Newest Insights About Sarcoidosis

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Sarcoidosis—Brief History

- First published descriptions by Dr. J. Hutchinson and Dr. Carl Boeck in 1869
  - Raised purple skin lesions on the face—“Boeck’s sarcoid”
- Dr. Caesar Boeck in 1899 finds that sarcoidosis can affect many organs (systemic disease)
  - Lungs, eyes, bone, lymph nodes, spleen, sinuses
- Cumulative experience associate physical findings with favorable prognosis (low mortality rate)
  - Heerfordt 1909 (uveitis, parotid, cranial neuropathy, fever)
  - Schaumann 1936 “lymphogranulomatosis benigna”
  - Löfgren 1953 (erythema nodosum, fever, arthritis, hilar adenopathy)
Chronic Sarcoidosis in the Lung

- Scadding classification of sarcoidosis chest x-rays
- In the US, sarcoidosis is often a chronic disease
- Long-term disease activity causes organ damage, scarring

What is Causing Sarcoidosis?

- Increased activity of the immune system
  - Triggered by specific protein targets (antigens)
  - Fueled by chemical signals (cytokines)
    - Fevers, fatigue, joint pain, weight loss
    - Recruitment of cells to form granulomas
- No evidence of active infection
- Improves with medications that suppress the immune system
  - Dose must be enough to cover signs of active disease
  - Cannot treat symptoms due to permanent damage (scarring)
Most Immune Responses Have Beginning and Ending Phases

Cold virus → Active infection → Eradication

\[ \text{Stimulation} \rightarrow \text{Disease} \rightarrow \text{Resolution} \]

Allergen → Allergic reaction → Allergen Clearance

\[ \text{↑ Chemical signals} \]

White blood cell activation

\[ \text{↓ Chemical signals} \]

WBC activation

Increased Immune System Activity Causes Sarcoidosis

Stimulation → Disease

\[ \text{Antigen Presenting Cell} \]

Sarcoidosis antigen mKatG

\[ \text{TCR} \]

MHC

IFNg, IL12, TNF

Inflammatory cytokines

Cellular recruitment

Granuloma formation

\[ \text{gene} \text{“sarcoidosis program”} \]

Other chemical signals

SAA
Can the Increased Immune System Activity Be “Shut Off”?

Disease \[\rightarrow\] Resolution

- Decreased cellular recruitment
- Cell death
- Chemical signals
- WBC activation

How Does the Increased Immune System Activity “Shut Off”?

Disease \[\rightarrow\] Resolution

- Decreased cellular recruitment
- Cell death
- Chemical signals
- WBC activation

- Clearing of antigens
- Other chemical signals

- Regulatory T cells
- Inhibitory cytokines
- IL-10, TGF-beta

- "garbage collector"
Finding Answers to Sarcoidosis From Within the Granuloma

- **Kveim reagent**: sarcoidosis tissue extract
  - Insoluble to neutral detergents
  - Relative resistance to heat, acidity, proteases and nucleases
  - Activity neutralized by strong denaturants and alkali
  - No microbial nucleic acids (DNA) present

- **Intradermal injection**
  - Epithelioid granulomas in 2-4 wks
  - Response in 80% of sarcoidosis pts.

Circulating Antibodies Identify Antigen Targets in Sarcoidosis Biopsies

- Antibodies in sarcoidosis blood recognize protein(s) in sarcoidosis biopsy extracts

- Mass spectrometry identifies a protein “fingerprint” consistent with a mycobacterial protein, *M. tb* catalase-peroxidase (mKatG)

A Sarcoidosis Antigen is Discovered in Tissue Extracts

- A prior eradicated infection leaves behind protein antigens (debris)
  - A non-infectious, microbial trigger for sarcoidosis
- mKatG is likely one of many antigens
  - Other proteins from mycobacteria
    - Drake (Vanderbilt), Dubaniewicz (Poland)
    - Other microbes? propionibacteria (Japan)
- Additional questions beyond mKatG:
  - What causes granulomas and scarring?
  - What else can we learn from Kveim reagent?

Host Modification of Antigen-Specific Responses

- Physical and chemical properties of Kveim reagent (limited solubility, resistance to degradation) contribute to its granuloma-inducing properties
  - Does mKatG have these properties to allow it to persist in tissues?
- Can antigens interact with natural (host) proteins that share properties similar to Kveim reagent?
  - The granuloma-inducing properties of disease-causing antigens may result from interactions between antigens and host proteins
- Amyloid-related proteins have physical and chemical properties similar to Kveim reagent
  - Can form poorly soluble protein aggregates and leave deposits
Expression of Serum Amyloid A in Sarcoidosis Granulomas

- SAA is deposited / located in cells of sarcoidosis granulomas
- SAA is not found in the same pattern / intensity in other diseases
- Other amyloid proteins, such as beta-amyloid, are not found in sarcoidosis granulomas

Role of SAA in Sarcoidosis?

- Serum amyloid A is an acute phase reactant
- SAA can act as a chemical signal through several receptors, including TLR2, RAGE, and others
- SAA binds matrix proteins and may serve as an important granuloma structural component
  - May contribute to how granulomas may function as an “antigen depot” for circulating proteins and microbes
SAA Enhances Cytokine Production in Sarcoidosis Lung Cells Through TLR2

- SAA causes the production of several chemical signals important to sarcoidosis, in part, due to binding with the TLR2 receptor.

Less Fibrosis Around Granulomas in Mice That Lack RAGE

- Immunize w/ mKatG
- Re-expose to mKatG
- Less fibrosis around granulomas in mice that lack RAGE.
A Model of Chronic Sarcoidosis

- Antigens left over from an eradicated infection trigger immune system activity
- SAA from an acute phase response to infection can enhance inflammation or promote scarring
- Ineffective clearance (antigen, SAA) provides a source for chronic stimulation of the immune system

Possible New Approaches to the Treatment of Sarcoidosis

- Reduce cytokine production by blocking binding of SAA to receptors
  - Identification of other SAA receptors
  - Reduce production of SAA
- Block important chemical signals that direct and fuel the inflammatory process
- Change or "re-educate" the immune system response to sarcoidosis antigens
SAA Possibly Linked to Stress?

- SAA is an acute phase reactant
- Persistent elevations in SAA 48 hours following ultra-distance Spartathon (246km)
- Is there a relationship between stress and inflammation?
- Need to collect SAA measurements along with surveys for stress and fatigue

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