The TH17 Cell, IL17, and IL23 in SpA: Pathobiology and Therapeutic Targeting

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Research and Education Association Memberships

Executive board GRAPPA, member of ASAS, SPARTAN, Scientific Director of CORRONA SpA/PsA registry, Co-chair OMERACT PsA working group
Rheumatology Steering Group - ICHOM
REVIEW

Interleukin-17 in Fashion, at Last

Ten Years After Its Description, Its Cellular Source Has Been Identified

Pierre Miossec

• 1995: Discovery of IL-17 in man
• 2005: Identification of Th17 cells in mouse
T Cell Differentiation Pathways

Native T cell

- IL-12
- TGF-β

Stat1
Stat4
T-bet

IFN-γ
IL-4

T H 1

Protection against intracellular pathogens (e.g. viruses, bacteria)
Autoimmunity, delayed-type hypersensitivity

Stat3
GATA3

IL-4
IFN-γ

T H 2

Protection against extracellular pathogens (e.g. parasites, bacteria)
Allergy, asthma

Stat3
RORγt

T H 17

Protection against extracellular pathogens (e.g. fungi, bacteria)
Autoimmunity

FoxP3

Treg

TGF-β
IL-10

Immunosuppression
Th17 cells produce multiple cytokines

- IL-17
- IL-17F
- IL-21
- IL-22
- TNF-α
- IL-6
- GM-CSF
Multiple cell types produce IL-17

- T cells
- Intra-epithelial lymphocytes
- Lung epithelial cells
- Cells of GI tract and uterus
- Eosinophils
- Basophils
- Mast cells
- Alveolar macrophages

- Th17 cells
- CD8+ T cells
- γδ T cells
- NK cells
- NK T cells
- LTi cells
- Neutrophils

- Keratinocytes
- Lung epithelial cells
- Colon epithelial cells

Under investigation

There are multiple IL-17R subtypes

<table>
<thead>
<tr>
<th>Member</th>
<th>Target Receptor</th>
<th>Main Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17A(^1,2)</td>
<td>IL-17RA and IL-17RC</td>
<td>Neutrophil recruitment, host defense against extracellular pathogens, autoimmune pathology</td>
</tr>
<tr>
<td>IL-17B(^1,2)</td>
<td>IL-17RB</td>
<td>Proinflammatory activity?</td>
</tr>
<tr>
<td>IL-17C(^1,2)</td>
<td>IL-17RE</td>
<td>Proinflammatory activity?</td>
</tr>
<tr>
<td>IL-17D(^1,2)</td>
<td>Unknown</td>
<td>Proinflammatory activity?</td>
</tr>
<tr>
<td>IL-17E(^1,2)</td>
<td>IL-17RB and IL-17RA</td>
<td>Stimulates Th2 responses Supresses Th17 responses</td>
</tr>
<tr>
<td>IL-17F(^1,2)</td>
<td>IL-17RA and IL-17RC</td>
<td>Neutrophil recruitment (?), host defense against extracellular pathogens (?), immunoinflammatory pathology (?)</td>
</tr>
<tr>
<td>IL-17A – IL-17F heterodimer(^2)</td>
<td>N/A</td>
<td>Autoimmune pathology (presumed), neutrophil recruitment, and immunity to extracellular pathogens</td>
</tr>
</tbody>
</table>

IL-17 receptor signaling

- Binding of IL-17A and/or IL-17F to the heterodimeric IL-17R leads to the recruitment of Act1 through homotypic interactions between SEFIR domains (red ovals in diagram)
- This in turn allows the incorporation of TRAF6 into the signaling complex and then 'downstream' activation of the NF-κB and mitogen-activated protein kinase pathways
IL-17A has effects on neutrophils

- IL-17 orchestrates the accumulation of neutrophils in mammals thereby contributing to host defense
- IL-17 stimulates the apoptosis of mouse neutrophils and simultaneously, the release of the microbiocidal compound, myeloperoxidase
- IL-17 also stimulates mouse macrophages to phagocytose aged neutrophils

Key Functions of IL-17 and Its Role in Inflammation and Matrix Destruction


G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte–macrophage colony-stimulating factor; TNF = tumor necrosis factor.
Structure of IL-17 and Its Interaction With IL-17R

mRNA = messenger ribonucleic acid; NF-κB = nuclear factor κB; TNFRI = tumor necrosis factor receptor type 1; TNFRII = tumor necrosis factor receptor type 2; TRAF6 = TNF receptor-associated factor 6.

Synergy Between TNF and IL-17A and F on IL-6 Expression and Production by Synoviocytes

IL-6 mRNA

IL-6 Protein

TNFα = tumor necrosis factor alpha.

IL-17 in a mouse model of ankylosing spondylitis (AS)

- Male (BXSB x NZB) F₁ mice develop seronegative ankylosing enthesitis in ankle/tarsal joints only when caged in groups, with the incidence reaching 83% at 7 months of age.

- Elevated popliteal lymph node T cells producing IL-17 and IFN-γ are significantly associated with joint ankylosis.

IL-17 expressing CD4+ cells are increased in peripheral blood of patients with (AS) or psoriatic arthritis (PsA)

- Peripheral blood was obtained from 10 PsA, 10 AS, 10 rheumatoid arthritis (RA), and 5 vitiligo (Vit) patients, as well as from 25 healthy donors (HD)
- Peripheral blood cells were analyzed by flow cytometry and immunohistochemistry
- Cytokine production was examined by enzyme-linked immunosorbent assay and intracellular cytokine staining using specific monoclonal antibodies

*** P<0.001 vs healthy donors


IL-17 expression is increased in T cells from patients with either AS or PsA

- This study assessed IL-23 receptor and IL-17 expression in patients with active AS (n=17), PsA (n=8), early RA (n=9), and healthy subjects (n=20)

- There was a nearly 2-fold increase in the proportion of T cells capable of IL-17 production in AS patients versus healthy controls

- Results of experiments with gating on CD4+ T cells, showed that classic Th17 cells in the periphery were expanded in patients with PsA and patients with early RA compared with controls

IL-17 is elevated in cells from facet joints in patients with AS

- *In situ* analysis of IL-17+ cells in facet joints of AS patients and patients with osteoarthritis (OA) was carried out using immunofluorescence microscopy
- Double-staining revealed that myeloperoxidase-positive (MPO+) and CD15+ cells are the major source of IL-17 expression
- The frequency of these cells was significantly higher in AS than in OA (P<0.05 in both cases). The population of MPO+ cells included mononuclear cells and cells with polysegmental nuclei
- Th17 cells and mast cells are also a source for IL-17+ expression, both of which were significantly higher in AS patients than in OA patients (P<0.05 in both cases)

![Ankylosing Spondylitis](image)

IL-17 is increased in synovial mast cells from patients with SpA

- Synovial tissue and fluid were obtained from patients with either non-psoriatic or psoriatic spondylarthritis (SpA) (n=82) and patients with RA (n=50)
- Synovial biopsy tissue was analyzed by immunostaining
- IL-17 and tryptase expression were both increased in synovial mast cells from patients with SpA vs those with RA

![Image of mast cell tryptase colocalization](image)

Arrows indicate colocalization of IL-17 and tryptase

* P<0.05 for difference between SpA and RA

"Enthesis" from the Greek word, "ἔνθεσις" or "ένθεσις," meaning insertion. The site of attachment of tendons, ligaments or joint capsule fibers to bone. Enthesitis is inflammation of the enthesis.
Normal Tendon Enthesis
Achilles Enthesitis

Doppler Signal at Enthesis


Courtesy of Dr GS Kaeley
IL-23 induces enthesitis and new bone formation in SpA animal model

Passive transfer CIA

IL-23 minicircle

IL-23 promotes enthesial inflammation and IL-22 osteoproliferation

CIA, collagen-induced arthritis

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

![Diagram of IL-23 and T-cell interactions promoting enthesitis and osteoproliferation.]

Gamma-delta T Cells in the entheses

Under IL-23 mediated inflammatory conditions $\gamma\delta$ T cells accumulate in the Achilles tendon; 50-80% of enthesal $\gamma\delta$ T cells are of a phenotype (V$\gamma$6+) that produce IL-17, $\gamma\delta$ T cells are the major producers of IL-17 in the enthesis.


IL-17-producing $\gamma\delta$ T Cells populate mechanically exposed tissues

$\gamma\delta$ T cells also accumulate in tissues with similar biomechanical properties to those present in the entheses such as the aortic valve and root, and the ciliary body within the eye in IL-23 overexpressing mice.

right: immunofluorescence; arrows: $\gamma\delta$ T cells; green: autofluorescence and $\gamma\delta$ T cell reporter; red: CD3/T cells; blue CD45/lymphocytes.

Enthesitis Indices

LEI
6 sites

SPARCC
18 sites; score of 16

MASES
13 sites

Achilles Enthesitis: US/MRI

Courtesy of Dr GS Kaeley
Tools for Targeting the IL-17–Th17 Pathway

Inhibitors of T<sub>H</sub>17 cell generation
- RORC
- STAT3
- IL-23p19-targeted antibody

Combination with TNF inhibition:
- Two molecules
- One molecule

IL-17A-targeted antibodies
- AIN-457
- LY2439821
- SCH-900117
- RG4934

IL-17RA-targeted antibody
- AMG 827

IL-17A–IL-17F targeted antibody
- RG7624

IL-17A–IL-17F

IL-17RA
IL-17RC

Target tissue

Inhibitors of IL-17R signal transduction

Biological effects
- Inflammation
- Matrix destruction
- Cell migration

RORC = Retinoid-related orphan receptor-γ; STAT3 = signal transducer and activator of transcription 3.
Ustekinumab: p40 inhibitor
Ustekinumab in AS (looked promising)
Prospective, open-label, single-arm, proof-of-concept trial

- 20 pts with active AS treated with ustekinumab 90 mg at baseline, week 4 & week 16
- 1st endpoint ASAS40 response at week 24
- 35% of the pts had an ASDAS inactive disease (ASDAS <1.3)
- Clinical response correlated with reduction of active inflammation on MRI and CRP levels

Ustekinumab is not moving forward in AS based on phase inadequately positive phase 3 results
IL-17 Inhibitors in SpA

Figure adapted from Strzepa A, et al. Pharmacol Reports. 2011;63(1):30-44, courtesy of Frank Nestle
MEASURE 2 (Secukinumab): Study Design

Loading

Week BL 1 2 3 4 8 12 16

Secukinumab 150 mg s.c. BL, Wks 1, 2, 3

Treatment

Primary Endpoint

Secukinumab 150 mg s.c. Wk 4 and q4wk

Final Injection Wk 256

Final Assessment/ Wk 260/ Wk 268

PBO s.c. BL, Wks1, 2, 3

Secukinumab 75 mg s.c. Wk 4 and q4wk

Secukinumab 150 mg s.c. Wk 16 and q4wk

Secukinumab 75 mg s.c. Wk 16 and q4wk

Randomization stratified by response to prior anti-TNF treatment (naive vs inadequate response or intolerance).

BL, baseline; PBO, placebo; q4wk, every 4 weeks; R, randomization; s.c., subcutaneous; TNF, tumor necrosis factor; Wk, Week.
MEASURE 2: Secukinumab ASAS20 Responses

NRI data through Week 52

NRI data to Week 16; Observed data from Week 20–52

Primary endpoint

Weeks

Percentage of responders

Secukinumab 150 mg (n = 72)
Secukinumab 75 mg (n = 73)
Placebo (n = 74)

*P < 0.0001; †P < 0.001; ‡P < 0.01; §P < 0.05 vs. placebo.
P-values at Week 16 adjusted for multiplicity of testing
NRI, Nonresponder imputation; ASAS20, 20% improvement in ASAS criteria.

MEASURE 2: Secukinumab ASAS40 Responses

NRI data through Week 52

NRI data to Week 16;

Observed data from Week 20–52

*P < 0.0001; †P < 0.001; §P < 0.01; ‡P < 0.05 vs. placebo.

P-values at Week 16 adjusted for multiplicity of testing

NRI, Nonresponder imputation; ASAS40, 40% improvement in ASAS criteria

MEASURE 2: Secukinumab  ASAS40 Responses in Anti-TNF naïve Subjects

NRI data through Week 52

NRI data to Week 16;
Observed data from Week 20−52

*P < 0.0001; †P < 0.001; §P < 0.01; ‡P < 0.05 vs. placebo.
NRI, Nonresponder imputation; ASAS40, 40% improvement in ASAS criteria.

Abstract OP0168;
Novartis Data on File 2014. MEASURE 2 Clinical Study Report;
Novartis on File 2015 Summary of Clinical Efficacy in ankylosing spondylitis
MEASURE 2: Secukinumab  ASAS40 Responses in Anti-TNF-IR Subjects

NRI data through Week 52

- Secukinumab 150 mg (n = 28)
- Secukinumab 75 mg (n = 28)
- Placebo (n = 29)

NRI, Nonresponder imputation; ASAS40, 40% improvement in ASAS criteria.

*P < 0.0001; †P < 0.001; §P < 0.01; ‡P < 0.05 vs. placebo.

MEASURE 1: Core Study Design

Randomization was stratified according to whether patients were anti-TNF-naïve or had previous intolerance or inadequate response to anti-TNF therapy.

ASAS20: ≥20% improvement in Assessment of Spondyloarthritis International Society criteria; BL: baseline; IV: intravenous; q4wk: every 4 weeks; R: randomization; SC: subcutaneous; TNF: tumor necrosis factor.


MEASURE 1: Approximately 80% of Subjects Receiving Secukinumab Experienced No Increase in mSASSS Over 2 Years

Baseline mSASSS score: Secukinumab 10 mg/kg i.v. \( \rightarrow \) 75 mg: 10.84; secukinumab 10 mg/kg i.v. \( \rightarrow \) 150 mg: 9.63
Data from subjects with x-rays at baseline and Week 104 (x-ray completers; observed data)

Emerging Therapies for SpA

- IL-17Ai
  - Ixekizumab
- IL-17A/Fi
  - Bimekizumab
- IL-23i?
  - Guselkumab
  - Tildrakizumab
- JAKi
  - Tofacitinib
  - Other JAKs?
    - Upacitinib?
    - Filgotinib?
    - Baricitinib?
    - TYK2i
Ixekizumab

- COAST-V  Biologic Naïve - AS
- COAST-W  TNF-i Experienced - AS
- COAST-X  Biologic Naïve nr – Axial SpA
## Pathogenic Pathways Relevant to JAKi

### Arthritis

#### Enthesitis

![Enthesitis Image]

### Pathogenic Cytokines are Mediated or Modified by Tofacitinib

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Function/Physical Signs and Symptoms</th>
<th>Activated/Maintained by Cytokines</th>
<th>Produce Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ and CD8+ cells</td>
<td>Enthesitis, skin inflammation, synovitis</td>
<td>IL-6, IL-7, IL-15, IL-12, IL-23</td>
<td>IL-17, IL-22</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>T cell activation</td>
<td>IL-15, IFNα</td>
<td>IFNγ, IL-12, IL-23</td>
</tr>
<tr>
<td>Innate lymphoid cells</td>
<td>Enthesitis</td>
<td>IL-7</td>
<td>IL-17, IL-22 and TNF</td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>Hyperkeratosis, systemic inflammation</td>
<td>IL-17, IL-22, IL-20 family</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte synoviocyte interaction</td>
<td>Synovial inflammation</td>
<td>IL-15, IFNγ, IL-17</td>
<td>RANKL, TNF</td>
</tr>
<tr>
<td>Osteoclast</td>
<td>Bone resorption</td>
<td>RANKL, IL-6, TNF</td>
<td></td>
</tr>
<tr>
<td>Osteoblast</td>
<td>Pathologic bone formation</td>
<td>IL-22</td>
<td></td>
</tr>
</tbody>
</table>

Cytokines in red are JAK dependent
Tofacitinib reduces the production or downstream effects of cytokines in blue.

CD=Cluster of Differentiation; IFN=Interferon; RANKL=Receptor Activator of Nuclear factor Kappa-B Ligand
Conclusions

• The IL17-IL23-TH17 axis is important in SpA
• Modulators of this pathway have shown efficacy in signs and symptoms of AS, PsA, and psoriasis.
• There exists the possibility of modulation of progressive ankylosis; absolute proof is pending