Immune Reconstitution Inflammatory Syndrome

Avindra Nath MD

Johns Hopkins University
Baltimore, USA
IRIS

- Definition and types of IRIS
- Risk factors
- Clinical manifestations and diagnosis
- Management
- Pathophysiology
Immune Reconstitution Inflammatory Syndrome

“IRIS is a worsening of a patient’s clinical condition that is paradoxically attributable to the recovery of the immune system after initiation of HAART”
EPIDEMIOLOGY of IRIS

15-25% Patients on HAART

20-45% Patients with OI on HAART

Shelburne et al., 2006
Types of IRIS

With OI
- Before ART
- After ART

Without OI
- Acute
- ?chronic
Terminology

• Hypersensitivity reactions
  – TB meningitis
  – Bacterial meningitis
  – Lepromatous leprosy

• JH reaction: syphilis
Time interval between Initiation of HAART and IRIS

Shelburne et al., AIDS, 2005
Risk Factors for IRIS

Antiretroviral naïve

Active or subclinical OI at HAART initiation

CD4 count (i.e. < 50 cells/mm$^3$)

Prompt decrease in HIV viral load with HAART

Host susceptibility genes
CASE

56 yr old woman with HIV infection

1994: CD4 count 7 cells; started on HAART

7/04 Change in HAART

7/04 Episode of aphasia; CD4 count 474; HIV viral load <200
CSF: 7 cells (100% mononuclear), protein 73; glucose 60;
HIV viral load 886
10/28/04 Readmitted

2 week history of seizures

Progressive decrease level of consciousness x 2 days
11/2 to 11/6 methylprednisone 1g/day

11/8 Dramatic improvement in mental status

Still significant and permanent impairment of short term memory

**Final diagnosis:** Immune Reconstitution Syndrome with HIV dementia

Riedel et al., Nature Neurol 2006
Acute encephalopathy with immune reconstitution

(Miller, Acta Neuropath 2004)

CD8+ T cells
Management of CNS-associated IRIS

No randomized treatment trials

Exclude drug effects, compliance and progression of underlying disease

Q 1) whether to discontinue HAART

Q 2) whether to give systemic corticosteroids

Reidel et al., Nature CI Prac Neurol, 2006
Lymphocytes (normal donor)

Anti-CD28  Anti-CD3

culture sups

MTT assay (O.D.)

- PBMC
- CD4
- CD8
- Ac-PBMC
- Ac-CD4
- Ac-CD8

P<0.01
Pathophysiology

Mechanism of T cell activation

Mechanism of T cell-mediated neuronal injury
Activated CD4 and CD8 cells produce granzyme B
An anti-Tat 125+IgG

GB (pg/ml)

Tat (nM)

P<0.05

GB (pg/ml)

Tat (nM)

0  15.6  31.2  62.5  125  250

0  125  125+Anti-Tat  125+IgG
Pt#9-220-79-31

VL=21777
CD4=204
Age=48y
Sex=M
ART (? compliance)

Pt #1-240-08-45

VL=8562
CD4=186
Age=29y
Sex=M
No ART

Pt#7-284-15-95

VL=ND
CD4=645
Age=52y
Sex=F
Stable ART

Pt#1-152-82-12

VL<50
CD4=663
Age=42y
Sex=F
Stable ART
Tat activates CD4 and CD8 cells to release GB
Repeat measures ANOVA with Dunnett correction

29-KCCFHCQVCFITKGL-43

Index (control = 1)

15 mer Tat peptides

* p<0.005
Effects of Kv Channel Blockers on Granzyme B production

A). Anti-CD3/CD28 beads

B). Anti-CD3 beads
Tat mediated GB release is NF-kB dependent
Pathophysiology

Mechanism of T cell activation

Mechanism of T cell-mediated neuronal injury
Granzyme alone is sufficient to cause neurotoxicity
Granzyme B is toxic to neurons not astroglia
Inhibition of proliferation of neural precursor cells by activated T cells

Wang and Nath, unpublished

BrdU positive cells (%)
Granzyme B acts via a G-Protein Coupled Receptor

Wang et al., FASEB J 2006
Granzyme B causes a decrease in cAMP levels in neurons and NPC

![Graph showing decrease in cAMP levels]

- ctrl
- forskolin
- GB+forskolin

P<0.05
untreated GrB treated

caspase 3 activation
resting cytosolic calcium

**SDF-1α**

- **vehicle** (blue circle)
- **10 nM granzyme** (red circle)

**Neuronal cell death (%)**

- **Control**
- **GrB**
- **GrB + Vit E**
- **GrB + 1046**

**[Ca^2+]_c (nM)**

- 0
- 200
- 400
- 600

- **Time (sec)**
  - 0
  - 50
  - 100
  - 150

**Means ± S.E.M.**

* p < 0.05
** p < 0.001
# p < 0.01
Future directions

• Need to establish clinical criteria for diagnosis
• Need biomarkers for recognizing the immune response
• Understand pathophysiology
• Need clinical trials with existing immunomodulatory drugs
• New modes of therapy that target the T cell responses against normal tissue but preserve those against infected cells
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