Rheumatoid Arthritis

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Goals

To learn:
1. What are the genetic factors?
2. What are the environmental factors?
3. What are the current therapies?
4. How do we distinguish RA from other forms of Arthritis?
Rheumatoid arthritis (RA)

Definition: a chronic autoimmune disease that symmetrically affects large and small joints with inflammation and ultimate deformity.
Rheumatoid Arthritis affects more than joints

May also affect other organs such as:
- **eye** (dry eyes - keratitis)
- **skin** (nodules and vasculitis)
- **lungs** (nodules and infiltrates)

and cause:
- **neuropathy** (disease of nerves)
- **anemia** (low red blood cells/hemoglobin)
- **fatigue** (due to sleep disturbance)

Heart disease - the main cause of death in RA is early atherosclerosis.
Schematic of Joint Inflammation

Normal Joint

Joint Affected by Rheumatoid Arthritis

Bone Loss/Erosion
Cartilage Loss

Bone Loss (Generalized)
Inflamed Synovium
Swollen Joint Capsule
History of RA - 1

• The first known traces of arthritis based on x-ray date back at least as far as 4500 B.C. from burial grounds of Native American Indians, found in Georgia and Tennessee.

• In the Old World (Europe), the disease is vanishingly rare before the 17th century.
• Anthropologists believe it spread across the Atlantic during the Age of Exploration with the slave trade.

• In 1859, the disease acquired its current name—“Rheumatoid Arthritis” by British rheumatologist Dr. Alfred Baring Jarrod.
Peter Paul Rubens first depicts the effects of RA.

*The Three Graces* -- 1658 by Reubens previously also showed RA in “The Miracle of St. Ignatius of Loyola (1618)"
Dr. Rubens’ Recommendations

Rubens himself had gouty arthritis, and recommended:
bleeding  bee venom  honey
rest      copper bracelets  vitamins
fasting  tooth extractions  magnets
nutmeg  apple & rhubarb diet
compression & elevation

“some light exercise every now and then”
“nettles” (stinging plant contact)
Infections and Arthritis - 1

- RA originally considered an infection, most likely a form of Tuberculosis (TBC), and treated with heavy metals used for “scrofula”

  - *Initially:* lead and mercury
  - *Later:* gold injections (which you may remember from 20 yrs ago). It worked but gold became too expensive
RA General Population Incidence

- About **0.6%** of the United States adult population has RA,
  - **women two to three times** as often as men.

- **ONSET** is most frequent during middle age, but people of *any age* can be affected.

- The worldwide incidence distribution and severity vary, but this may reflect access to therapy.
Very High Incidence of RA in American Indians
(the first Indian with RA gene about 5000 AD)
Overview of Clinical Presentation of Arthritis if symptoms last over 6 weeks

We look for:

- **Symmetry** in location (i.e., both hands or feet)
- **Positive rheumatoid factor** (RF) blood test
- **Positive anti-CCP** (anti-citrullinated peptide) blood test
- **Erosions of joints** visible on x-rays
Clinical Definition

We also exclude other arthritic conditions, such as the “sero-negative variants” (since they have different therapeutic responses)

Psoriasis
Inflammatory Bowel Disease (IBD)
Ankylosing Spondylitis
Reiter’s Disease
Lyme and other infectious causes
Osteoarthritis
Different Joints Are Predisposed

- DIP: OA, psoriatic, Reiter’s
- PIP: OA, SLE, RA, psoriatic
- MCP: RA, pseudogout, hemochromatosis
- 1st CMC: OA
- Wrist: RA, pseudogout, gonococcal arthritis, juvenile arthritis, ganglion cyst, carpal tunnel syndrome
- De Quervain’s tenosynovitis
Rheumatoid Arthritis is different than Osteoarthritis

It would be fine at age 80, but at earlier age, it represents a premature brittleness of the cartilage lining of the joint. At least, this is partly under genetic control of WNT genes.
Environmental factors and RA risk - 1

• Environmental factors in men and women:
  – – tobacco smoking
  – – periodontal disease
  – – silica dust, solvents, mineral oil
  – – air pollution
Diet and Smoking in RA

- **Diet** has been highly debated, but probably plays a role, as exemplified in **Celiac Sprue** (gluten intolerance). The peptide fits in the “groove” for a different HLA-DR

- **Smoking** is the most significant non-genetic risk with RA being up to *three times* more common in smokers.
SMOKING and OBESITY increase the risk of RA in Dutch Study.
The gene that smoking effects: Protein Tyrosine Phosphatase

This enzyme is involved in signalling pathways in lymphocytes.

The mutation Arg620Trp disrupts a binding site and serves as a target for molecular screening for drug candidates.
Screen for new drugs from herbal sources

A. Serotonin

B. Herbal analog of serotonin used in traditional medicine

C. Crystal model of serotonin IB binding pocket used for screening

D. Robotic throughput screening
Reproductive factors in women

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- OCP (oral contraceptive pill)
- perimenopausal, parity, young age at menarche, irregular menses, postpartum
- breastfeeding
We will first discuss “genetic” factors.

HLA-DR gene located on chromosome 13.
Rheumatoid Arthritis
Genetic Factors are only part of the process - 1

About **20%** of the risk for RA is believed to be genetic, which means that 80% is not simply due to your genes.

- **Disease genetic concordance in monozygotic twins** is approximately **15–20%** -- so about **80% of incidence is “epigenetic”** (viral and non-genetic events)
As we sequences genes of RA patients, the most important genetic factor

- The inherited tissue type major histocompatibility complex (MHC) on chromosome 13.

- The MHC are the same genes that get matched for tissue transplants.

- Their normal function is to allow the immune system to see “foreign” antigens or infections.
HLA-DR is the strongest gene predisposing to RA

- This transplantation antigen holds the “driving” viral particle (or “antigen”) that stimulates the T-cells.
The most important region of the HLA molecule that holds the “peptide” (10-12 amino acids) in a particular groove that can be recognized by other cells of the immune system.

This is the 3-D view with the important binding sites.
Current Candidates for Potential Pharmaceutical Therapy - 2

The molecule that fits in the groove is the “holy grail” of our search for cause of RA
Epigenetic factors alter gene expression (includes DNA recombination of genes, regulatory RNA’s, viruses, other infections and toxins)
Periodontal Disease and RA Risk - 1

- Long-standing association between periodontitis and RA

- Similar HLA-DRB1 risk factors

- Chronic inflammation adjacent to calcified tissue causes damage by similar mechanisms
Periodontal Disease and RA risk - 2

• *Porphyromonas gingivalis*, an anaerobic strep frequently associated with periodontitis, generates citrullinated antigens through PAD enzyme.

• 80% sequence homology between immuno-dominant epitope of PG and human α-enolase... CEP1 peptide.
However, the Periodontitis-RA association remains controversial

*P. gingivalis* association with ACPA:

Periodontitis in ERA, but *P. gingivalis* not specific:
- Common genetic risk; hypomethylation of IL-6 promoter:
  - Ishida, K, 2012

No association with periodontitis:
- Arkema E, et al, 2010
Epigenetic Factors and RA Risk

• **Effects of smoking** may be mediated through DNA methylation changes in loci such as F2RL3.

• **Hypo-methylation in critical genes** may be related to certain toxins found in foot or water in genetically susceptible people.

• **Viruses or other infections** may alter how certain genes are regulated in genetically susceptible individuals.
In addition to DNA and proteins...

A new player recently found after smoking and viral infections that alters gene regulation is a “regulatory RNA” molecule that does not become a protein but regulates other segments of DNA.

• miRNA (e.g., 155, 146a) levels in RA
The joint becomes a chaotic soup of inflammatory factors

- **T cell**
- **APCs**
- **B cell or macrophage**
- **Synoviocytes**
- **Articular cartilage**
- **Pannus**

**Inflammatory Factors**
- IFN-γ and other cytokines
- Production of collagenase and other neutral proteases
- Antibodies
- Immune complexes

**Cells and Factors**
- **Macrophage**
- **HLA-DR**
- **Chondrocytes**
Each of these factors is a potential target for therapy such as Enbrel (TNF), B-cells (Rituximab), IL-6.
Treatments - 1

• Treatments are *pharmacological* and *non-pharmacological*. 
  *Non-pharmacological* treatment includes:
  – physical therapy and occupational therapy  
  but these therapies do not stop progression.

• *Pain-relieving medicines* include:
  anti-inflammatory drugs and cortico-steroids.
Treatments - 2

• Disease-Modifying Anti-Rheumatic drugs (DMARDs) can slow or halt the progression of the disease.
  – The newer biologics are DMARDs, but are very expensive.

• The evidence for Complimentary and Alternative Medicine (CAM) treatments for RA related pain is weak, with the lack of high quality evidence leading to the conclusions that their use is currently not supported by the evidence.
The Players in RA

- The T-cell is the “conductor” of the orchestra.
- The B-cell makes the antibodies under the T-cell’s direction.
- The dendritic (synovial cell) makes the destructive enzyme.
- These cells intercommunicate through lymphocyte hormones called “interleukins” or “cytokines.”
Joint swelling

• **Bacterial arthritis** (such as streptococcus) is usually *asymmetric*, while **RA** usually involves *both sides of the body symmetrically*.

• **Gonococcal arthritis** (another bacterial arthritis) is also initially migratory, and can involve tendons around the wrists and ankles.
Into the Future

The screening for drug candidates

• First, crystallize the receptor and identify the 3-dimensional structure.

• Use rapid (through-put) screening to look for drug candidates that bind.

• Proceed to pre-clinical molecules for likely candidates.

• This is now largely computer automated.
The role of the rheumatologist is to give patients the permission to live at their highest functional level.

“I am only one, but still I am one.”
I cannot do everything, but still I can do something...
And because I cannot do everything, I will not refuse to do the something that I can do.”

-- Helen Keller
But from the patient’s perspective...

“I don't deserve this award,
but I have arthritis
and I don't deserve that either.”

-- Jack Benny
Thank you for inviting me

All slides are available on my website:

http://www.RobertFoxMD.com
Notable Knuckles (part 1 and 2): Evaluating Arthritic Conditions of the Hand

From our work with “Doctors without Borders” from India, China, and Tibet we have some case histories and photographs of arthritis

- www.medscape.com/features/slideshow/knuckles
- www.medscape.com/features/slideshow/knucklespart2
As we are all slowly developing Osteoarthritis...

• What are the current cures? So far, not many.
  – Weight loss, exercise, orthotics
• New candidates to try to help the joints re-surface themselves
• Lots of money spent on well-intentioned cures by naïve orthopedic surgeons
• A current focus of “regenerative” (stem cell) medicine to rationally regrow the damaged tissue
Osteoarthritis commonly affects:

- hands, feet, spine
- and the large weight-bearing joints—such as the hips and knees
- although in theory—any joint in the body can be affected.