Pathogenesis and Genetics of Psoriasis and Psoriatic Arthritis

Speakers

Laura Korb Ferris, MD, PhD
Associate Professor of Dermatology
University of Pittsburgh
Director of Clinical Trials
UPP Department of Dermatology
Pittsburgh, Pennsylvania

Sergio Schwartzman, MD
Associate Professor of Clinical Medicine
Weill Medical College of Cornell University
The Hospital for Special Surgery
New York Presbyterian Hospital
New York, New York

Content Developers

James G. Krueger, MD, PhD
Associate Professor
Medical Director
Laboratory for Investigative Dermatology
Rockefeller University
New York, New York

Christopher Ritchlin, MD, MPH
Professor of Medicine
Chief, Allergy, Immunology & Rheumatology Division
University of Rochester Medical Center
Rochester, New York

Psoriasis

Psoriasis Vulgaris

Histopathology of Normal Appearing Background Skin and a Psoriasis Plaque (both at same magnification)
Defining Parts of the Psoriasis Skin Lesions: Cellular Features

- A change in epidermal growth and differentiation, along with a vascular response that creates plaques on the skin.
- An underlying cellular immune response that involves myeloid dendritic cells and T-cells. Cytokines produced by these activated immune cells are key drivers of altered epidermal growth and skin structural changes.

Psoriasis Vulgaris: Clinical Pathological Correlates

- Clinical lesion is characterized by:
  A. Indurated plaques
  B. Scale
  C. Erythema
- Histological correlates are:
  A. Regular epidermal hyperplasia with elongated rete (regular acanthosis): increases epidermal thickness
  B. Reduced granular layer and keratinocyte maturation with retained nuclei (parakeratosis)
  C. Angiogenesis and dilation of superficial venules

Epidermal Reaction in Psoriasis

- Epidermal acanthosis results from excessive proliferation of keratinocytes.
  - Demonstrated by an increase in Ki67+ nuclei (next slide) in lesional skin
- Hyperplasia triggers a wound healing differentiation program in the epidermis.
  - Visualized by synthesis of keratin 16 in suprabasal keratinocytes next slide).

Factors That May Induce Keratinocyte Hyperplasia in Psoriasis

- Autocrine growth factors, especially EGF family (transforming growth factor-alpha, amphiregulin, and heparin-binding EGF) are all over-expressed in psoriasis
- Keratinocyte growth factor, other FGF family growth factors, and insulin-like growth factor-1 all have increased expression or activity in psoriasis lesions.
- Immune-related cytokines
  - IL-1 and IL-6
  - IL-10 family: IL-19, IL-20, IL-22, IL-24

Other Changes in the Epidermis

- At a molecular level, hundreds of genes in the epidermis have increased or decreased transcription in active psoriasis lesions
- Some changes reflect cell growth pathways of generalized hyperplasia
- Some changes are more specific to psoriasis—the following slide shows (red) genes with very high expression in psoriasis, but much lower expression in atopic dermatitis, another skin disease that has associated epidermal hyperplasia
Key Concepts in Pathogenesis

• Genes that are highly and selectively expressed in psoriasis are induced by immune cytokines produced by “polar” T-cell subsets: Th1, Th17, and Th22.
• Myeloid dendritic cells (CD11c+ DCs) regulate T-cell activation through antigen-presentation, co-stimulation, and production of cytokines such as IL-12 and IL-23 that drive activation, differentiation and survival of polar T-cell subsets.

CD3+ T-cells in Psoriasis

• Th1 (CD4+) and Tc1 (CD8+) T-cells that are defined by synthesis of interferon-gamma upon activation.
• Th17 (CD4+) and Tc17 (CD8+), including conventional T-cells and gamma-delta T-cells, synthesize IL-17A and IL-17F upon activation.
• Th22 (CD4+) and Tc22 (CD8+) synthesize IL-22 upon activation.

T-cell Subsets in Psoriasis

• Genes with high expression in psoriasis lesions all have low expression in non-lesional or normal skin.
• As shown by IHC at bottom for S100A7 and S100A9, the altered expression of these genes is created by over-production of corresponding proteins in epidermal keratinocytes.

Heatmap Slide

- Genes with high expression in psoriasis lesions all have low expression in non-lesional or normal skin.
- As shown by IHC at bottom for S100A7 and S100A9, the altered expression of these genes is created by over-production of corresponding proteins in epidermal keratinocytes.
“Polar” cytokines of Th1, Th22, and Th17 T-cells act on epidermal keratinocytes directly to change gene expression profiles and alter other properties of the skin that in the sum create the psoriasis phenotype at clinical, cellular, and molecular levels.

Interferon-γ binds to receptors that are highly expressed on epidermal keratinocytes. IFN-γ activates STAT1 and induces expression of many pro-inflammatory gene products.

- STAT1 activation
- STAT1 mRNA
- CXCL9, 10, 11 mRNAs
- MHC-II mRNAs
- ~1000 other mRNAs also regulated

Named genes strongly induced by IFN-γ, but not by IL-17 or IL-22

What features of psoriasis may be explained by polar T-cell cytokines (especially IL-17 and IL-22)?

IL-22 binds to receptors that are highly expressed on epidermal keratinocytes and induces transcription of several S100 genes including psoriasin (S100A7).

IL-22 stimulates:
- Acanthosis of epidermis
- Keratin 16
- S100A7 (psoriasin)
- S100A9
- Profilaggrin
- STAT3 nuclear translocation

IL-22 is shown to increase epidermal thickness (caused by keratinocyte hyperplasia) in reconstructed human epidermis by IL-19, IL-20 and IL-22

Increased expression of keratin 16, S100A7, and nuclear STAT3 is induced by each of these cytokines, with IL-22 showing the strongest effect.
IL-17 also binds to receptors that are highly expressed on epidermal keratinocytes. IL-17 induces transcription of many psoriasis-selective genes that encode proteins with pro-inflammatory functions. IL-17A and IL-17F bind to human keratinocytes (in vitro). S100A7 (psoriasin), CXCL1,2,3,8, CCL20, β-defensin and other anti-microbial peptides.

Polar T-cell subsets in psoriasis produce cytokines that drive differing responses in epidermal keratinocytes: epidermal hyperplasia and inflammation are stimulated by IL-22 and IL-17, Th17, and IL-17 (Th17). Keratinocytes have unique responses to IL-17 and IL-22.

IL-17 also binds to receptors that are highly expressed on epidermal keratinocytes. IL-17 induces transcription of many psoriasis-selective genes that encode proteins with pro-inflammatory functions. IL-17A and IL-17F bind to human keratinocytes (in vitro). S100A7 (psoriasin), CXCL1,2,3,8, CCL20, β-defensin and other anti-microbial peptides.

T-cells and DCs in Psoriasis

- As shown on next slides, there is a consistent and highly significant increase in myeloid DCs in psoriasis lesions.
- These inflammatory DCs produce cytokines such as IL-12 and IL-23 that drive polar T-cell differentiation.
- IL-23, composed of p19 and p40 subunits, is highly up-regulated in psoriasis lesions. CD3 cell counts, CD11c cell counts, Langerin cell counts. CD3 Cell Counts, CD11c Cell Counts, Langerin Cell Counts. 8-fold average increase, 7-fold average increase, no significant change. Concept of an inflammatory dendritic cell. CD11c+ DCs in psoriasis express high levels of TNF and iNOS, and in addition make other key inflammatory cytokines such as IL-23.

Genetic Links to IL-23 Axis in Psoriasis

- Chris has a slide that shows general genetic links in psoriasis.
- SNPs associated with IL-23 p40 and p19 genes are risk alleles for psoriasis.
- The IL-23R also has a risk allele for psoriasis.
- Functional studies by Frank Nestle’s group have shown IL-23R risk allele leads to more production of Th17 cells when differentiation is stimulated in vitro from naïve precursors.
**IL-23/Th17 Pathway: Essential for Psoriasis Pathogenesis**

- **Antimicrobial peptides**
  - β-defensins
  - Lipocalin
  - LL-37
  - S100A7

- **CXC chemokines**
  - CXCL 1, 2, 3, 5
  - IL-8

- **CCL20**

- **CCR6+ cells**


**Blockade of IL-17**

- The pathogenic contribution of IL-17 to psoriasis has been determined by antagonizing IL-17A or the IL-17 Receptor A subunit in clinical studies:
  - IL-17A Antibody Secukinumab/AIN457 (Novartis)
  - IL-17A Antibody Ixekizumab/LY2439821 (Lilly)
  - IL-17 Receptor A subunit antibody Brodalumab/AMG827 (Amgen)

- All IL-17 antagonists induce a PASI75 response in 70-80% of treated patients after 12 weeks. There is nearly complete reversal of cellular and molecular disease pathology after IL-17 blockade.

**Blockade of IL-23**

- The pathogenic contribution of IL-23 to psoriasis has been determined by antagonizing the p19 subunit of IL-23 in clinical studies:
  - IL23 Antibody Guselkumab (Janssen)
  - IL-23 Antibody Tildrakizumab (Merck)
  - IL-23 Antibody BI65066 (Boehringer)

- All IL-23 antagonists induce a PASI75 response in 70-80% of treated patients after 12 weeks. Production of IL-17 is strongly attenuated by IL-23 blockade. Effects are similar to IL-17 blockade—there is nearly complete reversal of cellular and molecular disease pathology.

**What Is the Role of TNF in the Pathogenesis of Psoriasis?**

- **In vitro**
  - Normal Human Keratinocytes growth with medium
  - Treated for 24h with:
    - Medium alone
    - IL-17 200 ng/mL
    - TNF 10 ng/mL
    - IL-17 + TNF

- Gene sequencing by Illumina Genechip
  - RT-PCR

- **IL-8**

- **S100A7**

- **IL-23**

- TNF interacts with this pathway at 2 points:
  - First, TNF induces IL-23 production in myeloid DCs.
  - Second, TNF and IL-17 interact synergistically and additively in keratinocytes to increase transcription of many psoriasis-related genes.
Psoriasis Immunopathogenesis

CCL = chemokine (C-C motif) ligand; CXCL = chemokine (C-X-C motif) ligand; DC = dendritic cell; IFN = interferon; IL = interleukin; LL3 = human cathelicidin; STAT = signal transducer and activator of transcription; TNF = tumor necrosis factor.


Initial response

Immune amplification

Disease phenotype: cytokine amplification of keratinocyte hyperplasia and inflammation via KCs

Central IL-23/Th17 pathway in psoriasis

Neutrophil chemoattraction and more inflammation

IL-23 Th17 T-cell

IL-17

TNF

DC

IL-17 (synergy with TNF)

IL-12

IL-23

TNF Th17

Th1

Th22

S100A7

IP-10

IP-10

CXCL1

CXCL2

CXCL3

CXCL8 (IL-8)

STAT1 activation

IFNγ

Hyperplasia

IL-36

γ

IL-19

TNF

IL-22

Feed forward activation of DC recruitment and activation

CCL20

LL37

IL-22

IL-19

IL-20

IL-24

STAT 3

activation

More S100A7

K16

Keratinocyte proliferation

IL-2

Vascular and Hepatic Inflammation in Psoriasis

FDG-PET


Landmarks in Psoriatic Arthritis

• 1850—Jean Louis Alibert’s monograph: association between Ps and arthritis published
• 1956—First publication by Dr. Wright on PsA
• 1964—ARA recognizes PsA as separate from RA
• 1973—Landmark paper by Drs. Moll and Wright describes the five subgroups
• 1978—Dr. Gladman establishes first cohort of patients in Toronto
• 1991—Original five subgroups of Drs. Moll and Wright challenged
• 1998—Dr. McGonagle paper published in Lancet
• 2000—First paper describing beneficial effect of anti–tumor necrosis factor drugs in psoriatic arthritis
• 2003—First meeting of GRAPPA
• 2006—Publication of classification criteria for psoriatic arthritis (CASPAR)
• 2008—Publication of PsA treatment guidelines


Is PsA an Autoimmune Disease?

Rheumatoid arthritis
• Autoantibody identified
• MHC Class II (shared epitope)
• SS, vasculitis, nodules
• Type II collagen
• Homogeneous tissue response

Psoriatic arthritis
• No autoantibodies
• MHC class I
• Psoriasis, uveitis, IBD
• Over expression/deletion of GF, cytokines, signals
• Heterogeneous tissue response

Clues to Pathogenesis:
• 40% with positive family history
• Male/Female ratio approximately 1:1
• Psoriasis usually precedes arthritis
• Association with Class I MHC alleles
  – B13, B17, B27, B39 and Cw6
• Environmental triggers:
  trauma (Koebner phenomena), infection (?microbiome), stress

Psoriasis and PsA

Psoriasis and PsA.
Genes in Psoriasis and PsA

Probandwise concordance estimates on PsO and PsA

<table>
<thead>
<tr>
<th></th>
<th>MZ Twins</th>
<th>DZ Twins</th>
<th>Difference (95% CI), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moll and Wright</td>
<td>1/10 (10%)</td>
<td>1/26 (3.7%)</td>
<td>6.3% (-11%, 34%)</td>
</tr>
<tr>
<td>CASPAR</td>
<td>1/9 (11%)</td>
<td>1/22 (4.5%)</td>
<td>6.6% (-12%, 39%)</td>
</tr>
<tr>
<td>PsO in Twins with PsA</td>
<td>6/11 (55%)</td>
<td>6/28 (21%)</td>
<td>34% (-2%, 60%), p&lt;0.05</td>
</tr>
</tbody>
</table>

Genes in which association of variants with Ps and PsA achieved GWA significance in Western cohorts

Obesity Is a Major Risk Factor for Incident Ps and PsA

Prospective examination of relationship between incident Ps and BMI in 78,626 women in NH study over 14 year period.

Cohort study of 75,395 subjects with psoriasis in the THIN database to examine the relationship between obesity and incident PsA

The Gut-Joint Axis in SpA/PsA

• HLA-B27 tg rats don’t develop colitis/Ps/arthritis under Germ-free conditions.

• ~2/3 of SpA patients have microscopic, subclinical gut inflammation; ~10% AS patients  clinical IBD

• PsA patients have subclinical gut inflammation (16-100%)

• Is there a role for Mucosal Inflammation/Microbiome in the pathogenesis of SpA (PsA)?

The Gut Microbiome in PsA

• IBD (and especially Crohn’s) patients have decreased diversity
  • Akkermansia, Ruminococcus and other beneficial commensals are also absent in IBD microbiome
  • Levels of protective MCFAs (hexanoate/heptanoate) are significantly lower in IBD/Ps/PsA

Decreased Diversity in PsA Gut Microbiome Resembling IBD

Scher JU, Ubeda C, et al., Arthritis Rheum 2014 (ePub)
**Model: Microbiome in PsA Etiopathogenesis**

- Genetic predisposition (HLA-B27, Cw*6)
- Environmental factors (Stress, Infection, Skin microbiome, trauma)
- ~30% Psoriatic Arthritis
- ~70% Skin Psoriasis

**Psoriatic Disease and the IL-23/Th17 Pathway**

- Psoriasis and Nail Disease
- MSK
- Diabetes
- Obesity
- CV Disease
- Uveitis
- Gut
- Enthesitis
- Dactilitis
- Peripheral Arthritis
- Axial DIP Mutilans

**Sites of Joint Inflammation**

- RA-synovium
- PsA-bone, enthesis and synovium
- AS-bone, enthesis

**Synovial Histopathology of PsA**

- SpA tissues (PsA, AS, USpA):
  - More vascularity, neutrophil and CD 163+ macrophage infiltration
  - No citrullinated proteins in polyarticular PsA
  - DC163+ macrophages, PMN and lining hyperplasia correlated with swollen joint count and acute phase reactants in PsA
  - Synovial histopathology of PsA (either oligo or poly) resembles other SpA subtypes more than RA
  - Both groups can be differentiated from RA

**Increased Synovial RANKL and Circulating OCP in PsA**

**Master Cytokines in Spondyloarthritis**

*Figure 1: Diagram showing the role of cytokines in spondyloarthritis.*

**Links Between Skin and Joint in PsA**

*Figure 2: Diagram illustrating the connection between psoriatic plaque and bone marrow.*

**CD8+ IL17+ Cells Expanded in PsA But Not RA Synovial Fluid**

*Figure 3A: Graph showing CD8+ IL17+ cell levels in PsA and RA.*

**Synovio-Enthesial Complex (SEC)**

*Figure 4: Diagram explaining the relationship between synovium and enthesis.*

**Relationship between the DIP Joint, Nail, and Enthesis**

*Figure 5: Image showing the anatomical relationship between the DIP joint, nail, and enthesis.*

**IL-23 Induces Enthesitis and New Bone Formation**

*Figure 6: Diagram illustrating the effects of IL-23 on enthesis and bone formation.*

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IL-23 and Resident T-cells Promote Enthesitis and Osteoproliferation


Three Pathways to Osteoproliferation


Phenotypic Diversity in PsA

Mutilans, Dactylitis, Synovitis, Ankylosis, Mutilans

Cutaneous Nociceptors in PsA Promote IL-23 Release


Questions & Answers