Conférences Bernoises de Médecine de Laboratoire

L'Inflammasome

candidat pour une analyse approfondie des états inflammatoires

UNIL | Université de Lausanne

Fabio.Martinon@unil.ch

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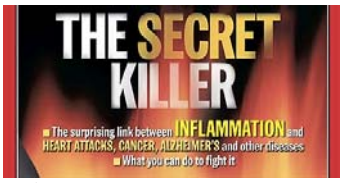
Inflammation contributes to diseases

clinically denoted by the suffix *itis*.

suffix that denote inflammation of an organ (***dermatitis***; ***arthritis***; ***colitis***; ***bronchitis; gastritis; neuritis…***)



www.Times.com

Definition:

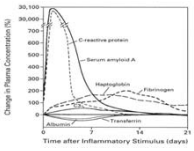
- Inflammation is the body' **natural** and **immediate** response to tissue injury.

Targets and Kinetics of the Inflammatory response

- **Local response**
  - Defense and healing

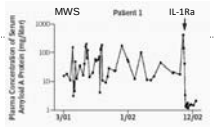
- **Systemic response**
  - Fever, Heart rate increase, Acute phase response, Abnormal white blood cell count..

- **Acute inflammation**
  - Short term
  - Usually results in healing



Gabay & Kushner NEJM. 1999, 340(6):448-54

- **Chronic inflammation** (parainflammation)
  - Prolonged
  - Dysregulated and maladaptative
  - Active inflammation, tissue destruction and attempts at tissue repair

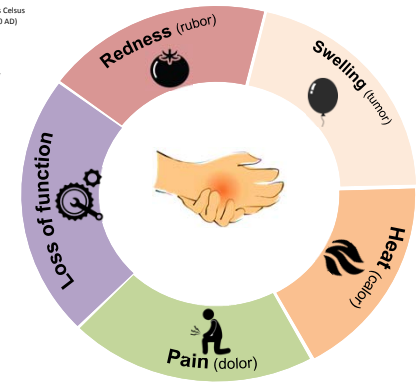


Hawkins et al. NEJM. 2003, 348(25):2583-4

Hallmarks of acute Inflammation

Aulus Cornelius Celsus (c. 25 BC – c. 50 AD)

Rudolf Virchow (1821 – 1902)



Causes of inflammation:

Tissue Death (Necrosis)

Microorganisms

- Mechanical trauma (tissues are crushed, pressure friction..)
- Corrosive Chemicals (acid reflux)
- Thermal injury (burns and frostbite)
- Radiation
- Ischemia
- Infection

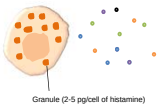
…

Cells that initiate inflammation:

Tissue resident **Macrophages**

- Cytokines
- Leukotrienes
- Prostaglandines
- ROS / NO
- Platelet activating factors

Tissue resident **Mast cells**



- Histamine
- Serotonin
- Lysosomal enzymes

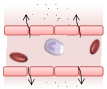
Vascular and cellular effects

Vasodilatation

Histamine, prostagandines, NO ..

Increased vascular permeability

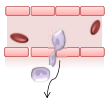
Histamine, ROS, leukotrienes, platelet activating factors



Fluid and protein leakage

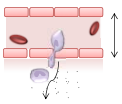
Chemotaxis

Chemokines, cytokines, leukotrienes



Neutrophils emigration

Events that contribute to the signs of Inflammation

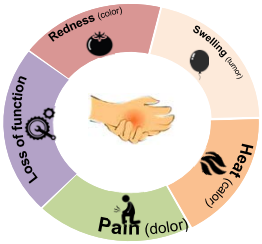


Vasodilatation

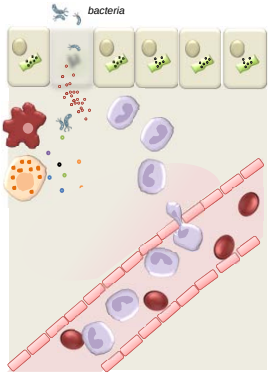
Increased vascular permeability

Emigration of White Blood Cells

Mediators (cytokines, ROS)



Overview of the inflammatory response



What are the signals detected by the sentinels ?

How are these signals integrated by the cell ?

Sensors of microbes and danger signals

Signals :

Pathogen associated molecular patterns (PAMPs)

LPS, peptitoglycans, nucleic acids …

Danger associated molecular patterns (DAMPs)

ATP, uric acid, HMGB1, IL-1α …

Sensors :

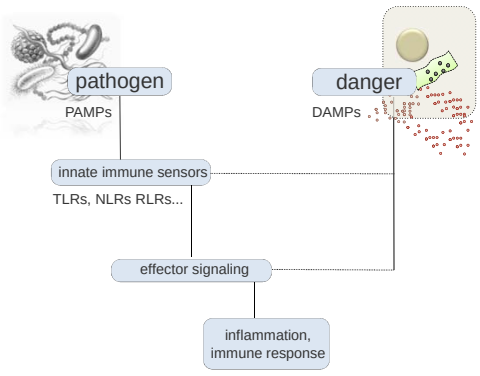
Membrane associated (sample surface and endosomes)

Toll-like receptors (TLRs) …

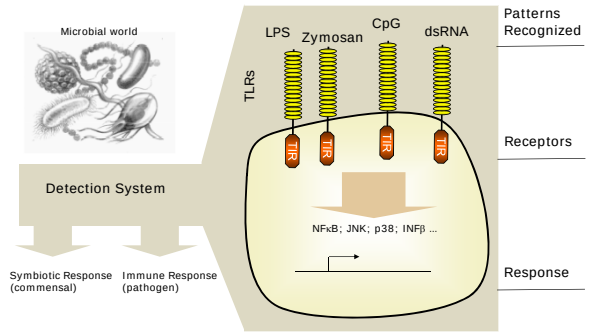
Cytosolic (sample the cytosol)

Nod-like receptors (NLRs); Rig-I-like receptors (RLRs); AIM2-like receptors (ALR)…

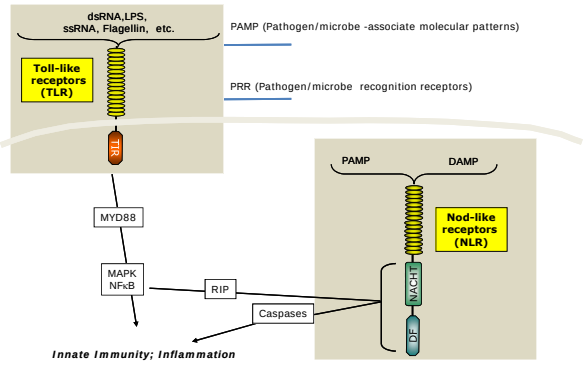
Mechanisms of innate immunity



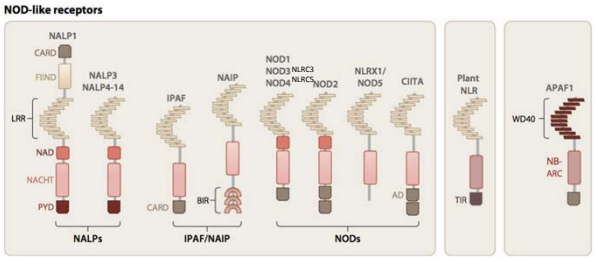
Systems for the sensing of Microbes



Toll-like receptors (TLRs) and Nod-like receptors (NLRs)

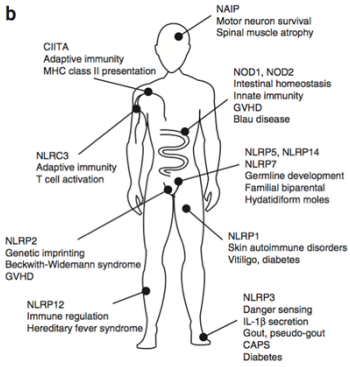


Nod-like receptors (NLRs)



Martinon, F., Mayor, A., & Tschopp, J. (2009). The inflammasomes: guardians of the body *Annual Review of Immunology*, *27*, 229–265

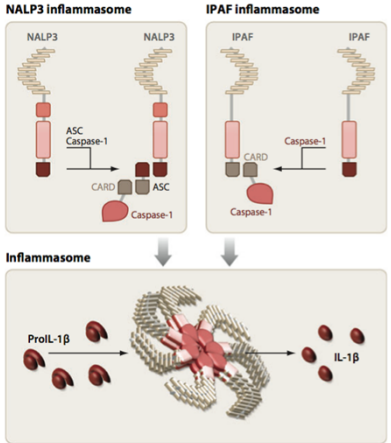
Nod-like receptors (NLRs) : Associated Diseases



Kufer, T. A., & Sansonetti, P. J. (2011). NLR functions beyond pathogen recognition *Nature Immunology*, *12*(2), 121–128.

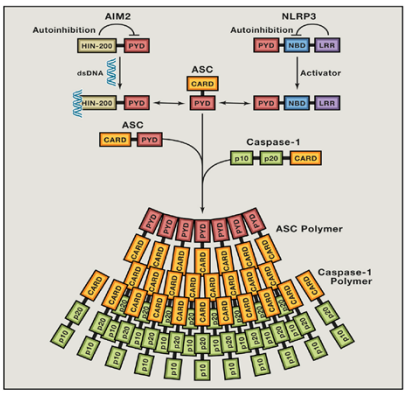
Molecular definition of the Inflammasomes

Inflammasomes

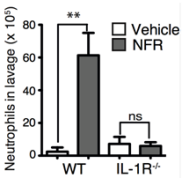


Martinon, F., Mayor, A., & Tschopp, J. (2009). The inflammasomes: guardians of the body *Annual Review of Immunology*, *27*, 229–265

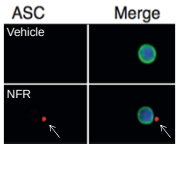
Inflammasomes prionisation



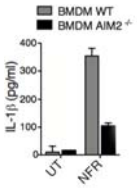
Visualization of the inflammasome



NFR-induced peritonitis



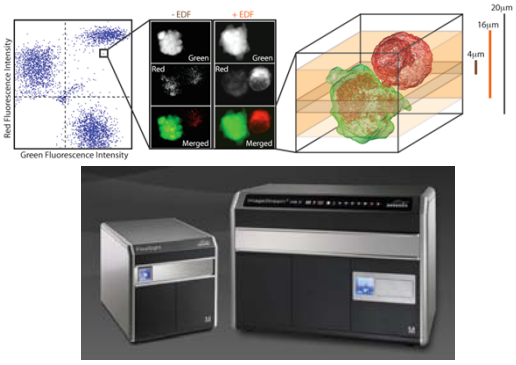
ASC specks



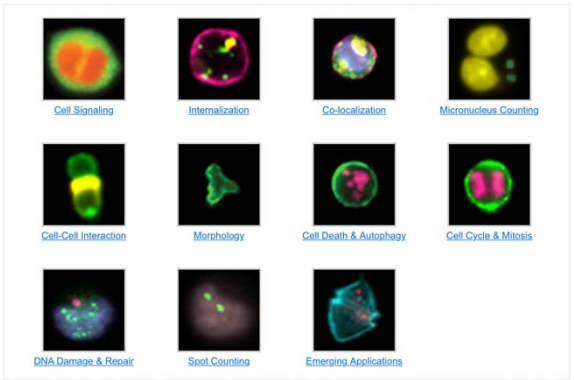
AIM2 is required

The AIM2 inflammasome is a guardian of Nuclear Envelope integrity, Di Micco et al. 2016 PNAS

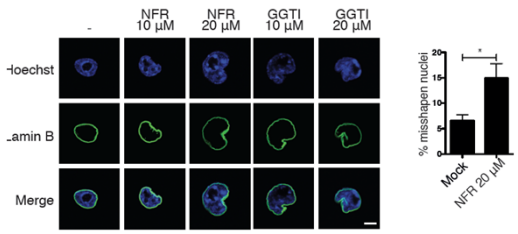
Imaging flow cytometry



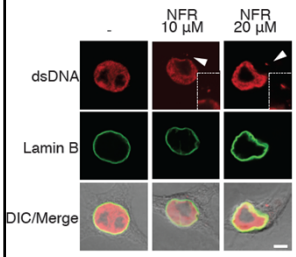
Imaging flow cytometry applications

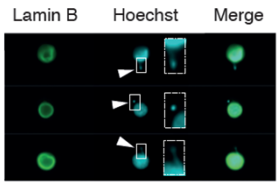


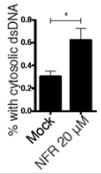
NFR affects nuclear shape



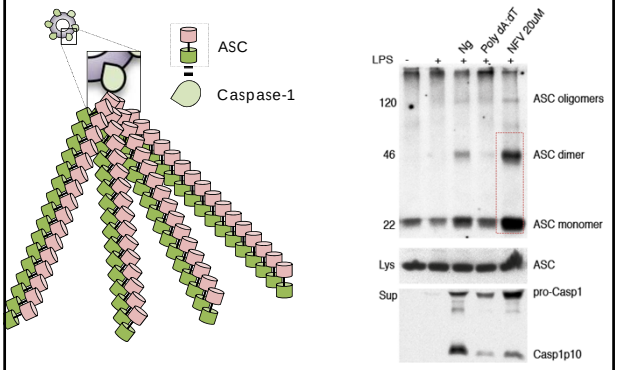
DNA release upon treatment with NFR



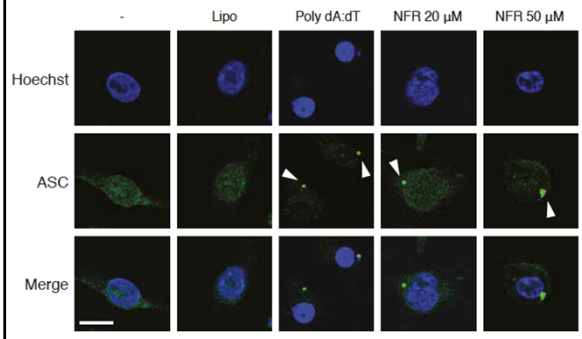




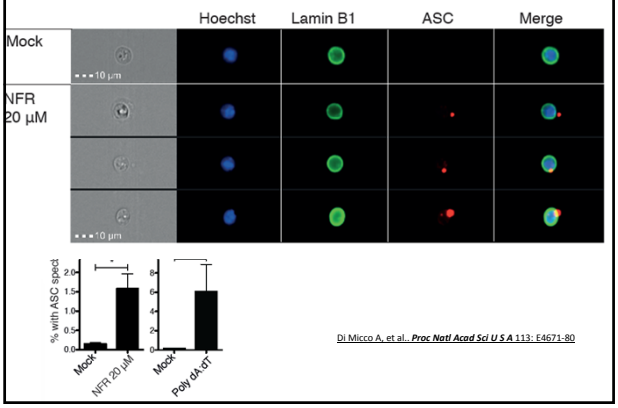
NFR mediates **ASC** oligomerization



NFR triggers **ASC** specks



Quantification of **ASC** specks using ImageStream



Di Micco A, et al., ***Proc Natl Acad Sci U S A*** 113: E4671-80

Interleukin-1 (IL-1β)

>Key player in Inflammation

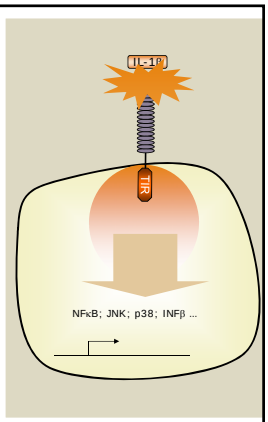
>Important player in various aspect of cell regulation

Known as

- Lymphocyte activating factor (LAF)
- Mitogenic protein (MP)
- T cell replacing factor III (TRFIII)
- B-cell activating factor (BAF)
- B-cell differentiation factor (BDF)
- "Heidikine"

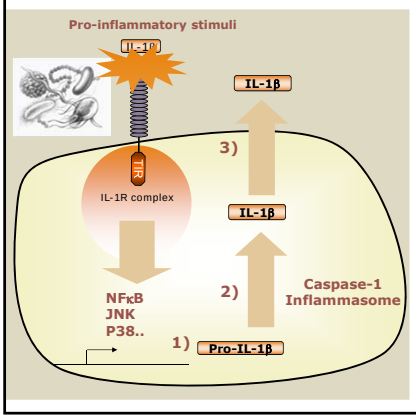
IL-1

- Endogenous Pyrogen (EP)



Burns, K., Martinon, F., Esslinger, C., Pahl, H., et al. (1998). MyD88, an adapter protein involved in interleukin-1 signaling *The Journal of biological chemistry*, *273*(20), 12203–12209.

IL-1β Production

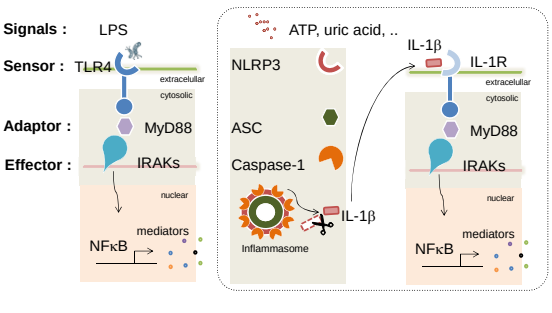


1) Transcription

2) Maturation

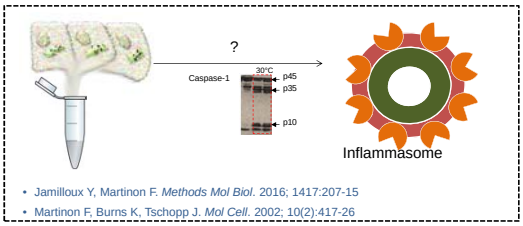
3) Export

The TLR and Inflammasome systems



TLRs *Inflammasome* -> *IL-1R*

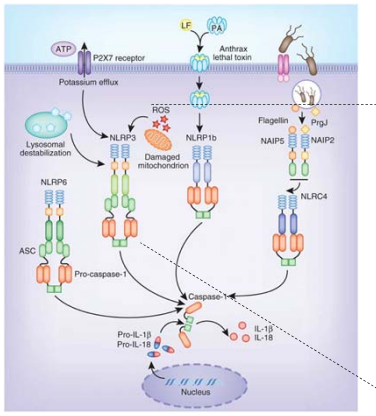
Inflammasomes as guardians of cellular integrity



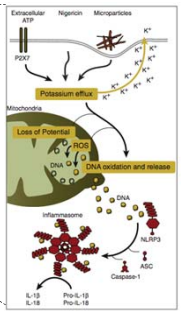
- Jamilloux Y, Martinon F. *Methods Mol Biol*. 2016; 1417:207-15
- Martinon F, Burns K, Tschopp J. *Mol Cell*. 2002; 10(2):417-26

What are the **cell-intrinsic** pathway of inflammasome activation?

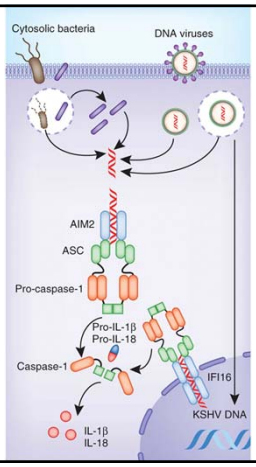
How is innate immunity affected by **cellular perturbations**?



Activation of NLR Inflammasomes



Rathinam VAK, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. Nat Immunol 2012;13:333–332.



Activation of PYHIN Inflammasomes

Rathinam VAK, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. Nat Immunol 2012;13:333–332.

Inflammasomes in Diseases

NLRP3 (CIAS1; cryopyrin) and autoinflammatory diseases

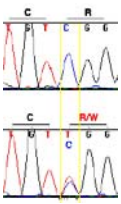
Localized on Chr: 1q44 a periodic fever locus

- Familial cold urticaria (FCU)
- Muckle-wells syndrome (MWS)
- Chronic infantile neurological cutaneous arthropathy (CINCA)

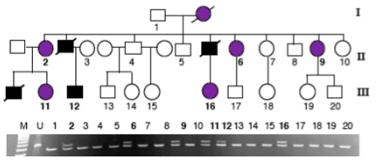
Suscseptibility locus
- 1q44

Pathology
- Rashes
- Fever
- Amyloidosis
- Sensorineural Deafness (MWS)
- Symptoms provoked in the cold (FCU)
- Neurological involvement (CINCA)

- Autosomal dominant



NLRP3 (NALP3; CIAS1; cryopyrin) and CAPS



periodic fever with amyloidosis
periodic fever without amyloidosis
Cold/sensivity/periodic fever without amyloidosis

Figure 6.4 . A) Pedigrees of family A (Indian) showing the results of *Taq* I restriction fragment length polymorphism assays for the R260W. B) family B (French Canadian), and *Alu* I

Hereditary autoinflammatory diseases

Table 1 The autoinflammatory diseases

	Diseases	Gene chromosome	Protein	Transmission	Clinical features
Periodic/ recurrent fevers	Familial Mediterranean fever	*MEVF* 16p13.3	Pyrin	AR	Short duration of fever episodes: 24–48 h Abdominal and chest pain. Erysipelas-like erythema High incidence of renal amyloidosis in untreated patients Good response to colchicine Possible response to IL-1 blockade
	Mevalonate kinase deficiency	*MVK* 12q24	Mevalonate kinase	AR	Early onset (usually <12 months) Mean duration of fever episodes: 4–5 days Poor conditions during fever episodes. Abdominal pain, vomiting, and diarrhea. Splenomegaly Good response to steroids. High rate of self-resolution during adulthood. Amyloidosis is rare
	TNF receptor-associated periodic syndrome	*TNFRSF1A* 12p13	p55 TNF receptor	AD	Prolonged fever episodes: 1–3 weeks Periorbital edema, monocytic fasciitis Incidence of renal amyloidosis: 15–25% Response to TNF and IL-1 blockade
	NALP12-associated periodic fever	*NLRP12*	NLRP12	AD	Periodic fever after cold exposure, hearing loss
Cryopyrinopathies	FCAS, MWS, CINCA	*NLRP3* 1q44	Cryopyrin	AD	FCAS: rash, fever, and arthralgia after cold exposure MWS: recurrent or sub-chronic urticaria-like lesions, sensorineural hearing loss, amyloidosis CINCA: as above + mental retardation, chronic aseptic meningitis, and bone deformities Dramatic response to IL-1 blockade
Granulomatous disorders	Blau's syndrome	*CARD15/NOD2* 16q12	CARD15	AD	Early onset (<5 years) Polyarticular granulomatous arthritis, uveitis, skin rash Good response to anti-TNF monoclonal antibodies
Pyogenic disorders	PAPA syndrome	*PSTPIP1* 15q24-q25.1	PSTPIP1	AD	Pyogenic sterile arthritis, pyogenic gangrenosum, and cystic acne Good response to IL-1 blockade
	Majeed's syndrome	*LPIN2* 18p	LPIN2	AR	Multifocal osteomyelitis, congenital dyserythropoietic anemia, inflammatory dermatosis
	DIRA	*IL1RN* 2q	IL1 receptor antagonist	AR	Neonatal-onset multifocal osteomyelitis, periostitis, and pustulosis Dramatic response to anakinra

AD, autosomal dominant; AR, autosomal recessive; CINCA, chronic infantile neurological cutaneous and articular syndrome; CRMO, chronic recurrent multifocal osteomyelitis; DIRA, deficiency of the interleukin-1 receptor antagonist; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome. Modified from [2].

Hereditary autoinflammatory diseases

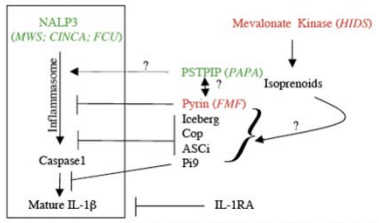
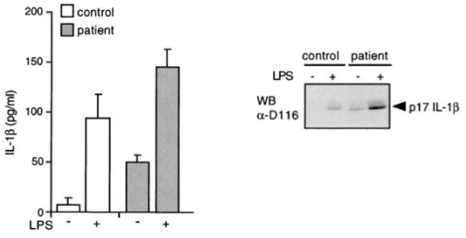


Figure 6.8 Model for the inflammasome deregulation in periodic fevers. Proteins highlighted in green represent mutated protein for gain of function, and proteins highlighted in red proteins were the function is believed to be disrupted in the patients.

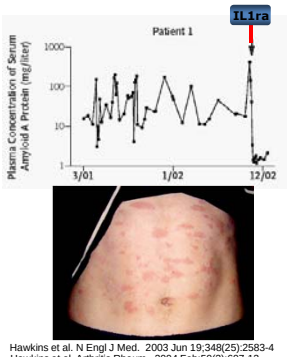
NALP3 mutation lead to increased IL-1 secretion

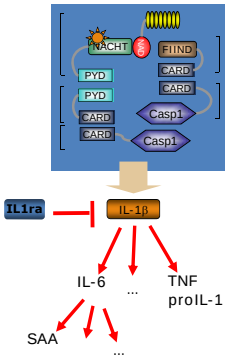


Agostini, L., Martinon, F., Burns, K., McDermott, M. F., Hawkins, P. N., & Tschopp, J. (2004) Immunity, 20(3), 319-325.

Martinon, F., Agostini, L., Meylan, E., & Tschopp, J. (2004). Current biology 14(21), 1929-1934.

Treatment of patients with IL1ra (Anakinra)

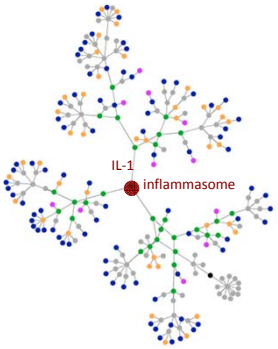




Hawkins et al. N Engl J Med. 2003 Jun 19;348(25):2583-4
Hawkins et al. Arthritis Rheum. 2004 Feb;50(2):607-12.

➢IL-1 a target for therapy

Inflammatory cascades:



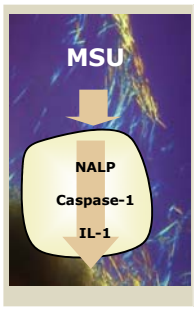
Linear model of inflammation

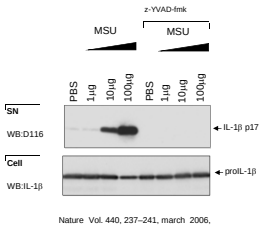
Uric acid crystals (MSU)....

...the etiologic agent of gout

- **-Autoinflammatory disorder**
- **-pain**
- **-inflammation of the articular and periarticular tissues**

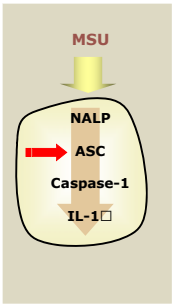
Does MSU activates the NALP3 inflammasome?

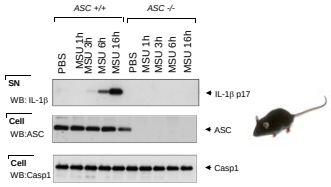




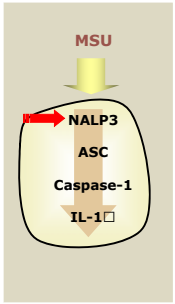
Nature Vol. 440, 237–241, march 2006.

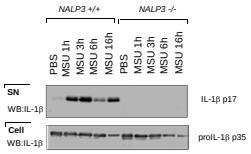
MSU activation of IL-1β is ASC dependent



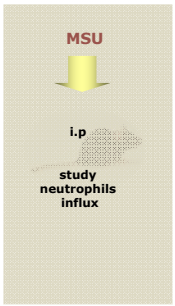


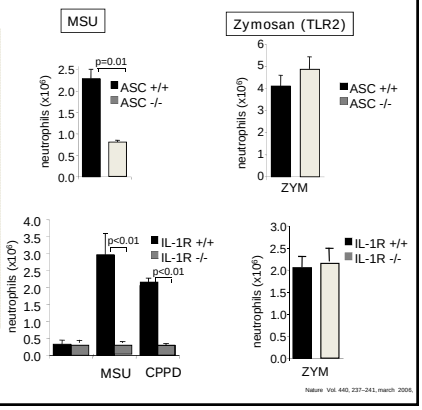
MSU activation of IL-1β is NALP3 dependent





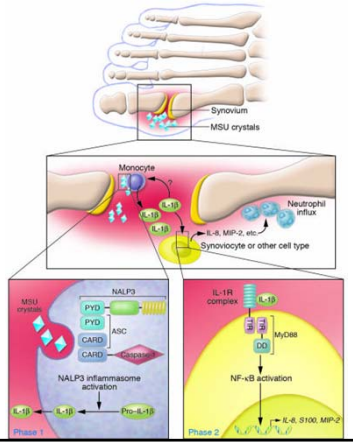
Inflammasome dependent MSU inflammation in vivo





Nature Vol. 440, 237–241, march 2006.

Gout

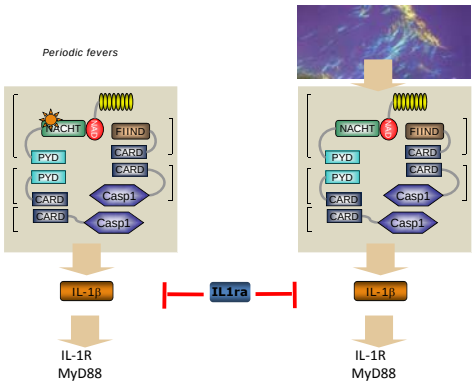


Martinon and Glimcher
J. Clin Invest. 116 (8) 2073-5

Autoinflammatory and chronic inflammatory diseases

Gout / Pseudogout/Asbestosis/ Silicosis

Periodic fevers



Use of IL-1 inhibitors in Gout patients

Prof.Alexander So

Table 1 Clinical summary of the 10 patients studied and their response to treatment

Patient	Clinical presentation	Affected joints	Serum uric acid (normal range, 160–390 μmol/l)	Serum creatinine (normal range, 44–80 μmol/l)	Hypouricemic treatment	Effect of anakinra (hours)	Patient assessment of improvement in pain (%)
Case 1 (female, 72 years old)	Chronic tophaceous gout, renal stones	Fingers, toes	637	79	Uricase	36	70
Case 2 (male, 70 years old)	Chronic tophaceous gout	Ankle, toes	564	202	Allopurinol	24	90
Case 3 (male, 72 years old)	Acute gout	Knee, ankle, foot	482	121	Allopurinol	24	90
Case 4 (male, 51 years old)	Acute gout	Ankle, toe	396	84	Allopurinol	24	100
Case 5 (male, 40 years old)	Acute gout	Ankle, toe	322	113	Allopurinol	36	100
Case 6 (female, 72 years old)	Acute gout	Feet, toe	572	72	None	36	80
Case 7 (male, 76 years old)	Acute gout	Ankle, foot	338	79	None	36	100
Case 8 (male, 70 years old)	Acute gout	Wrist, elbow, hand	779	406	None	48	50
Case 9 (male, 53 years old)	Chronic tophaceous gout	Elbow, finger, foot, ankle	660	84	Allopurinol	48	50
Case 10 (male, 38 years old)	Acute gout	Wrist, finger	540	84	None	24	60

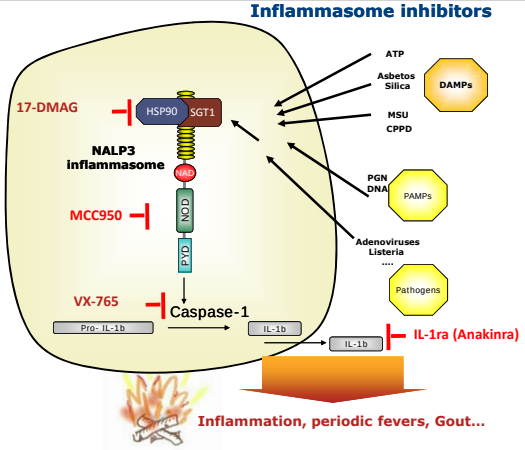
So et al. :
A pilot study of IL-1 inhibition by anakinra in acute gout

Table 3. Current approved anti-interleukin (IL)-1 therapies.

	Anakinra (Kineret)	Rilonacept (Arcalyst)	Canakinumab (Ilaris)
Nature	Recombinant IL-1Ra	Cytokine trap (fusion protein including IL-1R and IL-1Ra)	Humanized monoclonal antibody against IL-1β
Target	IL-1R	IL-1β (and IL-1α, IL-1RAcP)	IL-1β
Half-life	4–6 h	8·6 days	26 days
Administration	100 mg, daily, subcutaneous	320 mg loading dose then 160 mg maintenance, weekly, subcutaneous	150 mg, every 8 weeks, subutaneous (or intravenous)
Common side-effects	Major injection site reactions, URI, infections	Minor injection site reactions, URI, infections	URI, vertigo (MWS patients), negligible injection site reactions,
Indications	Second-line therapy for RA (FDA 2001, EMEA 2002). CAPS (off-label use)	FCAS and MWS patients aged more than 12 years (FDA 2008, EMEA 2009)	FCAS and MWS patients aged more than 4 years (FDA and EMEA 2009)

IL-1Ra: IL-1 receptor antagonist; IL-1R: IL-1 receptor; IL-1RAcP: IL-1 receptor accessory protein; URI, upper respiratory tract infections; CAPS; cryopyrin-associated periodic syndromes; RA: rheumatoid arthritis; FCAS: familial cold autoinflammatory syndrome; MWS: Muckle–Wells syndrome; FDA: Food and Drug Administration; EMEA: European Medicines Agency. Regarding NOMID/CINCA: the only currently approved therapy is Canakinumab (approved by the EMEA but not the FDA).

Inflammasome inhibitors



ARTICLES

nature medicine

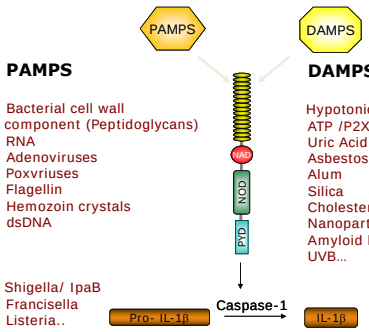
A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases

Rebecca C Coll[1,2], Avril A B Robertson[2], Jae Jin Chae[3], Sarah C Higgins[1], Raúl Muñoz-Planillo[4], Marco C Inserra[2,5], Irina Vetter[2,5], Lara S Dungan[1], Brian G Monks[6], Andrea Stutz[6], Daniel E Croker[2], Mark S Butler[2], Moritz Haneklaus[1], Caroline E Sutton[1], Gabriel Núñez[4], Eicke Latz[6–8], Daniel L Kastner[3], Kingston H G Mills[1], Seth L Masters[9], Kate Schroder[2], Matthew A Cooper[2] & Luke A J O'Neill[1]

Sterile inflammatory diseases-Infammasomes

1	MWS, FCU, CINCA/NOMID	*NALP3	IL1ra
	Familial Mediterranean Fever (FMF)	*Pyrin	IL1ra
	Pyogenic arthritis, pyoderma & acne syndrome (PAPA)	*PSTPIP1	IL1ra
	Systemic juvenile idiopathic arthritis (SOJIA)	*CLIC2?	IL1ra
	TRAPS	*TNFR1	IL1ra
	Gout	MSU/NALP3	IL1ra
	Pseudogout	CPPD/NALP3	IL1ra
	DIRA	IL1RA	IL-1ra
2	Asbestosis	Asbestos/NALP3	?
	Contact dermatitis (hypersensitivity)	Irritants/NALP3	?
	Malaria	HZ/NALP3	?
	Vitiligo	*NALP1	?
	Hydatidiform moles	*NALP7	?
	Hypertension	*NALP3	?
	Fever Syndrome	*NALP12	?
3	Schnitzler's syndrome	?	IL1ra
	Sweet syndrome	?	IL1ra
	Behçet's disease	?	IL1ra
	Type 2 diabetes	?	α-IL1β
	Rheumatoid Arthritis	?	(α-IL1β)
	Relapsing polychondritis	?	IL1ra
	Castleman disease	?	IL1ra

Activators of the NLRP3 Inflammasome



nature immunology

Fatty acid–induced NLRP3-ASC inflammasome activation interferes with insulin signaling

Haitao Wen[1,2,6], Denis Gris[1,2,6], Yu Lei[1,3], Sushmita Jha[1], Lu Zhang[1,3], Max Tze-Han Huang[1,3], Willie June Brickey[1] & Jenny P-Y Ting[1,2,4,5]

High-fat diet (HFD) and inflammation are key contributors to insulin resistance and type 2 diabetes (T2D). Interleukin (IL)-1β plays a role in insulin resistance, yet how IL-1β is induced by the fatty acids in an HFD, and how this alters insulin signaling, is unclear. We show that the saturated fatty acid palmitate, but not unsaturated oleate, induces the activation of the NLRP3-ASC inflammasome, causing caspase-1, IL-1β and IL-18 production. This pathway involves mitochondrial reactive oxygen species and the AMP-activated protein kinase and unc-51–like kinase-1 (ULK1) autophagy signaling cascade. Inflammasome activation in hematopoietic cells impairs insulin signaling in several target tissues to reduce glucose tolerance and insulin sensitivity. Furthermore, IL-1β affects insulin sensitivity through tumor necrosis factor–independent and dependent pathways. These findings provide insights into the association of inflammation, diet and T2D.

LETTERS

NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals

Peter Duewell[1,3]*, Hajime Kono[2]*, Katey J. Rayner[4,5], Cherilyn M. Sirois[1], Gregory Vladimer[1], Franz G. Bauernfeind[6], George S. Abela[8], Luigi Franchi[9], Gabriel Nuñez[9], Max Schnurr[3], Terje Espevik[10], Egil Lien[1], Katherine A. Fitzgerald[1], Kenneth L. Rock[2], Kathryn J. Moore[4,5], Samuel D. Wright[11], Veit Hornung[7]* & Eicke Latz[1,7,10]*

. Mature atherosclerotic lesions contain macroscopic deposits of cho- lesterol crystals in the necrotic core, but their appearance late in atherogenesis had been thought to disqualify them as primary inflam- matory stimuli. However, using a new microscopic technique, we revealed that minute cholesterol crystals are present in early diet- induced atherosclerotic lesions and that their appearance in mice coincides with the first appearance of inflammatory cells.

ARTICLES

nature medicine

Activation of the NLRP3 inflammasome in dendritic cells induces IL-1β–dependent adaptive immunity against tumors

François Ghiringhelli[1–4,18], Lionel Apetoh[1,2,5,6,18], Antoine Tesniere[2,5,7,18], Laetitia Aymeric[1,2,5,18], Yuting Ma[1,2,5], Carla Ortiz[1,2,5,8], Karim Vermaelen[1,2,5,9], Theocharis Panaretakis[2,5,7], Grégoire Mignot[1–4], Evelyn Ullrich[1,2,5], Jean-Luc Perfettini[2,5,7], Frédéric Schlemmer[2,5,7], Ezgi Tasdemir[2,5,7], Martin Uhl[10], Pierre Génin[11], Ahmet Civas[11], Bernhard Ryffel[12], Jean Kanellopoulos[13], Jürg Tschopp[14], Fabrice André[1,2,5], Rosette Lidereau[15], Nicole M McLaughlin[16], Nicole M Haynes[16], Mark J Smyth[16,18], Guido Kroemer[2,5,7,18] & Laurence Zitvogel[1,2,5,17,18]

The therapeutic efficacy of anticancer chemotherapies may depend on dendritic cells (DCs), which present antigens from dying cancer cells to prime tumor-specific interferon-γ (IFN-γ)–producing T lymphocytes. Here we show that dying tumor cells release ATP, which then acts on $P2X_7$ purinergic receptors from DCs and triggers the NOD-like receptor family, pyrin domain containing-3 protein (NLRP3)-dependent caspase-1 activation complex ('inflammasome'), allowing for the secretion of interleukin-1β (IL-1β). The priming of IFN-γ–producing $CD8^+$ T cells by dying tumor cells fails in the absence of a functional IL-1 receptor 1 and in Nlpr3-deficient (*Nlrp3*$^{-/-}$) or caspase-1–deficient (*Casp-1*$^{-/-}$) mice unless exogenous IL-1β is provided. Accordingly, anticancer chemotherapy turned out to be inefficient against tumors established in purinergic receptor *P2rx7*$^{-/-}$or *Nlrp3*$^{-/-}$or *Casp1*$^{-/-}$hosts. Anthracycline-treated individuals with breast cancer carrying a loss-of-function allele of *P2RX7* developed metastatic disease more rapidly than individuals bearing the normal allele. These results indicate that the NLRP3 inflammasome links the innate and adaptive immune responses against dying tumor cells.

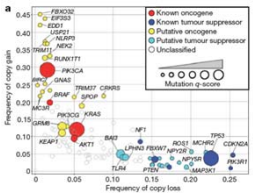
REPORTS

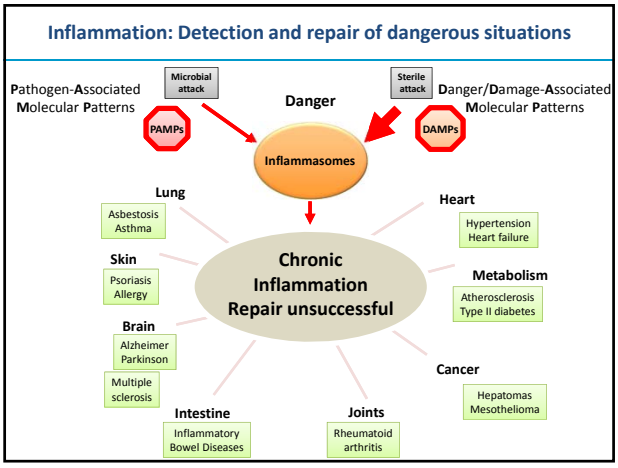
Innate Immune Activation Through Nalp3 Inflammasome Sensing of Asbestos and Silica

Catherine Dostert,[1] Virginie Pétrilli,[1] Robin Van Bruggen,[2] Chad Steele,[3] Brooke T. Mossman,[4] Jürg Tschopp[1]*

The inhalation of airborne pollutants, such as asbestos or silica, is linked to inflammation of the lung, fibrosis, and lung cancer. How the presence of pathogenic dust is recognized and how chronic inflammatory diseases are triggered are poorly understood. Here, we show that asbestos and silica are sensed by the Nalp3 inflammasome, whose subsequent activation leads to interleukin-1β secretion. Inflammasome activation is triggered by reactive oxygen species, which are generated by a NADPH oxidase upon particle phagocytosis. INADPH is the reduced form of nicotinamide adenine dinucleotide phosphate.) In a model of asbestos inhalation, Nalp3$^{-/-}$ mice showed diminished recruitment of inflammatory cells to the lungs, paralleled by lower cytokine production. Our findings implicate the Nalp3 inflammasome in particulate matter–related pulmonary diseases and support its role as a major proinflammatory "danger" receptor.

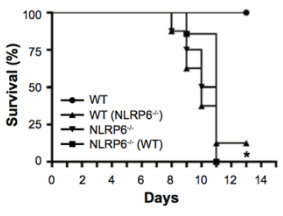
Diverse somatic mutation patterns and pathway alterations in human cancers





NLRP6 Inflammasome Regulates Colonic Microbial Ecology and Risk for Colitis

Eran Elinav,[1,8] Till Strowig,[1,8] Andrew L. Kau,[4,8] Jorge Henao-Mejia,[1] Christoph A. Thaiss,[1] Carmen J. Booth,[2] David R. Peaper,[3] John Bertin,[5] Stephanie C. Eisenbarth,[1,7] Jeffrey I. Gordon,[4] and Richard A. Flavell[1,6,*]
[1]Department of Immunobiology
[2]Section of Comparative Medicine
[3]Department of Laboratory Medicine
Yale University School of Medicine, New Haven, CT 06520, USA
[4]Center for Genome Sciences and Systems Biology
[5]Division of Allergy and Immunology, Department of Internal Medicine
Washington University School of Medicine, Saint Louis, MO 63108, USA
[6]Pattern Recognition Receptor Discovery Performance Unit, GlaxoSmithKline, Collegeville, PA 19426, USA
[7]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
[8]These authors contributed equally to this work
*Correspondence: richard.flavell@yale.edu
DOI 10.1016/j.cell.2011.04.022



single-housed versus cohoused WT and NLRP6mice.

NLRP6-Deficient Mice Harbor a Transmissible Colitogenic Gut Microbiota

LETTER

doi:10.1038/nature22967

Nlrp9b inflammasome restricts rotavirus infection in intestinal epithelial cells

Shu Zhu[1]*, Siyuan Ding[2,3]*, Penghua Wang[4], Zheng Wei[1], Wen Pan[5], Noah W. Palm[1], Yi Yang[1], Hua Yu[1], Hua-Bing Li[1], Geng Wang[1], Xuqiu Lei[1], Marcel R. de Zoete[1], Jun Zhao[1,6], Yunjiang Zheng[1], Haiwei Chen[1], Yujiao Zhao[4], Kellie A. Jurado[7], Ningguo Feng[4], Liang Shan[1], Yuval Kluger[6], Jun Lu[5], Clara Abraham[7], Erol Fikrig[2,8], Harry B. Greenberg[2,3] & Richard A. Flavell[1,8]

Bacteria/Inflammasome interaction

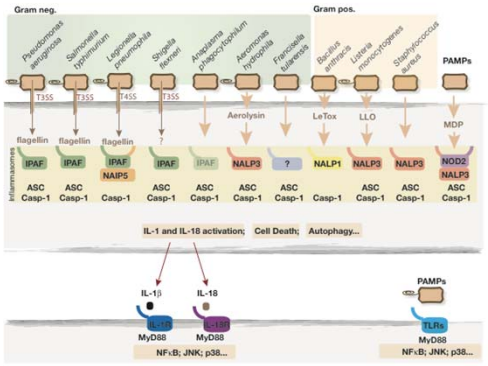


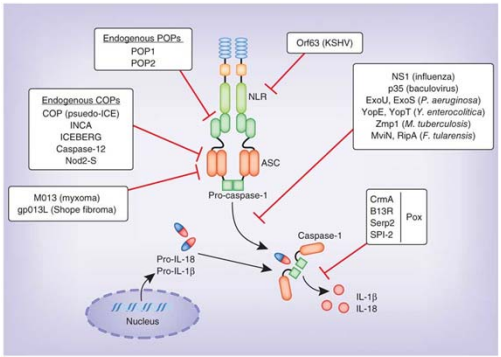
Table 1. The good: inflammasome control of pathogen infection.

Organism	PAMPS identified	Inflammasome activated	Inflammasome importance established *in vivo*†	Refs
Helminths				
Schistosoma mansoni	n.d.	NLRP3	Yes	[138]
Bacteria				
Mycobacterium tuberculosis	ESX-1 secretion system	NLRP3-dependent and -independent mechanism	Yes. *In vivo* IL-1 production is independent of caspase-1	[17,139–142]
Streptococcus pneumoniae	Pneumolysin	NLRP3	Yes	[143,144]
Streptococcus pyogenes	Streptolysin O	NLRP3	Yes. Not important *in vivo*	[145]
Streptomyces hygroscopicus	Nigericin	NLRP3	n.a.	[146]
Klebsiella pneumoniae	n.d.	NLRP3	Yes	[147]
Chlamycia pneumoniae	n.d.	NLRP3	Yes	[148]
Salmonella typhimurium	Flagellin and type III secretion system	NLRP3 and NLRC4	Yes	[149,150]
Francisella tularensis	DNA	AIM2	Yes	[146,151,152]
Legionella pneumophila	Flagellin	NLRC4	Yes	[153]
Listeria monocytogenes	Flagellin, Listeriolysin O, DNA	AIM2, NLRP3, NLRC4	Yes*	[146,154,155]
Pseudomonas aeruginosa	Flagellin, Type III secretion system	NLRC4	Yes	[156–158]
Shigella flexneri	Type III secretion system	NLRC4	Yes	[157,159]
Neisseria gonorrhoeae	Lipo-oligosaccharide	NLRP3	No	[160]
Staphylococcus aureus	Peptidoglycan Haemolysin	NLRP3	Yes	[146,161–165]
Vibrio vulnificus and *Vibrio cholerae*	Haemolysins	NLRP3	No	[166]
Bacillus anthracis	Anthrax lethal toxin	NLRP1	Yes	[167–170]
Escherichia coli	Type III secretion system, flagellin	NLRC4	No	[157]
Chlamydia trachomatis	Type III secretion system	NLRP3	No	[171]
Protozoa				
Toxoplasma gondii	n.d.	NLRP1	No	[172]
Plasmodium species; falciparum, berghei, chabaudi	Haemozoin, MSU	NLRP3	Yes†	[30,136,173]
Fungal				
Candida albicans	Hyphae, β-glucan	NLRP3	Yes	[174]
Aspergillus fumigatus	n.d., β-glucan	NLRP3	No	[175,176]
Saccharomyces cerevisiae	n.d., β-glucan	NLRP3	n.a.	[174]
Viruses				
Sendai virus	RNA	NLRP3	No	[177]
Influenza virus	RNA, M2 ion channel	NLRP3	Yes	[177–181]
Adenovirus	DNA	NLRP3	Yes	[182]
Vaccinia virus	DNA, RNA	AIM2	No	[23,155]
Mouse cytomegalovirus	DNA	AIM2	Yes	[155]
Vesicular stomatis virus	5′-triphosphate ssRNA	RIG-I‡, NLRP3	Yes. Not important *in vivo*	[24,183]
Encephalomyocarditis virus	RNA	NLRP3	Yes. Not important *in vivo*	[24,183]

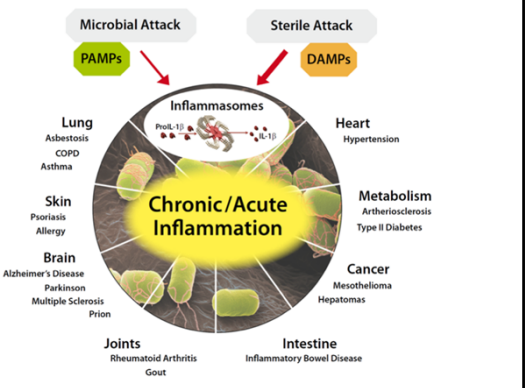
Menu, P., & Vince, J. E. (2011). The NLRP3 inflammasome in health and disease: the good, the bad and the ugly. *Clinical and experimental immunology*, Inflammasomes: the good, the bad and the ugly,

Inflammasome regulation

Inflammasomes regulators



Rathinam VAK, Vanaja SK, Fitzgerald KA. Regulation of inflammasome signaling. Nat Immunol 2012;13:333–332.


Microbial Attack
PAMPs
Sterile Attack
DAMPs
Inflammasomes
ProIL-1β
IL-1β
Chronic/Acute Inflammation
Lung
Asbestosis
COPD
Asthma
Heart
Hypertension
Skin
Psoriasis
Allergy
Metabolism
Artheriosclerosis
Type II Diabetes
Brain
Alzheimer's Disease
Parkinson
Multiple Sclerosis
Prion
Cancer
Mesothelioma
Hepatomas
Joints
Rheumatoid Arthritis
Gout
Intestine
Inflammatory Bowel Disease