Overview of Ankylosing Spondylitis
Genetics and pathogenesis

BSR Glasgow 3 may 2012

Paul Bowness
Consultant Rheumatologist and Professor of Experimental Rheumatology,
Oxford University.
No conflict of interest
Overview

1) Introduction
2) AS genetics
3) AS theories of pathogenesis
4) Immunotherapy of AS, clues to pathogenesis?
AS is

- A common inflammatory rheumatic disease characterized by sacroileitis and spinal inflammation (and HLA-B27)
Bamboo spine in Ankylosing Spondylitis
Sacroiliitis and hip involvement in a patient with AS
MRI showing sacroileitis
Extra-skeletal features of AS

- Iritis
- Gut inflammation
- Cardiac
- Lung
HSA B27-associated spondyloarthritides

The spondyloarthritides comprise a group of diseases sharing key clinical features and an HLA -B27 association.

- **Disease**                  HLA B27 frequency % (approximate)
- Ankylosing spondylitis       96%
- Undifferentiated spondyloarthropathy 70%
- Reactive arthritis          30-70%
- Colitis-associated spondyloarthritis 33-75%
- Psoriatic spondyloarthritis  40-50%
- Juvenile enthesitis-related arthritis 70%
Understanding pathogenesis will improve targeted treatment.

Lessons from Genetics and from trials of Biologic therapies are informative.
Overview

1) Introduction

2) AS genetics

3) AS theories of pathogenesis

4) Immunotherapy of AS, clues to pathogenesis?
Genetics of AS 1.

- Strong HLA-B27 association
  - 94% vs 9.4% controls
  - Odds ratio 171 (95% C.I. 135-218)
  - Brown et al 1996

The prevalence of AS around the world parallels the prevalence of HLA-B27

But B27 alone is not enough........
What causes Ankylosing Spondylitis?

- **AS major hereditary component >90%**.
- **HLA-B27 contributes about 1/3 of this.**
  - The recurrence risks in different degrees of relatives were: monozygotic (MZ) twins 63% (17/27), first degree relatives 8.2% (441/5390), second degree relatives 1.0% (8/834). Brown 2000
Genome-wide association study of ankylosing spondylitis identifies non-MHC susceptibility loci.

- a genome-wide association study in 2,053 unrelated ankylosing spondylitis cases among people of European descent and 5,140 ethnically matched controls, with replication in an independent cohort of 898 ankylosing spondylitis cases and 1,518 controls. In addition to strong association with the major histocompatibility complex (MHC; \( P < 10^{-800} \))…

- We also replicated previously reported associations at IL23R \( (P = 9.1 \times 10^{-14}) \) and ERAP1 \( (P = 5.3 \times 10^{-12}) \).

- This study identifies a major role for the interleukin (IL)-23 and IL-1 cytokine pathways in disease susceptibility.

Genetic study could produce a drug for cruel back condition

Mark Henderson Science Editor

A set of genes that influence a painful back and joint disorder affecting 200,000 Britons has been identified, offering hope of new treatments.

A study of more than 5,000 people with ankylosing spondylitis has linked eight new DNA variants to the autoimmune disease, which affects up to one in 200 men and one in 500 women.

One of the genes, called ERAP1, points to a biological mechanism that may explain many cases of the condition. This insight could lead to drugs that calm down the over-active immune system that causes ankylosing spondylitis and controls the disease.

"As we understand better how these genetic factors operate, we may be able to use that understanding to develop new therapies," said Professor Peter Donnelly, director of the Wellcome Trust Centre for Human Genetics at the University of Oxford, who led the international study.

Ankylosing spondylitis principally affects the spine, causing stiffness, inflammation, curvature and back pain in the ages of 15 and 35. While the inflammation and pain can be managed, there is no cure.

The results of the study, published in the journal Nature Genetics, linked three genetic variants conclusively to a raised risk of ankylosing spondylitis and found four more that were strongly associated with the disease.

"The study also found an interaction between the ERAP1 gene and a gene called HLA-B27, which has been known for almost 40 years to be a significant factor in ankylosing spondylitis. People with the HLA-B27 variant have up to 80 times the normal risk of developing it. But those with HLA-B27 who also have a certain version of ERAP1 have a risk four times lower than normal, suggesting that ERAP1 may have a powerful protective effect.

"It seems to slow down the immune system, so it can't work too hard any more," he said.

A lifelong test of endurance

First person Mike Atherton

I remember being dismissed by a doctor in my early teens. I had sharp pains below my ankle and in my knees, the latter so bad that for a year I could barely walk down the stairs. The doctor shrugged. "Growing pains," he said.

These "growing pains" got worse as I got older, and seemed to travel up the body until, by my early twenties, they had become a permanent "bad back". Still there was no diagnosis when on an England tour of Australia in 1991 I went to a renowned back surgeon in Perth with acute pain in the sacroiliac joint. I was told that only pregnant women got pain there.

Eventually, blood tests were taken, the faulty gene (HLA-B27) was identified and ankylosing spondylitis diagnosed. This should not have been surprising. I suppose, since my father suffered from it (it ended his professional football career with Manchester United before he was 20). As I, too, was playing professional sport, I had bypassed the GP stage and gone to specialists who did not ask about family history. Thereafter anti-inflammatories which, ironically, as sufferers of AS will know, is about as good a career choice as any. Anything to keep those stiff joints moving.

There were other problems associated with this autoimmune disease. Throughout my twenties I had bouts of colitis (inflammation of the bowel) which is truly debilitating. I know that I had it before my hundredth Test, because the photographs show an uncharacteristically fat face, the result of prednisolone, a powerful steroid to combat colitis. More recently, I have had a bout of iritis (inflammation of the eye).

The news, then, that gene research may have identified a way of halting this condition has been greeted with joy in the Atherton household. Of course, I realise that there are many worse afflictions and there are many people who suffer more acutely from AS than I do. Nevertheless, as a father of two children I am acutely conscious of the curse that I have a 50 per cent chance of passing on.
Latest GWAS. Interaction between ERAP1 and HLA-B27 in ankylosing spondylitis implicates peptide handling in the mechanism for HLA-B27 in disease susceptibility.

- ERAP in B27+
- IL23R, IL-12B (p40) and other genes involved in Th17 responses (e.g., STAT3)

What does genetics tell us about the immunopathogenesis of AS?

- AS is highly hereditary
- HLA-B27 critical (and not a linked gene)
- ERAP which is involved in antigen processing.
- Th17 T cells (+ Tumour Necrosis Factor)
What is the role of HLA-B27?
Overview

1) Introduction
2) AS genetics
3) AS theories of pathogenesis
4) Immunotherapy of AS, clues to pathogenesis?
Theories of B27 disease causation

1. Arthritogenic peptide

2. Intracellular stress following B27 misfolding (Colbert, Powis, Antoniou, Goodall, Gaston)

3. Innate immune recognition of aberrant B27
Ankylosing spondylitis (AS) – Theories of immune Pathogenesis

1. Arthritogenic peptide

2. Unfolded protein response

3. HLA-B27 homodimers interact with KIRs and LILRs on immune cells

Nat Rev Rheumatol 2010 6:399
Different Immune receptors can recognize B27

1) Classical immune/autoimmune

HLA-B27+ peptide
Molecular structure of HLA B27

Structure of the HLA-B27 molecule

Expert Reviews in Molecular Medicine © 1999 Cambridge University Press
Model of B27_2 homodimer
Different receptors can recognize B27:

2) NK and LILR recognition

- NK family receptor
- LILR receptor
- HLA-B27+ peptide
- CD8 T cell
- NK cell/CD4 T cell
- Monocytes/B cells
- Dendritic cells
KIR3DL2+ CD4 T cells are expanded in SpA

% expressing KIR3DL2

1= Healthy PBMC  2= RA PBMC  3a= B27- SpA PBMC  3b= B27+ SpA PBMC  4= ERA PBMC  5= RA SFMC  6= SpA SFMC  7= ERA SFMC  n= 28 controls, 35 SpA, 5 ERA

$\chi^{2}$, $\pi$, ### $p<0.001$  *, ** $p<0.005$
SpA synovial fluid KIR3DL2+CD4 T cells are enriched for IL17 production

Anna Ridley, Simon Kollnberger
KIR3DL2+CD4 T cells are enriched for IL17 production
related to HLA-B27
Increased T cell IL-17 production in the presence of cells expressing HLA-B27₂
Abnormal HLA-B27 forms can be detected and their functional effects inhibited by a monoclonal antibody HD6. HD6 stains AS synovial fluid and peripheral blood CD14+ monocytes.

IL17 secretion by AS but not healthy control PBMC stimulated with SEB is inhibited by HD6. Mean values±SEM (n=6 AS, n=3 HC). * P<0.05 students unpaired T test. Payeli et al Arthritis and Rheumatism in press 2012
Possible role of ERAP1 (endoplasmic reticulum aminopeptidase 1) in AS?

- Trimming of “arthritogenic” peptides
- Effect on B27 folding in ER
- Effect on stability of B27 on cell surface
ERAP K527R has altered function in trimming B27-presented peptide epitopes

Overview

1) Introduction
2) AS genetics
3) AS theories of pathogenesis
4) Immunotherapy of AS, clues to pathogenesis?
Anti TNF blockade is great in SpA, but...

- Not everyone responds
- ? Debate about effect on new bone formation, this may be “uncoupled” from inflammation
Anti TNF blockade is great in SpA, but...

- Not everyone responds
- ? Debate about effect on new bone formation, this may be “uncoupled” from inflammation

**ASSERT MRI Study: Example, Patient Before vs. After Therapy with Infliximab, STIR-Technique**

The future -

- Match phenotype with genotype
- Better understanding of gene function in disease
- Better earlier diagnosis (D van de Heide)
- New treatments (D Baeten)
  - Small molecule inhibitors…….

- New treatments to target new bone formation…….
Overview

1) Introduction
2) AS genetics
3) AS theories of pathogenesis
4) Immunotherapy of AS, clues to pathogenesis?
Acknowledgements

MRC HIU
Simon Kollnberger, Kirsty McHugh, Anna Ridley, Jackie Shaw, Isabel Wong-Baeza, Liye Chen, Joanna Giles, Antoni Chan

CCMP
Roman Fischer
Benedikt Kessler

Funders
Action Medical Research
Oxford NIHR Biomedical Research Centre

Arthritis Research UK
Providing answers today and tomorrow