Preventive Lupology

Diane L. Kamen, MD, MSCR
Associate Professor of Medicine
MUSC Division of Rheumatology
Outline

• Brief overview of known environmental contributions to SLE
• Introduce the SLE in Gullah Health (SLEIGH) community based study and touch on findings to date regarding 2 risk factors
• Describe future directions in the discovery & prevention of modifiable environmental risk factors for SLE

• Disclosures: None
Timeline of Autoimmune Pathogenesis

Environmental Triggers & Epigenetic Factors

Genetic Predisposition

Loss of tolerance to self antigens

Development of autoantibodies

Tissue damage & onset of symptoms

Clinical Autoimmune Disease

Evidence for Environmental Influences in Disease Etiology

- Disease concordance < 50% in monozygotic twins
- Dechallenge = disease improvement after agent removal
- Rechallenge = disease recurrence after re-exposure
- Geographic clustering in disease incidence or prevalence
- Changes in the prevalence or incidence of disease over time
- Seasonality in birth dates and disease onset
- Environmental response genes are major risk factors for disease
- Strong biologic plausibility from \textit{in vitro} data / animal models
- Epidemiologic associations between specific infectious and non-infectious exposures and certain diseases
Potential Environmental Triggers of SLE

- Drugs and hormones
- Crystalline silica exposure
- EBV and other infections, microbiome
- UV light
- Smoking
- Vitamin D deficiency
- Pesticides, persistent organic pollutants (POPs), metals, personal use products
- Dietary factors

The Human Exposome

- Methods being developed to determine an individual’s “exposome”
- Using “omics” technologies: a non-targeted approach for biomarker identification & individual profiling
  - Genomics, transcriptomics, proteomics, metabolomics
- Coupled with refined questionnaire-based approaches
- The 129 scrutinized EPA priority pollutants is tiny compared with the human metabolome

Rappaport SM. J Epi Comm Health 2012.
Disparities in Lupus

• **African Americans have:**
  - 3-fold increased incidence of SLE
  - A younger age of onset
  - More frequent & more severe kidney involvement
  - Increased overall morbidity and mortality

• **Yet, SLE is a rare disease in West Africa**
Gullah African Americans

- African Americans from the Sea Islands of SC (Gullah) are direct descendants of blacks from the Rice Coast of West Africa (primarily Sierra Leone).
- The Gullah are genetically and culturally distinct due to previous geographic isolation and low rates of genetic admixture.

Spruill I and Davis BL. OjHE; 2005.
Gullah Ancestral Origins

SLE in Gullah Health (SLEIGH)

- Ongoing population based case-control study of genetic and environmental risk factors for SLE
- Enrolling since 2003
- Visits in the CTRC
- African American Gullah men & women, all ages.
  - SLE patients (n=247)
  - Family members (n=233)
  - Unrelated controls (n=173)
Community Input and Support

- Community-Based Participatory Research (CBPR)
- Established relationship & trust with the Sea Island Families Project Citizen Advisory Committee (CAC) since conceptualization
Genetics of SLE in SLEIGH

• High prevalence of multi-patient families with SLE
  – 27% of SLEIGH patients with SLE are from multiplex families
  – 17% of SLEIGH patients with SLE have a first-degree relative with SLE (compared to 8% in other regions)
  – Suggests a strong genetic component, but doesn’t explain ~70% of the cases

• Susceptibility loci for SLE same for Gullah as other African Americans

• Interestingly, 35% of asymptomatic relatives of SLE patients were ANA positive (increased to 70% when they came back 3.5 years later)

Epigenetic & Environmental Studies in SLEI GH

The POPAI Study:
Persistent Organic Pollutants (POPs) & other potential environmental triggers of Autoimmunity (AI)
Potential Environmental Triggers of SLE

- Drugs and hormones
- Crystalline silica exposure
- EBV and other infections, microbiome
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High PFCs & PBDEs in Charleston Harbor
Bottlenose Dolphins – a sentinel species

- Ashley, Cooper & Wando Rivers
- Charleston Harbor
- Stono River Estuary

Persistent Organic Pollutants (POPs)

- Bioaccumulate & have become ubiquitous contaminants – detectable in the environment, in animals & humans
- Perfluorinated compounds (PFCs) used as surface treatments & surfactants
  - PFOS & PFOA – production phasing out since 2000
- Polybrominated diphenyl ethers (PBDEs) widely-used flame retardants
- Endocrine-disrupting effects
- Immune system targets of POPs toxicity
- Mixture effects are more than additive

Levels of Perfluorinated Compounds (PFCs) Higher than NHANES and Associated with ANA Positivity in Gullah Controls

• Preliminary results show that all have measurable serum levels of PFCs (specifically PFOS, PFOA and PFNA) from baseline and follow-up visits 7.3 ± 1.4 years apart.
  – Annual servings of seafood directly correlated with baseline serum PFOS (p=0.02) and PFNA levels (p=0.03) and the strongest correlation was with reported intake of seafood known to have the highest concentrations of PFCs.

• ANA positive controls (48% of controls at baseline) had higher median levels compared to ANA negative controls for PFOS (62.3 vs 46.4 ng/ml, p=0.05), PFOA (6.1 vs 5.4, p=NS) and PFNA (2.8 vs 1.6, p=0.03).

Levels of Perfluorinated Compounds (PFCs) Higher than NHANES and Associated with ANA Positivity in Gullah Controls

- Local serum levels of PFCs among the Gullah at baseline (~2003-2004) are higher compared to NHANES non-Hispanic black serum levels from 2003-2004. Gullah PFOS levels at follow-up (~2010-2011) are higher compared to NHANES non-Hispanic black PFCs from 2007-2008. p-values are given using Welch’s t-test for unequal population variances.

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<th>2003 - 2004</th>
<th>2010 - 2011</th>
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<td>PFOS (ng/ml) at baseline</td>
<td>PFOS (ng/ml) at follow-up</td>
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<td>Gullah AA controls</td>
<td>39.4 ± 2.4; n=48</td>
<td>17.8 ± 2.6; n=53</td>
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<td>NHANES blacks</td>
<td>21.6 ± 1.4; n=538</td>
<td>15.0 ± 1.4; n=419</td>
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<td>PFOA (ng/ml) at baseline</td>
<td>PFOA (ng/ml) at follow-up</td>
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<td>Gullah AA controls</td>
<td>5.0 ± 1.8; n=48</td>
<td>2.7 ± 3.5; n=53</td>
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<tr>
<td>NHANES blacks</td>
<td>3.4 ± 0.2; n=538</td>
<td>3.9 ± 0.2; n=419</td>
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<tr>
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<td>PFNA (ng/ml) at baseline</td>
<td>PFNA (ng/ml) at follow-up</td>
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<td>Gullah AA controls</td>
<td>1.9 ± 2.0; n=48</td>
<td>1.4 ± 3.4; n=53</td>
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<td>NHANES blacks</td>
<td>1.1 ± 0.2; n=538</td>
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<tr>
<td>p-value</td>
<td>&lt;0.01</td>
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Immune Actions of 1,25(OH)$_2$D$_3$

- Modulates dendritic cell maturation
- Influences T cell phenotype
  - Down-regulates inflammatory cytokines (IFN, IL17, IL21)
  - Up-regulates suppressor cytokines (IL4, IL5, IL10)
  - Promotes induction of T regs (expressing CTLA-4 & FoxP3)
- Reduces B cell hyperactivity in deficient patients
- Influences innate immune responses
  - Enhances production of anti-microbial peptides (LL-37 / cathelicidin & $\beta$-defensin-2)

Vitamin D in SLEIGH & Sierra Leone

- Very low 25(OH)D levels seen in Gullah - both SLE patients & controls:
  - Overall mean 13.3 ng/ml (N=187, sd 8.0)
  - 95% of subjects had 25(OH)D < 30 ng/ml
  - Higher lupus activity seen with lower 25(OH)D

- Normal 25(OH)D levels in Sierra Leone African women:
  - Overall mean 36.0 ng/ml (N=70, sd 9.2)
    - p < 0.001 compared to SLEIGH cohort
    - ANA+ had lower 25(OH)D than ANA+ Africans

Communication of Research Findings back to the Community

• Jan 21, 2012 – Sea Island Community Research Celebration on Johns Island
Current Study Design

Common Genetic Ancestry

- 100 Gullah Unrelated Controls
- 60 Gullah Patients
- 100 Sierra Leone Africans

Validation of Questionnaires in Population

Study Visit

Existing Data from 100 Gullah FDR Controls

Exposure Measures
- Diet/Lifestyle Questionnaires

Biomarkers
- 25(OH)D
- MeHg
- POPs
- Autoantibodies
Future Study Design

- Form interdisciplinary team
- Identify participants: high risk pre-clinical disease (GWAS data)
- Accurate measurement of exposures & effect of exposures (EWAS data)
- Independent validation
- Targeted “personalized” prevention of progression to clinical disease

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