Rheumatoid Arthritis, Redefined

What Do We Really Know About RA?
Key Learning Objectives

• Reevaluate the key drivers of rheumatoid arthritis (RA) pathogenesis
  – Highlight the role of pathogenic autoantibodies and proinflammatory cytokines in RA pathology

• Understand how persistent T-cell activation can perpetuate autoantibody production

• Recognize the importance of anti-citrullinated protein antibodies (ACPAs) as a diagnostic and prognostic biomarker in RA
The Breaking of Immune Tolerance
In Healthy Individuals, Immune Signaling Is Directed Against Foreign Antigens

**Primary Immune Response**

- **T cell**
- **Activated T cell**
- **APC**
- **Lymph node**

**Secondary Immune Response**

- **B cell**
- **Activated T cell**
- **Plasma cell**: immediate response
- **Memory B cell**: long-term response

**Co-stimulation**

- **APC = antigen-presenting cell; MHC = major histocompatibility complex; CD = cluster of differentiation; TCR = T-cell receptor.**


Healthy immune systems employ multiple tolerance mechanisms such as depleting self-reactive T and B cells.

- **Peripheral Anergy**
  - Sites: secondary lymphoid tissue and inflammation sites
  - Mechanism: cellular inactivation by signaling without co-stimulus

- **Regulatory T Cells**
  - Sites: secondary lymphoid tissue and inflammation sites
  - Mechanism: suppression by cytokines, intercellular signals

- **Antigen Segregation**
  - Sites: peripheral organs (e.g., thyroid, pancreas)
  - Mechanism: physical barrier to self-antigen access to lymphoid system

- **Activation-Induced Cell Death**
  - Sites: secondary lymphoid tissue and inflammation sites
  - Mechanism: apoptosis

- **Central Tolerance**
  - Sites: thymus & bone marrow
  - Mechanism: deletion & editing

Several Factors May Contribute to Loss of Immune Tolerance and the Onset of RA

- **Environmental Factors**
- **Susceptibility Genes** (i.e. Shared Epitope)
- **Epigenetic Modifications** (i.e. Methylation)
- Gut Microbiome
- Smoking
- Periodontal disease

Key Drivers of RA Pathogenesis and Disease Progression
The role of proinflammatory cytokines in RA is well known, and recent research has deepened our understanding of the role of pathogenic autoantibodies in disease.

**Cytokine production**

Proinflammatory cytokines released from T cells and macrophages are well known drivers of disease.

**Autoantibody production**

APCs present autoantigens to T cells, activating T cells and subsequently, B cells. Mature B cells produce pathogenic autoantibodies.

These Drivers Perpetuate Disease Through Persistent T-Cell–Initiated Immune Responses

- Cytokines
- Activated Macrophage
- B-cell activation

The release of T-cell–derived cytokines can lead to macrophage activation, resulting in further secretion of proinflammatory cytokines and T-cell activation.

- Activated T cell
- Dendritic cell

Another powerful effector is the immune complex. Immune complexes amplify the inflammatory response of macrophages.

- Macrophage
- Self-proteins

B-cell–derived autoantibodies further recognize an unlimited supply of self-proteins and perpetuate T-cell activation.

- B cell
- Macrophage

IL = interleukin; JAK = Janus kinase; TNF = tumor necrosis factor.

Autoimmunity Leads to Activation of Effectors That Break Down Bone and Cartilage

Complement Release

ACPA

MMP-12 = matrix metallopeptidase (macrophage metalloelastase); MMP = matrix metalloproteinase.

Breakdown of Bone and Cartilage Leads to Structural Damage and Functional Impairment

<table>
<thead>
<tr>
<th>Susceptibility to RA</th>
<th>Preclinical RA</th>
<th>Early RA</th>
<th>Established RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms or signs of autoimmunity</td>
<td>Asymptomatic autoantibody development</td>
<td>Early symptomatic autoimmunity</td>
<td>Undifferentiated arthritis</td>
</tr>
</tbody>
</table>

No detectable autoimmunity

Initiation of autoimmunity

Propagation of autoimmunity

No symptoms or signs of autoimmunity

Joint capsule

Synovium

Bone

Healthy joint

Possible immune cell infiltration, but often normal

Immune cell infiltration

Immune cell infiltration, hyperplasia of the lining layer and pannus formation

Autoantibodies in RA: Clinical Significance and Implications for Treatment
Autoantibodies Are Important Biomarkers Specific to RA

- Anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF) are well studied autoantibodies in RA\(^1,2\)

- ACPA has recently emerged as a key diagnostic and prognostic biomarker in RA\(^2\)

Autoantibody Detection Can Precede the Onset of RA Symptoms

Analysis of Blood Samples From 79 RA Patients Prior to the Onset of Disease Symptoms

IgM = immunoglobulin M.

IgM-RF or ACPA
49.4%

ACPA
40.5%

IgM-RF
27.8%

Positive patients, %

Years before the start of symptoms

15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
In ACPA+ Healthy Individuals, Bone Loss Is Exhibited Even Without Joint Inflammation

- Healthy individuals with ACPA with no concomitant signs of arthritis show alterations in cortical bone architecture
- Significant reduction in cortical thickness and widespread cortical porosity areas in the ACPA+ group than in ACPA–

Arrows show cortical thinning, cortical fenestration, as well as small bone erosions.
ACPA = anti-citrullinated protein antibody; MCF = metacarpal fingers.
After Clinical Onset, ACPA+ and ACPA− RA Patients Have a Different Disease Course

Bony erosions measured by Sharp–van der Heijde Score.

Furthermore, ACPA+ RA Patients Have Increased Comorbidity Risks

**RA Comorbidities**

- Psychiatric diseases
- Infections
- Cancer
- Gastrointestinal diseases
- Cardiovascular disease
- Pulmonary disease (specifically ILD)

ILD = interstitial lung disease.

ACPA+ RA Is Associated With an Increased Risk for Heart Disease and Death\textsuperscript{1a}

- In a prospective study of 937 RA patients, more ACPA+ RA patients had ischemic heart disease compared with ACPA-negative RA patients\textsuperscript{1}

\begin{itemize}
  \item Shared epitope alleles of MHC are also associated with an increased risk of death from cardiovascular disease\textsuperscript{2}
\end{itemize}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
 & Anti-CCP+ & Anti-CCP- & & & \\
\hline
Ischemic Heart Disease & 6.5 & 2.6 & & & \\
\hline
Acute Stroke & 4.4 & 3.3 & & & \\
\hline
Thrombosis & 5.2 & 3.3 & & & \\
\hline
Heart Failure & 7.2 & 6.4 & & & \\
\hline
Death & 11.2 & 6.8 & & & \\
\hline
\end{tabular}
\caption{Patients With Events, %}
\end{table}

\begin{itemize}
  \item OR 2.58 (1.17–5.65)\textsuperscript{b}
  \item NS
  \item NS
  \item NS
  \item 1.72 (1.01–2.91)\textsuperscript{c}
\end{itemize}

\textsuperscript{a} Values are the number (percentage) unless otherwise indicated; \textsuperscript{b} \(P<0.025\); \textsuperscript{c} \(P<0.05\).

Anti-CCP = anti-cyclic citrullinated peptide; CV = cardiovascular; MHC = major histocompatibility complex; OR = odds ratio; 95\% CI = 95\% confidence interval; NS = not significant.

A meta-analysis was performed to determine the risk conferred by ACPA seropositivity on RA-related ILD, IPF, AD, pleural disease, nodular lung disease, bronchiolitis obliterans, and arteritis.  
8 studies from 7 publications were used in the analysis, including 1685 RA patients.

**Risk of RA-related ILD and IPF with ACPA positivity**

<table>
<thead>
<tr>
<th>Overall</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I-squared = 45.3%, (P=0.140))</td>
<td>3.39 (1.67, 6.88) (P=0.001)</td>
</tr>
<tr>
<td>.01</td>
<td>.1</td>
</tr>
</tbody>
</table>

IPF = interstitial pulmonary fibrosis; AD = airway disease.
Understanding RA Initiation, Progression, and Prognosis May Aid in Treatment Decision Making

Risk of developing RA → Asymptomatic Autoimmunity → ACPA-associated disease → ACPA-positive RA

Genetic susceptibility and environmental challenges → Loss of immune tolerance

Co-stimulation and activation of T cells → Antibody production

• Pain
• Bone loss

• Pain
• Inflammation
• Erosions

• Osteoclast activation

IL = interleukin; PAD = peptidylarginine deiminase.
Figure reproduced with permission from Catrina AI, et al. Nat Rev Rheumatol. 2017;13:79-86.
Summary

• RA is a destructive autoimmune disease driven by pathogenic antibodies and proinflammatory cytokines
• Such autoimmunity is dependent on persistent T-cell–initiated immune responses
• Recent research into the role of autoantibodies in RA, particularly ACPA, has redefined our understanding of the disease
• Understanding the underlying factors behind the articular and extra-articular manifestations of RA is crucial for identification and selection of therapies that prevent or halt disease progression
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACPA</td>
<td>anti-citrullinated protein antibody</td>
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<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>AD</td>
<td>airway disease</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>anti-cyclic citrullinated peptide</td>
</tr>
<tr>
<td>APC</td>
<td>antigen presenting cell</td>
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<tr>
<td>CD</td>
<td>cluster of differentiation</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<tr>
<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<tr>
<td>HRCT</td>
<td>high-resolution computed tomography</td>
</tr>
<tr>
<td>JAK</td>
<td>Janus kinase</td>
</tr>
<tr>
<td>Ig</td>
<td>immunoglobulin</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>ILD</td>
<td>interstitial lung disease</td>
</tr>
<tr>
<td>IPF</td>
<td>idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>MHC</td>
<td>major histocompatibility complex</td>
</tr>
<tr>
<td>Micro-CT</td>
<td>micro-computed tomography</td>
</tr>
<tr>
<td>MMP</td>
<td>matrix metalloproteinase</td>
</tr>
<tr>
<td>MMP-12</td>
<td>matrix metallopeptidase</td>
</tr>
<tr>
<td>NS</td>
<td>not significant</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PAD</td>
<td>peptidylarginine deiminase</td>
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<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RF</td>
<td>rheumatoid factor</td>
</tr>
<tr>
<td>SE</td>
<td>shared epitope</td>
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<tr>
<td>SHS</td>
<td>Sharp/van der Heijde score</td>
</tr>
<tr>
<td>TCR</td>
<td>T-cell receptor</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
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</tbody>
</table>
References

References (cont’d)

• Song YW, Kang EH. Autoantibodies in rheumatoid arthritis: rheumatoid factors and anticitrullinated protein antibodies. QJM. 2010;103:139-146.