What Causes Sarcoidosis?

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Acknowledgements

- Dr. Marc Judson

No Financial Disclosures
What causes sarcoidosis?

- **Triggers**
  - Environmental/Occupational
    - Dust/Combustion products
    - Metals
    - Infectious organisms
    - Health care workers
    - US Military
    - ACCESS
  
- **Genetics**
  
  - Interaction between triggers and genetics

Background: Sarcoidosis

- **Systemic inflammatory disease**
  - Affects the lungs in ~90% of subjects
  - Affects many other organs as well

- **Clinical course (varies from person to person)**
  - ~1/3 remitting disease
  - ~1/3 stable persistent disease
  - ~1/3 progressive disease
Many Pulmonary Findings: highlighting the diversity of sarcoid

- Lymph Node enlargement
- Nodules
- Extensive disease
- Fibrosis/scarring

The finding on biopsy:
Granulomatous Inflammation

High power image from lung biopsy

Giant Cell with surrounding inflammation
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Potential Environmental Triggers: Combustion products

- Firefighters
  - Prezant DJ. Chest 1999; 116:1183

- World Trade CTR dust
  - Izbicki G. Chest 2007; 131:1414

- Wood stove exposure
  - Kajdasz DK. Ann Epidemiol 1999; 150:271

Provided by Dr. Marc Judson
Potential Environmental Triggers: Metals

- Titanium
  - Kucera GP. Chest 2003; 123:1527

- Photocopier toner (Si, Fe, Cu)
  - Rybicki BA. SVDLD 2004; 21:49

Potential Environmental Triggers: Infectious organisms

- Mycobacterial catalase-peroxidase (MKatG)
  - Present in sarcoid tissue.¹
  - T-cell response to MKatG in PBMC and lung of sarcoidosis patients.²,³

². Chen ES. J Immunol 2008; 181:8784
³. Oswald-Richter KA. Infect Immunol 2009; 77:3740
How can we tell that sarcoid isn't an infection due to TB?

- No one has ever been able to consistently grow TB or other organisms from sarcoid tissue
- Use steroids to treat sarcoid
  - This treatment would worsen an infection

Sarcoidosis: infectious agents

- Steroids improve sarcoidosis implies
  - Sarcoidosis is not an infection, per se
  - Sarcoidosis may be caused from a person's immune response to remnants of an infectious organism
  - "Antigen"
Potential Environmental Triggers: Infectious organisms

- Propionibacterium acne
  - Present in DNA of lymph of Japanese and Europeans with sarcoidosis.¹


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Potential Occupational Triggers: Health Care Workers

- Bresnitz, EA Ann NY Acad Sci 1986; 465:632
- Parkes, SA Thorax 1985; 40:284
- Edmondstone WM Thorax 1988; 43:342
Potential Occupational Triggers: U.S. Military

McDonough, C Mil Med 2000; 165:630
Cooch, JW Am Rev Respir Dis 1961; 84:103

Potential Occupational Triggers: Lumber Industry

Cummings, MM Ann Intern Med 1959; 50:879
Buck, AA Am J Hyg 1961; 74:137
ACCESS: A Case Control Etiologic Study of Sarcoidosis

- **Overall findings**
  - Positive associations between sarcoid and
    - Agricultural employment
    - Insecticides at work
    - Mold/mildew exposures
  - No single predominant exposure was found

Newman, LS Am J Respir Crit Care Med 2004; 170:1324

What causes sarcoidosis?

- **Triggers**
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    - Infectious
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- **Genetics**
Genetics: Important to understand basic immunology

- Terminology:
  - "Antigen"
    - A protein or molecule that can stimulate the immune system
  - MHC Class II proteins
    - Proteins that are on the surface of immune cells and bind to antigens
    - In humans, the MHC proteins are referred to as "HLA", human leukocyte antigen

MHC molecule has binding pockets for antigens

- Immune cell that displays Antigen to T cells
- Antigen: could be any of the triggers
- Different Antigens
- HLA protein
**Genetics: Important to understand basic immunology**

- **Antigen**
- HLA protein
- T cell
- **Antigen**
- T cell Receptor
- **Antigen**
- Cell that displays **Antigen** to T cells
- **Antigen:** could be any of the triggers
- granulomatous inflammation

**Concept of the Lock and Key**

- **Antigen**
- HLA protein
- T cell Receptor
- **Antigen**
- **Lock and Key**
- A person’s genetic DNA determines the shape of the “lock” and “key”
## Exposure-Genetics-Clinical findings

<table>
<thead>
<tr>
<th>exposure</th>
<th>genetics</th>
<th>sarcoidosis</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal</td>
<td>HLA DR3</td>
<td>+</td>
<td>Lung and skin</td>
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<tr>
<td>Metal</td>
<td>HLA B8</td>
<td>-</td>
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</tr>
<tr>
<td>TB</td>
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<td>Eyes and skin</td>
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</table>

## Cause of Sarcoidosis

Maybe there are multiple causes...

“The Sarcoidoses”
How do we deal with multiple causes of sarcoid?

- Study the similarities and differences of sarcoid inflammation between patients

Distinct inflammation patterns in sarcoidosis

- Indistinguishable from controls
- Up-regulated in sarcoid

Subjects
- Control
- Sarcoid

Genes
- IRF1
- STAT1
- GBP1
Thank You for your Attention!

Questions?

Similarities in the immune response of sarcoid and TB

Koth, LL. Am J Respir Crit Care Med 2011; 184:1153