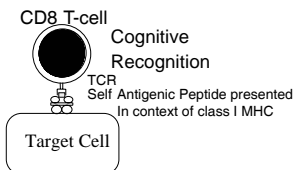


### Class I Associated Autoimmune Diseases:

A group of autoimmune diseases that appear to result almost exclusively from the activation of autoreactive CD8 T cells that recognize self peptides from various target cells presented in the context of class I MHC molecules



Theme: contrast with rheumatoid arthritis

### Class I Associated Autoimmune Diseases:

Immune mediated inflammatory diseases affecting

- joints,
- skin
- eyes
- mucous membranes

That share distinctive features:

1. Clinical:-characteristic joint involvement of arthritis plus:  
Spondylitis (inflammation of vertebral discs),  
Sacroiliitis (sacroiliac joints) and  
Enthesitis\* (tendon insertions).

All with

- Granulomatous fibrosis
- New bone formation

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

### Class I Associated Autoimmune Diseases:

2. Genetic:- Susceptibility to develop disease is associated with inheritance of certain MHC class I alleles, notably HLA-B27

3. Pathogenesis:- CD8 T cells are centrally implicated while CD4 T cells or B cells are not essential as shown by MHC class I HLA associations, plus:

- Occur at increased prevalence in those with advanced AIDS
- No Autoantibodies "Seronegative"
- CD8 T cells activated, clonally expanded and sometimes show antigen drive in sites of inflammation
- Often appear to be initiated or exacerbated by innate immune triggers (danger signals)

### Class I Associated Autoimmune Diseases:

#### Spondylitis Diseases

- Ankylosing spondylitis
- Reiter's syndrome / reactive arthritis
- Psoriatic arthritis
- Undifferentiated spondyloarthritis
- Enteropathic arthritis (ulcerative colitis, regional enteritis)

#### Psoriasis

#### Acute Anterior Uveitis

Spondylitis leads to the development of syndesmophytes and ankylosis



T cells invade the junction of annulus fibrosis and vertebral body forming granulation tissue (activated macrophages, T cells and fibroblasts)



Annulus fibers are eroded, then replaced by fibrocartilage that ossifies to form a syndesmophyte. Subperiosteal new bone formation ensues



Progressive cartilaginous and periosteal ossification forms a "bamboo spine", osteoporosis develops

#### Sacroiliitis



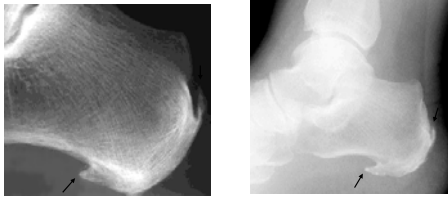
The subchondral regions of the synarthrotic SI joints are invaded by T cells leading to the formulation of granulation tissue



The cartilage on the iliac side is eroded first, causing bone plate blurring, joint space "widening" and reactive sclerosis. Ultimately the resultant fibrous ankylosis is replaced by bone, obliterating the SI joint

### Enthesitis (enthesopathy)

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



Infiltration of entheses by T cells, enthesitis, produces 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).

### Inflammatory back pain

Differential diagnosis from mechanical or degenerative spine disease

Seen in initial inflammation of spondylitis, sacroiliitis, or enthesitis involving paraspinous ligaments

- Onset before age 40
- Insidious dull deep buttock or low back pain
- Poorly localized, does not follow nerve root
- Persists > 3 months
- Stiffness/pain upon arising in the morning, or during sleep
- Improvement with exercise

### Spondylitis Disorders

Genetic epidemiology

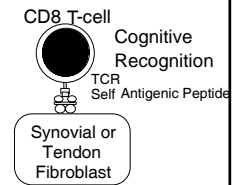
- HLA-B27 increased among nearly all spondylitis diseases

	HLA-B27 frequency (%)
Ankylosing spondylitis	95
Reiter's syndrome (reactive arthritis)	70
Enteropathic arthritis	50
Psoriatic arthritis	35
<u>Ethnically matched</u> controls	8

- The uneven association suggests recognition of different peptides
- Other class I alleles may also be involved
- Strong familial aggregation 10-25% 1st degree relatives
- Identical twin concordance ~50%

### Spondylitis Disorders

CD8 T cell effector mechanism of tissue injury



- The identity of autologous peptides /proteins driving the response still unknown
- Activated CD8 T cells may directly attack target cells
- Activated CD8 T cells, release  $\gamma$ -IFN, etc
- Secondarily activated macrophages release cytokines (TNF- $\alpha$ )
- Fibroblasts primarily have a fibrogenic program activated



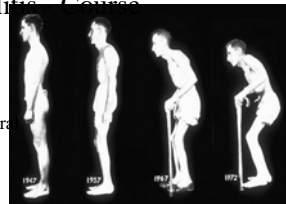
### Ankylosing spondylitis

- A progressive autoimmune inflammatory disease characterized by widespread spondylitis and sacroiliitis, mediated by CD8 T cells
- Culminates in bony ankylosis
- Onset, age 10-35 with dull pain in lumbar or gluteal regions, lasting 1-2 hours after arising. Then becomes persistent and bilateral
- Hip, shoulder knee arthritis in ~ 30%

- Epidemiology: follows distribution of HLA-B27 alleles, highest in circumpolar regions in Europe and Asia. No specific etiologic trigger
- Affects 1-3% of HLA-B27 individuals, >95% of these are HLA-B27
- Male: female =10:1

### Ankylosing spondylitis Course

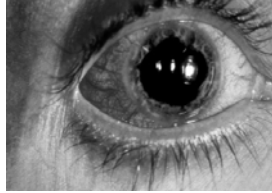
- Inflammatory back pain and tenderness or pain at central entheses (iliac crests, ischeal tuberosities) progresses over several months to years, with increasing stiffness and loss of mobility



- Highly variable progression rate
- 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 and enthesopathy may dominate the early phase of disease, while bony ankylosis predominates in the latter

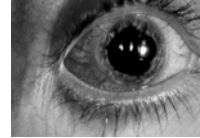
## Ankylosing spondylitis - systemic involvement

- Acute anterior uveitis may occur at any time (25%). High potential for synechiae 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



Extra articular features found in ankylosing spondylitis may occur without detectable evidence of spondylitis

Acute anterior uveitis indistinguishable from that in ankylosing spondylitis is commonly seen as an isolated inflammatory eye disease in individuals without detectable evidence of spondylitis



Ideopathic complete heart block developing in younger adults is indistinguishable from that occurring in ankylosing spondylitis and is also strongly associated with HLA-B27

## 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

Allele	Features	Ank.Spon
B*2701	Rare	Yes
B*2702	10% of AS in Europe and Middle East	Yes
B*2703	Rare West African allele	Yes
B*2704	Major HLA-B27 allele in China and India	Yes
B*2705	90% of AS, circumpolar Caucasians & Asians	Yes
B*2706	SE Asia	No
B*2707	Minor allele in SE Asia, China and India	Yes
B*2708	Rare, UK and Azores	Yes
B*2709	Sardinia, Italy	No

(It's the Allele, ... again!)

HLA-B27 alleles share the same P2 "B" pocket, but differ from one another in polymorphic amino acids at other regions, notably the "F" P9 pocket structure determined by  $\beta$ -chain amino acids 114 and 116

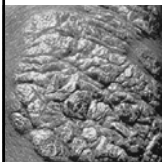
Allele	59	P9 Pocket			114	Ank.Spon
		77	80	116		
B*2701	Tyr	Agn	Thr	Asp	His	Yes
B*2702	Tyr	Agn	Ile	Asp	His	Yes
B*2703	His	Asp	Thr	Asp	His	Yes
B*2704	Tyr	Ser	Thr	Asp	His	Yes
B*2705	Tyr	Asp	Thr	Asp	His	Yes
<b>B*2706</b>	Tyr	Ser	Thr	<b>Tyr</b>	<b>Asp</b>	No
B*2707	Tyr	Asp	Thr	Asp	His	Yes
B*2708	Tyr	Ser	Ile	Asp	His	Yes
<b>B*2709</b>	Tyr	Asp	Thr	<b>His</b>	His	No

The HLA-B27 alleles not associated with susceptibility to ankylosing spondylitis may bind a different, non-inciting peptide

## Psoriasis / Psoriatic Arthritis

Psoriasis is characterized by retardation in keratinocyte differentiation induced by the presence of infiltrating T cells that are driven by keratinocyte peptides presented by class I molecules. Psoriatic arthritis is an often clinically distinctive complex of enthesitis and arthritis occurring in the setting of psoriasis. It may involve the spine or peripheral joints in a variety of patterns.

Both disorders may be initiated or exacerbated by stress or non specific inflammation or infection



### Psoriasis

Onset age 15-30 yrs  
Prevalence ~3%

10-30%  
10 years



### Psoriatic arthritis

% no  
psoriasis

## Psoriatic arthritis

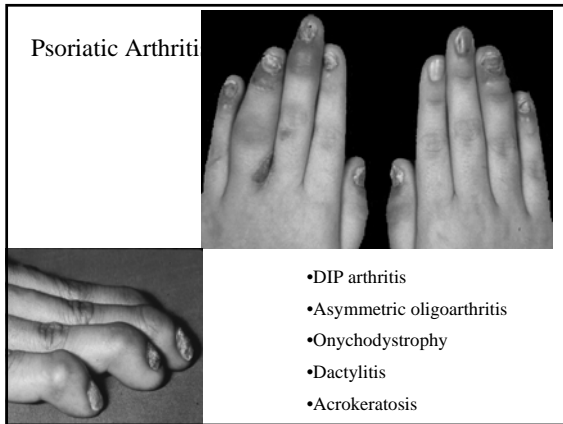
Patterns of Peripheral Arthritis (any peripheral joint)

- Symmetric polyarthritis generally similar to rheumatoid arthritis
- Asymmetric oligoarthritis of small and medium-sized joints
- DIP arthritis joints, where it characteristically also involves nails
- Arthritis mutilans

Dactylitis (Sausage digit)  
Spondylitis or sacroiliitis (40%)  
Enthesopathy and tenosynovitis  
Systemic features: leukocytosis, fever, night sweats, anemia




Psoriatic Arthritis



- DIP arthritis
- Asymmetric oligoarthritis
- Onychodystrophy
- Dactylitis
- Acrokeratosis

Psoriatic arthritis  
An ancient disease

During the Byzantine period the practice of expelling those with disfiguring diseases (biblical leprosy) from cities evoked a philanthropic response from the monasteries that took in the sick, forming the basis of the hospital

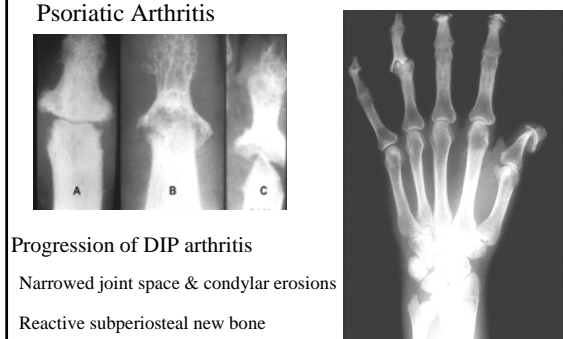


3 of 10 skeletons preserved in the Martyrius monastery outside of Jerusalem had classic features of psoriatic arthritis, 2 with arthritis mutilans

Biblical Leprosy included psoriasis and psoriatic arthritis

J. ZIAS and P. MITCHELL, Am J Phys Anthropology 101 (1996), 491-502

Psoriatic Arthritis



Progression of DIP arthritis

Narrowed joint space & condylar erosions

Reactive subperiosteal new bone

Pencil in cup appearance

Psoriatic arthritis-nature of immune process

- Susceptibility influenced by particular MHC class I alleles, e.g. HLA-B27, B57, B39, B38  
Implication: MHC class I molecules present peptide Ag to T cells in an adaptive immune response
- Disease develops in a setting of advanced AIDS  
Implication: Effector CD8 T cells are of central importance while B cells and CD4 T cells play a minimal role
- Stress and injury often precipitate or exacerbate arthritis  
Implication: Innate immune system signals are relevant to activation of effector T cell clones

**A genetically determined autoimmune arthritis with joint inflammation and destruction driven by CD8 T cells**

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 /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
- 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

A few similarities to ankylosing spondylitis, but basically 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

• Heart - 10% of chronic phase patients develop heart block (1°) from IV septum inflammation and /or aortic valve insufficiency due to granulomatous aortitis at aortic ring



### Reiter's syndrome /Reactive arthritis

Reiter's syndrome - triad of usually explosive arthritis, conjunctivitis and urethritis with keratodermic skin and nail lesions

Reactive arthritis refers to a somewhat milder and more self-limited post infectious arthritis without evidence of skin or eye involvement or urethritis

### Some features distinguishing the spondyloarthritis disorders from rheumatoid arthritis

- Spondylitis, sacroiliitis, enthesitis, dactylitis
- Arthritis distribution: usually involves large joints in asymmetric pattern, or DIP joints
- Male predominance, marked familial aggregation
- Cutaneous, mucosal, uveitis and nail involvement
- Susceptibility -certain class I MHC alleles
- CD8 T cells drive pathogenesis, no AIDS remission
- No autoantibodies, immune complexes, small vessel vasculitis or complement activation

### Reiter's syndrome- role of specific infection

Induction by particular pathogens

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 intestinal and other cells, presumably resulting in the expression of arthritogenic peptides in class I MHC

Develops 7-30 days after venereal infection with

- *Chlamydia trachomatis* or *C. psittaci*

Evidence for this is a little more controversial

### Reiter's syndrome /Reactive arthritis

• HLA-B27 present in 70% of Northern European Caucasoids, Alaskan Inuit and Northern Asians, e.g. Chuckchis (HLA-B27 frequency 25-40%) who develop Reiter's syndrome

• HLA-B27 0% in Zimbabwe, where reactive arthritis is a major health problem, occurring in association with HIV infection

• Penetrance: HIGH! In contrast to most other autoimmune diseases, up to 50% of HLA-B27 individuals develop RS / RA during major epidemics of dysentery by arthritogenic organisms

**Reiter's syndrome-Reactive arthritis -Mechanism Activation**

Disruption of "tolerance" of autoreactive CD8 T cells likely occurs through a combination of mechanisms:

- Molecular mimicry - Older theory...T cell clones involved in attack on microorganisms expand and initiate attack on cells expressing target proteins that contain peptides that mimic the amino acid sequence found in the microorganisms
- Provision of co-stimulatory signals by activated dendritic cells and macrophages in initial immune response to infection disrupts anergic or unreactive state of T cells
- CD8 T cells express NK and other receptors that foster the activation of these cells by "danger" signals recognized by innate immune system receptors

**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, now a very major problem in Africa and parts of Asia
- 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**

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



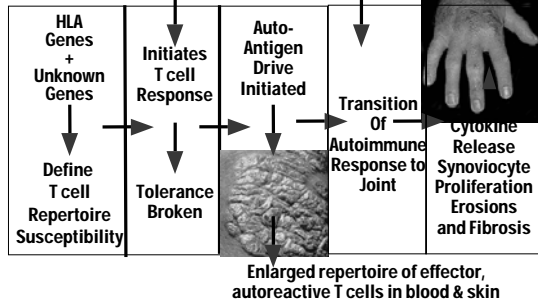
**Reiter's syndrome**

Progression to psoriasis pattern of skin disease in AIDS



**Hypothetical Scheme for Stages in Pathogenesis of Psoriatic Arthritis**

Microorganism, inflammation, trauma?



**Summary Pathogenesis scheme**

