Complementary medicine: The hunt for lupus biomarkers

Systemic lupus erythematosus (SLE) is an autoimmune disorder sometimes referred to simply as lupus. SLE can affect numerous organs, resulting in a confusing constellation of signs and symptoms including rash, joint pain, chest pain, hair loss, sun sensitivity, cognitive dysfunction, and renal failure. Consequently, patients are often misdiagnosed initially, leading to a delay of the correct diagnosis of up to five years after onset of symptoms on average.

Lupus affects approximately 1 in 1,000 people in the UK, and approximately five million people worldwide. The disease tends to disproportionately affect women and is more likely to be diagnosed in people of colour, with most cases spotted in early to mid-adulthood. At present, there is no cure for lupus and most patients are required to take immunosuppressive medications to counteract inflammation and manage symptoms. Symptoms of SLE can be distressing and can take a toll on a patient’s quality of life.

The immune system protects the body’s tissue by attacking foreign pathogens. In the case of autoimmune disorders such as SLE, the immune system attacks the patient’s own tissue, for reasons that remain largely unknown. Inflammation is a key weapon in the immune system’s arsenal, but when inflammation occurs chronically as a result of a long-term attack on healthy tissue, as in SLE, this can cause substantial damage.

In severe cases, inflammation as a result of SLE can interfere with the function of major organs including the kidneys, heart, and brain, causing a serious threat to life. A key characteristic of the disease, however, is its heterogeneity and patients present with tremendous clinical diversity. This heterogeneity has made it difficult to develop treatments that are suitable for all patients. Heterogeneity has also made it more difficult for researchers to characterise the mechanisms that underpin disease, causing SLE to remain poorly understood.

FLARE-UPS

Patients with SLE tend to experience symptoms in bouts, with its effects often remitting for many months. Flare-ups can vary in length, but their onset can be very unpredictable with triggers for flares remaining largely unknown. Detecting these stages of active disease are key to effectively managing symptoms, thus improving a patient’s quality of life and survival. Accurately pinpointing disease activity with tests utilising biomarkers – biological flags, such as a change in protein level or gene that specifically associates with disease pathophysiology – is key to ensuring the best outcomes for patients. Existing biomarkers available for SLE, however, lack sufficient specificity or sensitivity, making it difficult for clinicians to correctly associate the patient’s clinical presentation with SLE versus an alternative etiology.

The lack of sensitivity also impedes the interpretation of clinical trials, which are vital to finding much-needed treatments for patients. Biomarkers are essential to these studies as they act as a measurable factor that changes in the presence of an intervention, offering researchers a way to determine if a therapy is efficacious.

One researcher dedicated to improving biomarkers for SLE is Dr Alfred Kim, Assistant Professor of Medicine and Pathology & Immunology at the Washington University School of Medicine in St. Louis, Missouri. Dr Kim, who is also founder and co-director of the Lupus Clinic at Washington University, is working with collaborators to embark on the CASTLE trial – Complement Activation Signature Tunes in Systemic Lupus Erythematosus. The team aims to identify better biomarkers and nail down the role of key mechanisms that are central to the disease. They have fixed their sights on the complement system, a vital part of the immune system that could hold the key to effective biomarkers, and therefore better care for patients living with SLE.

COMPLEMENT SYSTEM

The complement system is an integral part of the innate immune system and its activation is a core hallmark of SLE. In SLE, the complement system is activated by autoantibodies bound to the patients’ cells, leading to inflammation that can cause tissue damage. Serum measures of complement components, known as C3 and C4, are currently used to detect disease activity as levels of both of these factors fall as the complement system is activated. However, these tests can be inaccurate as the genetic make-up of some patients can lead to lowered levels of C4. Furthermore, the liver generates higher levels of C3 and C4 during systemic inflammation as occurs in SLE, potentially masking low concentrations of these proteins.

Kim has teamed up with colleagues from Washington University, Saint Louis University and Stanford to use an innovative testing platform to understand more about the complexities of complement activation in SLE. Their aim is to fully delineate the numerous fragments that result from complement activation and that are found in patient immune cells and in blood. By characterising complement fragments that promote inflammation, the team hopes to create better measures of disease activity, which could lead to better outcomes for patients and better-informed decision-making for clinical teams. Furthermore, by identifying the key complement fragments that denote disease activity, the team will make it more difficult for researchers to characterise the mechanisms that underpin disease, causing SLE to remain poorly understood.

The CASTLE pilot study has shown the potential of the complement split product, iC3b, as a new biomarker for disease activity.

Lupus is a clinically heterogeneous syndrome with over 50 signs and symptoms involving multiple organs that are commonly observed in patients.
The lateral flow assay (LFA) design uses matched pair antibodies to either iC3b or C3 to form an immunochromatography assay. The cassette contains an anti-iC3b or anti-C3 specific monoclonal antibody conjugated to colloidal gold, and the antigen-specific capture antibody bound to the membrane strip to form the solid-phase enzyme immunoassay. iC3b and C3 values determined with the LFA reader correlate highly with ELISA results.

Over the course of CASTLE, Kim and colleagues will work towards establishing the long-term relationships between iC3b, C3, the iC3b/C3 ratio, disease activity and clinical observations in SLE. Importantly, the pilot study utilised a novel investigational device that relies on a lateral flow assay, a simple paper-based test. The lateral flow assay (LFA) design uses matched pair antibodies to either iC3b or C3 to form an immunochromatography assay. The cassette contains an anti-iC3b or anti-C3 specific monoclonal antibody conjugated to colloidal gold, and the antigen-specific capture antibody bound to the membrane strip to form the solid-phase enzyme immunoassay. iC3b and C3 values determined with the LFA reader correlate highly with ELISA results.

By characterising complement fragments, the team hopes to create better measures of disease activity, leading to better outcomes for patients with SLE.

**References**


**Personal Response**

Do you think that by characterising the complement signature, the CASTLE trial could potentially identify new targets for drug development?

I do for two reasons. First, complement split products have the potential to serve as a more effective biomarker of SLE disease activity. This has important implications for SLE clinical trials, as current outcome measures still lack the precision we desire. Measuring complement split products may improve our ability to assess treatment efficacy. Second, we suspect that subsets of patients with SLE utilise different pathways to activate complement. By identifying the pathway(s) utilised, it can be blocked by novel therapies under development. Thus, we may be able to predict which patients will respond to a particular complement inhibitor, serving as an example of personalised medicine.