Injectable stem cell assembly for cartilage regeneration

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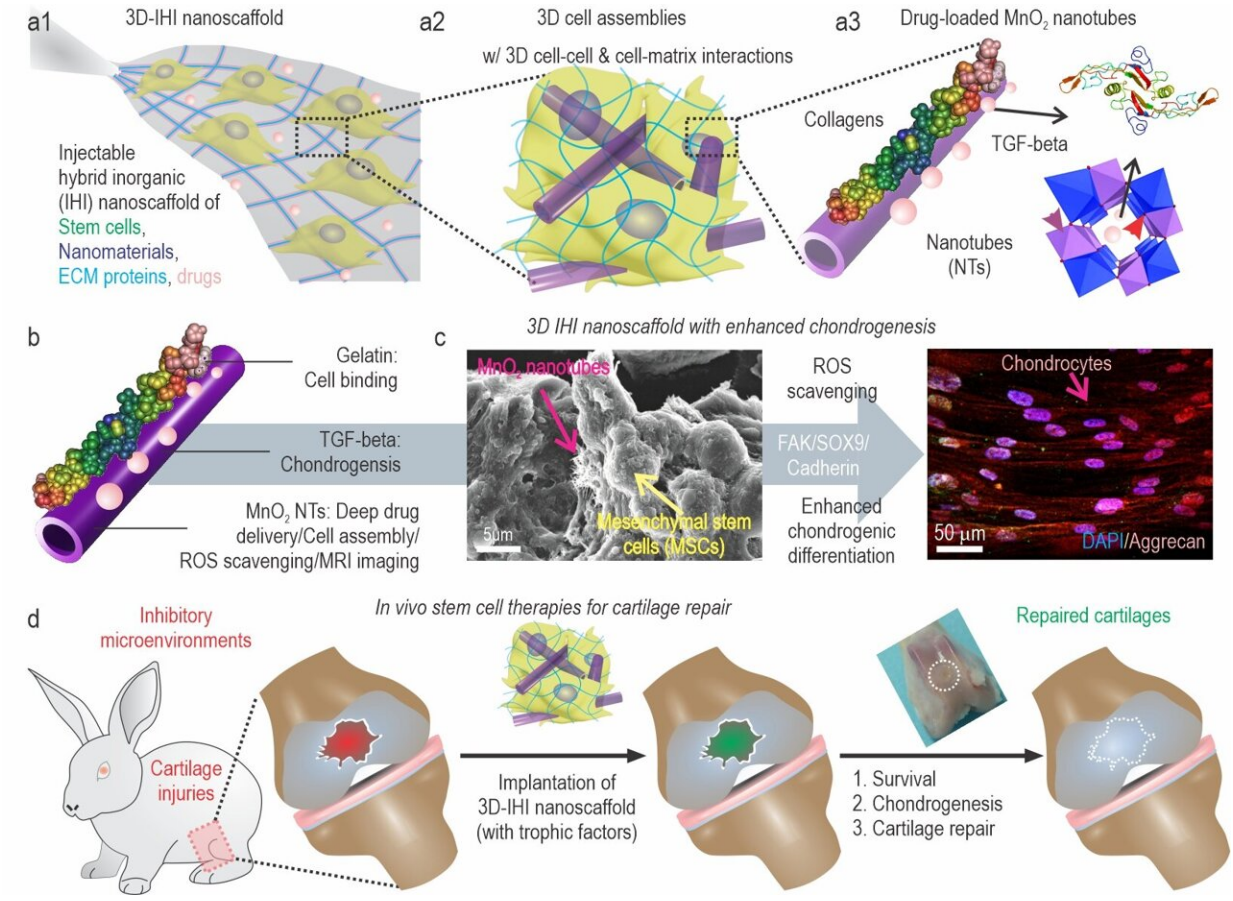


a) A schematic illustration of 3D TGFβ-BMSC-IHI nanoscaffold. b) The schematic illustration of gelatin-coated and TGF-β3-loaded MnO_2 NTs. c) The FESEM image indicated that most of the BMSCs form contacts with other cells and the 1D fibril-like structures, which was similar to the structures of natural tissues. d) By remodeling the oxidative microenvironment, enhancing cell viability, and chondrogenesis of transplanted cells, cartilage regeneration could be finally achieved. Credit: Science China Press

A study led by Prof. Qiuyu Zhang (Northwestern Polytechnical University), Prof. Ki-Bum Lee (Rutgers University), and Prof. Liang Kong (School of Stomatology, The Fourth Military Medical University) has established an injectable hybrid inorganic (IHI) nanoscaffold-templated stem cell assembly and applied it to the regeneration of critically-sized cartilage defects.

Cartilage injuries are often devastating and most of them have no cures due to the intrinsically low regeneration capacity of cartilage tissues. The rise of 3D stem cell culture systems has led to breakthroughs in developmental biology, disease modeling, and regenerative medicine. For example, stem cells, once transplanted successfully, could initially secret trophic factors for reducing inflammation at sites of cartilage injuries and then differentiate into cartilage cells (e.g., chondrocytes) for functional restoration.

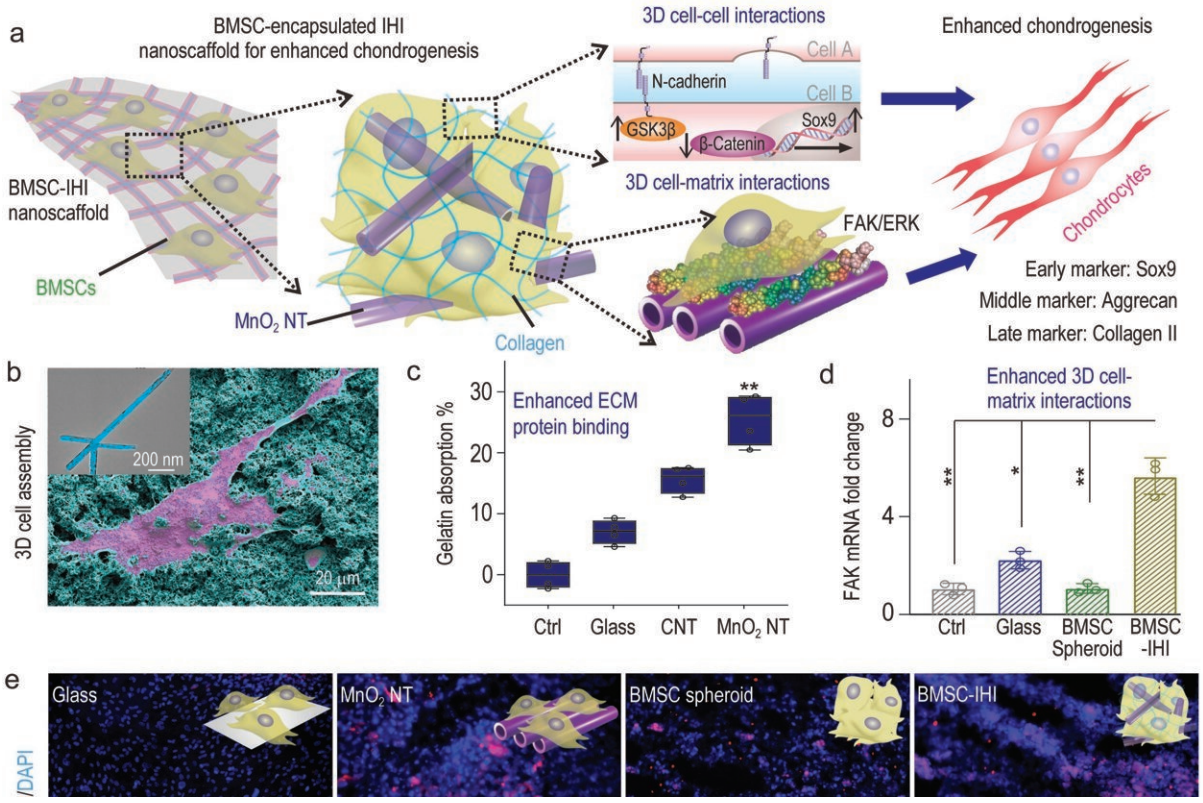
Nevertheless, there are critical barriers remaining to be overcome before the therapeutic potential of stem cell therapies can be realized. The limited control over the chondrogenic differentiation of stem cells in vivo has often resulted in compromised regenerative outcomes. Moreover, due to the prevalence of oxidative stress and inflammation in the microenvironment of injury sites, stem cells frequently undergo apoptosis after injection.

To address these challenges, the researchers demonstrated the development of a 3D IHI nanoscaffold-templated stem cell assembly system for advanced 3D stem cell culture and implantation. 3D-IHI nanoscaffold rapidly assembles stem cells into injectable tissue constructs through tailored 3D cell-cell and cell-matrix interactions, deeply and homogeneously delivers chondrogenic proteins in the assembled 3D culture systems, and controllably induces chondrogenesis

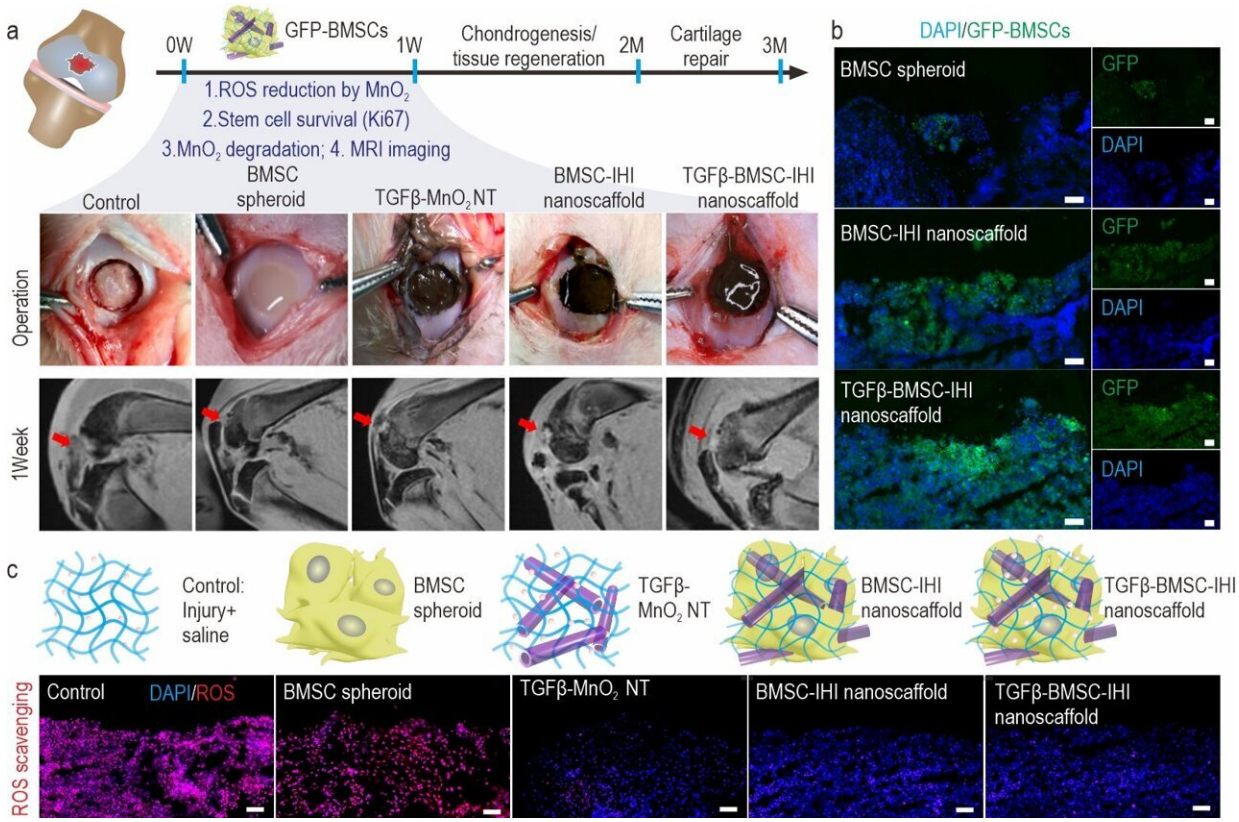
through nanotopographical effects.

Once implanted in vivo in a rabbit cartilage injury model, 3D-IHI nanoscaffold effectively modulates dynamic microenvironment after cartilage injury through the integration of the aforementioned regenerative cues, and simultaneously scavenges reactive oxygen species using a manganese dioxide-based composition. In this way, accelerated repair of cartilage defects with rapid tissue reconstruction and functional recovery is realized both in the short term and long term. Given the excellent versatility and therapeutic outcome of 3D-IHI nanoscaffold-based cartilage regeneration, it may provide promising means to advance a variety of tissue engineering applications.

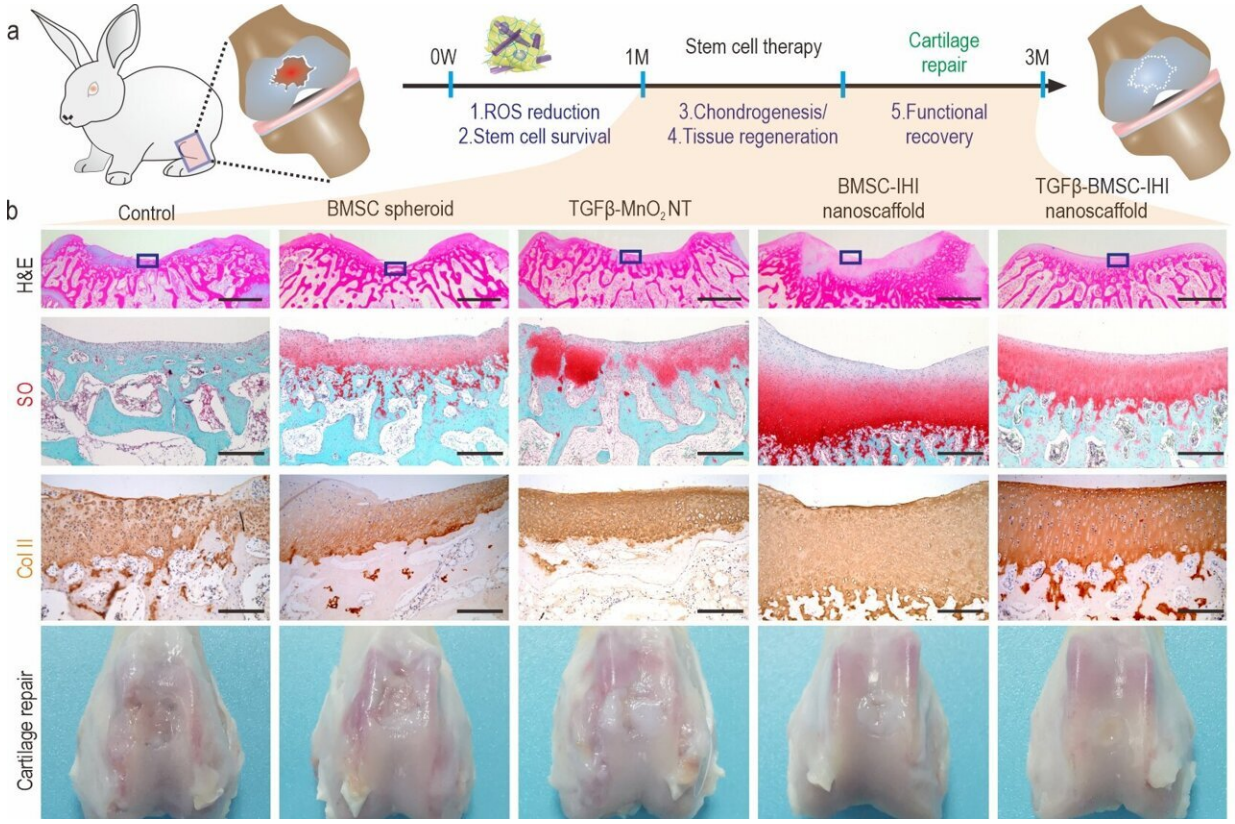
The research was published in *National Science Review*.



a) A schematic diagram showing the 3D-IHI nanoscaffold could enhance chondrogenic differentiation of BMSC through a synergy between N-cadherin and FAK-mediated pathways. b) The strong interactions between MnO_2 NTs and functional groups commonly existing in ECM proteins effectively supported cell attachment as demonstrated via SEM image. c) Bicinchoninic acid assay indicated the enhanced absorption toward gelatin from MnO_2 nanotube compared to control groups. d) The MnO_2 nanotube-templated assembly method significantly enhanced cell-matrix interaction as demonstrated through the up-regulated expression patterns of the FAK gene. e) Representative immunostaining images showing the improved chondrogenesis of BMSC in the BMSC-IHI nanoscaffold group compared to the control groups. Scale bar: 50 μm. f-h) The expression of chondrogenic genes, including SOX9 (f), Aggrecan (g), and Col-II (h) were characterized via qRT-PCR measurement. Credit: Science China Press



a) Schematic diagram illustrating the surgical process and timeline of cartilage repair. The degradation of MnO_2 NTs and the regeneration process could be monitored via MRI. b) To identify our transplanted cells, BMSCs were genetically labeled with a green fluorescent protein (GFP). Scale bar: 100 μm. c) The dramatically reduced red fluorescent signals of the ROS probe revealed that MnO_2 NTs in the IHI nanoscaffold could effectively scavenge ROS in the defect area. Promoted cell proliferation was confirmed by the higher expression of proliferative marker Ki67 immunostaining. Scale bar: 50 μm. d) The TGFβ-BMSC-IHI nanoscaffold could retain a significantly higher amount of cells after transplantation compared to other cell transplantation groups by quantifying the number of remaining GFP+ cells in (c). e) Histogram of the fluorescence intensity of ROS probe showed the effective consumption of ROS in the MnO_2 NTs containing groups. f) Quantification of Ki67+ cells in the defects. The quantifications in (e) and (f) were generated based on the fluorescence intensities in (c). Credit: Science China Press



a) A schematic diagram illustrating the long-term (3 months) cartilage regeneration process. b) The in vivo cartilage regeneration was characterized through H&E, Safranin O staining, Col-II immunochemistry staining, as well as macroscopic views. Zoom out scale bar: 2 mm, zoom in scale bar: 200 μm. c-h) Quantifications of cartilage thickness (by H&E staining) (c), cellular components (by Safranin O staining) (d), ECM components (by Col II immunostaining) (e). Results of International Cartilage Repair Society (ICRS) macroscopic (f) and histologic scores (g) indicated significantly improved defect repair qualities in the TGFβ-BMSC-IHI nanoscaffold group. The reduced Osteoarthritis Research Society International (OARSI) scores revealed the TGFβ-BMSC-IHI nanoscaffold could prevent the deterioration of osteoarthritis (h). Credit: Science China Press

More information: Shenqiang Wang et al, Injectable hybrid inorganic nanoscaffold as rapid stem cell assembly template for cartilage repair, *National Science Review* (2022). DOI: 10.1093/nsr/nwac037

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