Spondyloarthritis Diseases

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

- 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
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
Enthesitis (enthesopathy): the central inflammatory unit of spondyloarthritis

Classic example: Calcaneal spurs at plantar fascia and Achilles tendon (Lover’s heel)

Features of inflammation:

• Infiltration of entheses by activated T cells
• Granulation tissue forms (activated macrophages and fibroblasts)
• Bone erosions and heterotopic new bone formation
Annulus fibers eroded, then replaced by fibrocartilage:
- Subperiosteal new bone formation
- Fibrocartilage ossifies to form syndesmophytes

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

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

- 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

Strong familial aggregation
50-70% FHx +

High identical twin concordance

Genetically complex pattern of inheritance

Unifying features

50-70% FHx +

Genetically complex pattern of inheritance
Spondyloarthritis Diseases

Unifying features

Genetics

Susceptibility associated with certain Class I MHC alleles

- **HLA-B27 !!**

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA-B27 frequency (%)</th>
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</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>95</td>
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<tr>
<td>Reiter’s syndrome (reactive arthritis)</td>
<td>60-70</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>15-20</td>
</tr>
<tr>
<td>Ethnically matched controls</td>
<td>3-8</td>
</tr>
</tbody>
</table>

- Other class I alleles also involved
Spondyloarthritis Diseases

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*

Autoantibodies such as ANA or RF are *not* present, hence the term “seronegative arthritides”
Memory effector CD8 T cells lose CD28 and express natural killer receptors that bind Class I molecules and other ligands induced by stress and tissue injury.

**Triggers:**

- Increased expression of activating ligands reflecting tissue stress or danger (also loss of MHC I)
- IL-15
Spondyloarthritis Disorders

Unifying features

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 Disorders

Therapy

*Physical medicine*

*Anti inflammatory*
  NSAIDS

*Cytokine inhibition*
  Methotrexate
  TNF blockers

*T cell-directed*
  Biologics, e.g. anti CD28 (abatacept)
  Calcineurin inhibitors
Spondyloarthritis Diseases

- Ankylosing spondylitis (ASp)
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Ankylosing spondylitis

- Widespread spondylitis and sacroiliitis
- 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
Ankylosing spondylitis - Course

• Begins with sacroiliitis

• 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

- Acute anterior uveitis (25%) may occur at any time; (synchæae 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>
<thead>
<tr>
<th>Allele</th>
<th>Features</th>
<th>Ank.Spon</th>
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<tbody>
<tr>
<td>B*2701</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>B*2702</td>
<td>10% of AS in Europe and Middle East</td>
<td>Yes</td>
</tr>
<tr>
<td>B*2703</td>
<td>Rare West African allele</td>
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<tr>
<td>B*2704</td>
<td>Major HLA-B27 allele in China and India</td>
<td>Yes</td>
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<tr>
<td>➡️ B*2705</td>
<td>90% of AS, circumpolar Caucasians &amp; Asians</td>
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<tr>
<td>B*2706</td>
<td>SE Asia</td>
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<tr>
<td>B*2707</td>
<td>Minor allele in SE Asia, China and India</td>
<td>Yes</td>
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<tr>
<td>B*2708</td>
<td>Rare, UK and Azores</td>
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<tr>
<td>B*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.

<table>
<thead>
<tr>
<th>Allele</th>
<th>59</th>
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<th>80</th>
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<td>Agn</td>
<td>Thr</td>
<td>Asp</td>
<td>His</td>
<td>Yes</td>
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<tr>
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<td>Tyr</td>
<td>Agn</td>
<td>Ile</td>
<td>Asp</td>
<td>His</td>
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<tr>
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<td>Thr</td>
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<tr>
<td>B*2707</td>
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<td>Asp</td>
<td>His</td>
<td>Yes</td>
</tr>
<tr>
<td>B*2708</td>
<td>Tyr</td>
<td>Ser</td>
<td>Ile</td>
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<td>Yes</td>
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<tr>
<td>B*2709</td>
<td>Tyr</td>
<td>Asp</td>
<td>Thr</td>
<td>His</td>
<td>His</td>
<td>No</td>
</tr>
</tbody>
</table>
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
Cysteine in α-helix results in disulfide-linked HLA-B27 dimers.
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: spondloarthritis and psoriasis

Psoriasis
Onset age 15-30 yrs
Prevalence ~3%

Psoriatic arthritis
~15% no prior psoriasis

10-20% 0-20+ years between 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
- Sacroiliitis 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

**Dactylitis** (Sausage digit) widespread inflammatory edema due to:

- DIP and PIP arthritis of same ray
- Enthesitis
- Tenosynovitis (flexor > extensor)
- Periostitis
- Onychodystrophy

*Acral dystrophic state*
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
Progression of DIP arthritis

Narrowed joint space & condylar erosions

Reactive sub periosteal new bone

Pencil in cup appearance
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
Psoriatic Arthritis-Nail Involvement

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

Nail matrix abnormalities
  • Pitting
  • Onychodystrophy, crumbling
  • Transverse ridging (Beau's lines)
  • Subungual hyperkeratosis
  • Leukonychia
  • Onycholysis
  • Ectatic 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

$\lambda_R = 55$ (assuming prevalence 0.1%)
Psoriatic arthritis genetics

Genetic Heterogeneity in MHC associations

1. Psoriasis susceptibility HLA haplotypes containing: \textit{HLA-Cw*0602, (Psors I)} Account for \textasciitilde 30\% of PsA cases (and 70\% psoriasis cases)
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-B39 molecules very similar to HLA-B27 in peptide binding
No common HLA-C alleles
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%)

- **Sacroiliitis, stuttering spondyloarthritis**
Reiter’s syndrome
Spondyloarthritis

**Sub periosteal new bone formation a major feature**

- Infiltration of T cells
- Fluffy reactive new bone formation
- “Square” vertebrae but minimal paravertebral ossification
- Asymmetric involvement of only one or two vertebral units
Reiter’s syndrome - Clinical features II

• **Onychodystrophy**: subungual hyper- and para-keratosis

• **Conjunctivitis** (often first manifestation). Uveitis in recurrent disease

• **Non specific urethritis**

• **Painless circinate balanitis and mucosal ulcers, prostatitis**

• **Heart** - 10% of chronic phase 1° 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

- **Keratodermia blenorrhagicum** - pustular psoriasis-like lesions of palms and soles

- **Psoriasis-like lesions** (T cell infiltration, keratinocytes HLA-DR+ with delayed differentiation, parakeratosis, sterile microabscesses)
Progression to psoriasis pattern of skin disease in AIDS