The role of Matrix metalloproteinase-3 in Rheumatoid Arthritis

Ágnes Szappanos MD PHD

Semmelweis University Heart and Vascular Center

Semmelweis University Department of Rheumatology and Clinical Immunology

SEMMELWEIS UNIVERSITY 1769

Rheumatoid Arthritis

- Rheumatoid arthritis is a **chronic systemic inflammatory** rheumatological disorder that primarily affects the small joints of the hands and feet.
- The course of the disease is characterized by **progressive inflammation** and destruction involving the articular cartilage and bone. In the long term, it leads to limited movement and instability of the affected joints.
- The incidence of the disease is around **5-50 new cases** per hundred thousand inhabitants per year.
- The disease usually appears between **40 and 50 years** of age, the female/male ratio is **3:1.**
- Genetic predispositions, environmental factors and autoimmune processes play a role in the **development** of the disease.
- The course of the disease is characterized by an **introductory, central-proliferative** and final **destructive** phase.

- Inflammatory infiltration of the **synovia** plays a role in its pathogenesis. This leads to the appearance of **pannus** formation and then to extensive, **erosive** joint destruction on the affected cartilage and subchondral bone tissue.

Joint and radiological changes of rheumatoid arthritis

Joint deformities:

- Joint contractures, subluxation
- PIP hyperextension és DIP flexion
  „swan-neck deformity”
- PIP flexion contracture, DIP hyperextension
  „buttonhole deformity”
- Ulnar deviation
- Volar wrist subluxation

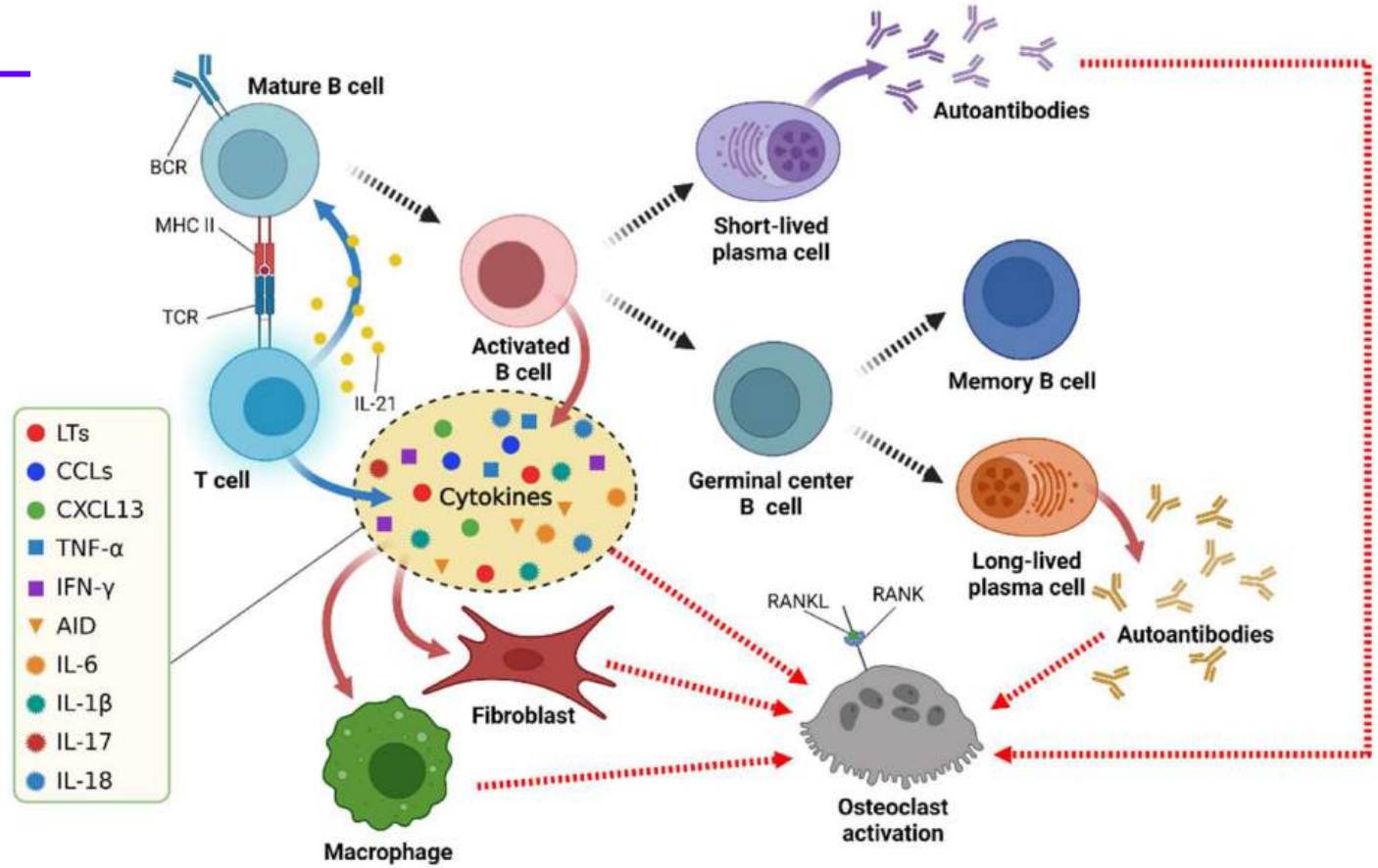
Radiological signs:

- Soft tissue thickening
- Banded osteopenia
- Joint space narrowing
- Marginal erosions
- Ulnar deviation

Conventional radiography of the hands and wrists in rheumatoid arthritis. What a rheumatologist should know and how to interpret the radiological findings. Alexandros A. Drosos et al, Rheumatology International volume 39, pages1331–1341 (2019)

Molecular mechanisms involved in the pathogenesis of Rheumatoid Arthritis

- Pathogenetic changes in the synovial membrane
- T Cell-Mediated Immune Response
- B Cell-Mediated Immune Response
  - Autoantibody Production
  - Antigen Presentation
  - Cytokine Secretion
  - Osteoclast Activation
- Innate Immunity-Mediated Immune Response
  - Macrophages
  - Dendritic cells
  - Natural killer cells

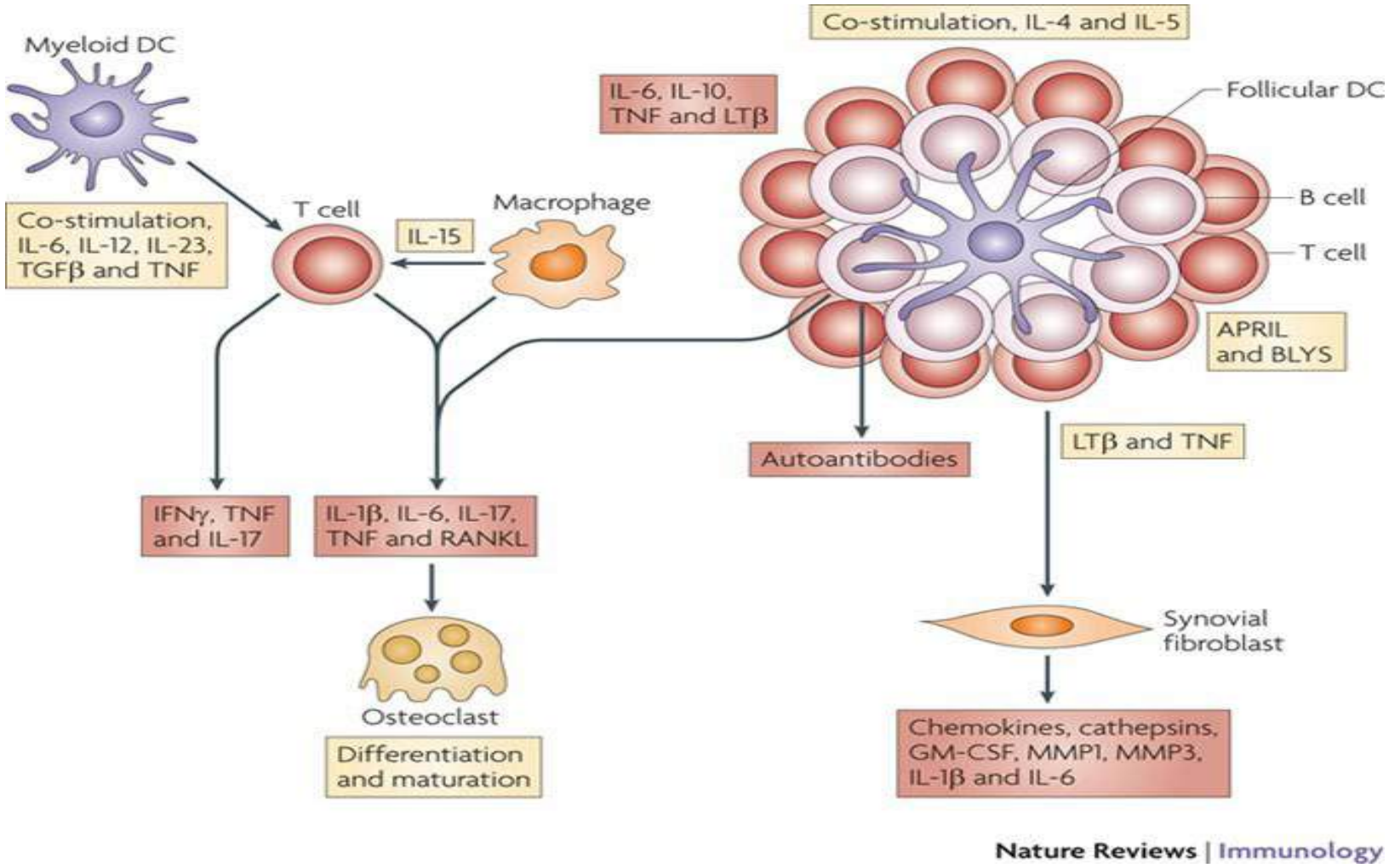


Jang S, Kwon EJ, Lee JJ. Rheumatoid Arthritis: Pathogenic Roles of Diverse Immune Cells. Int J Mol Sci. 2022 Jan 14;23(2):905.

Molecular mechanisms involved in the pathogenesis of Rheumatoid Arthritis

Synovial fibroblasts:

- Chemokines
- Cathepsins
- GM-CSF
- MMP1
- MMP3
- IL-1β
- IL-6



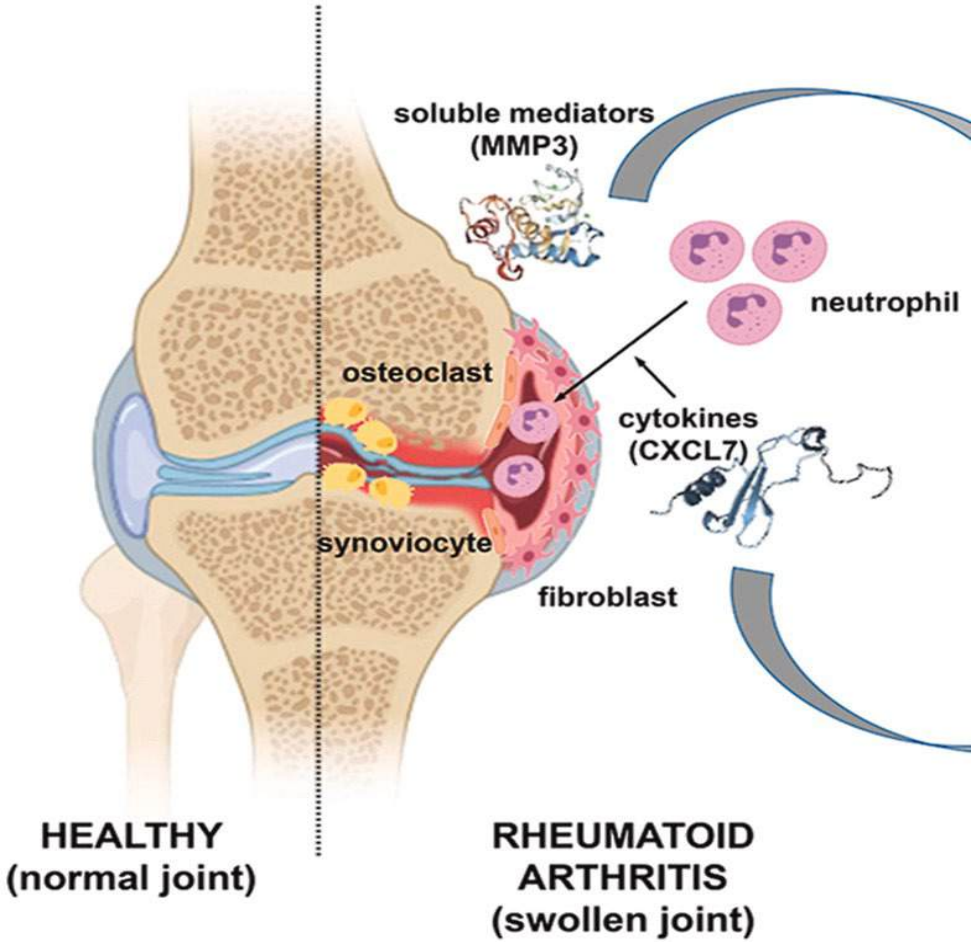
The changing face of rheumatoid arthritis: sustained remission for all? John D. Isaacs Nature Reviews Immunology volume 10, pages605–611 (2010)

Matrix metalloproteinase endopeptidase enzymes in the pathogenesis of Rheumatoid Arthritis

- Matrix metalloproteinase endopeptidase enzymes are of particular importance in the pathogenesis of RA in the creation of joint destruction. They are involved in the breakdown of extracellular matrix proteins during tissue remodeling in normal physiological processes.

- MMP3 is involved in connective tissue remodeling, primarily responsible for the degradation of collagen types II, III, IV, IX, X, proteoglycans, fibronectin, laminin, and elastin.

- In addition, it can activate other MMPs such as MMP- 1, MMP-7 and MMP-9 enzymes.



Simultaneous determination of CXCL7 chemokine and MMP3 metalloproteinase as biomarkers for rheumatoid arthritis. Guerrero S et al. Talanta. 2021 Nov 1;234:122705.

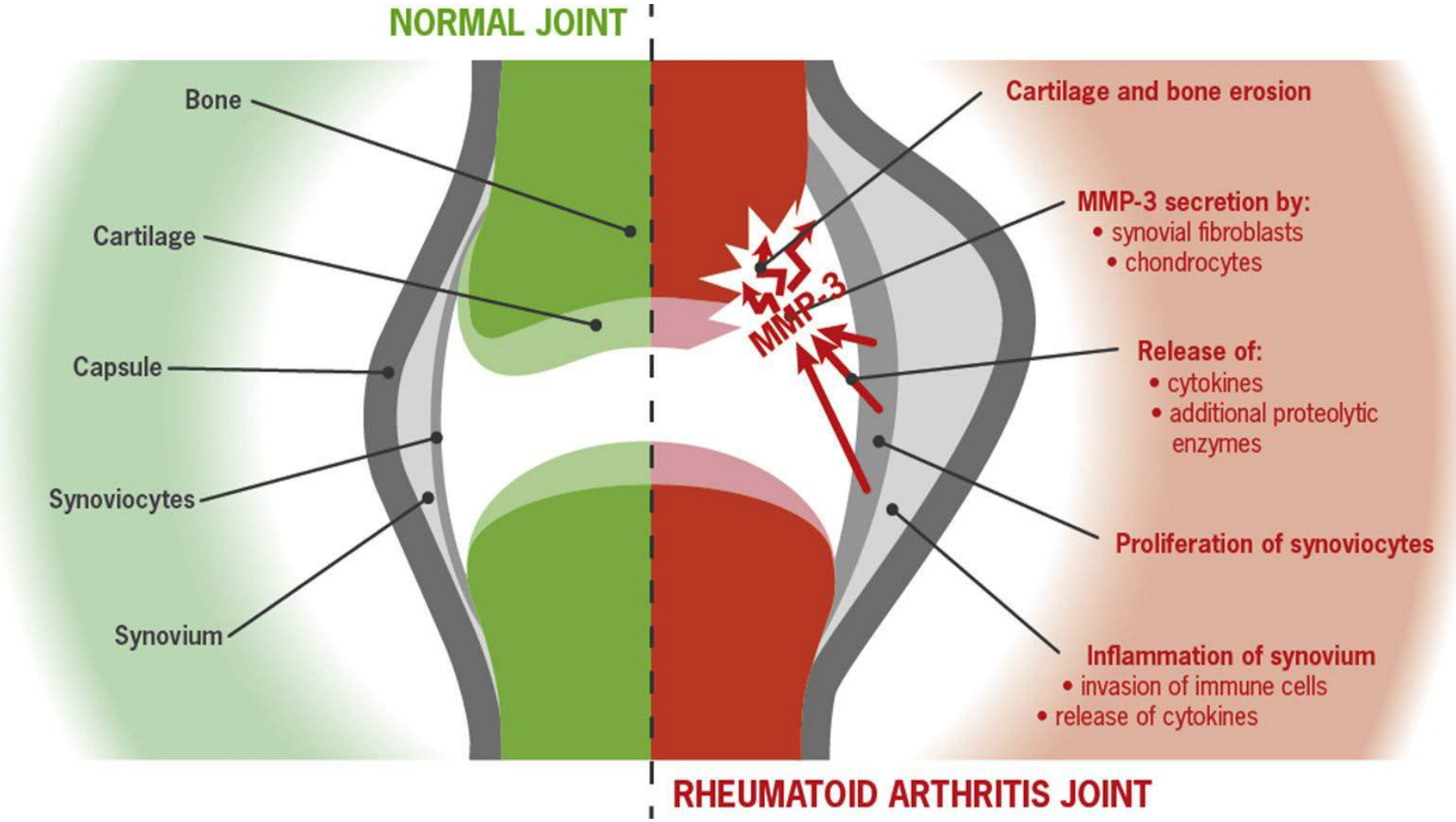
MMP3 in joint inflammation and destruction in Rheumatoid Arthritis

- MMP3 is a proteinase synthesized and secreted by synovial fibroblasts and chondrocytes in the joints.
- It is actively involved in joint destruction in RA patients.

MMP3 was extensively studied in:

- disease activity reflection
- monitoring progress
- therapeutic responsiveness

but did not gain enough attention by the professionals!



MMP3 is a reliable marker for disease activity, radiological monitoring, disease outcome predictability, and therapeutic response in rheumatoid arthritis. Lerner A, et al Best Pract Res Clin Rheumatol. 2018 Aug;32(4):550-562

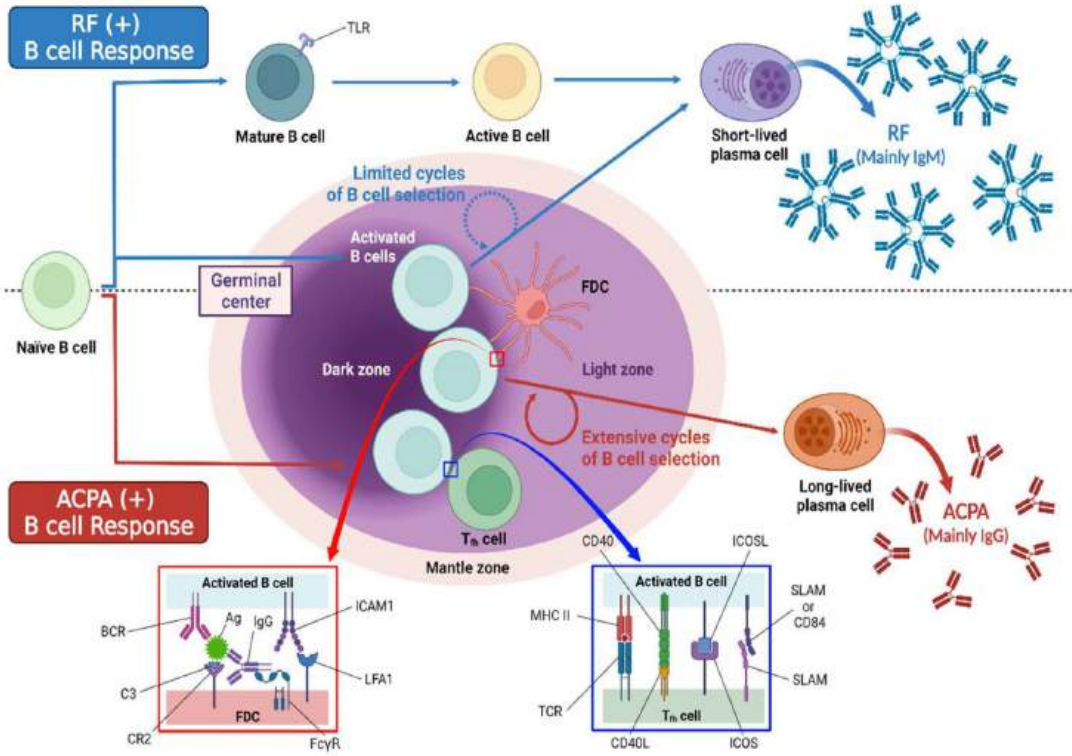
Autoantibodies involved in the pathogenesis of Rheumatoid Arthritis

Rheumatoid factor:

- Is an antibody that recognizes the Fc portion of IgG
- Can be found in almost all types of immunoglobulins
- RF occurs in 60–80% of established and 50–60% of early RA
- It may reflect disease activity but is less useful in patient's diagnosis
- In older age, IgM RF can be detected in 10-15% without the presence of RA
- False positive:
  - infectious diseases
  - induces false positive laboratory results (thyroglobulin, α feto protein, sex hormones binding proteins, troponin 1, various cytokines, HBV + HCV serology, and latex agglutination)

Antibodies against the cyclic citrullinated peptide (ACPA):

- It is an autoantibody against a citrullinated protein
- Currently the best laboratory indicator of RA
- It can be detected up to 5 - 10 years before the onset of the disease
- Pooled sensitivity of ACPA was 67% and specificity was 95%
- It can activate immune cells and upregulate pro-inflammatory cytokine production



Jang S, Kwon EJ, Lee JJ. Rheumatoid Arthritis: Pathogenic Roles of Diverse Immune Cells. Int J Mol Sci. 2022 Jan 14;23(2):905

2010 ACR/EULAR Classification Criteria

Target population: Patients who (i) have at least 1 joint with clinical synovitis and (ii) with the synovitis not better explained by another disease.

	Score
A. Joint involvement (tender/swollen)	
1 large joint	0
2-10 large joints	1
1-3 small joints (± involvement of large joints)	2
4-10 small joints (± involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
B. Serology	
Negative RF & ACPA	0
Low-positive RF/low-positive ACPA	2
High-positive RF/high-positive ACPA	3

	Score
C. Acute-phase reactants	
Normal CRP & ESR	0
Abnormal CRP & ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

Add score of categories A-D:

≥ 6/10 = definite RA

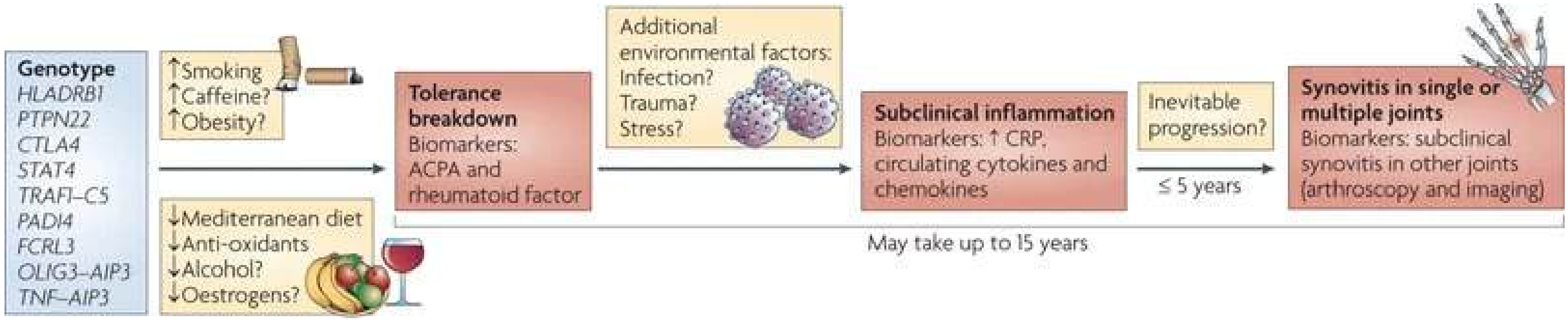
2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative D. Aletaha, Arthritis Rheum, 2010 Sep;62(9):2569-81.

Assessment of Rheumatoid Arthritis disease activity

- The **long-term treat-to-target** (T2T) treatment concept aims to achieve remission or low disease activity.
- Among the clinical indices validated for measuring disease activity, the **Disease Activity Score 28** (DAS28) is widely used.
- The DAS28 value can be **significantly affected** by changes in acute phase parameters and the use of therapies affecting their levels.
- Due to this, the obtained value **does not give a reliable result** in terms of measuring disease activity.
- In RA, the prediction of disease activity, response to treatment, and radiological progression has not been solved until now.

Biomarker

Significance of biomarkers in the course of Rheumatoid Arthritis



Biomarkers

Biomarkers

Biomarkers

The changing face of rheumatoid arthritis: sustained remission for all? John D Isaacs, Nat Rev Immunol, 2010 Aug;10(8):605-11.

Clinical significance of MMP3 in Rheumatoid Arthritis

Clinical correlations between MMP3 and RA:

- with the degree of synovial inflammation
- with disease activity
- with the radiological progression followed for one year
- with the number of newly formed erosions
- with the level of inflammatory parameters
- with different biomarker and interleukin levels (IL-8, IL-6, IFN γ, VEGF és COMP)
- with the degree of structural remission under methotrexate therapy

Biomarkers → **MMP3**

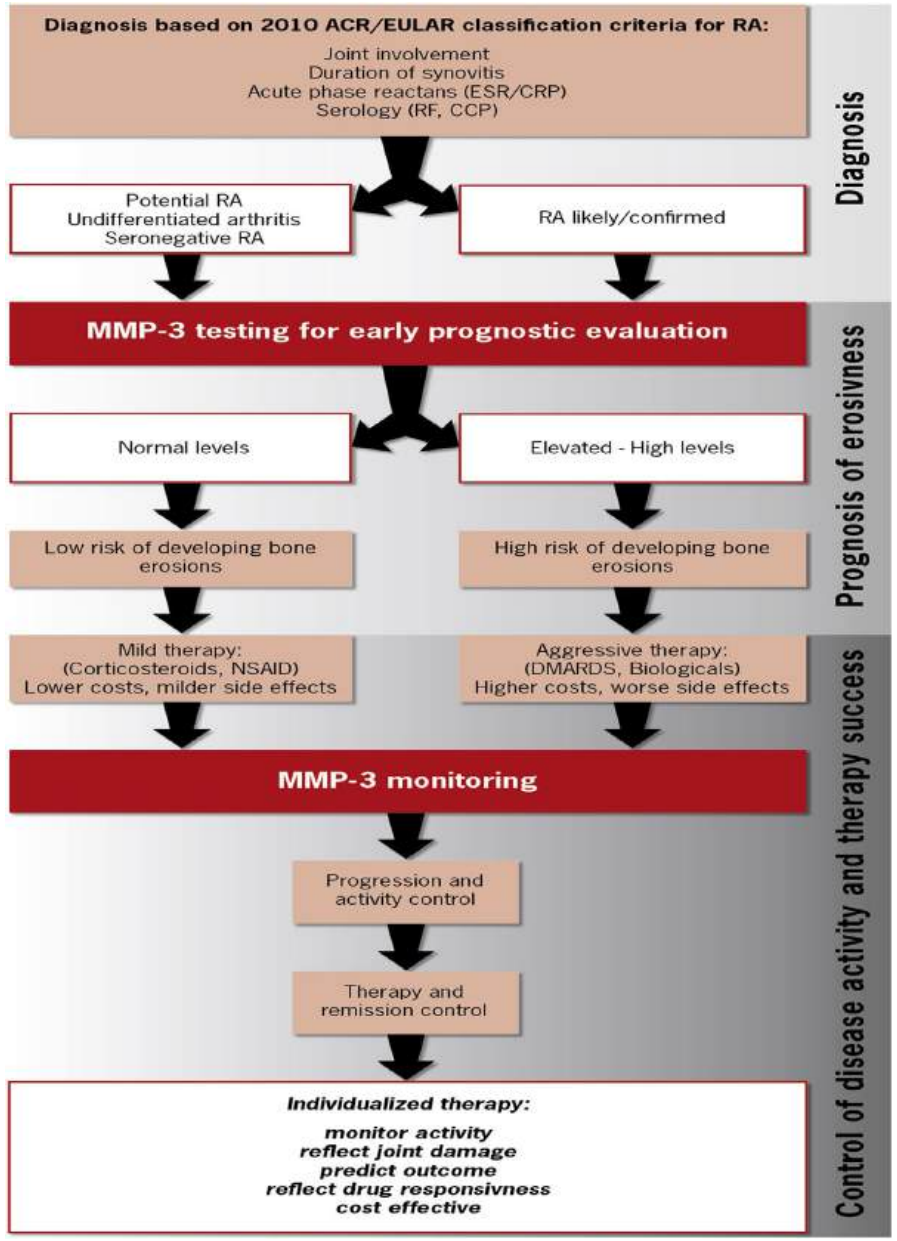
Clinical significance of MMP3 in Rheumatoid Arthritis

MMP3 may play a role in RA:

- Establishing a diagnosis
- In the prognosis of erosion rates
- Disease follow-up

It can play a prominent role in personalized RA therapy:

- Monitoring disease activity
- Determining the degree of joint damage
- Determination of disease outcome
- Monitoring of therapeutic response
- Cost effectiveness



MMP3 is a reliable marker for disease activity, radiological monitoring, disease outcome predictability, and therapeutic response in rheumatoid arthritis. Lerner A, et al Best Pract Res Clin Rheumatol. 2018 Aug;32(4):550-562.

Thank you for your attention!

SEMMELWEIS
UNIVERSITY 1769