Les biomarqueurs sériques de l’inflammation en 2017: dans la pratique ?

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Institut Central des Hôpitaux
Hôpital du Valais, Sion

Berne, le 22 aout 2017
From rubor, calor dolor to
(VIERGE AU CHANOINE, J. VAN EYCK, 1435)
GIANTOCELLULAR ARTERITIS - GCA
1. **Systemic Inflammatory Response, fevers and Acute phase response**
2. **CRP versus ESR: non-sense debate?**
3. **Use combined with clinical score**
   1. Examples: Gigantocellular Arteritis (GCA, Horton) and rheumatoid arthritis
4. **Procalcitonin (PCT) and bacteremia in emergency and intensive care units:**
   1. What is missing for personalized targeted therapy?
5. **Auto-inflammatory diseases and Inflammasomes:**
   1. More frequent than expected by the rare genetic diseases, Gout,
   2. Consequences: AA amyloidosis, but therapeutic options
6. **Unregulated cytokine storm:**
   1. Ferritin and macrophage activation syndrome (MAS)
7. **Low-grade inflammation (hsCR) and CV risk**
8. **Time to redefine inflammation:**
   - As innate immune response to insults to restablish homeostasis

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**Large scope of inflammation**

**Exemples of what is to me significant**

- Systemic Inflammatory Response, fevers and Acute phase response
- CRP versus ESR: non-sense debate?
- Use combined with clinical score
  1. Examples: Gigantocellular Arteritis (GCA, Horton) and rheumatoid arthritis
- Procalcitonin (PCT) and bacteremia in emergency and intensive care units:
  1. What is missing for personalized targeted therapy?
- Auto-inflammatory diseases and Inflammasomes:
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  1. Ferritin and macrophage activation syndrome (MAS)
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- Time to redefine inflammation:
  - As innate immune response to insults to restablish homeostasis

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**août 17**
SIRS (Systemic Inflammatory Response Syndrome)

• The systemic response to a wide range of stresses.
  - Temperature >38°C
  - Heart rate >90 beats/min.
  - Respiratory rate >20 breaths/min or PaCO₂ <32 mmHg.
  - White blood cells > 12,000 cells/ml or < 4,000 cells/ml or >10% immature (band) forms.

• Note
  - Two or more of the following must be present.
  - These changes should be represent acute alterations from baseline in the absence of other known cause for the abnormalities.

American College of Chest Physicians/Society of Critical Care Medicine Consensus.

Disease groups causing recurrent fevers

- **The big three**
  - Inflammatory, infectious:
    - persistent,
    - undertreated,
    - increased susceptibility
  - Inflammatory, non-infectious
    - Autoimmune
    - Autoinflammatory
  - Mostly inflammatory
    - Malignancies

- **The little three**
  - Mostly non inflammatory:
    - Munchausen,
    - Drug fever,
    - Benign hyperthermia

- **Miscellaneous**
  - Various mechanisms
    - Central fever
    - Dehydratation…

Kallinich T., Allergy 2013, EAACI Position paper
Systemic inflammatory response
Pathophysiological changes in systemic inflammatory response

**Neuroendocrine changes**
- Fever, somnolence, fatigue and anorexia
- Increased adrenal secretion of cortisol, adrenaline and glucagon

**Haematopoietic changes**
- Anaemia
- Leucocytosis
- Thrombocytosis

**Metabolic changes**
- Loss of muscle and negative nitrogen balance
- Increased Lipolysis
- Trace metal sequestration
- Diuresis

**Hepatic changes**
- Increased blood flow
- Increased acute phase protein production

*Gabay and Kushner, NEJM, 1999*
Acute phase response from hepatocytes

Figure 3 APR by IL-6
Complex interplay of cells and stimuli
• **ESR: global evaluation with many pitfalls**
  - Used for its negative predictive value (*no inflammatory syndrome*)
  - Depend of viscosity, cells, Ig and fibrinogen mostly
  - Most often concordant with CRP as screening
  - ESR >100 mm/Hour: infection 40%, endocarditis…
    - Malignant and renal 30%
    - Inflammatory systemic dis. 20%, Thyroid and Horton…

• **CRP: convenient, reactive acute phase protein marker**
  - Mostly produced by hepatocytes in response to IL-6
  - Highest increase in infections,
  - Very dynamic changes >1000 folds increase
  - Monitoring of the inflammatory state (resolution or treatment response)
  - hsCRP: useful to assess baseline CRP; associated with increased vascular risk
  - Low grade inflammation: 3-10 mg/L usually without clinical symptoms
<table>
<thead>
<tr>
<th>Increased ESR</th>
<th>ESR</th>
<th>Decreased ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Heavy Metal Poisoning</td>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Collagen Vascular Disease</td>
<td></td>
<td>Polycythemia</td>
</tr>
<tr>
<td>Carcinomas</td>
<td></td>
<td>Sickle Cell Anemia</td>
</tr>
<tr>
<td>Cell or tissue injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gout arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Factors causing false increases**

- Increased fibrinogen, globulin, cholesterol levels
- High room temperature
- Macrocytic anemia
- Menstruation
- Pregnancy
- Tilting or lying down of the ESR tube
- Drugs: Dextrane, methyldopa, methysergide, penicillamine, procainamide, theophylline, trifluoperidole, vitamin A

**Factors causing false decreases**

- Cachexia
- Coagulation of the blood sample
- Increase in bile salts
- Increase in phospholipids
- **Making the sedimentation sample wait more than two hours**
- Increase in adrenal steroids
- Hypofibrinogenemia
- Hyperglycemia
- Hyperalbuminemia
- Leukocytosis
- Microcytic anemia
- Drugs: ACTH, cortisone, ethambutol, quinine, salicylates

(Adapted from A Textbook of Natural Medicine, Pizzorno and Murray, 1992)
Acute phase proteins and the systemic inflammatory response

4 general stimuli:
1. Injury, trauma
2. Infection (Procalcitonin)
3. Inflammatory diseases (autoimmunity and autoinflammatory)
4. Many cancer

Gabay and Kushner, 1999
C-reactive protein in patients undergoing curative surgery for colorectal cancer

Crozier et al., 2004
### Assays of inflammatory markers and clinical use

<table>
<thead>
<tr>
<th>Marker</th>
<th>Stability</th>
<th>Assay availability</th>
<th>Standard available</th>
<th>Interassay variability</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>Unstable</td>
<td>everywhere</td>
<td>yes</td>
<td>10%-15%</td>
<td>low</td>
</tr>
<tr>
<td>hsCRP</td>
<td>Stable</td>
<td>everywhere</td>
<td>yes</td>
<td>&lt;10%</td>
<td>low</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>Stable</td>
<td>everywhere</td>
<td>yes</td>
<td>&lt;15%</td>
<td>high</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Stable</td>
<td>everywhere</td>
<td>yes</td>
<td>&lt;10%</td>
<td>low</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Stable</td>
<td>everywhere</td>
<td>yes</td>
<td>&lt;10%</td>
<td>medium</td>
</tr>
<tr>
<td>Serum amyloïd A</td>
<td>Stable</td>
<td>few</td>
<td>yes</td>
<td>&lt;10%</td>
<td>medium</td>
</tr>
<tr>
<td>Cytokines (IL-6, IL1RA, TNF)</td>
<td>Unstable except</td>
<td>few</td>
<td>yes</td>
<td>&lt;20%</td>
<td>high</td>
</tr>
</tbody>
</table>

*Assays of inflammatory markers and clinical use, Dayer, Nature clinical rheumatology practice, 2007*
Investigation of inflammatory syndromes
A daily clinical question for physicians
**Indication**

- Female 65 y, Febrile with inflammatory syndrom, **CRP: 122 mg/L** without clear clinical localisation.
- Nuccal headache irradiating in the temporal regions of the head
- Left carotid artery examination normal. Painful cervical spine mobilisation
- Differential diagnosis: **GCA (Horton), spondylodiscitis**?

**Investigations**

- Carotid and Temporal Doppler was normal, **NO halo sign**
- Uniteral temporal **biopsy was negative**

**CT scan conclusion**

- No carotid dissection found.
- **Circonferential peri-aortic hypodensity** of the aorta ascending, as well as thoracic, abdominal aorta, suggestive of large vessel vasculitis
PET computerized tomography was performed
CRITERIA ACR: Giganto-cellular Arteritis (GCA) Horton

1. Beginning of symptoms ≥50 years
2. New headache
3. Temporal arteritis anomaly (pain or no pulse)
4. High ESR(≥50 mm/H) or CRP > 50 mg/L
5. Temporal artery inflammation at the biopsy
   - monocellular inflammation or
   - granulomatosus inflammation, often with multinucleate giant cells

If >3 criteria = Sensitivity 93.5% and specificity 91.2%,
Giganto-cellular arteritis: « classical » Horton + large vessel vasculitis

If typical symptoms: headache, temporal artery modifications, TA biopsy +

-> classical diagnosis (ACR)

BUT isolated aortic or large vessel inflammation are often expressed only by inflammatory markers and no classical signs (> 50% of GCA have aortic involvement)

-> Need of radiologic evaluation (PET-CT / angioIRM)
Biomarkers in the management of Giant-Cell Arteritis and Polymyalgia Rheumatica.

A  Giant-Cell Arteritis

**Induction Therapy**
- Prednisone, 1 mg/kg/day
- Goal: resolution of laboratory and clinical abnormalities
- Course: generally 2–4 wk
- Begin bone-protective therapy
- Consider aspirin
- Consider gastroduodenal protection

**Maintenance Therapy**
- Taper prednisone by 10–20%/mo
- Monitor clinically
- Monitor acute-phase reactants (ESR and CRP)
- When dose <10 mg/day, taper by 1 mg/mo

**Management of Flares**
- Severe flare: repeat prednisone induction therapy
- Mild flare: increase prednisone by 10–20%
- Be cautious in treating elevated ESR or CRP level in absence of clinical symptoms
  - Glucocorticoid-sparing agents: methotrexate, marginal benefit; infliximab, no benefit; dapsone, adalimumab, leflunomide, hydroxychloroquine, tocilizumab, azathioprine, anecdotal use

B  Polymyalgia Rheumatica

**Induction Therapy**
- Prednisone, 15–20 mg/day
- Goal: remission of myalgias, stiffness, constitutional symptoms
- Course: generally 1–2 mo
- Consider bone-protective therapy

**Maintenance Therapy**
- Taper prednisone by 20%/mo
- Monitor clinically
- Monitor acute-phase reactants (ESR and CRP)
- When dose reaches 10 mg/day, taper slowly

**Management of Flares**
- Reassess diagnosis, rule out vasculitis, consider temporal-artery biopsy, and consider large-vessel imaging
- Increase prednisone by 10–20%
- Reattempt taper
- Glucocorticoid-sparing agents: methotrexate marginally effective
Disease activity score in rheumatoid arthritis

3 levels

HDA: high disease activity
LDA: low disease activity
Remission

Essential to define treat to target

DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable.

Fleischmann RMD Open 2017
## Acute phase proteins during infection

<table>
<thead>
<tr>
<th>Protein</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>Stimulated by both viral and bacterial infections, but reaches higher values during bacterial infections [44, 77, 78]</td>
</tr>
<tr>
<td>SAA</td>
<td>Elevated in viral infections [47, 56]</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>Decreased during infections [79]</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Not significantly different between neonates with and without an infection [80]</td>
</tr>
<tr>
<td>Retinol</td>
<td></td>
</tr>
<tr>
<td>Haptoglobin</td>
<td></td>
</tr>
<tr>
<td>α1-antitrypsin</td>
<td></td>
</tr>
<tr>
<td>LPS binding protein</td>
<td>Elevated in bacterial infections as compared to viral infections [68]</td>
</tr>
<tr>
<td>sTREM-1</td>
<td></td>
</tr>
<tr>
<td>Neutrophil lipocalin</td>
<td>More elevated in bacterial infections as compared to viral infections [81]</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; SAA: serum amyloid A; sTREM-1: soluble triggering receptor expressed on myeloid cells-1.
Table 1. Diagnostic Criteria for Sepsis, Severe Sepsis, and Septic Shock.*

**Sepsis (documented or suspected infection plus ≥1 of the following)**

**General variables**
- Fever (core temperature, >38.3°C)
- Hypothermia (core temperature, <36°C)
- Elevated heart rate (>90 beats per min or >2 SD above the upper limit of the normal range for age)
- Tachypnea
- Altered mental status
- Substantial edema or positive fluid balance (>20 ml/kg of body weight over a 24-hr period)
- Hyperglycemia (plasma glucose, >120 mg/dl [6.7 mmol/liter]) in the absence of diabetes

**Inflammatory variables**
- Leukocytosis (white-cell count, >12,000/mm³)
- Leukopenia (white-cell count, <4000/mm³)
- Normal white-cell count with >10% immature forms
- Elevated plasma C-reactive protein (>2 SD above the upper limit of the normal range)
- **Elevated plasma procalcitonin (>2 SD above the upper limit of the normal range)**

**Hemodynamic variables**
- Arterial hypotension (systolic pressure, <90 mm Hg; mean arterial pressure, <70 mm Hg; or decrease in systolic pressure of >40 mm Hg in adults or to >2 SD below the lower limit of the normal range for age)
- Elevated mixed venous oxygen saturation (>70%)
- Elevated cardiac index (>3.5 liters/min/square meter of body-surface area)

**Tissue-perfusion variables**
- Hyperlactatemia (lactate, >1 mmol/liter)
- Decreased capillary refill or mottling

**Severe sepsis (sepsis plus organ dysfunction)**

**Septic shock (sepsis plus either hypotension [refractory to intravenous fluids] or hyperlactatemia)**

*NEJM 2016*
Procalcitonin and bacterial infection

- Normally produced by parafollicular cells in thyroïd
- 100-1000 fold increase in response to endotoxin, produced by most cells.
- Appropriate to improve the diagnosis and followup of bacterial infections in specific settings
- Included in the evaluation of septic shock, predicts mortality in emergency and intensive care units
- Inappropriate to exclude bacterial infection in general practice
- Appropriate to exclude bacterial infection in emergency settings
- Appropriate to limit antibiotic use and follow resolution of infection in ICU
- Price issue to be solved (excessive usage in ICU has to be limited) : high laboratory reagent costs)
Procalcitonin and bacterial infection

- To rule out the presence of bacteraemia

**SUBGROUPS**

- Sensitivity ranging
  - from 66% in immunocompromised/neutropenic patients
  - to 89% in ICU patients
- Specificities ranging
  - from 55% in bacteraemia versus local infections
  - to 78% in immunocompromised/neutropenic patients

- Biomarker guided therapy?

Clin Microbiol Infect 2015; 21: 474–481

The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis

S. H. Hoeboer1, P. J. van der Geest1, D. Nieboer2 and A. B. J. Groeneveld1
**PCT (µg/l)**

**Ongoing infection?**

**Recommendation for Stopping AB**

**Important considerations and overruling criteria**

- **Consider the course of PCT**
- If antibiotics are continued:
  - Daily measurement of PCT; discontinue antibiotics when PCT decreases >80% of the peak level or an absolute PCT value <0.5 ng/ml is reached.
  - If PCT remains high, consider treatment failure.

- **Always consider clinical course of patients in addition to PCT levels.**
- If Antibiotics are discontinued, close clinical evaluation is recommended.
PCT (ng/ml)

- **Very likely:** 10.0
- **Likely:** 5.0
- **Yes:** 2.5
- **Unlikely:** 1.0
- **Very unlikely:** 0.5

Likelihood of bacterial infection

Recommendation for antibiotic treatment

Important considerations and overruling criteria

- Consider the course of PCT (dynamic monitoring)
- If antibiotics are initiated:
  - Repeat PCT on days 3, 5, 7; stop antibiotics using the same cut offs
  - If peak PCT levels are very high, then stop when 80-90% decrease of peak
  - If PCT remains high, consider treatment failure

- If antibiotics are withheld, control PCT after 6-24 hours
- Initial antibiotics can be considered in case of:
  - Respiratory or hemodynamic instability, severest comorbidities, ICU admission
  - PCT < 0.1 ug/L: CAP with PSI V or CURB >3, COPD with GOLD IV
  - PCT < 0.25 ug/L: CAP with PSI IV & V or CURB >2, COPD with GOLD III & IV
Procalcitonin retesting interval and datamining in our institution

Evaluation of the cost of early retesting of PCT

1. 18.2% under 48H set as Minimal Restesting interval (MRI)
2. 80% Due to significant biological variation

It appeared that the transition of PCT from normal to pathological values, at the beginning of the infection, occurred much faster than the inverse transition, when PCT returned to normal values.

USE different MRI in the ascending phase and in the recovery phase to lower the cost

Depending of this algorithm, reevaluation of non-conformity is done and the % of non-conformity pass from 18.2% to 11.9%:

- Initial PCT [μg/L]:
  - ≤ 0.25: MRI 6 h
  - > 0.25: MRI 48 h

Effort must be done for after initiation of antibiotics treatment when PCT is recheck.

MRI = Δt_min
Auto-inflammatory diseases and Inflammasomes:
1. More frequent than expected by the genetic diseases,
2. Exemple: Familial Mediterranean Fever
3. Consequences: AA amyloidosis, but therapeutic option
   - Knowledge from genetic disease such as periodic fevers
   - Inflammation occurring without pathogens or trauma
   - Recurrent state with spontaneous resolution in variable duration
   - Exemple: FMF = Familial Mediterranean Fever

**Table: Major criteria**

<table>
<thead>
<tr>
<th>Typical attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Peritonitis (generalized)</td>
</tr>
<tr>
<td>2. Pleuritic (unilateral) or pericarditis</td>
</tr>
<tr>
<td>3. Monoarthritis (hip, knee, ankle)</td>
</tr>
<tr>
<td>4. Fever alone</td>
</tr>
<tr>
<td>5. Favorable response to colchicine</td>
</tr>
</tbody>
</table>

**typical acute attack** =
More than 3 febriles identical episodes
And central 38°C
Duration: between 12 H et 3 D

And 1 criterium associated
FMF: Se 57% Sp 99%
## Autoinflammation: pathology of the innate immunity

<table>
<thead>
<tr>
<th>Autoinflammation</th>
<th>Autoimmunity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INNATE</strong></td>
<td><strong>Immune dysregulation</strong></td>
</tr>
<tr>
<td>Monocytes, macrophages, neutrophils</td>
<td><strong>Predominant cells</strong></td>
</tr>
<tr>
<td>IL-1, TNF, IL-12(IL-17), IL-18</td>
<td><strong>Cytokines target used</strong></td>
</tr>
<tr>
<td>Neutrophil and macrophage organ damage</td>
<td><strong>Pathogenesis of organ damage</strong></td>
</tr>
<tr>
<td>IL-1 mediated autoinflammatory dis.</td>
<td><strong>Diseases examples</strong></td>
</tr>
</tbody>
</table>

**Autoantibody, Ag specific T cells**

**Thyroiditis, RA, SLE, ALPS**
Pathogen? How are they recognized?

Receptors: -called: pattern recognition recepteurs = PRR

Ligands:
- **PAMPS**: pathogen associated molecular patterns
- conserved structures, essential to microbes,
- absent in mammals
- **LPS, RNA ds, flagellin, oxydative stress**, 
- **DAMPS**: danger associated molecular patterns
  ATP...
Physiopathology of FMF: Inflammasome

FMF

pathogènes

NLRP3

Pro-IL-1β

CASP-1

Active IL-1β

inflammation

AIM: absent in melanoma; BIRs: baculovirus IAP-repeats; CARD: caspase recruitment domain; CASP: caspase; LRRs: leucin-rich repeats; NACHT: nucleotide binding/oligomerization domain; NAIP: NLR family, apoptosis inhibitory protein; NLRP: nucleotide-binding domain, leucine-rich repeat-containing receptor protein; PYD: pyrin domain

Adapté de Swiss Med Wkly. 2012;142:w13590
Fig. 2 The pyrin inflammasome. At steady state, the phosphorylation of pyrin on serine residues S208 and S242 by the kinases PKN1/2 results in the interaction of pyrin with 14-3-3 protein, a chaperone which sequesters pyrin and blocks its ability to form an inflammasome. Decreased geranylgeranyl pyrophosphate (secondary to deficiency in mevalonate kinase, MVK) or addition of toxins A or B from Clostridium difficile or YopE/T from Yersinta pestis inactivate the Rho GTPases, leading to inactivation of the kinases PKN1/2. This inhibition results in the dephosphorylation of pyrin, its release from the 14-3-3 protein, the activation of the pyrin inflammasome and its interaction with microtubules, and the release of IL-1β. MEFV mutations associated with familial Mediterranean fever (red star) decrease the threshold of activation of the pyrin inflammasome. Colchicine inhibits the interaction of the pyrin inflammasome with the cytoskeleton.
Autoinflammatory diseases

Monogenic autoinflammatory diseases

- Cryopyrinopathies
  - FCAS, MWS, NOMID
- IL-1 mediated bone diseases
  - DIRA, Majeed

Classic hereditary fever syndromes

- FMF, TRAPS, HIDS
  - *PAPA
  - *PGA
  - *FCAS2

Autoinflammatory diseases with unknown genetics

- Schnitzler syndrome
- SoJIA/AOSD
- Behcet’s disease
- SAPHO/CRMO
- PFAPA

Metabolic diseases with proposed IL-1 mediated pathology

- Gout/pseudogout
- Type 1/Type 2 DM
- CAD/stroke/heart remodeling
- Metabolic syndrome

*Partial response to IL-1 inhibition suggests involvement of additional cytokine pathways.
Chronic Inflammation

**Pro-inflammatory markers**
- IL-1 beta
- IL-6
- TNF-α

**Anti-inflammatory markers**
- TGF-β
- IL-12
- Inducible IL-35

IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β
Fig. 1. Principaux mécanismes régulateurs de la voie de l’interleukine-1β. Un signal 1, ligand d’un toll-like receptor (TLR), est nécessaire pour pré-activer la voie de l’interleukine (IL)-1β et la transcription des gènes de l’IL-1 et du NOD-like receptor, pyrin domain containing 3 (NLRP3). Des micro-ARN peuvent inhiber par compétition les ARN de ces protéines. Un signal 2, spécifique, est ensuite requis pour activer chacun des récepteurs de l’inflammasome : efflux de potassium (K+), modification de l’AMP cyclique, ATP ou cristaux d’urate monosodique (MSU) pour le récepteur NLRP3 ; ADN double brin (ADNdb) pour le récepteur absent in melanoma 2 (AIM2) ; ou toxine B du C. difficile (TcdB) pour le récepteur pyrine. Diverses protéines peuvent inhiber ces récepteurs : les pyrin-only proteins (POP)1/2 pour les NLR et proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1) pour la pyrine. L’inflammasome activé entraîne l’activation de la caspase-1 et le clivage de la pro-forme de l’IL-1β. La caspase-1 peut être inhibée par les COP (CARD-only proteins). L’autophagie joue un rôle régulateur à différents niveaux : diminution de la quantité de pro-IL-1β disponible, dégradation de la caspase-1 et du complexe inflammasome, sécrétion de l’IL-1β activée via l’auto-phagosome. Une fois sécrétée, l’IL-1β exerce son effet via divers récepteurs, qui peuvent transduire ou inhiber le signal. Enfin, certains récepteurs solubles ou anticorps, endogènes ou synthétiques, ont un rôle inhibiteur sur la voie de l’IL-1β (comme l’IL-1Ra, le récepteur antagoniste du récepteur de l’IL-1).
Spontaneous recovery linked to autophagy.

Zhenyu Zhong, Atsushi Umemura, Elsa Sanchez-Lopez, ..., Maria T. Diaz-Meco, Jorge Moscat, Michael Karin

Correspondence
karinooffice@ucsd.edu

In Brief
NF-κB restraints its own inflammation-promoting activity in macrophages by promoting p62-mediated removal of mitochondria that have been damaged after macrophages encounter various NLRP3-inflammasome activators.
Schematic drawing depicting SAA synthesis and interaction with its receptors.

**SAA (blood)**
- **Bacteria**: Opsonizes Gram-negative bacteria, promotes bacterial clearance.
- **HDL**: Displaces apo A-1; participates in lipid metabolism.
- **SR-B1**: Facilitates cholesterol efflux, clears SAA; cleaves SAA to form AA.
- **FPR2**: Induces phagocyte migration, alters tumor microenvironment - metastasis, anti-apoptotic - prolongs neutrophil lifespan.
- **P2X7**: Activates NLRP3 inflammasome for IL-1β production.
- **TLR2**: Induces IRF7, IRF4, Jmjd3 (epigenetic regulation)
  - **TLR4**: Induces M2 markers, IL-33, IL-10, IL-1rm
  - **RAGE**: Promotes macrophage efferocytosis
- **Inflammation**
- **Cancer**
- **Surgery**
- **Trauma**
- **Infection**

**SAA (tissue)**
- **Activates NF-κB, AP-1 for NOS and NO production**
- **Activates NF-κB and induces inflammatory cytokines**


©2015 by Society for Leukocyte Biology
SAA for auto-inflammatory diseases

- Linked to inflammasome associated disease with persistent elevated levels
- Up to 40% of recurrent fevers develop secondary AA amyloïdosis
- Potent inducer of IL1 via TL2 and 4….
- But also an inducer of recovery mechanism like M2 macrophage, Il-10…
- Can be used as a marker of response to treatment
Inflammatory stimuli (infection, injury)

Macrophages

IL-1, TNF-α

Stromal cells

IL-6

Non-hepatic tissues

Hepatocytes

SAA

SAA

HDL

Phagocytes

Normal catabolism

(Impaired processing)

Initial amyloid fibril formation

Amyloid P component,
Apolipoprotein E,
Glucosaminoglycans
and other tissue components

Stable amyloid deposition
SAA-αA (removal of carboxyl terminus of SAA)

Fig. 2 Synthesis of SAA and catabolic pathway leading to amyloidogenesis.

Serum
Amyloid A
(SAA)
## Predictors of mortality in AA amyloïdosis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>P value</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at dx</td>
<td>&lt;0.001</td>
<td>1.53</td>
<td>1.34-1.74</td>
</tr>
<tr>
<td>Periodic fever syndroms</td>
<td>0.03</td>
<td>0.36</td>
<td>0.14-0.88</td>
</tr>
<tr>
<td>Median SAA (per doubling)</td>
<td>&lt;0.001</td>
<td>1.27</td>
<td>1.16-1.40</td>
</tr>
<tr>
<td>Onset of ESRF</td>
<td>&lt;0.001</td>
<td>2.97</td>
<td>2.10-4.21</td>
</tr>
<tr>
<td>Amyloid regression</td>
<td>0.04</td>
<td>0.13</td>
<td>0.02-0.94</td>
</tr>
<tr>
<td>Median survival under 13 years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lachmann HJ, NEJM 2007
Therapeutic blockade of interleukin-6 by tocilizumab in the management of AA amyloidosis and chronic inflammatory disorders: a case series and review of the literature

T. Lane, J.D. Gillmore, A.D. Wechalekar, P.N. Hawkins, H.J. Lachmann

- Response to anti-IL-6 lead to suppression of the inflammatory stimulus
- Decrease of amyloid deposition
Macrophage activation syndrome/ferritin

Classification of macrophage activation syndrome
in systemic juvenile idiopathic arthritis

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:

Ferritin >684 ng/ml

and any 2 of the following:

- Platelet count ≤181 x 10^9/liter
- Aspartate aminotransferase >48 units/liter
- Triglycerides >156 mg/dl
- Fibrinogen ≤360 mg/dl
Macrophage activation syndrome
Cytokines storm leading to extracellular ferritin release

Follow up and treatment of a macrophage activation syndrome
Chronic inflammation/High basal hsCRP

**Cardiovascular Diseases:**
- Atherosclerosis
- Cerebrovascular dis.
- Heart failure
- Cardiomyopathy
- Stroke

**Diabetic Complications:**
- Cardiomyopathy
- Atherosclerosis
- Chronic renal failure
- Retinopathy, Sepsis
- Neuropathy

**Neurological Disorders:**
- Alzheimer’s
- Parkinson’s
- AIS
- Dementia

**Metabolic Disorder Complications:**
- Fatty liver disease
- Heart disease
- Type 2 Diabetes
- CKD
- Sleep apnea

**Cancer:**
- Lung cancer
- Kidney cancer
- Gastric cancer
- Colon cancer
- Pancreatic cancer
- Lymphoma

**Bone, Muscular & Skeletal Disease:**
- Osteoporosis
- Osteoarthritis
- DDD
- Muscular dystrophy

**Chronic Inflammatory Dis:**
- IBD, COPD, RA, Psoriasis
- Chronic pancreatitis
- CIDP, CICTD
### hsCRP and cardiovascular risk

<table>
<thead>
<tr>
<th>Etude</th>
<th>Design</th>
<th>Sexe</th>
<th>Risque relatif cardiovasculaire selon le taux de hsCRP (4&lt;sup&gt;e&lt;/sup&gt; vs 1&lt;sup&gt;er&lt;/sup&gt; quartiles)</th>
<th>AUC des facteurs de risque traditionnels seuls</th>
<th>AUC pour la hsCRP combinée aux facteurs de risque traditionnels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman’s health study (Ridker et coll., 2002)</td>
<td>Prospective</td>
<td>Femmes</td>
<td>2.3</td>
<td>0.81</td>
<td>0.81</td>
</tr>
<tr>
<td>Rotterdam Study (van der Meer et coll., 2003)</td>
<td>Nested case-control</td>
<td>Hommes et femmes</td>
<td>1.2</td>
<td>0.746</td>
<td>0.748</td>
</tr>
<tr>
<td>MONICA Augsburg Study (König et coll., 2004)</td>
<td>Prospective</td>
<td>Hommes</td>
<td>2.2</td>
<td>0.735</td>
<td>0.75</td>
</tr>
<tr>
<td>Reykjavik Cohort Study (Danesh et coll., 2004)</td>
<td>Nested Case-Control</td>
<td>Hommes et femmes</td>
<td>1.4</td>
<td>0.64</td>
<td>0.65</td>
</tr>
<tr>
<td>Framingham Offspring Study (Rutter et coll., 2004)</td>
<td>Prospective</td>
<td>Hommes et femmes</td>
<td>1.9</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>Framingham Heart Study (Wilson et coll., 2005)</td>
<td>Prospective</td>
<td>Hommes et femmes</td>
<td>1.6</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>Cardiovascular Heart Study (Shipak et coll., 2005)</td>
<td>Prospective</td>
<td>Hommes et femmes</td>
<td>Non disponible</td>
<td>0.73</td>
<td>0.72*</td>
</tr>
</tbody>
</table>

### Practical implications:
1. Classical risk factors predict more than 90% of future myocardial infarcts
2. Patients with intermediate risk may benefit from hsCRP to start treatment
3. These biomarkers should not be used for population screening
4. Same for new biomarkers, so far as we know now
Association Between Carotid Atherosclerosis and Markers of Inflammation in Rheumatoid Arthritis Patients and Healthy Subjects

Inmaculada del Rincón,¹ Ken Williams,¹ Michael P. Stern,¹ Gregory L. Freeman,¹ Daniel H. O’Leary,² and Agustín Escalante¹

Table 6. Relationship between C-reactive protein (CRP) level and carotid artery plaque*

<table>
<thead>
<tr>
<th>CRP, mg/liter</th>
<th>No. of carotid vessels imaged</th>
<th>Carotid vessels with plaque, no. (%)†</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1.0</td>
<td>77</td>
<td>8 (10)</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>1.1–2.3</td>
<td>89</td>
<td>28 (31)</td>
<td>6.61</td>
<td>1.79–24.39</td>
</tr>
<tr>
<td>2.4–4.8</td>
<td>118</td>
<td>33 (28)</td>
<td>5.59</td>
<td>1.52–20.54</td>
</tr>
<tr>
<td>4.9–30</td>
<td>279</td>
<td>89 (32)</td>
<td>6.75</td>
<td>1.94–23.41</td>
</tr>
<tr>
<td>&gt;30</td>
<td>41</td>
<td>15 (37)</td>
<td>8.31</td>
<td>1.98–34.94</td>
</tr>
</tbody>
</table>

* See Table 2 for other definitions.
† P for trend = 0.001 unadjusted, ≤0.001 age- and sex-adjusted, ≤0.001 age-, sex-, and cardiovascular risk factor–adjusted.
Low grade « inflammation » : CRP 3-10 mg/L

Usually asymptomatic leading to latter consequences

Leading to a new definition of inflammation:

Inflammasomes in health and disease

Nature 481(7381):278-86 · January 2012
Redefining INFLAMMATION

INNATE immune response to potentially harmful stimuli such as pathogens, injury and metabolic stress To restore optimal homeostatic state

| TABLE 1. Comparison of acute, low-grade, and autoinflammatory inflammation |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Parameter                       | Infection       | Tissue injury   | Low-grade inflammation | Autoinflammatory diseases |
| Cause Mediators                 | Pathogens       | Trauma, tissue infarction | Metabolic malfunction | Usually spontaneous |
| Classic signs of inflammation   | Molecules and cells of the innate immune response | Molecules and cells of the innate immune response | Molecules and cells of the innate immune response | |
| CRP response                    | +++             | +++             | None              | +++             |
| Purpose                         | Defense healing and repair | Healing and repair | Restoration of homeostasis | None apparent |
| Triggering mechanism            | Pattern recognition molecules, notably for PAMPs and DAMPs | Pattern recognition molecules, notably for DAMPs | Sentinel cells that monitor for tissue stress, notably the UPR | Genetically based dysregulation |

DAMP: damage-associated molecular patterns; PAMP: pathogen-associated molecular pattern. Plus symbols indicate magnitude.
In conclusion

1. ESR as Inflammation biomarker to rule out inflammatory syndrome
2. Use of biomarkers in follow up alone or in clinical score of disease activity (GCA; DAS - RA)
3. PROCALCITONIN included in ICU septic shock evaluation and exclusion of bacteremia: not yet directing AB treatment
4. Chronic residual inflammation or recurrent fevers with long term consequence as AA amyloïdosis: Treatment options: anti-IL6 (monitoring with SAA)
5. Macrophage activation syndrome: FERRITIN as an essential marker of macrophage
6. Basal hs CRP levels and risk evaluation: screening limited
7. Time to redefine inflammation
Thank you for your attention

Any question?