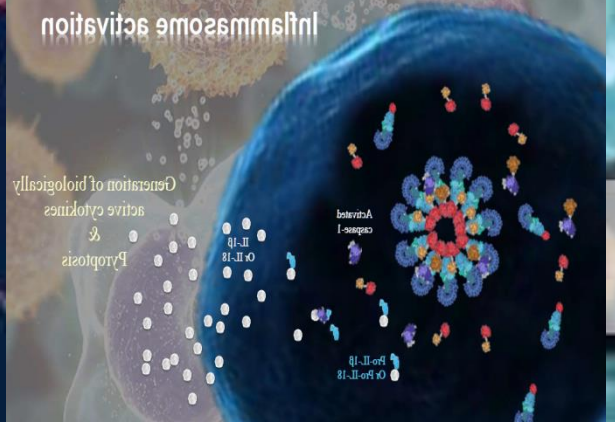
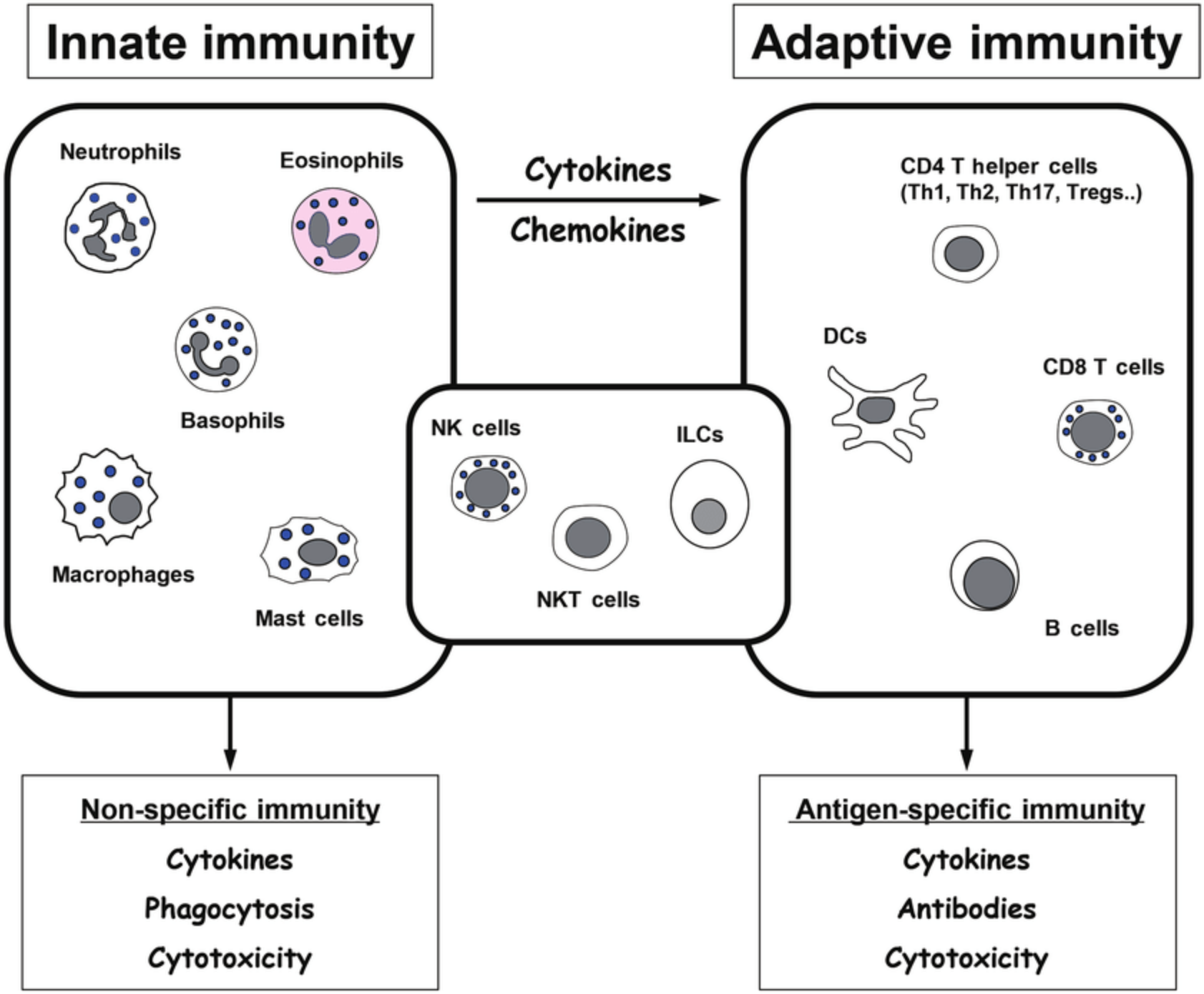


Φλεγμονόσωμα και παθήσεις αναπνευστικού

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)

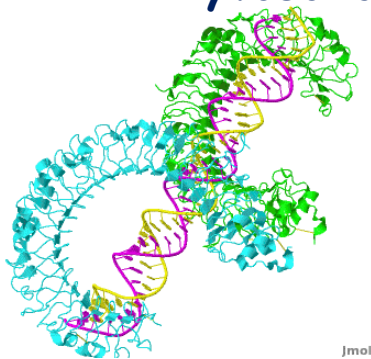
PRRs

- 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

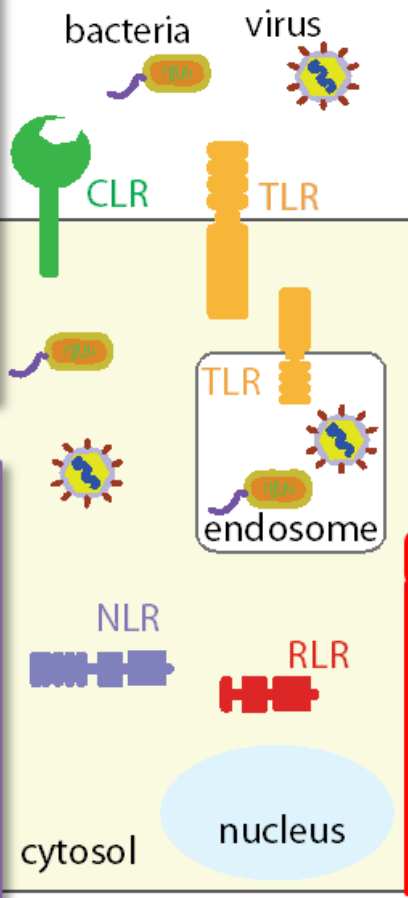
NLR

- **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



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 lipopolysaccharide (LPS) , a component of the gram-bacteria cell wall

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

NLRP3 inflammasome activators

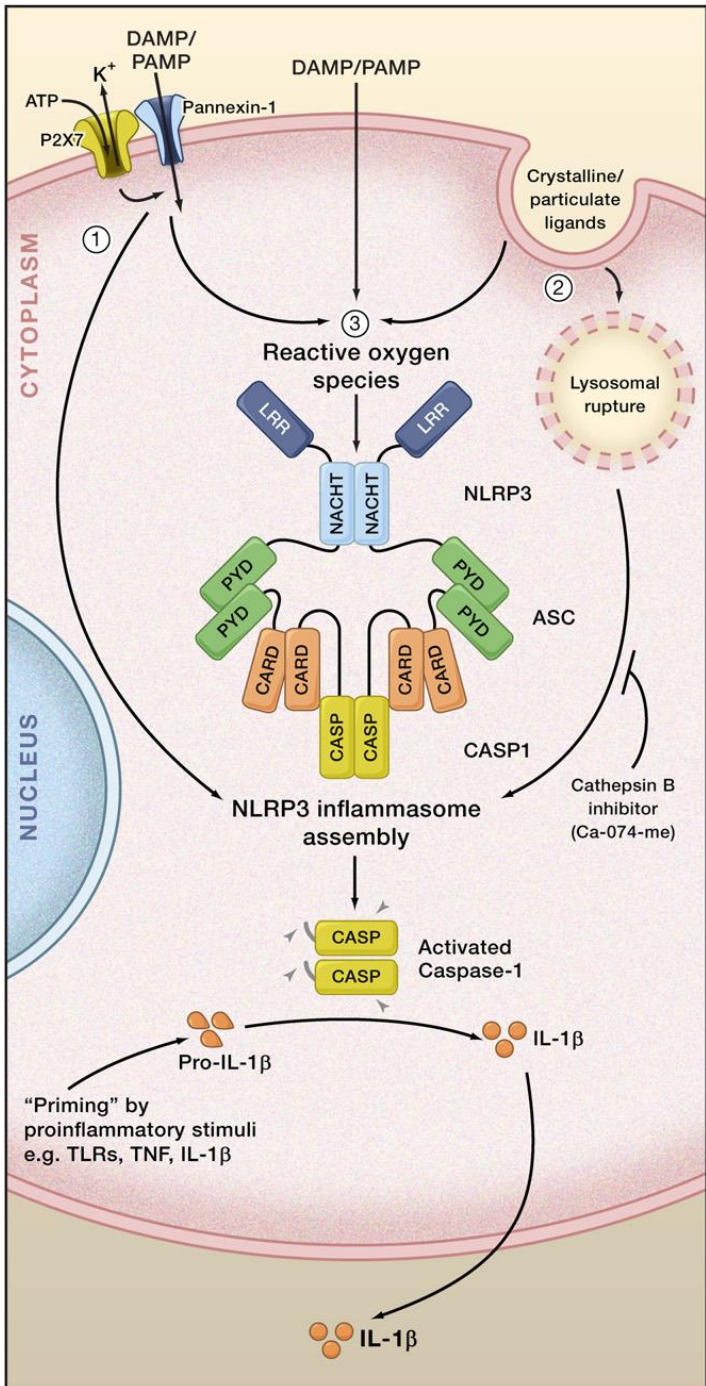
Activator	Source	Examples
DAMP	Self-derived	ATP, cholesterol crystals, monosodium urate crystals, calcium pyrophosphate dihydrate crystals, calcium oxalate crystals, soluble uric acid, neutrophil extracellular traps, cathelicidin, α-synuclein, amyloid-β, serum amyloid A, prion protein, biglycan, hyaluronan, 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

Nat Rev Immunol. 2019 Aug;19(8):477-489

Structures of the inflammasomes

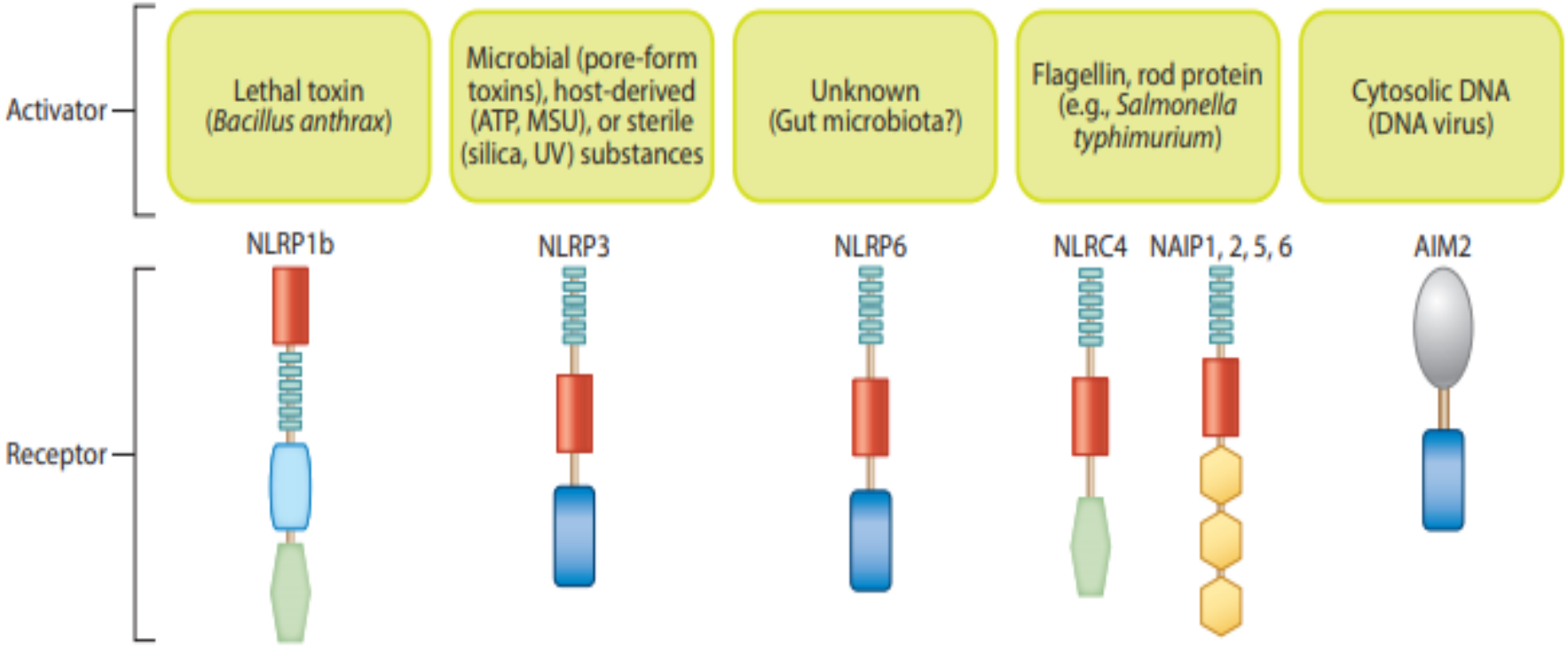
- **NLR family**
  - *a sensor - central nucleotide-binding* and oligomerization (NACHT) domain, which is commonly flanked by C-terminal leucine-rich repeats (LRRs)
  - *an adaptor molecule known as apoptosis-associated speck-like protein containing caspase activation and recruitment domain (CARD) (ASC),* or pyrin (PYD) domain
  - *the effector molecule caspase-1*

- NOD like receptors with a pyrine domain → NLRP (1,3)
- With a caspace recruitment domain → NLRC
- NLRP3 = NOD like receptor with a pyrine domain 3
- Best characterized



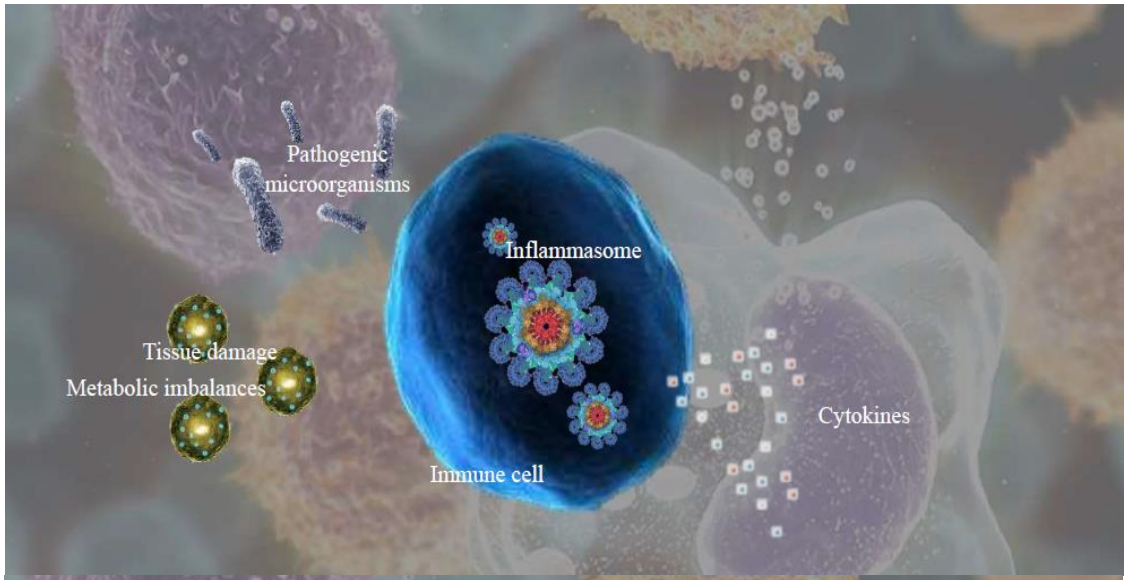
Schroder & Tschopp The inflammasomes Cell 2010

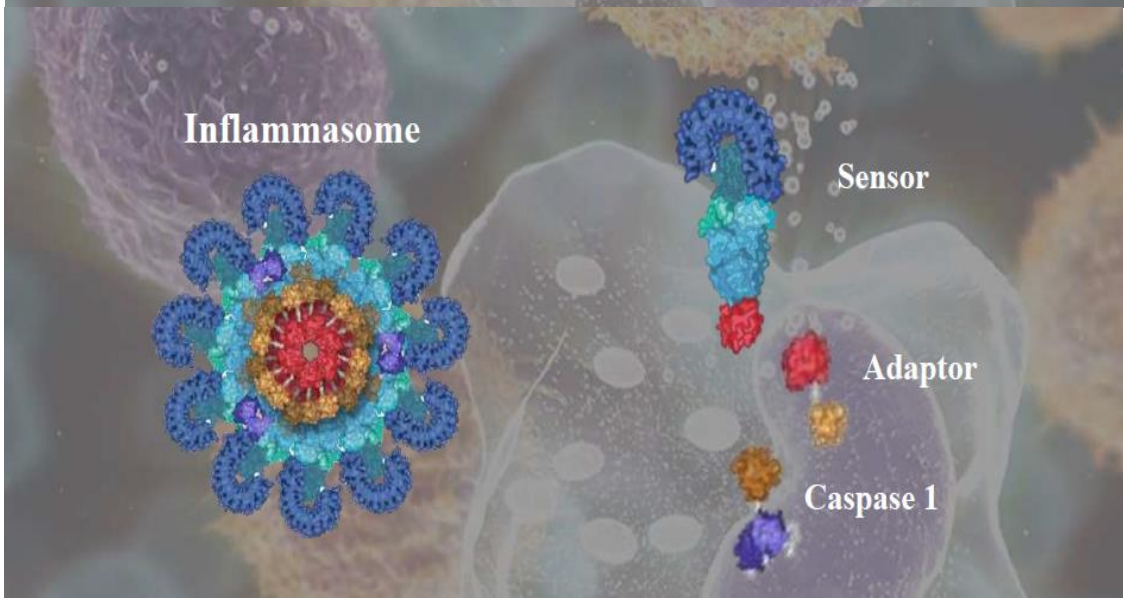
NOD-like receptors and their activators



Annu Rev Physiol. 2017 Feb 10;79:471-494

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





Μέλη της οικογένειας NLR σχηματίζουν μεγάλα κυτταροπλασματικά συμπλέγματα

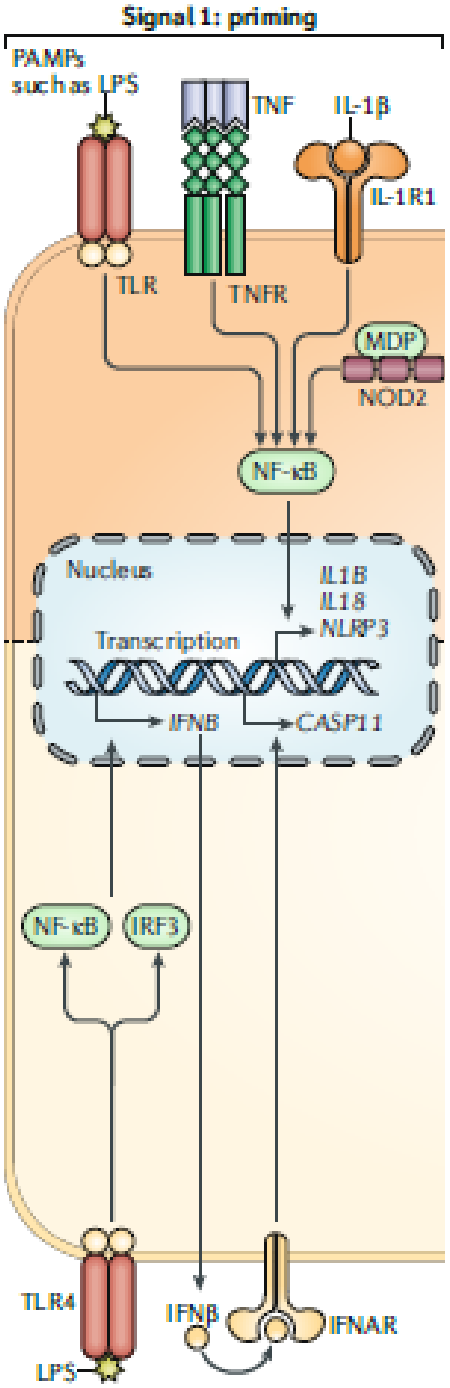
⬇

Φλεγμονοσώματα

Μοριακές πλατφόρμες που συνδέουν την αναγνώριση μικροβιακών/κυτταρικών προϊόντων μετά από λοιμώξεις ή καταστάσεις stress με την πρωτεολυτική ενεργοποίηση των φλεγμονωδών κυτταροκινών IL-1β και IL-18 μέσω της caspase-1

Alarmins

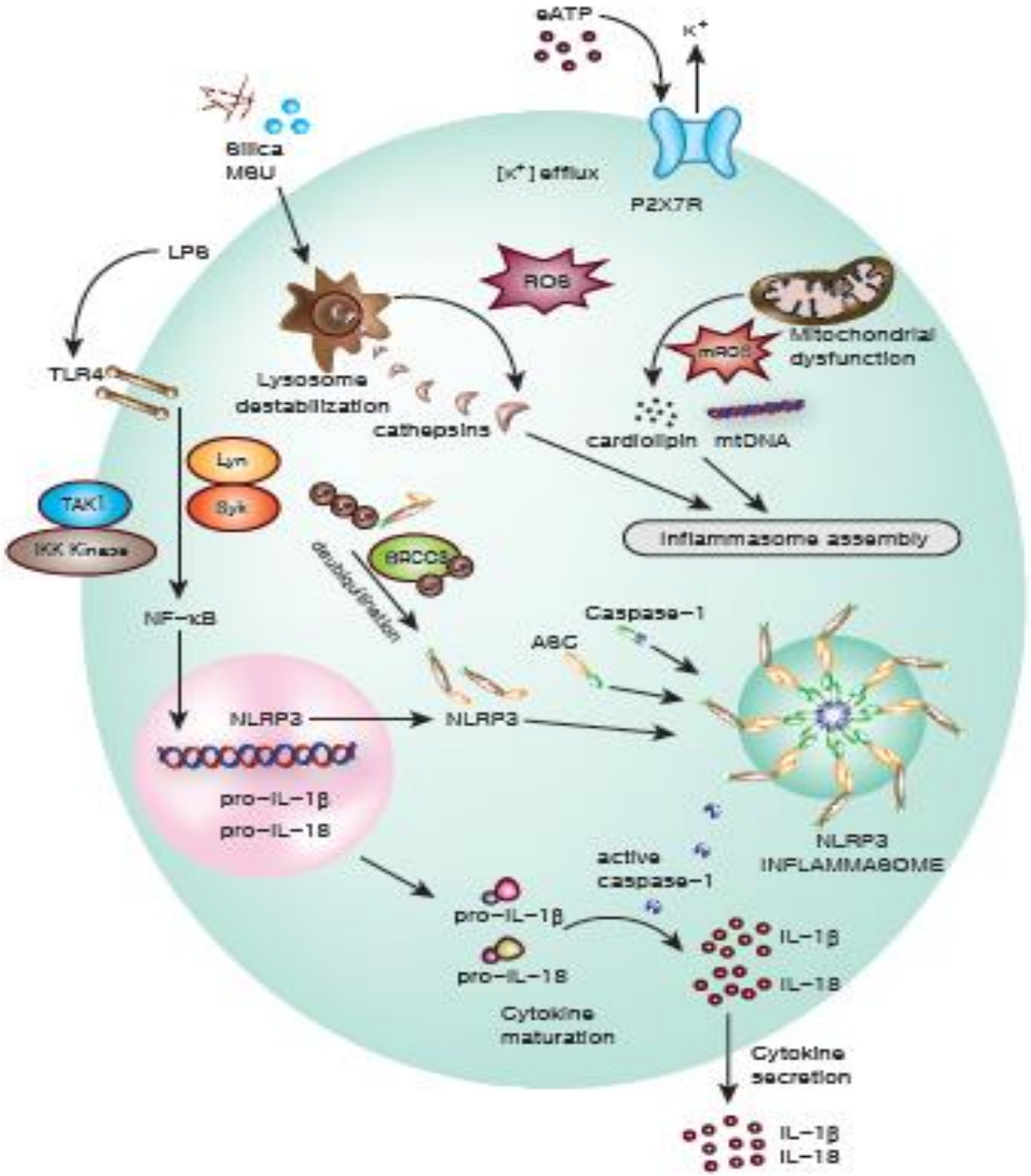
Loverdos et al. J Clin Med. 2019 Nov 14;8(11)



Priming is provided by the activation of cytokines or pathogen- associated molecular patterns (PAMPs), leading to the transcriptional upregulation of canonical and non- canonical NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome components.

Nat Rev Immunol. 2019 Aug;19(8):477-489

The NLRP3 inflammasome responds to activating signals through a two-step activation model



Step 1

Initiation is typically triggered by ligand binding (e.g., LPS) to Toll like receptors (e.g., TLR4) and related receptors. This results in activation of NF-κB which translocates to the nucleus and activates the transcription of inflammasome components, including NLRP3, and the pro-forms of inflammasome-related cytokines (i.e., pro-IL-1β and pro-IL-18).

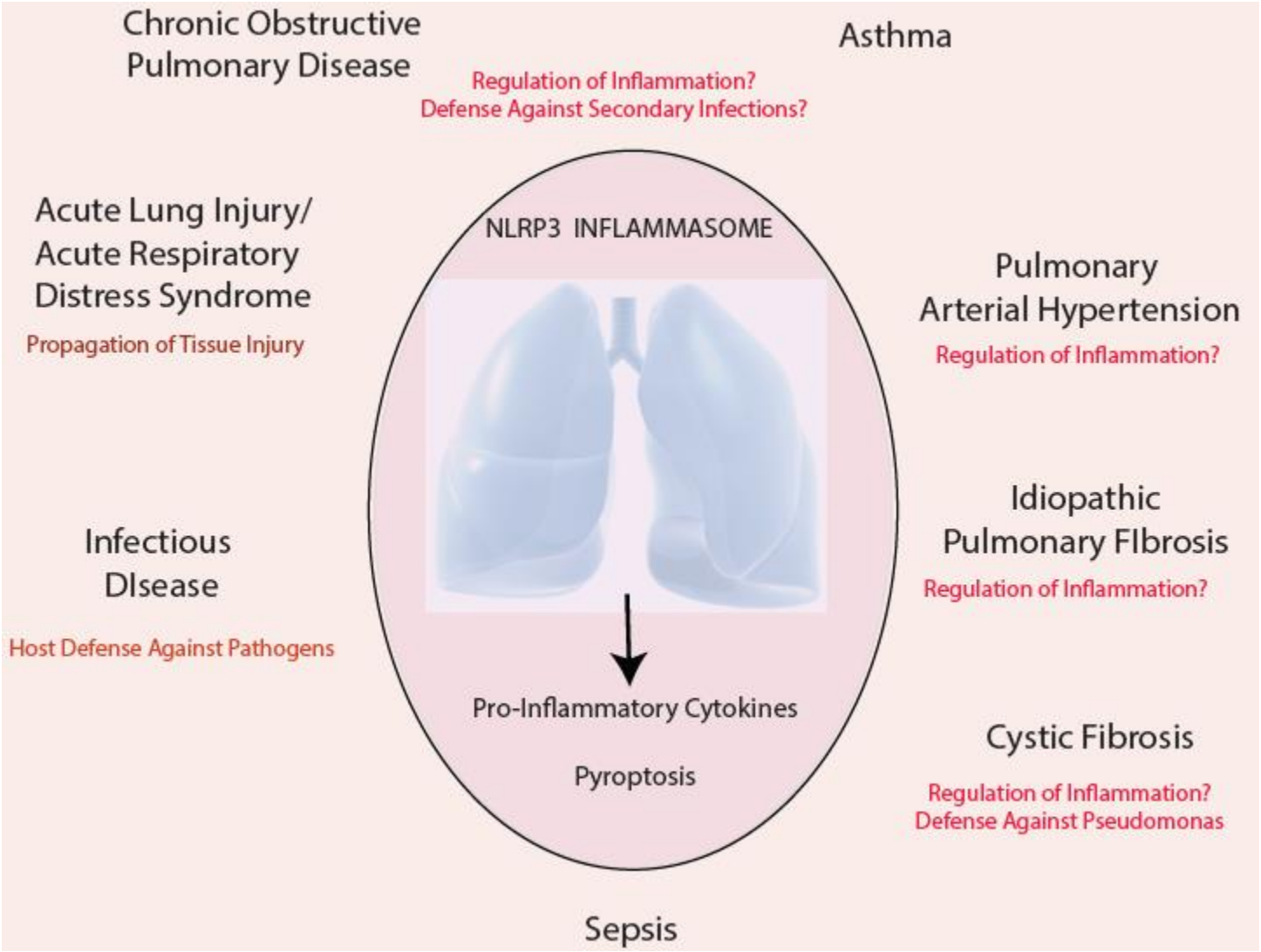
Step 2

A second signal is required for assembly of the inflammasome from its individual components (e.g., NLRP3, ASC, pro-caspase-1).

- The canonical signal is provided by P2X7 stimulation by ligand (e.g., eATP), which triggers potassium ion efflux.
- Additional contributory signals may include the destabilization of lysosomes after ingestion and phagocytosis of crystalline substrates such as monosodium urate crystals (MSU), and the disruption of mitochondria, leading to the release of mitochondrial DAMPs such as cardiolipin and mtDNA.
- Activation of inflammasome-associated caspase-1 results in the activation (cleavage) of pro-inflammatory cytokines (e.g., IL-1β, IL-18), prior to their secretion

Am J Respir Cell Mol Biol. 2016 Feb;54(2):151-60

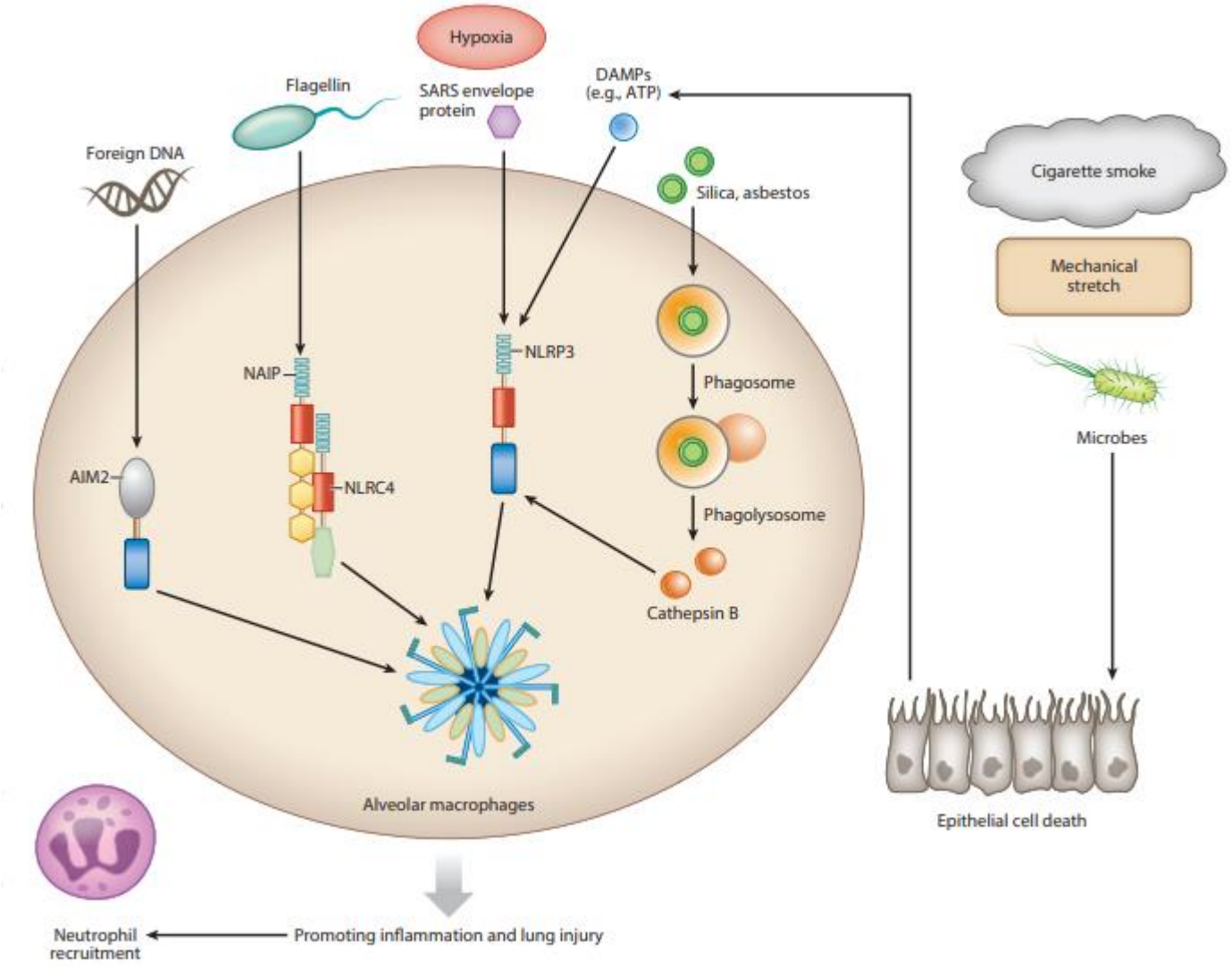
NLRP3 inflammasome in lung disease



Am J Respir Cell Mol Biol. 2016 Feb;54(2):151-60

Infectious disease

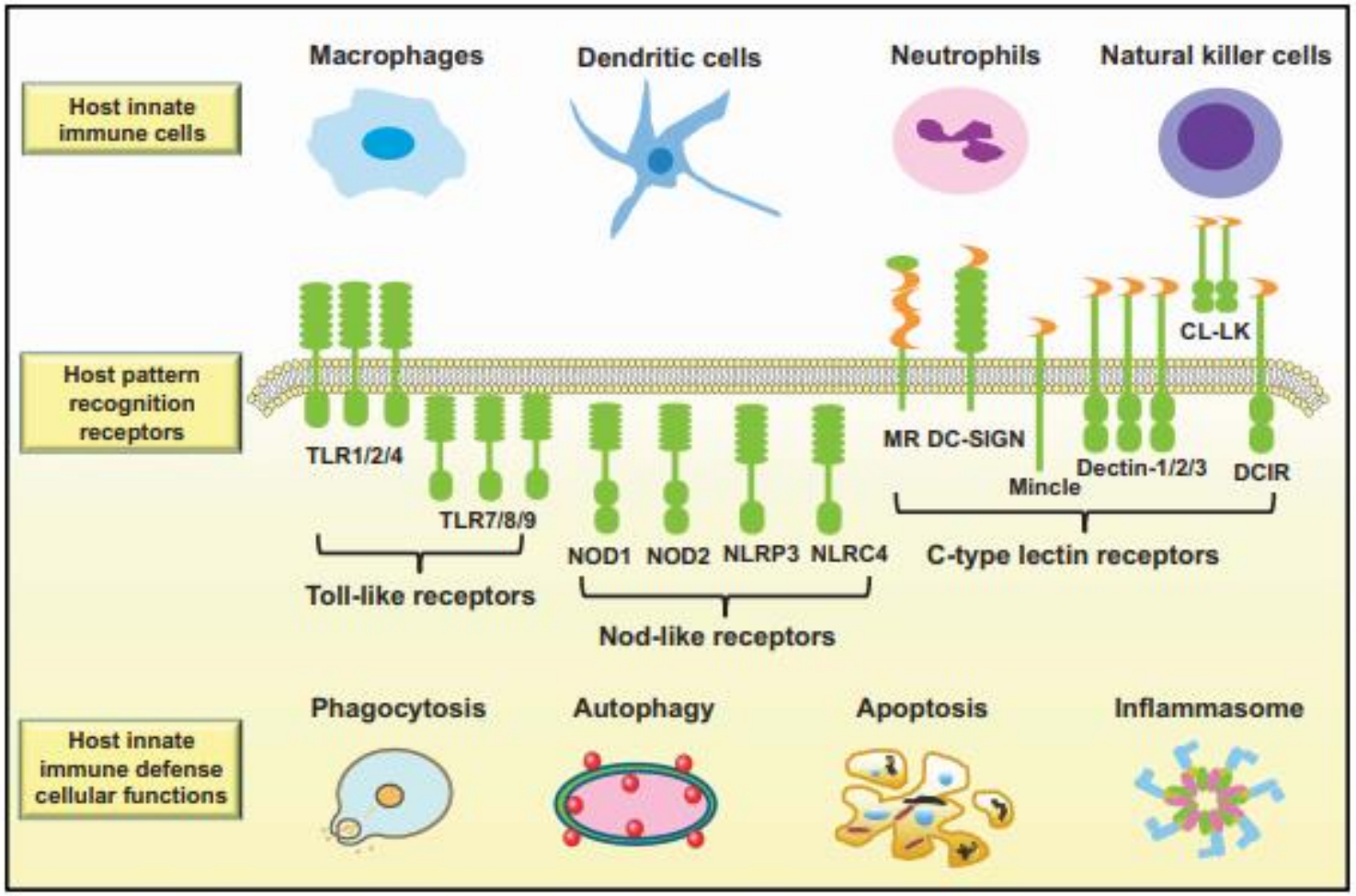
Environmental triggers of inflammasome activation in a pulmonary macrophage



Annu Rev Physiol. 2017 Feb 10;79:471-494

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

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



Cell Mol Immunol. 2017 Dec;14(12):963-975

PULMONARY PERSPECTIVE

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

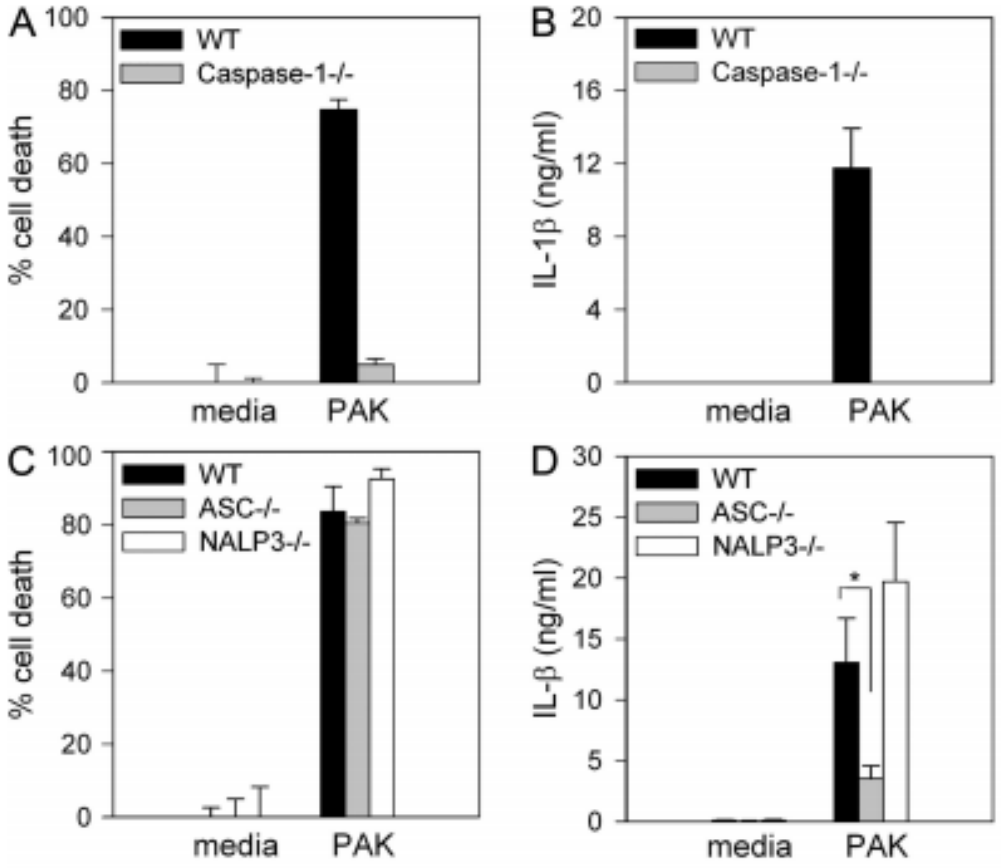
Mary Leissinger[1], Ritwij Kulkarni[1], Rachel L. Zemans[2], Gregory P. Downey[2], and Samithamby Jeyaseelan[1,3]

Bacteria	MAMP	NLR	Phenotype*
Bordetella pertussis	CyaA	Unknown	S*nd* N*nd* BB↑
		Inflammasome	BD*nd* (IL-R1$^{-/-}$ mice)
Chlamydophila (Chlamydia) pneumoniae	Unknown	Unknown	S↓ N*nd* BB↑ BD*nd*
		Inflammasome	(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*

Am J Respir Crit Care Med. 2014 Jun 15;189(12):1461-8

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] Barbara I. Kazmierczak,[2,4] and Richard A. Flavell[1,3]

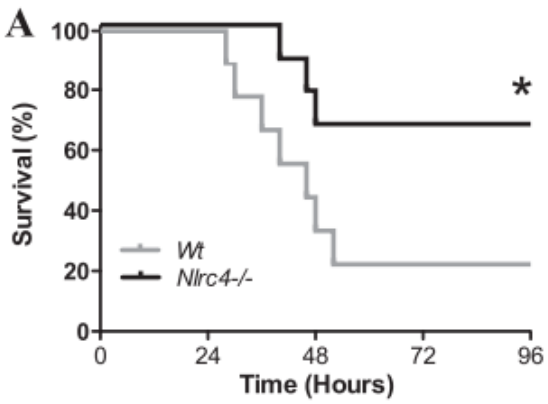


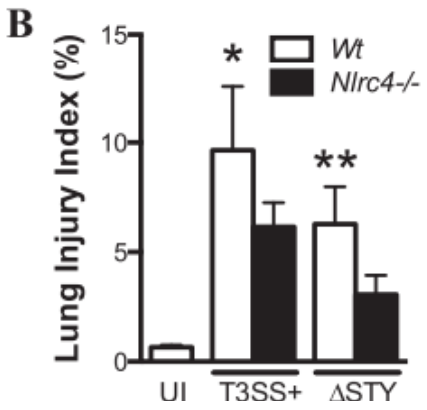
J Exp Med. 2007 Dec 24;204(13):3235-45

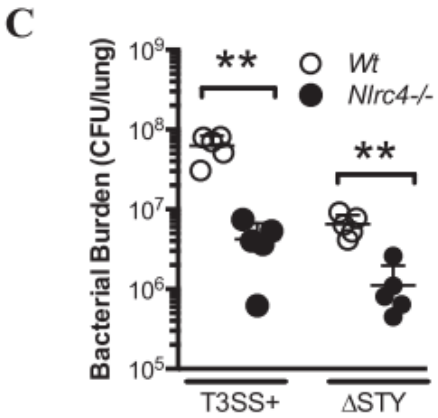
ORIGINAL ARTICLE

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

Emmanuel Faure[1,2*], Jean-Baptiste Mear[1,2*], Karine Faure[1,2], Sylvain Normand[2,3,4,5], Aurélie Couturier-Maillard[2,3,4,5], Teddy Grandjean[2,3,4,5], Viviane Balloy[6], Bernhard Ryffel[7,8], Rodrigue Dessein[1,2], Michel Chignard[6], Catherine Uyttenhove[7,8], Benoit Guery[1,2], Philippe Gosset[2,3,4,5], Mathias Chamaillard[2,3,4,5†], and Eric Kipnis[1,2†]







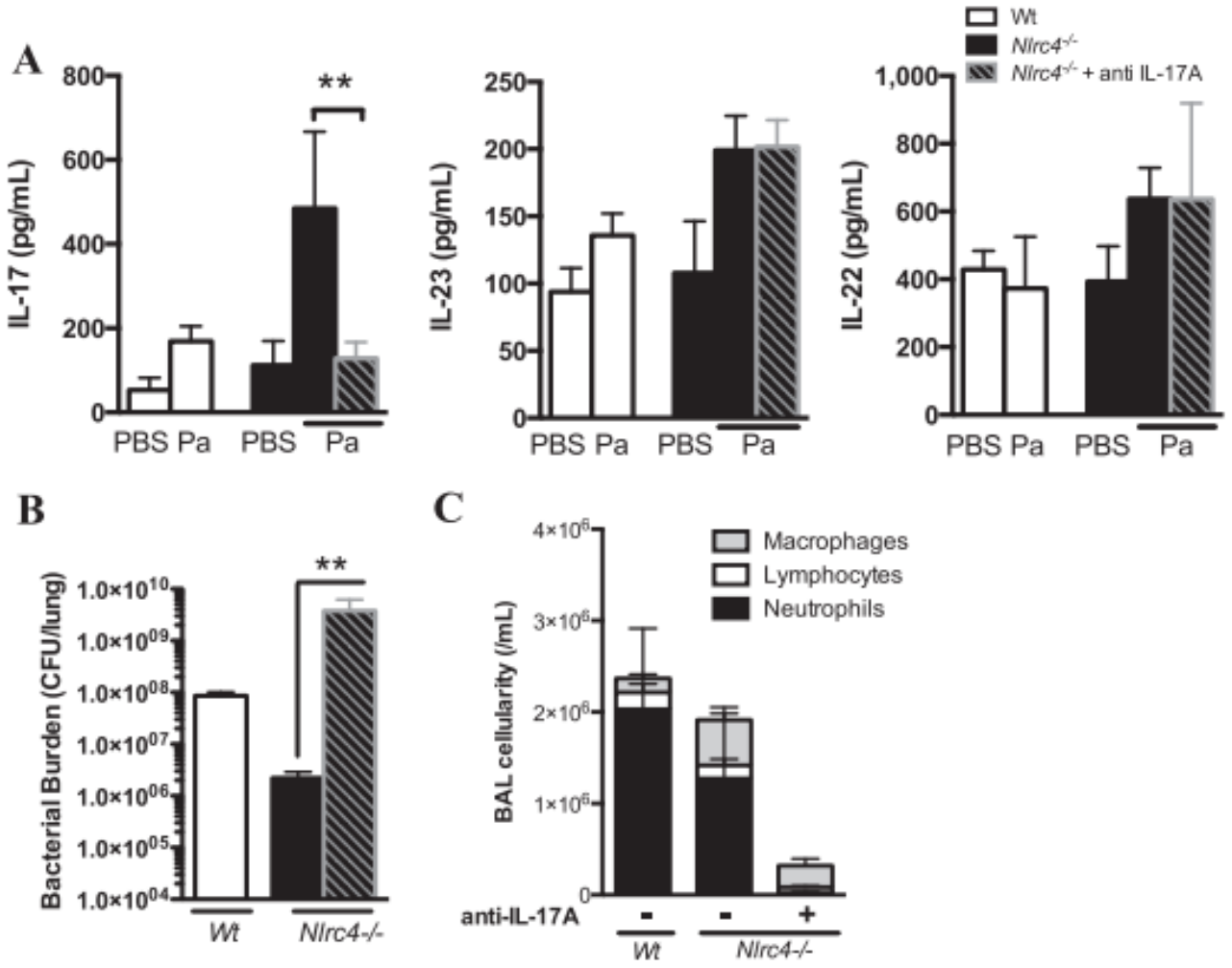
- Type-3 secretion system-positive (T3SS1) strain
- Srain lacking exotoxins (DSTY)

Pseudomonas aeruginosa triggers, through a functional type-3 secretion system (T3SS), the activation of NLRC4.

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

Am J Respir Crit Care Med. 2014 Apr 1;189(7):799-811

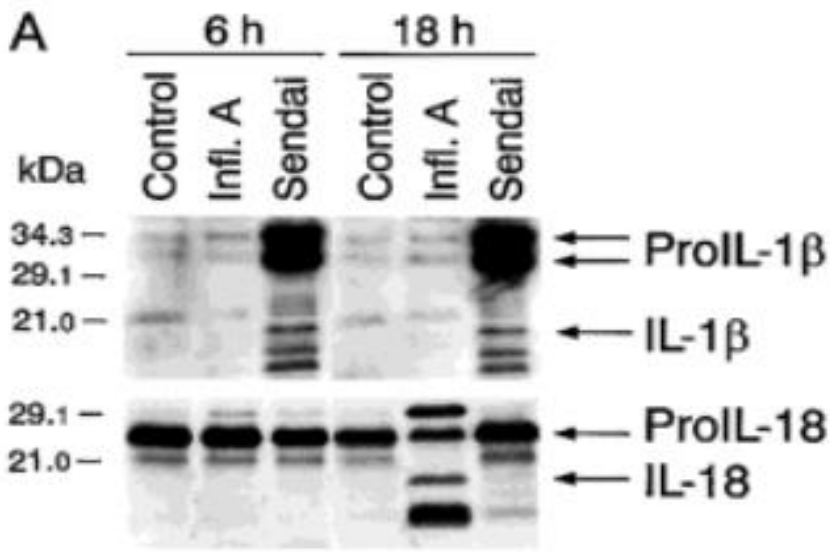
IL-17–mediated Host Response Is Increased in Nlrc4-/- Mice

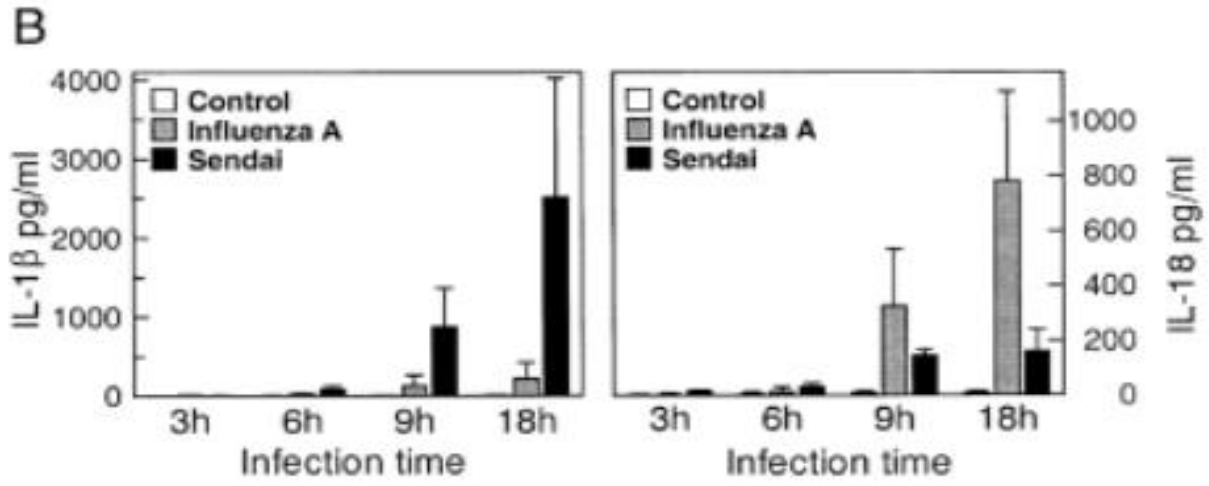


Am J Respir Crit Care Med. 2014 Apr 1;189(7):799-811

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





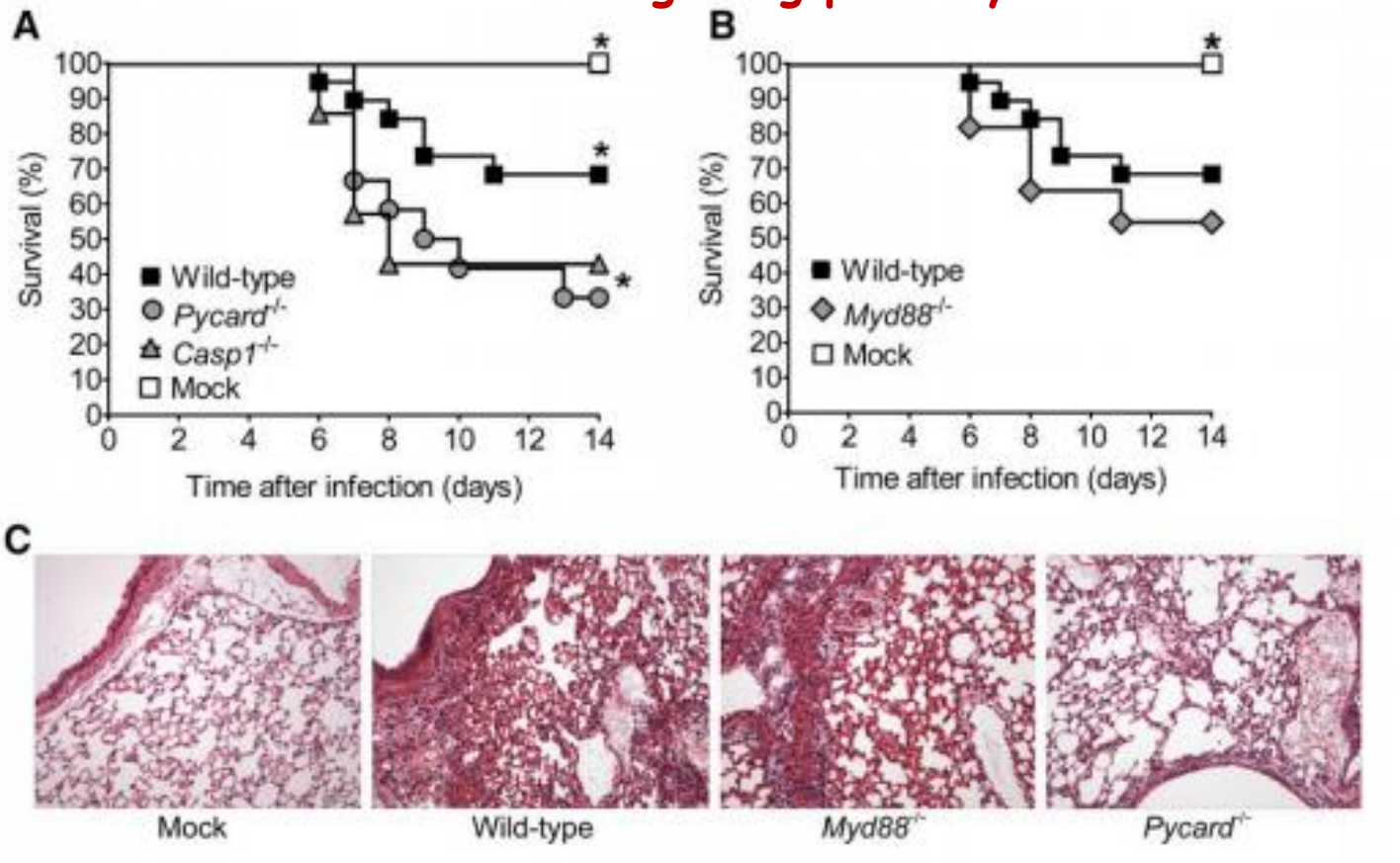
Virus infection induces the processing of pro-IL-1 and pro-IL-18 into their mature forms in macrophages

Eur J Immunol. 2001 Mar;31(3):726-33.

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]

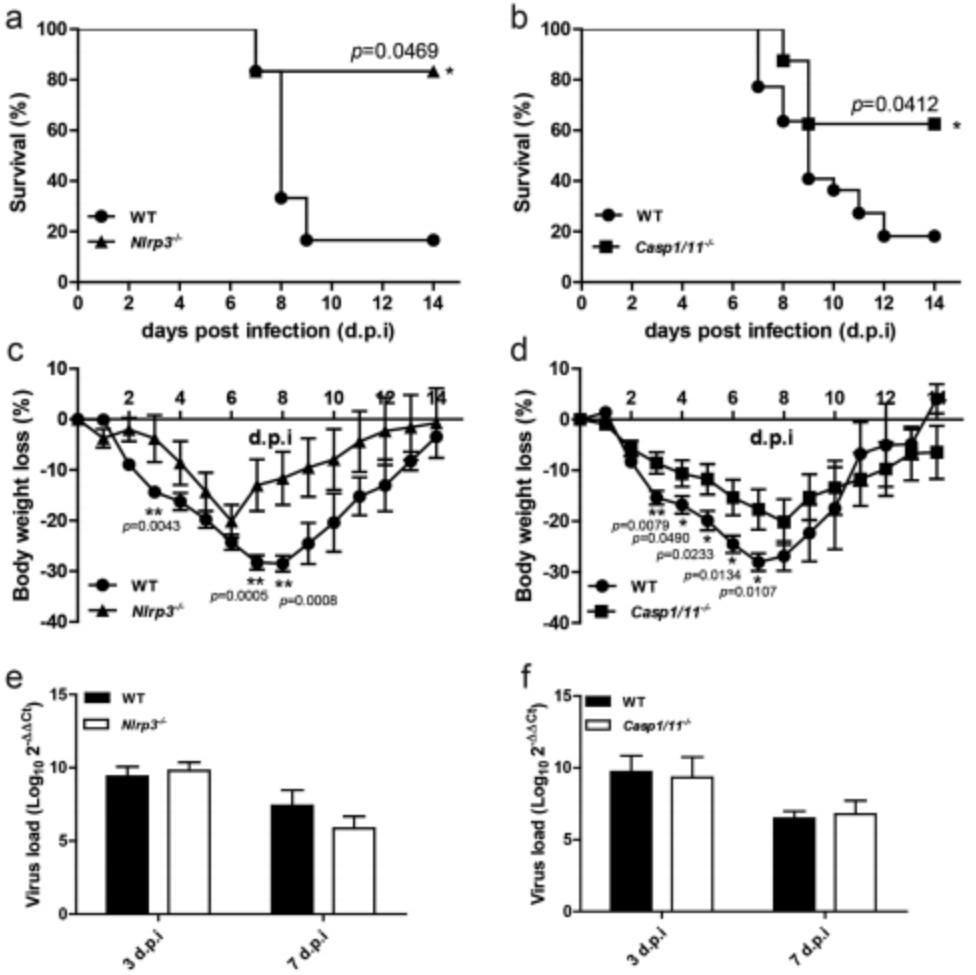
Pathogenicity and immune response in mice deficient in inflammasome signaling pathways



Immunity. 2009 Apr 17;30(4):556-65

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

Rongrong Ren[1], Shuxian Wu[2], Jialin Cai[4], Yuqin Yang[5], Xiaonan Ren[1], Yanling Feng[1], Lixiang Chen[1], Boyin Qin[1], Chunhua Xu[1], Hua Yang[1], Zhigang Song[1], Di Tian[1], Yunwen Hu[1,3], Xiaohui Zhou[1,3] & Guangxun Meng[2]



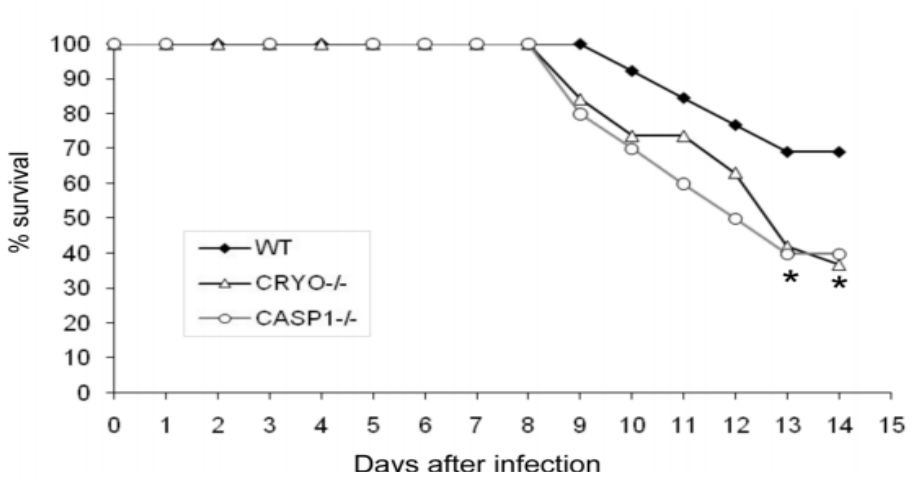
Mice deficient for NLRP3 inflammasome components, including NLRP3, caspase-1, and Apoptosis-associated speck-like protein containing a CARD (ASC), were less susceptible to H7N9 viral challenge than wild type (WT) controls.

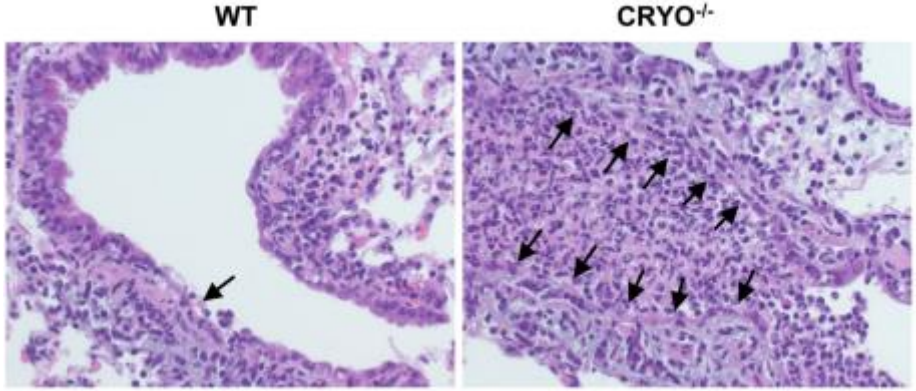
Sci Rep. 2017 Aug 8;7(1):7625

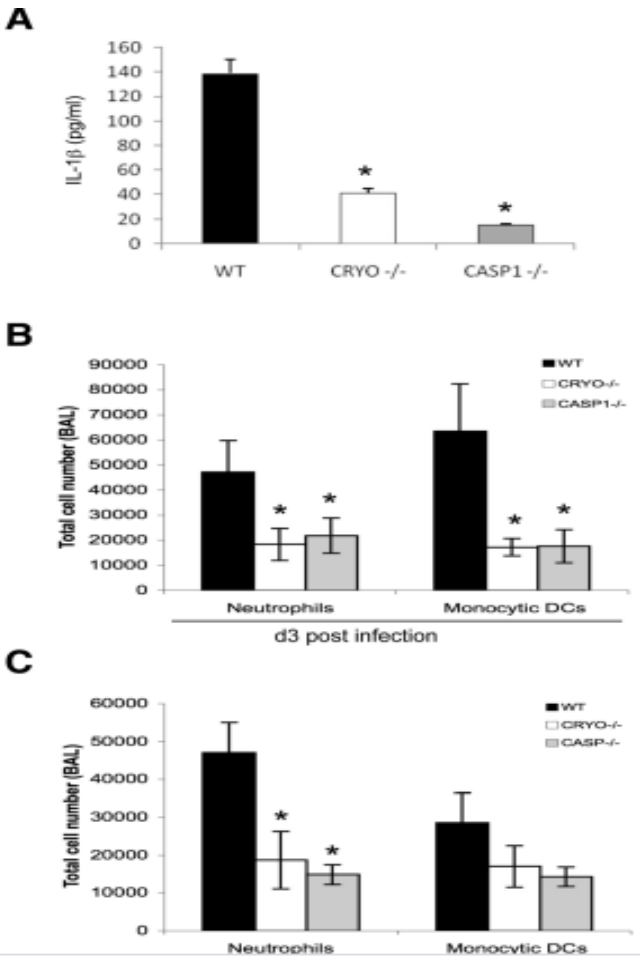
NLRP3 (NALP3/CIAS1/Cryopyrin) mediates key innate and healing responses to influenza A virus via the regulation of caspase-1

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





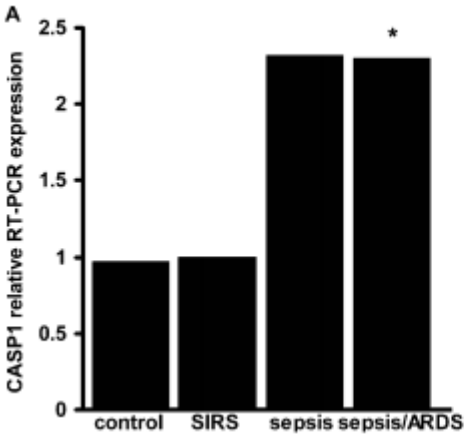


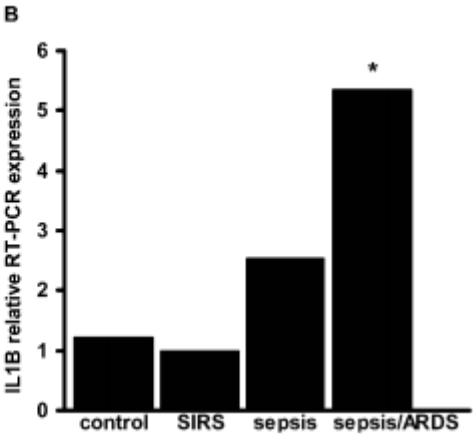
Immunity. 2009 Apr 17;30(4):566-75

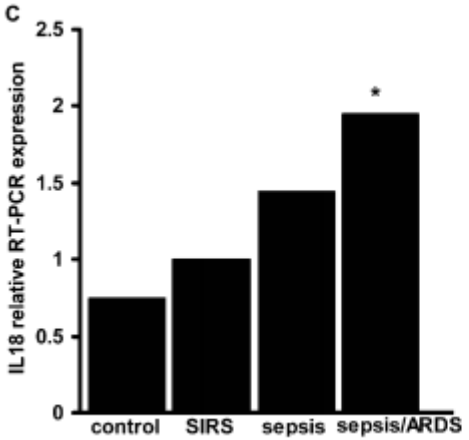
Acute lung injury and ARDS

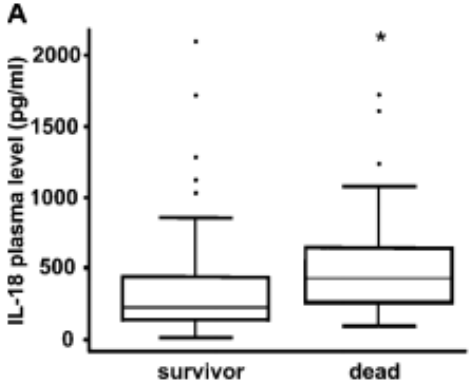
Inflammasome-regulated Cytokines Are Critical Mediators of Acute Lung Injury

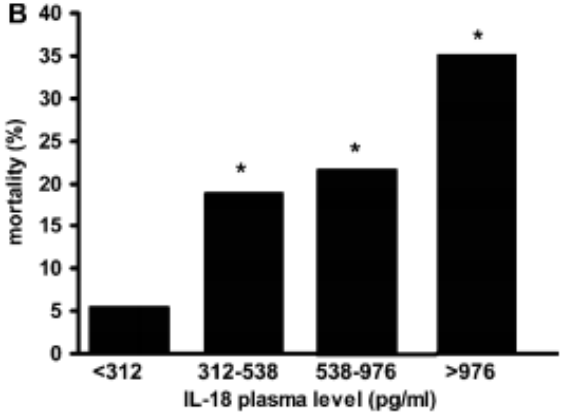
Tamás Dolinay[1], Young Sam Kim[1], Judie Howrylak[1,2], Gary M. Hunninghake[1,2], Chang Hyeok An[1], Laura Fredenburgh[1], Anthony F. Massaro[1], Angela Rogers[1,2], Lee Gazourian[1], Kiichi Nakahira[1], Jeffrey A. Haspel[1], Roberto Landazury[1], Sabitha Eppanapally[3], Jason D. Christie[4], Nuala 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]







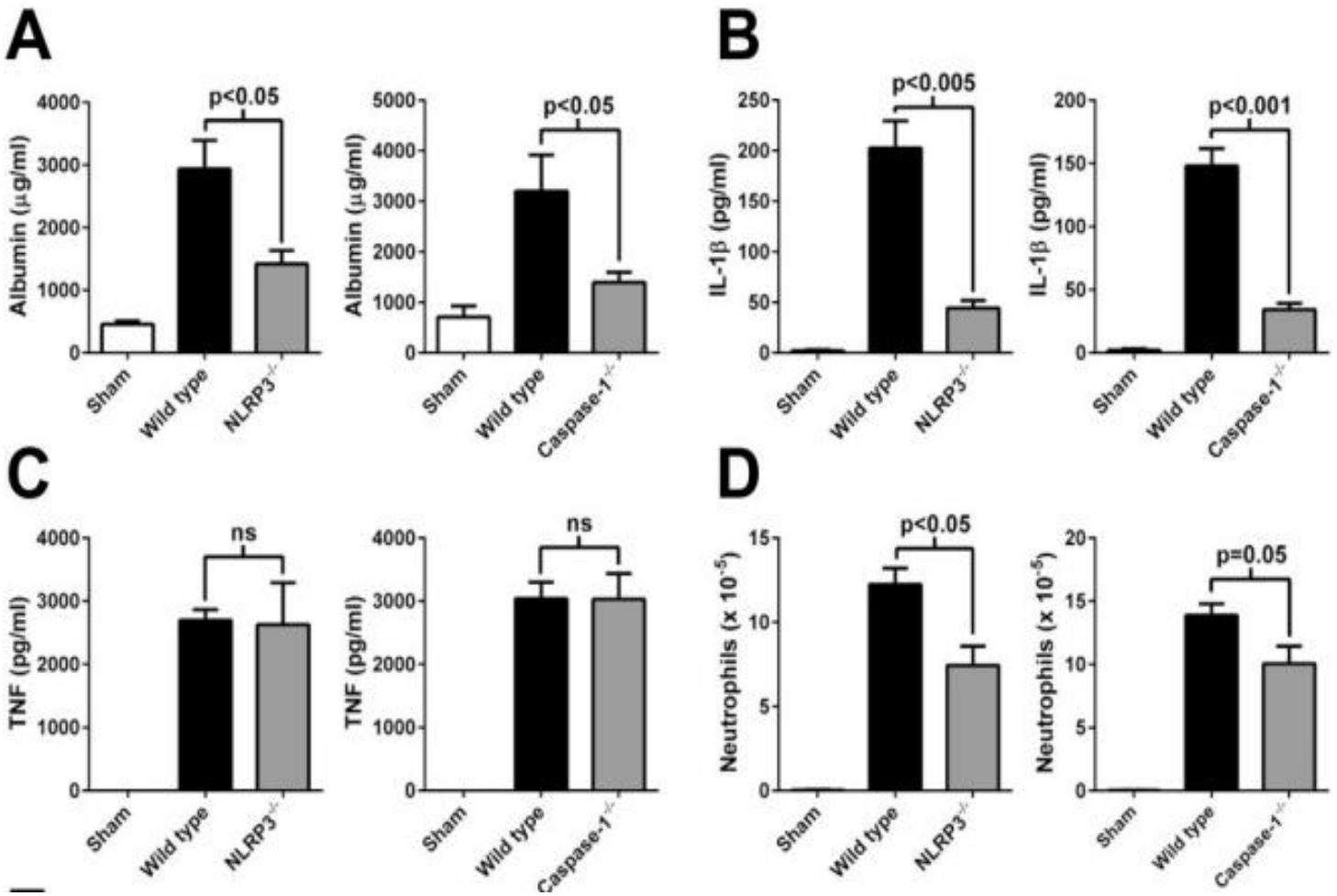




Am J Respir Crit Care Med. 2012 Jun 1;185(11):1225-34

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

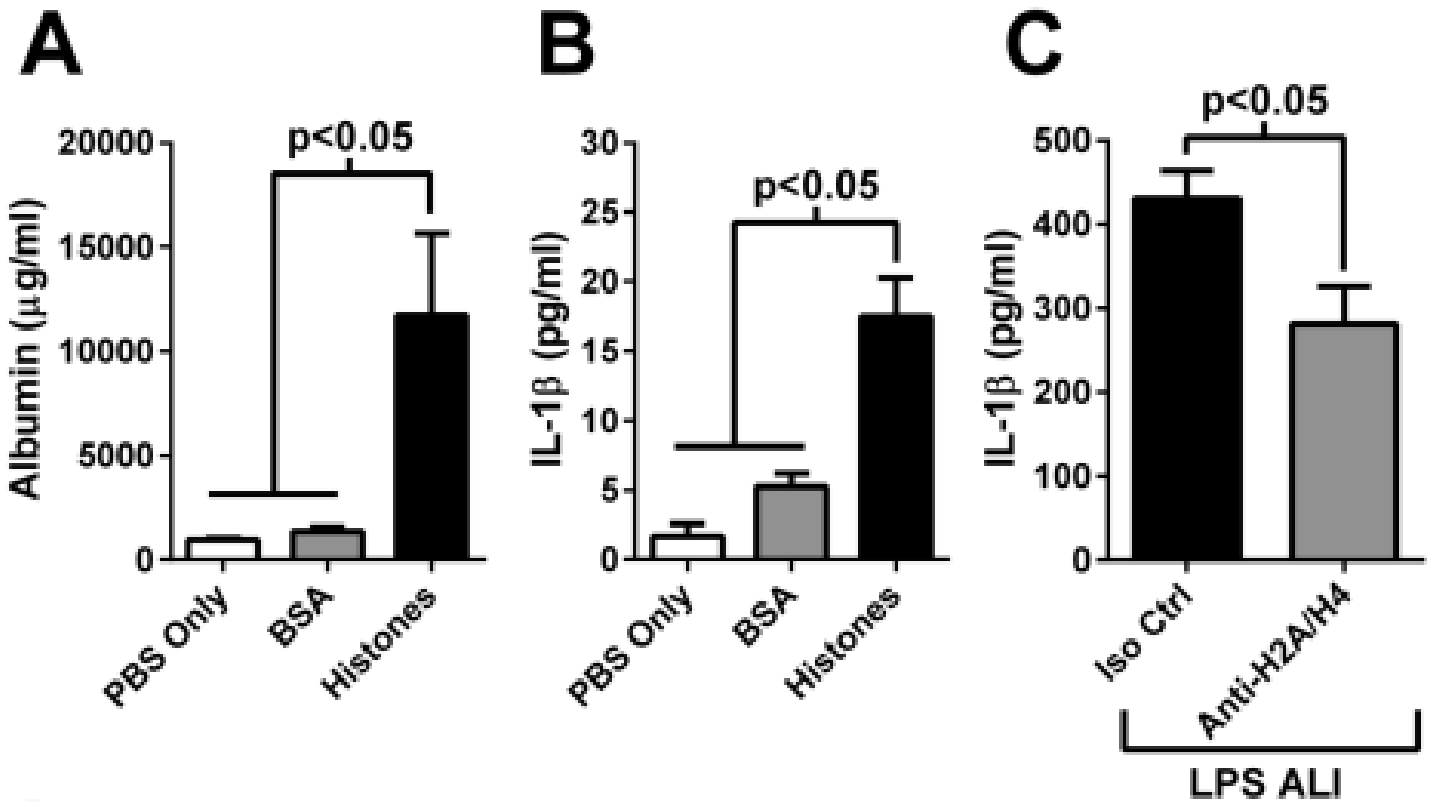
Jamison J. Grailer, Bethany A. Canning, Miriam Kalbitz, Mikel D. Haggadone, Rasika M. Dhond, Anuska V. Andjelkovic, Firas S. Zetoune, and Peter A. Ward*



J Immunol. 2014 Jun 15;192(12):5974-83.

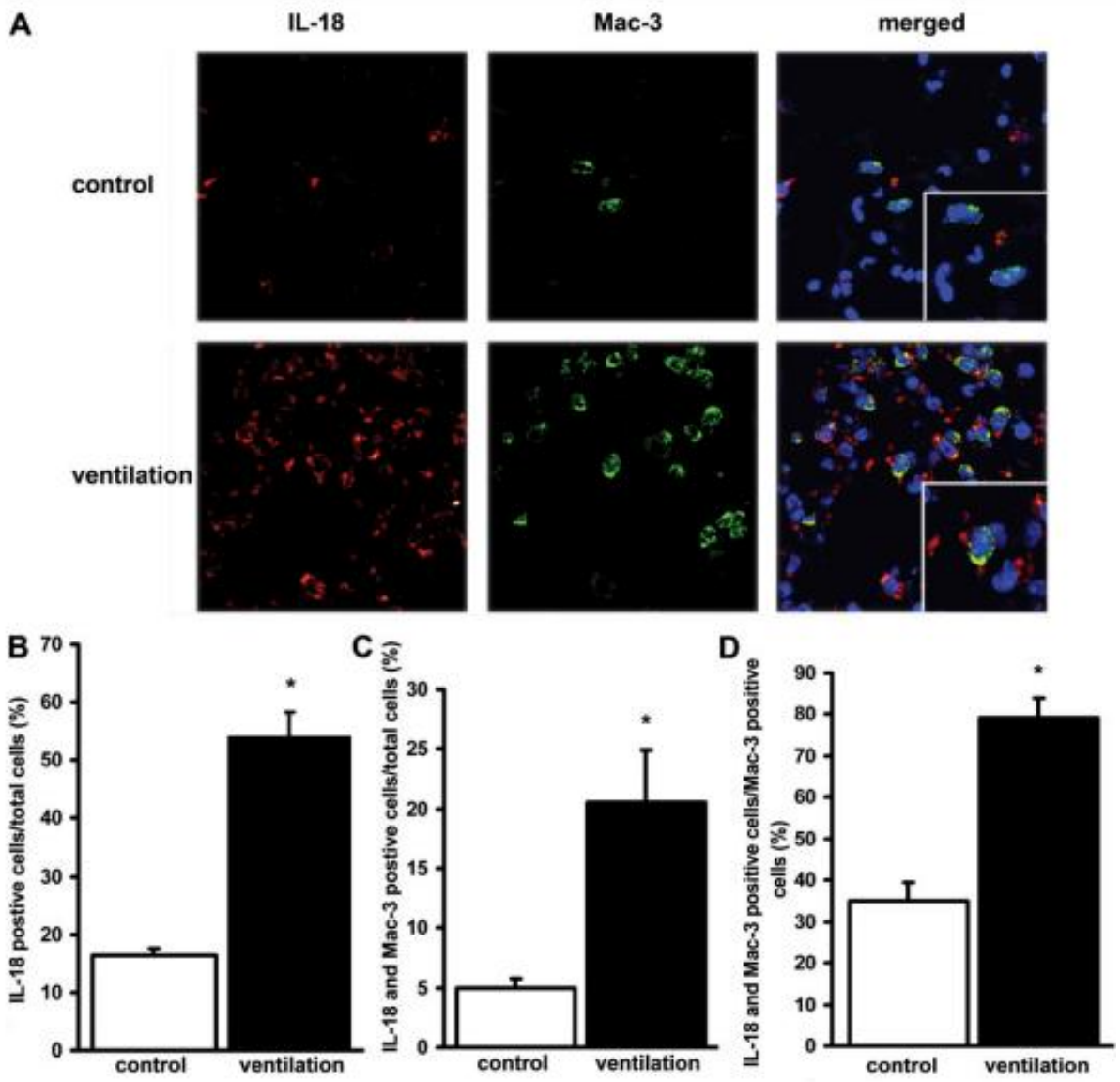
Extracellular histones activate the inflammasome

These data indicate an interaction between extracellular histones and the NLRP3 inflammasome, resulting in ALI. Such findings suggest novel targets for treatment of ALI, for which there is currently no known efficacious drug.



J Immunol. 2014 Jun 15;192(12):5974-83.

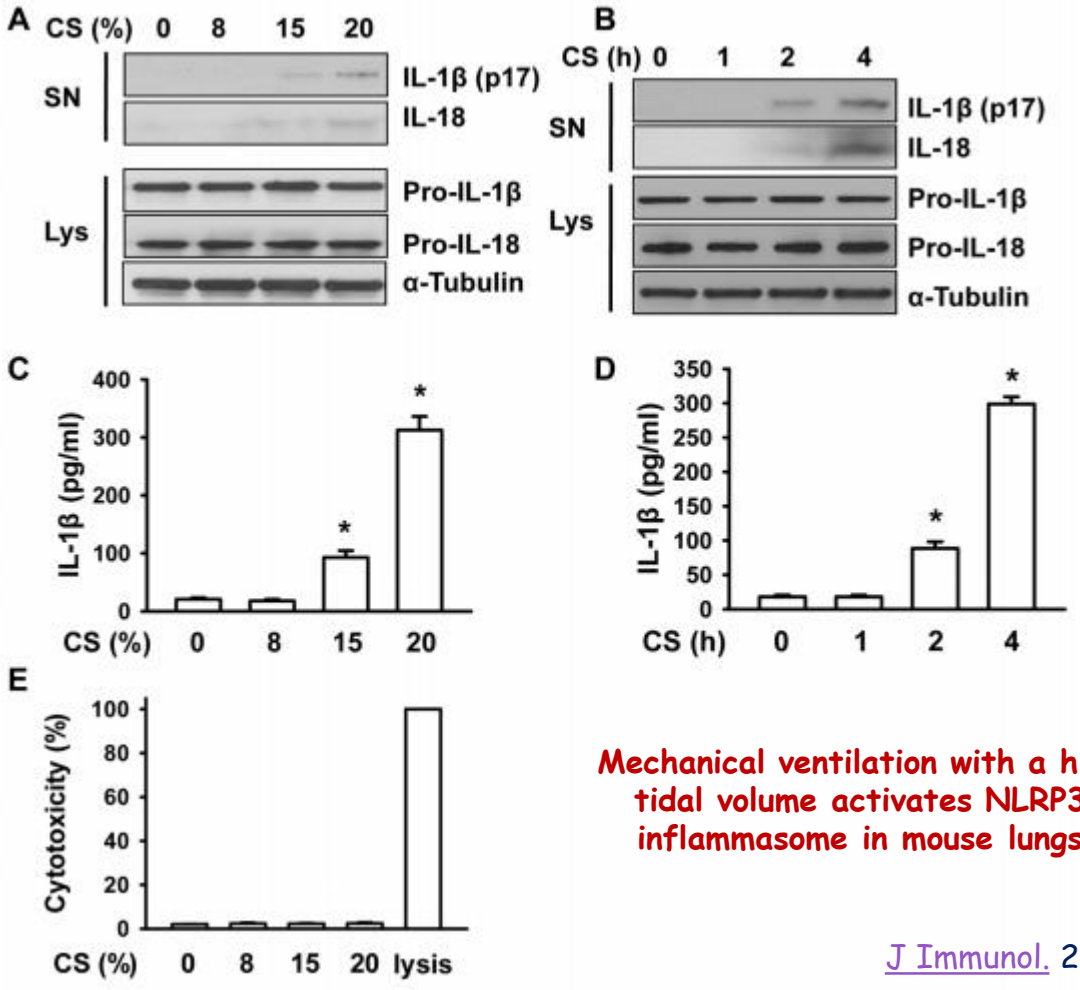
Mechanical ventilation (MV) increases the expression of the cleaved form of IL-18 in alveolar macrophages



Am J Respir Crit Care Med. 2012 Jun 1;185(11):1225-34

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[*,‡]

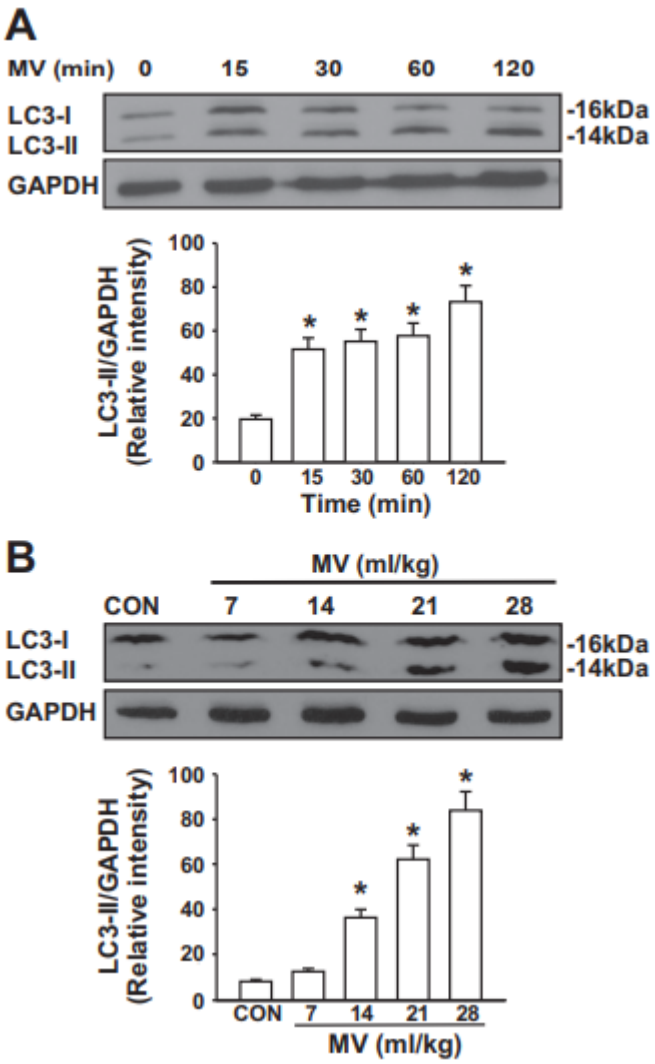


Mechanical ventilation with a high tidal volume activates NLRP3 inflammasome in mouse lungs

J Immunol. 2013 Apr 1;190(7):3590-9

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]



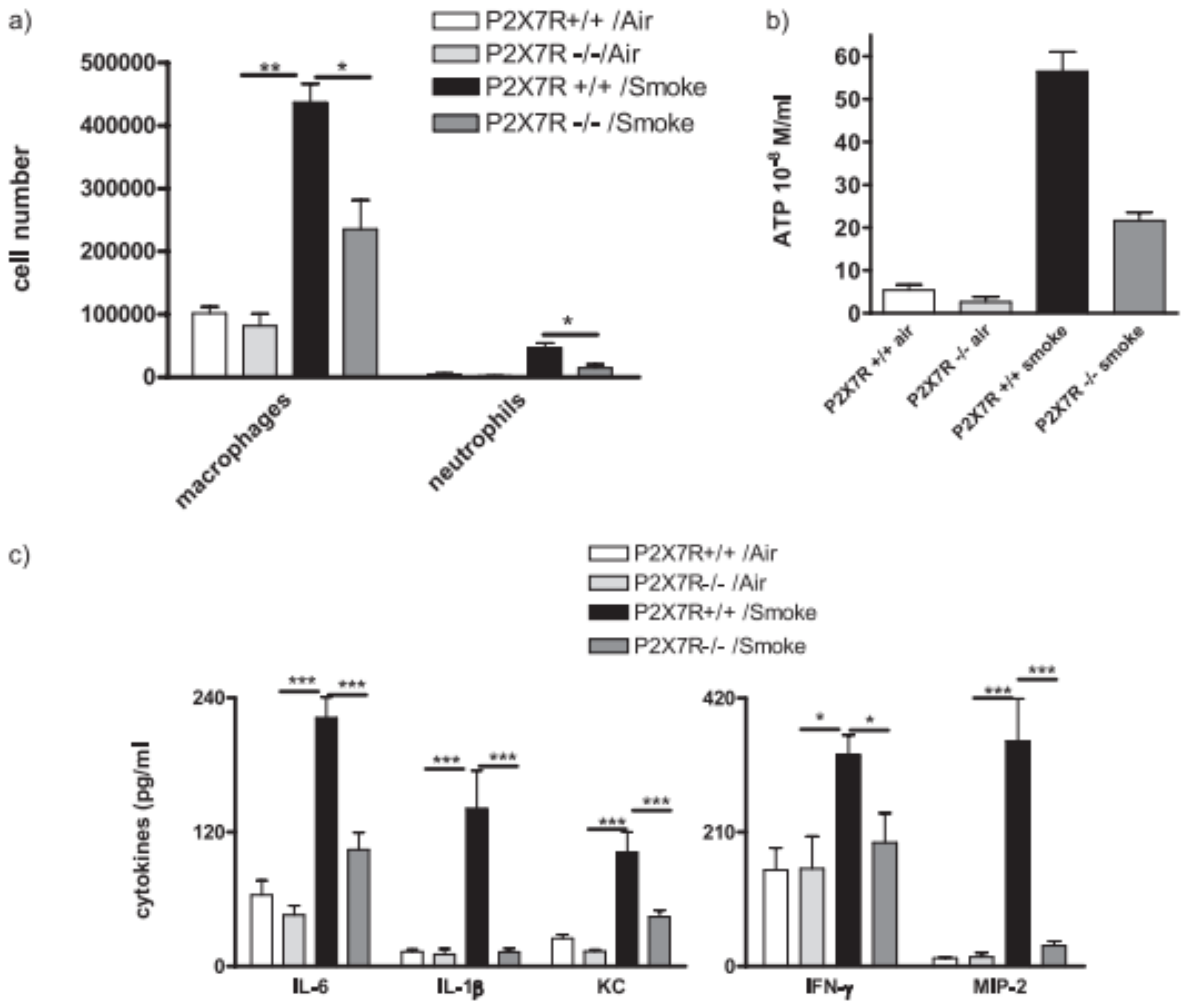
The cytosolic form of microtubule-associated protein 1A/1B-light chain 3 (LC3-I) is conjugated to phosphatidylethanolamine to form LC3-II, which is recruited to autophagosomal membranes, the process of which is essential for the autophagosome formation

Am J Physiol Lung Cell Mol Physiol. 2014 Jul 15;307(2):L173-85

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]

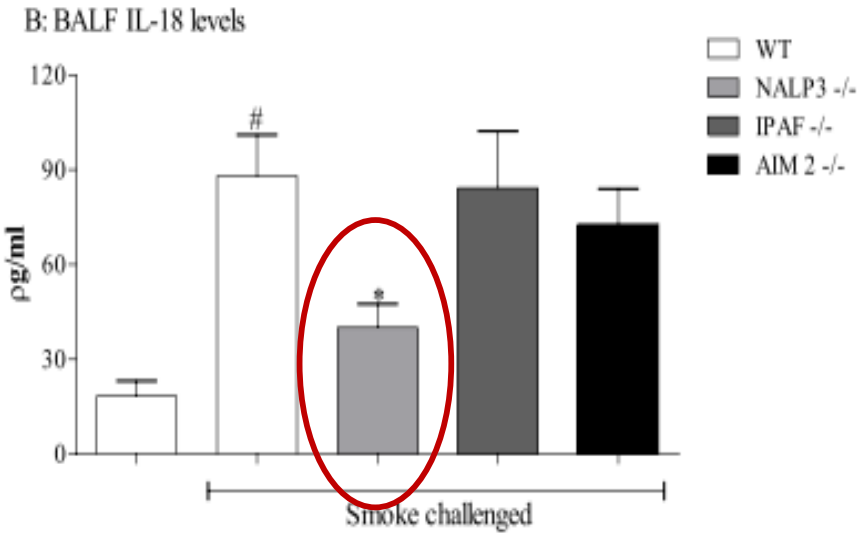


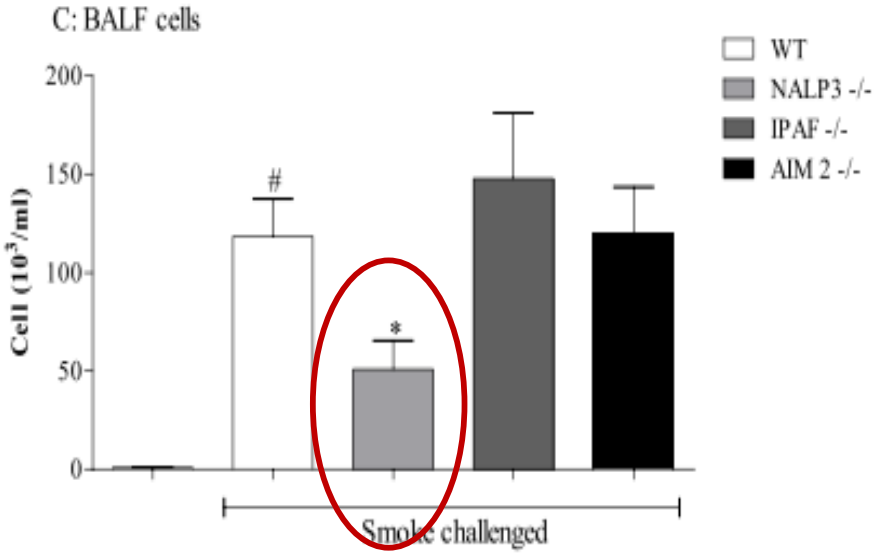
P2X7R-deficient animals are partially protected from cigarette smoke (CS)– induced lung inflammation

Am J Respir Cell Mol Biol. 2011 Mar;44(3):423-9.

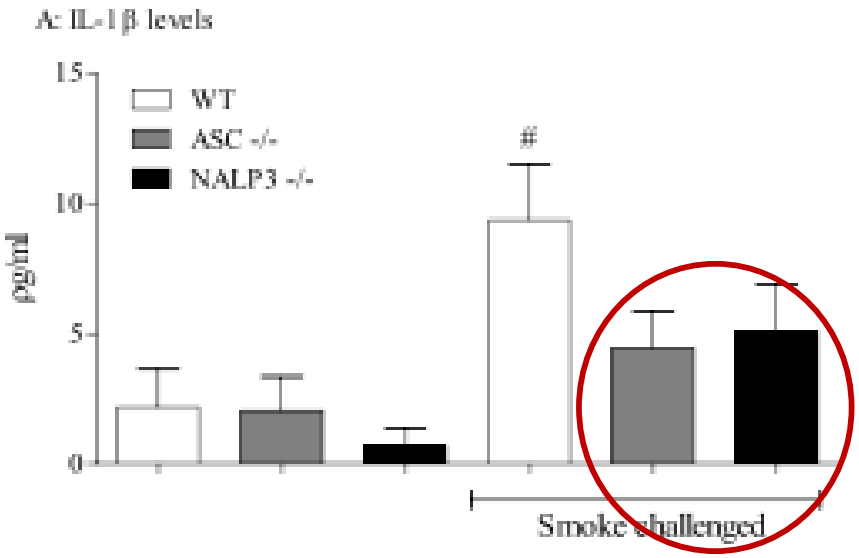
Role of the Inflammasome-Caspase1/11-IL-1/18 Axis in Cigarette Smoke Driven Airway Inflammation: An Insight into the Pathogenesis of COPD

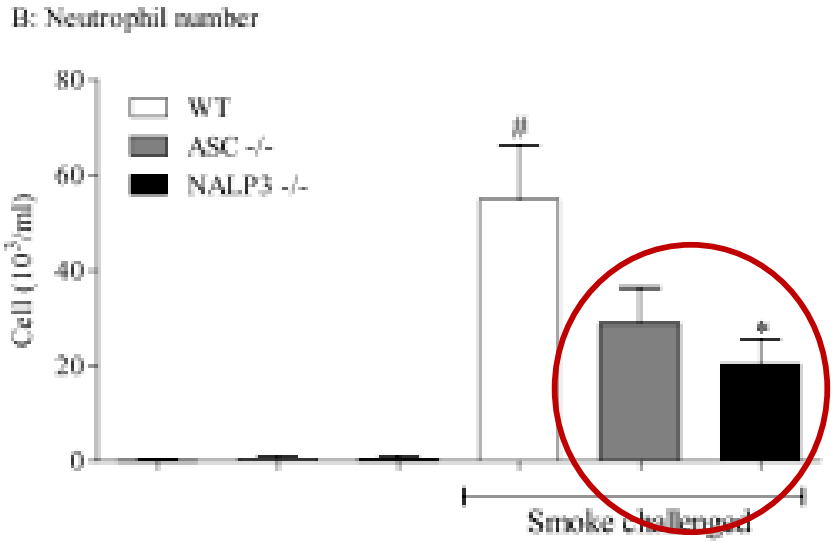
Suffwan Eltom[1], Maria G. Belvisi[1], Christopher S. Stevenson[2¤], Sarah A. Maher[1], Eric Dubuis[1], Kate A. Fitzgerald[3], Mark A. Birrell[1]*

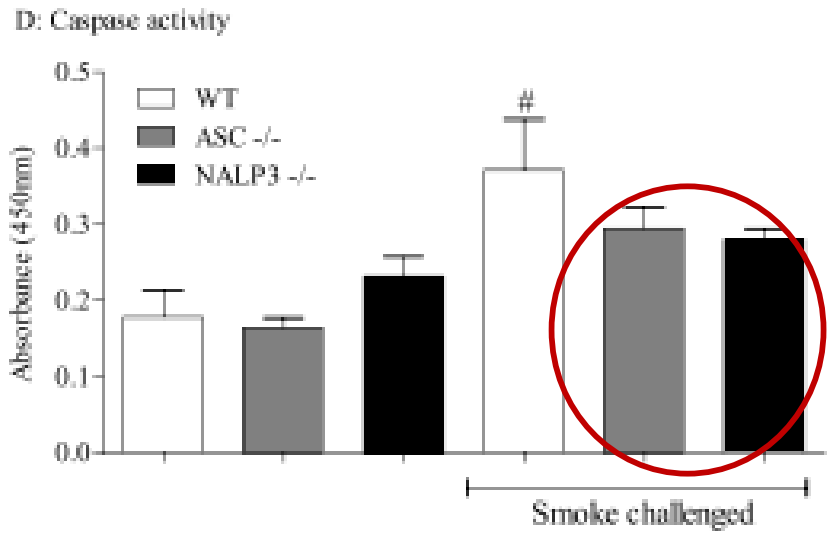




PLoS One. 2014 Nov 18;9(11):e112829.



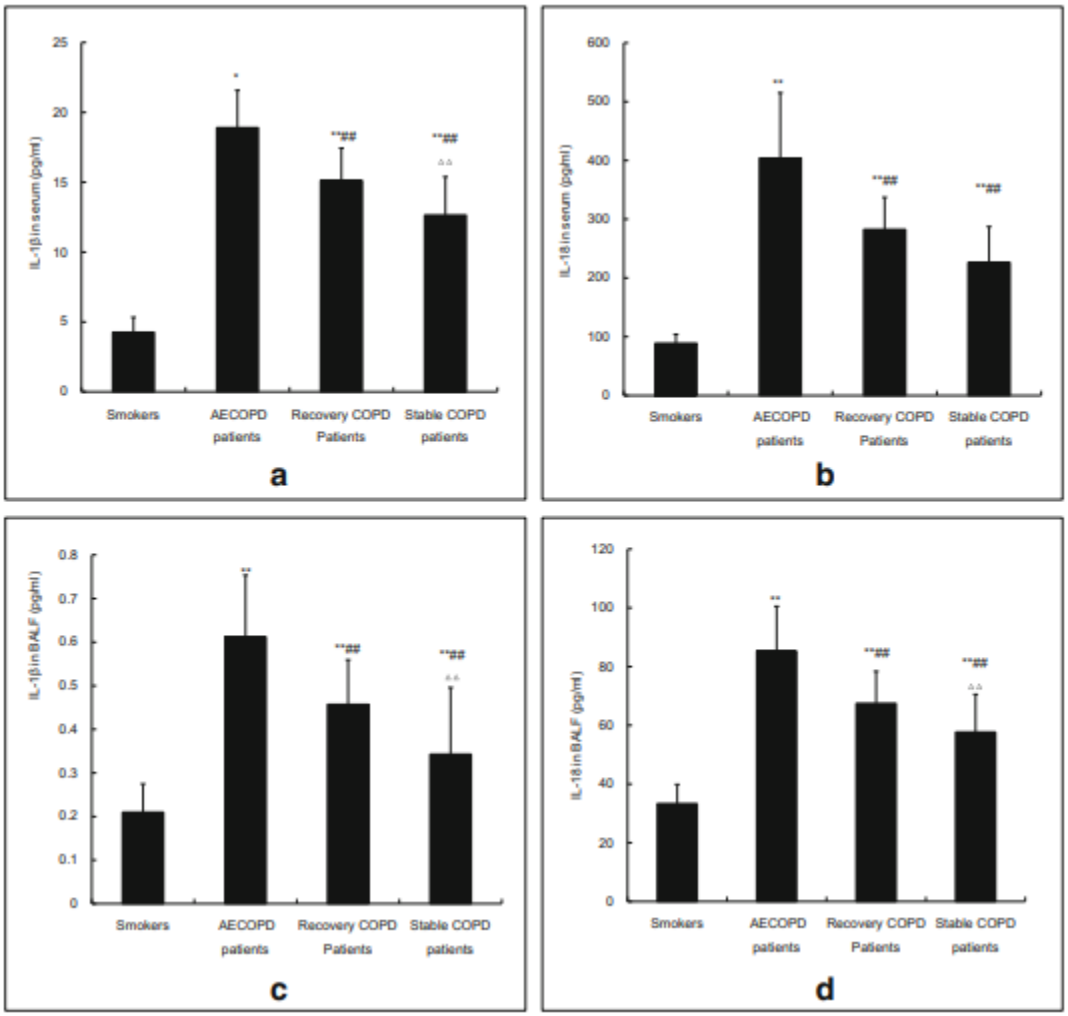




PLoS One. 2014 Nov 18;9(11):e112829.

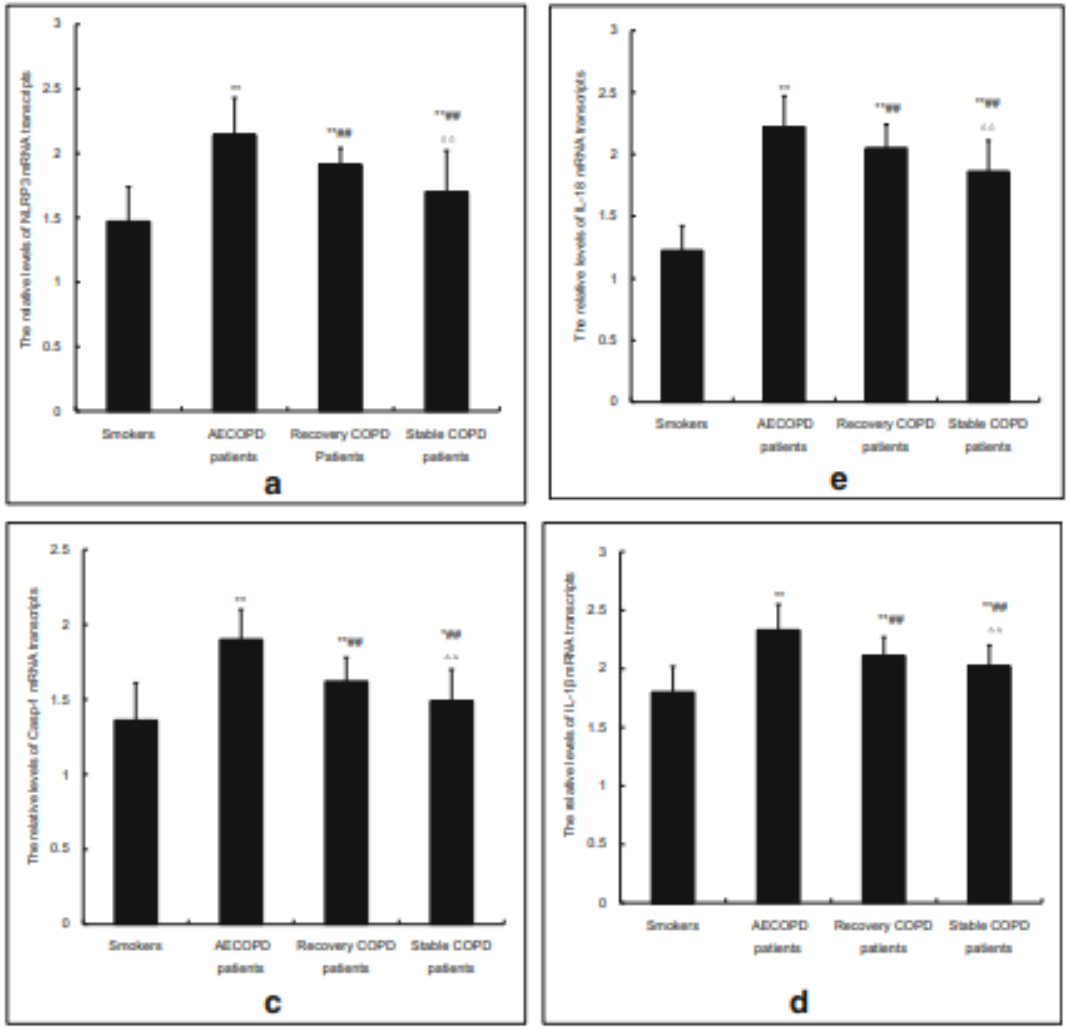
NLRP3 Inflammasome Involves in the Acute Exacerbation of Patients with Chronic Obstructive Pulmonary Disease

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



Inflammation. 2018 Aug;41(4):1321-1333

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



Inflammation. 2018 Aug;41(4):1321-1333

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

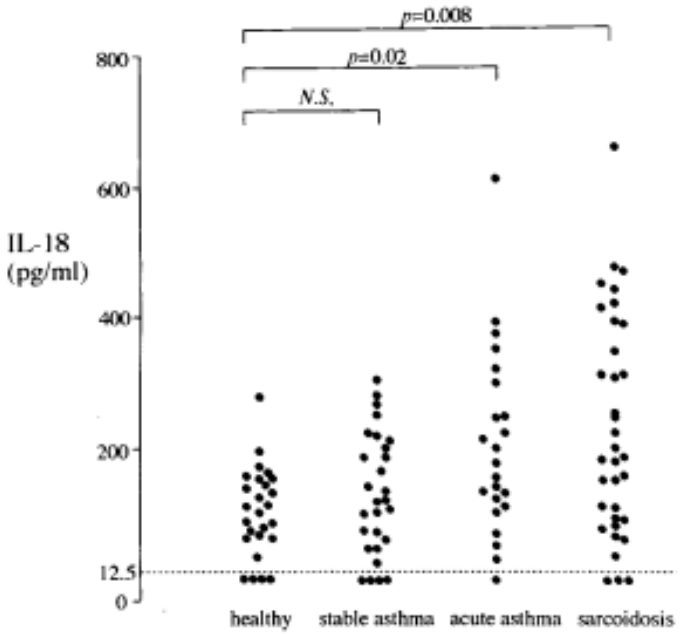
	Staphylococcus aureus (log CFU/ml)		*Klebsiella pneumoniae* (log CFU/ml)		*Streptococcus pneumoniae* (log CFU/ml)		*Pseudomonos aeruginosa* (log CFU/ml)		*Haemophilus influenzeae* (log CFU/ml)		*Moraxella catarrhalis* (log CFU/ml)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
NLRP3	0.299	0.001	0.438	< 0.01	0.295	0.001	0.355	< 0.01	0.563	< 0.01	0.425	< 0.01
ASC	0.352	< 0.01	0.512	< 0.01	0.331	< 0.01	0.281	0.002	0.498	< 0.01	0.350	< 0.01
Casp-1	0.248	0.006	0.456	< 0.01	0.213	0.020	0.330	< 0.01	0.462	< 0.01	0.364	< 0.01
IL-1β	0.316	< 0.01	0.335	< 0.01	0.270	0.003	0.375	< 0.01	0.530	< 0.01	0.416	< 0.01
IL-18	0.584	< 0.01	0.549	<v0.01	0.468	< 0.01	0.568	< 0.01	0.642	< 0.01	0.599	< 0.01

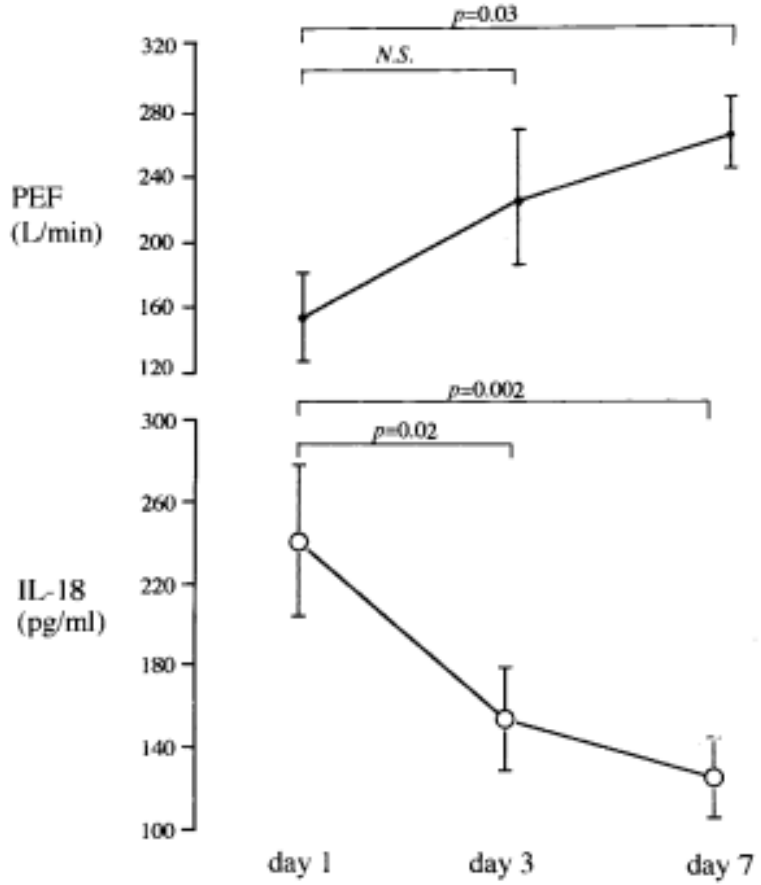
Inflammation. 2018 Aug;41(4):1321-1333

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*

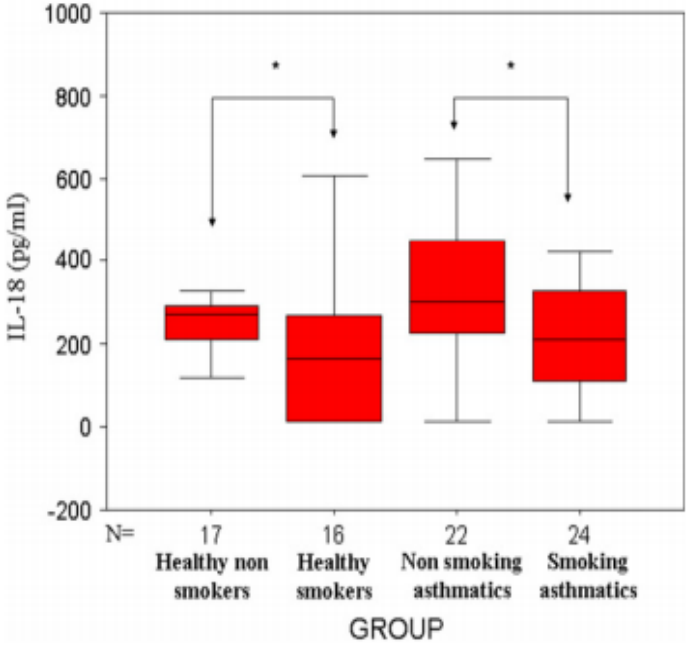


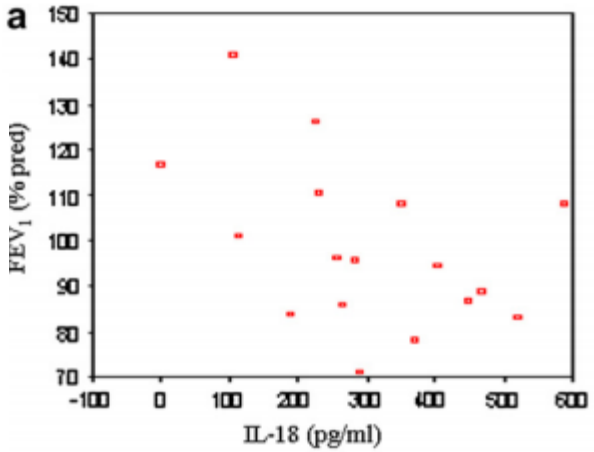


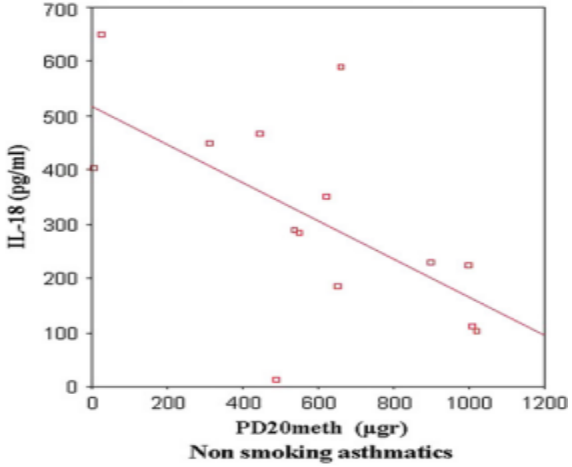
J Allergy Clin Immunol. 2001 Feb;107(2):331-6

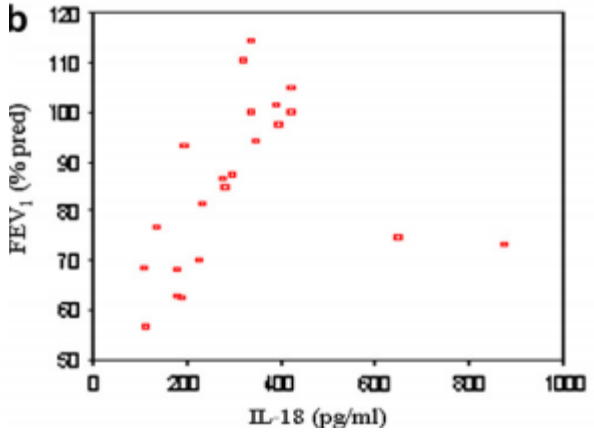
IL-18 in induced sputum and airway hyperresponsiveness in mild asthmatics: Effect of smoking

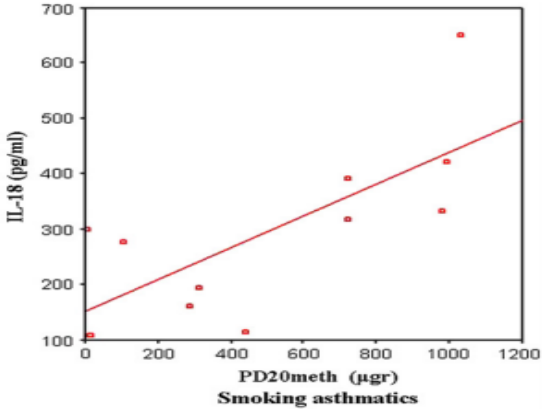
Nikoletta Rovina [a,c,*,d], Efrossini Dima [a,c,d], Christina Gerassimou [c], Androniki Kollintza [c], Christina Gratziou [b,c], Charis Roussos [a,b,c]







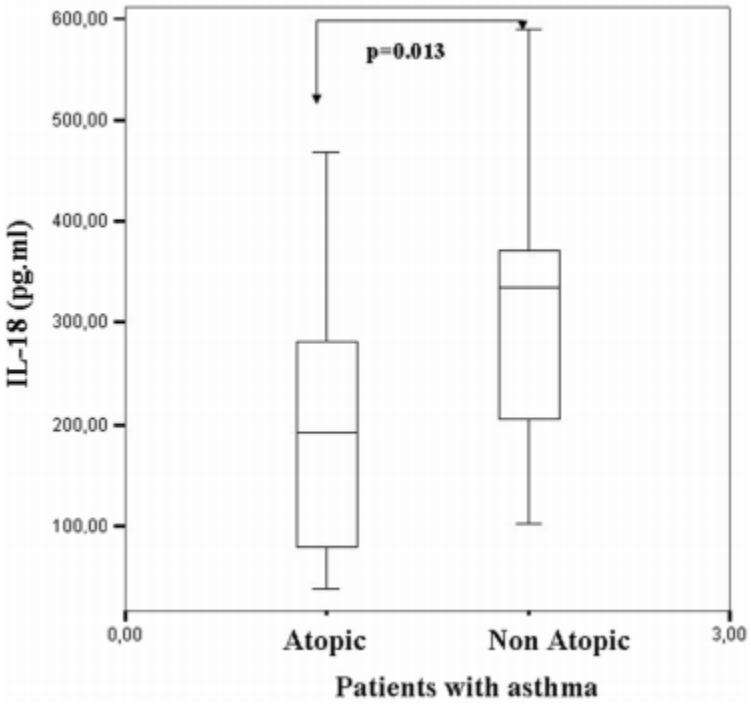


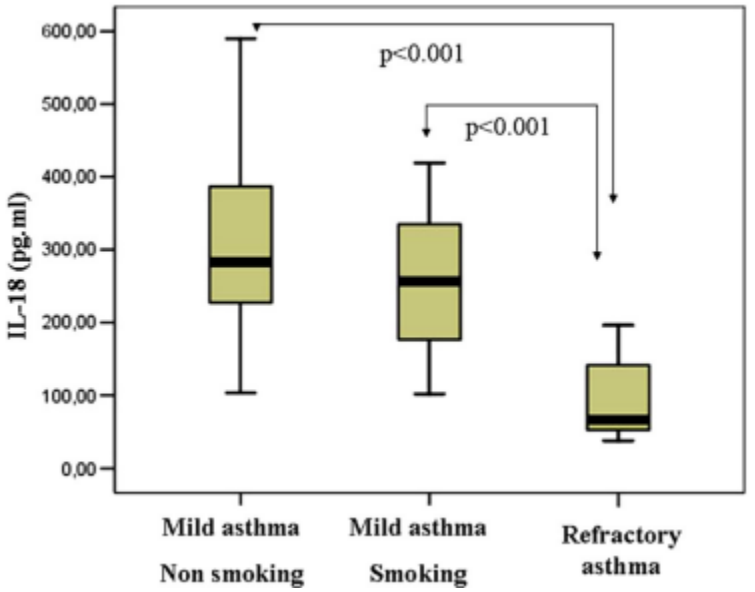


Respir Med. 2009 Dec;103(12):1919-25

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

Nikoletta Rovina [a,*], Efrossini Dima [a], Petros Bakakos [a], Eleni Tseliou [a], Konstantina Kontogianni [a], Spyros Papiris [b], Antonia Koutsoukou [a], Nikolaos G. Koulouris [a], Stelios Loukides [b]





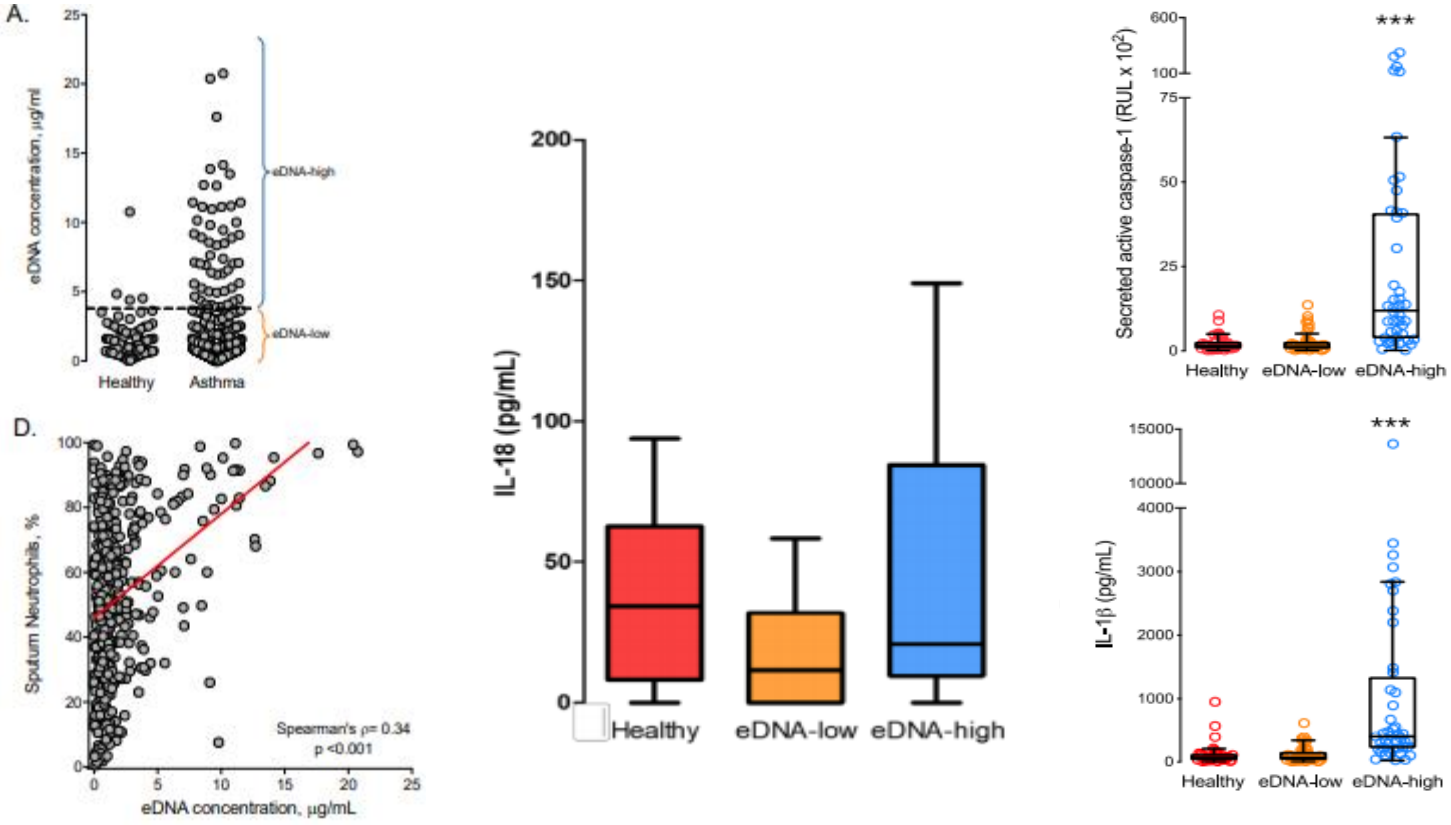
Respir Med. 2015 May;109(5):580-7

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

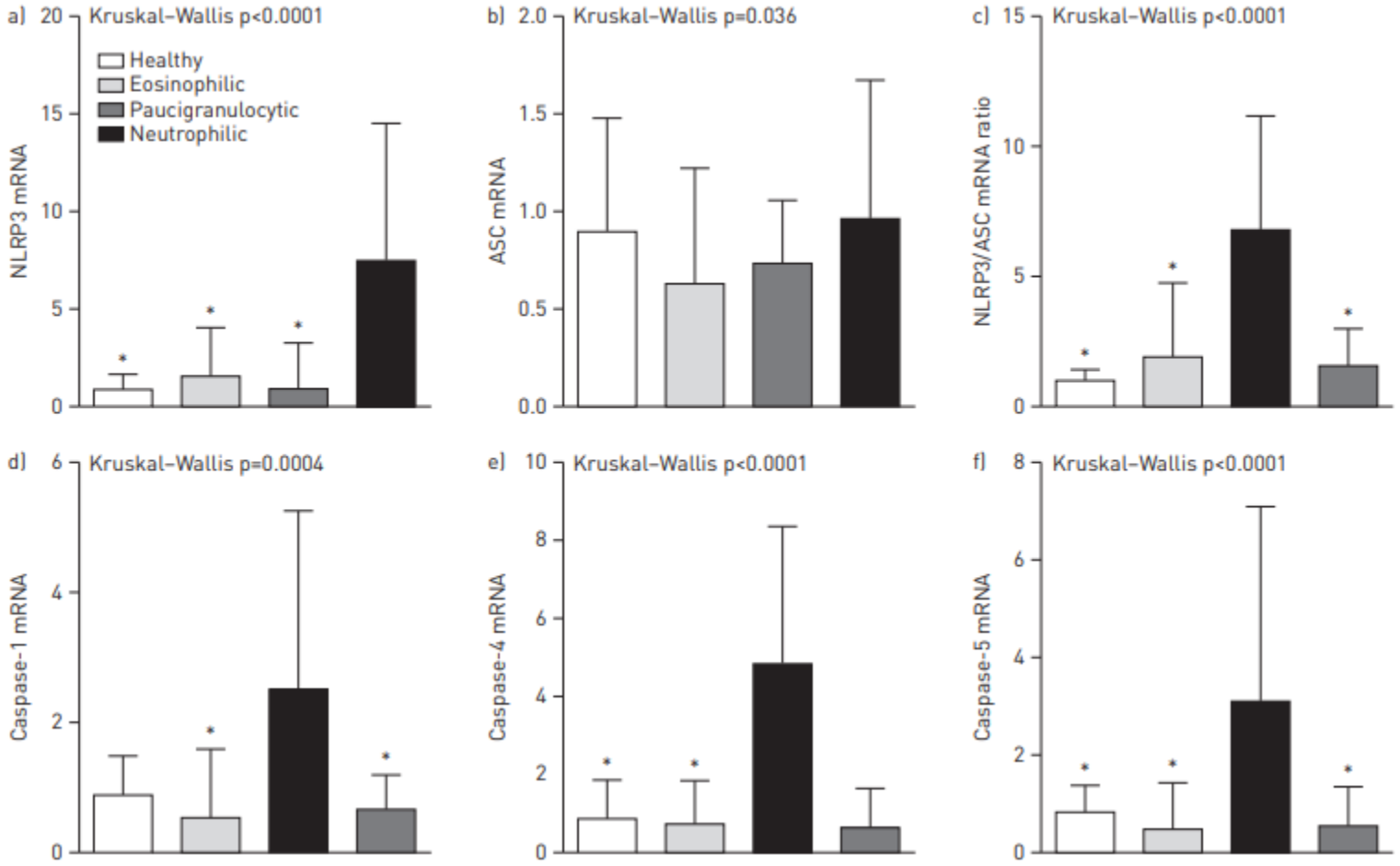
Increased extracellular DNA (eDNA) in sputum from a subset of asthmatics reflects neutrophil activation



Am J Respir Crit Care Med. 2019 May 1;199(9):1076-1085

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]

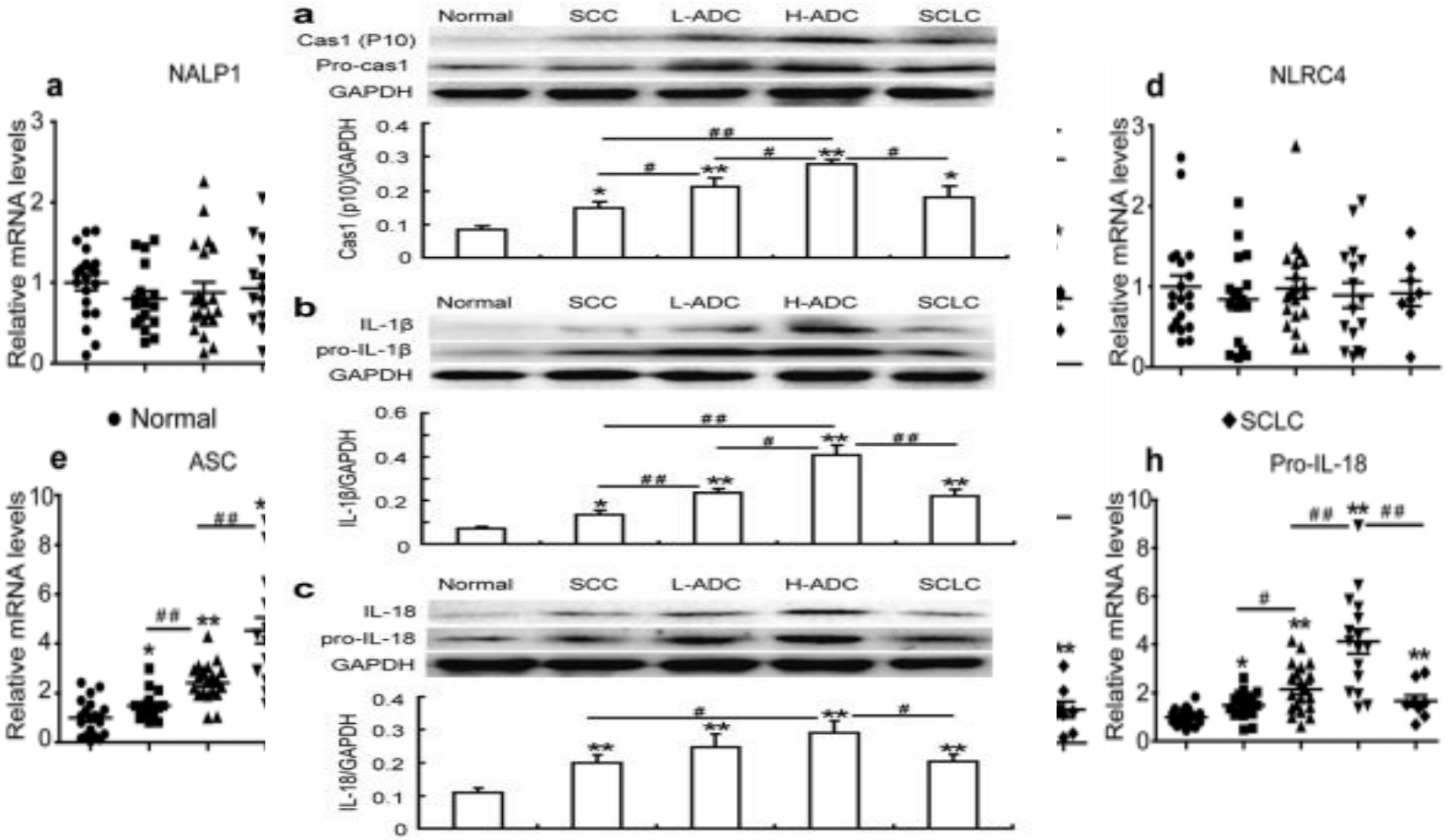


Eur Respir J. 2014 Apr;43(4):1067-76

Lung cancer

Differential expression of inflammasomes in lung cancer cell lines and tissues

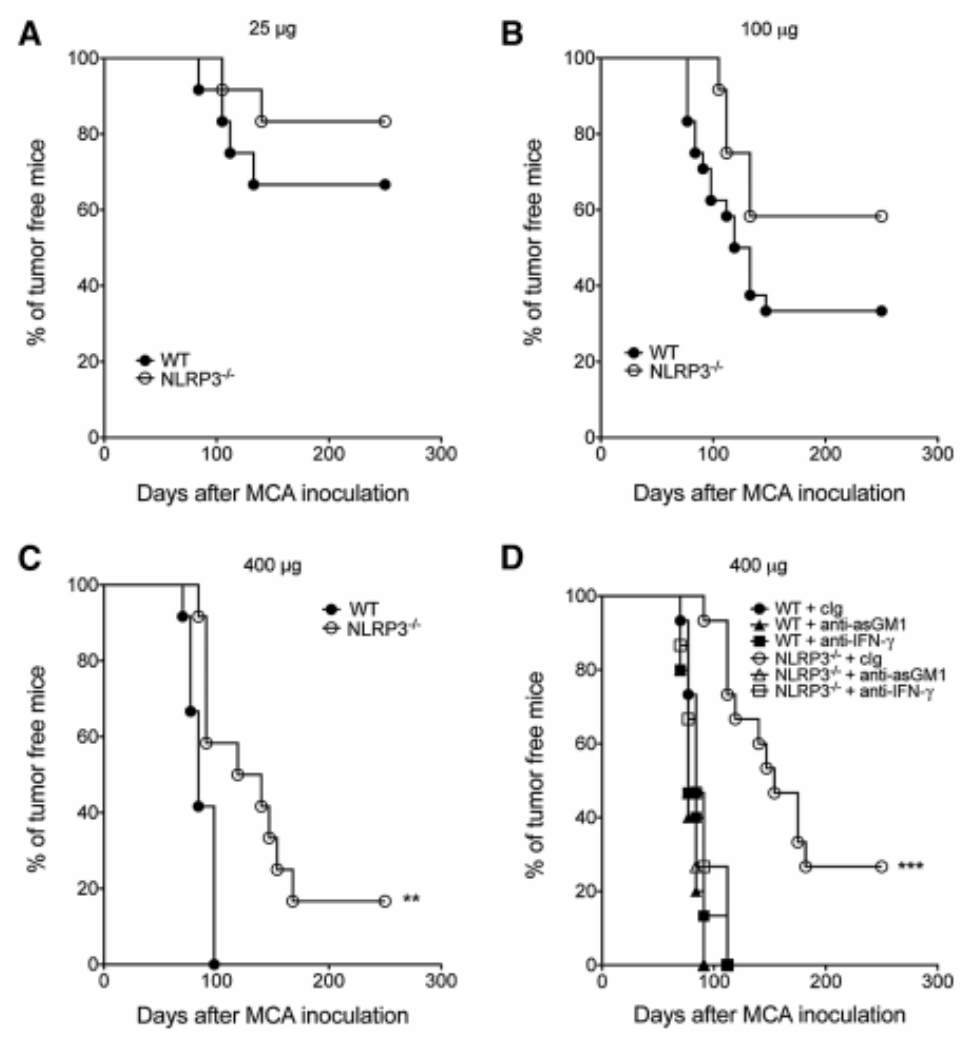
Hui Kong[1] · Yanli Wang[1] · Xiaoning Zeng[1] · Zailiang Wang[1] · Hong Wang[1] · Weiping Xie[1]



Tumour Biol. 2015 Sep;36(10):7501-13

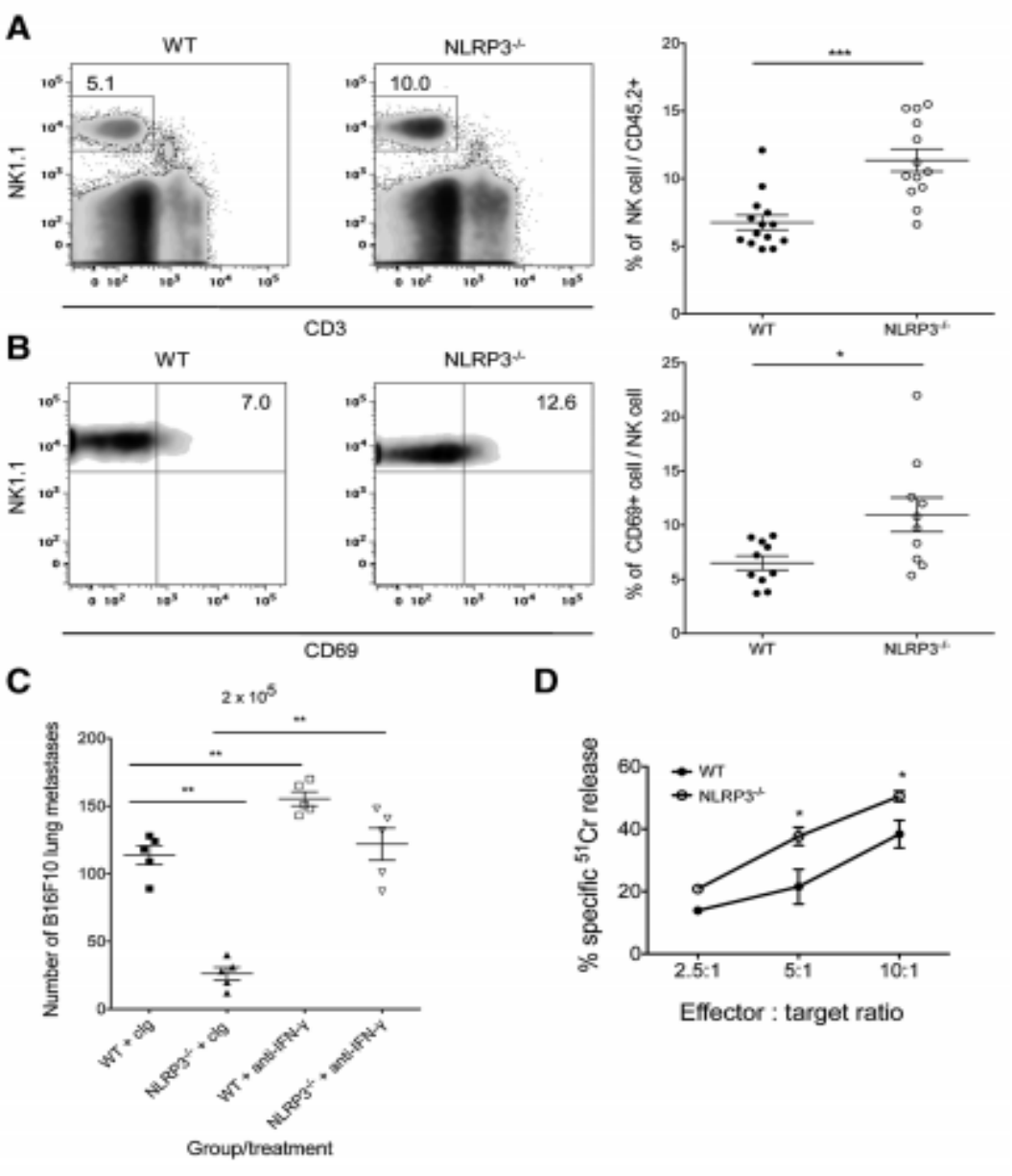
NLRP3 Suppresses NK Cell–Mediated Responses to Carcinogen-Induced Tumors and Metastases

Melvyn T. Chow[1,3], Jaclyn Sceneay[2,3], Christophe Paget[1], Christina S.F. Wong[2], Helene Duret[1], Jürg Tschopp[4,†], Andreas Möller[2,3], and Mark J. Smyth[1,3]



Cancer Res. 2012 Nov 15;72(22):5721-32

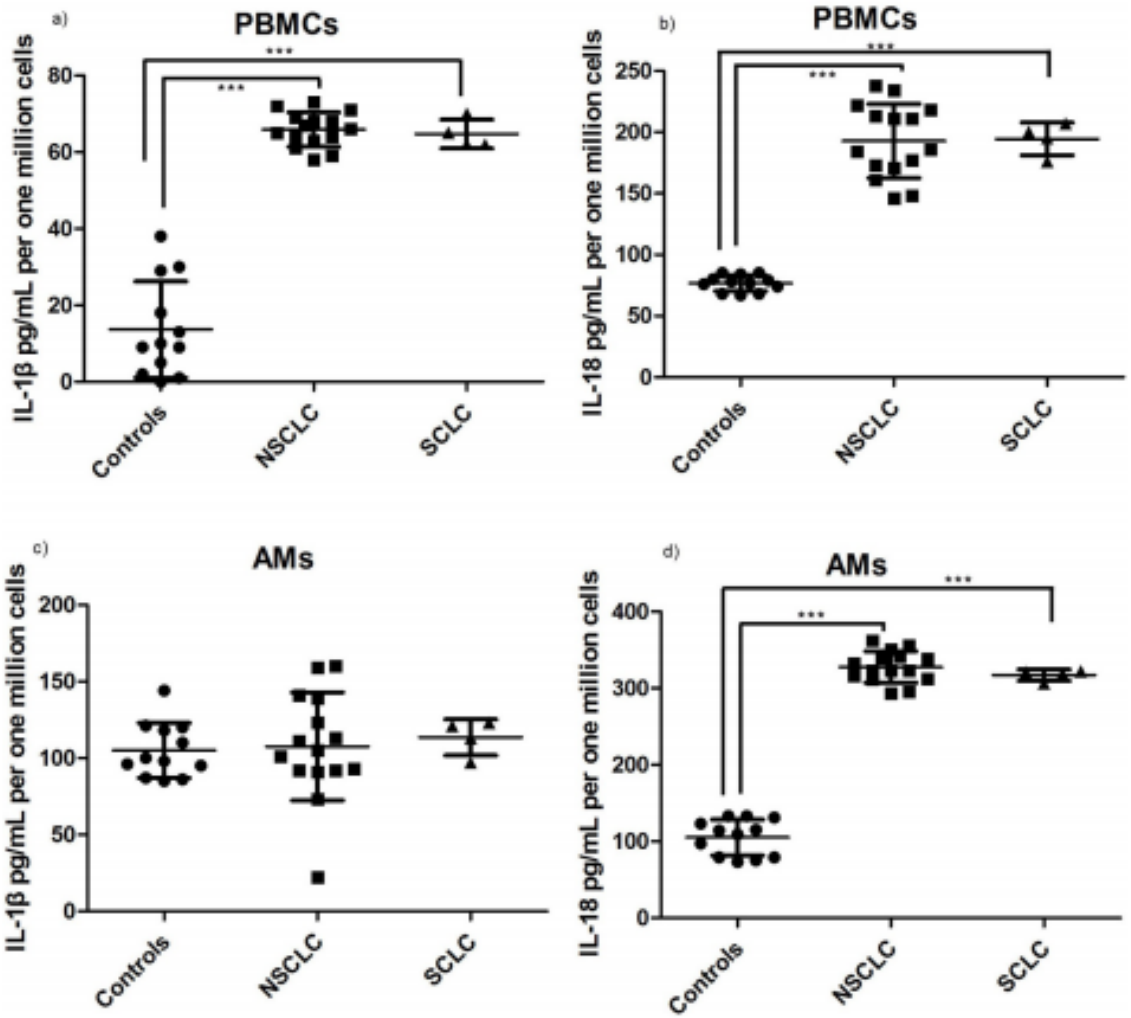
Greater NK cell frequency and activity in the B16F10-bearing lungs of NLRP3/ mice



Cancer Res. 2012 Nov 15;72(22):5721-32

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]*

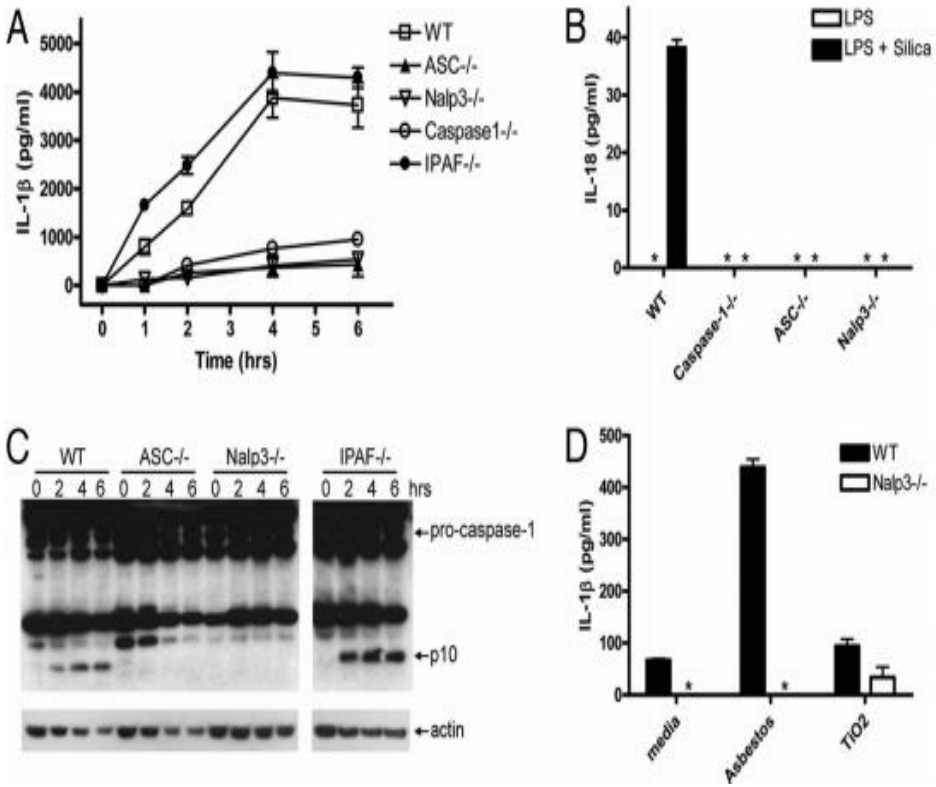


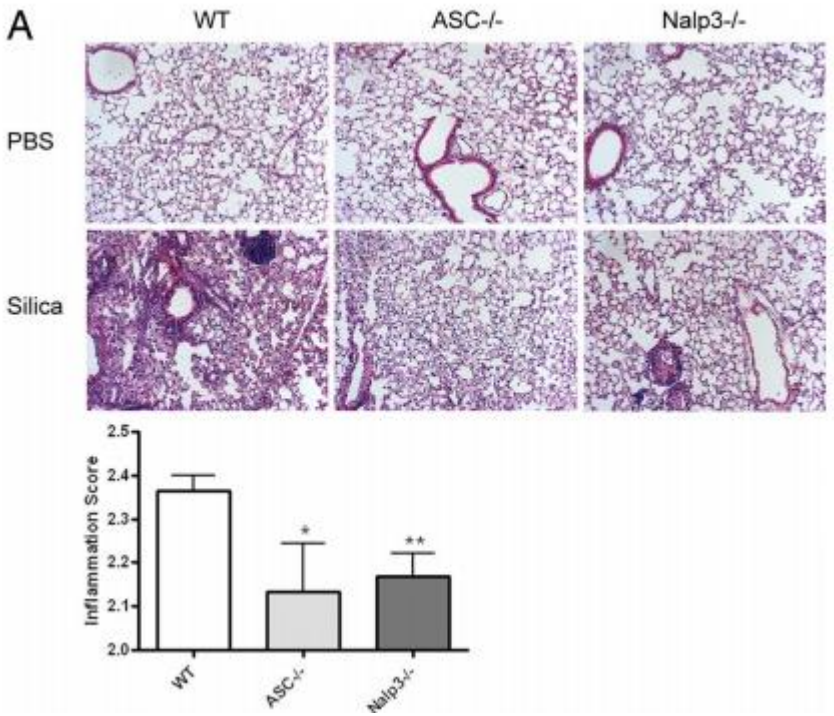
PLoS One. 2018 Oct 26;13(10):e0205242

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]

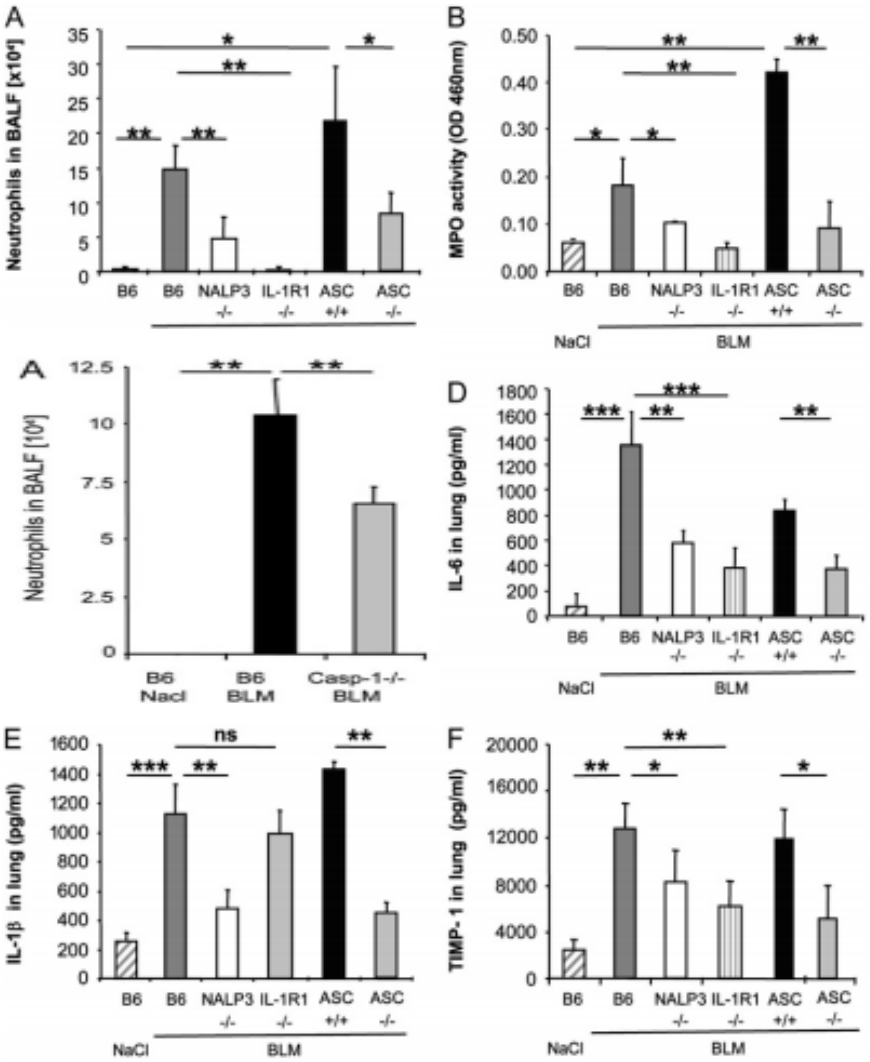




PNAS 2008 Jul 1;105(26):9035-40

Uric Acid Is a Danger Signal Activating NALP3 Inflammasome in Lung Injury Inflammation and Fibrosis

Pamela Gasse[1*], Nicolas Riteau[1*], Sabine Charron[1], Sandra Girre[1], Lizette Fick[2], Virginie Pétrilli[3], Jürg Tschopp[3], Vincent Lagente[4], Valérie F. J. Quesniaux[1], Bernhard Ryffel[1], and Isabelle Couillin[1,5]

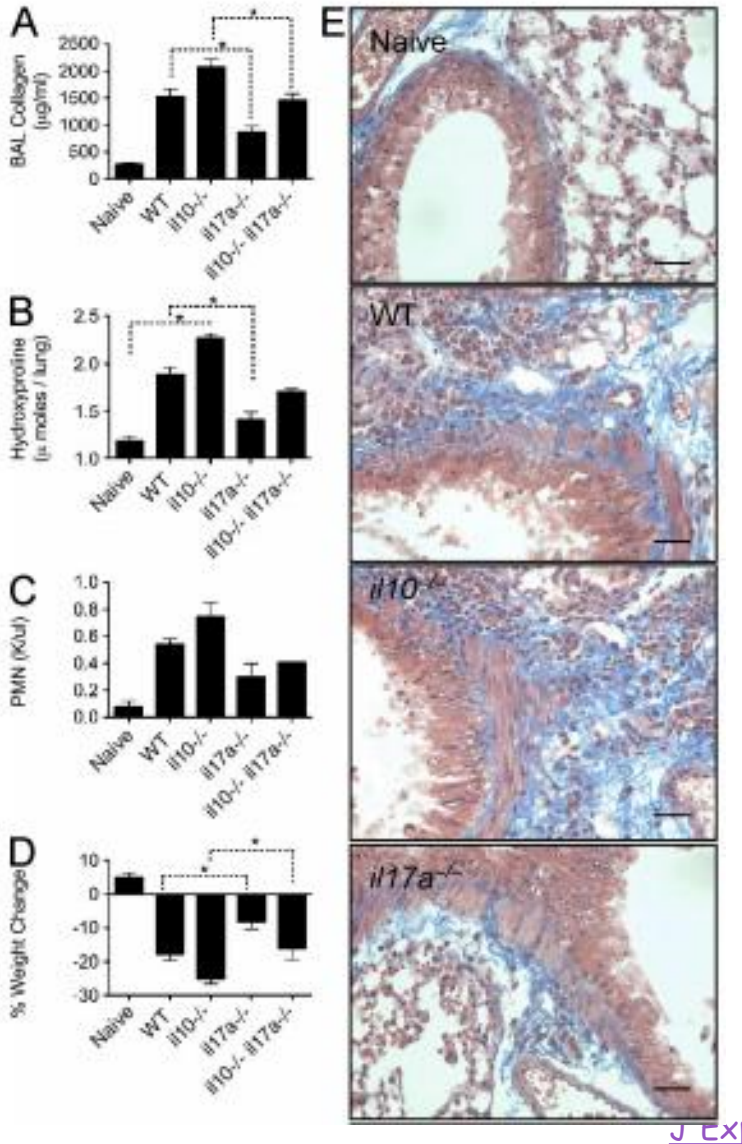


Bleomycin (BLM)-induced pulmonary inflammation and remodeling are dependent on NALP3, caspase-1, and ASC proteins

Am J Respir Crit Care Med. 2009 May 15;179(10):903-13

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]

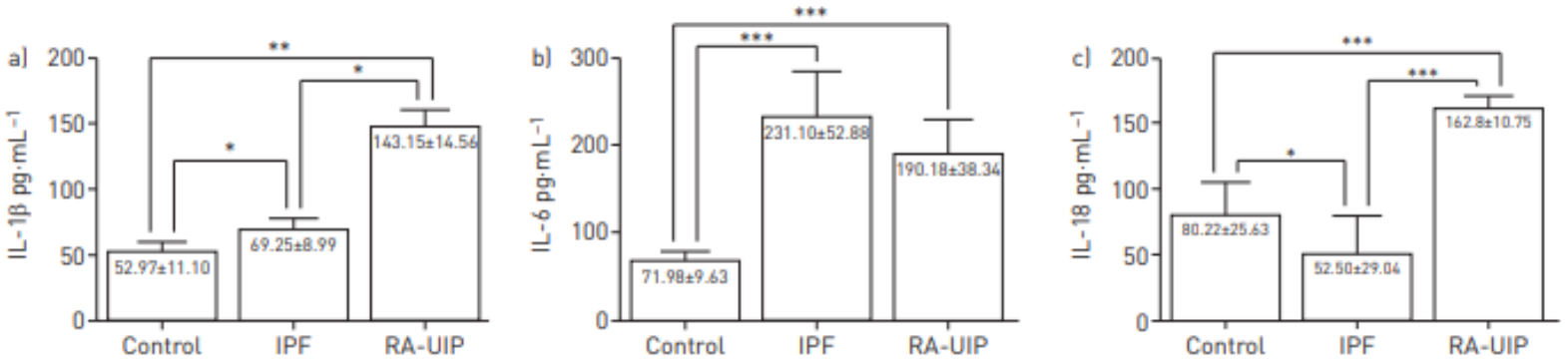


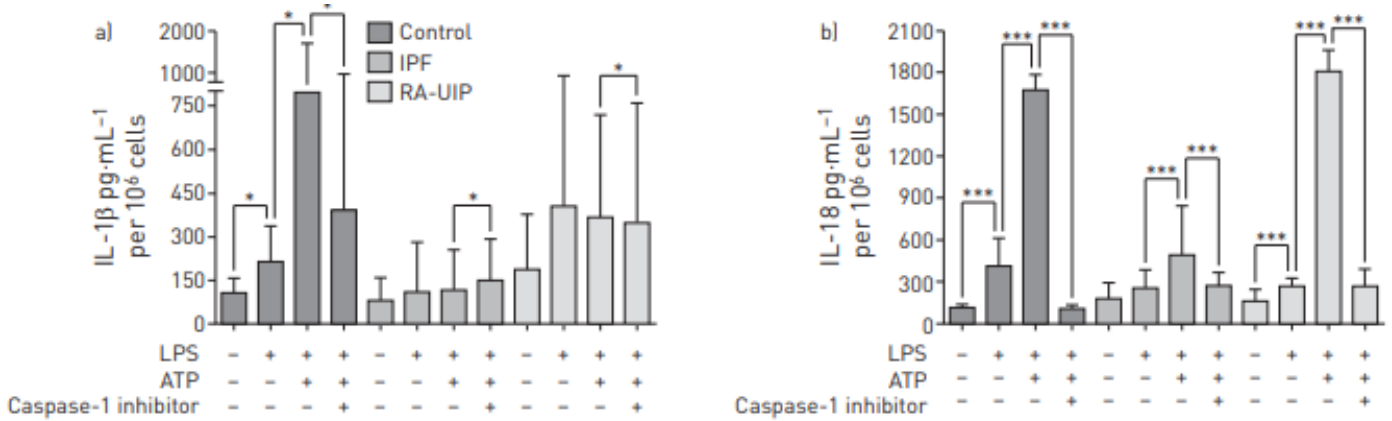
J Exp Med. 2010 Mar 15;207(3):535-52

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

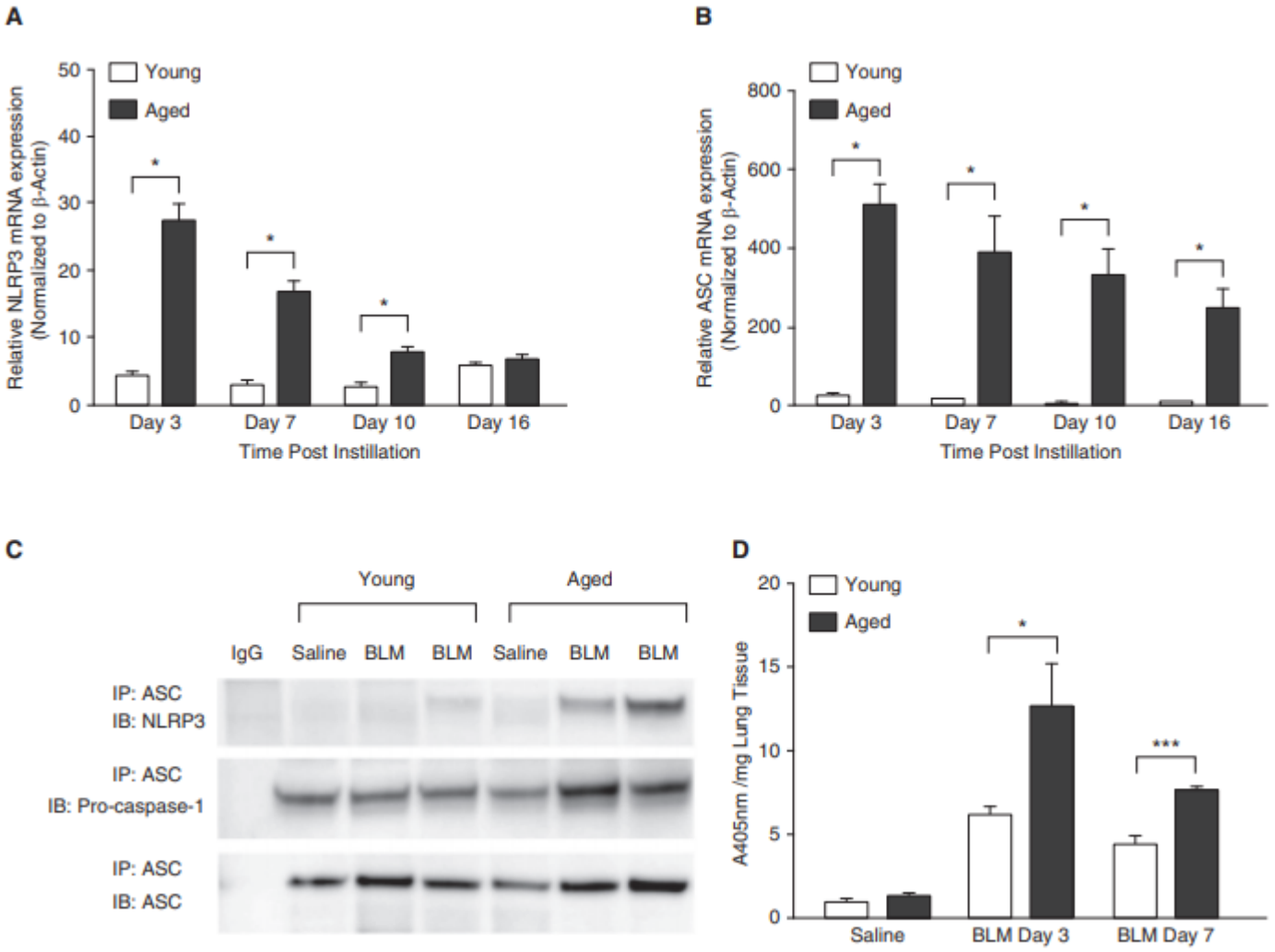




Eur Respir J. 2016 Mar;47(3):910-8

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]

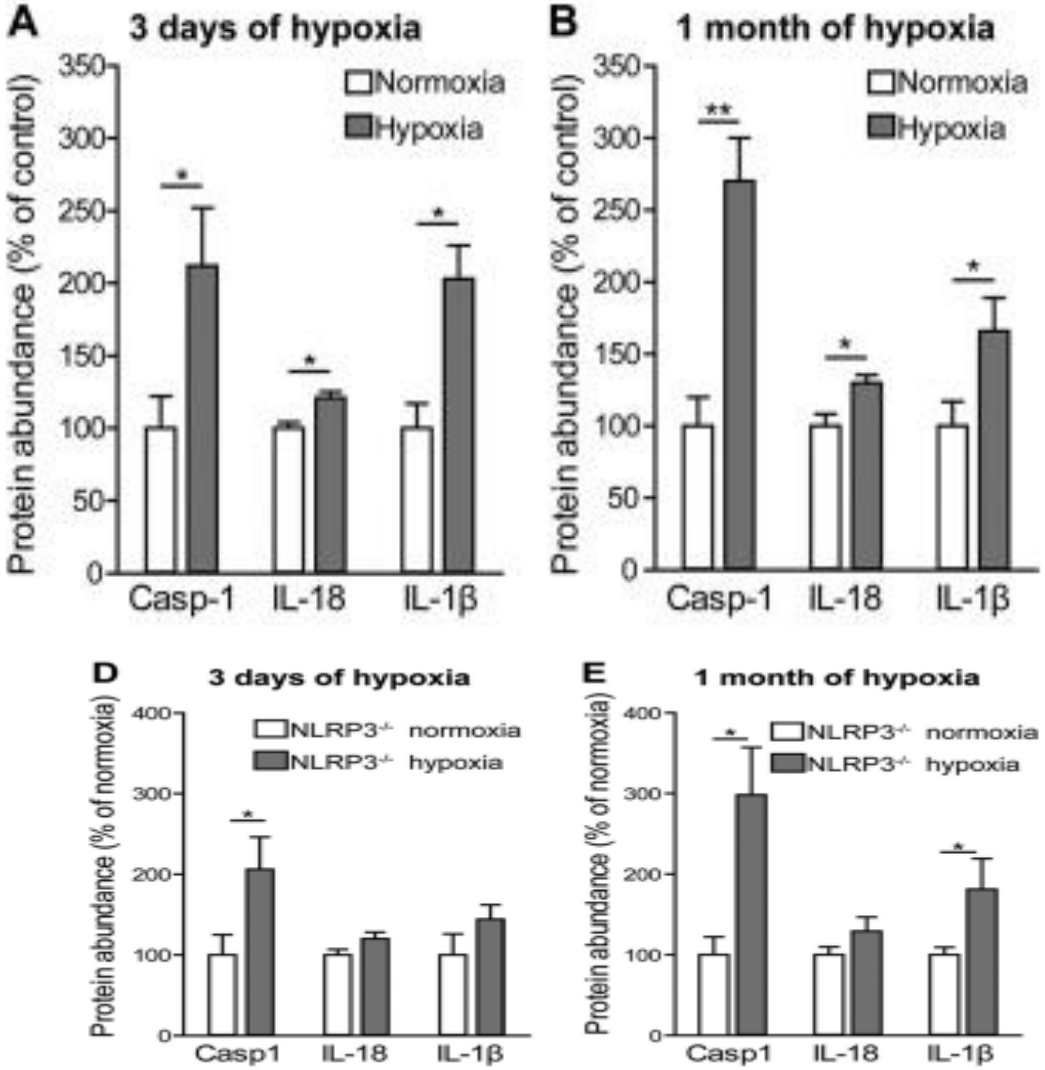


Am J Respir Cell Mol Biol. 2016

Pulmomary hypertension

Absence of the inflammasome adaptor ASC reduces hypoxia-induced pulmonary hypertension in mice

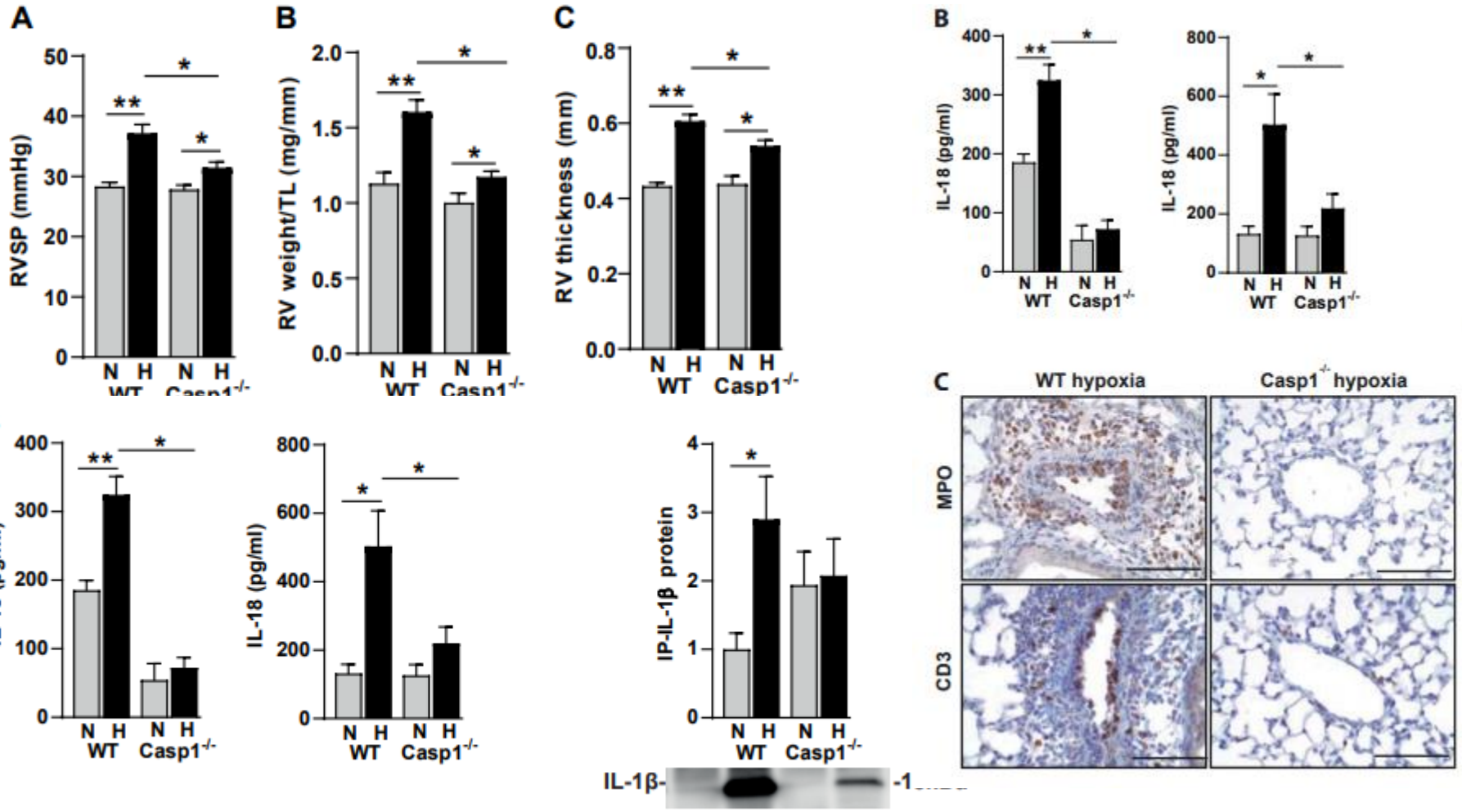
Fadila Telarevic Cero,[1,2,3] Vigdis Hillestad,[2,3] Ivar Sjaastad,[2,3,5] Arne Yndestad,[3,4,5] Pål Aukrust,[4,5,6] Trine Ranheim,[3,4,5] Ida Gjervold Lunde,[2,3,7] Maria Belland Olsen,[3,4] Egil Lien,[8,9] Lili Zhang,[2,3] Solveig Bjærum Haugstad,[2,3] Else Marit Løberg,[10] Geir Christensen,[2,3] Karl-Otto Larsen,[1,3] and Ole Henning Skjønsberg[1]



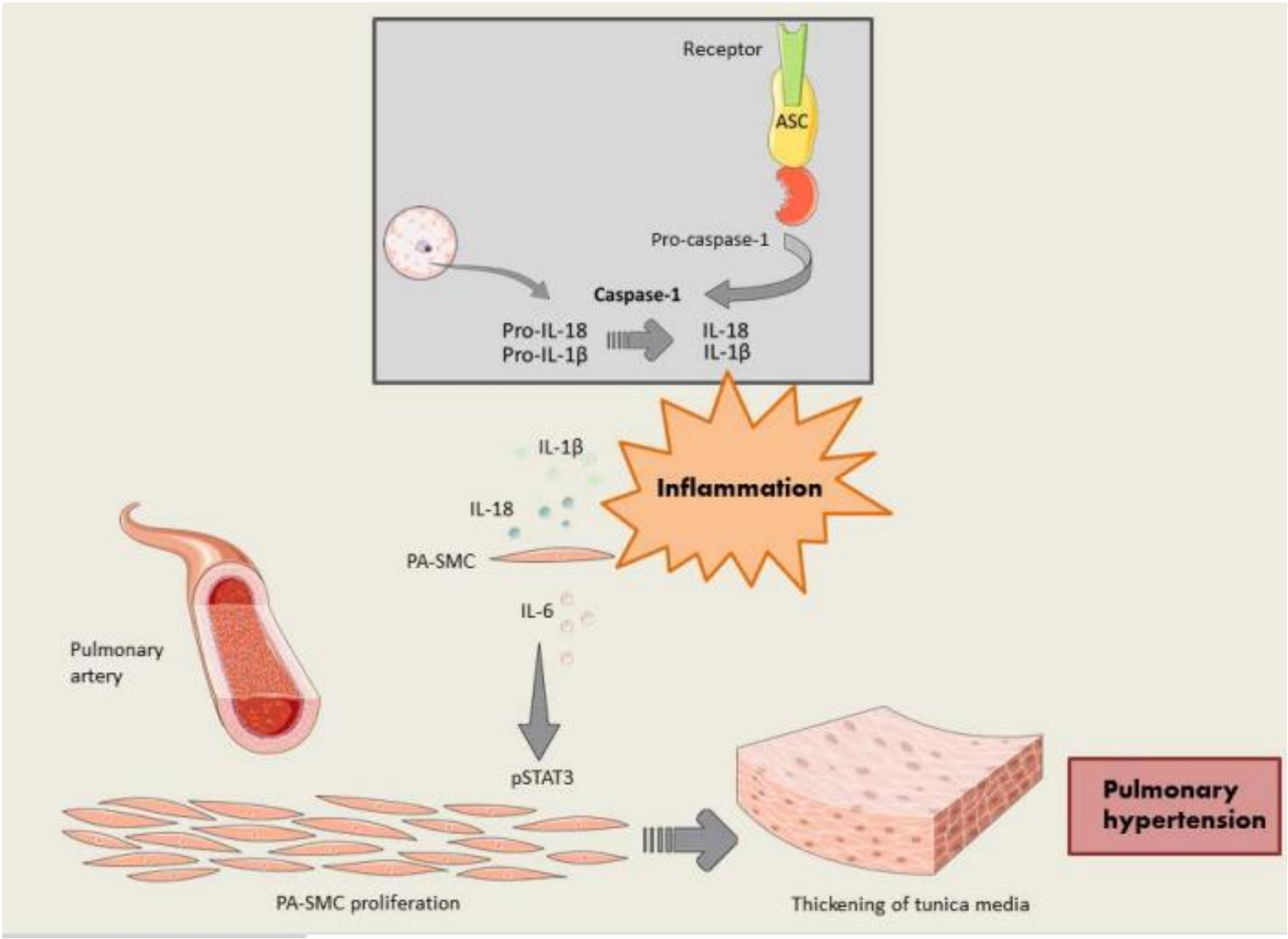
Am J Physiol Lung Cell Mol Physiol. 2015 Aug 15;309(4):L378-87

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]



Am J Physiol Lung Cell Mol Physiol. 2019 Jun 1;316(6):L999-L1012



Am J Physiol Lung Cell Mol Physiol. 2019 Jun 1;316(6):L999-L1012

Conclusion

- PRRs constitute an integral component of the immune system of the lung and are necessary for inflammatory processes involved in defense against invading pathogens and for restoration of tissue homeostasis
- Acutely, activation of NLRP3 is important for the clearance of viral and bacterial lung infections
- However, sustained activation of NLRP3 after inhalation of irritants can lead to more chronic and deleterious inflammatory effects in the lung
- The partially redundant and complementary roles of inflammasome effector molecules in lung pathologies also warrant the search for novel therapeutics that directly target the NLRP3 inflammasome or mechanisms that control its activation

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