Pathogenesis of Psoriasis
Integrating Pathogenesis and Treatment of Psoriasis

AAD 2017 Structure & Function Course

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Conflicts

• Research support, consulting, or lecture fees by most pharma and biotech companies with a psoriasis product or investigational agent
• No patents, ownership, or financial gain from any psoriasis product or drug
• In this talk, therapeutic agents are discussed only to illustrate disease pathogenic mechanisms
Psoriasis vulgaris
(2017 mechanistic definition)

• An autoimmune disease where IL-17 induces or regulates auto-
  antigens that stimulate Th17 (CD4+) & Tc17 (CD8+) T-cells and
• Where IL-17 activates keratinocytes and other cell types to produce
  “feed forward” cytokines and other inflammatory molecules that
  control epidermal hyperplasia, tissue structure, and mixed immune
  infiltrates (dendritic cells, T-cells, and neutrophils), including other
  “polar” T-cell subsets that actively synthesize unique inflammatory
  cytokines.
• Thus cutaneous immunity, through cytokine elaboration, alters
  structure and function of the skin.

Can also be viewed as activation of cellular/molecular pathways
induced normally to control Candida infections
Uninvolved Skin

Psoriasis Plaque
CD3+ T-cells in Psoriasis

Uninvolved Skin

Psoriasis Plaque
Epidermal hyperplasia in psoriasis is triggered by CD25+ (activated) T-cells interacting with keratinocytes.

**Homeostasis**
(low proliferation & complete differentiation)

**Regenerative Growth**
(high proliferation & incomplete differentiation) + Induction of immune-related surface proteins

- IGF-1
- KGF
- IL-6
- TGF-α

CD25+ T-lymphocyte (mainly CD8+ within epidermis)

K16-  

K16+  

K16-  

K16+  

CD40

ICAM-1

IL-10

CD40

IGF-1

KGF

IL-6

TGF-α
Myeloid (CD11c+) Dendritic Cells in Psoriasis
NON-LESIONAL PSORIASIS PLAQUE
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.
Inflammatory Dendritic Cells in Psoriasis Lesions

TIP-DC
TNF and iNOS Producing -DC
(within CD11c+ or myeloid DC subset in psoriasis lesions)

TIP-DC (Inflammatory CD11c+ DC) extended phenotype

TRAIL
TLR1 & TLR2
TNF

iNOS

Nitric Oxide (NO)

S100A12
IL-20
IL-23
IL-12 and IL-23 --“p40” cytokines-- control activation of “polar” T-cell subsets

IL-12

Th1
Tc1

IFN-γ

IL-23

Th17

IL-17
IL-22

Th22
Consistent up-regulation of p40 and p19 mRNAs (IL-23 subunits) in psoriasis plaques, as detected by real-time RT-PCR (normalized to HARP mRNA).

Lee et al JEM (2005). In this work, IL-23 synthesis traced back to CD11c+ DCs.
Th17 T-cells increased in psoriasis lesions.
Gene expression during cyclosporine treatment

- **K16 mRNA**
  - NL: 1000
  - Ps: 2000
  - D14: 3000
  - D42: 4000
  - D56: 5000

- **IFNg mRNA**
  - NL: 20
  - Ps: 40
  - D14: 60
  - D42: 80
  - D56: 100

- **IL-17 mRNA**
  - NL: 5
  - Ps: 10
  - D14: 15
  - D42: 20
  - D56: 25

- **IL-22 mRNA**
  - NL: 1
  - Ps: 2
  - D14: 3
  - D42: 4
  - D56: 5
What features of psoriasis may be explained by Th17 T-cell products (especially IL-17 and IL-22)?
Normal

LS Psoriasis

S100A9 (calgranulin B)

S100A7 (psoriasin)
What is potential significance to activated Th17 T-cells to biology of psoriasis lesions?

IL-22

human keratinocytes (in vitro)

S_{100}A7 (psoriasin)
S_{100}A8
S_{100}A9
&
profilaggrin

Strongly induced by IL-22, not by γ-interferon

Genes up-regulated by IL-17 in keratinocytes

<table>
<thead>
<tr>
<th>Innate defense molecules</th>
<th>FCH</th>
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<tbody>
<tr>
<td>DEFB4 defensin, beta 4</td>
<td>238.549</td>
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<td>S100A7 psoriasin</td>
<td>189.381</td>
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<td>S100A12 S100 calcium binding protein A12</td>
<td>30.707</td>
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<td>S100A8 S100 calcium binding protein A8</td>
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<td>S100A9 S100 calcium binding protein A9</td>
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<table>
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<tr>
<th>Cytokines</th>
<th>FCH</th>
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<tr>
<td>IL1F9 interleukin 1 family, member 9</td>
<td>15.062</td>
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<tr>
<td>IL8 interleukin 8</td>
<td>14.529</td>
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<td>IL1B interleukin 1, beta</td>
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<table>
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<tr>
<th>Chemokines</th>
<th>FCH</th>
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<tr>
<td>CCL20 chemokine (C-C motif) ligand 20</td>
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<td>CXCL6 chemokine (C-X-C motif) ligand 6</td>
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<td>CXCL1 chemokine (C-X-C motif) ligand 1 (m)</td>
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<tr>
<td>CXCL2 chemokine (C-X-C motif) ligand 2</td>
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<tr>
<td>CXCL5 chemokine (C-X-C motif) ligand 5</td>
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<tr>
<td>CXCL3 chemokine (C-X-C motif) ligand 3</td>
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</table>

IL-22 stimulates:

- Acanthosis of epidermis
- Keratin 16
- S100A7 (Psoriasin)
- STAT3 nuclear translocation

IL-17 and IL-22 induce key molecular features of psoriasis
IL-22 promotes acanthosis and impairs terminal differentiation

Full thickness skin rafts (epidermis + fibroblasts/dermis)

- Confirms effect of IL-22 on acanthosis of epidermis
  (Sa et al J Immunology 2007)

*Parakeratosis

The TIP-DC $\rightarrow$ IL-23 $\rightarrow$ Th17-Th22 Pathway

Keratinocytes have unique responses to IL-17 & IL-22.
Effects are distinct from those of Th1-cytokines.

S100A7 “psoriasin” parakeratosis

IL-17

IL-22
$(&$ other IL-20 family cytokines)$

Th17

Th22

TIP-DC
Th1, Th17 and Th22 T-cells drive cellular and molecular features of psoriasis through complex cytokine circuits.

Figure adapted from: Nestle FO, et al. N Engl J Med. 2009;361:496-509
The IL-23/Th17 axis is essential sustaining disease activity.

NKT cell → IFN-α → activation → TIP-DC → TNF-α → IL-1β, IL-6, TNF-α, IL-12 (p40/p35) → Th1

Th/Tc22 → IL-23 (p40/p19) → keratinocyte

IL-21 → macrophage

IL-17A/F → Th17

TNF-α, IFN-γ, Antimicrobial peptides

S100, CXCL8, CXCL9, CXCL10, CXCL11, CCL20

Figure adapted from: Nestle FO, et al. N Engl J Med., 2009;361:496-509
IL-23/Th17 pathway in psoriasis

DC \[\rightarrow\] IL-23 \[\rightarrow\] T17 \[\rightarrow\] IL-17

Th17
Tc17
Tgamma-delta 17
ILC 17

KC

Anti-microbial peptides
β-defensins
Lipocalin
LL-37
S100A7, S100A8
CXC chemokines
CXCL 1, 2, 3, 5
IL-8
CCL20

neut

CCR6+ cells
BI655066 is a human p19 monoclonal antibody (IL-23 blocker)
Data published March 2015 J. Allergy Clin Immunol (online).

Week 12*
PASI 75 = 87%
PASI 90 = 58%
p < 0.01 vs. Placebo (0%)

* i.v. and s.c. BI 655066 groups combined
Clearing of Psoriasis Lesions with BI 655066

Week 0

Week 12
Consistent improvements in psoriasis induced by multiple IL-23 antagonists

- Guselkumab (human antibody to p19 subunit)
- Tildrakizumab (human antibody to p19 subunit)
- BI655066 (human antibody to p19 subunit)
IL-23/Th17 pathway in psoriasis

- Th17
- Tc17
- Tgamma-delta 17
- ILC 17

IL-23

IL-17

KC

CCL20

Anti-microbial peptides
β-defensins
Lipocalin
LL-37
S100A7, S100A8
CXCL 1, 2, 3, 5
IL-8

CXC chemokines
Study Design

Study Treatment Period

Screening Period

All Subjects

Study Period Follow Up

W0
Dose 1
Biopsy

W2
Dose 2
Biopsy

W4
Dose 3

W6

W12

W16

W20
End of Study

Ixekizumab 150 mg SC (n=8)

Ixekizumab 50 mg SC (n=8)

Ixekizumab 15 mg SC (n=8)

Ixekizumab 5 mg SC (n=8)

Placebo SC (n=8)

SC=subcutaneous; W=week
Expression of IL-17 Target Genes (RT-PCR)

log2(expression /hARP) = mRNA expression (RT-PCR) normalized to the housekeeping gene human acidic ribosomal protein gene (hARP)
Immunohistochemical Analysis of Skin Biopsy (150 mg ixekizumab)
Proportion of Patients with PASI 75

- **Placebo SC (n=8)**
- **LY 150 mg SC (n=8)**

The graph shows the proportion of patients with PASI 75 over weeks for two different treatment groups. The red line represents LY 150 mg SC (n=8), which shows an increase in the proportion of patients with PASI 75 from 0% at week 0 to 100% at week 6, after which it remains steady until week 16, and then begins to decrease. The black line represents Placebo SC (n=8), which remains at 0% throughout the entire duration of the study.
Genes Modulated by ixekizumab (FCH>6)

LS= Lesional Skin Biopsies at Baseline

NL= Non-Lesional Skin Biopsies at Baseline
Psoriasis Lesions at Weeks 0, 2 and 6

Placebo, Baseline

Ixekizumab 150 mg, Baseline

Placebo, Week 2

Ixekizumab 150 mg, Week 2

Placebo, Week 6

Ixekizumab 150 mg, Week 6

Consistent improvements in psoriasis induced by multiple IL-17 antagonists

- Secukinumab (anti-IL17 monoclonal antibody)
- Ixekizumab (anti- IL-17A monoclonal antibody)
- Brodalumab (antibody to IL-17 Receptor A subunit, blocking IL-17A & IL-17F signaling)
What is the role of TNF in the pathogenesis of psoriasis?
TNF interacts with the IL-23/Th17 pathway at two points. First, TNF induces IL-23 production in myeloid DCs. Second, TNF & IL-17 interact synergistically and additively in keratinocytes to increase transcription of many psoriasis-related genes.
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
Panel of induced genes with synergistic induction by IL-17 and TNF

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>IL-17 alone</th>
<th>TNF-α alone</th>
<th>IL-17+TNF-α</th>
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<tbody>
<tr>
<td>IL19</td>
<td>interleukin 19</td>
<td>0.84</td>
<td>-0.12</td>
<td>5.77</td>
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<td>IL8</td>
<td>interleukin 8</td>
<td>1.39</td>
<td>1.88</td>
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<td>IL23A</td>
<td>interleukin 23, alpha subunit p19</td>
<td>0.74</td>
<td>0.47</td>
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<td>CCL20</td>
<td>chemokine (C-C motif) ligand 20</td>
<td>1.05</td>
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<td>interleukin 6 (interferon, beta 2)</td>
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<td>0.33</td>
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<td>CXCL1</td>
<td>chemokine (C-X-C motif) ligand 1</td>
<td>0.80</td>
<td>0.20</td>
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<td>TNF</td>
<td>tumor necrosis factor (TNF superfamily, member 2)</td>
<td>-0.13</td>
<td>0.95</td>
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<td>IL17C</td>
<td>interleukin 17C</td>
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<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>IL-17 alone</th>
<th>TNF-α alone</th>
<th>IL-17+TNF-α</th>
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<tbody>
<tr>
<td>DEFB4</td>
<td>defensin, beta 4</td>
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<td>complement factor B</td>
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<td>PLAT</td>
<td>platelet-derived growth factor receptor-like</td>
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<td>TNFAIP6</td>
<td>tumor necrosis factor, alpha-induced protein 6</td>
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<td>0.25</td>
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<td>MAP2K3</td>
<td>mitogen-activated protein kinase kinase 3</td>
<td>0.11</td>
<td>-0.05</td>
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<td>PTGE2</td>
<td>prostaglandin E synthase 2</td>
<td>0.12</td>
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<td>TFAP2C</td>
<td>transcription factor AP-2 gamma</td>
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<td>MAP2K13</td>
<td>mitogen-activated protein kinase kinase 13</td>
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<td>0.00</td>
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<tr>
<td>CSF3</td>
<td>colony stimulating factor 3</td>
<td>0.10</td>
<td>0.17</td>
<td>0.84</td>
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Total number: 160
Correlation with psoriasis transcriptome

Genes synergistically induced by IL17 and TNFα resulted overexpressed in psoriatic lesional skin

They strongly correlated with psoriasis transcriptome

\[ r = 0.79 \]
\[ p < 10^{-10} \]

1 Yao Y et al. Plos One 2008
Pathway: TNF $\Rightarrow$ IL-23 $\Rightarrow$ IL-17 (single and synergistic effects)
But, how do we get from IL-17 to a complex tissue phenotype?

Figure adapted from: Nestle FO, et al. N Engl J Med. 2009;361:496-509
IL-17 directly or indirectly regulates psoriasis autoantigens

Central IL-23/T_{H}17 pathway in psoriasis
Ki-67

NON-LESIONAL

LESIONAL

S100A7

psoriasin
HBD-2
(β-defensin)

LCN-2
(lipocalin-2)
New age of molecular medicine where translational research will accelerate therapeutic development for many different skin diseases

Understanding of Pathogenesis

Targeted Therapeutics
Idea of “digital” inflammatory diseases

• Psoriasis vulgaris– An IL-17 dominated inflammatory disease (Type 17 T-cells) with co-activation Th1 and Th22 T-cells with CD11c+ DCs

• Atopic dermatitis– An IL-4/IL-13 dominated inflammatory disease (Th2 T-cells) with co-activation of Th1 and Th22 with CD11c+ DCs

• Cutaneous Lupus– An interferon dominated inflammatory disease (Th1 T-cells) and co-activation of innate interferon producing cells (myeloid and plasmacytoid DCs)
Thank you