Plain language summary

What is the problem?

Systemic lupus erythematosus (lupus) is an autoimmune disease where the body begins to attack itself. People with lupus develop severe inflammation and tissue damage that affects many different organs and tissues throughout the body including the skin, joints, heart, kidney, nerves, and blood vessels. Over 20,000 Australians and 5 million people worldwide are estimated to be living with this disease. Despite recent advances in our understanding of what causes lupus and some improvement to available treatments, the prognosis for many patients remains poor and quality of life is severely impacted. Treatments for this disease can be ineffective, non-specific, have many serious side effects and can leave patients susceptible to life threatening infections. In fact, only two new drugs have been approved for lupus in the past 20 years and these new treatments unfortunately have limited use in the clinic as only a very small group of patients benefit from their use. Therefore, there is a need to identify new causes of this disease so we can develop new and better therapies to treat lupus.

Identification of a new population of disease-causing immune cells in lupus

One type of white blood cells thought to contribute to the inflammation and organ damage in lupus are neutrophils. Neutrophils are the most abundant immune cells in the blood and play an essential role in protecting the body against infection. On the other hand, hyperactive neutrophils can cause chronic inflammation and tissue damage in a range of autoimmune diseases. Indeed, recent research in both human patients and animal models of lupus have shown that neutrophils can release toxic molecules and signals that cause inflammation, organ, and tissue damage, all of which are associated with lupus. Importantly, while neutrophils were long considered to be a homogenous population of cells, there is compelling evidence that certain subsets of neutrophils are disease causing and can promote inflammation and tissue damage in human disease but are absent in healthy people.

Using advanced technologies, we were the first to identify a new neutrophil population that is present in the blood of lupus patients with active disease. These neutrophils can be identified by a protein on their cell surface called CD98. CD98 can transport a type of fuel called amino acids into cells, and these amino acids are then used by cells to generate energy.

Our idea

We propose that CD98 neutrophils cause inflammation and tissue damage in lupus and that targeting these disease-causing neutrophils could be a new way to treat this debilitating autoimmune disease. We will address our aims using blood collected from human lupus patient as well as from mouse models of lupus.

What did we discover?

Biomarkers are something that doctors can assess in patients that tells them how severe disease is, whether treatments are working, whether patients are in remission or are having a flare of symptoms. Biomarkers in lupus are severely lacking and this hinders the way doctors can properly manage these patients and impedes development of new therapeutics. Using funding from Arthritis Australia, we collected blood from human lupus patients and showed that CD98 neutrophil levels correlated with "disease activity" (Martin et al, 2023, Clinical and Translational Medicine). This means that patients with severe lupus symptoms had more of these neutrophils in the blood when compared to patients with mild disease and this population was completely undetectable in healthy people. This exciting finding suggests that the levels CD98 neutrophils could represent a "biomarker" to be used by doctors as a simple and effective test to help guide patient care or to assess whether treatments are working. In addition to showing that CD98 neutrophils correlate with the severity of lupus, we also show that they can cause an inflammatory response in patients. For example, we showed that CD98 neutrophils produce proinflammatory signals, release toxic molecules that cause cellular and tissue damage and are more metabolically active which enhances their ability to cause damage.

To understand exactly how CD98 neutrophils contribute to lupus and to determine if targeting this population could be new way to treat this autoimmune disease, we turned to a mouse model that develops many of the same clinical features as human lupus. These mice develop systemic inflammation, produce of self-targeting proteins called autoantibodies and show damage to organs such as the kidney. These mice develop mild lupus symptoms at 24 weeks of age and show severe signs of disease at 36 weeks of age. Given that in human disease, CD98 neutrophils are found in patients with lupus but not in healthy people, we asked the

question of whether these cells were also found in the mouse model of lupus. We looked at mice with no disease symptoms (12 weeks of age), mild (24 weeks of age) or severe symptoms (36 weeks of age) and compared them to normal mice. In these experiments, we found that before disease developed (12 weeks), the lupus mice had equivalent levels of CD98 neutrophils as normal healthy mice. Similar to human patients, lupus mice with mild or severe disease symptoms had a large increase in the number of CD98 neutrophils in their blood compared to normal healthy mice. This indicated that CD98 neutrophils are behaving similarly in the lupus mouse model as they are in human patients and means we can use these mice better understand the role these neutrophils playing in disease and find ways to target them and limit their disease causing capacity.

Where to next?

We have strong evidence to show that CD98 neutrophils contribute to lupus. We also have exciting data to show that if we target CD98 on this neutrophil population in a test tube we can limit the amount of damage they can cause. The next step of this project is to determine if targeting CD98 on the disease causing neutrophil population can prevent or treat lupus. To do this, we have used funds from Arthritis Australia to purchase genetically modified mice that do not have CD98 on the surface of the neutrophils. Our next step is to breed these mice with the lupus mice and determine whether absence of CD98 can limit the damage these neutrophils can cause and decrease the severity of lupus symptoms.

How will this benefit people with lupus?

Biomarkers represent an essential part of clinical practice and are used in almost every step of patient care. Biomarkers that predict disease outcomes, remission, and long-term adverse events in lupus are severely lacking and this hinders the way doctors can properly manage these patients and impedes development of new therapeutics. We have developed an easy and simply test clinicians can use to guide the way they treat patients. Furthermore, we are providing the proof-of-concept evidence that CD98 on these disease causing neutrophils represents an exciting new therapeutic target to treat lupus.