Spondyloarthritis Diseases

A group of individually distinctive diseases with common, unifying features

Spondylitis Diseases

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

Undifferentiated spondyloarthritis (USpA)

Enteropathic arthritis (ulcerative colitis, regional enteritis)

Psoriasis
Spondyloarthritis Diseases

**Unifying features**

**Clinical**

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

Entheses are the specialized fibrocartilagenous region of bone where ligaments, tendons, fascia or joint capsules insert

Infiltration of entheses by T cells initiates granulation tissue producing a combination of bone erosions and heterotopic new bone formation. Calcaneal spurs at insertion of plantar fascia and Achilles ligament are classic examples (Lover’s heel).
Annulus fibers are eroded, then replaced by fibrocartilage that ossifies to form a syndesmophyte. Subperiosteal new bone formation ensues. Subchondral regions of the synarthrotic SI joints are invaded by T cells leading to the formulation of granulation tissue.
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
Identical twin concordance
Susceptibility associated with certain class I MHC alleles

HLA-B27 is a common denominator

Class I-associated autoimmune diseases
Spondyloarthritis Diseases

Unifying features

Genetics

• HLA-B27 increased, but unevenly, among spondylitis diseases

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

• Other class I alleles may also be involved, especially in PsA and RS

Spondyloarthritis Diseases

Unifying features

Mechanism

Appearance to primarily result from the 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
Spondylitis Disorders

CD8 T cell effector mechanisms of tissue injury

- Activated CD8 T cells injure target cell and release cytokines including γ-IFN that reprogram gene expression of nearby cells
- CD8 T cells are CD28-negative, memory / effector cells that receive a “signal 2” from engagement of NK receptors by stress-induced ligands
- The identity of autologous peptides /proteins driving the response is still unknown…aggrecan?
- Macrophages activated by γ-IFN release cytokines (TNF-α)
- Fibroblasts usually have fibrogenic and osteoblastic program activated

Specific Spondyloarthritis Diseases

Ankylosing spondylitis

First disease shown to be related to occurrence of a particular HLA allele

Uniquely high relationship between susceptibility and HLA-B27
Ankylosing spondylitis

- A progressive autoimmune inflammatory disease characterized by 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 distribution of HLA-B27 alleles, highest in circumpolar regions in Europe and Asia
- Affects 1-3% of HLA-B27 individuals,
- No evidence for triggering by microorganisms

Ankylosing spondylitis - Course

- Begins with sacroiliitis
- Inflammatory back pain and tenderness or pain at central entheses (iliac crests, ischeal tuberosities) progresses and ascends over several months to ~10 years, with increasing stiffness and loss of mobility
- Postural changes include loss of lumbar lordosis, buttock atrophy and thoracocervical kyphosis, chest expansion compromised
- Peripheral joints, notably the hips may develop flexion contractures or ankylosis. Compensatory knee flexion
- Peripheral arthritis (~30%) and peripheral enthesopathy (~30%) may dominate the early phase of disease, while bony ankylosis predominates later
Ankylosing spondylitis - systemic involvement

- Acute anterior uveitis may occur at any time (25%). High potential for synchiae and glaucoma
- Apical pulmonary fibrosis often with cavitation, uncommon (<<5%)
- Restrictive pulmonary disease due to costovertebral ankylosis, ~10%
- Symptomatic complete heart block due to interventricular septum inflammation and/or aortic insufficiency due to granulomatous aortitis occurring in ~5% of patients. These may appear early, even developing in HLA-B27 individuals without detectable spondylitis

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>
<td>Yes</td>
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<tr>
<td>B*2704</td>
<td>Major HLA-B27 allele in China and India</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>
<td>Yes</td>
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<tr>
<td>B*2709</td>
<td>Sardinia</td>
<td>No</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>
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<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>
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<tr>
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<td>Asp</td>
<td>Thr</td>
<td>Asp</td>
<td>His</td>
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<td>Thr</td>
<td>Asp</td>
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<td>Tyr</td>
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<td>Thr</td>
<td>Tyr</td>
<td>Asp</td>
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<td>B*2707</td>
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<td>Thr</td>
<td>Asp</td>
<td>His</td>
<td>Yes</td>
</tr>
<tr>
<td>B*2708</td>
<td>Tyr</td>
<td>Ser</td>
<td>Ile</td>
<td>Asp</td>
<td>His</td>
<td>Yes</td>
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<tr>
<td><strong>B*2709</strong></td>
<td>Tyr</td>
<td>Asp</td>
<td>Thr</td>
<td>His</td>
<td>His</td>
<td><strong>No</strong></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 may misfold and elicit an altered protein stress response
Ankylosing Spondylitis

Therapies

Physical medicine: posture and mobility

Antiinflammatory (NSAIDS)

TNF blockers

Psoriasis / Psoriatic Arthritis

Psoriasis is characterized by retardation in keratinocyte differentiation induced by the presence of activated T cells that are seemingly driven by keratinocyte peptides presented by class I molecules.

Psoriatic arthritis is an often clinically distinctive complex of spondloarthritis occurring in the setting of psoriasis. It may involve the spine or peripheral joints in a variety of patterns.

Initiated or exacerbated by stress or non specific infection.

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
- Enthesitis
- Ankylosed joints, e.g. hallux rigidus
- Juxta-articular new bone formation
- Sacroiliitis and/or spondyloarthritis
- DIP joint arthritis
- Onychodystrophy
- Dactylitis

*Supporting features:*
- Convincing past history and/or family history for psoriasis
- Peripheral arthritis, often asymmetrical at onset

*Exclusions:*
- Fibromyalgia, seronegative or seropositive rheumatoid arthritis
- Intercurrent arthritides, e.g. Lyme disease
- Repetitive motion-induced musculoskeletal syndromes

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 - features

- Presentation: with obvious skin lesions, sometimes with subtle skin involvement (eg, scalp, umbilicus, intergluteal cleft, ear), only nail manifestations, or no psoriasis; usually between ages 25 and 45

- Early onset psoriatic arthritis occurs in a setting of strong family history

- Onset typically insidious with stiffness predominating, but may be acute mimicking gout if localized to the foot or toe, sometimes seeming to following a joint injury

- Dactylitis and pitting edema of the hands or feet, sometimes asymmetrical, secondary to enthesitis and tenosynovitis, and or inflammatory back pain at onset

- Sex: Men and women are affected equally

Enthesitis

- May be quite subtle and relatively easy to overlook

- Nonspecific foot pain, "tennis elbow" in the non-dominant hand, or isolated posterior tibial tendinitis

- When more widespread and symmetric, the distribution differentiates it from posttraumatic or occupational tendon injury

- Can be fulminant and combined with intense tenosynovitis
Psoriatic arthritis-peripheral synovitis patterns

• Asymmetric oligoarthritis of small and medium-sized joints
  Classic, with time more joints accumulate, blurring asymmetry
  Digits of the hands and feet often affected first, characteristically with dactylitis

• DIP arthritis joints, where it characteristically also involves nails
  Classic and unique to psoriatic arthritis, but not common as isolated form, primarily males
  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 in early-onset disease

Progression of DIP arthritis

Narrowed joint space & condylar erosions

Reactive sub periosteal new bone

Pencil in cup appearance
Psoriatic Arthritis-Nail Involvement

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

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

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

Psoriatic arthritis-peripheral synovitis patterns

- **Symmetric polyarthritis**
  
  Most common reported pattern at onset, but if isolated has lowest specificity for PsA
  
  Not easily distinguished from coincident rheumatoid arthritis, especially seronegative
  
  Hands, wrists, ankles, and feet
  
  Female preponderance
  
  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
  
  *In absence of distinguishing features not a criterion of certain PsA*

Important to distinguish RA from PsA because steroids contraindicated
Mixed multifactorial pattern, partially dominant mode of inheritance, incompletely penetrant

~40% have strongly positive family histories, most often with first degree relatives affected by psoriasis

\[ \lambda_R = 55 \text{ (assuming prevalence 0.1\%)} \]

\[ \lambda_R = 12.2 \text{ (assuming prevalence 0.45\%)} \]

Psoriatic arthritis genetics

Multiple studies implicate several class I HLA alleles

**Genetic Heterogeneity**

Psoriasis susceptibility HLA alleles: HLA-Cw*0602, *Psors 1*

~ 60% in most series, and a group of HLA-B alleles that are in linkage disequilibrium: HLA-B57, HLA-B37, HLA-B13

HLA-B alleles HLA-B27, HLA-B38, HLA-B39 (not strongly associated with psoriasis, no common HLA-C allele in linkage disequilibrium)
Psoriatic Arthritis Therapy

- NSAIDS + Methotrexate
- Anti TNF-α receptor blockade

No systemic steroids!

Specific Spondyloarthritic Diseases

Reiter’s syndrome / Reactive arthritis

Directly triggered by specific pathogenic microorganisms in susceptible persons that carry 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 polyarthritis 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 /Reactive arthritis - features

• **Onset** 7-30 days after self limited specific enteric or venereal infection

• **Course**-Initial episode usually regresses completely after weeks to months, but occasionally can return in a series of sometimes increasingly intense recrudescences and become sustained and chronic

• **Peripheral arthritis**: acute, highly inflammatory asymmetric arthritis involving knees, ankles, toes, and fingers.
  - All affected joints usually synchronous in abrupt fulminant onset
  - Usually an oligoarthritis with 2-4 joints involved

• **Enthesitis** - notably plantar fascia and Achilles tendon (40%)

• **Dactylitis** (Sausage digit) (40%)

• **Sacroiliitis**, stuttering spondylitis with asymmetric involvement of only one or two vertebral units (50%). More extensive vertebral “squaring”
Reiter’s syndrome-Reactive arthritis

Sub periosteal new bone formation a major feature

Infiltration of lymphocytes followed by fluffy reactive new bone formation, similar to process occurring in entheses.

May produce “square” vertebrae and other features of paravertebral ossification

Some similarities to ankylosing spondylitis, but different

Reiter’s syndrome /Reactive arthritis - Clinical features

• Onychodystrophy with hyper- and para-keratosis. Often subungual

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

• Non specific urethritis

• Painless circinate balanitis and mucosal ulcers, prostatitis

• Heart - 10% of chronic phase patients develop heart block (1st) from IV septum inflammation and/or aortic valve insufficiency due to granulomatous aortitis at aortic ring, rarely see aortic dissection
Reiter’s syndrome- role of specific infection

Induction by particular pathogens, intriguing host-pathogen relationships

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*
- *Yersineae enterocoliticas*
- *Campylobacter jejuni* or *C. fetus*

These organisms typically invade and kill intestinal M cells, perhaps resulting in the expression of arthritogenic peptides in class I MHC by dendritic cell cross presentation (?)

Develops 7-30 days after venereal infection with

- *Chlamydia trachomatis* or *C. psittaci*

Obligate intracellular eubacteria

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HIV and the spondylitis diseases

- Early in the course of the HIV epidemic, a marked increase in instances of very severe Reiter’s syndrome or psoriatic arthritis-psoriasis appeared in North America in patients with frank AIDS. This is still a major problem in Africa and parts of Asia
- However, intriguingly, ankylosing spondylitis not seen with AIDS
- Sometimes the Reiter’s syndrome or psoriatic arthritis was the first finding and therapy with immunosuppressant drugs accelerated AIDS
- The paradox of a disease treated with immunosuppression appearing *de novo* in a profound immune deficiency state was an experiment of nature that eliminated the role of CD4 T cells from the pathogenesis of RS /PsA
- It also suggested that these spondylitis diseases arise from clones of previously expanded memory rather than naïve CD8 T cells

( Rheumatoid arthritis and SLE are ameliorated in advanced AIDS)
Reiter’s syndrome in the setting of AIDS

• Keratodermia blennorrhagica - pustular psoriasis-like lesions of palms and soles

• Psoriasis-like lesions (T cell infiltration, keratinocytes HLA-DR+ with delayed differentiation, parakeratosis, sterile microabscesses

Reiter’s syndrome
Progression to psoriasis pattern of skin disease in AIDS