National Institute of Environmental Health Sciences

Finding the Genetic Causes of Lupus

NIEHS-supported research is shedding light on how mutations in genes controlling DNA repair may drive autoimmune disorders.

Research funded by the National Institute of Environmental Health Sciences (NIEHS) is unraveling the genetic basis of autoimmune conditions, such as systemic lupus erythematosus, or lupus. Lupus affects potentially 1.5 million Americans, mostly women, and has no known cure.[1] People with lupus may suffer painful flares affecting their skin, joints, and organs. Lupus also damages the immune system, leaving sufferers highly vulnerable to infections, such as pneumonia.

Joann Sweasy, Ph.D., an NIEHS-funded researcher at the University of Nebraska Medical Center, is an internationally recognized expert in the genetics, cell biology, and biochemistry of DNA repair. Funded by an NIEHS Revolutionizing Innovative, Visionary Environmental health Research (RIVER) award, Sweasy studies the connection between DNA repair and the development of lupus. Her background in tracing links between DNA repair and cancer, plus a mouse model experiment that went awry, positioned Sweasy to pivot to researching lupus.

Sweasy hopes her work will lead to improved therapeutic or preventive approaches for lupus, including identifying potential drug targets. She is optimistic that, if we know that individuals with certain DNA repair variants are affected by certain environmental exposures, we can prevent the disease in some way.

"Our major goals are precision, prevention, and population health. What's so important to us, and to the National Institutes of Health, is that interactions between genes and the environment can be prevented," Sweasy said. "I hope our work in this area is bringing attention to the need to understand who is likely to develop lupus and what is going to trigger it."

Sweasy, an NIEHS grant recipient since 2002, is conducting pioneering research on DNA mutagenesis and repair.

How Cancer Research Led to a Lupus Discovery

While Sweasy was breeding mice for her research into the role of DNA damage and repair in cancer, something unexpected happened. She had bred the mice with a mutated variant of a key mouse DNA repair gene, POL B, predicting they would develop cancers that she could then study. Instead of cancer, the mice developed symptoms remarkably similar to lupus. This unexpected result sparked a decade of research on DNA repair and autoimmunity.

Impacts of Finding the Genetic Causes of Lupus

- Revealed that abnormal DNA repair mechanisms were linked to autoimmunity.[2, 3]
- Identified several DNA repair variants present in higher numbers in people with lupus.[4]
- Created four mouse models, which carry different DNA repair gene variants, to study lupus.
- Found that a reduction in DNA glycosylase, enzymes that recognize and remove damaged DNA bases in mice, led to decreased severity of lupus-like symptoms, indicating glycosylase could play a role in future therapeutics.[5]
- Revealed that a chromatin sleeve that encases DNA inside a cell may have a link to autoimmune disease, opening up a new avenue of study and potential for therapeutics.

Then and Now

- **Then:** Estimates state more than 1.5 million Americans suffer from some form of lupus, but clinicians have little knowledge of the root causes of lupus.
- **Now:** Sweasy is identifying which gene variations contribute to lupus and mapping those genes to environmental triggers.
- **Then:** Lupus is ranked among the top 20 leading causes of death in females between 5 and 64 years of age from 2000 to 2015, and is thought to have contributed to 28,411 female deaths during that period.[6]
- **Now:** Sweasy's research is pinpointing the genetic mechanisms that can lead to autoimmune disease, with the goal of informing targets for therapeutics for lupus treatment and symptom control.

Research Timeline

2014

Fundamental Questions

A study in mice genetically primed for cancer revealed that a mutation in the POL B gene, which is involved in repairing single-strand DNA breaks, resulted in lupus-like symptoms.[3]

2014

Fundamental Questions

Demonstrated that slow activity of the DNA polymerase beta protein, a key enzyme in DNA damage repair, leads to lupus-like disease in mice and potentially lupus in humans.[3]

2014 - Present

Implementation and Adjustment

Began collaborating with a rheumatologist geneticist, who identifies inherited changes — called germline variants — in DNA repair genes that occur more frequently in people with lupus.

2017

Fundamental Questions

Reviewed more than 100 lupus studies and reported mutations in a range of DNA repair genes, especially in genes associated with immune system cells. These mutations could lead to accumulation of misplaced DNA and inappropriate immune responses, which could trigger lupus.[7]

2021

Application and Synthesis

Discovered a DNA glycosylase deficiency in one of her mouse models led to decreased severity of lupus-like symptoms, indicating glycosylase could play a role in future lupus therapeutics.[5]

2022

Policy and Practice

Isolated a DNA germline variant MSH6 associated with lupus-like disease in mice.[4]

2022

Implementation and Adjustment

Revealed that expression of a DNA polymerase beta protein, Y265C, plays a critical role in whether the organs where it is expressed will develop lupus symptoms.[8]

2025

Policy and Practice

One of Sweasy's lab's mouse models exhibits significantly faster DNA repair, compared to other models' test groups and controls. Research on this feature is underway.

2025

Implementation and Adjustment

Found evidence the way the chromatin sleeve encasing DNA inside a cell opens and closes, to start and stop the process of RNA replication and protein creation, may have a link to autoimmune disease, opening up a new avenue of study and potential for therapeutics. Research is underway.

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Mouse Models Advance Lupus Research

Sweasy's lab has developed mouse models based on human lupus to understand the disease at a molecular level. By introducing different DNA repair gene variants into these models, her team can study how these changes affect the immune system. This research provides a unique opportunity to accelerate mechanistic studies of lupus by:

- Allowing in-depth investigation of different genetic variants at the same time.
- Enabling comparative analysis of lupus development across multiple models.
- Reducing time and resources typically spent searching for promising mouse models.
- Providing a broader range of genetic contexts to understand how lupus develops.
- Focusing research on the specific mechanisms driving lupus symptoms in each variant.

Sweasy's team is using their mouse models to conduct detailed genomic characterization and immune profiling, and to explore DNA repair mechanisms. The wide range of symptoms between models offers insights into how different genetic variants contribute to lupus development in different ways.

Research Challenges and Solutions

Challenge:
Sweasy's 2014 experiments breeding mice to develop cancer instead results in mice with no cancer, but lupus-like skin lesions and organ damage.

Solution:
Following the advice of her graduate and doctoral mentors, Sweasy "followed her nose" and transitioned from studying how faulty DNA repair affects cancer to how it affects autoimmunity.

Challenge:
Sweasy's research into lupus demanded more genetics knowledge than her background provided.

Solution:
Sweasy began collaborating with geneticist and rheumatologist Lindsey A. Criswell, M.D., M.P.H., D.Sc., now the director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Criswell's lab identified variants in multiple genes associated with DNA repair that commonly occur in people with lupus, providing Sweasy target genes to investigate.

Occupational Exposures May Increase Lupus Risk

NIEHS-funded researchers study how the chemicals people are exposed to in the workplace may affect their risk of developing lupus. For example, exposure to agricultural pesticides, silica dust, and some industrial solvents have been linked to an increased risk of lupus.[9]

- **Pesticides:** In a study of licensed pesticide applicators and their spouses, participants who used the herbicide metribuzin or who applied pesticides at least 20 days per year had increased risk of developing lupus.[10]
- **Silica dust:** Workers in the mining, construction, farming, and manufacturing industries may be exposed to silica dust, which is linked to lupus and other diseases.[11] One study found that exposure to medium or high levels of silica dust at work was associated with a threefold increased risk of lupus.[12] Importantly, dietary supplementation with docosahexaenoic acid — an omega-3 fatty acid found in salmon and some other fish — reduced lung inflammation and other biological changes associated with silica-induced lupus, offering a promising intervention for the disease.[13]
- **Industrial solvents:** Trichloroethylene (TCE) is widely used as an industrial solvent for metal degreasing. In studies using mice, exposure to TCE was associated with key processes driving lupus development, such as inducing oxidative stress and increasing autoimmune response.[14] Treatment with an antioxidant that naturally occurs in cruciferous vegetables, like broccoli, reduced TCE-induced immune responses, pointing to a potential therapy for lupus.[15]