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Effetti delle polveri ultrafini e delle nanoparticelle a livello cellulare e molecolare

Effect of ultrafine particles at the cellular and molecular level

F. Di Virgilio

Particulate air pollution increases chronic obstructive lung diseases, congestive heart failure, myocardial infarction, and in general hospital admissions for cardiorespiratory symptoms

- Hourly peaks in air pollution more than double stroke risk (American Heart Association, British Medical Journal)
- People with diabetes, cardiovascular diseases, COPD, rheumatoid arthritis have an increased death risk in polluted environments (American Thoracic Society)
- Children with obesity and asthma are more affected by air pollution than other kids (American Thoracic Society)
- Lung development is better in children who stay away from pollution (American Journal of Respiratory and Critical Care Medicine)

In October 2006 WHO said that by enforcing more restrictive guidelines on air quality it may be possible to save as many as 300 000 lives each year around the world.

INFLAMMATION

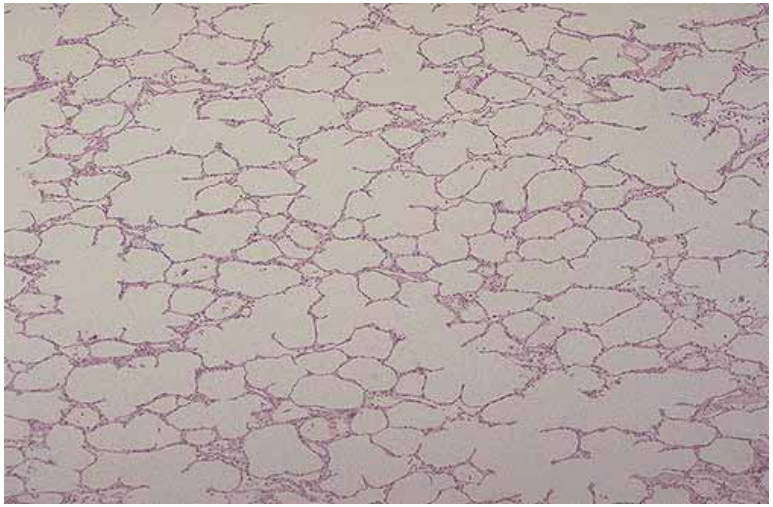
Inflammation as a response to pathogens…….

Inflammation as the key pathogenetic mechanism in lung pathology:

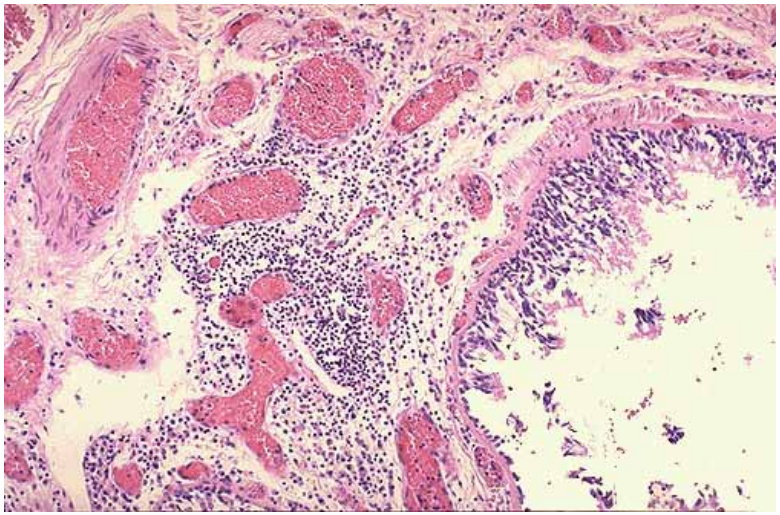
obstructive (Chronic bronchitis, Emphysema, asthma, cystic fibrosis, bronchiectasia) and restrictive (sarcoidosis, Pneumoconiosis, interstitial fibrosis, ARDS) lung diseases.

Inflammatory changes in the lung

Healthy lung

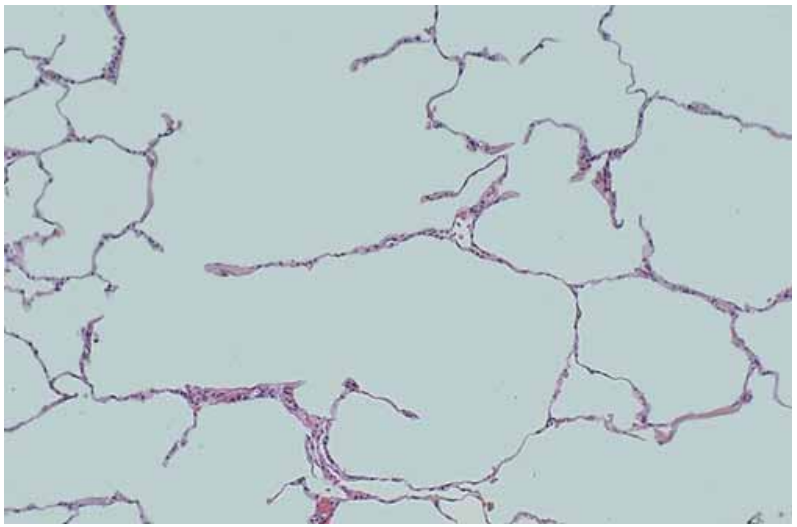


Chronic bronchitis with inflammatory infiltrate

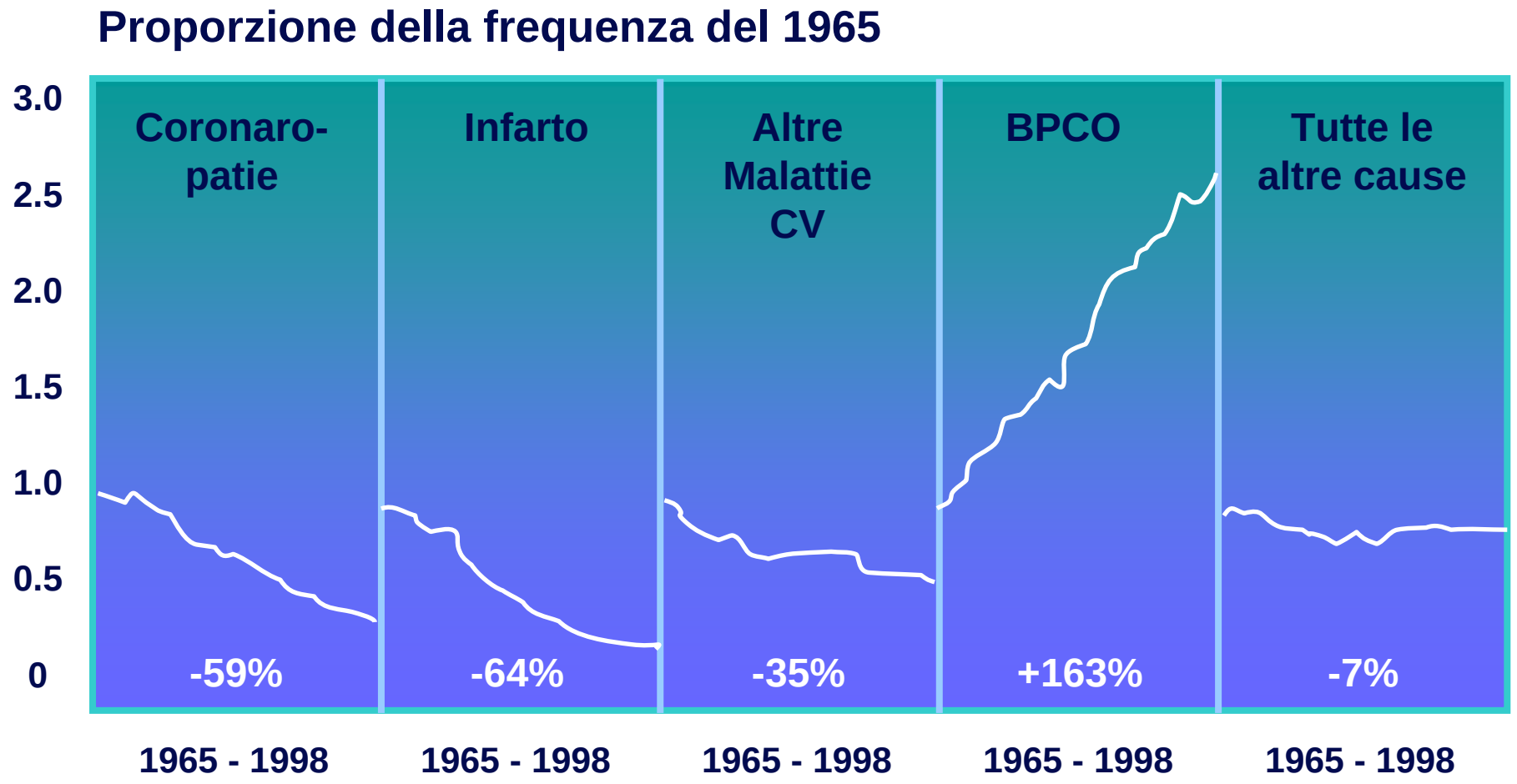


COPD/BPCO

Emphysema

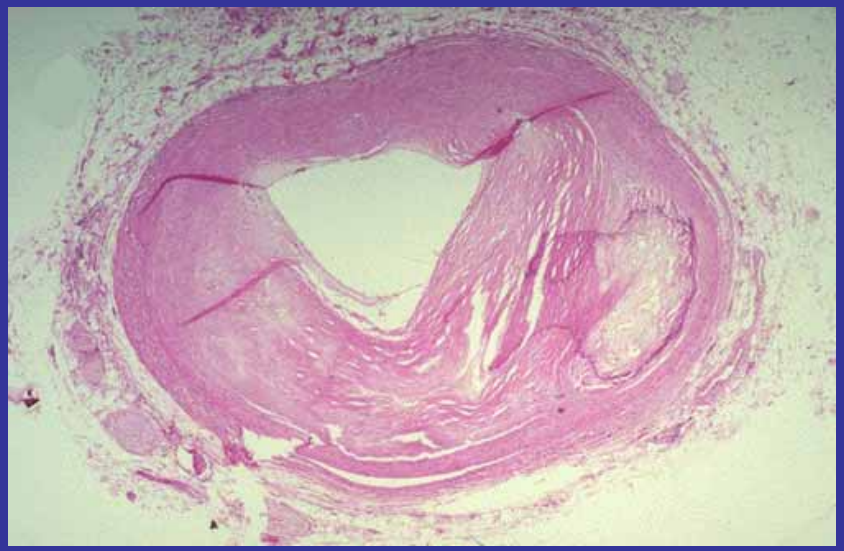


Variazione percentuale della mortalità aggiustata per l'età in U.S.A.



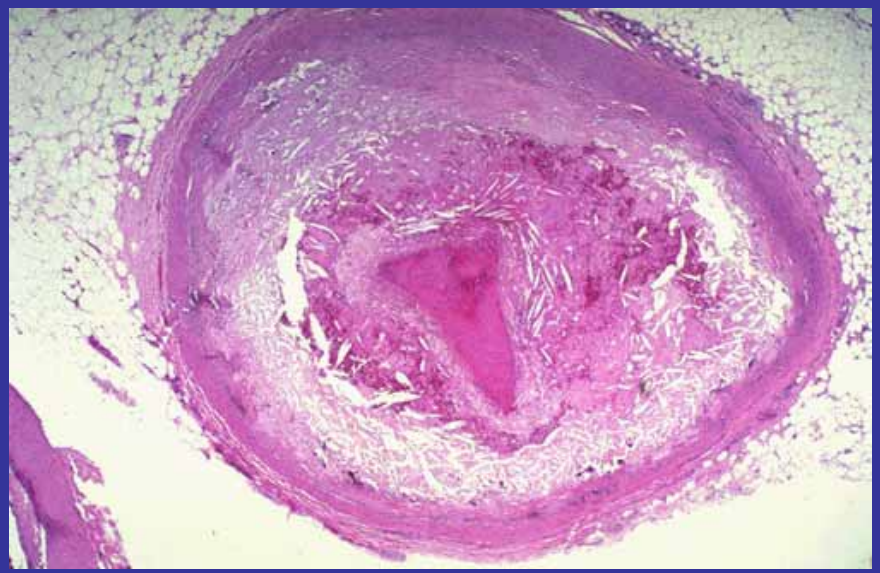
But also in Cardiovascular diseases:

inflammation is crucial not only for plaque development
but also for destabilization of the plaque thus converting a chronic vascular disease into a thrombo-embolic disorder

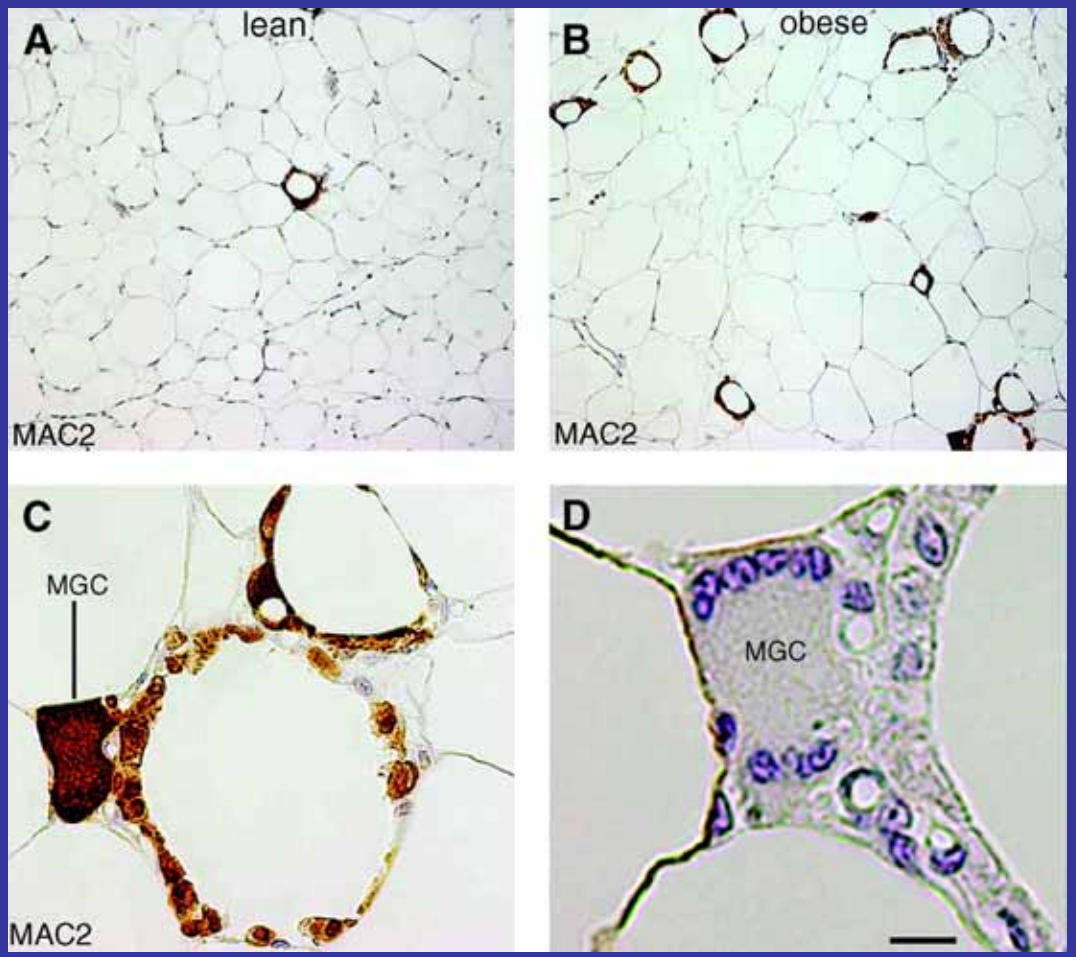


Coronary atherosclerosis-non obstructive

Coronary atherosclerosis-recent thrombus



Inflammation is a key disease factor in obesity or metabolic diseases, probably due to the accumulation of visceral fat tissue



Visceral fat in infiltrated with monocyte-like inflammatory cells

Cinti, S. et al. J. Lipid Res. 2005;46:2347-2355

Inflammation as a concurrent/causative factor in age-related deterioration (microcirculation insufficiency, muscle waste, cognitive impairment), Alzheimer

“inflammageing”

Inflammation and cancer: back to Virchow

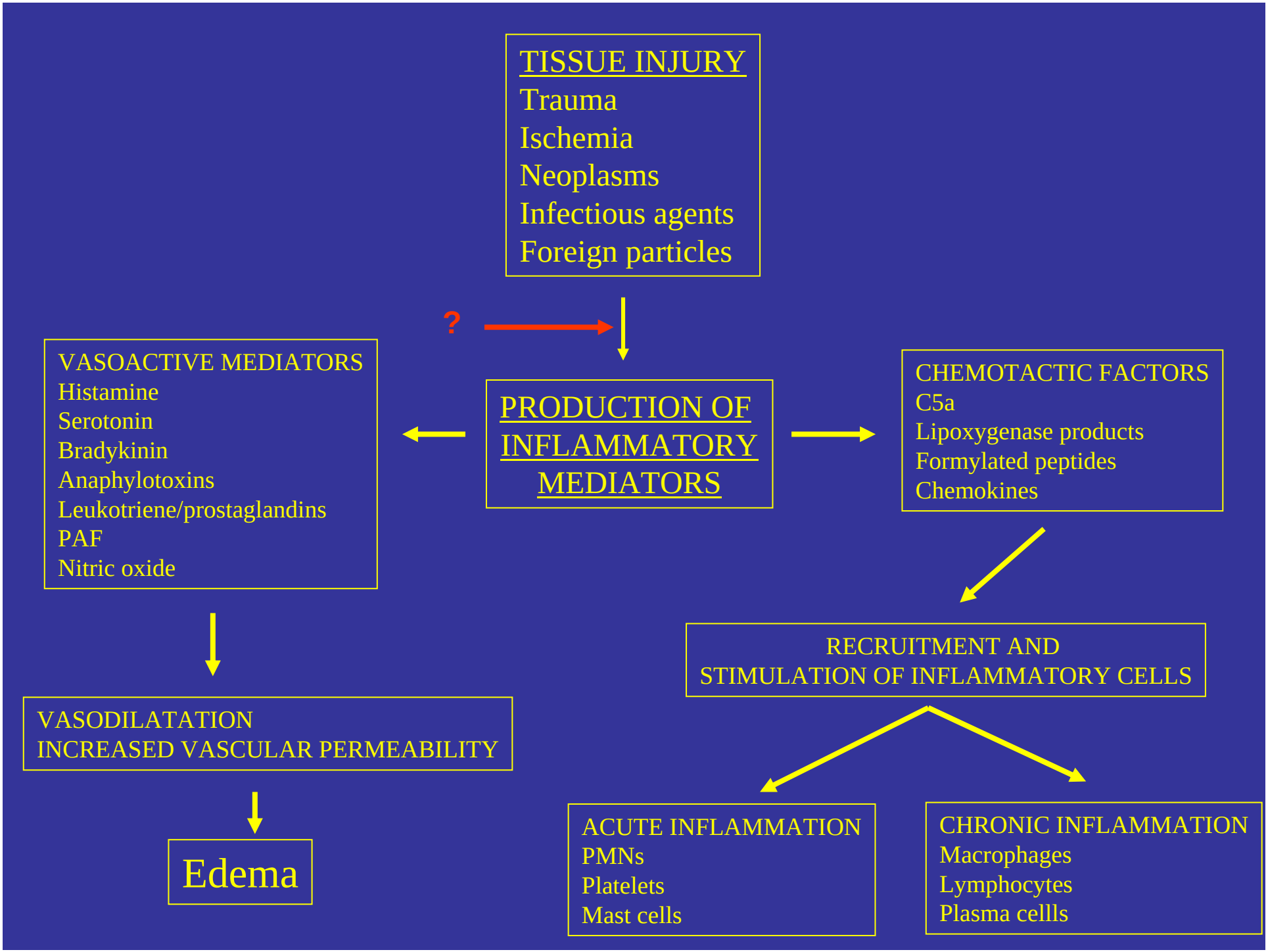
What is inflammation?

A homeostatic, monotonous, body response elicited by any noxious agent.

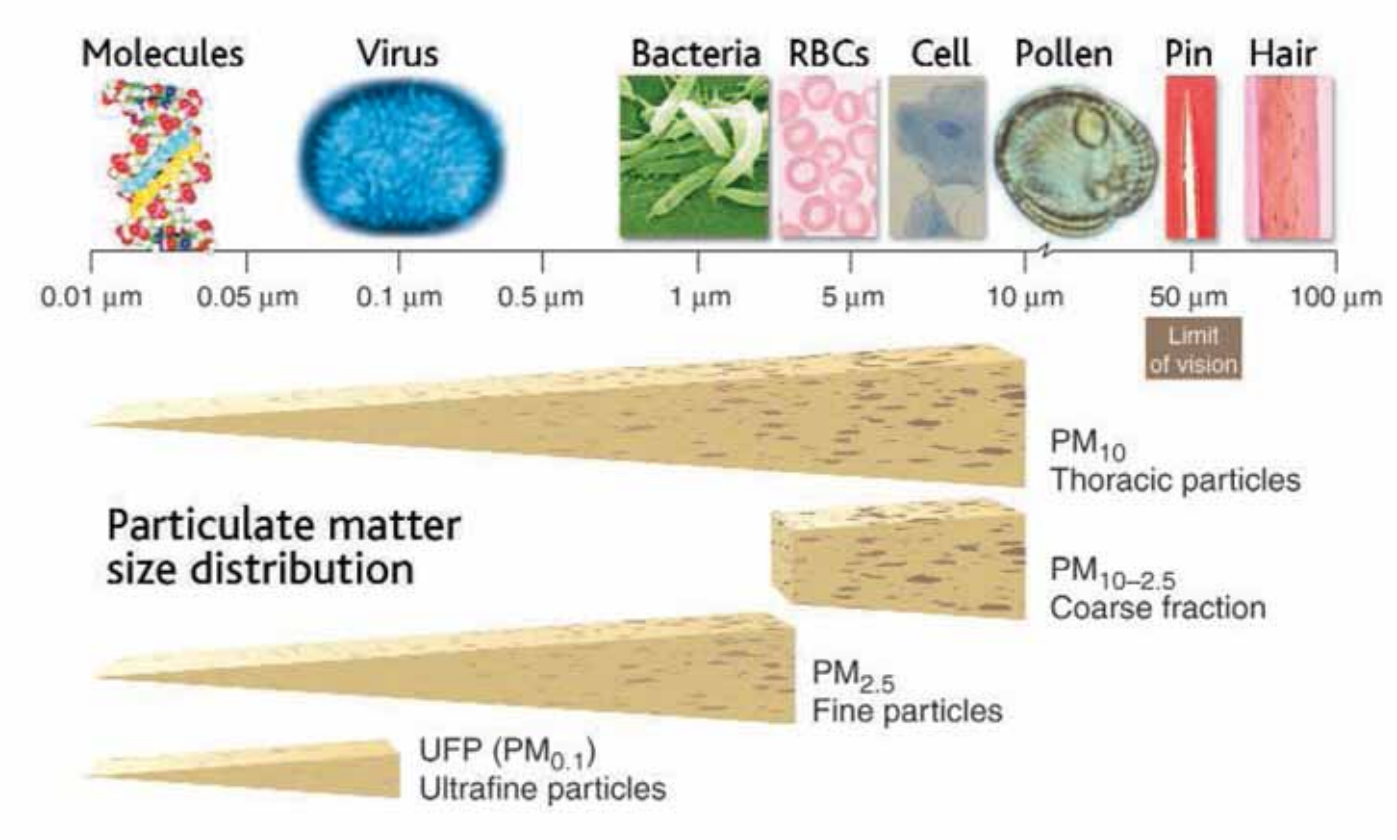
In principle is a protective mechanism, but very often it goes too far.

“Notae vero inflammationis sunt quatuor: rubor et tumor cum calore et dolore”

Cornelio Celso


TISSUE INJURY
Trauma
Ischemia
Neoplasms
Infectious agents
Foreign particles
?
PRODUCTION OF INFLAMMATORY MEDIATORS
VASOACTIVE MEDIATORS
Histamine
Serotonin
Bradykinin
Anaphylotoxins
Leukotriene/prostaglandins
PAF
Nitric oxide
CHEMOTACTIC FACTORS
C5a
Lipoxygenase products
Formylated peptides
Chemokines
VASODILATATION
INCREASED VASCULAR PERMEABILITY
Edema
RECRUITMENT AND
STIMULATION OF INFLAMMATORY CELLS
ACUTE INFLAMMATION
PMNs
Platelets
Mast cells
CHRONIC INFLAMMATION
Macrophages
Lymphocytes
Plasma cellls

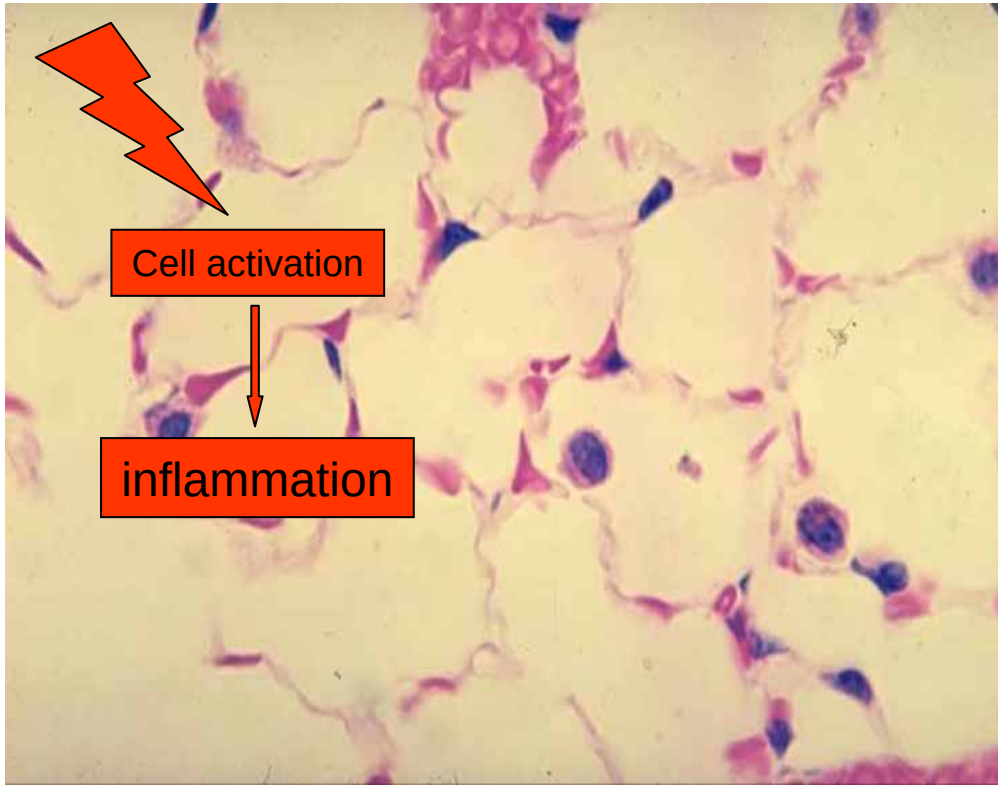
Particulate Matter



UFPs hurt the lung as well as the heart

HOW?

- Type I Pneumocytes (Epithelial cells)
- Type II Pneumocytes (Surfactant cells)
  - secrete surfactant
  - BIG, at corners of alveoli
- Macrophages
  - within the alveolar space (alveolar macrophages)

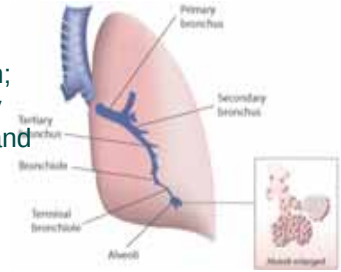


Alveolar macrophages and type II pneumocytes release ROS, RNS and inflammatory cytokines

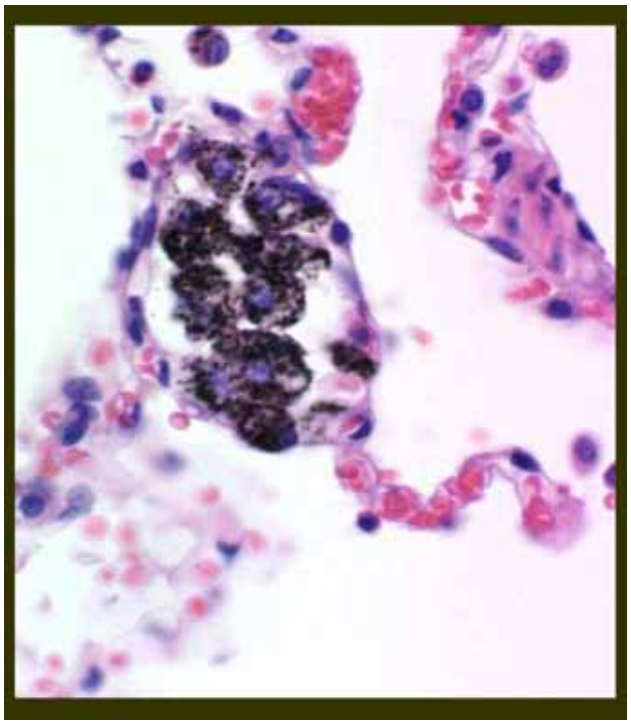
Reactive oxygen and nitrogen species

Mainly local effects

airway irritation; cough; phlegm; decreased lung function; airway inflammation; asthma attacks; and chronic bronchitis



Protein kinase activation
Transcription factor activation

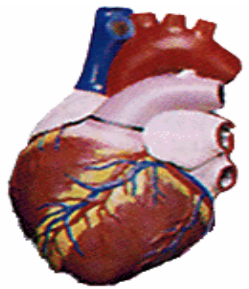


Cytokine and Chemokine release

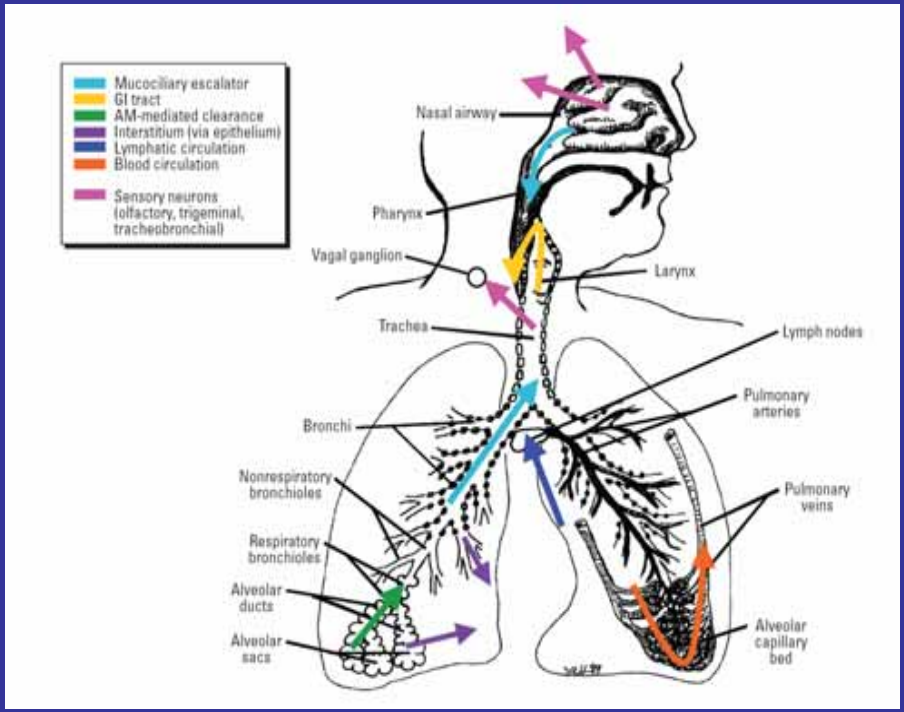
Interleukin-1β
Interleukin-6
Interleukin-8
TNFα

Local and distal effects

Arrhythmias and changes in heart rate. Increased risk of thrombosis and ischemic heart disease

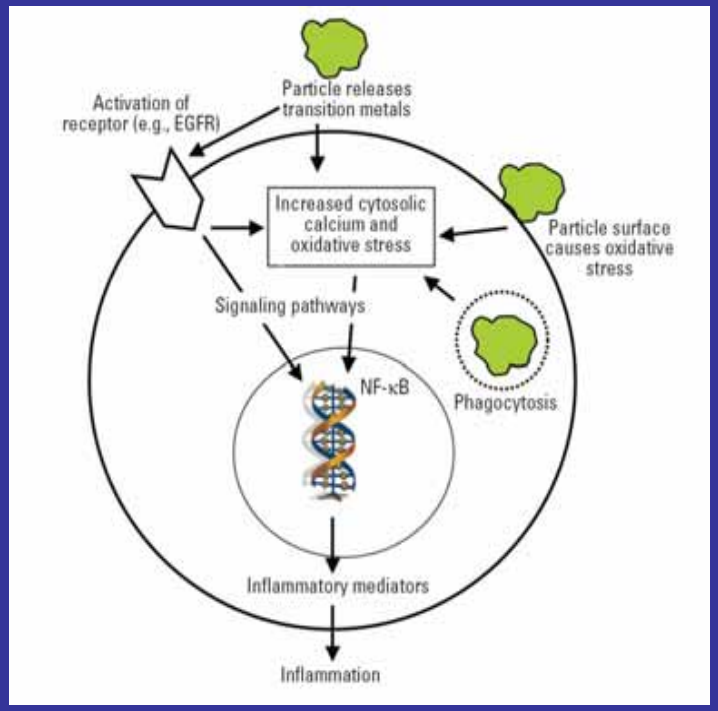


Particle clearance



From Oberdoster et al., 2005

Particle effect



From Oberdoster et al., 2005

The Monty Python Flying Circus: and now for something completely different/and now more of the same

How do NSPs trigger inflammation?

Complement activation

Increased ICAM-1 and EGFR-ligand (amphiregulin) expression

Increased sensitivity to antigen mediated by local production of IL-5 and eotaxin

ROS/RNS

Aggregate formation, induction of granulomas

PMN recruitment

Pro-coagulant activity

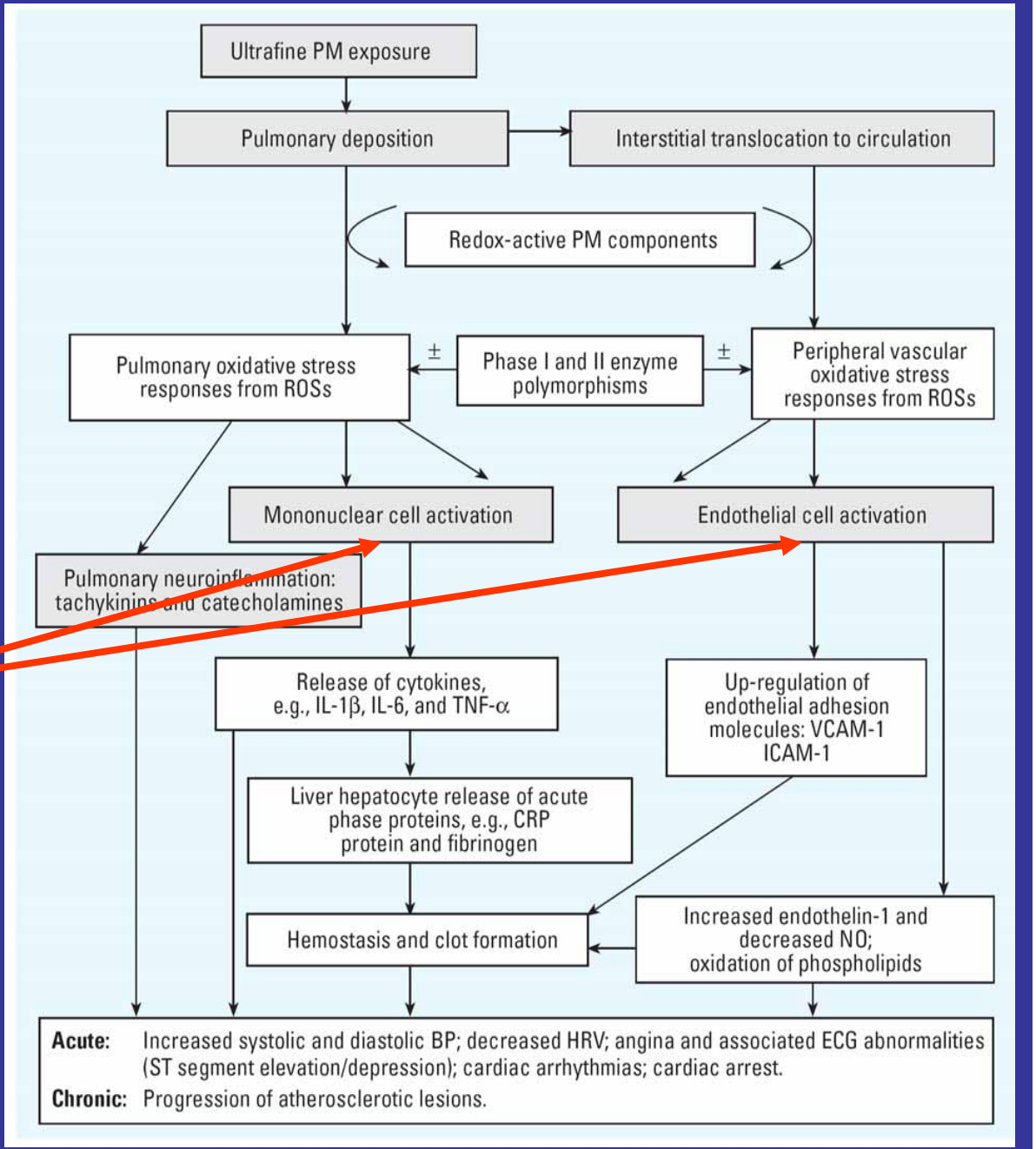
Stimulation of release of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF….)

?????????????

HOW?

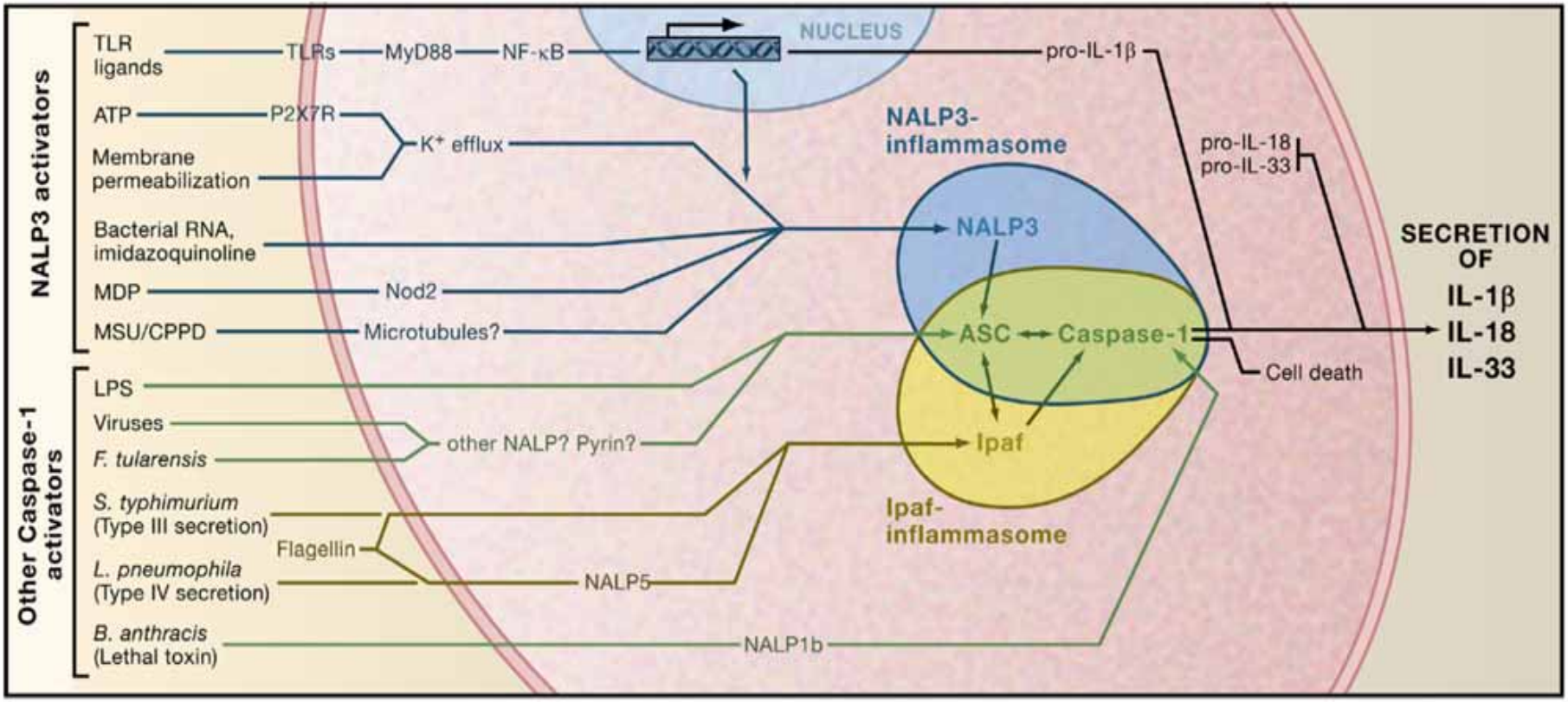
Mononuclear cell activation

Endothelial cell activation



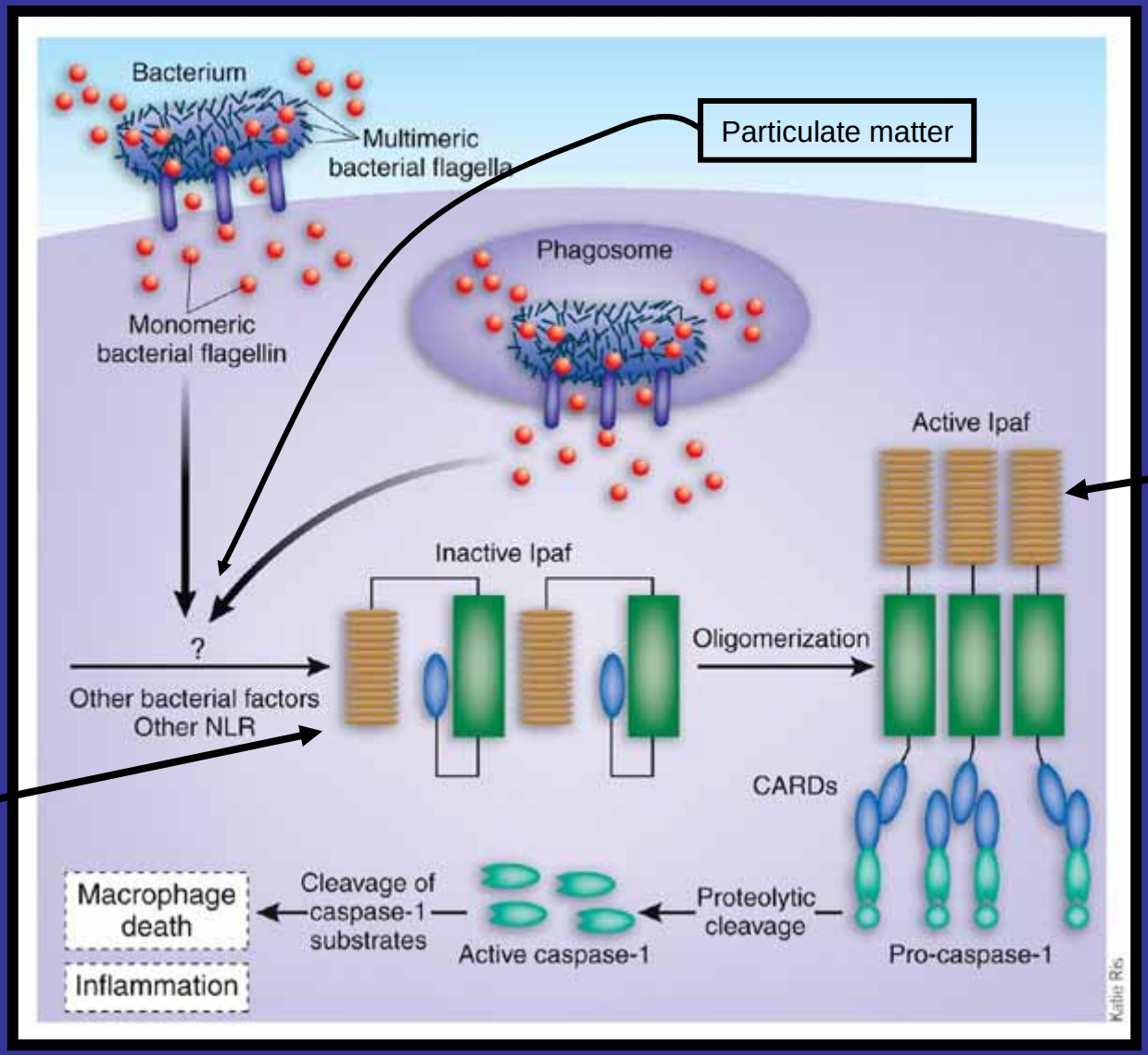
Modified from Delfino et al., 2005

The inflammasome: first line of defense to cell stress



Ogura et al., 2006, Cell 126:659-662

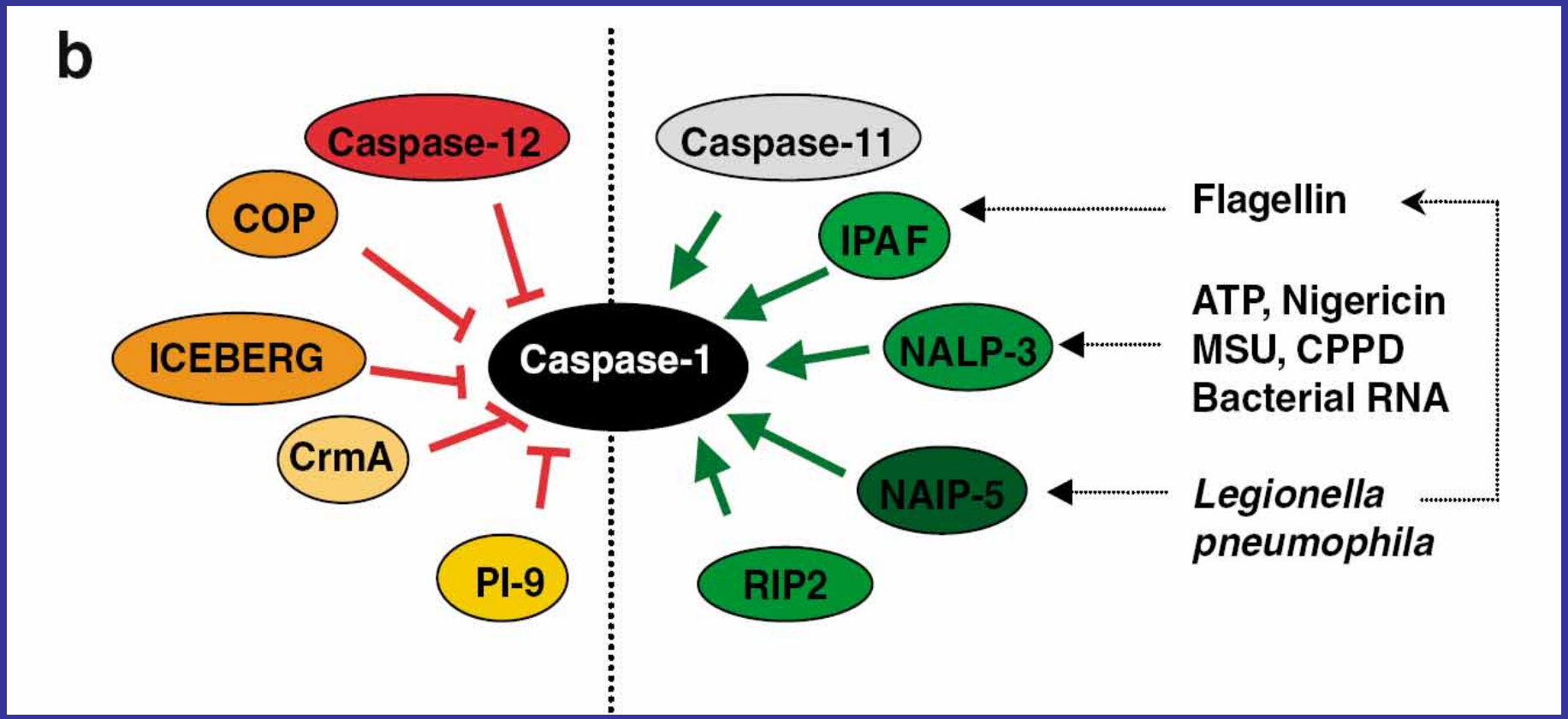
Pathogen detection by the IPAF Inflammasome



Leucin Rich Repeat (LRR): -L-X-X-L-X-L-

Modified from Roy and Zamboni, 2006, Nat Immunol 7:549-551

NLR make the inflammasome sensitive to danger signals



Cytoplasmic sensors of danger
or
cellular transducers of noxious signals

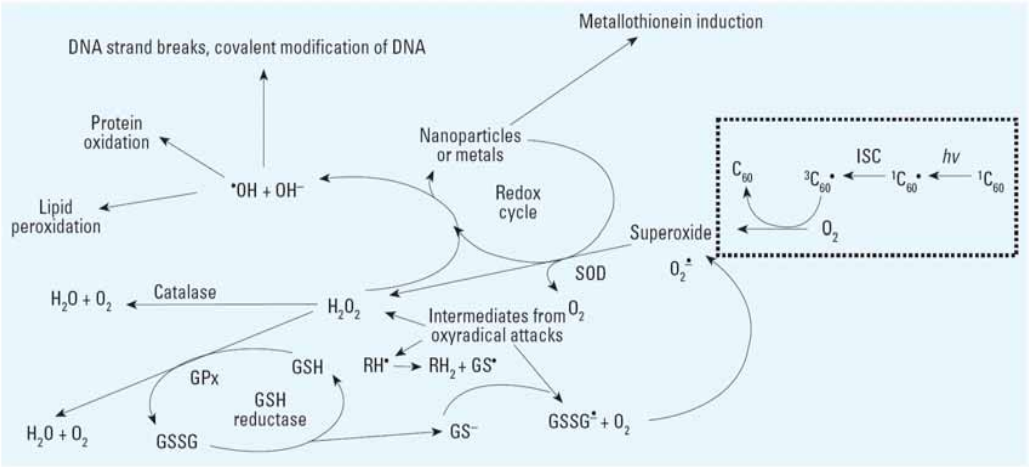
From Scott and Saleh, 2006, Cell Death Diff, in press

Take-home message/morale della favola

- Small is not always beautiful
- We have been exposed to very small particulate matterfor hundred thousands of years and we have learned to detect (cellular sensors) and (possibly) fight them
- Inflammation is our key defense mechanism
- However, sometimes it may go awry
- Thus, it would be helpful for human health to understand what goes wrong

However

“Prevenire è meglio che curare”



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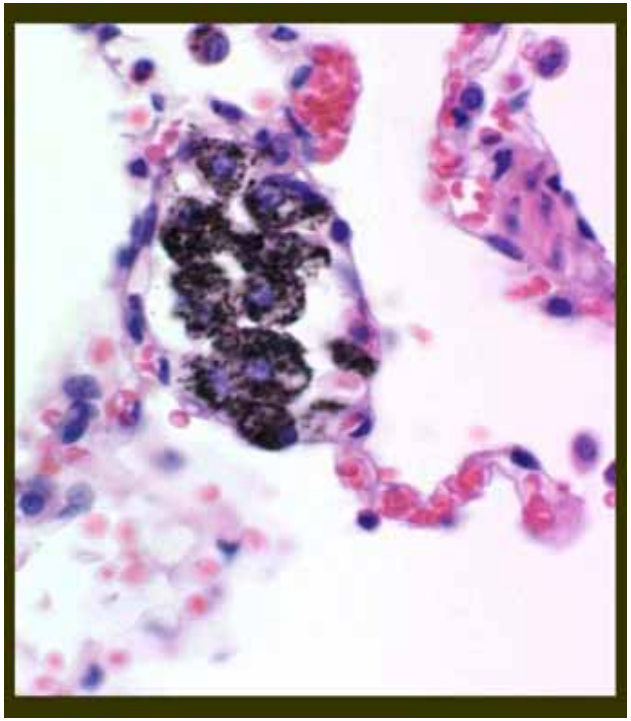

Cytokine and Chemokine release

Interleukin-1β
Interleukin-6
Interleukin-8
TNFα

Local and distal effects

Inflammation is becoming an increasing concern for physicians (and patients!)

Why?

Cytoplasmic sensors of danger
or
cellular trasnducers of noxious signals

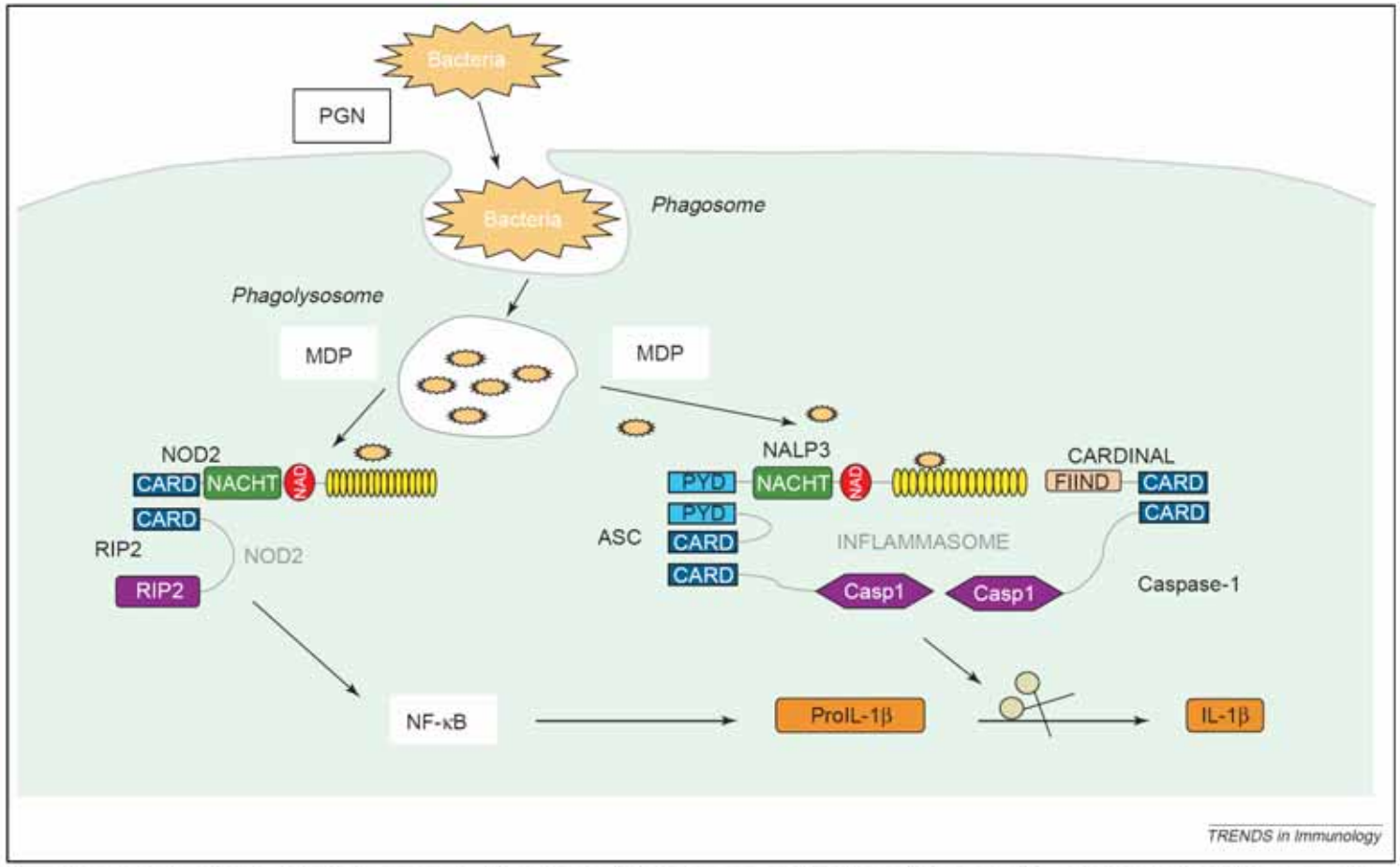

Figure 3. Model for the activation of the inflammasome by PGN. When bacteria are phagocytosed, PGN present in the bacterial wall is degraded to produce muropeptides, which are similar to MDP. Subsequent translocation of MDP into the cytoplasm (by an enigmatic mechanism) leads to the direct or indirect activation of NOD2, which results in NOD2–RIP2 complex formation. The resulting RIP2 activation leads to NF-κB activation and proIL-1β synthesis. Release of MDP also triggers NALP3 (Cryopyrin) activation, which results in the formation of the inflammasome complex (NALP3, cardinal, ASC and caspase-1). Caspase-1 activation then induces cleavage and maturation of IL-1β. Abbreviations: FIIND, function to find; NAD, NACHT-associated domain.