U021: Monogenic autoinflammatory syndromes

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DISCLOSURES

We do not have any relevant relationships with industry.

We will be discussing off-label use of many medications.
Objectives

• Formulate a framework for understanding monogenic autoinflammatory syndromes

• Recognize targeted therapies for autoinflammatory conditions based on pathways involved

• Describe clinical features of monogenic autoinflammatory syndromes due to alterations in the inflammasome, the NF-kB pathway, and the interferon pathway.
Autoinflammatory Disease

- Disorders of the innate immune system
  - Autoimmune disease: adaptive immune system
- Seemingly unprovoked episodes of intense inflammation
- No high-titer autoantibodies or antigen specific T-cells
<table>
<thead>
<tr>
<th>Disease</th>
<th>Year mutation published</th>
<th>Gene/protein</th>
<th>Inheritance pattern</th>
<th>Disease onset</th>
<th>Flare/flare pattern</th>
<th>Specific organ inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMF (MIM 249100)</td>
<td>1997</td>
<td>MEFV/pyrin</td>
<td>AR</td>
<td>80% of the cases occur before the age of 20 y</td>
<td>1-3 d</td>
<td>Skin, joints, peritoneum, pleura</td>
</tr>
<tr>
<td>TRAPS (MIM 191190)</td>
<td>1999</td>
<td>TNFRSF1A/TNFRSF1A, TNFR1, p55</td>
<td>AD</td>
<td>Median age at onset of 3 y</td>
<td>1-6 wks</td>
<td>Skin, eyes, joints, peritoneum, pleura</td>
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<tr>
<td>CAPS FCAS (MIM 120100)</td>
<td>2001</td>
<td>CHIAsi or NLRP3/cryopyrin or NLRP3 or NALP3</td>
<td>AD</td>
<td>First 6 mo of life, cold &lt;24 h induced</td>
<td></td>
<td>Skin, eyes, joints</td>
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<tr>
<td>MWS (MIM 191900)</td>
<td>2001</td>
<td>CHIAsi or NLRP3/cryopyrin or NLRP3 or NALP3</td>
<td>AD</td>
<td>Infancy to adolescence</td>
<td>24-48 h</td>
<td>Skin, eyes, joints, inner ears, meninges (mild)</td>
</tr>
<tr>
<td>NOMID (MIM 607115)</td>
<td>2002</td>
<td>CHIAsi or NLRP3/cryopyrin or NLRP3 or NALP3</td>
<td>ADide novo</td>
<td>Neonatal or early infancy</td>
<td>Continuous with flares</td>
<td>Skin, eyes, joints, acrora, prominant lymph nodes</td>
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<tr>
<td>HIDS (MIM 260920)</td>
<td>1999</td>
<td>MUK/involution kinase (MK)</td>
<td>AR</td>
<td>Median age at onset 6 mo</td>
<td>3-7 d</td>
<td>Skin, eyes, joints</td>
</tr>
<tr>
<td>PGA (MIM 136580)</td>
<td>2001 and 2005*</td>
<td>NOID2 or CARD15/NOD2 or CARD15</td>
<td>ADide novo</td>
<td>Early childhood</td>
<td>Continuous</td>
<td>Skin, eyes, joints</td>
</tr>
<tr>
<td>PAPA (MIM 604416)</td>
<td>2002</td>
<td>CD2BP1 or PSTPIP3/CD1BP1 or PSTBP1</td>
<td>AD</td>
<td>Early childhood</td>
<td>Prolonged flares</td>
<td>Skin, joints</td>
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<tr>
<td>Majed syndrome (MIM 609628)</td>
<td>2005</td>
<td>LPIN2/LPIN2</td>
<td>AR</td>
<td>Early infancy (1-19 mo)</td>
<td>Weeks to months</td>
<td>Bones, peritoneum, anemia</td>
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<tr>
<td>Chénetion (MIM 118400)</td>
<td>2001</td>
<td>SH3BP2/E3BP2</td>
<td>AD</td>
<td>Childhood spontaneous remission by 3rd decade</td>
<td>Continuous early in life</td>
<td>Jaws, eyes (rare)</td>
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<tr>
<td>FCAS2 (MIM 611762)</td>
<td>2008</td>
<td>NLRP12/NLRP12 or NALP12</td>
<td>AD</td>
<td>Childhood, cold induced</td>
<td>2-10 d, 1-3 x per month</td>
<td>Continuous with flares</td>
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<tr>
<td>DIRA (MIM 612852)</td>
<td>2009</td>
<td>IL1RI/IL-1Ra</td>
<td>AR</td>
<td>Neonatal or early infancy</td>
<td>Continuous with flares</td>
<td>Skin, bones, lungs (rare), vasculitis (rare)</td>
</tr>
</tbody>
</table>
Comparison Chart of Systemic Autoinflammatory Diseases (SAID)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>SADT</th>
<th>Synonym</th>
<th>Clinical Features</th>
<th>Laboratory</th>
<th>Diagnosis</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>CAPS1</td>
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<td>CAPS2</td>
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<td>CAPS3</td>
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<td>CAPS4</td>
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<td>CAPS5</td>
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<td>WJS</td>
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<td>FMF</td>
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<tr>
<td>PAPA</td>
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<td>TRAPS</td>
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<tr>
<td>Muckle-Well Syndrome</td>
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<tr>
<td>Perozyne Syndrome</td>
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</tbody>
</table>

http://www.autoinflammatory.org/compchart.php
The Growing List of Autoinflammatory Diseases

- Familial Mediterranean Fever (MEFV)
- Tumor necrosis factor receptor associated periodic syndrome (TRAPS) (TNFRSF1A)
- Hyper IgD Syndrome/Mevalonate Kinase Disease (MVK)
- Cryopyrin Associated Periodic Syndromes (NLRP3)
- Deficiency of IL-1 Receptor Antagonist (DIRA) (IL1RN)
- Deficiency of IL-36 receptor antagonist (DITRA) (IL36RN)
- Pyogenic Arthritis Pyoderma Gangrenosum and Acne (PAPA) (PSTPIP1)
- PAPA-like disorders (PASH, PPASH, PAPASH)
- Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO)
- Proteasome Associated Autoinflammatory Syndrome (PRAAS) (PSMB8)
- Deficiency of Adenosine Deaminase Type 2 (DADA2) (ADA2)
Inflammasome and IL-1β production

- FMF
- DIRA
- CAPS
- PAPA
Familial Mediterranean Fever syndrome

• Mutation of *MEFV* gene, which encodes the protein pyrin
• Periodic fevers lasting 1-3 days
• Inflammation of the serosal membrane: abdomen, heart, lungs
• Monoarticular arthritis of large joints
• Amyloid deposition in organs → mortality
• Treatment: Colchicine, anti-IL-1
FAMILIAL MEDITERRANEAN FEVER

Signs and Symptoms

CARDINAL

% in our cohort of patients with mutations (47)

96% Fever

57% Pleurisy

2% Amyloidosis

91% Sterile Peritonitis

45% Arthritis/Arthralgia

13% Erysipelas-Like Erythema

During Attacks

ESR
WBC
Fibrinogen
Microscopic Hematuria/Proteinuria

Other

Headache
Aseptic Meningitis
Pericarditis
Splenomegaly
Polyarteritis Nodosa
Glomerulonephritis

Henoch Schönlein Purpura
Acute Scrotum
Febrile Myalgia

Proteinuria
Scattered Purpura

Samuels et al., Medicine (Baltimore) 77:268, 1998
Familial Mediterranean Fever

- Autosomal Recessive
- MEFV

The Pyrin Inflammasome

IL-1β Converting Enzyme (ICE)
Cutaneous Manifestations of FMF

• Erysipeloid erythema histopathology:
  o Superficial dermal edema and sparse perivascular infiltrate composed of neutrophils and few lymphocytes
  o Direct immunofluorescence: C3 deposits in vessel walls

• Treatment:
  o Colchicine
  o IL-1 blockade
The Cryopyrinopathies

“Neutrophilic dermatoses” due to mutation in NLRP3

Histology:
- Neutrophilic infiltrate
- Interstitial/perivascular neutrophils and lymphocytes
- Absence of dermal edema and vasculitis
The Cryopyrinopathies

• Familial Cold Autoinflammatory Syndrome

• Muckle-Wells Syndrome

• Neonatal Onset Multisystem Inflammatory Disease
FCAS: Familial cold autoinflammatory syndrome

• Cold-induced inflammation: urticaria, arthralgias, conjunctivitis, headaches
• Episodes < 24 hours
• No organ damage

http://www.autoinflammatory.org/fcas.php
MWS: Muckle-Wells syndrome

- Continuous inflammatory symptoms: fever, urticaria, arthritis, conjunctivitis, episcleritis
- Sensorineural hearing loss in 2\textsuperscript{nd}-4\textsuperscript{th} decade
- 25% develop amyloidosis

Nguyen et al. JAAD. 2013;68:834-853
NOMID/CINCA: Neonatal onset multisystem inflammatory disease

- Urticarial rash with fever
- Arthropathy: overgrowth patella, epiphyses of long bones; joint contractures
- Chronic aseptic meningitis \(\rightarrow\) intracranial pressure, ventriculomegaly, cerebral atrophy, seizures, vision loss
- Sensorineural hearing loss
- Short stature, frontal bossing
- Risk of amyloidosis

CAPS treatment

- Mutations in *NLRP3* gene → constitutive inflammasome activation (more IL-1β)
- IL-1RA blocks IL-1 mediated signaling
- IL-1 blocking agents as therapy

Goldbach-Mansky, Kastner. JACI. 2009;124:1141-9
Beer et al. JID. 2014;134:1805-1810
Could This be NOMID?

DIRA: Deficiency of IL-1 receptor antagonist

- AR mutation in *IL1RN* $\rightarrow$ unopposed IL-1
- Neonatal onset:
  - Fetal distress
  - Pustulosis
  - Oral mucosal lesions
  - Joint swelling/pain
  - Skeletal disease
- No fever

Aksentijevich et al. NEJM. 2009;360:2426-37
Deficiency of the IL-1 Receptor Antagonist (DIRA)

- Histopathology:
  - Epidermal acanthosis
  - Hyperkeratosis
  - Epidermal and dermal neutrophilic infiltrate with pustule formation along hair follicles

- Treat with the IL-1 receptor antagonist: anakinra

DIRA: Response to anakinra

Askentijevich et al. NEJM. 2009;360:2426-2437
Pyogenic Arthritis with Pyoderma Gangrenosum and Acne Syndrome (PAPA)

- Autosomal Dominant
- $PSTPIP1$
The Alphabet Soup of PAPA-like disorders
Treatment of PAPA and PAPA-like Diseases

- Glucocorticoids
- Anti-TNF agents
- Anti-IL-1 agents
- For \textit{PSTPIP1} positive
  - IL-18 blockade?
- IL-17 inhibition
- IL-23 inhibition
NF-κB signaling disorders

HA20
Haploinsufficiency of A20: Behçet’s-like

- Childhood onset
- Typical findings:
  - Skin lesions
  - Oral/genital ulcers
  - Ocular inflammation
  - Arthralgia/arthritis
  - GI inflammation

Function of A20
NF-κB Pathway

• Common low-penetrance coding and non-coding polymorphisms in associated with autoimmune diseases.

• A20 is an anti-inflammatory protein.
  • Cleaves K63 Ub chains, disrupting the signaling complex.
  • Adds K48 Ub chains, targeting proteins for proteasome degradation.
A20 is a potent inhibitor of NF-κB
Anakinra treatment

Initial experience in a patient (P6) with an agent targeting IL-1β has been positive.
Haploinsufficiency of A20 treatment

- Our NIH cohort is treated with:
  - Anti-TNF therapy
  - Anti-IL-1 therapy (continuous versus prn)
  - Prednisone prn or daily
  - Varying combinations of the above
    - Anti-IL-6 therapy
  - Other?

EXTENDED REPORT

A20 inhibition of STAT1 expression in myeloid cells: a novel endogenous regulatory mechanism preventing development of enthesitis

Katelijne De Wilde,1,2 Arne Martens,3,4 Stijn Lambrecht,1,2 Peggy Jacques,1,2 Michael B Drennan,1,2 Karlijn Debusschere,1,2 Srinath Govindarajan,1,2 Julie Coudryns,1,2 Eveline Verheugen,1,2 Fien Windels,1,2 Leen Catrysses,3,4 Rik Lories,5,6 Dennis McGonagle,7 Rudi Beyaert,4,8 Geert van Loo,3,4 Dirk Elewaert,1,2
Interferonopathies

CANDLE

SAVI
Proteasome-associated autoinflammatory syndromes (PRAAS)

- 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)
**Case & Review**

**Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome**

Antonio Torrelo, MD, Sapna Patel, MD, Isabel Colmenero, MD, Dolores Gurbindo, MD, Francisco Lendínez, MD, Angela Hernández, MD, Juan Carlos López-Robledillo, MD, Ali Dadban, MD, Luis Requena, MD, and Amy S. Paller, MD

*Madrid and Almería, Spain; Chicago, Illinois; and Amiens, France*
CANDLE: Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature syndrome

• Perinatal
  o Fever, persistent erythematous annular plaques
• Late infancy
  o Periorbital erythema, digital edema
• Early childhood
  o Lipodystrophy, LAD, anemia, arthritis/arthritis
• Late childhood
  o Hepatomegaly, cardiomyopathy
IFN signaling: JAK-STAT pathway

- Cytokines bind TM receptors associated with Jaks
- Binding activates Jaks
- Jaks phosphorylate receptors
- STATs bind receptors
- Jaks phosphorylate STATs
- STAT translocates to the nucleus
- STATs bind DNA and regulate transcription
Cytokines associated with Jaks

- First generation Jak inhibitors: ruxolitinib, tofacitinib, baricitinib
  - Block multiple Jaks
  - Multiple cytokines
  - Inhibit adaptive, innate responses
  - Small molecules
  - Varying half-lives
  - Varying effects on different cytokines
Preliminary response to Janus kinase inhibition with baricitinib in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE)

G Montealegre1, A Reinhardt2, P Brogan3, Y Berkun4, A Zlotogorski4, D Brown5, P Chira6, L Gao7, J Dare8, S Schalm9, R Merino10, D Chapelle1, H Kim1, S Judd1, M O’Brien1, A Almeida De Jesus1, Y Kim11, B Kost1, Y Huang1, S Paul12, A Brofferio13, C-C Lee14, C Hadigan15, T Heller11, C Minniti13, K Rother11, R Goldbach-Mansky1

From 8th International Congress of Familial Mediterranean Fever and Systemic Autoinflammatory Diseases Dresden, Germany 30 September - 3 October 2015
Activated STING in a Vascular and Pulmonary Syndrome

SAVI: STING-associated vasculopatthy with onset in infancy

• Autosomal dominant, mutation in TMEM173
  o Encodes adaptor protein STING
  o Mediates production of IFNβ
  o Elevated IFN → autoinflammation similar to PRAAS

• Cardinal features
  o Early-onset systemic inflammation
  o Severe cutaneous vasculopathy
  o Pulmonary inflammation
  o Poor response to steroids, DMARDs
Violaceous scaling lesions

Nail dystrophy and loss

Ulcerated lesions

Microthrombotic vasculopathy/Gangrene

Hyperkeratotic cornified skin

Ulcerated lesions with scabs

Tissue loss and scarring
Constitutive phosphorylation of STAT1 was blocked by JAK inhibitors

Liu et al. NEJM. 2014;371:507-518
SAVI: Prognosis

- High mortality (3/7)
- Unresponsive to multiple agents
  - Pred, CYP, AZA, CSA, MTX, MMF, IVIG, belimumab, HCQ, TNF-α inhibitor, leflunamide, RTX, ASA, nifedipine
- Interferon pathway-specific Tx: baricitinib
JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies


CANDLE syndrome

SAVI syndrome
Summary

• We have reviewed monogenic autoinflammatory disorders related to:
  o Inflammasome and IL-1β production
  o NF-κB signaling disorders
  o Type I Interferonopathies

• We discussed the clinical manifestations and pathogenesis of these disorders

• Knowing the genes, pathways, and cytokines involved has led to use of rationale treatments
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