Autoinflammatory Diseases

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Faculty Disclosure

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I will be discussing products that are investigational or not labeled for use under discussion.
Outline

• The autoinflammatory concept

• Hereditary fever disorders
  • Clinical features
  • Pathophysiology
  • Therapy

• Expanding family of monogenic autoinflammatory diseases
Immunologic Diseases

Classical Categories

- Immunodeficiency
- Allergic Diseases
- Autoimmune Diseases

Several immunologic diseases do not fit nicely into this standard classification system
Unclassified
Inflammatory Diseases

- Gout
- Crohn’s Disease
- Sarcoidosis
- Behcet’s Disease
- Still’s Disease
  - Juvenile (Systemic onset juvenile idiopathic arthritis)
  - Adult onset
- Hereditary Angioedema
- Recurrent Fever Disorders
Autoinflammatory Diseases

Definition

Disorders with recurrent episodes of inflammation

- No evidence of pathogenic infection or IgE mediated dz
- No high titer auto-antibodies or antigen specific T cells
- Disturbances of homeostasis of cytokine responses
- Aberrant bacterial sensing
- Predominance of monocytes/neutrophils rather than lymphocytes as effector cells
Hereditary Fever Disorders

- Familial Mediterranean fever (FMF)
- Hyper IgD syndrome (HIDS)
- TNF Receptor Assoc. Periodic Syndrome (TRAPS)
Hereditary Fever Disorders
Clinical Characteristics-Shared

• Intermittent episodes of inflammation with intervals that are relatively symptom-free
  – Fever
  – Musculoskeletal symptoms
  – Rash

• Laboratory evidence of inflammation
  – ESR
  – CRP
  – SAA - amyloidosis
Familial Mediterranean Fever (FMF)

- More common in Jews, Arabs, Turks, Armenians, but also in other Mediterraneans
- Usually autosomal recessive inheritance
- Episodes last 1-3 days
- Symptoms - severe abdominal or chest pain, monoarthritis, erysipelas rash on legs
- Responsive to colchicine
FHF

Erysipelas-like rash on legs

Simon et al 2005
**Hyper IgD syndrome (HIDS) with periodic fever**

- Founder effect in Northern Europe
- Autosomal recessive inheritance
- Episodes last 3-7 days
- Episode intervals are periodic (3-6 weeks)
- Symptoms - abdominal pain, vomiting, arthralgia, rash, lymphadenopathy, splenomegaly, aphthous ulcers
- Labs - Increased IgD level ( >100 IU/ml or 14 mg/dl)
  - Increased urinary mevalonate
HIDS

Maculopapular Rash

Aphthous ulcers

Simon et al 2005
TRAPS

- No specific populations
- Autosomal dominant inheritance
- Episodes last 1 - 4 weeks
- Symptoms - arthralgia and localized myalgia, conjunctivitis and periorbital edema, abdominal pain, migrating painful rash
- Some response to corticosteroids
TRAPS

Centrifugal migratory painful erythematous rash

Photo courtesy of D. Kastner
TRAPS - Ocular Findings

Photo courtesy of D. Kastner
Hereditary Fever Disorders
Clinical Characteristics

• Familial Mediterranean fever (FMF)
• Hyper IgD syndrome (HIDS)
• TNF Receptor Assoc. Periodic Syndrome (TRAPS)

• Other disorders
  • Familial cold autoinflammatory syndrome
  • Muckle Wells Syndrome
  • Neonatal Onset Multisystem Inflammatory Disease
68 year old with lifelong history of urticaria-like rash, fever, and joint symptoms following cold exposure.

Photo courtesy of R. Shpall
Familial Cold Autoinflammatory Syndrome

- Autosomal dominant inheritance
- Episodes last < 1 day - daily symptoms
- Symptoms - urticaria-like rash, arthralgia, myalgia, conjunctivitis after cold exposure
Skin biopsy of A affected Area

Shpall et al, Br J Derm 2004
MWS

Urticaria like rash

Progressive Hearing Loss
Muckle Wells Syndrome

- Autosomal dominant inheritance
- Daily symptoms - episodes last 1 - 2 days
- Symptoms - urticaria-like rash, arthralgia, myalgia, progressive hearing loss
NOMID

Urticaria-like rash

Enlarged knees

CNS involvement

Courtesy of R Goldbach-Mansky
NOMID

- Primarily sporadic, but also autosomal dominant inheritance
- Chronic inflammation with flares
- Symptoms - urticaria-like rash, deforming arthropathy, dysmorphic features, growth and developmental delay, seizures
Hereditary Fever Disorders
Clinical Characteristics-Unique

- Ethnicity
- Inheritance Pattern
- Pattern and length of episodes
- Specific symptoms
- Type of Rash
- Treatment responsiveness
PATTERN OF EPISODES
LENGTH OF EPISODES

- FMF
- HIDS
- FCAS
- TRAPS
- MWS

Graphs showing body temperature over time for different episodes.
Autoinflammatory Diseases
Genetics

- Familial Mediterranean Fever
  - *MEFV* - Pyrin
- Hyper IgD syndrome
  - *MVK* - Mevalonate Kinase
- TNF receptor associated periodic syndrome
  - *TNFSRIA* - TNF Receptor p55
Cleaved TNFR1

Free TNFα

↑ Inflammation
TNF

Normal

Reduced receptor shedding

apoptosis

NF-κB

inflammation

increased mitochondrial ROS

Collection in cytosol and ligand independent signaling

Retention in ER and lack of surface expression
Therapy in TRAPS

- Some response to high dose corticosteroids during attacks
- Successful prospective trials of Etanercept (soluble TNF receptor) in TRAPS patients
  - Hull et al 2003
  - Drewe et al 2003
- Some patients do not respond adequately
  - Symptom breakthrough
  - Development of amyloidosis
- Other TNF directed therapies (antibodies) were ineffective or made it worse
Acetyl CoA + Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl CoA → Mevalonate → Mevalonate phosphate → Mevalonate diphosphate → Isopentenyl-PP → Geranyl-PP → Farnesyl-PP → Squalene → Cholesterol → Excreted in urine

HIDS (HMG CoA reductase deficiency) → Lack of isoprenoids leads to inflammation

- Isopentenyl adenine (DNA replication)
- Farnesylated proteins, Dolichol, Heme A, Ubiquinone
- Steroid hormones, Bile Acids, Lipoproteins, Vitamin D
HIDS
Potential Mechanisms?

• Decreased stability of Mevalonate Kinase protein leading to reduced, but not absent enzyme function (Mevalonic Aciduria)
  – Remaining function may be affected by elevated temperature (immunization and infection)

• Increased IL-1B mediated inflammation
• Decreased apoptosis of lymphocytes
Therapy in HIDS?

- High dose corticosteroids at attack onset
  - Some reduction in severity of attacks

- Statins (HMG coA reductase inhibitors)
  - Reduce mevalonate
  - Some potential improvement in attack frequency

- Etanercept (soluble TNF receptor)
  - Reduced acute phase reactants
  - Reduced attack severity and frequency
Heterozygous Mutations in FCAS and MWS patients

Chromosome 1p

Chromosome 1q

1q44

Genetic Mapping

Markers

Genes

DNA Bases

GAGCCGCC

GTCGGCTCCG

Sequencing
Gene and Protein Structure

Cold Induced Autoinflammatory Syndrome 1

CIAS1 (NLRP3)

Mutations

Cryopyrin (NALP3)

Hoffman et al, Nature Genetics 2001
NLRP3 Mutations - 82

FCAS  MWS

NOMID

Infevers – Touitou et al
Cryopyrin Associated Periodic Syndromes:

A Spectrum of One Disease
Modeling mutations
Nucleotide binding Leucine rich Repeat (NLR) family

- NLRP1
- NLRP2-14
- NOD1
- NOD2
- Ipaf
- Naip
- CIITA
- Apaf-1
- RIP2
- ASC
- CARDINAL

Adaptors

PYD  NACHT  NAD  LRR  FIND  CARD
WD40
Inflammasome

Monocyte
Macrophage

Urate/CPPD crystals

Silica and Asbestos

Cholesterol

Islet amyloid

Secretory Lysosome

Cleaves

Pro-IL-1β

IL-1β

IL-6

Agostini et al, Immunity 2004
**FMF & CAPS - Pathogenesis**

- Structurally related proteins (pyrin and cryopyrin) both have Pyrin domains involved in protein-protein interactions.
**CAPS and FMF Pathogenesis**

**Inflammasome**

- Monocyte Macrophage
- Cryopyrin
- Pyrin
- ASC
- Cardinall
- Caspase 1
- Activated caspase 1

**Cytokine expression**

- P2X7
- K channel
- K efflux
- HSP90
- SGT1
- LRR
- ILK1
- SGT1
- β
- LRR
- COLD

**Secretory Lysosome**

- Cleaves
- Pro-IL-1β
- NF-κB
- IL-6
- IL-1β

**IL-1 Receptor**

Agostini et al, Immunity 2004
Targeted Therapy for CAPS

Monocyte Macrophage

Cryopyrin

ASC

Caspase 1

Cardinal

Inflammasome

Cleaves

Pro-IL-1β

Cytokine expression

NFS-κB

IL-6

IL-1β

Anakinra

ATP

P2X7

K channel

K efflux

Secretory Lysosome

Nucleus
Anakinra

Approved for Rheumatoid Arthritis in 2001

Hoffman JACI 2009
Experimental Cold Challenges

- 4°C room for greater than 30 minutes
- Serial monitoring of vital signs and symptoms for 24 hours
- Collection of blood and skin tissue before and during development of symptoms and after resolution.
Skin following cold challenge

Hoffman et al, Lancet 2004
Oral temperatures

![Oral temperatures graph showing temperature changes over time with different groups compared.](image-url)
White Blood counts

- **Patients** (n=4)
- **Patients after anakinra** (n=3)
- **Controls** (n=3)

1000/ml vs Time (hours)
IL-6 serum levels

- Patients (n=4)
- Patients after anakinra (n=3)
- Controls (n=3)

(pg/ml vs Time (hours))
Anakinra in MWS

Hawkins et al, 2003

- Reduced symptoms in MWS patients
- Decreased systemic inflammation SAA levels
Significant Efficacy in NOMID

Goldbach-Mansky et al 2007

- Reduced symptoms
- Improved growth/development
- Decreased systemic inflammation
- Improved CNS signs

Figure 1. Inflammatory Organ Manifestations in Neonatal-Onset Multi-system Inflammatory Disease before (Panels A, C, E, and G) and after (Panels B, D, F, and H) Treatment with Anakinra.
Anakinra in CAPS

- Clinical trials demonstrating remarkable efficacy in
  - FCAS (Ross et al 2008)
  - MWS (Leslie et al 2006)
  - NOMID (Goldbach-Mansky et al 2007)

- Unfavorable features
  - Short half life (< 12 hours)
  - Painful injection reactions
  - No interest by pharmaceutical company
Rilonacept

**IL-1 TRAP**

- Rilonacept: a dimeric fusion protein (251 kDa) that is a specific blocker of IL-1 - incorporating components required for IL-1 signalling
  - IL-1 receptor subtype
  - IL-1 receptor accessory protein
- Prolonged circulation half-life in-vivo (8.6 days)
Canakinumab

- Fully human IgG1 anti-IL-1β mAb

Action
- Direct binding to IL-1β
- Half life > 21 days
- No cross-reactivity with human IL-1α or IL-1Ra
FDA approved

Canakinumab

Rilonacept

IL-1β

Anakinra or IL-Ra

IL-1R

Inflammation; Fever, rash, pain

Hoffman JACI 2009
Translational research model in the monogenic autoinflammatory diseases

Patients/Families

Disease Characterization

Gene identification

Protein function

Inflammatory Pathways

Novel Therapy

Gene identification
Anakinra in other recurrent fever disorders

- **Successful trials of Anakinra in TRAPS patients**
  - Simon et al 2004
  - Gattorno et al 2008
  - Sacre et al 2008

- **Successful trials of Anakinra in HIDS patients**
  - Bodar et al 2005
  - Calliez et al 2006

- **Successful trials of Anakinra in FMF patients**
  - Gattringer et al 2007
  - Calligaris et al 2008
Summary

• Autoinflammatory diseases are a new category of inflammatory diseases

• The hereditary fever disorders are excellent examples of translational research success

• IL-1 targeted therapy has demonstrated proven efficacy in CAPS, but also other autoinflammatory diseases