Autoinflammatory Diseases:
A Primer

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Disclosures

Nothing to disclose

Learning Objectives

• Discuss the distinction between autoinflammatory and autoimmune diseases
• Enumerate various autoinflammatory diseases and list their most common clinical manifestations
• Discuss the diagnosis and pathophysiology of selected autoinflammatory diseases
• Delineate treatment options for selected autoinflammatory diseases
The Systemic Autoinflammatory Diseases: What Are They and Why Should You Care?

- Recurring episodes of seemingly unprovoked localized and systemic inflammation, without high titer autoantibodies, antigen-specific T cells, or evidence of overt infection
- Dramatic evidence of inflammation
- Disorders of innate immunity, providing new insights into human biology

Positional Cloning of \( \text{MEFV} \), the Gene Mutated in Familial Mediterranean Fever (FMF)

Cell

TNFR and Autoinflammatory Syndromes
The Inflammasomopathies

Manthiram et al. Nat Immunol 18:832, 2017

FMF: Clinical Features
- Peritonitis (air-fluid levels)
- Pleurisy (left pleural effusion)
- Posterior pericardial effusion
- Chronic arthritis of the hip
- PMNs, synovial fluid
- Renal amyloidosis
- Erysipeloid erythema

IL-1 Inhibition in FMF Amyloidosis

Chae et al. PNAS 103:9682, 2006
Pyrin S242R in a Family with a Severe Dominantly Inherited Autoinflammatory Disease: PAAND


The Inflammasomopathies

Manthiram et al. Nat Immunol 18:832, 2017

Hyperimmunoglobulinemia D with Periodic Fever Syndrome (HIDS)

- 3 – 7 day febrile episodes
- Abdominal pain
- Arthritis/arthritisia
- Diffuse maculopapular rash
- Prominent cervical adenopathy
- Aphthous ulcers
- Onset within first year of life
- Episodes sometimes induced by childhood immunizations
- Amyloidosis very rare

Rheumatology 5th edn, 1648, 2011
Familial Cold Autoinflammatory Syndrome (FCAS)

- Fever, hives-like skin rash upon generalized exposure to cold
- Rash occurs about 2 hr after cold exposure
- Not true urticaria: neutrophils, not mast cells
- Dominant inheritance

Muckle-Wells Syndrome

- Inflammatory episodes
  - Fever
  - Limb pain
  - Urticarial rash
- Sensorineural hearing loss
- Systemic amyloidosis

Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/Chronic Infantile Neurologic Cutaneous and Articular Syndrome (CINCA)
The Inflammasomopathies

Deficiency of the IL-1 Receptor Antagonist (DIRA)

The TNF Receptor-Associated Periodic Syndrome (TRAPS)
Mutations in proteasome subunit β Type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity


NF-κB-Mediated Autoinflammation

Disorders of deubiquitination

Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease

Biallelic hypomorph mutations in a linear deubiquitinase define otulipemia, an early-onset autoinflammatory disease
Zhou et al., PNAS 113:10127, 2016
Summary

- The systemic autoinflammatory diseases are disorders of innate immunity
- Several autoinflammatory diseases are disorders of IL-1β signaling, with significant therapeutic response to IL-1 inhibitors
- The interferonopathies are disorders of type I interferon signaling, and may respond to JAK inhibitors
- Disorders of NF-κB signaling include oteilipenia and Blau syndrome, which may respond to TNF inhibitors
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