Objective
Describe mechanisms for autoinflammation and briefly review autoinflammatory diseases
Understand the role therapeutic agents play in targeting the innate immune system
Review applications of biologics targeting autoinflammation in challenging inflammatory dermatoses

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

Disclosure
Celgene (I, Janssen (I, A), Lilly (I, A), MC2 Therapeutics (I), Pfizer (I, S), Abbvie (S, A), Regeneron/Sanofi (S,A), Sun Pharma (S), UCB Pharma (I, A), Boehringer Ingelheim (I), LEO Pharma (A), Ortho (A), Bond Avillion (I), Athenex (I), Angen (I, A), BMS (A), BI (A)
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>
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</table>

IL-1β and IL-18

Both activated by inflammasome activation, central to autoinflammation

Both released as precursors and require activation

- IL-1β induces interferon-γ
  - Requires IL-12 or IL-15 also
  - Not a strong pyrogen (less activation of NFκB)

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 decay),

- 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 in CAPS
- FDA approved for CAPS, systemic JIA, TRAPS, FMF
Pipeline for Targeting IL-1

Gevokizumab (anti-IL-1β mAb) purchased by Novartis, more likely being studied in oncology
LY2189102 was in development, studied in diabetes, but no new information
P2D7KK - similar to Canakinumab but 11x more potent; still in preclinical trials
Bermekimab is an IL-1α inhibitor licensed from Xbiotech to Janssen with promising early data in HS treatment
  - IL-1α has been shown to have different effects on neutrophilic inflammation apart from the inflammasome
  - It has been postulated that IL-1α and β have different roles in inflammatory responses, may work in different organ systems, and possess diverse biological effects

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

PRR recognizes stimuli → ASC linked to procaspase-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

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, $S_{100}$
Complicated relationship with tumorigenesis

Classical 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>Erythematous macules/patches and urticaria</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>
</tbody>
</table>

Juvenile Autoinflammatory Diseases

| Various                                      | Various, including severe acne, HS, PG, pustular psoriasis | Various |

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
  - 60% have one episode by age 10
  - As early as 3 months of age
- 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

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

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
(A) NLRP3 inflammasome
(B) Microtubules mediate NLRP3 inflammasome formation by bringing the mitochondrially-based ASC into apposition with NLRP3, located on the surface of the endoplasmic reticulum
(C) 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)

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

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

More common conditions featuring autoinflammation
Numerous conditions also feature autoinflammation as a major cause of disease pathogenesis
HS, PG, Psoriasis, Acne
Pyoderma Gangrenosum

IL-1β 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, PAPASH, 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>Systemics</th>
<th>Local</th>
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<tbody>
<tr>
<td>Corticosteroids (60-80mg daily)</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>
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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
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

Rituximab weekly shown to have benefit in a particularly recalcitrant case on the face

Apremilast used in one reported case

Biologics in PG

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

Ustekinumab 45mg dosing: Weeks 0, 4, 10, and 14
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

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

Cytokines in HS
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

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 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.

Thank you!
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