Updates on Lupus 2016

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Outline

• Research at UR
• What’s new in diagnosis?
• Pathogenesis (leads to treatment)
• Treatment
Research in Lupus

- The more that is known about clinical outcomes and immune abnormalities associated with lupus, the better equipped we are to fight the disease!
What we’re doing at the U of R:

• NIH funded networks
  • Autoimmunity Center of Excellence for clinical trials and basic mechanisms of lupus and clinical trials
  • Accelerating Medicines Partnership

• Clinical Cohorts/Consortiums
  • Lupus Clinical Trials Consortium (LCTC): Collaborative Longitudinal Lupus Registry of 20 centers- UR is one
  • LuCIN (Lupus Clinical Investigators Network- LRI/ALR collaboration, repurposing drugs)

• Clinical Trials
  • The AIR unit has an active program in clinical trials in SLE
  • Investigation of new, targeted biological interventions in SLE
Systemic Lupus Erythematosus (SLE)

- **Systemic** inflammatory disease of **autoimmune** etiology and **unknown** cause.
- **Chronic** disease characterized by unpredictable **exacerbations** and **remissions**.
- It can affect virtually **any organ**, singly or in combinations that change from patient to patient.
- Accordingly, its severity ranges **from mild** in some cases to **life-threatening** in others.
SLE - Epidemiology

• World-wide prevalence: 10-50/100,000
• US prevalence: 24-100/100,000
• African-Americans > Caucasians (3x)
  - Caucasian women (15-64 years of age): 1/700
  - African-American women (15-64): 1/245

• Age at diagnosis:
  - 16-55 years of age: 65% of cases
  - < 16: 20%
  - > 65: 15%

• Female/male ratio:
  - Age 14-65: 6-10 / 1
  - Age <14 or >65: 2-3 / 1
Lupus presenting symptoms

- Painful Joints
- Fever
- Swollen Joints
- Extreme Fatigue
- Skin Rash
- Anemia
- Renal
- Pleurisy
- Facial Rash
- Photosensitivity
- Hair Loss
- Clotting
- Raynauds
- Seizures
- Ulcers
Episode 408:
“You don’t want to know”
It is lupus!
### How do we diagnose lupus?:

**American College of Rheumatology (ACR) criteria**

<table>
<thead>
<tr>
<th>Skin criteria</th>
<th>Systemic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Malar rash</td>
<td>5. Arthritis</td>
</tr>
<tr>
<td>2. Discoid Rash</td>
<td>6. Serositis</td>
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</tbody>
</table>

**Lab criteria**

9. Anti-nuclear antibody  
10. Immunologic  
11. Hematologic

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For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any **4 or more of the 11 criteria** are present, serially or simultaneously, during any interval of observation.
Newer SLICC criteria

1) Fulfillment of at least four criteria, with at least one clinical criterion AND one immunologic criterion
   • Broader skin, neurologic, alopecia, immunologic criteria include low complements and direct coombs

2) OR Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.
SLE Diagnosis: Autoantibodies

- **ANA**
  - Seen in 99% of SLE
  - Not specific for SLE
  - Seen in many inflammatory, infectious, and neoplastic diseases
  - Seen in 5% to 15% of normal persons

- Other more specific autoantibodies - antiDNA, antiSmith
Multiplex detection of multiple autoantibodies

- Autoantigen specific beads
- Mix patient serum and beads
- Each bead subjected to lasers
- Characterizes 200 beads for each analyte
Autoantibodies precede diagnosis

![Graph showing the time course of positive test results for different autoantibodies before diagnosis.](image-url)

*Arbuckle...Harley. NEJM 349: 1526, 20036*
Can we treat before disease?

- Identify 'at risk' individuals
- Balance risks of treatment:
  - Emerging data for
    - Vitamin D
    - Omega-3-fatty acids

The Future of Diagnosis

- Identify and detect more lupus specific autoantibodies-
  Next generation proteomics

- Stanford silicon chip with thousands of histone related proteins
- Rochester collaboration with CDI-19,000 human proteins on a single microscope slide

*Stanford- Scientific Reports 2016; Nature Medicine 2012*
The Future of Diagnosis

- Combine autoantibody panels with other tests
  - AVISE SLE- diagnostic test for SLE, includes a panel of autoantibodies+cell-bound complement activation products
  - May increase sensitivity and specificity

Earlier diagnosis=lower number of hospital visits, better clinical outcomes, fewer disease flares, reduced healthcare costs
- Clinical/transcriptional profiling of 158 lupus patients for 4 years
- Neutrophil signatures associate with progression to active nephritis
- Molecular correlates of disease activity stratify patients into seven major groups
- Molecular stratification may improve the outcome of clinical trials in SLE

Banchereau et al. Cell 2016
Cause/Pathogenesis

- genetics
- hormones
- environment

The 'exposome'
Genetics

- Polygenic - each single gene contribution is very small
- Genetic burden
- Many polymorphisms are in non-coding regions (ENCODE)
Epigenetics

- Changes in gene expression resulting from changes in DNA structure that influence transcription
- DNA or protein (histone) modification
- Many examples emerging about how epigenetics affects immune cell function and risk of lupus

Microbiome

- Total population of bacteria and other microorganisms in the gut
- Aid in digestion but also influence the immune system
- Can transfer obesity to mice with microbiota
- Emerging data on risks of lupus in mouse models and altered microbiota in lupus patients
- ...BUT it is a big step to understand how to modify the microbiome!!

SLE pathogenesis and treatment targets

Stages of autoimmunity

Loss of tolerance
Sle1, CD22, C1q, BANK, BAFF

Innate and adaptive dysregulation
Sle2 (B), Sle3 (T, DC), PTPN22

End organ targeting
FcR, ITGAM

Stages of autoimmunity:
- Loss of tolerance
- Innate and adaptive dysregulation
- End organ targeting

Autoantibodies:
- Proteasome inhibitors
- Anti-B cell antibodies
- TLR inhibitors
- IFNα blockade

Immune complexes:
- PC

BAFF inhibitors:
- mBAFF
- sBAFF

CTLA4-Ig Abatacept

Lymphocyte signaling:
- Small molecule inhibitors

TNF blockade
- IL-6 blockade

N

T

B

pDC

IFNα

CD40

CD40L

CD28

B7.1/2

B7.1/2

TLR9

IFNα

TNF

CTLA4-Ig

Abatacept

IL-1β

IL-6

IL-17
B cells behaving badly

B-cell \rightarrow \text{Plasma cell}

SLE Controlled

\begin{align*}
\text{CD27} & \quad \frac{\text{IgD}}{10^4} \\
\text{SLE Active} & \quad \frac{\text{CD27}}{10^4} \\
\end{align*}

(Auto)-antibody production

Protective B cell functions

Pathogenic B cell functions

Anolik et al. AR 2007
Palanichamy et al. JI 2010
B cells behaving badly

- B cells that normally regulate inflammation get signaled to become pro-inflammatory instead in part by IFN.
Epigenetics and B cells come together

- Changes in DNA accessibility in B cells in SLE that influence B cell activation
Normal healthy turnover of mammalian cells, which die, break up and have their parts, including DNA, recycled.

Researchers found that an enzyme, DNASE1L3, normally digests the DNA within small particles coming from disintegrating cells, thereby preventing lupus.

Many forms of cell death—apoptosis, autophagy, mitophagy.

The spectrum of lupus treatment

Treating inflammation or autoimmunity
  • Anti-inflammatory agents
  • Antimalarials
  • Immunosuppressive/cytotoxic agents

Other
  • Prevention: management of cardiovascular risk, immunization
  • Anti-thrombotic therapy
  • Dialysis and kidney transplantation
The ‘traditional treatment armamentarium’

FDA Approved drugs
- glucocorticoids
- hydroxychloroquine
- low dose ASA
- Benlysta

‘Off-label’ but standard of care
- azathioprine
- cyclophosphamide
- NSAIDs

Immunosuppressives developed for other diseases
- mycophenolate mofetil
- methotrexate
- cyclosporin
- leflunomide
- tacrolimus
- fludarabine
HOW DO WE IDENTIFY NEW TARGETS? Accelerating Medicines Partnership (AMP) Initiative

- New venture between lupus and RA scientists, NIH, biopharmaceutical companies and non-profit organizations
- UR is one of the 9 sites
- Goal is to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets of disease in TARGET TISSUE

- The ultimate goal is to increase the number of new diagnostics and therapies for patients and reduce the time and cost of developing them
Boosting Success by Improving Efficacy: Phase II Clinical Trials

Current targets
- Animal models
- Cell lines

AMP targets
- Emerging Technologies
  - DNA sequencing
  - Proteomics
  - Single-cell analysis
  - Bioengineered cells
  - Imaging
- Extensive Human Data
  - Tissue/blood samples
  - Clinical information
  - Demographics
- Big Data Tools

Adapted from: Arrowsmith J, Miller P. Nat. Rev. Drug Discov. 12, 569, August 2013
AMP Initiative: Tissue is the Issue!

RA synovium
Lupus kidney

RNA profiling
More on clinical trials and new treatment strategies
Rituximab = anti-CD20 = B cell depletion

- Initial promising studies
- Two large trials of anti-CD20 (rituximab) in SLE failed to meet their primary outcomes
- Advances in the field on how to successfully do lupus clinical trials
- Rituximab is still thought to be effective in lupus and indicated for a subset of refractory patients (personalized medicine)
B cell targeted 2016 What’s new?

• Innovative ways to combine rituximab with benlysta

• Other B cell targeted therapies:
  • Anti-CD22: phase III completed, did not meet endpoints
  • Other anti-CD20s-approved for lymphoma
  • Anti-CD19

• Cytokine blockade
  • Benlysta for nephritis, black patients, pediatric, long-term safety, treatment holiday/restart, SQ (BLISS-SC + Phase 3)
  • Different forms of BAFF blockade in Phase 3- blisibimod (Anthera- CHABLIS study begun 7/2016), atacicept (EMD Serono) Phase 2
Interferon and Toll-like receptors

Current Opinion in Rheumatology 2003 Pascual
IFN and TLR blockade

• Blocking IFN (discussed by Dr. Furie)- positive results with anifrolumab (Phase 2)

• Other approaches:
  • TLRs are key receptors of the innate immune system that can induce strong inflammatory responses- important in production of IFN. Interest in small molecule inhibitors of Toll-like Receptors (TLRs) 7, 8, and/or 9
Is it important to eliminate autoantibodies?

Protective vs pathogenic antibodies
- Anti-microbial
- Anti-ds DNA
- Anti-RBP antibodies (Ro, La, Sm/RNP)
Proteasome inhibitors

- Targeting autoreactive plasma cells
- Most current therapies do not effectively decrease autoantibodies
- Amgen acquires Onyx: Kyprolis=carlfizomib for myeloma

Itohkitawa...Anolik; Arthritis and Rheum 2012
Intracellular signaling pathways

• Mitogen-activated protein kinases (MAPK), tyrosine kinases (TK), Janus kinases (JAK) and nuclear factor κB (NFκB)
• Interesting therapeutic targets
• Experience in RA (tofacitinib=JAK3 inhibitor)
• Anolik lab work with SINEs
SINEs halt disease in lupus prone mice and eliminate plasma cells.
Currently enrolling trials at UR

• Inhibition of intracellular signaling with small molecule oral agents
  • Inhibitor of ubiquination in Phase II placebo controlled, multi-center trial by Celgene CC-220
  • We are CURRENTLY enrolling
  • May have particular efficacy in skin disease

• Cell based therapies
  • Mesenchymal stem cell transfer
Concluding points

- We are learning how to “borrow” drugs used to treat other diseases
- Some drugs may provide clues about how lupus develops
- Despite barriers, novel mechanism-based therapies are in development for SLE
- Therapy will attempt to target specific pathways in the body
- Eventual treatments may involve combination therapies, i.e., “cocktails” of targeted and semi-targeted therapies
- Personalized medicine
Thank You!
Learn More

- www.lupusresearch.org/research/research_update.html
- LupusTrials.org
- www.clinicaltrials.gov
- The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the Office on Women’s Heath have developed a strategic plan for reducing health disparities. Lupus is included as an area of research focus. Recent first-ever National Public Health Agenda for Lupus in collaboration with the National Association of Chronic Disease Directors (NACDD). Further information on disparities in lupus and educational material at:
  - http://thelupusinitiative.org
  - www.couldihavelupus.gov