Update on autoinflammatory diseases

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Acting Chief, Dermatology Branch
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National Institutes of Health
Turning Discovery Into Health
Autoimmunity
- Adaptive immune response
  - Autoreactive T-cells, autoantibodies

Autoinflammation
- 1997 FMF = MEFV: pyrin
- 1999 Innate immune response
  - TNF, IL-1β
  - Fever: absence of infectious trigger
  - Skin, joints, bones, GI, serosa, CNS

Daniel Kastner, MD, PhD
Scientific Director, NHGRI
Pyoderma gangrenosum
Acne vulgaris
Hidradenitis suppurativa
Organ-specific autoimmune diseases
Multiple sclerosis
Inflammatory bowel disease
Spondyloarthropathies
Gout and other crystal arthropathies
Systemic lupus erythematosus
Systemic juvenile idiopathic arthritis
Familial fever syndromes
Autoimmune
Organ-specific
Systemic
Autoinflammatory
APCED
IPEX
ALPS
Mendelian disorders
Polygenic diseases
## Comparison Chart of Systemic Autoinflammatory Diseases (SAID)

<table>
<thead>
<tr>
<th>Condition</th>
<th>SIGS</th>
<th>MNS</th>
<th>SCD</th>
<th>SCD-TX</th>
<th>TRAPS</th>
<th>IBMR</th>
<th>FBMR</th>
<th>FMF/MEH</th>
<th>MTPH</th>
<th>IBD/xLP</th>
<th>MA</th>
<th>NAPSA/PAPA</th>
<th>HABP/SCAR</th>
<th>FAPA/PAFO</th>
<th>RAPA/CAPS</th>
<th>TTP/PAPA</th>
<th>PAPA/PHOC</th>
<th>PAPA/SEPS</th>
<th>SLA/BMx</th>
<th>GLAN/CGA</th>
<th>PSNA/BMx</th>
<th>BAM/SCD</th>
<th>AILNM/CSBM</th>
<th>AILNM/CSBM</th>
<th>AILNM/CSBM</th>
<th>AILNM/CSBM</th>
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</thead>
<tbody>
<tr>
<td><strong>JUXTACORTICAL INFLAMMATION</strong></td>
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<td><strong>ARTHRITIS</strong></td>
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<tr>
<td><strong>IMMUNE MEDIATED</strong></td>
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<tr>
<td><strong>MUTATION</strong></td>
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</tbody>
</table>
Update on autoinflammatory diseases

- Autoinflammatory disease
- Monogenic disease
- Skin
Update on autoinflammatory diseases

- Inflammasomopathies
- Interferonopathies
Update on autoinflammatory diseases

Inflammasomopathies
- CAPS → NUD, NUSI, Schnitzler S.
- DIRA/DITRA and pustular psoriasis
- PAAND → neutrophilic skin disease
- NLRP1-associated skin diseases

Interferonopathies
### Cryopyrin-associated periodic fever syndromes (CAPS)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease onset</th>
<th>Duration of episodes</th>
<th>Abdominal pain</th>
<th>Skin rash</th>
<th>Arthralgia/arthritis</th>
<th>Bone involvement</th>
<th>CNS inflammation</th>
<th>Lymph node involvement</th>
<th>SAA amyloidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial cold autoinflammatory syndrome</td>
<td></td>
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</tr>
<tr>
<td>Muckle-Wells syndrome</td>
<td>Early childhood</td>
<td>2–3 days</td>
<td>Possible</td>
<td>Urticaria-like</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neonatal onset multisystem inflammatory disease</td>
<td>Neonatal or early infancy</td>
<td>Continuous with flares</td>
<td>Rare</td>
<td>Urticaria-like</td>
<td>Yes</td>
<td>Bony overgrowth</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- **Clinical features**
  - Neutrophilic urticaria w/ fever (FCAS/MWS/NOMID)
  - Cochlear, CNS inflammation (MWS/NOMID)
  - Arthralgia/arthritis (NOMID)

Nat Rev Rheumatol 2011;7469-77.
NLRP3 ‘Inflammasome’

Autosomal dominant

– *NLRP3*, ‘cryopyrin’
Dramatic response to IL-1 blockade

FDA approval for CAPS:
- Anakinra
- Rilonacept
- Canakinumab

Neutrophilic urticaria w/ systemic inflammation

Schnitzler syndrome
Neutrophilic urticaria
Fevers
Bony lesions/pain
Monoclonal IgM

Still’s disease/sJIA
Neutrophilic urticaria
Fevers
Arthritis
↑ Ferritin

Urticarial Vasculitis
Chronic urticaria
Arthralgias
Systemic involvement
Leukocytoclastic vasculitis

Eiling, et al. JAAD 2007;57
Schnitzler S.

Mean age onset: 60 yrs

Table 2  Strasbourg diagnostic criteria of Schnitzler syndrome according to Allergy 2013;68:562–568

<table>
<thead>
<tr>
<th>Obligate criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic urticarial rash and</td>
</tr>
<tr>
<td>Monoclonal IgM or IgG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent fever&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Objective findings of abnormal bone remodeling with or without bone pain&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>A neutrophilic dermal infiltrate on skin biopsy&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Leukocytosis and/or elevated CRP&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Definite diagnosis if

Two obligate criteria AND at least two minor criteria if IgM and three minor criteria if IgG

Probable diagnosis if

Two obligate criteria AND at least one minor criteria if IgM and two minor criteria if IgG

<sup>a</sup> Must be >38 °C and otherwise unexplained. Occurs usually—but not obligatory—together with the skin rash

<sup>b</sup> As assessed by bone scintigraphy, MRI, or elevation of bone alkaline phosphatase

<sup>c</sup> Corresponds usually to the entity described as “neutrophilic urticarial dermatosis” (Medicine 2009;88:23–31); absence of fibrinoid necrosis and significant dermal edema.

<sup>d</sup> Neutrophils >10,000/mm³ and/or CRP >30 mg/l
Management (29 pts)

- Treatment of choice: anakinra → response 100%
- AE: Neutropenia (3); infection (6)
- Rapid return of symptoms after missed dose (36-48hrs)
- ‘Tx failures should lead to reconsidering Dx’
Cryopyrin somatic mosaicism

‘Atypical’ Schnitzler syndrome
- 2 pts. severe phenotype
- Low/no IgGk paraprotein
- Myeloid-lineage restricted somatic mosaicism (NLRP3)

Adult onset FCAS

NOMID
- 70% mutation ( - ) = somatic mosaicism
- Older age of onset
- Milder CNS disease

NRLP3 Inflammasome

CAPS: cryopyrin-associated periodic syndromes
PAPA syndrome
Familial Mediterranean fever

DIRA

IL-1β
IL-1Ra
IL-1RaCp

Normal situation

Beer HD, et al. *JID* 2014; 134
An Autoinflammatory Disease with Deficiency of the Interleukin-1–Receptor Antagonist
DIRA

- Autosomal recessive
- Onset birth-3 wks
- Fetal distress
- Joint swelling/pain
- Pustulosis
- Skeletal disease
  - Multifocal osteolytic lesions (8/9)
  - Heterotopic ossification (7/9)
  - Widening of rib ends (9/9)

No fever; limited response to steroids
2 deaths: multiorgan failure (2mo, 21mo)
1 death: progressive interstitial fibrosis

NRLP3 Inflammasome

CAPS: cryopyrin-associated periodic syndromes
PAPA syndrome
Familial Mediterranean fever

DIRA

IL-1β
IL-1RA
IL-1RAcP
PSTPIP1
(Anakinra)
IL-1R1

Mutated NLRP3
LRRs
CARD
NACHT
PYD
PYD

ASC
CASP-1
Caspase-1
Pro-IL-1β

Normal situation

Beer HD, et al. JID 2014; 134
DIRA: response to treatment with anakinra

Before anakinra  5 months after anakinra

## Monogenic AI forms of pustular psoriasis

<table>
<thead>
<tr>
<th>Disease*</th>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance pattern</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency of IL-1 receptor antagonist (DIRA)</td>
<td><em>IL1RN</em></td>
<td>IL-1 receptor antagonist</td>
<td>Autosomal recessive</td>
<td>Fevers, pustular skin rash, osteolytic bone lesions</td>
</tr>
<tr>
<td>Deficiency of IL-36 receptor antagonist (DITRA)</td>
<td><em>IL36RN</em></td>
<td>IL-36 receptor antagonist</td>
<td>Autosomal recessive</td>
<td>Generalized pustular psoriasis</td>
</tr>
</tbody>
</table>

DIRA vs. DITRA

Interleukin-36–Receptor Antagonist Deficiency and Generalized Pustular Psoriasis
DITRA

- Autosomal recessive
- Acute flares generalized pustular psoriasis
- Fevers, malaise, leukocytosis, ↑ CRP
- Childhood → adulthood (impetigo herpetiformis)

DITRA: spectrum of disease

- Null mutants (severe GPP/AGEP)
- Decreased/nl protein (hypomorphhic)
  - Localized or generalized PP
- Psoriasis vulgaris + PP = not DITRA
- Geographic tongue *is associated* with DITRA (w/ or w/o PP)


GT detected in both GPP and non-GPP DITRA family members
GT semi-dominant inheritance
Tongue biopsy: IL-36Ra/IL-36 expression decreased cp. to controls (including pts. w/o DITRA)
DITRA: treatment with anti-IL-17 therapy

Figure. Clinical Images of a Patient With Generalized Erythrodermic Pustulosis Due to DITRA Before and After Treatment With Secukinumab

A  Before treatment

B  After treatment
DITRA: treatment with anti-IL-12/23 therapy

1-1.5mg/kg ustekinumab every 2 months

Ann Rheum Dis, 2017 Sep 2. [Epub ahead of print]
Anakinra for pustular psoriasis

2 GPP pts. (adult, pediatric onset)
Rapid response to anakinra
Normalization of IL-6, IL-1β levels

13-AR-0071: A Phase 2 Study of Anakinra in Inflammatory Pustular Dermatosis: Evaluation of Therapeutic Efficacy and Validation of Pathogenic Mechanisms

3 month dose-escalation study
Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation

- Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)
  - Recurrent fever, arthralgias/myalgias, myositis
- Elevated acute phase reactants
- Neutrophilic dermatoses
  - Acne, HS, PG, vasculitis
- Features resemble PAPA (Pyogenic arthritis, PG, acne [PSTPIP1])
**PAAND**
- Autosomal dominant
- Recurrent fever
- Arthralgias/myalgias
- Myositis
- Neutrophilic dermatoses

Tx: IL-1, TNF blockade

**FMF**
- Autosomal rec. or dom.
- Fever
- Abdominal pain
- Erysipeloid erythema
- Amyloidosis

Tx: colchicine
Pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH)—a new autoinflammatory syndrome distinct from PAPA syndrome

Braun-Falco M, et al. JAAD 2011;66
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>PG</th>
<th>Acne</th>
<th>Pyogenic Arthritis</th>
<th>HS</th>
<th>Ulcerative Colitis</th>
<th>Seroneg spondylo-arthritis</th>
<th>PSTPIP1 mutation</th>
<th># of cases</th>
<th>Response to IL-1 blockade</th>
<th>Response to TNF blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>7 mutations</td>
<td>11 families</td>
<td>+ joints</td>
<td>+ skin</td>
<td></td>
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<tr>
<td>PASH</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>↑CCTG microsatellite</td>
<td>3</td>
<td>+ in 1</td>
<td>+ in 1</td>
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<tr>
<td>PAPASH</td>
<td>+</td>
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<td>E277D</td>
<td>1</td>
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<td>PAC</td>
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<td>G403R</td>
<td>1</td>
<td>+</td>
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<td>PASS/ PsAPASH</td>
<td>+</td>
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<td>Not done</td>
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<td>HS + PG</td>
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<td>&gt;30</td>
<td>+</td>
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2 pts. w/ FMF and HS (Turkey)

21 pts. complex HS (HIII or HII w/ other inflammatory condition(s))
  – PG, arthritis, IBD, acne conglobata
  – 8/21 (38%) pathogenic *pyrin* mutations
**Association of pyrin mutations and autoinflammation with complex phenotype hidradenitis suppurativa: a case–control study**


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**Table 3** Odds ratio (OR) for additional clinical features in the complex hidradenitis suppurativa group vs. normal population, and standardized morbidity ratio (SMR) calculation for clinical familial Mediterranean fever (FMF) disease

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Number of patients</th>
<th>Allele frequency of MEFV variants</th>
<th>OR**</th>
<th>95% CI</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Clinical FMF disease,a</td>
<td>5/119</td>
<td>NA</td>
<td>45b</td>
<td>16.50–99.84</td>
<td>&lt; 0.001</td>
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<tr>
<td>Hurley stage III</td>
<td>13/21</td>
<td>34.6%</td>
<td>4.17</td>
<td>1.75–9.94</td>
<td>0.001</td>
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<tr>
<td>Arthritis</td>
<td>8/21</td>
<td>31.3%</td>
<td>3.58</td>
<td>1.19–10.81</td>
<td>0.023</td>
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<tr>
<td>Acne</td>
<td>15/21</td>
<td>26.6%</td>
<td>2.87</td>
<td>1.20–6.84</td>
<td>0.018</td>
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<tr>
<td>Pyoderma gangrenosum</td>
<td>4/21</td>
<td>50%</td>
<td>7.88</td>
<td>1.9–32.67</td>
<td>0.004</td>
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<tr>
<td>Dissecting cellulitis of the scalp</td>
<td>5/21</td>
<td>30%</td>
<td>3.38</td>
<td>0.84–13.65</td>
<td>0.09</td>
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</table>

NA, not applicable. An OR with a lower boundary of the 95% confidence interval (CI) above one is equivalent to a significance level of P < 0.05. **OR is calculated using allele frequency of 11.2 in the healthy population. SMR is calculated using population data. Clinical prevalence of FMF in Turkey is one per 1075.**

Germline NLRP1 Mutations Cause Skin Inflammatory and Cancer Susceptibility Syndromes via Inflammasome Activation

- Gain of function $\rightarrow$ NLRP1

*Proliferative* inflammasome disorders
- Multiple self-healing palmoplantar carcinoma
- Familial keratosis lichenoides chronica
Germline NLRP1 Mutations Cause Skin Inflammatory and Cancer Susceptibility Syndromes via Inflammasome Activation
Germline NLRP1 Mutations Cause Skin Inflammatory and Cancer Susceptibility Syndromes via Inflammasome Activation
1. Neutrophilic urticaria: NLRP3 mutations, atypical Schnitzler’s syndrome → IL-1 inhibition

2. DIRA/DITRA: Pustular Pso with geographic tongue and absence of plaque disease are clues to DITRA

3. PAAND is new PAPA-like neutrophilic dermatosis w/ muscle involvement, distinct from FMF

4. Consider *pyrin* mutations in pts. with complex HS

5. NLRP1 inflammasome activation may cause skin hyperplasia/CA
Update on autoinflammatory diseases

- Inflammasomopathies
- Interferonopathies
Update on autoinflammatory diseases

Inflammasomopathies

Interferonopathies
  – Proteosome-associated AI disease
  – SAVI
<table>
<thead>
<tr>
<th>Mechanism of disease</th>
<th>Gene</th>
<th>Protein function</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal accumulation of nucleic acids</td>
<td>TREX1</td>
<td>Three prime repair exonuclease 1; cytosolic DNase</td>
<td>Aicardi-Goutières syndrome (AGS), Familial chilblain lupus (CHBL), Retinal vasculopathy with cerebral leukodystrophy (RVCL), Aicardi-Goutières syndrome (AGS)</td>
</tr>
<tr>
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<td>RNASEH2A</td>
<td>Ribonuclease H2, subunits A, B, C; ribonucleotide excision repair</td>
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<td>SAMHD1</td>
<td>SAM domain and HD domain-containing protein 1; dNTP triphosphohydrolase, RNase</td>
<td>Aicardi-Goutières syndrome (AGS), Familial chilblain lupus (CHBL)</td>
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<tr>
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<td>POLA1</td>
<td>DNA polymerase α; synthesis of RNA-DNA primer during DNA replication</td>
<td>X-linked reticulate pigmentary disorder (XLRPD)</td>
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<td>ADAR1</td>
<td>Adenosine deaminase, RNA-specific; deamination of adenosine to inosine in dsRNA</td>
<td>Aicardi-Goutières syndrome (AGS)</td>
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<tr>
<td></td>
<td>TMEM173</td>
<td>Stimulator of interferon genes protein; IFN-β induction in response to cytosolic DNA</td>
<td>STING-associated vasculopathy, infantile-onset (SAV), Familial chilblain lupus (CHBL)</td>
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<tr>
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<td>IFIH1</td>
<td>IFN-induced helicase C domain-containing protein 1; pattern recognition receptor for dsRNA</td>
<td>Aicardi-Goutières syndrome (AGS), Singleton-Merten syndrome (SGMRT)</td>
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<tr>
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<td>DDX58</td>
<td>Retinoic acid-inducible gene 1 protein; pattern recognition receptor for dsRNA</td>
<td>Singleton-Merten syndrome (SGMRT)</td>
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<td>ISG15</td>
<td>Interferon-stimulated gene 15; ubiquitin-like protein, modifies proteins by ISGylation</td>
<td>ISG15 deficiency</td>
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<td>USP18</td>
<td>Ubiquitin specific peptidase 18; de-ISGylation</td>
<td>USP18 deficiency</td>
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<td>ACP5</td>
<td>Tartrate-resistant acid phosphatase, type 5; dephosphorylation of osteopontin</td>
<td>Spondyloenchondrodysplasia (SPENCD)</td>
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<tr>
<td></td>
<td>PSMB8</td>
<td>Proteasome subunit beta type-6; antigen processing in immunoproteasome</td>
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<td>PSMB4</td>
<td>Proteasome subunit beta type-4; antigen processing in immunoproteasome</td>
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<td></td>
<td>PSMA3</td>
<td>Proteasome subunit alpha type-3; antigen processing in immunoproteasome</td>
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<tr>
<td></td>
<td>PSMB9</td>
<td>Proteasome subunit beta type-9; antigen processing in immunoproteasome</td>
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<tr>
<td></td>
<td>POMP</td>
<td>Proteasome maturation protein; formation of immunoproteasome</td>
<td>Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)</td>
</tr>
</tbody>
</table>
Aicardi-Goutières syndromes (AGS1-7)

- **TREX1, RNASEH2A-C, SAMHD1 and ADAR**
- Encephalopathy
- Retinal vasculopathy/cerebral leukodystrophy
- Dyschromatosis symmetrica hereditaria
- Familial chilblain lupus: acrocyanosis, purpura, petechiae

Aicardi-Goutières S. 2 yo girl with mild developmental delay, white matter changes, +ANA, homozygous missense mutation in SAMHD1. Courtesy Julie Schaffer, MD
Activated STING in a Vascular and Pulmonary Syndrome


SAVI
(STING-Associated Vasculopathy with onset in Infancy)

OMIM: 615934
Autosomal dominant (*de novo*)
- *TMEM173*: STimulator of Interferon Genes (STING)
- Gain-of-function mutation $\rightarrow$ constitutive activation
- Elevated *INFB1* transcription $\rightarrow$ autoinflammation

Cardinal features
- Early-onset systemic inflammation
- **Severe cutaneous vasculopathy**
- Pulmonary inflammation
- Poor response to steroids, DMARDs
# SAVI

**Neonatal onset**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>6 (1 day to 8 wk)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 3, Female 3</td>
</tr>
<tr>
<td>Symptom at initial presentation</td>
<td>Rash 4, Tachypnoea 2</td>
</tr>
<tr>
<td>Features of systemic inflammation</td>
<td>Increased acute-phase reactant level 6, Fever 6</td>
</tr>
<tr>
<td>Features of peripheral vascular inflammation</td>
<td>Acral violaceous plaques 6, Nodules on face, nose, or ears 6, Distal ulcerative lesions with infarcts 6</td>
</tr>
<tr>
<td>Manifestations of vascular and tissue damage</td>
<td>Nail dystrophy or loss 6, Gangrene of fingers or toes 4, Nasal-septum perforation 4</td>
</tr>
<tr>
<td>Pulmonary manifestations</td>
<td>Paratracheal adenopathy 6, Abnormal pulmonary-function test 5, Interstitial lung disease observed on CT 5, Lung fibrosis 3</td>
</tr>
<tr>
<td>Low-titer autoantibodies</td>
<td>Antinuclear antibody 3, Antiphospholipid antibodies 5, c-ANCA 1</td>
</tr>
<tr>
<td>No response or incomplete response to treatment</td>
<td>Glucocorticoid 6, DMARD 6, Biologic agents 6</td>
</tr>
</tbody>
</table>

*NEJM 2014;371:507-18.*
SAVI: facial features

- Nasal involvement (6/6)
- Septal perforation (4/6)

<table>
<thead>
<tr>
<th>CLINICAL FEATURES OF VASCULITIS</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acral violaceous plaques and nodules on the face, nose and ear lobes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful distal ulcerative lesions with purulent discharge or tissue infarcts</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral ulcers, pustules or vesicles</td>
<td>Yes</td>
<td>ND</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Generalized pustules</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Eschars</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Erythema</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL FEATURES OF VASCULAR/TISSUE DAMAGE</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livedo reticularis (localized to extremities and transient during cold exposure)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>Yes</td>
<td>ND</td>
<td>Yes</td>
<td>ND</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Telangiectasia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nailfold capillary tortuosity and/or periungual erythema</td>
<td>Yes / Prominent violaceous periungual erythema</td>
<td>Yes / 2+ tortuosity and 2+ capillary loop loss</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Yes</td>
</tr>
<tr>
<td>Gingival capillary dilatation</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nail dystrophy or loss</td>
<td>Yes / Clubbing</td>
<td>Yes / Dystrophy of finger and toenails</td>
<td>Yes / Dystrophy</td>
<td>Yes / Dystrophy</td>
<td>Yes / Dystrophy</td>
<td>Yes / Dystrophy and loss</td>
<td></td>
</tr>
<tr>
<td>Amputation of extremities/onset</td>
<td>No</td>
<td>No</td>
<td>Yes / 3yr</td>
<td>Yes / 18mo</td>
<td>Yes / 8yr</td>
<td>Yes / 1yr (noticed to have shortened digits, sclerosis and acral osteolyis)</td>
<td></td>
</tr>
<tr>
<td>Nasal septum perforation</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
### Lung/musculoskeletal

<table>
<thead>
<tr>
<th>PULMONARY MANIFESTATIONS</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial lung disease on CT</td>
<td>Yes / Chest CT with diffuse interstitial edema (Bmco), lung biopsy / interstitial chronic inflammation, multifocal lymphoid formations, alveolar hyperplasia and mild pulmonary fibrosis, Paratracheal adenopathy</td>
<td>Yes / PFT with moderate-severe restrictive defect Paratracheal adenopathy</td>
<td>Yes / Mild interstitial lung disease PFT with mild restrictive defect Hilar adenopathy</td>
<td>No / Recurrent wheezing episodes Mild mediastinal adenopathy</td>
<td>Yes / Bilateral lung infiltrates, patchy interstitial lung disease, Prominent hilar lymphadenopathy</td>
<td>Yes / Pneumonias from 2-4 yrs and from 12-14 yrs; mild interstitial lung disease PFT with mild restrictive defect Paratracheal adenopathy</td>
</tr>
<tr>
<td>Lung fibrosis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

| MUSCULOSKELETAL MANIFESTATIONS | |
| Myositis | ND | Yes | No | No | Yes | No |
| Arthritis/arthralgia | No / Arthralgia with strenuous exercise | No / Yes | No / No | No / No | Erosive RF+ Rheumatoid Arthritis | No / No |
| Chronic deforming arthritis | No | No | No | No | Yes | No |
| Joint stiffness | No | Yes | No | No | Yes | No |

### Images

- **J**: Bone resorption
- **K**: Surgical amputation
- **L**: Seropositive RA
- **M**: 12-14 yrs; mild interstitial lung disease
Prognosis

- High mortality (3/7)
- Unresponsive to multiple agents
  - Pred, CYP, AZA, CSA, MTX, MMF, IVIG, belimumab, HCQ, anti-TNF, leflunamide, RTX, ASA, nifedipine
- Interferon pathway-specific Tx?
The STING-Interferon-β pathway

Type 1 interferon receptor

STING-positive cell

dsDNA

cGAS

cGAMP

STING

STAT1

STAT2

TYK2

JAK1

Inhibition

Inhibition

STAT1

STAT2

TBK1 and IRF-3 activation

Transcription of type 1 interferon genes and interferon-response genes

Other interferon-responsive cells

↑ Type 1 interferons
Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature syndrome

- **Perinatal**
  - Fevers, persistent erythematous, annular plaques
- **Late infancy**
  - Periorbital erythema, digital edema
- **Early childhood**
  - Lipodystrophy, LAD, anemia, arthritis/arthralgia
- **Late childhood**
  - Hepatomegaly, cardiomyopathy, contractures

Dense dermal infiltrate of ‘atypical’ mononuclear cells
− Immature neutrophils/myeloid precursors
− Activated macrophages

Panniculitis

DDX:
− Histiocytoid Sweet’s syndrome
− Rheumatoid neutrophilic dermatosis
− Palisaded neutrophilic and granulomatous dermatitis
Proteasome-associated AI diseases

- Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)
- Nakajo-Nishimura syndrome (NNS)
- Japanese autoinflammatory syndrome with lipodystrophy (JASL)
- Joint contracture, muscle atrophy, panniculitis-induced lipodystrophy (JMP)

**Proteasome diseases**

- **Autosomal recessive:** *Proteasome subunit beta type-8 (PSMB8)*

- Defective assembly of immunoproteasome complex → increased cellular stress


IFN inducible genes are up-regulated in SAVI patients

JAK kinase inhibitors suppress STAT1 phosphorylation in SAVI patients

CD4 T cells

CD19 B cells

- Healthy control
- No inhibitor
- Tofacitinib 1 μM
- Ruxolitinib 100nM
- Baricitinib 200nM
JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies

- 18 patients (CANDLE, SAVI) → IFN positive gene signatures
- Failed corticosteroids, other immunosuppression, biologics
- CANDLE > SAVI
- Genetically negative patients also responded to therapy
Interferonopathy update: take home points

1. SAVI: severe acral vasculopathy, early-onset systemic inflammation, pulmonary inflammation

2. CANDLE: periorbital, acral erythema, panniculitis, immature PMNs, lipodystrophy, organomegaly, joint contractures

3. JAK inhibitors are an important new therapy for IFN-driven skin and systemic disease

4. Immunologic gene signature may guide therapy for difficult, complex/polygenic inflammatory disease

Contact information

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- cowene@mail.nih.gov
- 301-827-2328