Autoinflammatory Diseases
For the Dermatologist

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Disclosure

• I have no relevant conflicts of interest with regards to the topic of this talk

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?

- 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), LV2189102 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
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

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

Outline

• What is autoinflammation?
  • Classical/Monogenic Autoinflammatory Diseases
  • Common Dermatologic Conditions featuring Autoinflammation
  • Case Discussions
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>CIAS/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>Urticarial lesions</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 figurate</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

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)
Cryopyrin Associated Periodic Syndromes

- 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

Cryopyrin Associated Periodic Syndromes

- 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

CAPS Treatment

- Mutation in Mevalonate Kinase (MVK) gene leading to reduced enzyme function
- Recurrent fevers, cervical lymphadenopathy, arthralgias, abdominal pain, rash
- 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
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

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

- 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

- 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

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)
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 autoinflammatory 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

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

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
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

Autoinflammation in Dermatology

• HS, PG, and other neutrophilic dermatoses (including Sweet’s Syndrome) clearly 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
Outline

- What is autoinflammation?
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Case 1

- 35 yo Jewish man presenting with recurrent episodes of arthralgia and rash of ankles since childhood.
- Also with monoarticular shoulder, knee, and foot pain for 10 years, episodic, for weeks at a time
- Sometimes with testicular pain/swelling, abdominal pain, and oral ulcers
- Fever 1-2 days with beginning of episodes

Case 1

- CRP elevated to 3 mg/dL
- Negative RF
- Trace proteinuria
Case 1

• Genetic testing ordered; positive for a single V726A mutation in MEFV
• Diagnosis of Familial Mediterranean Fever was made
• Patient started on colchicine 0.6mg PO TID with significant improvement however treatment had to be stopped due to severe diarrhea
• Pentoxifylline started but attacks persisted

• What next?

Case 1

• Etanercept 25mg twice weekly started
• Reduction of frequency, duration, severity of joint episodes
• No further abdominal/testicular attacks

*Note that the testicular pain/swelling is not a typical finding of FMF

Case 2

• 27yo woman presenting with nephritic syndrome noting a history of recurrent attacks of fever and abdominal pain since 18 months of age, requiring intermittent oral prednisolone
  – Increase severity/frequency of attacks in 6 months prior to presentation
  – Also a/w erythematous plaques of neck and arms
  – Fevers with episodes lasting weeks
  – Father with similar disease leading to renal failure
Case 2

• 24 hour urine protein excretion elevated, serum albumin 24 g/L (nl 30-48)
• CRP/ESR elevated
• Serum Amyloid P Scan – amyloid in kidneys and spleen

Case 2

• Genetic testing ordered; positive for C33Y TNFRSF1A mutation
• Diagnosis of TRAPS was made
• Twice weekly etanercept 25mg injections were started
• 4 months later, 24 hour urinary protein declined by 80%, serum albumin was WNL, serum amyloid P scan suggested regression of amyloid
• Symptoms much improved over 2 years later

Case 2

• 25yo German woman presented with renal failure, progressive over 3 yrs requiring dialysis
• AA amyloid found on renal biopsy
• Periodic febrile attacks from infancy, worse in the winters, lasting a little under a week each time
• Other symptoms included headache, cervical and inguinal lymphadenopathy, and vomiting/diarrhea
• IgG2/4 deficiencies noted in adolescence led to treatment with IVIG without benefit
Case 3

- Serum IgD checked and was elevated to 104 mg/L
- Genetic testing showed MVK V377I and MVK L234P mutations
- Diagnosis of Hyper-IgD Syndrome was made
- Etanercept started with good response and attenuation of attacks (however renal failure persisted)

Case 3

- IgG deficiency was a red herring (not common)
- Lack of arthralgia is abnormal

Case 4

- 22yo woman presents for evaluation of joint pains, rash on legs, and conjunctivitis
- R great toe arthritis presented at age 8 and patient started having transient urticarial rashes, conjunctivitis, and arthralgia with fever lasting a few days only at a time
  - Flares occurred every 3-4 years since then
  - Also with occasional synovitis
- At about age 9, she started having progressive high frequency hearing loss
  - Hearing aids required at age 19
Case 4

- CRP elevated to 60mg/L (normal <3)
- WBC count 19,000 /mm³
- NSAIDs given for symptom relief, helped with the joint pain but CRP and WBC count remained elevated

Case 4

- Genetic studies ordered; heterozygous E311K mutation in CIAS1 gene identified
- Diagnosis of CAPS/Muckle Wells Syndrome was made
- Patient started on anakinra 100mg SQ daily
- CRP reduced by half within 1 month, approaching normal by 2 months
- WBC count normalized
- Repeat audiogram after 3 months of treatment revealed nearly complete regression of deafness and hearing aids not needed anymore

Case 4

- After several months, anakinra dosage reduced to 100mg every other day since patient was stable but CRP levels began to rise so she resumed 100mg daily dosing
Case 5

- 41 yo Hispanic woman presented with breast lesions for several weeks unresponsive to systemic antibiotics
- Pt had a bilateral breast reduction surgery prior to development of these lesions

Case 5

- Pt had breast reduction surgery 10 days prior to presentation at surgery clinic where she was started on Bactrim and Ciprofloxacin PO for cellulitis
- The next day, she presented to the ER with fever, intense pain, and leukocytosis
- Antibiotics were given, including vancomycin, aztreonam, metronidazole, daptomycin, and amikacin
- Multiple cultures negative, CT scan showing lack of loculated infection
- Daily fevers persisted
- Dermatology consulted 2 weeks later
Case 5

- Biopsy taken; consistent with pyoderma gangrenosum (as was the clinical presentation)
- Patient was started on prednisone, topical diflorasone, and doxycycline

Case 5

- EKG showed prolonged QT and labs revealed increased K (5.5)
- Doxycycline discontinued due to QT prolongation
- Cyclosporine not considered due to hyperkalemia and coincident altered renal function
- Lesions not improving

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.

Case 5

- Colchicine 0.6mg BID and Dapsone 12.5mg QD added to regimen
- Pt gradually improved over the next few months and lesions healed
Acknowledgment

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Thank you!

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