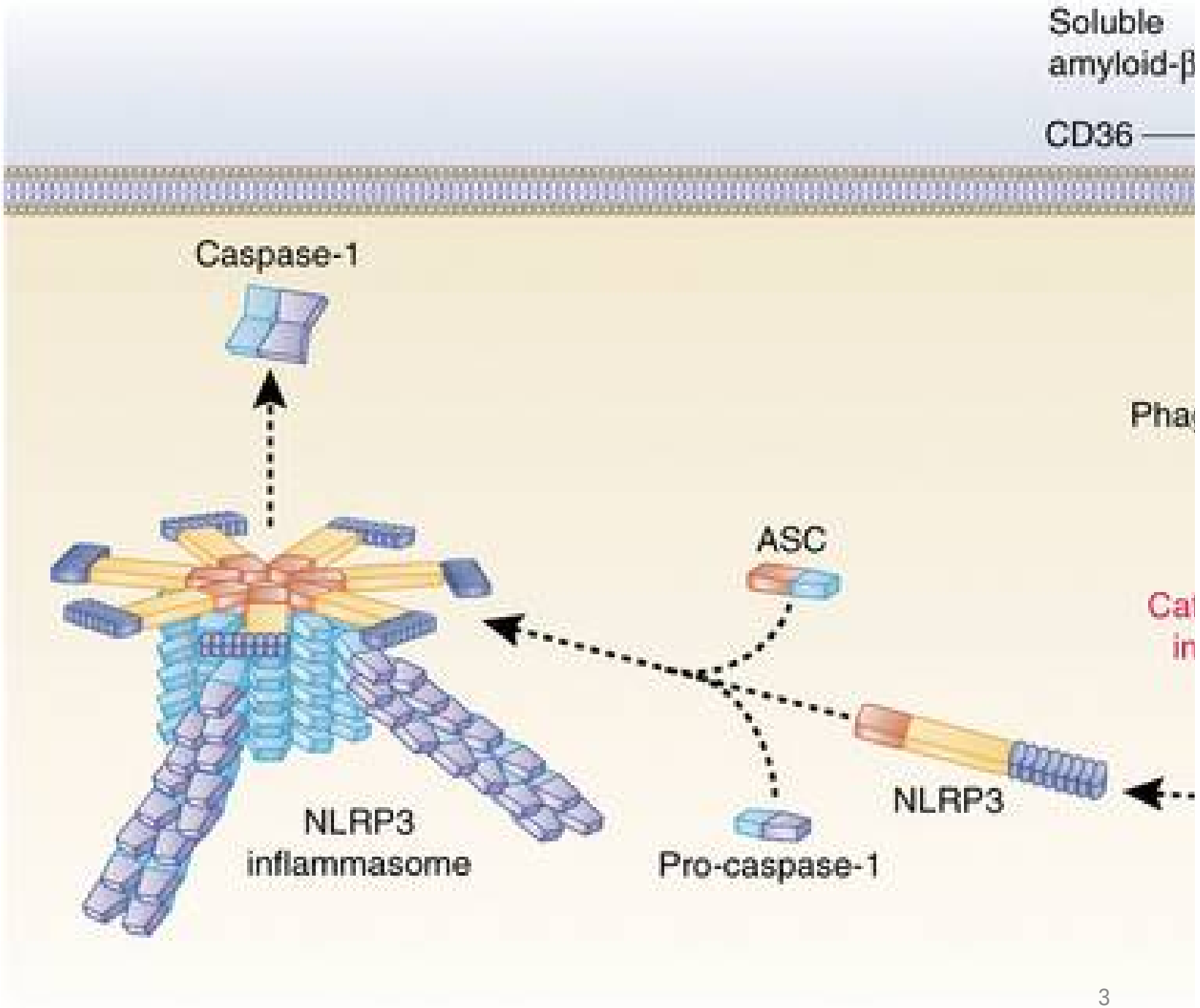
Inflammasomes

Dr.Shrilekha.S

What are Inflammasomes?

- Complexes present in cell cytoplasm
- Formed by oligomerization of a type of peptide…….associates with another protein =multi-protein complex
- This structure when formed, promotes procaspase-1 activation to caspase-1


Soluble
amyloid-β
CD36
Caspase-1
ASC
NLRP3
inflammasome
Pro-caspase-1
NLRP3

Types of Inflammosomes

Nomenclature

Understanding the Nomenclature Of Inflammasomes

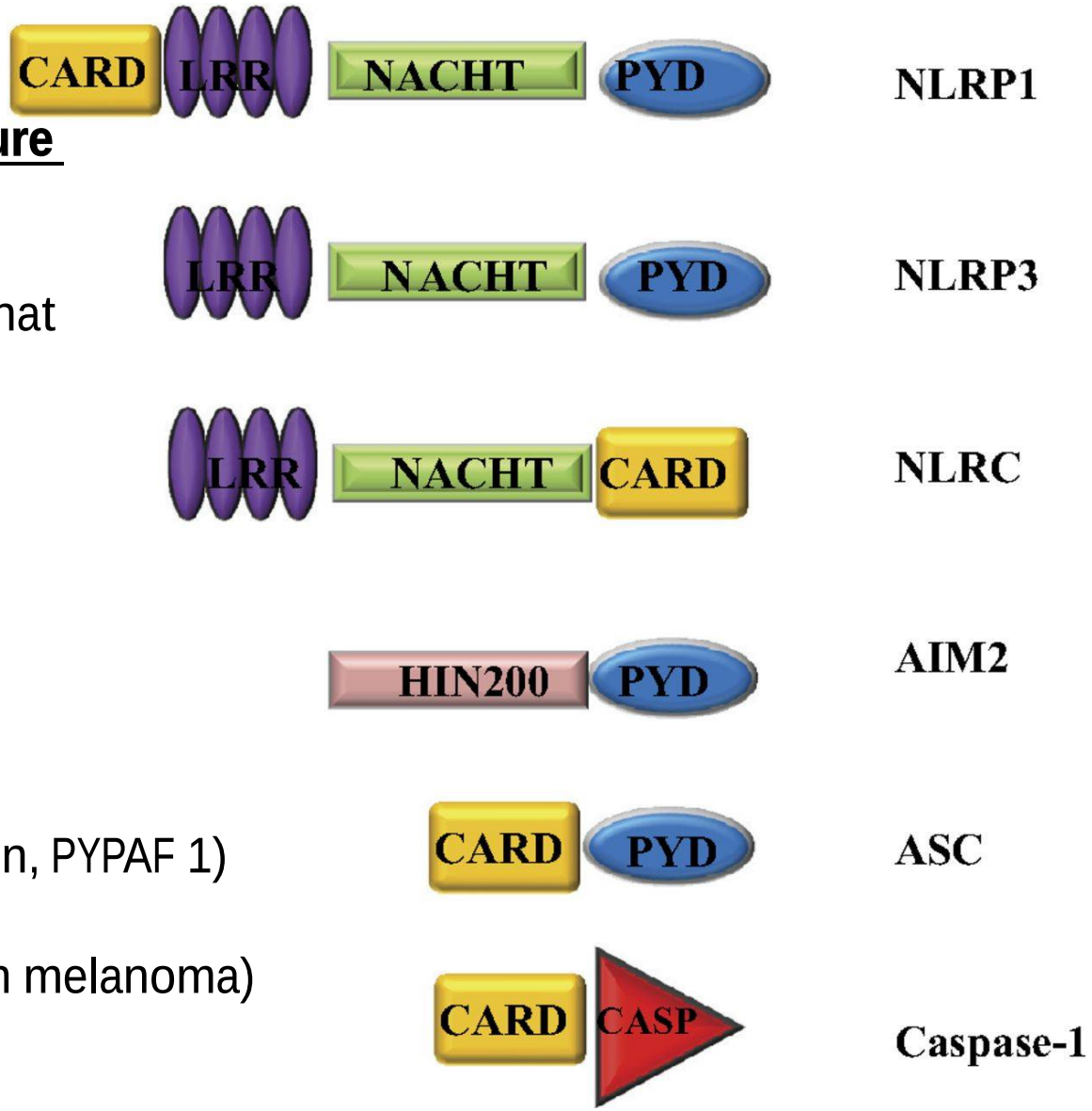
Based on the primary peptide that oligomerizes

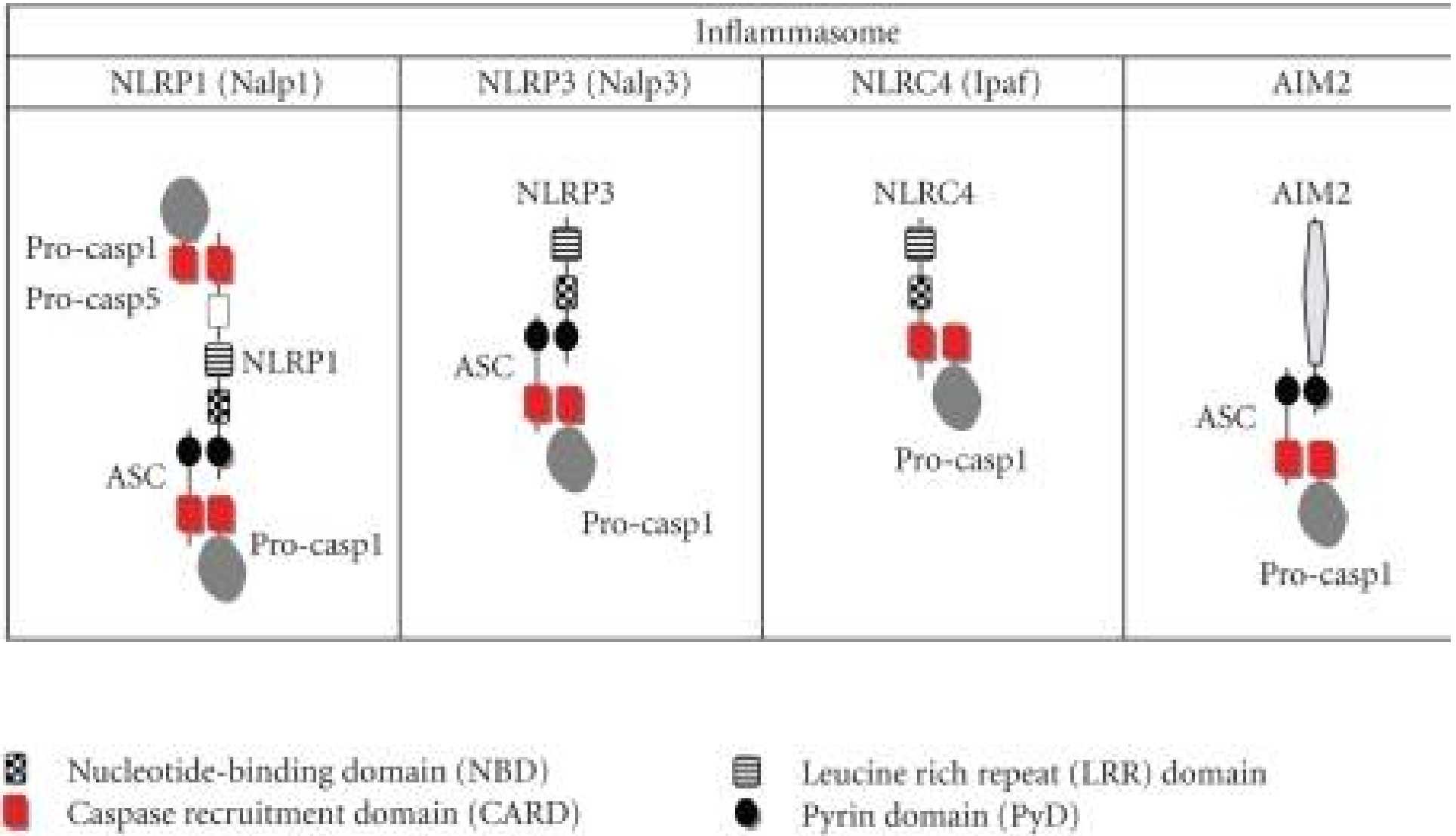
NLR: NOD like receptor
P: Pyrin domain
C: Card domain

Different Inflammasomes

NLRP1 inflammasome
NLRP3 inflammasome (Cyropyrin, PYPAF 1)
NLRC inflammasome (IPAF)
AIM 2 inflammasome (Absent in melanoma)
NLRP2, NLRP7,NLRP12, IFI16

ASC: Apoptosis associated Speck like protein Containing CARD




Inflammasome
NLRP1 (Nalp1)
NLRP3 (Nalp3)
NLRC4 (Ipaf)
AIM2
Pro-casp1
Pro-casp5
NLRP1
ASC
Pro-casp1
NLRP3
ASC
Pro-casp1
NLRC4
Pro-casp1
AIM2
ASC
Pro-casp1
Nucleotide-binding domain (NBD)
Caspase recruitment domain (CARD)
Leucine rich repeat (LRR) domain
Pyrin domain (PyD)

Functions of Inflammasome

- Formation of inflammasome complex results in procaspase undergoing auto proteolysis to caspase resulting in

- Activation of cytokines IL1β, IL18, IL33
- Pyroptosis: Inflammatory cell death
- Blocks glycolysis

- Inflammasomes differ in the number of caspase recruitment, some recruit caspase 5

Activated Caspase-1

- Inflammatory role: Cytokine and DAMP production
- Pyroptosis: Inflammatory cell death
- Procaspase7- --Caspase 7
- SREBPs: Sterol regulatory element binding protein: fatty acid and glucose metabolism, also promotes growth factors

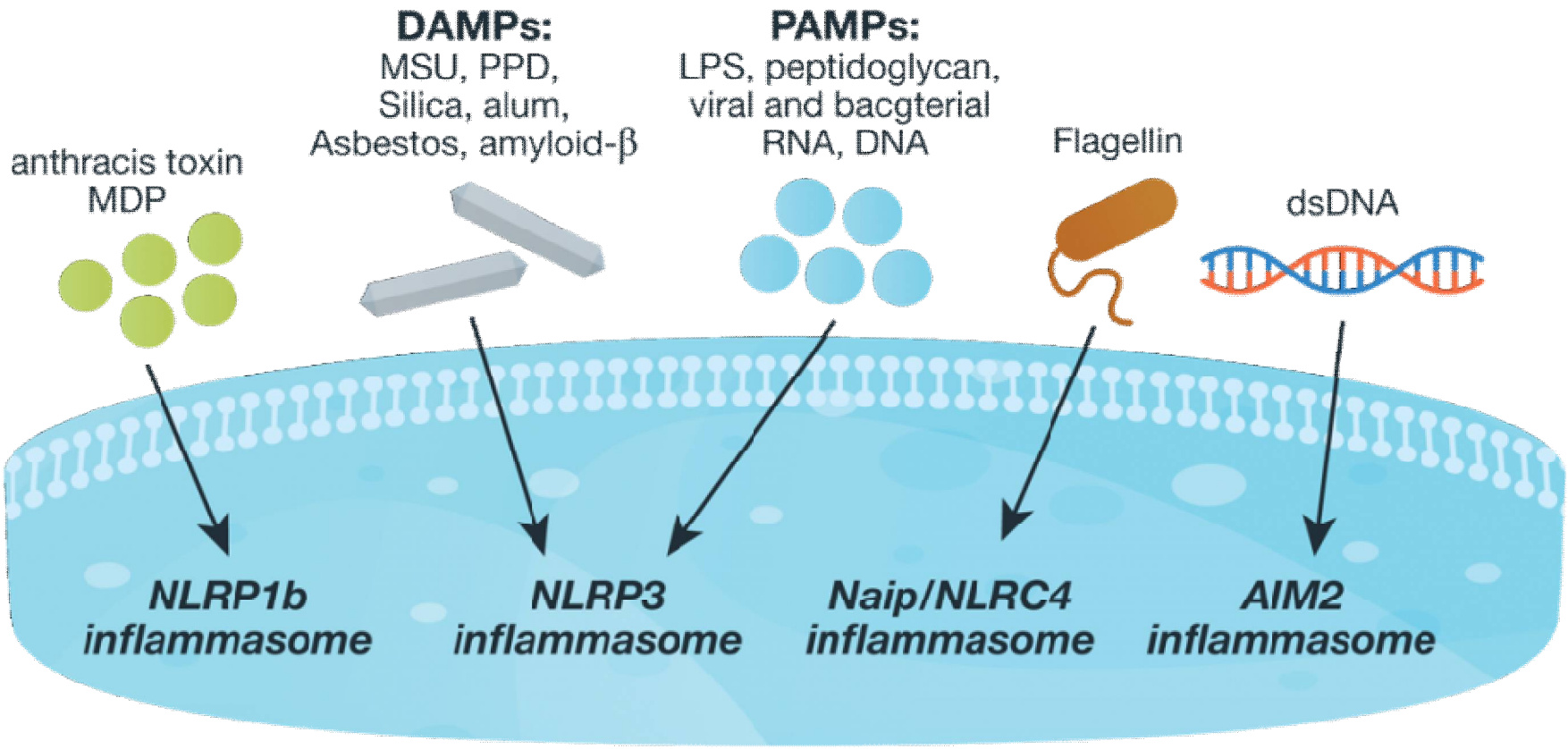
- Inflammasome spreading: Produced DAMPs cause other inflammasome to be activated

Activation Triggers of Inflammasomes

- What causes/stimulus for the formation of inflammasomes?

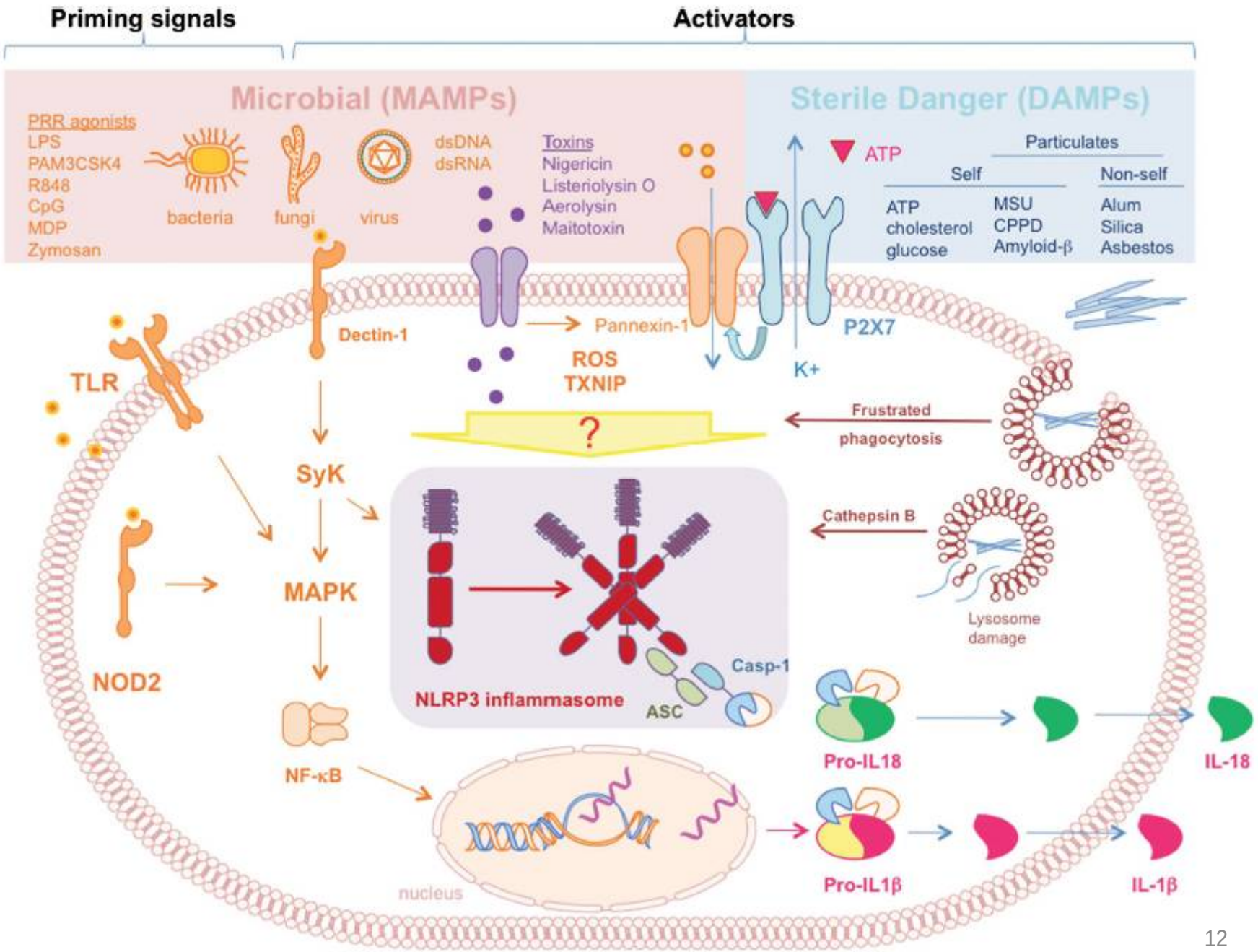
- Following stimulus, how is it formed?
  - Priming: Transcription of NLRP3 protein, pro-IL1β, Pro-IL-18
  - Activation and Assembly: Activate the NLRP3 protein, phosphorylates ASC, assembly

DAMPS: Danger associated molecular patterns
PAMPS: Pathogen associated molecular patterns
Part of Innate immunity : PRR- Pattern recognition receptors



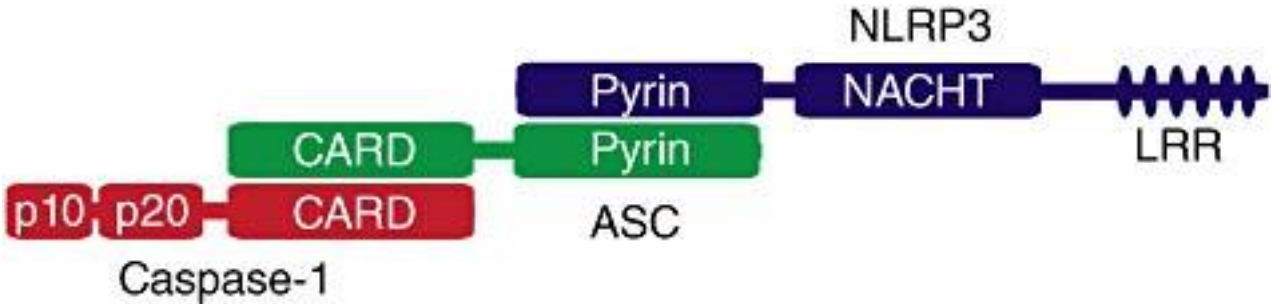
Extra-cellular stimulus—Intra-cellular changes

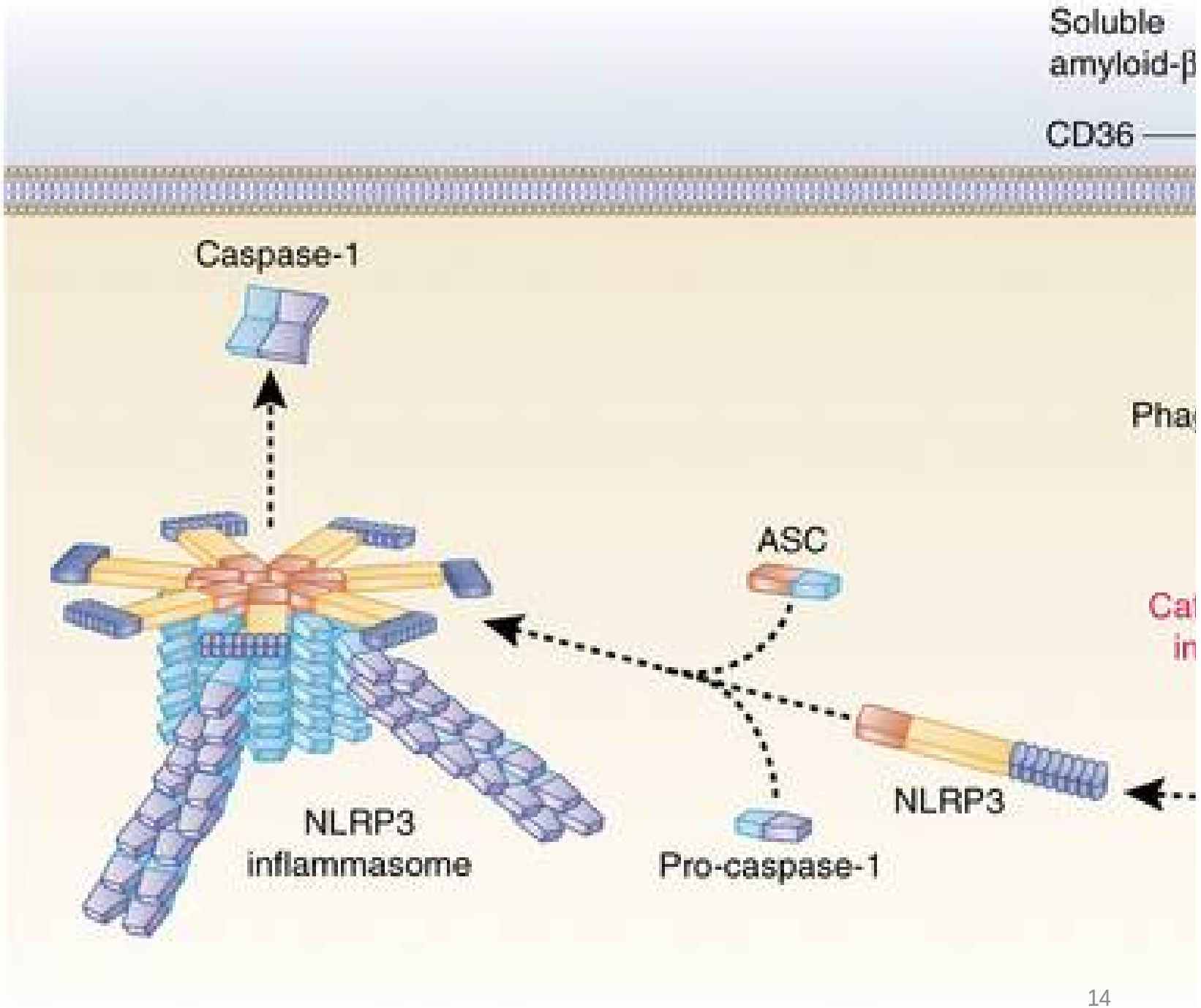
- Transmembrane receptors: P2X7; Pannexin
- Phagocytosis: lysosomal fusion
- Signals in cytosol:
  K+ Efflux and reduced incellular levels : regulated by P2X7 receptor
  Cathepsin- P : Lysosomal damage
  Reactive oxidation species :TXNIP (Thioredoxin interacting protein): protein that binds with thioredoxin (anti-oxidant)
- Priming and formation of necessary protiens via activation of transcription
- Phosphorylation of ASC protein


Priming signals
Activators
Microbial (MAMPs)
Sterile Danger (DAMPs)
PRR agonists
LPS
PAM3CSK4
R848
CpG
MDP
Zymosan
bacteria
fungi
virus
dsDNA
dsRNA
Toxins
Nigericin
Listeriolysin O
Aerolysin
Maitotoxin
ATP
Particulates
Self
Non-self
ATP
cholesterol
glucose
MSU
CPPD
Amyloid-β
Alum
Silica
Asbestos
Dectin-1
TLR
Pannexin-1
P2X7
K+
ROS
TXNIP
?
Frustrated
phagocytosis
SyK
Cathepsin B
MAPK
Lysosome
damage
NOD2
NLRP3 inflammasome
Casp-1
ASC
NF-κB
Pro-IL18
IL-18
nucleus
Pro-IL1β
IL-1β

Inflammasome Assembly

- Oligomerization of the protein: NLRPs or AIM
- Association with the adaptor protein (ASC)
- Clustering of the procaspase-1
- Auto-cleaved to caspase-1
- Pro-IL 1, 18 activated




Soluble
amyloid-β
CD36
Caspase-1
ASC
NLRP3
inflammasome
Pro-caspase-1
NLRP3

Inflammasome Regulators, de-activators

- Pyrin domain only proteins (POP 1,2,3,4)
- CARD only proteins (COP)
- ASC isoforms: ASC b,c,d: ASC c reduces inflammasome activity

- Some drugs: NRTI, Glyburide, 25 Cholesterol hydroxylase, MCC 950, B-hydroxy butyrate

Inflammasomes and Diseases

- Auto-inflammatory diseases: 90 mutations in NLRP3 causes excess activation and hence increases caspase-1, IL1β, IL18 expression
- Metabolic diseases: Type 2 Diabetes, atherosclerosis, MI: NLRP3 activation observed
- Neurodegenerative disorders: Alzheimer's, Multiple sclerosis
- AIM2 inflammasome prevents Inflammatory bowel disease

Clin Sci (Lond). 2016 Jul 1;130(14):1237-46. doi: 10.1042/CS20160090. Epub 2016 Apr 21.

Colchicine therapy in acute coronary syndrome patients acts on caspase-1 to suppress NLRP inflammasome monocyte activation.

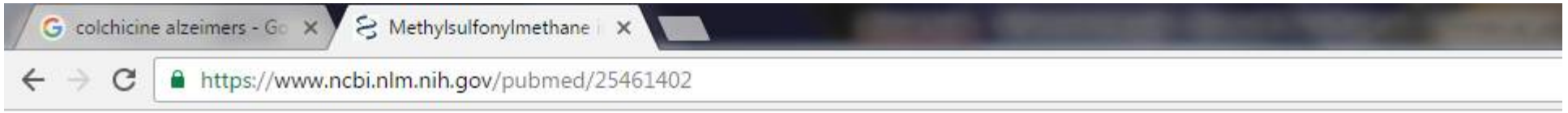
Robertson S[1], Martínez GJ[2], Payet CA[3], Barraclough JY[4], Celermajer DS[4], Bursill C[5], Patel S[6].

Author information

Abstract

Inflammasome activation, with subsequent release of pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18, has recently been implicated in atherosclerosis-associated inflammation. This study aims to assess in acute coronary syndrome (ACS) patients (1) inflammasome activation in circulating monocytes and (2) whether short-term oral colchicine, a recognized anti-inflammatory agent that has been shown to be cardio-protective in clinical studies, might acutely suppress inflammasome-dependent inflammation. ACS patients (n=21) were randomized to oral colchicine (1 mg followed by 0.5 mg 1 h later) or no treatment, and compared with untreated healthy controls (n=9). Peripheral venous blood was sampled pre- (day 1) and 24 h post- (day 2) treatment. Monocytes were cultured and stimulated with ATP. Analysis of key inflammasome markers was performed by ELISA. IL-1β secretion increased by 580.4% ($P<0.01$) in ACS patients compared with controls but only with ATP stimulation. Untreated ACS patients secreted significantly higher levels of IL-18 compared with healthy controls independent o ATP stimulation ($P<0.05$). Colchicine treatment in ACS patients markedly reduced intracellular and secreted levels of IL-1β compared with pre-treatment levels ($P<0.05$ for both), as well as significantly reducing pro-caspase-1 mRNA levels by 57.7% and secreted caspase-1 protein levels by 30.2% compared with untreated patients ($P<0.05$ for both). Monocytes from ACS patients are 'primed' to secrete inflammasome-related cytokines and short-term colchicine acutely and markedly suppresses monocyte caspase-1 activity, thereby reducing monocyte secretion of IL-1β.

KEYWORDS: acute coronary syndromes; atherosclerosis; colchicine; inflammasome; monocytes



Format: Abstract

Send

Cytokine. 2015 Feb;71(2):223-31. doi: 10.1016/j.cyto.2014.11.001. Epub 2014 Nov 21.

Methylsulfonylmethane inhibits NLRP3 inflammasome activation.

Ahn H[1], Kim J[1], Lee MJ[1], Kim YJ[2], Cho YW[3], Lee GS[4].

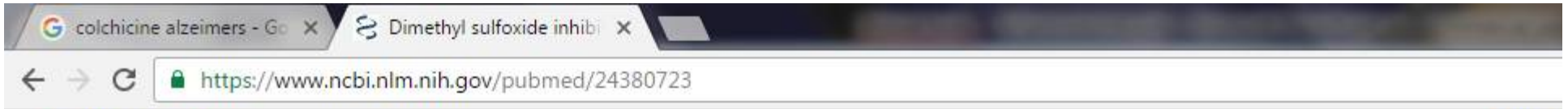
Author information

Abstract

Methylsulfonylmethane (MSM) is an organosulfur compound and the health benefits associated with MSM include inflammatio Although MSM has been shown to have various physiological effects, no study has yet focused on inflammasome activation. The inflammasome is a multiprotein complex that serves as a platform for caspase 1-dependent proteolytic maturation and secretion of interleukin-1β (IL-1β). In this study, we tested the effect of MSM on inflammasome activation using mouse and human macrophages. In our results, MSM significantly attenuated NLRP3 inflammasome activation in lipopolysaccharide-primed macrophages, although it had no effect on NLCR4 or AIM2 inflammasome activation. Extracts of MSM-enriched vegetables presented the same inhibitory effect on NLRP3 inflammasome activation as MSM. MSM also attenuated the transcriptional expression of IL-1α, IL-1β, IL-6, and NLRP3. Taken together, these results show that MSM has anti-inflammator characteristics, interrupts NLRP3 inflammasome activation, and inhibits pro-cytokine expression. We further confirmed the intracellular mechanism of MSM in relation to NLRP3 inflammasome activation, followed by comparison with that of DMSO. Both chemicals showed a synergic effect on anti-NLRP3 activation and attenuated production of mitochondrial reactive oxyger species (ROS). Thus, MSM is a selective inhibitor of NLRP3 inflammasome activation and can be developed as a supplement control several metabolic disorders.

KEYWORDS: DMSO; Inflammasome; Interleukin-1beta; MSM; Macrophages

PMID: 25461402 DOI: 10.1016/j.cyto.2014.11.001



Format: Abstract **Send**

Immunobiology. 2014 Apr;219(4):315-22. doi: 10.1016/j.imbio.2013.11.003. Epub 2013 Nov 22.

Dimethyl sulfoxide inhibits NLRP3 inflammasome activation.

Ahn H[1], Kim J[1], Jeung EB[2], Lee GS[3].

Author information

Abstract

Dimethyl sulfoxide (DMSO) is an amphipathic molecule that is commonly/widely used as a solvent for biological compounds. In addition, DMSO has been studied as a medication for the treatment of inflammation, cystitis, and arthritis. Based on the anti-inflammatory characteristics of DMSO, we elucidated the effects of DMSO on activation of inflammasomes, which are cytoplasmic multi-protein complexes that mediate the maturation of interleukin (IL)-1β by activating caspase-1 (Casp1). In the present study, we prove that DMSO attenuated IL-1β maturation, Casp1 activity, and ASC pyroptosome formation via NLRP3 inflammasome activators. Further, NLRC4 and AIM2 inflammasome activity were not affected, suggesting that DMSO is a selective inhibitor of the NLRP3 inflammasomes. The anti-inflammatory effect of DMSO was further confirmed in animal, LPS-endotoxin sepsis and inflammatory bowel disease models. In addition, DMSO inhibited LPS-mediating IL-1s transcription. Take together, DMSO shows anti-inflammatory characteristics, attenuates NLRP3 inflammasome activation, and mediates inhibition of IL-1s transcription.

KEYWORDS: Cytokine; DMSO; Inflammasome; Interleukin-1; Macrophages; NLRP3

Comment in

Effects of dimethyl sulfoxide on the NLRP3 inflammasome. [Immunobiology. 2015]

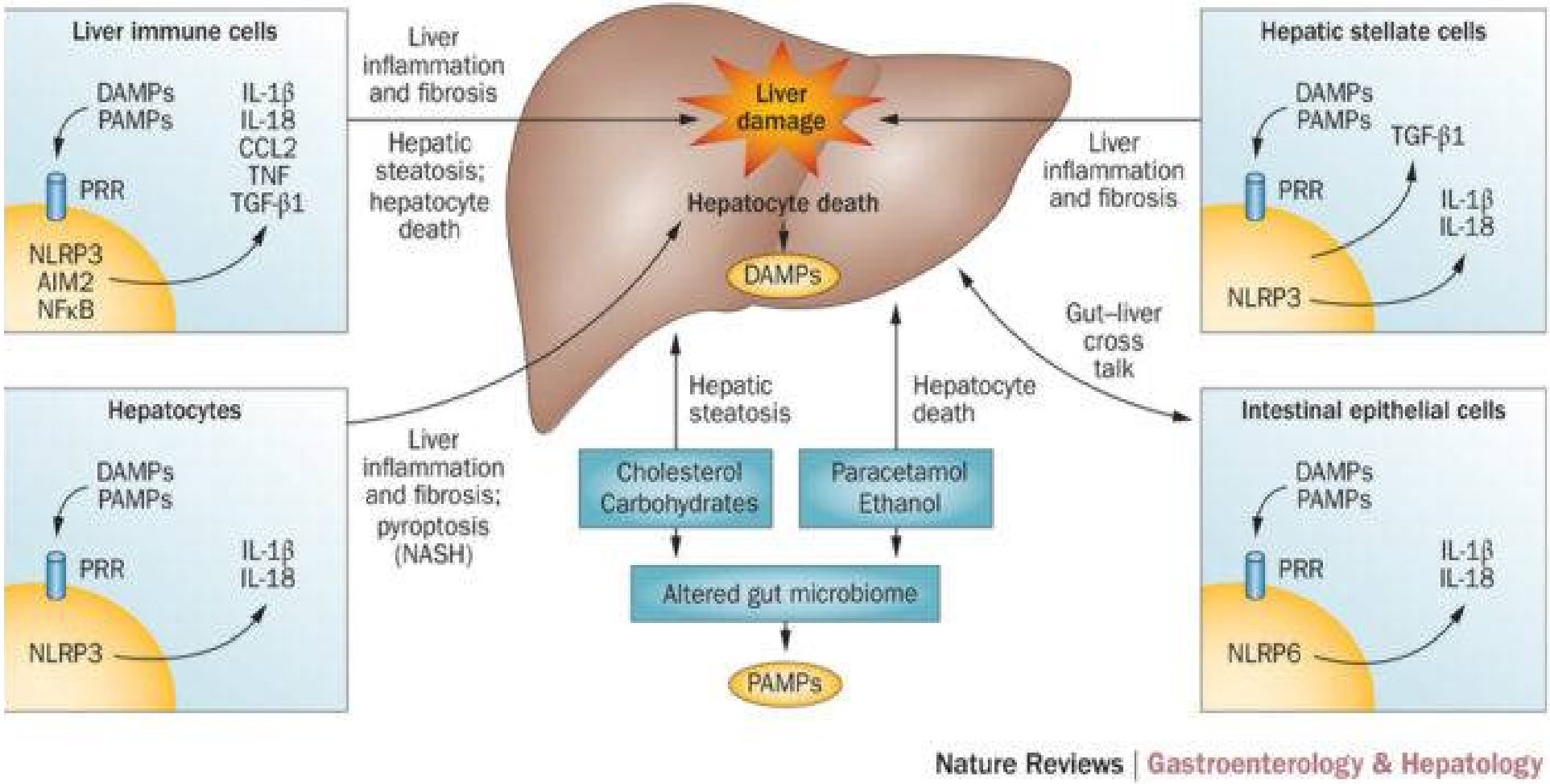
PMID: 24380723 DOI: 10.1016/j.imbio.2013.11.003

[PubMed - indexed for MEDLINE]

Summary/ Goal

- Nomenclature of inflammasomes
- Pathways of activation
- Different in-vitro studies as well as animal studies suggest inflammasomes have a regulatory role several diseases
- Certain nutraceuticals and medications have shown in small studies to have anti-inflammasome activity- ? translates to clinical benefit and extent of benefit remains to be seen

MCQ: How many different types of inflammasome is mentioned here



Nature Reviews | Gastroenterology & Hepatology

NLRP3, AIM2, NFkB, NLRP6, DAMP, PAMP, PRR

a) 1

b) 2

c) 3

d) 4

Thank you