Mouse study points way to shut down harmful immune response in lupus

17 August 2016

Molecules that scavenge debris from dying cells appear to halt the cycle of chronic inflammation in lupus, while also enhancing the body's ability to combat flu, according to Duke Health studies in mice.

The molecules, called polymers, have commonly been used in gene-transfer experiments because they bind to the nucleic acid in DNA and RNA. When deployed directly in mice with lupus or an acute flu infection, the polymers home in on the DNA and RNA refuse from dying cells, halting the damaging immune attack.

"This debris left by dead cells can mistakenly signal to the body that there is an infection that warrants immune action, triggering the innate immune system," said Bruce A. Sullenger, Ph.D., director of the Duke Translational Research Institute. Sullenger is senior author of a study published online this week in the *Proceedings of the National Academy of Sciences*.

"By selectively targeting the source of the immune activation rather than shutting off the innate immune system downstream, these nucleic acid scavengers are able to limit pathological inflammation without compromising one's ability to fight a viral infection," Sullenger said.

Pathological inflammation, a major cause of illness and death around the world, is a hallmark of autoimmune diseases, including lupus and diabetes, as well as chronic conditions such as heart disease and some cancers. It also fuels the organ failure associated with severe infectious diseases such as Ebola or even flu.

Current therapies to treat pathological inflammation generally focus on quieting the overactive immune response, but in suppressing the immune system, patients are vulnerable to severe infections arising from other sources.

Intrigued by the ability of certain polymers to mop up DNA and RNA for gene transfer, Sullenger and colleagues tested the idea that these chemical compounds might also be effective targeting such nucleic acids as they arise in cell death.

"Essentially what you have in an autoimmune disease is a vicious cycle," said lead author Eda K. Holl, Ph.D., assistant professor in Duke's Department of Surgery. "Our goal was to break this cycle at its onset. What we saw in animals with lupus when we used these compounds was a dramatic reduction in inflammation, which gave the body a chance to heal."

Sullenger and Holl said the approach was further tested to see if it compromised the mice's ability to fight outside infections. When they exposed the treated mice to the influenza virus, the animals recovered from the illness even better than healthy mice infected with flu that had not undergone the treatment.

"This approach has the potential to treat a wide range of inflammatory conditions —from lupus to diabetes to even obesity," Sullenger said.

He said the research team is continuing studies in animal models and working to start a company to develop and commercialize the scavenger approach.

More information: Eda K. Holl et al. Scavenging nucleic acid debris to combat autoimmunity and infectious disease, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1607011113

Provided by Duke University Medical Center