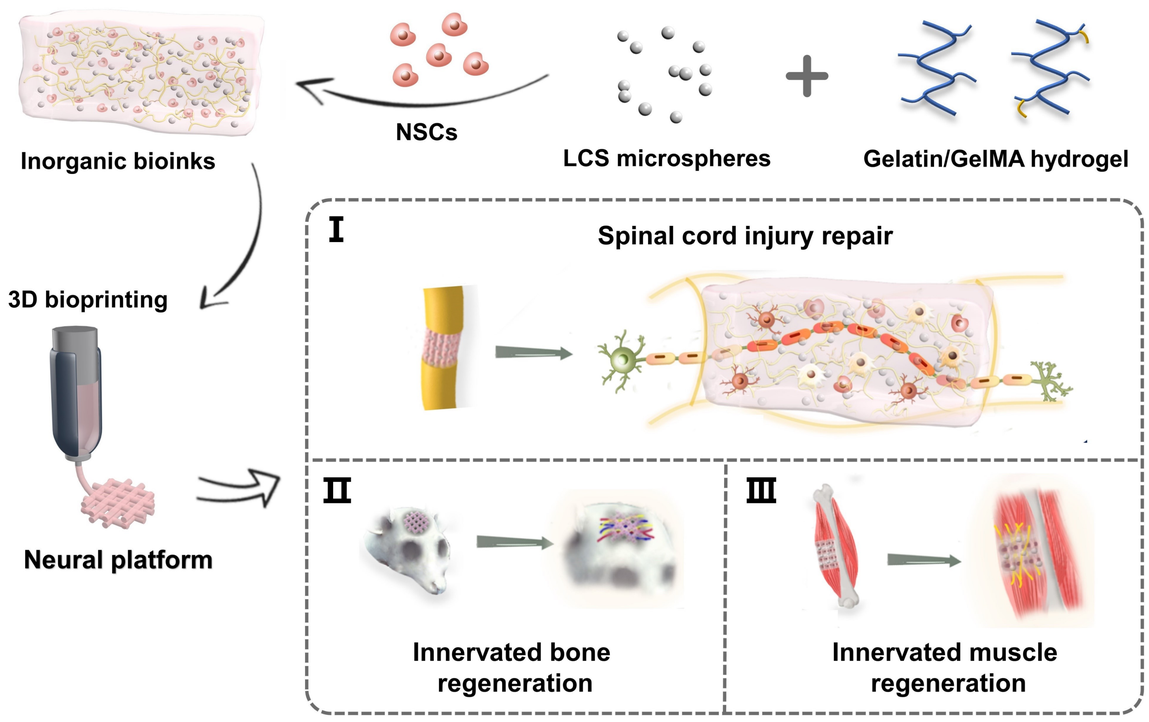
Inorganic biomaterials inducing innervated multi-tissue regeneration

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Introduction

Nervous system acts as a commander, orchestrating the homeostasis, physiological functions and regeneration of multiple tissues/organs. Herein, from the perspective of neural induction, we propose a new generation of engineered neural constructs for multiple tissue regeneration. Neural constructs consist of Li-Ca-Si (LCS) bioceramic and neural stem cells (NSCs), exhibited suitable neural activities. Animal experiments showed that neural constructs could act as a versatile platform for repairing central nervous system injuries with functions recovery, as well as promoting bone and skeletal muscles regeneration. These findings suggest that the inorganic-biomaterial/NSCs-based neural platform represents a promising avenue for inducing the regeneration and function recovery of varying tissues and organs.



Scheme. Schematic illustration of the preparation and application of inorganic biomaterials based neural constructs.

Results---1

LCS bioceramic act as an inorganic bioactive agents, which could build a beneficial ionic microenvironment through sustained release of bioactive Li, Ca and Si ions, thereby inducing the neuronal differentiation and maturation of encapsulated NSCs via activating PI3K-AKT signal pathway.

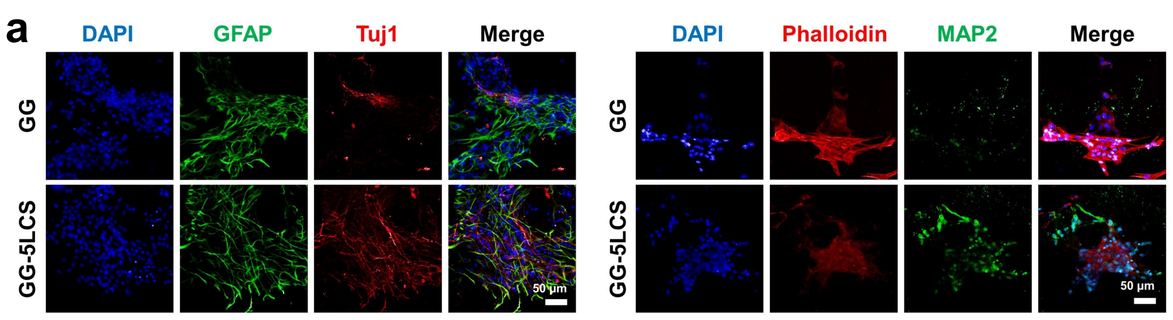


Fig. 1. (a) Representative immunofluorescence staining images of GFAP, Tuj1 and MAP2 of NSCs within GG and GG-5LCS constructs. (b) Western blot analysis of proteins expression related to PI3K-Akt signaling pathway and neuronal differentiation. (c) Schematic illustration of the potential underlying mechanism of LCS microspheres inducing the neuronal differentiation of NSCs within bioprinted constructs.

Results---2

Neural constructs were implanted into the defects of spinal cord injury to evaluate its capacity of repairing neural tissues. The results showed that neural constructs obviously induced neural regeneration, decreased glial scars formation, and angiogenesis, thereby recover its locomotor functions.

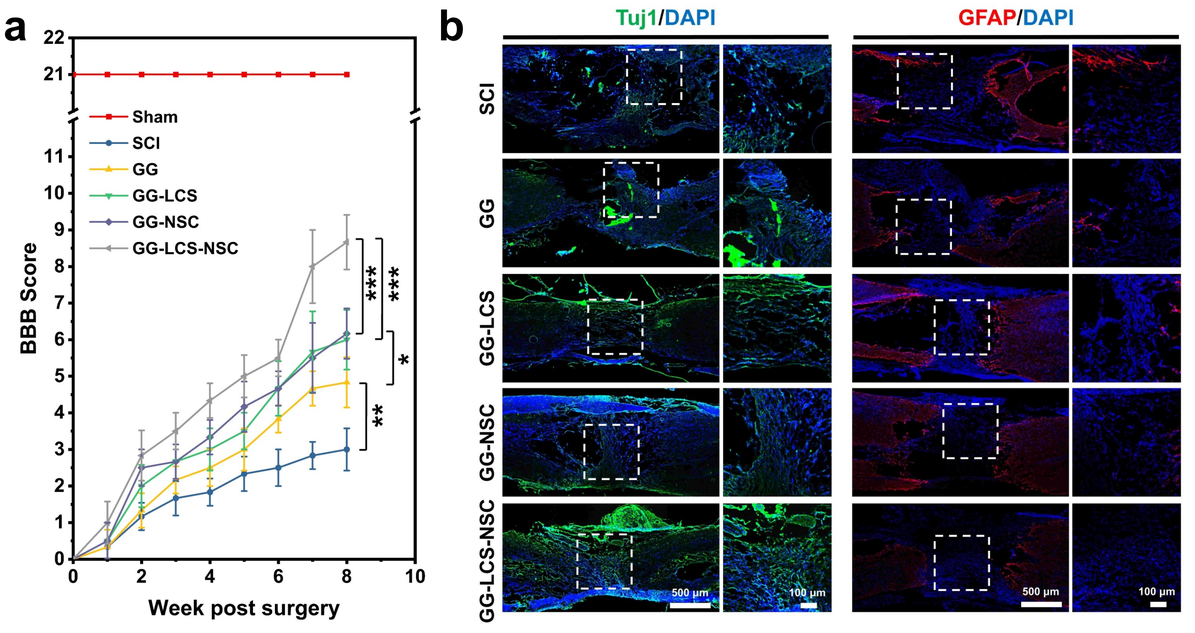


Fig. 2. (a) The BBB score of SCI rats in total 8 weeks of treatment. (b) Representative immunofluorescence staining images of Tuj1 and GFAP of the longitudinal sections of spinal cords.

Results---3

Neural constructs were implanted into the critical bone and skeletal muscle defects to evaluate its capacity of repairing nerve-innervated tissues. The results showed that neural constructs obviously induced neuro-vascularized bone regeneration, and regenerated the skeletal muscles with neural integration and vascularization.

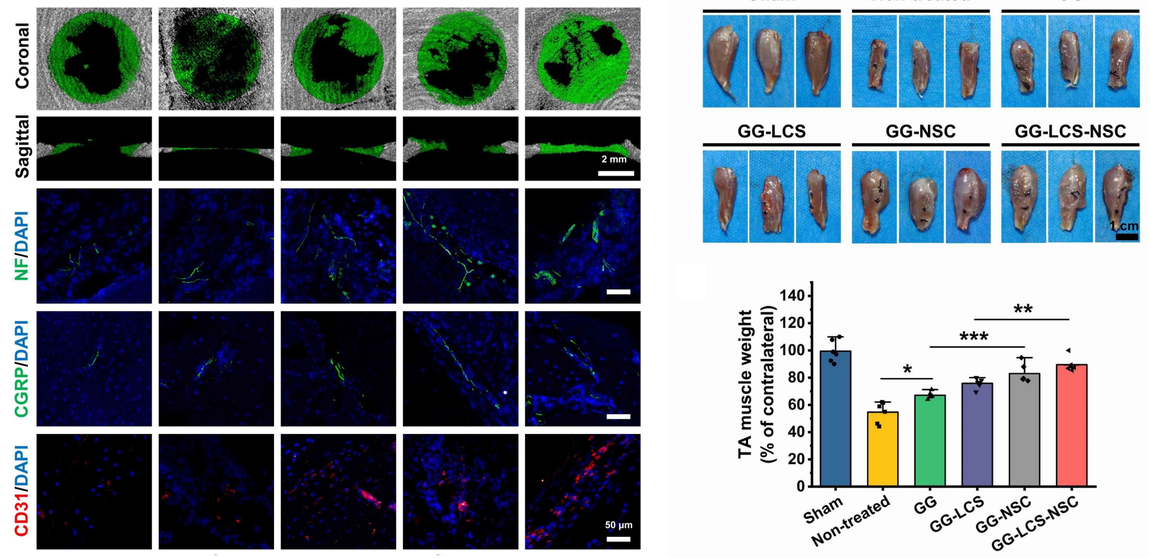


Fig. 3. (a) Representative micro-CT reconstruction images and immunofluorescence staining images of NF, CGRP and CD31. (b) Optical images and weight of retrieved TA muscles after 8 weeks of implantation.

Conclusions

An inorganic biomaterial/NSCs-based neural construct prepared by 3D bioprinting technology could act as a versatile platform for promoting multiple tissue regeneration with functional recovery including spinal cord, bone and muscles. This study provide a new way of thinking and a new approach to promoting tissue regeneration from the point of view of neural modulation, which will shed light on biomaterials design for regenerative medicine.

References

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