Horror Autoinflammaticus: The Expanding Spectrum of Systemic Autoinflammatory Disease

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NHGRI/NIH/DHHS
UTHSCSA Pediatrics Grand Rounds
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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 infection
- Dramatic evidence of inflammation
- Disorders of innate immunity, providing new insights into human biology

Kastner et al., Cell 140:784-790, 2010.
Samuels et al., Medicine (Baltimore) 77:268, 1998

Positional Cloning of MEFV, the Gene Mutated in Familial Mediterranean Fever (FMF)

Kastner et al., Cell 140:784-790, 2010.
The PYRIN Domain: A Cognate Interaction Motif

PYRIN
CARD
ASC
CASPASE-1
IL-1β

PYRIN

Pro-IL-1β

IL-1β

Converting Enzyme (ICE)

Richards et al., J Biol Chem 276:39320, 2001

Human and Mouse NLR Family Members

Schröder and Tschopp, Cell 140:821, 2010

Ancestral Mutations in FMF

Kastner, Hospital Practice 33:131, 1998


Smallpox: The Selective Pressure?

• Origins in the Nile valley?
• Requires high population density
• 25–30% mortality


FMF Knockin Mice: IL-Dependent Inflammation

WT

V726A

Chae et al., Immunity, in press.

IL-1 Inhibition in FMF Amyloidosis

Chae et al. PNAS 103:9882, 2006
**FMF Variant or New Disease?**

Periodic fever in the Irish: an allelic variant of FMF in descendants of ship-wrecked sailors from the Spanish Armada?

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**TNFRSF1A Mutations Can Cause Dominantly Inherited Periodic Fever**

The TNF Receptor-Associated Periodic Syndrome (TRAPS)

TRAPS: Shedding Defect or Constipated Monocytes?

TRAPS

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<tr>
<th>Human PBMCs</th>
<th>TNFR1(YFP)</th>
<th>GalT(Golgi)-CFP</th>
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Simon et al. PNAS 107:9801, 2010

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**Death domain**

CRD1
CRD2
CRD3
CRD4

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**TNFRSF1A**

13
12
11.12
12
13
14
15
21
22
23
24.1
24.3

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TNFRSF1A Mutations Can Cause Dominantly Inherited Periodic Fever

Rheumatology 5th edn. 1637-57, 2011

The TNF Receptor-Associated Periodic Syndrome (TRAPS)


TRAPS: Shedding Defect or Constipated Monocytes?

Human PBMCs

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**TRAPS**

ROS

p38

TNF-α, IL-1, other cytokines

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**TRAPS**

ROS

p38

TNF-α, IL-1, other cytokines

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TRAPS-Etanercept Trial

Protein-Misfolding Disorders


CAPS: Three Diseases Caused by Mutations in One Gene

Common clinical features: fever and urticarial rash

- FCAS (familial cold urticaria) – cold-induced fever and urticarial rash
- Muckle-Wells – fever, urticarial rash, arthritis, sensorineural deafness, amyloidosis
- NOMID/CINCA – fever, urticarial rash, bony overgrowth, CNS disease

Mutations in a Gene in the Pyrin Family Cause Muckle-Wells Syndrome (MWS) and Familial Cold Autoinflammatory Syndrome (FCAS)

Rheumatology 3rd edn, 1730, 2003

SoJIA?

NLRP3 Mutation in NOMID/CINCA

Ivona Aksentijevich
Raphaela Golubach-Mansky

Fever

Inflammation

Cryopyrin (NLRP3)
inflammasome

IL-1β

pro-IL-1β

CARD

PYD

Pyrin

Cryopyrin

p10

p20

ASC

PYD

CARD

p10

p20

pro-caspase-1
caspase-1

complex

Treatment of 18 NOMID Patients with the IL-1 Receptor Antagonist Anakinra

Response to Canakinumab, as Compared with Placebo

Could This be NOMID?

Age 9 months, before therapy

3 days post treatment initiation

7 days post treatment initiation

Deficiency of the IL-1 Receptor Antagonist (DIRA)
Frequency of the mutation in the founder population

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<tbody>
<tr>
<td>Caucasian Controls (NY)</td>
<td>Neg in 364 DNA samples</td>
<td>Neg in 364 DNA samples</td>
<td>Neg in 364 DNA samples</td>
<td>Not done DNA samples</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>0.4%</td>
<td>Not done DNA samples</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Neg in 364 DNA samples</td>
<td>Neg in 364 DNA samples</td>
<td>Neg in 364 DNA samples</td>
<td>Not done DNA samples</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>2.6%</td>
<td>Neg in 364 DNA samples</td>
<td>Neg in 364 DNA samples</td>
<td>Not done DNA samples</td>
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Extending the Pyrin Pathway:
Proline Serine Threonine Phosphatase Interacting Protein 1 (PSTPIP1/CD2BP1)

IL-1β Activation Disorders

Familial Shar-Pei Fever

A-C: Meatmouth variety
D: Traditional variety

Selective sweeps (regions identified by reduced heterozygosity)

FSF-disease association

The NIH Autoinflammatory Cohort

Genome-wide SNP genotype analysis identifies a region on chromosome 13 with evidence of recent selection and that is associated with FSF

B: FSF-disease association


Olsson et al. PLoS Genetics, 2011
Targeted next generation sequencing reveals increased frequency of reads in a region 5' of the HAS2 gene.

*Olsson et al.* PLoS Genetics, 2011

An Inflammasome Signature in PFAPA Flares

*Stojanov et al.* PNAS 108:7148, 2011

Anakinra in PFAPA

*Stojanov et al.* PNAS 108:7148, 2011

Behçet’s Disease: A Genetically Complex Disorder with an Autoinflammatory Component


<table>
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<tr>
<th>Allele freq</th>
<th>cases</th>
<th>Allele freq controls</th>
<th>Chi-squared</th>
<th>ChiSq P-value</th>
<th>Odds ratio (95% CI)</th>
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<tr>
<td>rs1518111 A/G</td>
<td>0.38</td>
<td>0.30</td>
<td>31.62</td>
<td>1.88E-08</td>
<td>1.41 (1.25 - 1.59)</td>
</tr>
<tr>
<td>rs924080 A/G</td>
<td>0.67</td>
<td>0.61</td>
<td>20.71</td>
<td>5.35E-06</td>
<td>1.31 (1.17 - 1.47)</td>
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*Breslow-Day Test for Homogeneity of the Odds Ratios: P = 0.54 and 0.71, for rs1518111 and rs924080, respectively.
Homozygotes for the Behçet’s Risk Allele Produce Reduced Amounts of IL-10


Gout as an Autoinflammatory Disease

Martinon and Glimcher JCI 116:2073-2075, 2006

Type 2 Diabetes Mellitus as an Autoinflammatory Disease


Atherosclerosis as an Autoinflammatory Disease


Summary

- The autoinflammatory diseases manifest constitutive or easily triggered innate immune activation
- Mendelian autoinflammatory diseases have provided important insights into the regulation of inflammation
- IL-1β activation and protein misfolding are two important mechanisms of Mendelian autoinflammatory disease
- Genome-wide association studies allow the identification of susceptibility loci for the more common but genetically complex autoinflammatory disorders
- Based on the demonstration of an important role for the inflammasome in their pathophysiology, a number of common disorders have been shown to have an autoinflammatory component
"It's a genome world . . .

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Wurstboro – Linda Tritle
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Nobuhisa Mizuki

Suggested Reading

• Stojanov S, Lapidus S, Chitkara P, et al. (2011) Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. PNAS 108:7148–7153.