Spondyloarthritis Diseases

A group of individually distinctive diseases with common, unifying clinical, genetic and pathophysiological features

- Ankylosing spondylitis (ASp)
- Psoriatic arthritis (PsA)
- Reiter’s syndrome (RS) / reactive arthritis (ReA)
- Undifferentiated spondyloarthritis (USpA)
- Enteropathic arthritis (ulcerative colitis, regional enteritis)

Psoriasis, a related condition

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Spondyloarthritis Diseases

**Unifying features**

**Clinical:**
Each distinguished by three main target sites of inflammation

- **Enthesitis:** fibrocartilage insertions of ligaments, tendons & fascia
- **Spondyloarthritis:** spine and sacroiliac joints
- **Synovitis:** peripheral joints

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Spondylitis: syndesmophytes and ankylosis

**ASp**

Activated T cells invade the junction of annulus fibrosis and vertebral body, triggering granulation tissue response

Annulus fibers eroded, then replaced by fibrocartilage:
- Subperiosteal new bone formation
- Fibrocartilage ossifies to form syndesmophytes

Inflammation resolves, but progressive cartilaginous and periosteal ossification forms a “bamboo spine”

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Sacroiliitis

- Subchondral regions of synarthrotic SI joints invaded by Activated T cells and granulation tissue
- Erosion of cartilage on iliac side
- Bone plate blurring, joint space “widening” and reactive sclerosis
- Fibrous ankylosis replaced by bone obliterating SI joint

Resolution of inflammation by heterotopic bone formation
Inflammatory back pain
Due to the initial inflammation of enthesitis, spondylitis or sacroiliitis

- Onset before age 40
- Insidious persistent (> 3 mo) dull deep buttock or low back pain
- Poorly localized, does not follow nerve root
- Stiffness/pain upon arising in the morning, or awakens from sleep
- Improves with exercise

Spondyloarthritis Diseases
Unifying features
Genetics
Susceptibility associated with certain Class I MHC alleles

- **HLA-B27**
- HLA-B27 frequency (%)
  - Ankylosing spondylitis 95
  - Reiter’s syndrome (reactive arthritis) 60-70
  - Psoriatic arthritis 15-20
  - Ethnically matched controls 3-8
- Other class I alleles also involved

Unifying features
Pathophysiologic Mechanism
A clue from clinical medicine

Unlike other autoimmune diseases that regress during development of AIDS, most spondyloarthritis diseases worsen or develop *de novo* at this time

Implication:
CD4 T cells not required for development of symptomatic disease

Spondyloarthritis Diseases
Pathophysiology
Activation of autoreactive CD8 T cells that recognize self-peptides in the context of class I MHC molecules

Autoantibodies such as ANA or RF are not present, hence they are sometimes called “seronegative arthritides”

Pathogenesis incompletely understood but seems to be at the interface of triggering CD8 T cell clones of the adoptive immune system by receptors recognizing innate immune system ligands

Memory effector CD8 T cells loose CD28 and express natural killer receptors that bind Class I molecules and other ligands induced by stress and tissue injury

Triggers:
Loss of self-MHC (missing self) or increased expression of ligands reflecting tissue stress or danger

IL-15
### Spondyloarthritis Disorders

**CD8 T cell effector mechanisms of tissue injury**

- Activated CD8 T cells injure target cell and release cytokines (γ-IFN), reprogramming gene expression of nearby cells
- CD8 T cells are CD28-negative, memory / effector cells that receive "signal 2" from NK receptor engagement by stress-induced ligands
- Macrophages activated by γ-IFN release cytokines (TNF-α)
- Fibroblasts usually have fibrogenic and osteoblastic program activated resulting in heterotopic bone formation

### Spondyloarthritis Diseases

- **✓** Ankylosing spondylitis (ASp)
- **✓** Psoriatic arthritis (PsA)
- **✓** Reiter’s syndrome (RS) / reactive arthritis (ReA)

### Ankylosing spondylitis - Course

- Begins with sacroilitis
- Inflammatory back pain and tenderness worsens and over several months to years ascends, with increasing stiffness and loss of mobility
- Postural changes: loss of lumbar lordosis, buttock atrophy and kyphosis; chest expansion compromised
- Peripheral joints, notably hips develop flexion contractures or ankylosis; compensatory knee flexion
- Peripheral arthritis (~30%) and peripheral enthesopathy (~30%) dominate the early phase of disease, then bony ankylosis predominates

### Ankylosing spondylitis - systemic involvement

- **✓** Widespread spondylitis and sacroilitis
- Male: female =3-10:1
- Culminates in boney ankylosis of spine
- Onset, age 10-25 with dull pain in lumbar or gluteal regions
- Hip, shoulder knee arthritis in ~30%
- Epidemiology: >95% of those affected are HLA-B27
- Disease prevalence follows circumpolar distribution of HLA-B27
- Affects 1-3% of HLA-B27 individuals,
- No evidence for triggering by microorganisms

### Therapy

- **T cell-directed**
  - Biologics, e.g. anti CD28 (abatacept)
  - Calcineurin inhibitors
- **Cytokine inhibition**
  - Methotrexate
  - TNF blockers
- **Anti inflammatory**
  - NSAIDS
- **Physical medicine**

### Ankylosing spondylitis

- Acute anterior uveitis (25%) may occur at any time; (syncheae and glaucoma)
- Apical pulmonary fibrosis, often with cavitation (<5%)
- Restrictive pulmonary disease due to costovertebral ankylosis (~ 10%)
- Granulomatous aortitis: complete heart block due to interventricular septum inflammation and/or aortic insufficiency (~5%)
Ankylosing spondylitis—different types of HLA-B27

HLA-B27 alleles differ from one another in polymorphic amino acids, in ethnic distribution and, importantly, whether they determine disease susceptibility

<table>
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<tr>
<th>Allele</th>
<th>Features</th>
<th>Ank Spon</th>
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<tr>
<td><em>B</em>2701</td>
<td>Rare</td>
<td>Yes</td>
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<tr>
<td><em>B</em>2702</td>
<td>10% of AS in Europe and Middle East</td>
<td>Yes</td>
</tr>
<tr>
<td><em>B</em>2703</td>
<td>Rare West African allele</td>
<td>Yes</td>
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<td><em>B</em>2704</td>
<td>Major HLA-B27 allele in China and India</td>
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<tr>
<td><em>B</em>2705</td>
<td>90% of AS, circumpolar Caucasians &amp; Asians</td>
<td>No</td>
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<tr>
<td><em>B</em>2706</td>
<td>SE Asia</td>
<td>No</td>
</tr>
<tr>
<td><em>B</em>2707</td>
<td>Minor allele in SE Asia, China and India</td>
<td>Yes</td>
</tr>
<tr>
<td><em>B</em>2708</td>
<td>Rare, UK and Azores</td>
<td>Yes</td>
</tr>
<tr>
<td><em>B</em>2709</td>
<td>Sardinia</td>
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A self-peptide likely drives ankylosing spondylitis

HLA-B27 alleles share the same P2 “B” pocket, but differ from one another in the “F” P9 pocket

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<th>P9 Pocket</th>
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<td><em>B</em>2701</td>
<td>Tyr 59</td>
<td>Asp 80</td>
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<td>Tyr 77</td>
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Current theories of why HLA-B27 predisposes to Ankylosing Spondylitis

Peptide binding properties of HLA-B27

Distinctive chemical state of HLA-B27 molecules

- Transgenic rats expressing >100 copies of HLA-B27 develop a disease with some features of ankylosing spondylitis
- HLA-B27 misfolds and elicit an altered protein stress response in endoplasmic reticulum

Psoriasis / Psoriatic Arthritis

Psoriasis: skin disease with retardation in keratinocyte differentiation induced by activated T cells
Perhaps keratinocyte peptides are presented by class I molecules?

Psoriatic arthritis: spondiloarthritis and psoriasis

Psoriasis
Onset age 15-30 yrs
Prevalence ~3%
10-20% of patients between Ps & PsA

Psoriatic arthritis
Onset age variable
10-20% of patients have Ps & PsA

Clinical Diagnostic Features of Psoriatic Arthritis

Characteristic features:
- Psoriasis present or documented
- Enthesitis
- Ankylosed joints, e.g. hallux rigidus
- Juxta-articular new bone formation
- Sacroiliatis and/or spondyloarthritis
- DIP joint arthritis
- Onychodystrophy
- Dactylitis

Exclusions:
- Fibromyalgia, RF positive rheumatoid arthritis
- Intercurrent arthritis, e.g. Lyme disease
- Repetitive motion-induced musculoskeletal syndromes
Psoriatic arthritis - features

- Presentation: with obvious, subtle or no psoriasis, sometimes only isolated nail disease
- Onset typically insidious with stiffness; sometimes acute mimicking gout; can follow joint injury
- Sex: Male = female
- Early onset (<40 yrs) psoriatic arthritis has strong family history

Psoriatic arthritis

Enthesitis

- Sometimes subtle and easy to overlook
- Nonspecific foot pain, “tennis elbow” in the non dominant hand, or isolated posterior tibial tendinitis
- Widespread and symmetric, distribution differentiates from posttraumatic or occupational tendon injury
- Can be fulminant and combined with intense tenosynovitis

Psoriatic arthritis-peripheral joint patterns

- Asymmetric oligoarthritis of small and medium-sized joints
  
  Classic, with time more joints accumulate

- DIP arthritis joints, also involves nails
  
  Classic and unique to psoriatic arthritis, but only ~5-10%
  
  Associated paronychia and swelling of the digital tuft may make appreciation of arthritis difficult; DDx Heberden’s nodes

- Arthritis mutilans
  
  Osteolytic dissolution of joint with redundant overlying skin and telescoping digits (opera-glass hand)
  
  Typical but uncommon; males and early-onset disease

Psoriatic arthritis-peripheral synovitis patterns

- Symmetric polyarthritis
  
  Most common pattern at onset, but is least specific for PsA
  
  Hands, wrists, ankles, and feet
  
  Differentiated from RA by enthesopathy and dactylitis, DIP joint involvement, relative asymmetry, new bone formation, pencil in cup deformity, absence of subcutaneous nodules, and negative RF

  Important to distinguish RA from PsA because steroids contraindicated
Psoriatic Arthritis—Nail Involvement

- ~80-85% PsA, vs. 20-30% in Ps

Nail matrix abnormalities
- Pitting
- Onychodystrophy, crumbling
- Subungual hyperkeratosis
- Leukonychia
- Onycholysis
- Eccrine capillaries

Acral dystrophy
- Nail matrix abnormalities
- Acrokeratosis
- Often seen in digit involved with DIP arthritis

Psoriatic Arthritis Genetics

~60% strongly positive family histories, most often first degree relatives affected by psoriasis

Mode: mixed multifactorial pattern, partially dominant, incompletely penetrant

Psoriatic arthritis genetics

Genetic Heterogeneity in MHC associations

1. Psoriasis susceptibility HLA-alleles containing: HLA-Cw*0602, (Psors 1) Account for ~30% of PsA cases (and 70% psoriasis cases)

HLA-Cw*0602
HLA-B17
HLA-Cw*0602
HLA-B17
HLA-Cw*0602
HLA-B17

Psors 1
Psors 1
Psors 1
Psors 1
Psors 1
Psors 1

Psors 1
Psors 1
Psors 1
Psors 1
Psors 1
Psors 1

Psoriatic arthritis genetics

Genetic Heterogeneity in MHC associations

2. Second group of HLA-B alleles, e.g. HLA-B27 and HLA-B39

Account for ~30% of psoriatic arthritis (not as strongly associated with psoriasis)

HLA-Cw*0202
HLA-B*2705
HLA-Cw*0101
HLA-B*2705
HLA-Cw*1203
HLA-B*3901

Psors 1
Psors 1
Psors 1
Psors 1
Psors 1
Psors 1

Psoriatic arthritis genetics

Genetic Heterogeneity in MHC associations

Imply susceptibility governed by different interactions with genes outside MHC
e.g. genes encoding NK receptors expressed on memory-effector CD8+ T cells (KIR system)

Imply different pathophysiologic mechanisms and the possibility of clinical differences

These are now being identified

Specific Spondyloarthritis Diseases

Reiter’s syndrome / Reactive arthritis

Directly triggered by specific pathogenic microorganisms in genetically susceptible persons (HLA-B27)

First example of a MHC allele controlling an immune response in humans (1974 Brewerton)
Reiter’s syndrome / Reactive arthritis

“On August 21, 1916 a lieutenant in the Prussian army developed abdominal pain and diarrhea. This episode lasted 48 hours and was followed by a latent period of 7 days at which time urethritis and conjunctivitis occurred. “The following day he developed polyarthralgias and arthritis of the knees, ankles, elbows, wrists and several interphalangeal joints. “Within a few days the symptoms remitted and the patient remained well for 3 weeks. “A relapse followed with a recurrence of urethritis and uveitis”

H. Reiter (Andre Calin)

Triad of Reiter’s syndrome

Reiter’s syndrome - Clinical features I

- Onset 7-30 days after specific enteric or venereal infection
- Course: Initial episode completely regresses, occasionally returns as increasingly intense recrudescences becoming chronic
- Peripheral arthritis: acute, highly inflammatory asymmetric arthritis involving knees, ankles, toes, and fingers (2-4 joints)
  - All joints synchronous in abrupt fulminant onset
- Enthesitis - notably plantar fascia and Achilles tendon (40%)
- Dactylitis (Sausage digit) (40%)
- Sacroiliits, stuttering spondylarthritis

Reiter’s syndrome - Clinical features II

- Onychodystrophy: subungual hyper- and para-keratosis
- Conjunctivitis (often first manifestation). Uveitis in recurrent disease
- Non specific urethritis
- Heart - 10% of chronic phase 1st heart block from IV septum inflammation;
  - Aortic valve insufficiency due to granulomatous aortitis at aortic ring, rarely aortic dissection

Reiter’s syndrome - role of specific infection

Develops 7-30 days after enteric infection with certain Gram neg. rods

- *Salmonella typhimurium*, and occasionally *S. paratyphi* or *S. heidelbergii*
- *Shigella flexneri* 2a and 2b, but not *S. sonnei*
- *Yersinia enterocolitica*
- *Campylobacter jejuni* or *C. fetus*

These organisms typically invade and kill intestinal M cells, perhaps arthritogenic peptides cross-presented in class I MHC

Develops 7-30 days after venereal infection with

- *Chlamydia trachomatis* or *C. psittaci*
  - Obligate intracellular eubacteria

Psoriasis / Reiter’s syndrome in the setting of AIDS

Provided major clue pointing to importance of CD8 T cells in pathogenesis

Major source of disability in otherwise relatively well HIV+ patients in developing countries where HIV therapy is inadequate
Psoriasis / Reiter’s syndrome in the setting of AIDS

- Keratoderma blennorrhagicum - pustular psoriasis-like lesions of palms and soles
- Psoriasis-like lesions (T cell infiltration, keratinocytes HLA-DR+) with delayed differentiation, parakeratosis, sterile microabsesses

Progression to psoriasis pattern of skin disease in AIDS