Auto-inflammatory Syndromes

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DISCLOSURE/CONFLICTS OF INTEREST

COI: None

Off-label Medications: All
Currently no "on-label" treatments for auto-inflammatory disorders

Overview of Talk

- Definition
- Why I got interested in AIS
- Cryopyrin-Associated-Periodic syndrome as a model of auto-inflammation
- The auto-inflammatory diseases, their genes, and pathogenesis
- Specific therapies
- Future trends

Autoinflammatory diseases

- Inherited group of diseases
- Cytokine Disregulation
- Absence of autoreactive lymphocytes or antibodies
- Often have skin manifestations
- Chronic inflammation with end-organ damage

Hull et al (2003) Curr Opin Rheum. 15: 61-69
Ting et al (2006) Nature Reviews Immuno. 6: 183-195

Case #1

"We describe a girl with NOMID who presented with typical neonatal rash, arthropathy, fever, and failure to thrive, but has not developed evidence of ocular or CNS involvement. This case illustrates the spectrum of involvement seen in NOMID. Histopathology of the skin demonstrated neutrophilic eccrine hidradenitis, a unique finding, which may serve as a diagnostic clue in patients with this rare disorder."

Neonatal onset multisystem inflammatory disease. Huttenlocher A, Frieden IJ, Emery H. J Rheumatol. 1995 Jun;22(6):1171-3.

Case 3 history

- Urticarial skin lesions since first few days of life, never resolving completely
- Recurrent fevers, adenopathy, non-deforming arthropathy
- History of pericarditis, papilledema, elevated CSF pressure
- Growth retardation
- Sensorineural hearing loss

Note from Ped Rheum UCSF

"As far as his rash is concerned, the mom reports that a previous skin biopsy was not helpful, but she states that he is going to be seen by Dermatology here, which I think is a great idea, and maybe they will have some idea as to how to put this together."

My A & P

- Findings c/w NOMID
- NOMID is a hereditary condition
- Cool website, GeneDx lists lots of tests for unusual genetic conditions and another one Genetests for many not on GeneDx
- Plan to look and see if there is a genetic test for NOMID yet

Further history

- Noted in early infancy –seen by me age 9 months
- Referred to ped rheum as infant: no abnormalities found
- Virtually never without rash
- Antihistamines ± help but not particularly itchy
- Presented at age 10 because rash was becoming a cosmetic concern to patient

Further History

- Severe headaches "migraines"
- Hearing loss – unclear etiology
- Arthralgias

Cases #3 and #4

- Gene testing sent: Both had mutations (different ones) in the 3rd exon of CIAS-1 gene

Refs:
Kilcine et al. Arch Dermatol. 2005 Feb;141:248-53.
Shinkai et al. Arch Dermatol. 2005 Feb;141:242-7.

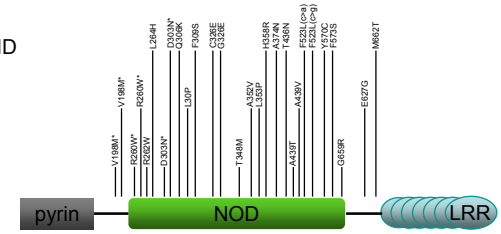
Cryopyrin associated periodic syndromes (CAPS)

mild phenotype — intermediate phenotype — severe phenotype

FCAS	MWS	NOMID
cold-induced urticaria fever arthralgia	urticaria amyloidosis deafness	Neonatal-onset urticaria CNS disease arthropathy

Mutations in *CIAS-1* do not predict phenotype

NOMID

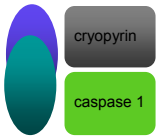


- All mutations lie in the same region
- Mutations do not predict clinical phenotype

Kilcline et al (2005) Arch Derm. 141:248-253

CIAS1 encodes Cryopyrin
Cryopyrin is essential part of an *Inflammasome*

Inflammasome:
a multi-protein signaling complex that leads to inflammation



The cryopyrin inflammasome

Ogura Y et al (2006) Cell, 126(4): 659-662.

Clinical Features

Onset at birth (19/22)

Daily febrile symptoms (20/22)

Arthralgia (19/22)

Finger clubbing (4/22)

Infertility (6/22)

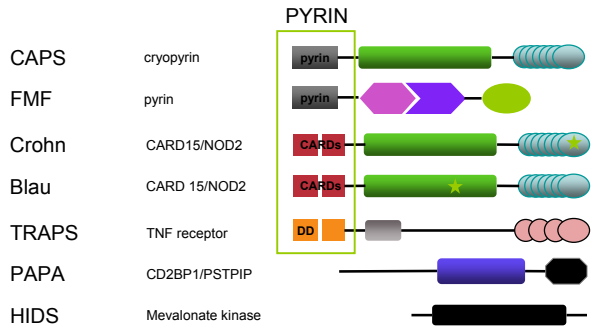
Why Should You (or we) Care About Such Rare Diseases?

- Can look very smart if you do diagnose *and* effective treatments are now available
- Auto-inflammatory disorders are a group diseases
- New way to think about inflammation and inflammatory skin diseases especially those with neutrophils e.g. neutrophilic urticaria
- Concepts of inflammation may apply to diseases we see much more commonly

Syndrome	Skin findings	Other Clinical
NOMID/CINCA/Muckle-Wells	Chronic waxing and waning neutrophilic urticaria	Hearing loss, aseptic meningitis, ± cold provoked
Familial Mediterranean fever	Erysipelas-like erythema at acral sites, atypical urticaria, HSP and non-specific purpuric lesions	Episodes 1-3 days; polyserositis; amyloidosis common
Pyogenic arthritis, PG, Acne (PAPA)	Acne, PG	Pyogenic arthritis
Blau syndrome	Papular rash with sarcoidal granulomas on histology	Granulomatous arthritis uveitis
TNF receptor-associated periodic syn.	Migratory erythematous macules, papules, edematous plaques, purpura	Long episodes >1 weeks, periorbital edema, myalgia
Hyper-IgD syn	Intermittent morbilliform rash	Lymphadenopathy, attacks after immunizations

Syndrome	Inheritance	Gene	Protein
NOMID/CINCA/ Muckle-Wells	AD	CIAS1	Cryopyrin
Familial Mediterranean fever	AR	MEFV	Pyrin
Pyogenic arthritis, PG, Acne (PAPA)	AD	PSTPIP1 (CD2BP1)	PSTPIP1
Blau syndrome	AD	NOD2 (CARD15)	NOD2 (CARD15)
TNF receptor-associated periodic syn.	AD	TNFRSF1A	TNF-receptor type 1(p55, CD120a, TNFR1)
Hyper-IgD syn	AR	*Mevalonate kinase*	Mevalonate kinase

The genes of autoinflammatory diseases



Hull et al (2003) Curr Opin Rheum. 15:61-69
Shinkai et al (2005) Arch Derm. 141: 242-247

Pathogenic links I

- Collectively these genes play critical role in the regulation of innate immunity.
- Both pyrin and cryopyrin are involved in regulation of IL-1beta; may influence the activity of the transcription factor, NFkappaB.
- NOD2 shares domains with cryopyrin and appears to be a sensor of intracellular bacteria. (Nod2/Card 15 mutations also found in some cases of Crohn's disease)

Pathogenic links II

- PSTPIP1, (gene mutated in PAPA) interacts both with pyrin and a protein tyrosine phosphatase to regulate innate and adaptive immune responses.
- Mutations in the p55 TNF receptor (TRAPS) lead dramatic inflammatory disease - the mechanisms still under investigation.
- Hyperimmunoglobulinemia D with periodic fever syndrome caused by mutations in cholesterol biosynthesis pathway

What does aberrant cryopyrin in CAPS actually do?

• Not completely understood

- genetic data suggests constitutive activation
- altered threshold of activation = greater sensitivity
- appropriate "ON", but aberrant "OFF"

Martinon, F (2004) Cell. 117: 561-574.

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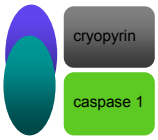

The cryopyrin inflammasome

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What is an Inflammasome?

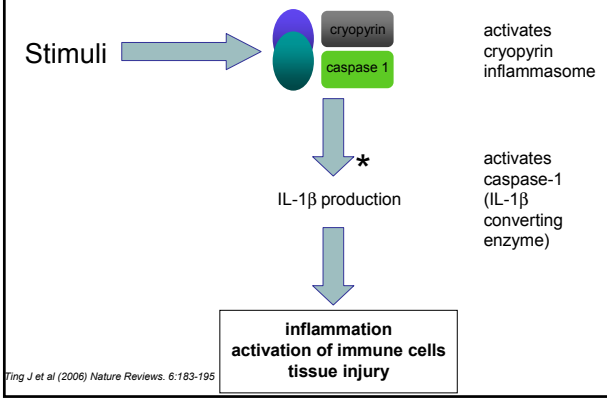
- Cytoplasmic multiprotein complex >700kDa is the molecular platform responsible for activation of caspases 1 & 5 leading to processing/secretion of cytokines IL-1β and ILF-18
- Similar to Toll-like receptors, activation thought to occur via recognition of pathogen-associated molecular patterns (PAMPs)

Drenth J and van der Meer J. NEJM 2006; 355:730-732

Inflammasome: A "sensor" for inflammatory stimuli

Drenth J and van der Meer J. NEJM 2006;355:730-732

Activation of inflammasome leads to inflammation



Ting J et al (2006) Nature Reviews. 6:183-195

Previous Treatments

Modest Benefit:	High dose corticosteroids Cyclosporine A Mycophenylate Mofetil Thalidomide
No Benefit:	Antihistamines NSAIDS Colchicine Dapsone Azathioprine Cyclophosphamide IVIG

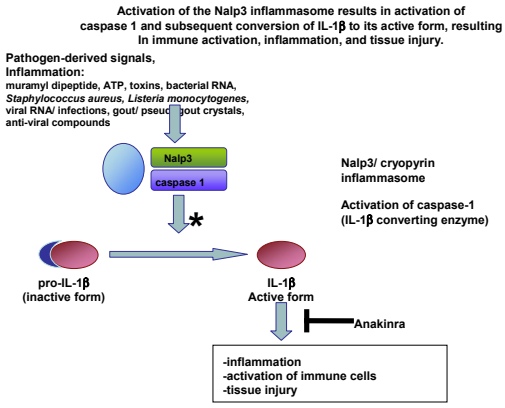
Interleukin-1 blockade is a treatment for CAPS

Interleukin 1-receptor antagonist in the Muckle-Wells syndrome

Hawkins PN et al.
NEJM 2003, 348: 2583-2584

The NEW ENGLAND JOURNAL of MEDICINE

2006: IL-1 blockade as a treatment



Shinkai et al, Cryopyrin-associated periodic syndromes(CAPS) and autoinflammation CED-2006-00525

What is Anakinra (Kineret®)?

- Interleukin 1 receptor antagonist
- Indication is for Rx of rheumatoid arthritis
- Given as SQ injection

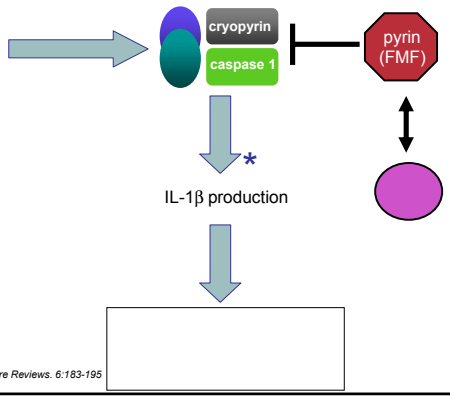
On The Horizon: Other indications

- Anakinra for type II diabetes – improved glucose tolerance
- Refractory systemic JRA
- Ischemic brain injury (animal model)

Hyper-IgD Syndrome (HIDS) Mevalonate kinase deficiency

- Dutch/French heritage
- Onset in infancy
- Febrile attacks
- 4-5 days
- Cervical lymphadenopathy
- Abdo pain & diarrhea
- Treatment: simvastatin

Do pyrin genes work in the same pathway?



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Lessons learned from Autoinflammatory syndromes

- Group of inherited diseases with mainly *neutrophilic* inflammation
- Seem "auto-immune" superficially but no true auto-antibodies
- Rare diseases BUT they provide insights into molecular pathways of inflammation and possible therapies for other diseases

On the Horizon: Other Drugs

- Rilonacept (Regeneron) IL-1 trap in priority review phase by FDA for CAPS.
- Estimate total of 200-500 CAPS patients in U.S.
- Other IL-1 blockers in clinical trials
- Major uses will be for other inflammatory diseases

What else might be auto-inflammatory?

- Neutrophilic urticaria
- Acne, especially severe variants
- Hidradenitis suppurativa
- Folliculitis decalvans
- Psoriasis
- ??

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Genetic determinants of autoinflammatory disease

- Meet the family: PYRIN genes
  - -PYRIN 

  - -Death domains 

  - -CARDs (caspase-recruitment domain) 

- pyrin domain: mediates protein-protein interactions
  - -bind each other via pyrin : pyrin interactions

Shinkai et al (2005) Arch Derm. 141: 242-247