Engineers Build Nanostructures That Fight Inflammation

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Approach avoids side-effects of current anti-inflammatories in mouse study. Monoclonal antibody treatments offer significant benefit for those suffering a range of auto-immune disorders, but such biologicals often have side-effects. Now, engineers are building nanofiber-based treatments that stimulate the body to mount its own biological attack on immune disorders.

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Biological treatments for autoimmune diseases consist of monoclonal antibodies that search out and destroy factors in the immune system that mistakenly mount immune attacks against the body and cause serious, often chronic disorders including Crohn’s disease, rheumatoid arthritis, and psoriasis.

Graphic of the peptide nanofiber with attached pieces of C3dg and TNF that stimulate the immune system to make antibodies against TNF to block auto-immune diseases such as psoriasis.

One immune factor that is commonly overproduced in such diseases is tumor necrosis factor (TNF). Thus biological treatments consist of injections of monoclonal antibodies that bind to and rid the body of excess TNF. Unfortunately, in addition to side-effects, monoclonal antibody treatments can have varying degrees of effectiveness in different individuals. Finally, the monoclonal antibodies that attack TNF are eventually recognized by the immune system, which destroys them, making subsequent treatments ineffective. This is particularly

problematic when the disease is chronic and needs repeated treatment.

Bioengineers at the Pratt School of Engineering at Duke University set out to develop a new approach that has the advantages of consistent neutralization of TNF, without side-effects. Joel Collier, Ph.D., Professor of Biomedical Engineering and his graduate student, Kelly Hainline, carried out the study, which was funded by the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

The strategy involved building nanostructures on which they could chemically tether protein subunits that could stimulate the type of biological response necessary to sequester the disease-causing excess of TNF.

“With some 24 million Americans suffering from autoimmune diseases, there is a great clinical need to find effective treatments for these disorders that are less expensive and more effective than the existing treatments,” said David Rampulla, PhD, director of the Division of Discovery Science and Technology at the NIBIB. “Nanobiology is a promising approach to coaxing the body to mount its own immune response to fight these complex diseases. This work in mice is an elegant demonstration of potential therapies using cleverly designed and synthesized nanofibers.”

The Duke engineers used a chemical process called supramolecular self-assembly. It sounds complicated but it makes things simpler. The technique is used for making many copies of complex molecules with many different parts, with each part having a different function (supramolecular). The chemistry is cleverly designed so the added parts find each other and stick together spontaneously (self-assembly).

They made a nanostructure, called a nanofiber, with a central backbone of repeated units of a protein. That backbone was used to add on the parts that interact with the immune system—the business ends of the super molecule. One of the main business parts is a piece of TNF. The other business part was a piece of a protein that ramps up the immune system, called C3dg.

When they put the nanofiber into mice with psoriasis it worked as well as the gold-standard monoclonal antibody treatment. The nanofiber with the pieces of TNF caused the mouse immune system to make antibodies against TNF. They found that adding the C3dg enhanced the treatment because C3dg augments B cell responses, so that more TNF-neutralizing antibodies are produced. Even more surprisingly, they found that the C3dg component had anti-inflammatory properties by itself, a finding that they are exploring in follow-on studies.

Collier succinctly explains the strategy. “We’re using the nanomaterials to induce the body’s immune system to become an anti-inflammatory antibody factory. It’s essentially an anti-inflammatory vaccine.”

The team is continuing to study how their nanomedicines stimulate the immune system to optimize treatment and adapt the technique to treat other inflammatory diseases. They next plan to test the approach in a mouse model of rheumatoid arthritis.

“Eventually using this approach in patients would be a whole new way of treating inflammatory disease,” explains Collier. “Patients would need fewer doses than with the current monoclonal antibody treatments, and at less expense—which is critical for reaching all patients, especially those in underserved settings and communities.”

The study appears in the Proceedings of the National Academy of Science (1).

Read the original article on National Institute of Biomedical Imaging and Bioengineering (NIBIB).