Pre-Activity Question 1
How confident are you in describing the pathogenesis of psoriasis?
1. Very confident
2. Confident
3. Somewhat confident
4. Not confident

Pre-Activity Question 2
How confident are you in describing the pathogenesis of PsA?
1. Very confident
2. Confident
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Pre-Activity Question 3
Genes that are highly and selectively expressed in psoriasis are induced by immune cytokines produced by "polar" T-cell subsets: Th1, Th17, and Th22.
1. True
2. False
Psoriasis

Psoriasis Vulgaris

Unaffected Skin

Psoriasis Lesion

Histopathology of Normal Appearing Background Skin and a Psoriasis Plaque (both at same magnification)

2 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 K67+ 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**

Uninvolved Skin

Psoriasis Plaque

“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.

**T-cell Subsets 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

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 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)
- STAT3 nuclear translocation

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-17 stimulates:
- Keratinocytes have unique responses to IL-17 and IL-22.
- Effects are distinct from those of Th1 cytokines (anti-proliferative for keratinocytes).

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.

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
NL
LS
0
50
100
150
200
250
300
350

CD11c cell counts
NL
LS
0
100
200
300
400
500
600

Langerin cell counts
NL
LS
0
25
50
75
100
125

8-fold average increase
P<0.0001

7-fold average increase
P<0.0001

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

8-fold average increase
P<0.0001

7-fold average increase
P<0.0001

no significant change

IL-23/Th17 Pathway:
Essential for Psoriasis Pathogenesis

\[ \text{IL-23} \rightarrow \text{IL-17} \rightarrow \text{CCL20} \rightarrow \text{CCR6+ cells} \]

\[ \text{CXCL 1, 2, 3, 5, IL-8} \]

\[ \text{Anti-inflammatory peptides} \]

\[ \text{β-defensins} \]

\[ \text{Lipocalin} \]

\[ \text{LL-37} \]

\[ \text{S100A7} \]

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

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

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
  - IL-23 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 10
• Gene sequencing by Illumina Genechip
• RT-PCR

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

Vascular and Hepatic Inflammation in Psoriasis

Psoriatic Arthritis
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
- 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?

<table>
<thead>
<tr>
<th>Rheumatoid arthritis</th>
<th>Psoriatic arthritis</th>
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</thead>
<tbody>
<tr>
<td>Autoantibody identified</td>
<td>No autoantibodies</td>
</tr>
<tr>
<td>MHC Class II (shared epitope)</td>
<td>MHC class I</td>
</tr>
<tr>
<td>SS, vasculitis, nodules</td>
<td>Psoriasis, uveitis, IBD</td>
</tr>
<tr>
<td>Type II collagen</td>
<td>Over expression/deletion of GF, cytokines, signals</td>
</tr>
<tr>
<td>Homogeneous tissue response</td>
<td>Heterogeneous tissue response</td>
</tr>
</tbody>
</table>

Psoriasis and PsA

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

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.

<table>
<thead>
<tr>
<th>BMI</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29.9</td>
<td>1.4 (1.13-1.73)</td>
</tr>
<tr>
<td>30-34.9</td>
<td>1.5 (1.51-1.91)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>2.7 (2.12-3.4)</td>
</tr>
</tbody>
</table>

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

<table>
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<tr>
<th>BMI</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29.9</td>
<td>1.09 (1.93-1.28)</td>
</tr>
<tr>
<td>30-34.9</td>
<td>1.28 (1.02-1.47)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>1.48 (1.20-1.81)</td>
</tr>
</tbody>
</table>

*Compared to BMI of 21-22.9.

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

- Scher JU, Ubeda C, et al., Arthritis Rheum 2014 (ePub)
- Decreased Diversity in PsA Gut Microbiome Resembling IBD

Psoriatic Disease and the IL-23/Th17 Pathway

- Psoriasis and Nail Disease
- MSK Disease
- Diabetes

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

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

- In RA: only CD4+ IL17+ are elevated in SF
- In PsA: CD4+ and CD8+ IL17+ are elevated in SF
- Levels of CD8+ IL17+ correlate with disease activity and erosions in PsA


Links Between Skin and Joint in PsA


Master Cytokines in Spondyloarthritis
Synovio-Enthesial Complex (SEC)

- In PsA, synovium and enthesis are closely related (concept of SEC).
- Stressing of SEC (danger signals due to cell injury) triggers innate immune response, which dictates clinical expression of disease.
- Primary basis for pathogenesis of PsA could be biomechanical rather than autoimmune.
- Spondyloarthritis could be an ‘auto-inflammatory’ disease.

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

- IL-23 Induces Enthesitis and New Bone Formation
  - While IL-23 promotes Osteoproliferation

Relationship between the DIP Joint, Nail, and Enthesis

SL = Superficial lamina; DL = Deep lamina.

Three Pathways to Osteoproliferation

Phenotypic Diversity in PsA
Cutaneous Nocioceptors in PsA Promote IL-23 Release

Post-Activity Question 1

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