Inflammation contributes to diseases

Clinically denoted by the suffix itis.

Suffix that denotes inflammation of an organ (dermatitis; arthritis; colitis; bronchitis; gastritis; neuritis, ...).

Inflammation contributes to diseases

www.Times.com

Definition:

• Inflammation is the body’s 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

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

Hallmarks of acute Inflammation

Causes of inflammation:

Tissue Death (Necrosis)

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

Microorganisms

Causes of inflammation:
Cells that initiate inflammation:

- Tissue resident Macrophages
- Tissue resident Mast cells

Cytokines
Leukotrienes
Prostaglandines
ROS / NO
Platelet activating factors
Histamine
Serotonin
Lysosomal enzymes

Vascular and cellular effects

- Vasodilatation
  Histamine, prostaglandines, NO...
- Increased vascular permeability
  Histamine, ROS, leukotrienes, platelet activating factors
- Chemotaxis
  Chemokines, cytokines, leukotrienes

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, peptidoglycans, nucleic acids...
- Danger associated molecular patterns (DAMPs)
  ATP, uric acid, HMGB1, IL-1β...

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 (ALRs)

Mechanisms of innate immunity

Pathogen

DAMPs

Innate immune sensors

TLRs, NLRs, RLRs...

Effector signaling

Inflammation, immune response
Microbial world

Detection System

Systems for the sensing of Microbes

Patterns Recognized

Receptors

Response

Symbiotic Response (commensal)

Immune Response (pathogen)

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

Nod-like receptors (NLRs): Associated Diseases

Molecular definition of the Inflammasomes
Inflammasomes primisation

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

NFR-induced peritonitis
ASC specks
AIM2 is required

Visualization of the inflammasome

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

Quantification of ASC specks using ImageStream

Interleukin-1 (IL-1β)

IL-1β Production

The TLR and Inflammasome systems
Inflammasomes as guardians of cellular integrity

What are the cell-intrinsic pathway of inflammasome activation?

How is innate immunity affected by cellular perturbations?

Activation of NLR Inflammasomes

Activation of PYHIN Inflammasomes

Inflammasomes in Diseases

NLRP3 (CIAS1; cryopyrin) and autoinflammatory diseases

Susceptibility locus
- 1q44

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

NLRP3 (NALP3; CIAS1; cryopyrin) and CAPS
Hereditary autoinflammatory diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene Mutation</th>
<th>Phenotype</th>
<th>Symptoms</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
<td>NOD2</td>
<td>Pernicious</td>
<td>Arthritis</td>
<td>Abdominal pain</td>
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<tr>
<td>Pyogenic liver abscess</td>
<td>IL-1B</td>
<td>Pyogenic</td>
<td>Fever</td>
<td>Systemic symptoms</td>
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<td>Primary hyperparathyroidism</td>
<td>CASP1</td>
<td>Hypercalc</td>
<td>Bone pain</td>
<td>Renal stones</td>
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<td>Familial Mediterranean Fever</td>
<td>MEFV</td>
<td>Mediterranean</td>
<td>Fever</td>
<td>Acute attacks of inflammation</td>
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<tr>
<td>Enzymatic deficiencies</td>
<td>NALP3</td>
<td>Pyomyositis</td>
<td>Fever</td>
<td>Musculoskeletal pain</td>
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<tr>
<td>Familial cold urticaria</td>
<td>TNFA</td>
<td>Cold urticaria</td>
<td>Fever</td>
<td>Urticaria</td>
</tr>
</tbody>
</table>

NALP3 mutation lead to increased IL-1 secretion

Treatment of patients with IL1ra (Anakinra)

Inflammatory cascades:

Uric acid crystals (MSU)....

...the etiologic agent of gout

Does MSU activates the NALP3 inflammasome?

**MSU activation of IL-1β is ASC dependent**

**MSU activation of IL-1β is NALP3 dependent**

Inflammasome dependent MSU inflammation in vivo

Gout

Autoinflammatory and chronic inflammatory diseases
**Use of IL-1 inhibitors in Gout patients**

Prof. Alexander So

**Table 4.** Use of IL-1 inhibitors in Gout patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Nausea</th>
<th>Chills</th>
<th>Diarrhea</th>
<th>Erythema</th>
<th>Rash</th>
<th>Generalized malaise</th>
<th>Sanction with fever</th>
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<td>Yes</td>
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</tr>
</tbody>
</table>

**Inflammasome inhibitors**

- Adenosine/Alo 2
- NALP3
- IL-1ra

**IL-1β (Anakinra)**

-Inflammation, periodic fevers, Gout...

**Activators of the NLRP3 Inflammasome**

<table>
<thead>
<tr>
<th>PAMPS</th>
<th>DAMPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial cell wall component (Peptidoglycans)</td>
<td>Hypotonic stress</td>
</tr>
<tr>
<td>RNA</td>
<td>ATP</td>
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<tr>
<td>Adenoviruses</td>
<td>P2X7</td>
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<tr>
<td>Poxviruses</td>
<td>UVC</td>
</tr>
<tr>
<td>Flagellin</td>
<td>Adeninar</td>
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<tr>
<td>Bacterial cell wall component (Peptidoglycans)</td>
<td>Alum</td>
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<tr>
<td>DNA</td>
<td>Silica</td>
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<tr>
<td>Adenoviruses</td>
<td>Cholesterol crystals</td>
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<tr>
<td>Poxviruses</td>
<td>Nanoparticles</td>
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<tr>
<td>Flagellin</td>
<td>Amyloid beta</td>
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<tr>
<td>Bacterial cell wall component (Peptidoglycans)</td>
<td>UVB</td>
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</tbody>
</table>

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

Mature atherosclerotic lesions contain macroscopic deposits of the 'deadly crystals in the necrotic core, but their appearance late in atherogenesis had been thought to disqualify them as primary inflammatory 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**

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

François-Christiaen**1,2,4,5, Lionel Aparisi**1,2,4,5, Kathleen Terwstra**1,2,4,5, Laurent Aymeric**1,2,4,5, Thibault Dehousse**1,2,4,5, Emmanuelle Filletti**1,2,4,5, Elsa Peretti**1,2,4,5, Jean-Canard Fiaschi**1,2,4,5, Renée Courbon**1,2,4,5, Florence Fabre**1,2,4,5, Marie Bouwens**1,2,4,5, Xavier Seoane**1,2,4,5, Marie-Catherine Fouque**1,2,4,5, Pierre Comb**1,2,4,5, Anne Chateau**1,2,4,5, Bertrand Thony**1,2,4,5, Xavier Pernin**1,2,4,5, Nicolas M. Lagadic**5, Nicole M. Harvey**5, Mark I. Smyth**5, Gisèle Kornbluth**1,2,4,5, Lionel Zitvogel**1,2,4,5

The therapeutic efficacy of antitumor chemotherapies may depend on dendritic cells (DCs), which present antigens from dying cancer cells to prime tumor-specific T lymphocytes. We identified a pathway. Here we show that dying tumor cells release ATP, which acts as an NALP3 inflammasome activator. Antitumoral DCs may prime T cells in the absence of non-tumor-specific T cells.

**NLRP6 Inflammasome Regulates Colonic Microbial Ecology and Risk for Colitis**


NLRP6 inflammasome lesions contain macroscopic deposits of dead crystals in the necrotic core but their appearance late in atherogenesis had been thought to disqualify them as primary inflammatory 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.
Bacteria/Inflammasome interaction

Table 1. The good, inflammasome control of pathogen infections.

<table>
<thead>
<tr>
<th>Organism</th>
<th>NLRP1 identifies</th>
<th>Inflammation required in vivo</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>Salmonella enterica</td>
<td>Yes</td>
<td>Yes</td>
<td>Role</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Yes</td>
<td>Yes</td>
<td>Role</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Yes</td>
<td>Yes</td>
<td>Role</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>Yes</td>
<td>Yes</td>
<td>Role</td>
</tr>
<tr>
<td>Inflammasome regulators</td>
<td>Yes</td>
<td>Yes</td>
<td>Role</td>
</tr>
</tbody>
</table>

Inflammasome regulation