Peptide hydrogels could help heal traumatic brain injuries

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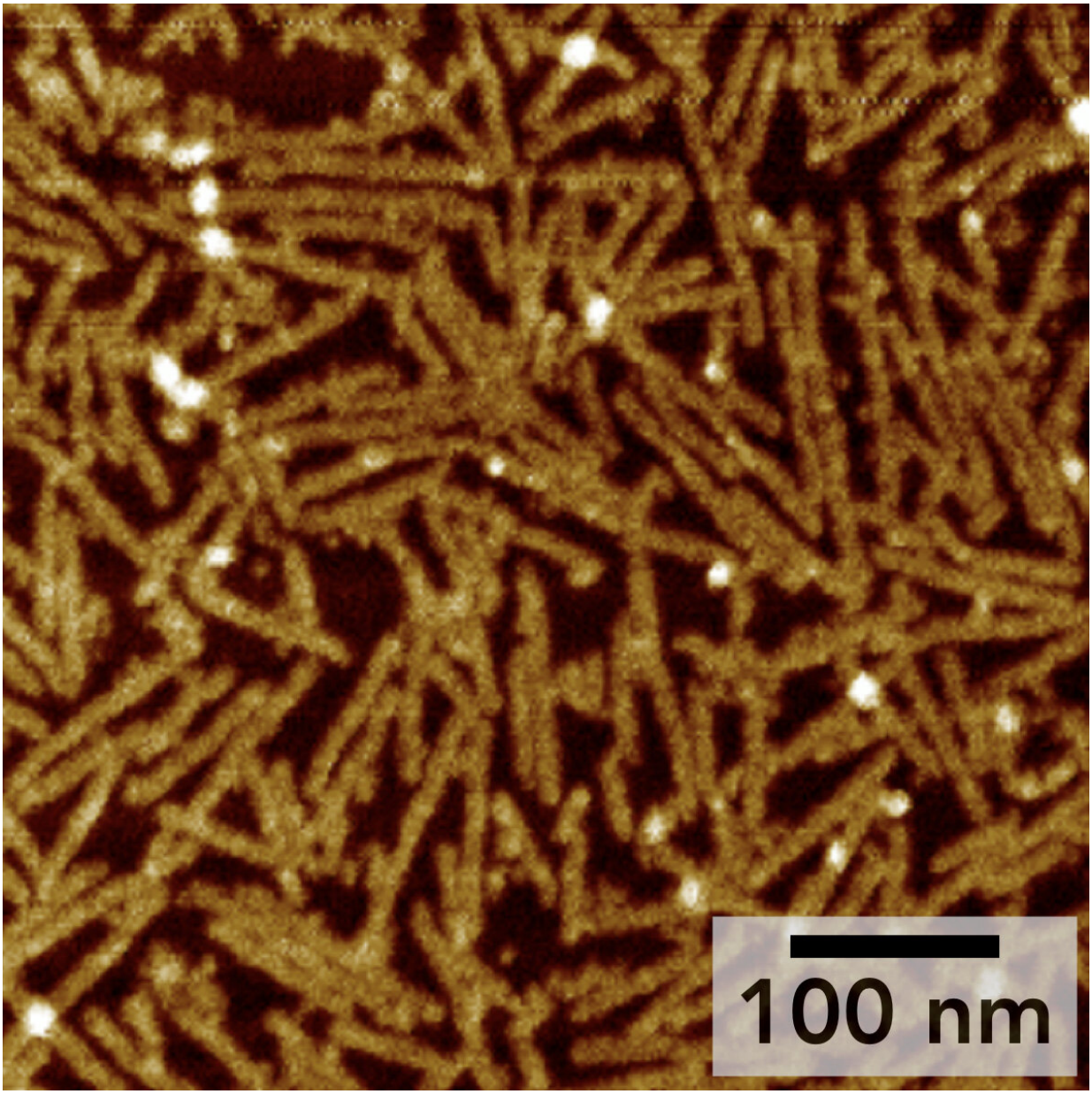

Self-assembled peptide nanofibers, shown here, form a hydrogel that improves survival of cortical neurons after a traumatic brain injury in rats. Credit: Biplab Sarkar and Vivek Kumar

Traumatic brain injury (TBI)—defined as a bump, blow or jolt to the head that disrupts normal brain function—sent 2.5 million people in the U.S. to the emergency room in 2014, according to statistics from the U.S. Centers for Disease Control and Prevention. Today, researchers report a self-assembling peptide hydrogel that, when injected into the brains of rats with TBI, increased blood vessel regrowth and neuronal survival.

The researchers will present their results at the American Chemical Society (ACS) Fall 2019 National Meeting & Exposition.

"When we think about traumatic brain injuries, we think of soldiers and athletes," says Biplab Sarkar, Ph.D., who is presenting the work at the meeting. "But most TBIs actually happen when people fall or are involved in motor vehicle accidents. As the average age of the country continues to rise, the number of fall-related accidents in particular will also increase."

TBIs encompass two types of injuries. Primary injury results from the initial mechanical damage to neurons and other cells in the brain, as well as blood vessels. Secondary injuries, which can occur seconds after the TBI and last for years, include oxidative stress, inflammation and disruption of the blood-brain barrier. "The secondary injury creates this neurotoxic environment that can lead to long-term cognitive effects," Sarkar says. For example, TBI survivors can experience impaired motor control and an increased rate of depression, he says. Currently, there is no effective regenerative treatment for TBIs.

Sarkar and Vivek Kumar, Ph.D., the project's principal investigator, wanted to develop a therapy that could help treat secondary injuries. "We wanted to be able to regrow new blood vessels in the area to restore oxygen exchange, which is reduced in patients with a TBI," Sarkar says. "Also, we wanted to create an environment where neurons can be supported and even thrive."

The researchers, both at the New Jersey Institute of Technology, had previously developed peptides that can self-assemble into hydrogels when injected into rodents. By incorporating snippets of particular protein sequences into the peptides, the team can give them different functions. For example, Sarkar and Kumar previously developed angiogenic peptide hydrogels that grow new blood vessels when injected under the skin of mice.

To adapt their technology to the brain, Sarkar and Kumar modified the peptide sequences to make the material properties of the hydrogel more closely resemble those of brain tissue, which is softer than most other tissues of the body. They also attached a sequence from a neuroprotective protein called ependymin. The researchers tested the new peptide hydrogel in a rat model of TBI. When injected at the injury site, the peptides self-assembled into a hydrogel that acted as a neuroprotective niche to which neurons could attach.

A week after injecting the hydrogel, the team examined the rats' brains. They found that in the presence of the hydrogel, survival of the brain cells dramatically improved, resulting in about twice as many neurons at the injury site in treated rats than in control animals with brain injury. In addition, the researchers saw signs of new blood vessel formation. "We saw some indications that the rats in the treated group were more ambulatory than those in the control group, but we need to do more experiments to actually quantify that," Sarkar says.

According to Kumar, one of the next steps will be to study the behavior of the treated animals to assess their functional recovery from TBI. The researchers are also interested in treating rats with a combination of their previous angiogenic peptide and their new neurogenic version to see if this could enhance recovery. And finally, they plan to find out if the peptide hydrogels work for more diffuse brain injuries, such as concussions. "We've seen that we can inject these materials into a defined injury and get good tissue regeneration, but we're also collaborating with different groups to find out if it could help with the types of injuries we see in soldiers, veterans and even people working at construction sites who experience blast injuries," Kumar says.

More information: Injectable neuroprotective peptide hydrogels, the American Chemical Society (ACS) Fall 2019 National Meeting & Exposition.

Abstract

The trauma caused by brain injury can lead to a pathologic cascade resulting in local inflammation and neuronal death. Current tissue engineering approaches have focused on developing implantable biomaterials that can stem the pathologic sequelae and aid in tissue regeneration in vivo. However, intricate surgical procedures involved in the implantation limit the potential of the therapeutic route. We report an injectable peptide-based hydrogel that can be injected intracranially in a non-invasive fashion into the injury site and demonstrate marked improvement in neuronal survival. The self-assembly of the peptide into nanofibers is mediated by non-covalent interactions among the peptide strands (hydrogen bonds, hydrophobic interaction, van der Waals interaction), and the nanofibers are ionically cross-linked into the bulk hydrogel. These underlying non-covalent bonds render the hydrogel sensitive to shear-thinning, however they can regain their elasticity almost immediately after a shearing event. Thus, the therapeutic hydrogel can be easily syringe-aspirated and injected directly into the

brain injury site. The peptide nanofibers were functionalized with a neuroprotective domain (ependymin mimic sequence) and have shown efficacy in an in vitro cortical neuron model. We used a fluid percussion injury (FPI) model in rodents and injected our beta-sheet-based nanofibrous hydrogels in situ, after the injury. We demonstrated therapeutic efficacy of the injected hydrogel through immunohistochemistry (VWF, alpha-SMA, NeuN, and myelin basic protein). Injectable peptide-based biomaterials may prove to be excellent tools to arrest and even reverse some of the pathological sequences after a traumatic brain injury.

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