Hemophagocytic lymphohistiocytosis: A unique immunoregulatory disorder

Michael B. Jordan, MD
Divisions of Immunobiology, and Bone Marrow Transplantation and Immune Deficiency
Cincinnati Children’s Hospital Medical Center/ Univ. of Cinci.
michael.jordan@cchmc.org

The immune system is a powerful machine

Essential for survival, remarkably flexible, and potentially very dangerous

What is HLH?

Mouse models: Immune regulation and immunopathology
Human disease: correlations, interventions, and complexity

Immune regulation and human disease

Initiation / Context cues
- Danger sensing
- Modulate ‘innate’ inflammation
CAPS
TRAPS
auto-inflammatory

Inborn errors of immune regulation

Hemophagocytic Lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis (HLH): a highly fatal disorder treated with immune suppression/marrow transplantation, often associated with genetic impairment of perforin-mediated cytotoxicity

Dr. Jordan declares he is a consultant for Novimmune.
Mouse Model of HLH:

Infect with LCMV → prf-/- → HLH?

LCMV-infected prf-/- mice display clinical and laboratory features of HLH

Modeling HLH:

Infection → HLH

Perforin: 1. Immune effector function: kill infected cells
2. Immune regulatory function?

Immune activation and viral burden do not correlate in cytotoxic mutant (Ctx-) mice after LCMV infection.

In vivo CD8+ T-cell activation is heightened in Ctx-/- mice after LCMV infection.
CD8+ T-cells in prf-/- mice have cell-signalling patterns suggesting heightened antigenic stimulation after LCMV infection.


T cell activation is selectively heightened in lymphoid tissues of prf-/- mice after infection

Lykens et al, 2011
Terrell et al, 2013

Dendritic cells and T cell activation in prf-/ - mice

Anomalous antigen presentation by dendritic cells drives heightened T cell responses in cytotoxic deficient mice

Abnormal antigen presentation by dendritic cells drives heightened T cell responses in cytotoxic deficient mice

Terrell et al, 2013

Both CD8+ T cells and IFN-γ are necessary for the development of an HLH-like disorder in LCMV-infected prf-/- mice

Sustained elevation of IFN-γ is sufficient to induce acute anemia


....and hemophagocytosis.

Sustained exposure to IFN-γ in vivo and macrophage endocytic phenotypes

Human HLH: macrophages in the CSF

What do recently activated T cells look like in humans?

• Antigen presentation
• T cell phenotypes
• IFN as disease mediator/target of therapy

Miller et al, 2008
Characterizing T cells in patients with HLH vs. sepsis

Phenotyping activated CD8+ T cells in HLH

Activated CD8+ T cells in HLH patients are terminally differentiated

Activated CD8+ T cells in HLH produce IFN-γ

Tissue infiltrating CD8+ T Cells are activated: BM

Tissue infiltrating CD8+ T Cells are activated: CSF
IFN-γ is necessary for the development of an HLH-like disorder in LCMV-infected prf-/- mice

**IFN-γ** and downstream chemokines are elevated in patients with HLH

Tang et al., Br J Haematol. 2008

100 1000 10000 100000

IFN-γ

CXCl9   CXCL10   CXCL11

(1/3>100pg/ml)

Data courtesy of Novimmune

NI-0501, an Anti-interferon Gamma (Anti-IFNγ) Monoclonal Antibody, in Paediatric Patients with Primary HLH

- Phase 2/3 International, multicenter, open-label, single-arm study
- Open in Europe and in the United States
- Study population: children with pHLH receiving NI-0501 as 1st or 2nd line therapy

US Principal Investigator – Michael Jordan
E-mail: michael.jordan@cchmc.org
EU Principal Investigator – Franco Locatelli
E-mail: franco.locatelli@phple.net

Sites open

Site activation ongoing

Patient enrolment in the NI-0501-04 study
**Cut-off date October 10th, 2016**

Rapid normalization of fever
**Hours after first infusion of NI-0501**

Patients with body temperature > 37.5 °C at initiation of NI-0501 treatment
Response to NI-0501: disease features

Immune regulation, Immunopathology, and HLH: etiologic variation

Flood the system with antigen (immun suppression, malignancy).

Altering T cell signalling (can't suppress antigen presentation, but can still activate)

Overwhelming innate immune stimuli: disseminated DNA viruses (HSV, Adeno), mycobacteria, or leishmania directly activating macrophages

Macrophages

Overwhelming innate immune stimuli: disseminated DNA viruses (HSV, Adeno), mycobacteria, or leishmania directly activating macrophages

Dendritic cells

Cytokine T cells

IFN-γ

Artificially sustained T cell activation (CAR or lymphoma)

Impairing perforin-dependent negative feedback

Make T cells more prone to produce IFN-γ and/or make macrophages hypersensitive to it

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A proposal for HLH diagnostic criteria informed by pathophysiology:

Evidence of type I
T cell activation
- Elevated iCD25
- Elevated CXCL9

For treatment, assess the presence of other diagnoses suggesting alternative adjunctive therapies
- Viral infection: HSV, Adeno, CMV, EBV
- Other: mycobacterial, leishmanial, or fungal
- Malignancy, esp. leuk/lymphoma
- Drug reactions (eg. DRESS syndrome)

> 2 corroborating findings of immune activation/dysregulation

Clinical:
- Fever >38.5
- Splenomegaly
- Personal/family history
- Lab:
  - Ferritin>2000
  - elevated granzyme B MFI
  - Ferritin>2000
  - increased granulocyte B MFI
  - Decreased CD107 neg.

> 2 signs of abnormal immunopathology
- > 2 cytopenias
- ALT >3 ULN
- ferritin>150
- Hemophagocytosis
- CNS: pleocytosis, elevated protein, seizure, defects

Acknowledgements: NI-0501-04

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<tr>
<th>Principal Investigator, Co-Investigators</th>
<th>Principal Investigator, EU</th>
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<tr>
<td>M. Jordan, Cincinnati Children's Hospital, Cincinnati, Ohio</td>
<td>Michael Jordan</td>
</tr>
<tr>
<td>F. Locatelli, Istituto Bambino Gesù, Rome</td>
<td>Francesco Locatelli</td>
</tr>
<tr>
<td>C. Allen, Texas Children’s Cancer Center, Houston, Texas</td>
<td></td>
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<tr>
<td>S. Casero, Pediatrico Bambino Gesù, Rome</td>
<td></td>
</tr>
<tr>
<td>M. Herry, Phoenix Children’s Hospital, Phoenix, Arizona</td>
<td></td>
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<tr>
<td>M.C. Foli, University Hospital, Padova</td>
<td></td>
</tr>
<tr>
<td>C. Risso, Istituto Bambino Gesù, Rome</td>
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<tr>
<td>C. Roosig, University Children's Hospital, Münster</td>
<td></td>
</tr>
<tr>
<td>I. Smolka, University Children’s Hospital, Milan</td>
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<td>M. Gattegno, Scientific Steering Committee</td>
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<td>Patients and families</td>
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Christiane Lavelle

Familial / Genetic Predisposition
Infections
Rheumatologic Conditions
Malignancy

Common Pathophysiology (T cell activation and IFN-γ)

Overwhelming innate immune stimuli: disseminated DNA viruses (HSV, Adeno), disseminated mycobacterial or leishmanial infection

Iatrogenic (CAR T cell)

Common Pathophysiology (T cell activation and IFN-γ)
HLH: trigger vs. mimic?

A definition: HLH is a disorder of immune regulation... when typically benefits from immunosuppressive therapies

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<th>Triggers:</th>
<th>Anti-HLH therapy:</th>
<th>Mimics:</th>
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<td>• Viruses: EBV, CMV, others</td>
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<td>• Other specific infections: leishmania, mycobacteria</td>
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<td>• Rheumatologic conditions: esp. JIA</td>
<td>• Malignancy: if undiagnosed</td>
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