AUTOIMMUNITY –CLINICAL CORRELATES

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AUTOIMMUNITY

- Definition:

  When the normally effective tolerant state of the immune system to “self” antigens breaks down resulting in damaging or potentially fatal autoimmune reactions.
AUTOINFLAMMATORY

Autoinflammatory diseases are a relatively new category of diseases that are different from autoimmune diseases. However, autoimmune and autoinflammatory diseases share common characteristics in that both groups of disorders result from the immune system attacking the body’s own tissues, and also result in increased inflammation.

- Examples include Behcet’s disease, Familial Mediterranean Fever, Tumor Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS)
AUTOIMMUNITY - BREAKDOWN IN TOLERANCE TO “SELF”

- Occurs when Treg have diminished function or
- Th increases or is augmented or
- Foreign antigens “cross react” with “self”
- Release of the sequestered antigens
- Or

- Normal regulators of TOLERANCE are deficient
  - Clonal deletion in the thymus does not occur
    - Rheumatoid arthritis – persistent ”arthritogenic antigen”
  - Receptor not blocked
  - Treg deficient
AUTOIMMUNITY - BREAKDOWN IN TOLERANCE TO “SELF”

- Tolerance is not perfect
  - Healthy individuals have auto-reactivity - i.e., low levels of autoantibodies (antibodies to “self” antigens)
  - Aging - immuno-senescence - increased auto-reactivity as one ages because of the inefficient regulatory immune system –

- Organ specific Autoimmune diseases and non organ specific Autoimmune diseases -
  - Rheumatoid Arthritis
  - Systemic Lupus Erythematosus
WHY SHOULD THE CLINICIAN BE INTERESTED IN IMMUNOLOGY AND GENETICS?

Genetic Info → Immune Pathways → Clinical Disease → Targeted Therapies

Sub A → Sub B → Sub C → Sub D
Chronic systemic inflammatory disease of undetermined etiology involving primarily the synovial membranes and articular structures of multiple joints.

- Pain, stiffness, and swelling of joints leading to deformity and ankylosis.

- Significant extra-articular manifestations most due to systemic inflammation.
RHEUMATOID ARTHRITIS

- 1% population
- 3:1 female to male
- Two peaks incidence
- Morbid disease
- Description dates to the 16th century
- Waxes and wanes
- Am stiffness
- Pattern of involvement
EARLY RHEUMATOID ARTHRITIS
RHEUMATOID ARTHRITIS – JOINT DAMAGE
The synovium serves as an important source of nutrients for cartilage. Two types of synovial cells A and B.

- Cartilage itself is avascular.
- Synovial cells synthesize joint lubricants such as hyaluronic acid, as well as collagens and fibronectin that constitute the structural framework of the synovial interstitium.
RHEUMATOID ARTHRITIS - JOINT

SYNOVIAL CAVITY

EROSIONS JOINT DESTRUCTION
Synovial lining infiltrated with inflammatory cells
T and B lymphocytes, plasma cells, follicular dendritic cells, macrophages and mast cells, CD4+ (memory CD45RO+)
Tumor-like tissue
RHEUMATOID ARTHRITIS WASTING DISEASE

- Fever spikes
- Weight loss
- Fatigue
- Anorexia
- Muscle wasting
RHEUMATOID NODULES
RHEUMATOID ARTHRITIS

- Rheumatoid nodules
- Lung – Caplan’s syndrome
- Lung Fibrosis
- Rheumatoid vasculitis
- Pleuritis
- Pericarditis

*Autoimmunity and
*Autoinflammation
RHEUMATOID ARTHRITIS - EYE

Scleral thinning

Scleromalacia perforans
RHEUMATOID VASCULITIS DIGITAL INFARCTS
DIGITAL GANGRENE
LAB CLUES RHEUMATOID ARTHRITIS

- High titer
  Rheumatoid factor
- Elevated
  Sedimentation rate
- Lower Hemoglobin
- GI bleeding
HOW DO RHEUMATOLOGISTS DIAGNOSE CLINICAL RHEUMATOID ARTHRITIS?

- Four of Seven Criteria* OLD ACR CRITERIA
  - Morning stiffness > 1 hour
  - 3 or more swollen joints present for 6 weeks
  - symmetric joint involvement for 6 weeks
  - joints of the hands and wrists for 6 weeks
  - erosions on Xray
  - presence of Rheumatoid nodules
  - Rheumatoid factor

* these criteria were replaced by the EULAR/ACR criteria
EULAR CRITERIA 2010 – WHY CHANGE THE CRITERIA?

- Patients must achieve a total score of 6 or greater (of a possible 10) from the individual scores in four domains:
  - number and site of involved joints (range 0–5),
  - serological abnormality (range 0–3),
  - elevated acute-phase response (range 0–1)
  - symptom duration (two levels; range 0–1).

- So that the subgroup of patients with erosive and persistent disease could be identified earlier and receive more aggressive therapy.
RHEUMATOID FACTOR
“AUTOANTIBODY”

80% of all RA patients
A human antibody against Fc portion human immunoglobulin
Usually IgM directed against IgG (but any combo has been noted)
High titer (quantity)
Also binds Complement
Found in Serum and Joint fluid
Not diagnostic of RA, found in other diseases with polyclonal stimulation of B Cells
RHEUMATOID VASCULITIS AND RF

- Suggests autoreactive B cells
- Adaptive immunity is involved
- RF antibodies against the Fc portion Ig
- Highly avid in RA patients vs. normals
- Variable domains of RF light chains have somatic mutations encoding for high affinity molecules
- Form Immune complexes
RHEUMATOID ARTHRITIS    RF
WHO IS SUSCEPTIBLE TO DEVELOPING RHEUMATOID ARTHRITIS? (GENES)

- 1970’s noted Association with MHC II-HLA DR4
- Multiple studies have noted only certain alleles of HLA DR4 confer susceptibility
- Susceptibility – located HLA DRB1 gene
- All RA associated alleles “share” an amino acid sequence – the shared epitope
- In all populations RA susceptibility is conferred by the shared epitope
- YAKIMA
RHEUMATOID ARTHRITIS
INDIVIDUAL ALLELES AND THE SHARED EPITOPE

- **HLA-DRB1*0401** — present in 50 to 61 percent with a relative risk of 5 to 11.
- **HLA-DRB1*0404** — present in 27 to 37 percent with a relative risk of 5 to 14;
- **HLA-DRB1*0101** — present in 13 to 27 percent with a relative risk of 1 to 2.
- **HLA-DRB1*10** — present in 1.5 percent of RA patients with a relative risk of 2.3

All “share” an amino acid sequence--
HOW DO HLA CONFER SUSCEPTIBILITY?

- Shaping the T cell repertoire during development
- Shaping the peripheral T cell repertoire
- Determining which antigenic peptides are bound and therefore presented to the immune system for recognition
- Generating molecular mimicry between self antigens and either the HLA molecule itself or peptides that it recognizes.
- HLA proteins present either foreign or self antigenic peptides to autoreactive T cells
HOW DO HLA CONFER SUSCEPTIBILITY?

- Infection, exogenous agents or "molecular mimicry" may reactivate silenced T cells in autoimmune diseases.
- The loss of HLA gene expression because of viral infection, somatic mutations or other causes may also have important effects on immune suppression and cancer development.
- Antigen processing and presentation.
RHEUMATOID ARTHRITIS HLA

- Genetics and autoimmune diseases - rapid and unprecedented expansion
- Multiple genes contribute to each of the major autoimmune disorders, with significant genetic overlaps among them.
- Rheumatoid arthritis genetic data reveal
  - new diagnostic subgroups
  - complex overlapping relationships with other autoimmune disorders
  - potential new targets for therapy.
- Genome-wide association scans (GWAS) - major common genetic risk factors
GENES AND AUTOIMMUNITY

- Genome for DNA polymorphisms associated with many autoimmune diseases.
  - celiac disease
  - Crohn's disease
  - multiple sclerosis
  - rheumatoid arthritis
  - systemic lupus erythematosus
  - type-1 diabetes

- GWAS have increased the number of genetic risk variants associated with these autoimmune diseases from 15 before 2006 to over 68
RHEUMATOID ARTHRITIS

- Advances in defining genetic susceptibility to RA suggest that aberrant pathways of T-cell activation, differentiation, and persistence are key.

- Disease associated genes
  - *HLA-DRB1*
  - *PTPN22*—Protein tyrosine phosphatase, non-receptor type 22 (lymphoid)
  - *CTLA4*—Cytotoxic T-Lymphocyte Antigen 4
  - *IL2RA*—Interleukin-2 receptor alpha chain
  - *IL2RB*—Interleukin-2 receptor beta chain
  - *STAT4*—transcription factors
  - *TRAF1* locus—(encoding tumor necrosis factor receptor-associated factor 1) and *C5* (encoding complement component 5).
Chronic Synovitis

Rheumatoid Factors

B-cell receptor (BCR)

Mitosis and Differentiation

Lymphokines

Rheumatoid Factors

Antibodies

Secretion

Plasma cell

IL 6

Macrophage

Helper T cell

CD 4

B cell
RHEUMATOID ARTHRITIS SUMMARY

- RA is perhaps best described as a prototype chronic inflammatory disease with features of autoimmunity.
- The target of autoreactivity remains unclear, immune reactions to inflammation arising as a consequence of tissue damage and cell death.
- Defects in antigen receptor signaling that probably have impacts on both central thymic and peripheral pathways of tolerance.
- Over-exuberant conventional pathways of antigen-specific activation.
- Selective approaches for targeting adaptive immunity have been more successful than those based on more conventional immunosuppression.
Newest autoantibody found in RA patients
Associated with the shared epitope
RA-associated HLA-DR4 molecules (DR4) can bind and present citrullinated peptides much more efficiently
RA disease - CVD, more joint destruction

What is a citrullinated peptide?

the exchange of the charged arginine for the non charged citrulline
WHY ARE ACPA IMPORTANT IN RA?
WHAT IMMUNE PROCESSES ARE IN RA?

- Autoreactive Polyclonal B cells
- Autoantibodies RF and ACPA
- Complement cascade activated
- Immune complexes are formed
- Susceptibility conferred on HLA DR4, HLA DRB1
- Production of certain cell products that activate inflammation and destruction - CYTOKINES
  - Tumor necrosis factor
  - Interleukin 6
THE IMMUNE CASCADE IN RA

- Dendritic
- Co-stimulation required

- T
  - Co-stimulation required
  - TNF alpha

- Macrophage
  - TNF
  - IL-1
  - IL-6

- B
  - Anti-CCP
  - Anti-GPI
  - Anti-RA33
T Cell Model for Synovitis in RA

- **Arthritogenic antigen**
- **T cell activation**
- **Regulation by cytokines**
- **Effector mechanisms for joint destruction**

**Activation**
- TNFα
- IL-1
- IL-2
- IFNγ
- IL-8
- TNFβ
- iNOS
- IL-6

**Inhibition**
- IL-4
- IL-10
- IL-11
- TGF-β
- sIL-8R
- sTNFR

**Activation of synoviocytes**
- Metalloproteinases

**Activation of vascular adhesion molecules**
- PMNs, lymphocytes, macrophages into joint

**B cells**
- Immunoglobulin
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HOW DO WE TRANSLATE WHAT WE KNOW INTO TREATMENT FOR RHEUMATOID ARTHRITIS?

- Targeted therapies to specific immune responses and how their success tells us about the disease
TREATMENTS

- Steroids and antimetabolites such as Methotrexate
- Targeted therapies Monoclonal antibodies
  - Anti Tumor Necrosis factor
  - Interleukin 1
  - Anti Co stimulatory molecules
  - Anti B cell
  - Interleukin 6
  - Anti T cell therapies
RA IMMUNE CASCADE

Cytokine release and proliferation

Activated T cell

Activated Macrophage

Activated B cell

Upstream mechanisms

T cell co-stimulation – abatacept

Anti-CD20 – rituximab

IL-6

TNF-α

IL-1

Autoantibodies, e.g. RF

Osteoclast

Chondrocyte

Downstream effects

Inflammation and destruction

Anti-TNF-α – etanercept, infliximab, adalimumab
Anti-IL-1 – anakinra
Anti-IL-6R – tocilizumab
RHEUMATOID ARTHRITIS SUMMARY

- Autoimmune disease resulting in symmetric joint destruction, systemic disease with autoinflammatory features
- Unknown Antigen trigger
- MHC II HLA DR 4 HLA DRB1 “Shared” epitopes
- Autoantibodies rheumatoid factor and anti cyclic citrullinated peptides- define subclasses of RA
  - Have pathogenic and prognostic significance
- Involves the Adaptive and Innate Immune system
RHEUMATOID ARTHRITIS
SUMMARY

- Multiple Effector cells release cellular products that result in joint and multiple organ destruction
- Immune complexes and complement are active
- Multiple theories have been proposed to explain the findings
- Suppression of the autoreactivity improves Rheumatoid arthritis
RHEUMATOID ARTHRITIS SUMMARY

- But Targeted therapies have changed the course of Rheumatoid arthritis
- Information from Targeted therapy suggest T cell or IL 1 suppression not helpful once the disease is apparent
- Targeted therapies Rheumatoid arthritis is not one disease and autoimmune processes overlap between autoimmune diseases
WHY SHOULD THE CLINICIAN BE INTERESTED IN IMMUNOLOGY AND GENETICS?

- Genetic Info
- Immune Pathways
- Clinical Disease
- Sub A
- Sub B
- Sub C
- Sub D
- Targeted Therapies
RHEUMATOLOGY
HARD TO SPELL
HARDER TO PRACTICE

thank you for your kind attention