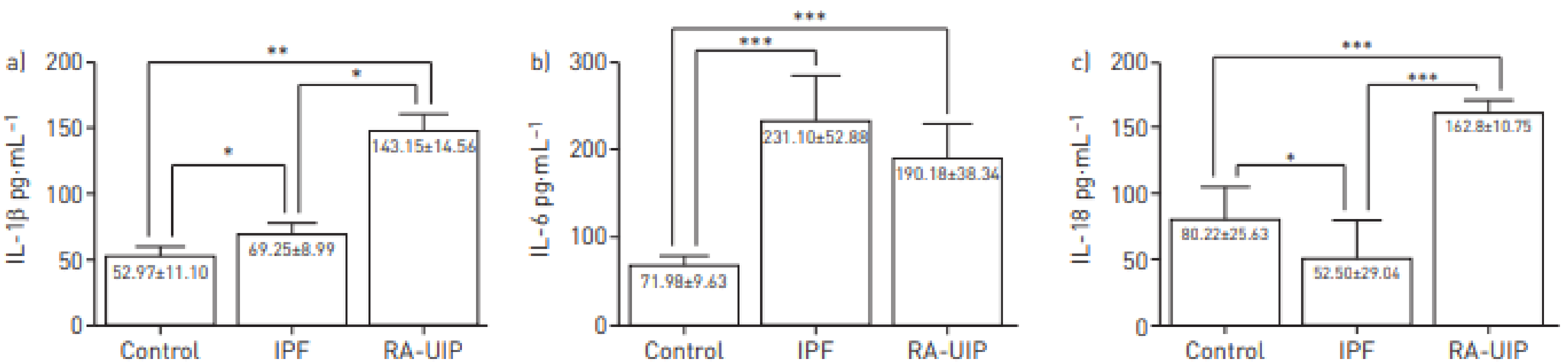


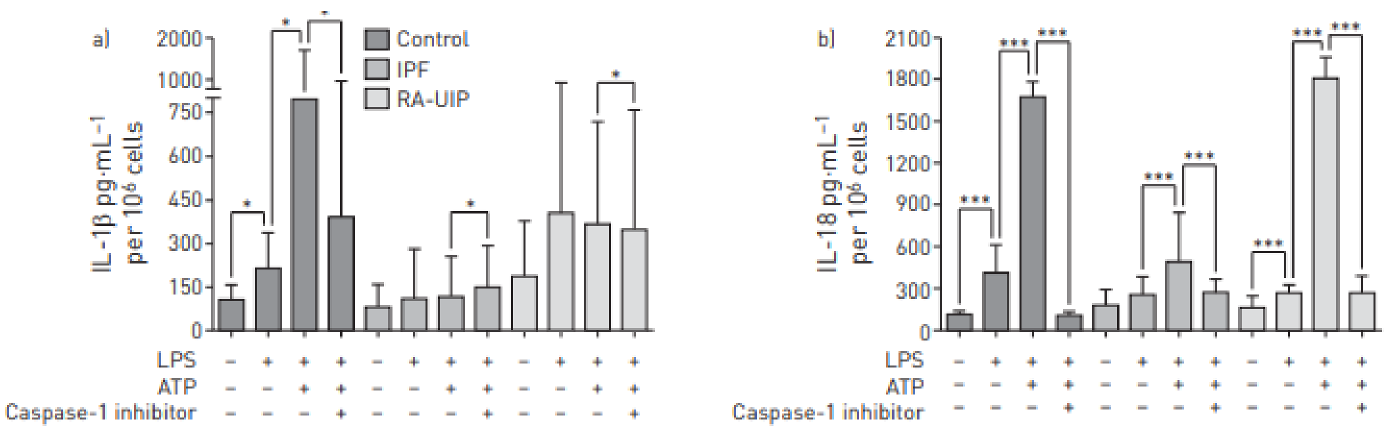
WR - ; = =- n - BH=D5 6B B:B

NLRP3 inflammasome expression in idiopathic pulmonary fibrosis and rheumatoid lung

Ismini Lasithiotaki[1,5], Ioannis Giannarakis[1,2,5], Eliza Tsitoura[1], Katerina D. Samara[1], George A. Margaritopoulos[1], Christiana Choulaki[3], Eirini Vasarmidi[1], Nikolaos Tzanakis[1,2], Argyro Voloudaki[4], Prodromos Sidiropoulos[3], Nikolaos M. Siafakas[2] and Katerina M. Antoniou[1,2]

BAL

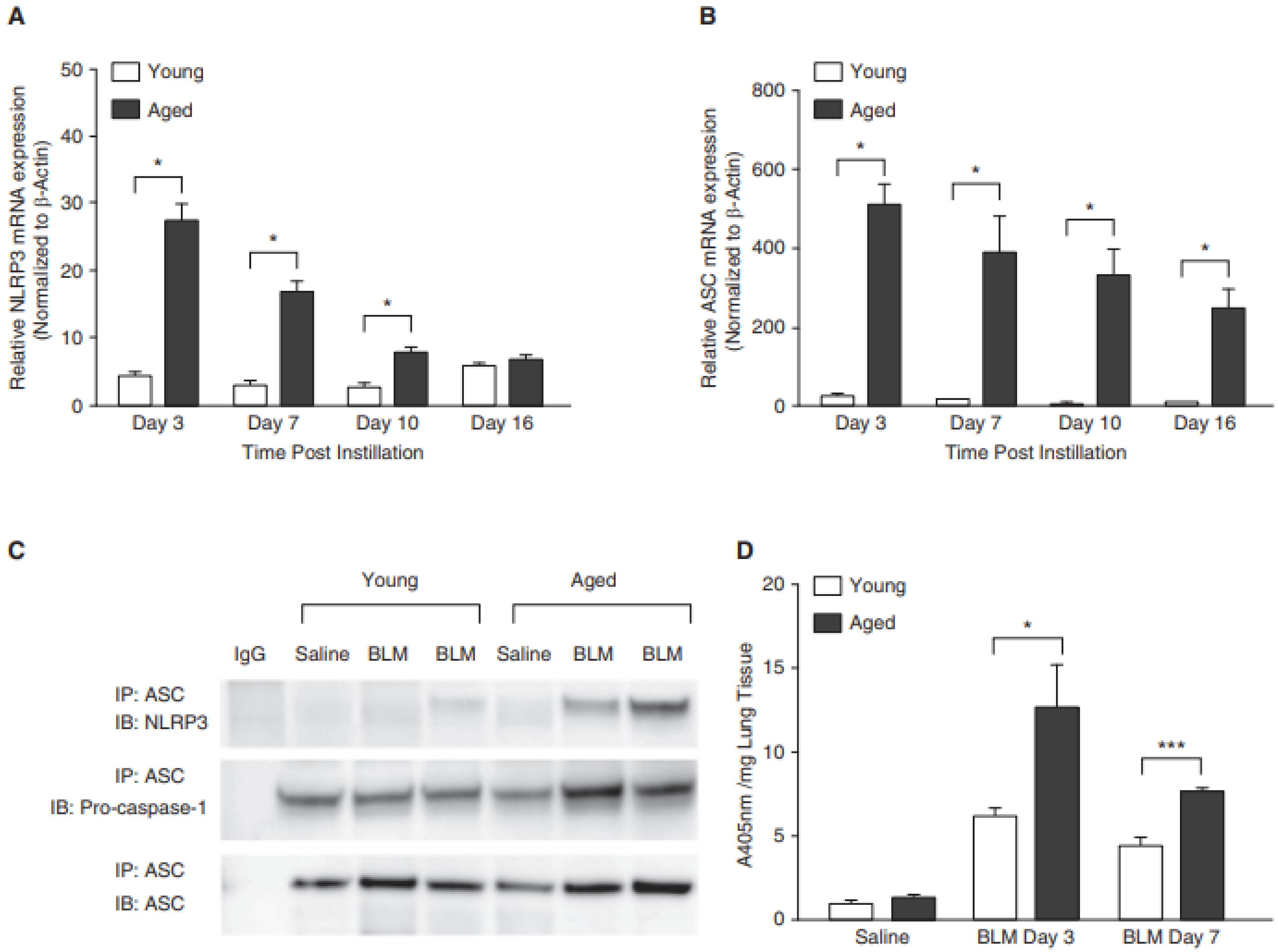




R - -W = C- n HAD5 6F =:E

Age-Dependent Susceptibility to Pulmonary Fibrosis Is Associated with NLRP3 Inflammasome Activation

Heather W. Stout-Delgado[1,2], Soo Jung Cho[1], Sarah G. Chu[3], Dana N. Mitzel[2], Julian Villalba[2,3], Souheil El-Chemaly[2,3], Stefan W. Ryter[1,3], Augustine M. K. Choi[1,3] and Ivan O. Rosas[2,3]

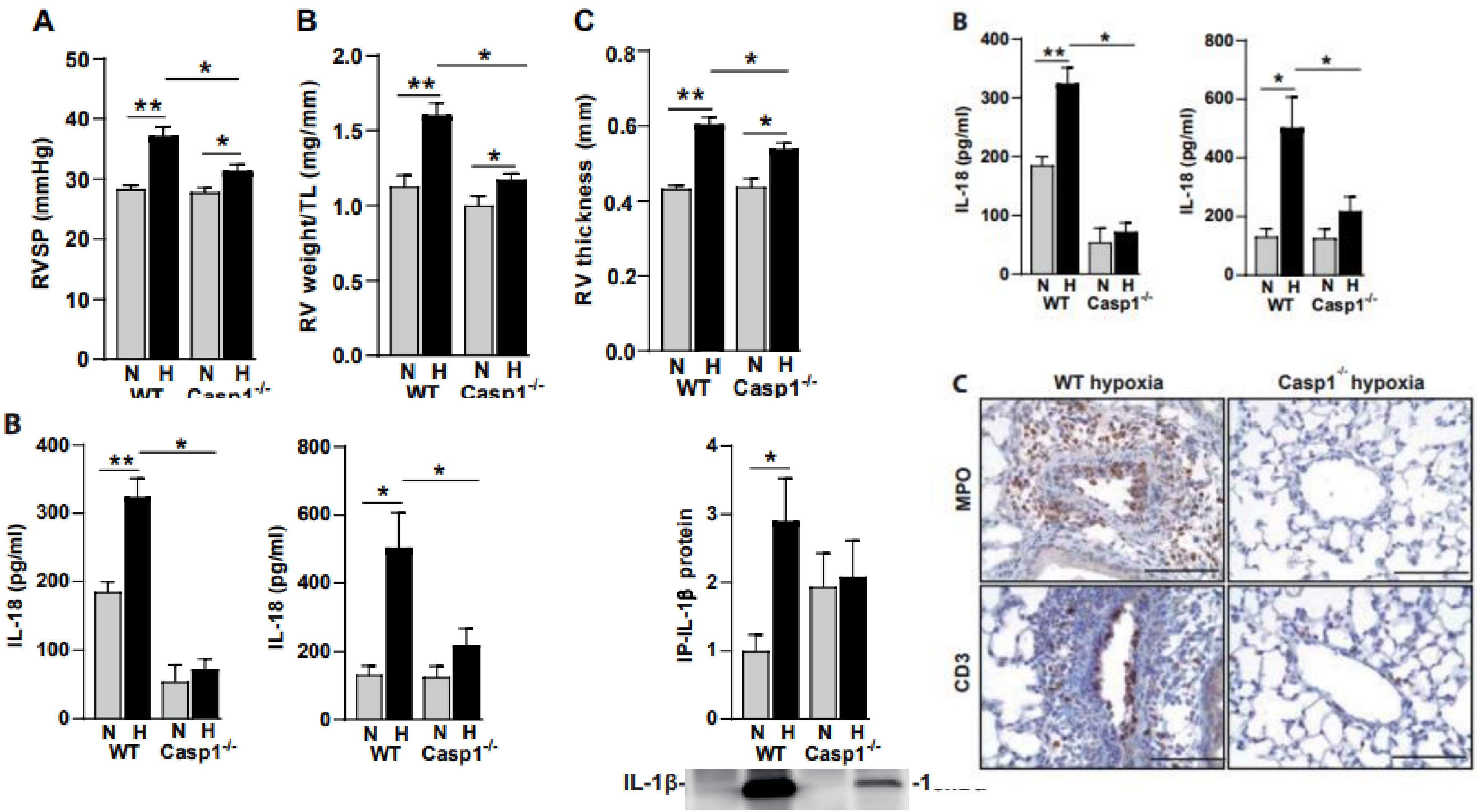


N -W -P - -O ; = C-

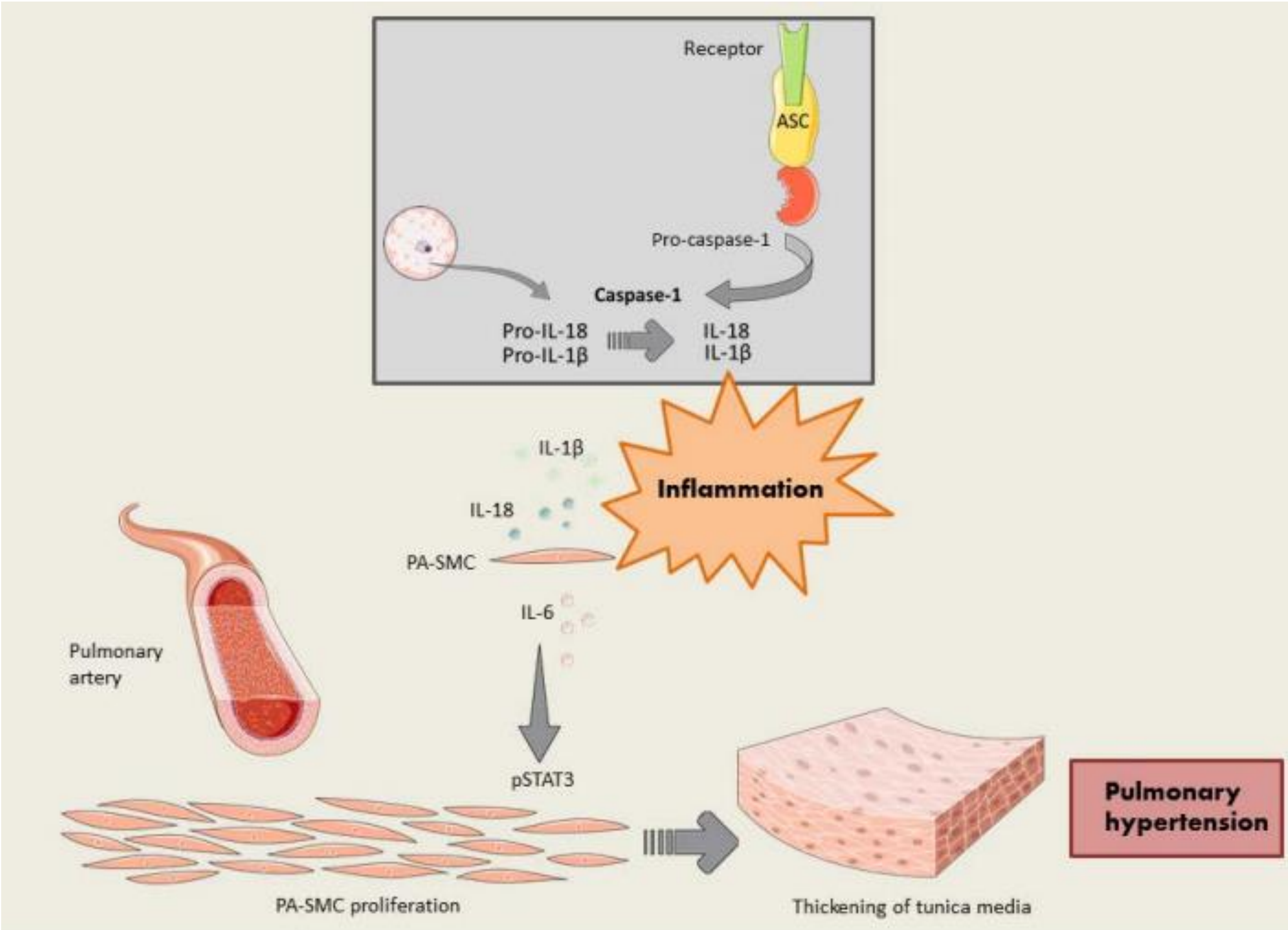
Pulmomary hypertension

Caspase-1 induces smooth muscle cell growth in hypoxia-induced pulmonary hypertension

C. Udjus,[1,2,3] F.T. Cero,[1,2,3] B. Halvorsen,[4] D. Behmen,[2,3] C.R. Carlson,[2,3] B.A. Bendiksen,[2,3] E.K.S. Espe,[2,3] I. Sjaastad,[2,3] E.M. Løberg,[6] A. Yndestad,[3,4] P. Aukrust,[4,5] G. Christensen,[2,3] O.H Skjønsberg,[1] and K.O. Larsen[1,3]



N -W -Y -P - - ; = F-W - H C5C6YFFF:Y =


Receptor
ASC
Pro-caspase-1
Caspase-1
Pro-IL-18
Pro-IL-1β
IL-18
IL-1β
Inflammation
IL-1β
IL-18
PA-SMC
IL-6
Pulmonary
artery
pSTAT3
PA-SMC proliferation
Thickening of tunica media
Pulmonary
hypertension

Conclusion

- -p -n - n -p - - - - - - - -
  n -n - p n - - n n - p - - - -
  n n - n - n -n - - n - - - n
- Np 9np n - - Y - - n - - -p n n p - - n -n -
  onp n - - p -
- U 9 n -np n - - Y -n - n n - - n -pn -
  n - - -p p-n - - n n - p - - -
- a - n n - n -n -p n - - - n n
  p - p - - - n -n - n n - - n p - - -
  n p - n - p - n - - Y - n n -
  p n - n -p - -np n

;