Autoinflammatory Diseases

For the Dermatologist

George Han, MD, PhD
Chairman, Department of Dermatology
Mount Sinai Beth Israel
Assistant Professor and Director of Teledermatology
Icahn School of Medicine at Mount Sinai

Objective

- Describe mechanisms for autoinflammation
- Identify and manage cutaneous and systemic manifestations of autoinflammatory conditions
- Treat autoinflammatory syndromes with an understanding of the role therapeutic agents play in targeting the innate immune system

Outline

- What is autoinflammation?
- Classical/Monogenic Autoinflammatory Diseases
- Common Dermatologic Conditions featuring Autoinflammation
- Case Discussions

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- What is autoinflammation?
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What is autoinflammation?

- Autoinflammatory syndromes are conditions characterized by:
  - Exaggerated innate immune system response
  - Episodes of spontaneous inflammation affecting multiple organ systems
  - Primarily neutrophil-mediated response
  - Usually involving IL-1 pathways

Autoinflammation vs Autoimmunity

<table>
<thead>
<tr>
<th>Autoinflammation</th>
<th>Autoimmunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate immune system</td>
<td>Adaptive immune system</td>
</tr>
<tr>
<td>Neutrophil-mediated</td>
<td>Lymphocyte-mediated</td>
</tr>
<tr>
<td>No detectable autoantibodies</td>
<td>Characteristic autoantibodies in serum</td>
</tr>
<tr>
<td>Linked to inflammasome activation</td>
<td>Less clear link to inflammasomes</td>
</tr>
<tr>
<td>Classically IL-1 mediated</td>
<td>Mediated by T- and B- cells, with variable interleukin activation (including IL-1)</td>
</tr>
<tr>
<td>Host vs. Danger signals</td>
<td>Self vs. Non-self</td>
</tr>
</tbody>
</table>

IL-1β and IL-18

- Both activated by inflammasome activation, central to autoinflammation
- Both released as precursors and require activation

IL-1β

- IL-1β – discovery first started in 1948
  - Substance from rabbit leukocytes able to cause fever, later identified in 1970's as IL-1
  - Secreted by immune cells
    - Monocytes/macrophages, dendritic cells, neutrophils, NK cells, lymphocytes
    - Also secreted by keratinocytes
  - Acute phase reactant and pyrogen
  - Upregulates secretion of COX-2, IL-6, TNF-α, and IL-1
    - Activation of NFκB and subsequent expression of COX-2 leads to fever
  - Multiple types of receptors, including soluble receptors
Medications Targeting IL-1β

- **Anakinra** - competitive inhibitor of IL-1; binds to IL-1R
  - Short half-life necessitates daily SQ injections
  - FDA approved for RA, CAPS
- **Rilonacept** - fusion protein of IL-1R which binds IL-1 (soluble decoy),
  - Stronger binding to IL-1β than IL-1α; FDA approved for CAPS
  - Weekly injections
- **Canakinumab** - anti-IL-1β monoclonal antibody
  - Half life of ~25 days allows for injection q2mo
  - FDA approved for CAPS, systemic JIA, TRAPS, FMF
- **Gevokizumab** (anti-IL-1β mAb), LY2189102 were in development but not progressing
- **P2D7KK** - similar to Canakinumab but 11x more potent; still in preclinical trials

IL-18

- Induces interferon-γ
  - Requires IL-12 or IL-15 also
- Not a strong pyrogen (less activation of NFκB)
- Possible role in inflammation of IBD, heart disease, metabolic syndrome
- Blocking IL-18 reduces metastasis in a mouse model of melanoma

Inflammasomes

- Regulates immunologic response to either exogenous stimuli (pathogens) or endogenous stimuli (neoplasia)
- Intracellular multi-protein complexes
  - Molecular pattern recognition receptor (PRR)
  - Apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) adaptor protein
  - Caspase-1 enzyme
Inflammasome

PRR recognizes stimuli → ASC linked to pro-caspase-1 which is cleaved → caspase-1 activation → pro-IL-1β and pro-IL-18 cleaved to active forms

Autoinflammation as Aberrant Host Defense

- Pathogen-associated molecular patterns (PAMPs) activate inflammasomes
- Prototype of PAMP is Lipopolysaccharide, an endotoxin found on gram-negative bacterial cell walls
- Also flagellin, lipoteichoic acid (Gram+), peptidoglycan, dsRNA (viruses)
- Necessary for innate immune response to microbial invaders

Autoinflammation as Aberrant Host Defense

- Danger-associated molecular patterns (DAMPs) part of host response to non-pathogenic danger signals
- During cell death, some nuclear/cytosolic proteins are broken down → activate inflammasome to clear away cellular debris or react to possible neoplasia
- Examples include DNA/RNA, Heat Shock Protein, ATP, adenosine, S100
- Complicated relationship with tumorigenesis

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Categories of Autoinflammatory Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mutation</th>
<th>Clinical</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Mediterranean Fever (FMF)</td>
<td>MEFV (AR)</td>
<td>Erysipelas-like lesions on lower extremities, vasculitis</td>
<td>Colchicine, Anakinra, TNF inhibitors</td>
</tr>
<tr>
<td>Cryopyrin-Associated Periodic Syndromes (CAPS)</td>
<td>CAS/NLRP3 (AD)</td>
<td>Urticarial lesions</td>
<td>Anakinra, Rilonacept, Canakinumab, Thalidomide</td>
</tr>
<tr>
<td>Hyper-IgD Syndrome (HIDS)</td>
<td>MVK (AR)</td>
<td>Erythematous macules/patches and urticaaria</td>
<td>Prednisone, Colchicine, IVIG, Cys, Anakinra, TNF inhibitors</td>
</tr>
<tr>
<td>TNF Receptor Associated Periodic Syndrome (TRAPS)</td>
<td>TNFRSF1A (AD, sporadic)</td>
<td>Erythematous patches/plaques, sometimes figureate</td>
<td>TNF inhibitors, prednisone, anakinra</td>
</tr>
<tr>
<td>Juvenile Autoinflammatory Diseases</td>
<td>Various</td>
<td>Various, including severe acne, HS, PG, pustular psoriasis</td>
<td>Various</td>
</tr>
</tbody>
</table>

Familial Mediterranean Fever

- Most common systemic autoinflammatory disease
  - Primarily affects patients with Jewish, Arab, Armenian, Turkish, and Italian lineage
  - AR; Carrier frequency in Middle Eastern populations as high as 1:3
  - Almost all have at least one episode by age 20
  - Fever 6 hours – 3 days, erysipelas-like lesions of lower extremities, monoarthritis, abdominal pain, pleurisy

Familial Mediterranean Fever

- Mutation in MEFV which encodes for pyrin
- Distinguishing clinical finding is erysipelas-like lesions of lower extremities in up to half of patients
  - Warm, erythematous, edematous, well-demarcated
  - Below knee, dorsal foot, anterior leg
  - Symmetric or unilateral
  - Generally less than 15cm in size
- Histology shows dermal infiltrate of neutrophils and nuclear dust
- Higher likelihood of vasculitis such as HSP (5%), PAN

Familial Mediterranean Fever

- Systemic manifestations common and may vary between episodes
  - Most common – abdominal pain (95%)
  - Monoarthritis (75%) with effusions – knee, ankle, hips
  - Pleuritic chest pain (30%)
  - Scrotal pain/swelling in boys
  - Amyloidosis in untreated
Familial Mediterranean Fever

- Treatment of choice – colchicine
- Reduces frequency/severity of attacks
- Remission in up to ¾
  – Prevents development of amyloidosis
- Reports of anakinra and TNF inhibitors also helping
  – RCT in 2016 from Israel – anakinra reduced frequency of attacks, especially helpful in joints

Colchicine and Inflammasomes

- NLRP3 inflammasome
- Microtubules mediate NLRP3 inflammasome formation by bringing the mitochondrially based ASC into apposition with NLRP3, located on the surface of the endoplasmic reticulum
- Colchicine blocks NLRP3 inflammasome formation and activation by inhibiting microtubule polymerization, thereby disallowing formation of the ASC-PRR complex and thus the inflammasome

Cryopyrin Associated Periodic Syndromes

- Encompasses a spectrum of severity and diseases previously classified separately
- Collectively referred to as CAPS or cryopyrinopathies
  – Familial Cold-Associated Syndrome (FCAS)
  – Muckle-Wells Syndrome (MWS)
  – Neonatal-onset multisystem inflammatory disease (NOMID)/Chronic infantile neurologic cutaneous articular syndrome (CINCA)

Cryopyrin Associated Periodic Syndromes

- FCAS and MWS found in 2001 to share the same mutation – susceptibility gene is CIAS1 which encodes for cryopyrin
  – Later found to also underlie NOMID/CINCA
  – Mutations mostly localized to exon 3
  – Some mutations can lead to different manifestations and severity
Cryopyrin Associated Periodic Syndromes

- NOMID/CINCA — earlier onset, most severe end of the spectrum
  - Triad of disabling arthropathy, skin eruption, CNS inflammation
  - 2/3 with urticaria-like eruptions at birth, most of the rest have it by 6 months
    • Biopsy showing dermal infiltrate of neutrophils, lymphocytes, occasional eosinophils but no mast cells as in true urticaria
  - Neurologic manifestations and arthropathy common and variable; also conjunctivitis and hearing loss
  - Treatment of choice is now anakinra (steroids, Cys much less effective)

- FCAS (aka familial cold urticaria) least severe — cold-induced bouts of fever, urticaria, and arthralgia
- MWS — fever, urticaria, and limb pain; also associated with amyloidosis and deafness
- Urticarial lesions provoked by generalized exposure to cold in FCAS; delay of 2-3 hours, lasting up to 12 hours
- Urticarial lesions in MWS persist for longer (up to 3 days)
- Dermal edema, infiltrate of neutrophils on histology
- In MWS, progressive sensorineural hearing loss in adolescence in 2/3 to 3/4; nephropathy due to amyloid in up to 1/4

For FCAS/MWS, NSAIDs and systemic steroids can be used during attacks to attenuate them and help with joint pain

IL-1 blockade can limit number of attacks and prevent amyloidosis so should be considered especially in MWS

Treatment may help or reverse the hearing loss but not yet clear whether this is consistent
Hyper-IgD Syndrome

- Mutation in Mevalonate Kinase (MVK) gene leading to reduced enzyme function
- Recurrent fevers, cervical lymphadenopathy, arthralgias, abdominal pain, rash
- Can have amyloidosis (AA) – kidney dysfunction
- At least 2 IgD levels above 100mg/L one month apart
  - Can also be seen in FMF, TRAPS, others
  - Genetic testing also available; mevalonic acid in urine elevated during attacks

Hyper-IgD Syndrome

- Skin eruption usually consists of erythematous macular eruption; biopsy may show vasculitic lesions
- Attacks up to 1 wk of lymphadenopathy, abdominal pain, rash, splenomegaly
- Treatment with steroids, IVIG, cyclosporine, statins
- Anakinra works well; from 1 to 5 mg/Kg per day
- Canakinumab 4mg/Kg q4-6 wk
- Newer reports of TNF inhibitors successfully treating HIDS

TNF-Receptor Associated Periodic Syndrome

- Mutation in TNF-Receptor superfamily 1A (TNFRSF1A) gene which encodes for the TNF receptor
- Skin lesions consist of erythematous macules/papules which then expand and coalesce into serpiginous or annular patches and plaques associated with deep pain beneath these areas (not usually seen in CAPS)
  - “painful erythemas”
- Upper extremities most commonly affected, migrates proximal to distally

TNF-Receptor Associated Periodic Syndrome

- Skin lesions may resolve with ecchymoses
- Attacks can last for weeks, with fever persisting for days to weeks
- Steroids can help during attacks
- TNF inhibitors (etanercept) may work however patients might lose efficacy over time
- IL-1 inhibitors (anakinra, canakinumab) more effective
- IL-6 inhibitor also reported effective (tocilizumab)
Juvenile Autoinflammatory Diseases

- Many described with more being reported frequently in the literature (often with just a few cases)
- Blau, PAPA, PASH, SAPHO, CANDLE, DIRA
- Blau syndrome – mutation in NOD2/CARD15
  - Granulomatous arthritis, uveitis, skin lesions: “Tapioca grain-like papules”
  - Tx with steroids, MTX, Cys, anakinra, TNF inhibitors

Juvenile Autoinflammatory Diseases

- PAPA/PASH
  - PAPA = PG, Acne, Pyogenic Arthritis
  - PASH = PG, Acne, HS (suppurative hidradenitis)
  - Mutation in PSTPIP1 for the former (possibly for the latter)
  - PAPA more periodic, a/w fever, flares of joint pain, starting in childhood and improving into adulthood
  - PASH starts with HS/acne in adolescence with PG coming later in life, less episodic/fevers
  - Treatment with TNF inhibitors (helps more with cutaneous manifestations) or IL-1 inhibitors (help more with joint pain)
  - Recalcitrant cases of PASH responded to infliximab + dapsone + cyclosporine

Juvenile Autoinflammatory Diseases

- SAPHO – Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis
  - Clinically on a spectrum with CRMO (Chronic Recurrent Multifocal Osteomyelitis)
  - May present with bone pain, worse at night, associated with fevers
  - No specific cause identified
  - Often coincides with other inflammatory skin diseases (Psoriasis/Palmoplantar Pustulosis, Sweet’s Syndrome, Vasculitis) or IBD
  - Treat with acitretin/isotretinoin, biologics, DMARD’s

Juvenile Autoinflammatory Diseases

- Deficiency of the IL-1 Receptor Antagonist (DIRA)
  - Mutation in IL1RN (AR)
  - Neonatal onset; osteomyelitis; pustular eruptions; treat with anakinra
  - Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (CANDLE)
    - Annular purpuric plaques, periorbital edema, partial lipodystrophy; typical facies
    - Mutation in PSMB8, involved in proteasome formation
    - Aberrant IFN signaling
      - Possible benefit of IFN inhibition

Summary: Monogenic Systemic Autoinflammatory Diseases

- Numerous autoinflammatory diseases
  - Multiple types and variations
- Treatments with IL-1 inhibitors tend to be effective as steroid-sparing agents
- Colchicine only consistently effective against FMF
- Genetic testing important to establish diagnosis
- Early treatment may prevent later sequelae such as amyloidosis

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More common conditions featuring autoinflammation

- Numerous conditions also feature autoinflammation as a major cause of disease pathogenesis
- HS, PG, Psoriasis, Acne

Hidradenitis Suppurativa

- Recent studies show increase in IL-1β and IL-17 in lesional skin of HS
- Lesional DAMPs (S100A8/A9) are upregulated and the NLRP3 inflammasome is activated
- Early lesions show increased IL-17+ cells which in turn promotes release of IL-1β from keratinocytes
**Biologics in HS**

- Widespread evidence of good treatment results with both infliximab and adalimumab (now FDA-approved to treat HS)
- No such evidence for etanercept
  - Randomized double-blind trial showed no difference from control
- Newer reports and studies with ustekinumab
- 12 patients completed protocol, half achieved HS Clinical Response 50 (corollary to PASI-50)

*British Journal of Dermatology*

**Hidradenitis Suppurativa**

**Anakinra and HS**

- Anakinra may be a treatment option in recalcitrant HS
- Successful treatment in a patient who failed oral antibiotics, azathioprine, cyclosporine, adalimumab, and infliximab

**Pyoderma Gangrenosum**

- IL-1β recently shown to be elevated in lesional skin
  - In the context of normal levels of TNF-α and IFN-γ
- Numerous autoimmune syndromes feature PG (PAPA, PASH, SAPHO — which can be a/w PG as well)
- Unclear etiology — could be that a persistent activation of inflammatory cascade (DAMP/PAMP, i.e. autoinflammation) may lead to the prolonged and unproductive inflammation in PG
**Pyoderma Gangrenosum**

<table>
<thead>
<tr>
<th>Systemics (60-80mg daily)</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Topicals (steroids, cyclosporine, tacrolimus)</td>
</tr>
<tr>
<td>Immunosuppressants (MTX, cyclophosphamide, immunoglobulin, cyclosporine, colchicine)</td>
<td>Wet compresses</td>
</tr>
<tr>
<td>Antimicrobials (dapsone, clofazimine, minocycline)</td>
<td>Hydrophilic occlusive dressing</td>
</tr>
<tr>
<td>Biologics (infliximab, other TNF-α inhibitors)</td>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>IVIG</td>
<td>Skin graft/flap</td>
</tr>
<tr>
<td>Thalidomide</td>
<td></td>
</tr>
</tbody>
</table>

**Canakinumab for PG**

- Dosed once, with optional doses at week 2 and week 8 depending on response
  - All patients received at least 2 doses
- 3/5 complete clearance, 1 partial response
- Previous treatments included steroids in all, and cyclosporine, azathioprine, cyclophosphamide, dapsone, IVIG, infliximab
- Sfx fatigue in 1, worsening of a lesion in 1

**Canakinumab for PG**

- Canakinumab dosed 150mg once monthly for 3 months in a patient with PG refractory to systemic steroids, cyclosporine, infliximab, and adalimumab
Traditional Biologics for PG

- Many case reports of successful treatment with infliximab and one randomized, double-blind, placebo-controlled trial
  - Several reports in populations with IBD

Biologics in PG

- Etanercept and adalimumab – results are more mixed
  - Case reports of success with either
  - Case reports of failure with both
  - One report of failure with etanercept but successful treatment upon switching to adalimumab

Biologics in PG

- One study found increased IL-23 expression in PG and successful treatment with ustekinumab

Ustekinumab for PG
Biologics in PG

- Need a balanced approach considering risk of infection (and immunosuppression) and area/severity of disease
  - Should take into account underlying conditions (such as IBD) as well
  - Relapse is common, loss of effect is common
  - Keep in mind that ustekinumab has a slower onset of action than infliximab, systemic steroids, or cyclosporine
  - IL-1 inhibitors may represent a good therapeutic option in challenging cases

Autoinflammation in Psoriasis

- Increased levels of Caspase-1 in psoriasis lesional skin
- Polymorphisms of NLRP1/3 and CARD8 associated with susceptibility towards psoriasis
  - CARDs are Caspase Recruitment Domains

Autoinflammation in Psoriasis

- Mutations in CARD14 recently shown to be involved in the pathogenesis of psoriasis in multiple studies
  - Familial and sporadic
  - Found to be the locus for PSOR2
- IL-1 inhibitors not consistently effective in psoriasis
- May be better for pustular psoriasis

Autoinflammation in Acne

IL-1β drives inflammatory responses to Propionibacterium acnes in vitro and in vivo.


IL-1β drives inflammatory responses to Propionibacterium acnes in vitro and in vivo. Acne vulgaris is a potentially severe skin disease associated with inflammation of the pilosebaceous unit by the commensal species Propionibacterium acnes. The inflammatory P. acnes infection is mediated by IL-1β, which potentiates the inflammatory response through recruitment of other pro-inflammatory mediators. In vivo, the inflammatory response to P. acnes is partially dependent on IL-1β and the NLRP3 inflammasome-stimulated cytokines. These findings show that the continuous P. acnes infection leads to a massive inflammatory response in the skin, thus establishing the NLRP3 inflammasome and IL-1β as possible therapeutic targets in acne.

Autoinflammation in Acne

Autoinflammation in Dermatology

- HS, PG, and other neutrophilic dermatoses (including Sweet’s Syndrome) clearly linked to autoinflammation
- Emerging evidence that acne is linked to autoinflammation
- Psoriasis also characterized by some degree of autoinflammation
- Other entities reported to feature autoinflammation include Schnitzler’s Syndrome, Behçet’s Disease, generalized vitiligo, SLE, systemic sclerosis, acne, rosacea, and atopic dermatitis

Suggested References

- Fenini G, Contassot E, French LE. Potential of IL-1, IL-18, and Inflammasome Inhibition for the Treatment of Inflammatory Skin Diseases. Front Pharmacol. 2017; 8: 278.