Immune cell's role in lupus nephritis demonstrated

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National Institutes of Health scientists have discovered that the activation of immune cells called basophils causes kidney damage in a mouse model of lupus nephritis. These findings and the team's associated research in humans may lead to new treatments for this serious disease, a severe form of systemic lupus erythematosus (SLE) that affects the kidneys and is difficult to treat.

In earlier research, the team found that mice engineered to be deficient in a protein called Lyn kinase had exaggerated responses to allergens in early life and developed a lupus-nephritis-like disease in later life. This was determined by monitoring the increase of immunoglobulin E (IgE) responses to normally harmless substances. The new study, published online in Nature Medicine, demonstrates for the first time, in the context of this mouse model, how basophils activated by self-reactive IgE antibodies (antibodies that attack the self instead of germs) might contribute to the kidney damage associated with SLE.

Specifically, the team showed that self-reactive IgEs attached to the surface of basophils, causing them to home to the mouse's spleen and lymph nodes, where they promoted a cascade of cellular events that enhanced the production of more self-reactive antibodies. These antibodies are already known to cause kidney damage by binding with other proteins to form immune complexes that are deposited in the kidneys. Here, they caused inflammation, damage and progressive loss of kidney function.

Furthermore, the scientists demonstrated that inducing the absence of self-reactive IgEs or depleting the population of basophils relieved many of the kidney disease features seen in the mouse model.

To explore the implications of their results in humans, the scientists examined blood samples from 44 people with SLE and found the presence of self-reactive IgEs, as well as an increase in activated basophils, features not seen in healthy controls. Both factors were strongly associated with disease activity and lupus nephritis in the people with SLE, suggesting a potential therapeutic benefit in reducing the levels of self-reactive IgE or of activated basophils.

One such potential treatment, the asthma medicine omalizumab, is already on the market. It blocks IgE from binding to the surface, and potential activation, of basophil cells, which might prevent basophils from promoting kidney inflammation. The NIH team is currently planning a safety study of omalizumab in people with SLE.

"We are excited by the potential of these findings in the treatment of lupus. Obviously, whether omalizumab treatment or other strategies to reduce basophil activation in lupus will prove efficacious remains to be seen. Nonetheless, this work opens new avenues of investigation in lupus and, at the very least, we have gained an understanding of how autoantibody production is enhanced in this disease," said Juan Rivera, Ph.D., the study's senior author and deputy scientific director at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the NIH institute that conducted the study. Support for the effort was also provided by the National Institute of Dental and Craniofacial Research.

In addition to testing omalizumab's potential and safety for treating lupus nephritis, Rivera says the group's future research will explore other ways that IgEs can be prevented from binding with basophils. They will also

attempt to determine whether or not depleting or inactivating the basophil population might reduce the production of self-reactive antibodies that can lead to kidney damage in SLE.

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