Immunology for the Rheumatologist

Alan L. Epstein, MD
Clinical Professor of Medicine
University of Pennsylvania School of Medicine
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We spend much of our time as rheumatologists dealing with the immune system gone awry. We rarely study the normal function of the immune system. Why is it important to have an understanding of immunology? Abnormal immune responses are the cause of many of our inflammatory diseases with serious morbidity and mortality. Antibodies are in widespread use to treat immunologic diseases. Understanding immunology helps us to better understand the diseases that we treat and their current therapies. It also prepares us for advances in understanding the immune mechanisms of inflammatory and autoimmune diseases and therapeutic options for these diseases in the future.

1) Review the innate immune system
2) Discuss acute gout as an example of a disease driven by aberrant innate immune function
3) Review the adaptive immune system
4) Discuss the details of T-cell function
5) Discuss the immunopathogenesis of rheumatoid arthritis
6) Review the treatment of rheumatoid arthritis from an immunologic perspective
Disclosures

• Speakers’ Bureau: Abbvie, Amgen, BMS, Janssen, Lilly, Merck, Novartis, Pfizer, Quest, Sanofi-Regeneron
Role of the immune system

- **Defense against infection**
- Surveillance against tumors
- Recognizes and reacts against foreign proteins and tissues

- How do perturbations in the normal immune system result in disease?
- How can we modulate the aberrant immune response to help our patients?
Components of the Immune System

- **Physical Barriers** - part of innate immune system
  - Skin
  - Epithelial membranes

- **Innate Immune System**
  - "Non-specific" response
  - Involves both immune & non-immune cells
  - Immediate response
  - Response = **inflammation** cytokines/chemokines & co-stimulatory molecules

- **Adaptive Immune System**
  - Specific recognition
  - Immune cells only (T-, B-cells)
  - Delayed response
  - Response = clonal expansion & effector cytokine secretion
  - Memory
Mechanisms of inflammation
Compare and contrast gout and rheumatoid arthritis
Two arms of the immune system

Innate (acute) Immunity:
• First response—12+ hours
• Gout is an example of a disease driven by aberrant innate immune function

Adaptive (acquired) immunity
• Takes time to develop
• RA is an example of a disease driven \textit{(in large part)} by aberrant adaptive immune function
Cells of the Immune System (Leukocytes)

**Innate response**
- Neutrophil (Phagocytosis, Degranulation)
- NK cell (ADCC)
- Basophil (Histamine Release)
- Eosinophil (IL-5 producers)
- Macrophage (APC)

**Adaptive response**
- Dendritic cell (APC)
- Tc lymphocyte (CD8+)
- Th lymphocyte (CD4+)
- B lymphocyte

Adapted from Goldsby, Kindt, Osborne and Kuby, Immunology 5th Ed. 2003 p25
Two Arms of the Immune System: Innate and Adaptive Immunity

Prevent infections
Eliminate microbes

Antibodies block infections and eliminate microbes
T lymphocytes eradicate intracellular microbes
Innate Immunity: General features

1) Initial response to microbes
   - Recognizes structures shared by classes of microbes
   - Receptors encoded in germline, limited diversity
   - Consists of epithelial barriers, phagocytes (neutrophils, monocytes and macrophages), NK cells, dendritic cells
   - Complement system
   - Cytokines + chemokines such as TNFα, IL-1, IL-6, IL-10, IFNγ

All defenses without MEMORY

2) Activates the adaptive immune response
Danger Is All Around Us

- Physical Damage
  - Tissue injury
  - Cell death

- Chemical Insults
  - Environmental toxins
  - Self-inflicted toxins

- **Infection**
  - Bacteria
  - Viruses
  - Parasites
  - Fungi
Sensing Danger/Danger Signals
a.k.a. “pathogen-associated molecular patterns” (PAMPS)
“danger-associated molecular patterns” (DAMPS)

- Unique microbial structures
  - Bacterial cell wall components (LPS, PGN)
  - Microbial proteins (flagellin, zymosan, toxins)

- Nucleic acids
  - Double stranded RNA
  - CpG DNA
  - Viral and Microbial RNA

- Necrotic cell ATP

- Uric acid

- Hyaluronan fragments

- Cytochrome c

PAMPs= Molecular structures that are part of microbial pathogens
DAMPs= Endogenous molecules released from damaged cells
**Pattern Recognition Molecules (PRMs)**
Present on cell surfaces
Present in blood and extracellular fluids

- **Toll-like Receptors (TLRs)**
- NOD-like Receptors (NLRs)
- RIG-I-like Receptors (RLRs)
- Pentraxins
- **Complement cascade**
- Collectins
- Ficollins
- C-type lectins
- Scavenger receptors

Inflammation
Opsonization
Phagocytosis
Recognition of pathogens by Toll-like receptors

- TLRs mediate innate immune response
- Found on macrophages, neutrophils, and dendritic cells
- Recognize distinct pathogen-associated molecular patterns conserved in microbes, e.g., lipopolysaccharides, lipoproteins, viral ds-RNA
TLR Signalling

Adapter proteins recruited
Signal transduction pathways activated
Drives gene transcription

Kawai et al. Nature Immunology. 11(5) 373-384. 2010
Macrophage Function

a) receptors for bacterial components
b) can bind and be activated by immune complexes

The macrophage expresses several receptors specific for bacterial constituents

- mannose receptors
- TLR
- LPS receptor (CD14)
- glucan receptor
- scavenger receptor
- CR3

Bacteria bind to macrophage receptors

Macrophage engulfs and digests bound bacteria

- phagosome
- lysosome
- phagolysosome

Figure 2.19 The Immune System, 3ed. (© Garland Science 2009)
Macrophage Function

On sensing microbial products, macrophages secrete a variety of pro-inflammatory cytokines

**Local effects**
- **IL-6**: Activates vascular endothelium and increases vascular permeability, which leads to increased entry of complement and cells to tissues and increased fluid drainage to lymph nodes
- **TNF-α**: Activates vascular endothelium
- **IL-1β**: Activates lymphocytes
- **CXCL8**: Local tissue destruction
- **IL-12**: Increases access of effector cells

**Systemic effects**
- **Fever**: Induces acute-phase protein production by hepatocytes
- **Fever**: Mobilization of metabolites
- **Fever**: Production of IL-6
- **Fever**: Shock
- **Chemotactic factor recruits neutrophils and basophils to site of infection**
- **Activates NK cells**

*Figure 2.27 The Immune System, 3rd ed. © Garland Science 2009*
COMPLEMENT - 3 distinct ways to activate all lead to C3b
Both Classical and Alternative Complement Pathways Coat Microbe With C3b

Classical Pathway
- Antigen–antibody complex
- C1, C2, C4
- 3 subcomponent proteins

Alternative Pathway
- Cell wall polysaccharides
- Factor B + Factor D
- C3b circulating in serum
- Factor P

Inflammation:
- Increase of blood vessel permeability, chemotactic attraction of phagocytes

Opsonization:
- Immune adherence

C5, C6, C7, C8, C9

Cytolysis:
- Loss of cellular contents through transmembrane channel formed by membrane attack complex C5–C9

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Classical Complement Pathway is Triggered by Antibodies Binding to Foreign Cells

1. Once antibodies recognize and attach to the antigen, complement protein C1 binds to two adjacent antibodies.

2. C1 acts as an enzyme that splits the C2 and C4 proteins into fragments. Fragments C2b and C4b combine to form another enzyme, which splits C3 into two fragments. The active fragment is called C3b.
Classical and Alternative Complement Pathways Cause *Inflammation, Opsonization, and Cytolysis*

**Classical Pathway**
- Antigen–antibody complex
- 3 subcomponent proteins
  - C1
  - C2
  - C4

**Alternative Pathway**
- Cell wall polysaccharides
- Factor B
- Factor D
- C3b circulating in serum
- Factor P

**Inflammation:**
- Increase of blood vessel permeability, chemotactic attraction of phagocytes

**Opsonization:**
- Immune adherence

**Cytolysis:**
- Loss of cellular contents through transmembrane channel formed by membrane attack complex C5–C9

© BENJAMIN/CUMMINGS
The Membrane Attack Complex

C5 → C5a

C5 → C6 → C5b → C7 → C8 → 70-180 Å
Functions of NK Cells

(A) NK cell

Virus-infected cell

Killing of infected cells

(B) Macrophage

Killing of phagocytosed microbes

IL-12

IFN-γ
Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)

1. Antibody binds antigens on the surface of target cell
2. Fc receptors on NK cell recognize bound antibody
3. Cross-linking of Fc receptors signals the NK cell to kill the target cell
4. Target cell dies by apoptosis

Figure 9.43 The Immune System, 3ed. (© Garland Science 2009)
Mechanisms of Acute Gouty Inflammation: Disorder of Innate Immunity

- Acute onset, self limited

- Urate is the inflammatory stimulus, resolves when urate is removed

- Predominant neutrophil response. No lymphocytic reaction

- No autoantibody formation
How Does a Crystal Incite Inflammation?

Interaction of crystals with synovial lining cells triggers neutrophil ingress.
Components of the Innate Immune System that Respond to DAMPS**

**DAMPs = Danger-Associate Molecular Patterns

**Toll-like receptors**
- Lipoteichoic acid
- Endotoxin
- Flagellin
- Viral RNA
- Viral/bacterial DNA
- MSU/CPPD crystals

**Nod-like receptors**
- Bacterial products (S. aureus, Listeria, anthrax lethal toxin, flagellins, etc.)
- Stress
- K⁺ efflux inducing agents
- MSU/CPPD crystals
Innate Immunity Sensors – Pattern Recognition Molecules (PRMs)

Toll-like receptors

Toll-Like Receptors (TLRs)
14 members of TLR family
How TLR senses the presence of DAMPs is not clear

Toll/IL-1 receptor (TIR) domain
Death domain
Leucine-rich domain
Innate Immunity Sensors – Pattern Recognition Molecules (PRMs)

NOD-like receptors (NLR)

Cytoplasmic equivalent of TLR

22 members of the NLR family in humans - Ligands include:

NALP1: anthrax lethal toxin
NALP3: S. aureus, Listeria, uric acid crystals, “stress”
NOD2: muramyl dipeptide
IPAF and NAIP5: Legionella flagellin

NALP1  NALP3  NOD2  IPAF  NAIP

- Nucleotide binding (NACHT) domain
- Pyrin domain
- Leucine-rich repeat
- Caspase recruitment domain
- Apoptosis inhibition domain
Edwards NL. Crystal-Induced Joint Disease, ACP Medicine Textbook, 2012
Adaptive Immunity

- Delayed response to an antigen demonstrating the features of **SPECIFICITY** and **MEMORY**

- Consists of lymphocytes and their products

- Utilizes specific receptors (T & B) *generated by somatic mutation* during development- ie system learns from what it sees

- Must be re-invented every generation!!
Time course of innate and adaptive immune responses

Mouse model of a viral infection
Classes of Lymphocytes - Recognize Different Types of Antigens

- Recognize soluble or cell surface Ags
- Recognize Ags on surface of APC's
- Recognize Ags on infected cells
- Recognize changes on surface of infected cells

Diagram:

1. **B lymphocyte**
   - Antigen recognition: Microbe
   - Effector functions: Neutralization of microbe, phagocytosis, complement activation

2. **Helper T lymphocyte**
   - Antigen recognition: Microbial antigen presented by antigen-presenting cell
   - Effector functions: Activation of macrophages, Inflammation, Activation (proliferation and differentiation) of T and B lymphocytes

3. **Cytotoxic T lymphocyte (CTL)**
   - Antigen recognition: Infected cell expressing microbial antigen
   - Effector functions: Killing of infected cell

4. **Natural killer (NK) cell**
   - Antigen recognition
   - Effector functions: Killing of infected cell

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Three Strategies to Combat Microbes

• Secreted antibodies bind to extracellular microbes, block their ability to infect host cells, and promote their ingestion and subsequent destruction by phagocytes

• Phagocytes ingest and kill microbes—helper T cells enhance the killing by phagocytes

• Cytotoxic T cells destroy cells infected by microbes that are inaccessible to antibodies
T Cell Immunity (cell-mediated)

- T lymphocytes mature in the Thymus

- They express a specific receptor that binds antigen, called the T Cell Receptor (TCR)

- There are 2 main types:
  - CD8+ Cytotoxic T cells (Tc)
    Induce cell death in target cells via cytotoxic granule release
  - CD4+ Helper T cells (Th)
    Help B cells to produce antibodies
    Help phagocytes to destroy ingested microbes

Adapted from Goldsby, Kindt, Osborne and Kuby, Immunology 5th Ed. 2003
CD4 Subsets: Generation and Function

Naive CD4+ T cell

- IFN-γ, IL-12
- IL-4
- TGFβ, IL-6
- IL-6, IL-21

Th1
- IFN-γ, TNF-α
- Defense against intracellular parasites

Th2
- IL-4, IL-5, IL-6, IL-13
- Allergy, Asthma
- Controls parasites and extracellular pathogens

Th17
- IL-17A, IL-17F, IL-21, IL-22
- Defense against pathogens, Autoimmunity, Transplantation rejection and Cancer

Treg
- TGFβ, IL-10
- Immune homeostasis, Maintains tolerance

Tfh
- FcεR1, CXCL13
- Help germinal centre B cells to make antibodies, Affinity maturation and antibody class switching
<table>
<thead>
<tr>
<th>Types of effector T cell</th>
<th>CD8 cytotoxic T cells</th>
<th>CD4 T&lt;sub&gt;H&lt;/sub&gt;1 cells</th>
<th>CD4 T&lt;sub&gt;H&lt;/sub&gt;2 cells</th>
<th>CD4 T&lt;sub&gt;H&lt;/sub&gt;17 cells</th>
<th>CD4 regulatory T cells (various types)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CTL</td>
<td>T&lt;sub&gt;H&lt;/sub&gt;1</td>
<td>T&lt;sub&gt;H&lt;/sub&gt;2</td>
<td>T&lt;sub&gt;H&lt;/sub&gt;17</td>
<td>T&lt;sub&gt;reg&lt;/sub&gt;</td>
</tr>
<tr>
<td>Main functions in adaptive immune response</td>
<td>Kill virus-infected cells</td>
<td>Activate infected macrophages</td>
<td>Provide help to B cells for antibody production, especially switching to IgE</td>
<td>Enhance neutrophil response</td>
<td>Suppress T-cell responses</td>
</tr>
<tr>
<td>Pathogens targeted</td>
<td>Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria</td>
<td>Microbes that persist in macrophage vesicles (e.g. mycobacteria, Listeria, Leishmania donovani, Pneumocystis carinii) Extracellular bacteria</td>
<td>Helminth parasites</td>
<td>Extracellular bacteria (e.g. Salmonella enterica)</td>
<td></td>
</tr>
</tbody>
</table>
T follicular helper cells migrate to follicles.
T follicular helper cells

Trigger formation and maintenance of germinal centers
Stimulate plasma cell development
Stimulate development of memory B cells
B cells and Humoral Immunity

- **Major limb of adaptive immunity**

- Immunoglobulin is structurally homologous to T cell receptor and also produced via somatic recombination

- Provides surveillance against blood born pathogens (bacteria, virus, parasites etc)

- Directly linked to innate immunity through complement activation
B cells develop in the bone marrow and migrate to the peripheral lymphoid organs, where they can be activated by antigens.

Activated B cells proliferate and differentiate into long-lived memory cells and antibody-secreting plasma cells.

B-Cell Activation

**Recognition phase**
- Helper T cells, other stimulus
- Antigen
- Resting IgM⁺, IgD⁺ mature B cell
- Activated B cell

**Activation phase**
- IgM
- Clonal expansion
- High-affinity Ig-expressing B cell
- Memory B cell
- Affinity maturation
- IgG
- IgG-expressing B cell
- IgG
- Isotype switching
- Antibody secretion

**Key events**
- **B-Cell Activation**
- **Resting IgM⁺, IgD⁺ mature B cell**
- **Activating antigen**
- **Clonal expansion**
- **High-affinity Ig-expressing B cell**
- **IgG-expressing B cell**
- **Memory B cell**
- **Affinity maturation**
- **Isotype switching**
- **Antibody secretion**
Roles of Mature B Cells

Role of B cells in immune-mediated inflammation in the RA synovium

- Cytokine production
- Autoantibody production and self-perpetuation
- Antigen presentation

Antigen presentation

- Autoreactive B cell
- Immune-complexed antigen

Autoantibody production

- B cell
- RF
- RF immune complexes
- Antigen presentation
- Autoreactive B cells
- Plasma cells
- Anti-CCP
- Anti-GPI
- Anti-RA33
- RF

Cytokine production

- B cell
- Dendritic cell
- Lymphotoxin
- IL-6
- IFN-γ
- TNF-α

Formation of new lymphoid structures

Amplification of inflammation and damage

- Osteoclast
- Bone
- Cartilage

Role of B cells in immune-mediated inflammation in the RA synovium
Targeting of Rituximab

Expression of CD20 During B-Cell Maturation

(CD=cluster of differentiation)

- Rituximab binds specifically to the CD20 antigen located on pre-B and mature B lymphocytes
- CD20 is not found on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissues
- Long-lived plasma cells do not express CD20 and are not directly targeted by Rituximab

Antibody Function

Specific antibody

Bacterial toxins
- Cell with receptors for toxin
- Neutralization
- Ingestion and destruction by phagocyte

Bacteria in extracellular space
- Macrophage
- Opsonization
- Ingestion and destruction by phagocyte

Complement

Figure 1-29 The Immune System, 2/e (© Garland Science 2005)
T Cell Function
MHC Based Antigen Presenting Cell-Lymphocyte Interactions

MHC II interacts with CD4+ lymphocyte

MHC I interacts with CD8+ lymphocyte
MHC Restriction

MHC restriction

T cell

TCR

HLA-A*0201

antigen-presenting cell

Recognition

X

No recognition

T cell

TCR

HLA-B*5201

antigen-presenting cell

Recognition

X

No recognition

T cell

TCR

HLA-A*0201

antigen-presenting cell

Recognition

Y

No recognition

Figure 3-30 The Immune System, 2/e © Garland Science 2005
T cell activation

TCR ligation alone is insufficient to activate T cells

Safety control

Second signal is essential CO-STIMULATORY

Failure to co-stimulate results in ignorance, anergy or apoptosis
Co-stimulation

**APC**  
- CD40  
- PD-1L  
- ICOS-L  
- CD80/86  
- MHC  
- CD80/86  
- PD-2L  
- B7-H3

**T Cell**  
- CD40-L  
- PD-1  
- ICOS  
- CTLA4  
- TCR  
- CD28  
- ?  
- ?

**Effect**  
+  
-  
+  
-  
+  
?  
?  
?

T Helper Cell Differentiation Driven by the Cytokine Milieu

- IL-12 → Th1
- IL-4 → Th2
- TGFβ, IL-6 → Th17
- TGFβ → Treg

Curtsinger et al., 1999 Journal of Immunology, 162:3256–3262
Abatacept: A Human Immunoglobulin Receptor Fusion Protein

CTLA4

Abatacept (CTLA4Ig)

IgG1

External domain

External

Cell membrane

Internal

Heavy-chain constant region

IgG1 = immunoglobulin G1.
Mechanism of Action of Abatacept

Without Abatacept

Activated T cell

CD28

CD80/86

DC

T

With Abatacept

Abatacept
Specificity of Immune Response

Antigen X
- Activated B cells
- Naive B cells
- Primary anti-X response

Antigen X + Antigen Y
- Secondary anti-X response
- Activated B cells
- Primary anti-Y response

Serum antibody titer

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Cytokine Biology

- Definition: Secreted proteins that function as mediators of immune and inflammatory reactions.
- Allow communication between immunocompetent cells.
- Innate immune response-produced mainly by macrophages and NK cells.
- Adaptive immune response-produced mainly by T cells.
Cytokines in RA

• Drive inflammation

• Drive joint damage

• Drive systemic manifestations
Targeted Therapies

• Treatments for rheumatoid arthritis (RA) prior to 1998 were discovered fortuitously.

• Now, due to a greatly improved understanding of the immunopathogenesis of the disease, we have developed targeted therapies.

• These include tumor necrosis factor α (TNFα), Interleukin-6, and Intracellular Signaling.
Tumor Necrosis Factor $\alpha$ (TNF$\alpha$)

- Expressed as a transmembrane protein
  - Cleaved by TACE on cell surface
- Active protein is trimeric
  - 157 amino acids / monomer
  - Unglycosylated
  - One intrachain disulfide per monomer for stability
- Binds p55 (ubiquitous) and p75 receptors (hematopoietic cells)
  - Receptors present on virtually all cells (200 – 10,000!!)

Synthesis and Function of TNFα

Activated macrophage

pathogens
Interferon γ

Transmembrane TNFα

Soluble TNFα

Receptors crosslinked by TNFα

Target cell

Induction of mediators

TNF receptors phosphorylate each other—induces signaling

Key Actions of TNFα in RA

- Macrophages:
  - proinflammatory cytokines
  - chemokines
  - Increased inflammation

- Endothelium:
  - adhesion molecules
  - vascular endothelial growth factor
  - Increased cell infiltration
  - Increased angiogenesis

- Synoviocytes/Chondrocytes:
  - acute phase response
  - metalloproteinase synthesis
  - Increased CRP in serum
  - Articular cartilage degradation

References:
INTERLEUKIN 6 IS AN IMPORTANT CYTOKINE IN RA
Functions of IL-6

Source: Am J Health Syst Pharm @2008 American Society of Health-System Pharmacists
IL-6 affects a broad range of cells and tissues. It can do so because of its unique signaling mechanism. Classical (cis-) signaling.
Trans-signaling

Probably more important in chronic inflammatory diseases
Intracellular Signaling
7 different cytokine receptors

- IL-17 cytokine receptors
- Types I and II cytokine receptors
- TNF receptors
- Chemokine G protein coupled receptors
- Ig receptors
- TGF-B receptors
Cytokine Receptors Use Different Signaling Pathways
Cytokines Signal Through Different Pathways
JAK-STAT Signaling

1. Cytokine binds to cell membrane receptor.
2. Receptor dimerizes.
3. STAT recruitment.
4. Tyrosine phosphorylation.
5. STAT dimerization.
6. DNA binding.
7. Induction of transcription.
Signaling by Different Cytokines Requires Unique JAK Pairings

Insights into the Initiation and Progression of RA
Etiopathogenesis of RA

- Genetic predisposition
  - *HLA-DRB1* ¹
  - *PTPN22* ²

- Environment
  - Prior infections ³
  - Hormones ⁴
  - Smoking ⁵

- Autoimmunity ³
  - CD4+ helper and TH17 T cells ⁶
  - B cells, plasma cells, and autoantibodies ⁷-⁹
  - Proinflammatory cytokines: TNF-α, IL-1, IL-6, IL-17 ⁹


Genetic Predisposition to RA

• Strongest genetic factor associated with an increased risk of developing RA:
  - Polymorphisms at the \textit{HLA-DRB1} locus (chr. 6p21.3) encoding HLA Class II β-chain molecules\textsuperscript{1}

• Proteins (MHC molecules) involved in antigen presentation to T cells\textsuperscript{2}

• MHC molecules containing the \textit{shared epitope} are able to accommodate citrullinated peptides in the binding site

Shared Epitope--part of the binding site of an MHC class II molecule
Immunologic Tolerance

• Definition:
  - specific unresponsiveness to an antigen that is induced by exposure of lymphocytes to that antigen

• Significance:
  - All individuals are tolerant of their own antigens (self-tolerance); breakdown of self-tolerance results in autoimmunity
HOW IS TOLERANCE BREACHED??

IE-WHY DOES THE RA PATIENT RECOGNIZE SELF AS FOREIGN??
PADI Citrullination is the Target Resulting in Breaching Tolerance in RA

- Citrullination occurs at sites of inflammation\(^1\)
- PADI post-translationally modifies proteins\(^1-3\)
- Peptidyl **arginine** amino acid residues are modified to **citrulline** residues\(^1-3\)
- This process occurs in multiple proteins\(^3\)

**RA in many pts characterized by autoantibodies that target citrulline-containing proteins**

CITRULLINATION

A

\[
\begin{align*}
&\text{L-arginine (charged)} \\
\rightarrow &\quad \text{PAD, Ca}^{2+} \\
&\quad \text{Citrullination} \\
&\quad + \text{NH}_3 + \text{H}^+ \\
\end{align*}
\]

B

1) Protein unfolding
2) Proteolytic degradation
3) Lost intramolecular interactions
Shared Epitope

- Part of the MHC class II molecule
- Able to bind citrullinated self-antigens
Etiopathogenesis of Rheumatoid Arthritis

**Genetics Environment**

**Adaptive Immunity**

**Innate Immunity**

- Rheumatoid factor
- Autoantibodies
  - Activates
  - Inflammation
  - Joint damage

- Cytokines
- MMPs

- Plasma cells
- B cells
- FLS
- Macrophages
- T cells
- B cells

- Dendritic cells
- Activates

**RA-associated Self-antigens**


FLS = fibroblast-like synoviocyte; MMP = matrix metalloproteinase; Mφ = macrophage.
There are multiple cell types and cytokines involved in RA. RA involves the entire integrated immune response—T, B, Innate. Understanding immunology allows a better understanding of the disease and its treatment.

Key cytokines in chronic inflammatory arthritis:

- TNF-α
- IL-1
- IFN-γ
- IL-6
- RANK-ligand
- IL-17
QUESTIONS ?