American Autoimmune Related Diseases Association, Inc.
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A nonprofit association bringing a national focus to autoimmunity, the major cause of chronic disease

AARDA Scientific Colloquium Highlights

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Toward an Integrated Theory of Autoimmune Disease Causation- Dr. Robert Root-Bernstein

- Self-non-self – possible cause of autoimmunity wherein pathogens and immune responses mimic self-antigens
- Two principles of autoimmunity: complementarity and molecular mimicry
    - Antigenic complementarity predicts that antibody or TCR sequences may mimic initiating infectious agents

Multiple facets of the hit and run hypothesis in the causation of autoimmune disease- Dr. Jay Reddy

- In a mouse model of CVB3-induced myocarditis, is there a role for cross-reactive T cells, and if so, what is it?
- Myhc-α 334-352 reactive T cells generated in the CVB3-infected mice are pathogenic
    - This encompasses both CD4 and CD8 T cell epitopes, both of which contribute to myocarditis
- CVB3 virus may lead to generation of T cells with multiple antigen-reactive species
- Possibility of creating a vaccine to prevent CVB infection, thus preventing CVB3 induced myocarditis

Autoimmunity in Neuropsychiatric Syndromes- Dr. Madeline W. Cunningham

- Syndenham chorea as a model of autoimmunity in the brain: targets neuronal cells, develops into dopamine-receptor encephalitis
- Human rheumatic carditis Mab cross-reacts with N-acetyl-β-D-glucosamine; dominant IgG2 subclass antibody
    - This dominates in rheumatic fever
- Rheumatic valve model
    - Valve becomes injured as one repeatedly is infected with strep
        - Breakdown of valve proteins (particularly collagen)
        - Epitope spreading
        - Avascular valve eventually becomes neovascularized, which activates TLR2 and 8 → may trigger cross-reactivity

Contribution of cardiac fibroblasts to post-infectious autoimmunity- Dr. Daniela Cihakova

- IL-17A KO mice did not show any decrease in EAM disease severity, implying that IL-17A is not required for autoimmune myocarditis
    - However, IL-17A does control progression to dilated cardiomyopathy
- Sca-1+ cardiac fibroblasts respond to helper T cells in the microenvironment; produce eotaxin 1 (CCL2) in response to IL-17A
    - IL-17A elicits myelotropic growth from cardiac fibroblasts, leading to fibrosis and further inflammation from more production of eotaxin 1

Combating Lyme Disease- Dr. Kim Lewis

- Lyme disease caused by *B. burgdorferi*- small subpopulations of persister cells may be resistant to antibiotic treatment of lyme disease
    - Persister mechanisms include ATP drop (cessation of metabolic activity)
- Heritable drug tolerance to antibiotics may also result in acute lyme disease
    - Possibly coming from highly persistent mutants among commensals
- Possible treatments for killing persisters:
    - Protease regulators such as ADEP
    - Vulnerability of cell wall in constantly remodeling persister cells

Bystander activation of T lymphocytes in persistent Lyme arthritis- Dr. Janes Weis

- CD4 an CD8 T cells are expanded in lymph nodes, responsible for promoting IFN-γ production in *B. burgdorferi* infected IL10 KO mice
    - Yet, *B. burgdorferi* is extracellular and is not expected to be presented to CD8+ T cells → bystander activation of CD8 T cells
- TLR2 expression increases during infection, which enhances IFN-γ production and lyme arthritis severity

Immunobiological Features of Patients with Persistent Symptoms Following Diagnosis and Treatment of Human Lyme Disease- Dr. Mark Soloski

- Study of Lyme Disease Immunology and Clinical Events (SLICE)- follow patients for 1 to 2 years to study post-treatment lyme disease syndrome (PTLDS)
- RNAseq data analysis on these patients revealed that CCL19 is always elevated and persistent in PTLDS patients
    - CCL19 drives immune cells to a site
- Some PTLDS patients also experience regional neuroinflammation caused by microglial-based activation

Manipulation of Treg Homeostasis and Function in vivo- Dr. Ethan M. Shevach

- Depletion of Foxp3+ T cells from adult mice leads to catastrophic autoimmunity
- Anti-IL-2 decreases the percentage and absolute numbers of Ly6C+ Tregs, but does not affect proliferation of Tregs
    - Anti-IL-2 increases the proliferation of CD4+Foxp3- and CD8 T cells
- Anti-MHC-II treatment expands Ly6C-Foxp3+ T cells
- CTLA-4 (coinhibitory receptor) deletion results in enhanced suppression of Treg response and prevents autoimmunity

Autoimmune risk alleles: improving fitness during infectious challenge- Dr. Eric Allenspach

- IFIH1 is a innate immune receptor that recognizes viral nucleic acids
    - $IFIH1^{A946T}$ variant mediates interferon program that limits viral infection but increases the risk for autoimmunity
    - Certain haplotypes of IFIH1 are associated with type 1 diabetes, exhibit enhanced autoantibody responses and enhanced ligand-dependent signaling
- SH2B3 protein regulates signaling pathways related to cell migration and inflammation
    - Certain haplotypes which include hypomorphic point mutations are associated with reduced mortality; other haplotypes developed in mouse models are protected from severe sepsis

A nanoparticle based negative T cell vaccine for tolerogenic therapy of autoimmune disease- Dr. Stephen D. Miller

- Antigen associated PLG nanoparticles serve as surrogates for apoptotic membranes for efficient induction of peripheral tolerance
- Tolerance induced by PLP-coupled PLG nanoparticles prevent and treat established PLP R-experimentally induced encephalitis
- P31-PLG induces systemic expansion of Tregs and regulates trafficking of effector Th1 cells, preventing them from going into the pancreas and possibly inducing diabetes

Deconvolution of pan-viral serology- Dr. Benjamin Larman

- Phage immune-precipitation sequencing (PhIPseq)
    - Antibodies from sera combined with a phage library, amplified
        - Look to find peptide enrichments to discover new disease associations
- AVARDA: Anti-Viral Antibody Deconvolution Algorithm
    - Find how peptides are related to each other- identify greatest set of non-overlapping peptide enrichments
    - Align all hits against human viruses
    - Remove overlapping peptides

Periodontitis in the pathogenesis of rheumatoid arthritis- Dr. Felipe Andrade

- Patients with RA have antibodies to citrullinated proteins
    - Synovial fluid shows hypercitrullination, major source is from neutrophils
- Hypercitrullination can be found in periodontitis; caused by *A. actinomycetemcomitans*
    - Bacteria might trigger hypercitrullination to protect themselves, inactivate antimicrobial proteins, RA genetic susceptibility

Linking gut microbial immunity with autoimmunity in joints in patients with rheumatoid arthritis- Dr. Allen Steere

- In mice, gut-residing segmented filamentous bacteria drive autoimmune arthritis
    - Gut dysbiosis in RA patients might activate autoreactive T cells

Infections can prime or protect against autoimmune disease- Dr. Robert Fujinami

- Multiple sclerosis migration studies show that moving to a high-risk area before age 15 increases MS risk
    - Vaccinia virus and CNS proteins have molecular mimicry, infecting with virus may lead to robust meningitis and perivascular cuffing
- Found differences between autoclaved and irradiated mouse food
    - High *Lactobacillus* load prevented EAE, while low load was associated with high EAE
    - Protection of mice from developing experimental autoimmune encephalitis

Killer cell induced neo-epitopes as drivers of autoimmune disease- Dr. Erika Darrah

- Rheumatoid arthritis- autoantigen peptidylarginine deiminae 4 (PAD4) is cleaved by granzyme B
  - Could alter immunogenicity
  - Levels of granzyme B increased in peripheral blood and synovial fluid in patients with rheumatoid arthritis
  - Possibly use granzyme B inhibitors as therapeutic targets for RA