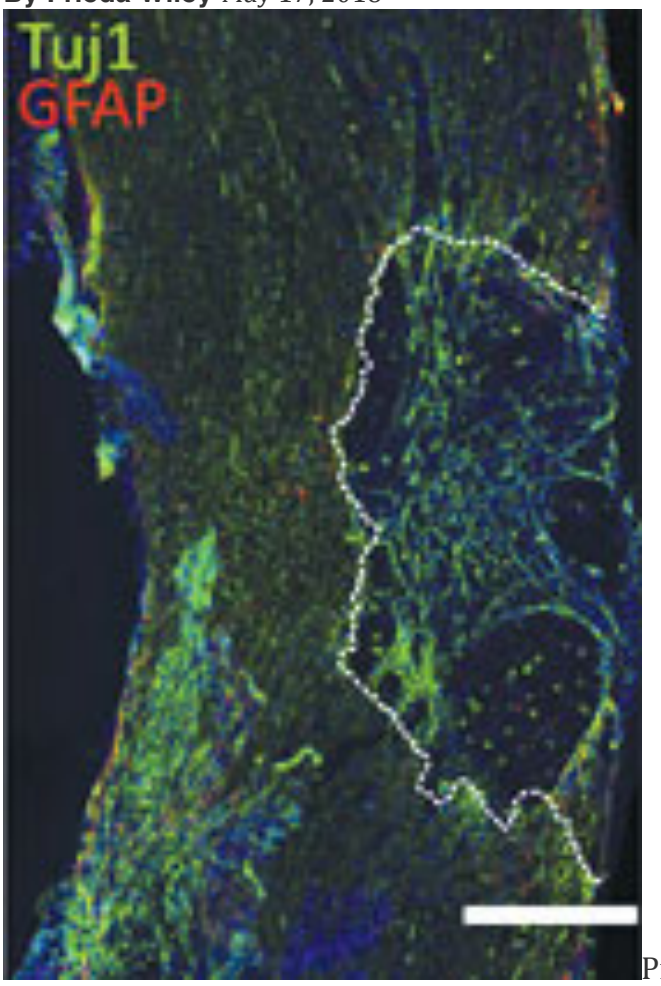
Biological, Biomedical, Biomaterials

Astrocyte-derived extracellular-matrix-containing hydrogel gives hope in spinal cord tissue injury

By Frieda Wiley May 17, 2018



Protoplasmic extracellular-matrix incorporation increases neural fiber staining within a spinal cord tissue lesion. The neurons are green; the dashed line denotes lesion boundary; and the scale bar is 500 μm. Credit: Biomaterials

Inhibition of tissue regeneration continues to present major challenges especially for spinal cord injuries (SCIs), often translating to poor outcomes for patients. However, recent research may carve a different path in regenerative medicine for SCIs. A group of researchers has recently discovered

that hydrogels containing an extracellular matrix derived from astrocytes—star-shaped cells of the central nervous system—reduced the size of scar tissue when introduced after spinal cord injury.

According to their study, published in a recent issue of *Biomaterials*, the previous discovery that astrocytes can take on inhibitory or pro-regenerative properties in rodents prompted further investigation. For example, a lipopolysaccharide-induced injury can yield a pro-inflammatory effect that results in inhibitory behavior by reactive astrocytes in which they change morphologically, express inflammatory protein markers, and induce inflammatory signaling cascades ; conversely, one cytokine (a protein), such as IL-10, encourages pro-regenerative activity.

Following trauma, glial cells—that surround neurons and provide support and insulation between them—actually form scars around spinal cord lesions and are one of the major factors that inhibit regeneration of spinal cord tissue. This occurs by the formation of a physical barrier by reactive astrocytes as well as proteoglycans (a protein compound) that inhibits astrocyte growth. Reactive astrocytes and proteoglycans also propagate the formation of biochemical barriers, which inhibit regeneration. Researchers are exploring the circumstances under which astrocytes engage in pro-regenerative activities.

“What makes the tissues young and why children’s repair easier than adults’ are the questions,” says Tatiana Segura, a professor in the Department of Biomedical Engineering at Duke University, who was not involved in this study. “Tissue, in general, change their composition in life, and you can see that the extracellular matrix (ECM) changes with time.”

Shelly Sakiyama-Elbert, professor of biomedical engineering at the University of Texas at Austin, and colleagues from the university, Washington University, and the University of Toronto, conducted two studies, the first exploring the effects of hyaluronic acid independent of other factors and the second study explored the effects of hyaluronic acid containing different combinations of the gel with other chemicals. In the first study, hyaluronic acid was injected into animals immediately following spinal cord injury. An acellular transplantation study, researchers partitioned rats into four groups: the sham implant, or placebo, group; those receiving hyaluronic acid (HA) alone; those receiving protoplasmic ECM (P-ECM); and those receiving fibrous ECM (F-ECM). Protoplasm is the colorless liquid that bathes the organelle of the cell. Fibrous ECM is ECM containing the fibrous proteins and proteoglycans that are bathed in the interstitial fluid between cells. In the second study, the investigators divided the animals into five groups: sham implant, HA-methylfuran alone, HA + P-ECM, HA + cells, and HA + P-ECM + cells.

Upon assessing motoneuron growth 48 hours after injection of the hydrogels, researchers noted that 1:25 F-ECM:HA and 1:100 and 1:25 P-ECM:HA gel concentrations yielded better, motoneuron neurite extension, or growth of the nerve cell projecting from the beyond the cell body, in comparison to HA gels that contained no ECM. Higher doses of ECM seemed to generate better neurite growth. P-ECM proved more potent than F-ECM. Delaying injection of P-ECM resulted in decreased activity.

It is important to note that in this study, the researchers resorted to using a crosslinked ECM that served as a scaffold because ECM harvested *in vitro* failed to form a hydrogel with sufficient crosslinking. To overcome this challenge, Sakiyama-Elbert’s group incorporated polyethylene glycol

(PEG) into the ECM to achieve crosslinking. Like HA, PEG is not a pro-inflammatory moiety. Also of interest was the potential immunogenicity of the murine-derived ECM, which produced negligible immunogenic response, suggesting utilization of tissue from a different animal species may not produce an inflammatory response in which the body rejects foreign tissue.

Additionally, researchers investigated the degree by which HA hydrogels retained ECM *in vivo* and *in vitro* by using antibodies against collagen XIIαI, the most abundant protein contained within the ECM. They assayed collagen XIIαI to determine whether P-ECM was still present two weeks post-SCI implantation. The investigators not only found collagen XIIαI aggregates in animals treated with HA-alone gels, they also detected some diffuse collagen XIIαI after staining in HA alone and P-ECM:HA gels, which demonstrates that some native cells found in the SCI lesion must engage in collagen XIIαI production.

“These studies are proof of concept to show that cells survive,” says Sakiyama-Elbert.

The findings of this research suggest the need for long-term studies investigating the regenerative properties of HA hydrogels containing astrocyte-derived ECM.

Read the abstract in *Biomaterials*.