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Evaluation of In Situ Gelling Chitosan-PEG Copolymer For Use in the Spinal Cord

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Purpose

To combat syringomyelia, new therapies are needed. An ideal treatment would involve a biomaterial vehicle delivering a drug or protein, over an extended period of time, aimed at combating specific cell processes to alleviate or treat symptoms. The first step in this process is to find the delivery vehicle before adding drug delivery. The ideal material delivery system should gel in the native environment and remain in place, induce minimal inflammation, match the tissue mechanical properties, release its treatment in an appropriate time-frame, and resorb over time so that native tissue can replace the cavity. The goal of the present work was to characterize a hydrogel material for localized spinal cord delivery.

Methods

An injectable in situ gelling system was tested utilizing a simple, effective, and rapid cross-linking method via Michael addition. Thiolated chitosan material and maleimide-terminated PEG material were mixed to form a hydrogel and evaluated in vitro and in vivo. Three distinct thiolated chitosan precursors were made by varying reaction conditions, with the most promising selected for animal study. After confirming low cellular toxicity in vitro, the hydrogel was injected into the spinal cord of rats for one or two weeks to assess host reaction.

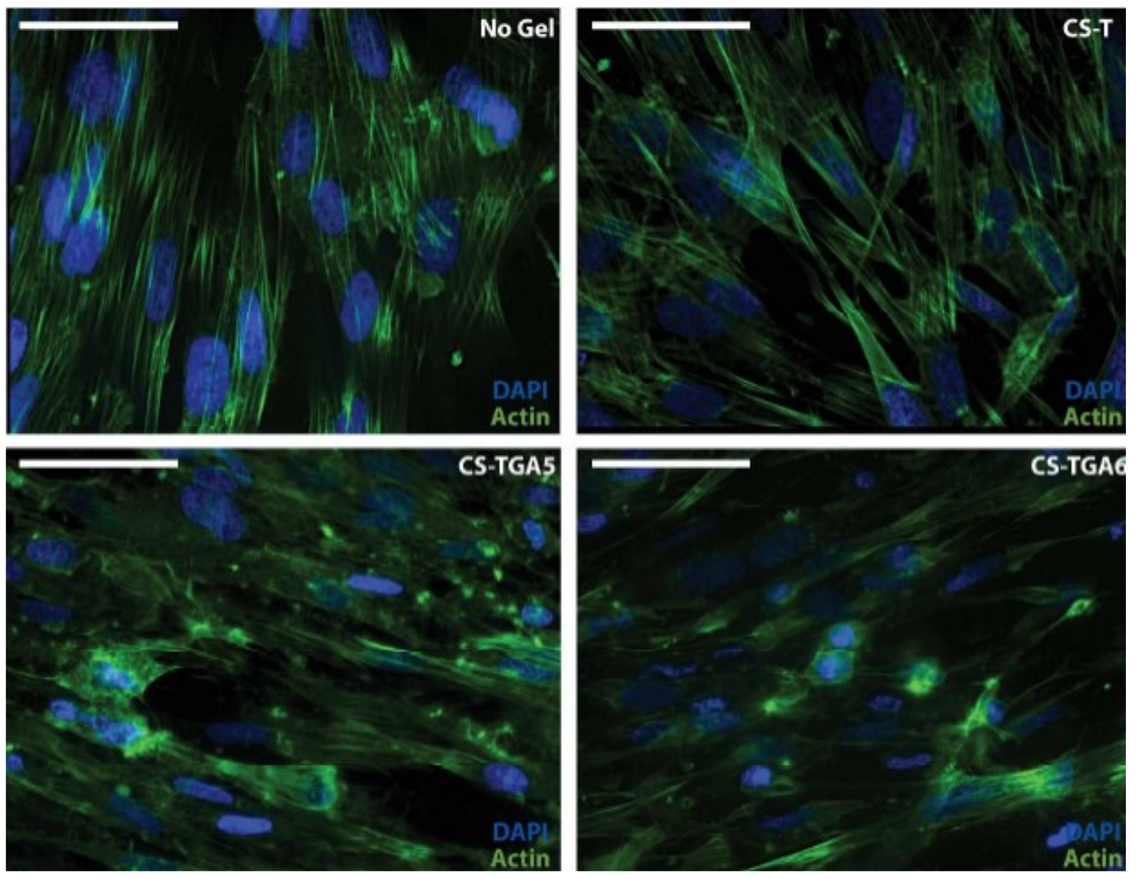
Results

The rats displayed no functional signs of injection following initial surgical recovery and throughout the 2 week period after for both the saline injected group and hydrogel injected group. The saline and hydrogel injected animals both showed a similar response from ED1+ microglia and GFAP expression. No significant differences were found between saline injected and hydrogel injected groups for any of the measures studied.

Conclusions

An in situ cross-linking hydrogel was successfully synthesized and characterized in this study. The hydrogel had appropriate mechanical properties for the CNS including a low complex modulus with high elasticity, and minimal threat of swelling damage. The material was non-toxic to fibroblasts in vitro and showed a similar muted host response to a saline sham group when injected directly in the spinal cord of rats. Taken together, we believe the chitosan-PEG copolymer may be an appropriate base biomaterial for future injectable spinal cord delivery strategies. Further testing is needed to evaluate its use in an injured spinal cord.

Images of fibroblasts during test, comparing control wells with wells containing gels.



Representative images from saline injected (A, B) and CS-T injected (C, D) spinal cord samples at one week post-surgery. In part C, a representative three dimensional rendering from µCT data shows the hydrogel (arrow) within the spinal column, slightly caudal to the injection site. WM: white matter; GM: grey matter.