A Method for Treating and Diagnosing Autoimmune Disease Exacerbated by Host Immune Response to Commensal Bacteria

An innovative strategy for better diagnosing and safely treating Systemic Lupus Erythematosus, particularly Lupus Nephritis.

Technology

The Silverman Lab at NYU Langone Health has identified a novel contribution of a commensal bacterial species, and developed a novel approach to safely diagnose Systemic Lupus Erythematosus (SLE), particularly Lupus Nephritis (LN), that is a severe and debilitating kidney complication. Additionally, the researchers have developed a groundbreaking approach to use this diagnostic data to treat LN by targeting the elevated levels of the responsible gut microbe. This approach provides new ways for the diagnosis and treatment of this serious and often life-threatening autoimmune disease.

Some commensal species have been implicated in the pathogenesis of inflammatory and autoimmune diseases. Therefore, the Silverman lab investigated whether Lupus patients have disease-associated gut expansions of certain bacteria. Comparison of fecal samples from SLE patients in different disease stages revealed that individuals with high-disease activity have lower diversity of bacterial species in their gut compared to low-disease activity patients and healthy people. Comparisons of bacterial taxa from SLE patients, as well as data from lupus renal disease patients, found that the gut species *Ruminococcus gnavus* is elevated. They invented a means to measure the serum antibodies that recognize these bacteria, and discovered that the serum from many SLE patients had much higher IgG anti-*R. gnavus* activity than healthy individuals. High-disease activity patients had higher specific antibody responses than in patients with low disease activity. These responses are specific to a unique lipoglycan bacterial antigen that they discovered acts *in vivo* as a toxin.

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- The Silverman group has found a strong correlation between *R. gnavus* gut blooms in LN patients and a host immune gene expression pattern that has not been previously linked to this disease process.
- The Silverman group has developed a biomarker-based method to assess the elevated risk of many lupus patients developing LN or other renal complications of SLE, leveraging the role of *R. gnavus* lipoglycan in vascular and innate immune system profiles. This is not found in other forms of renal disease.
- For potential use as a therapeutic (either protein-based or vaccine) or as part of a diagnostic, the Silverman group has developed a set of monoclonal antibodies against the *R. gnavus* lipoglycan. In this species, the lipoglycan is attached to the bacterial cell wall and is believed to be secreted, where it interacts with the immune system and the kidneys, leading to lupus disease exacerbation.

Background

Systemic Lupus Erythematosus (SLE) is a severe autoimmune disease in which the body attacks healthy cells. Some SLE symptoms may include skin rashes, arthritis, nerve problems, and inflammation of the heart and lungs. A common lupus complication is kidney disease, also known as lupus nephritis (LN), which can be life-threatening and often causes renal failure. In most cases, diagnosis of LN requires a renal biopsy, which is an invasive procedure associated with defined morbidity and complications. The majority of current therapies for SLE are drugs that suppress the immune system, making the human body more susceptible to infections. Additionally, these therapies have many side effects.

Applications

- Diagnosing and stratifying SLE, LN, and other autoimmune diseases.
  - These data can be used to stratify patients with suspected lupus or immune renal disease, based on their gut microbiome, and determine whether they are in the high disease activity lupus group (as symptoms are varied), and are high-risk for kidney problems.
  - The disease-associated bacteria can be targeted with antibacterial drugs to selectively reduce or eliminate the harmful species.
  - These methods may identify patients who are non-responders to therapeutic interventions due to continued innate immune stimulation from the microbiome.
  - Early, accurate, and safe diagnosis of SLE, LN, and other autoimmune diseases contributes to improved patient outcomes.

Advantages

- **Safer Diagnosis of LN:** The biomarker-based diagnostic method offers a noninvasive alternative to the traditional renal biopsy, which is typically required to diagnose LN but is associated with significant morbidity.
- **Reduced susceptibility to opportunistic infections:** A targeted approach to reduce the amount of *R. gnavus* in the gut with antibacterial agents lowers the risk of opportunistic infection, unlike many current SLE drugs.
- **Specific treatment with fewer side effects:** The disease-causing lipoglycan product of *R. gnavus* can be targeted using small-molecule or biologic approaches.

Intellectual Property

- Issued U.S. patent on method and compositions for treating and diagnosing autoimmune diseases (NYU Ref. SIL02-05US) that includes detection of lipoglycan antibodies.
- Pending U.S. non-provisional application on anti-lipoglycan antibodies (NYU Ref. SIL02-10US).
- Pending PCT application on gene signatures associated with microbial blooms in SLE and LN patients (NYU Ref. SIL02-12PCT).
- Pending provisional application on biomarker-based diagnostics (NYU Ref. SIL02-15PRO).

References

1. Gregg Silverman, MD, et al. , https://pubmed.ncbi.nlm.nih.gov/30782585/