Drug Deliverable Nano-Matrix for Growth Plate Cartilage Repair

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Introduction

Growth plate fractures are significant problems for children in the clinic. Damage to the growth plate cartilage may result in chondrocyte hypertrophy, cartilage ossification, angiogenesis, and bony bridge formation, which leads to growth cessation and deformity in patients. As of right now, there are no pharmaceutical treatments to promote growth plate cartilage regeneration and inhibit bone bridging after a growth plate fracture. Surgery is the only available treatment where the bony bridge is removed and autologous fat or cartilage tissue is inserted into the empty space to discourage bony bridge reformation. However, surgery occurs after the bony bridge is formed. Moreover, surgery is an intensive procedure and the clinical success rate for severe cases is only 15-38%. This is why there is a great need to investigate less invasive & more effective methods after growth plate fractures to both prevent ossification and to stimulate chondrogenesis in the defect.

In order to achieve growth plate fracture repair, we designed a novel nano-matrix combining tissue engineering and drug delivery approaches. The nano-matrix consists of biomimetic rosette nanotubes (RNTs) and matrilin-3 (MATN3) protein. MATN3 and RNT are able to self-assemble to form a hybrid MATN3/RNT nano-matrix (Figure 1). Our previous studies have found that this hybrid matrix served as a cell growth scaffolding for cartilage repair and presented an anti-osteogenesis effect in inhibiting bony bridge formation [1]. However, the nano-matrix was not able to achieve complete growth plate cartilage regeneration. Therefore, we aimed to develop the growth factor delivery ability of the nano-matrix for improved chondrogenesis. IGF-1 has been shown to enhance chondrogenesis and MATN3 has been shown to specifically bind to IGF-1 via a calcium ion mediated mechanism [2]. In this study, we hypothesize that MATN3 will bind to IGF-1 to create a MATN3/RNT/IGF-1 nano-matrix and with this added growth factor, the nano-matrix will improve chondrocyte growth and function for advanced growth plate cartilage repair.

Methods

IGF-1 binding and release: We loaded 100 ng/mL IGF-1 into the different doses of nano-matrix. Then, we measured the drug release curve over 2 weeks.

Cell growth and function study: Chondrogenic cells (ATDC5) are seeded on agarose gel with or without MATN3/RNT matrix and with or without IGF-1 in a 24-well plate. After 48 hours, their proliferation rate was measured via a cell proliferating assay.

Results

After 13 day release, we found that ~50% IGF-1 was retained in the 500ng/mL MATN3/RNT nano-matrix, and ~90% IGF-1 was retained in the 1000ng/mL MATN3/RNT nano-matrix (Figure 2). Results demonstrated that the nano-matrix presented a strong binding ability with IGF-1.

In vitro cell proliferation study demonstrated that MATN3/RNT with IGF-1 increases chondrocyte cell proliferation more than MATN3/RNT alone or IGF-1 alone (Figure 3). Results demonstrated that the IGF-1 bound with the nano-matrix is bioactive.

Discussion

When growth factor, IGF-1, was added to the MATN3/RNT nano-matrix, IGF-1 was bound with the nano-matrix. With higher dose of the nano-matrix, the majority of the growth factor retained in the matrix. The growth factor binding ability of the nano-matrix can achieve a local high concentration of the growth factor to deliver it into the injury site. Moreover, IGF-1 bound with the nano-matrix is bioactive. There was an increase in chondrocyte cell proliferation with MATN3/RNT/IGF-1 compared to MATN3/RNT nano-matrix alone and IGF-1 alone. In future studies, we will test the drug delivery ability and therapeutic outcomes of the nano-matrix in an animal model.

Significance

There is no therapeutic treatment available for growth plate fractures. Surgery is invasive and can only be preformed after a bony bridge has formed in the defect. This hybrid nano-matrix in combination with different growth factors, such as IGF-1, is a potential treatment that can be administered after a growth plate injury occurs without the need for surgery.

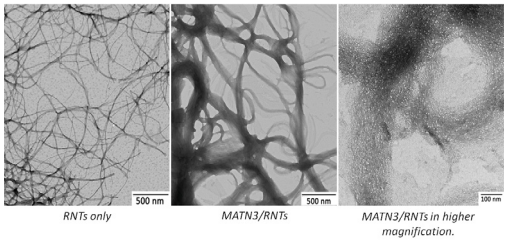

Figure 1. Self-assembly and morphology of MATN3/RNT matrix

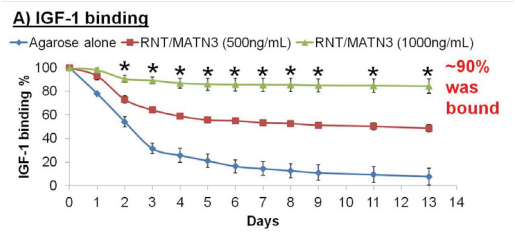

Figure 2. IGF-1 loading on MATN3/RNT nano-matrix

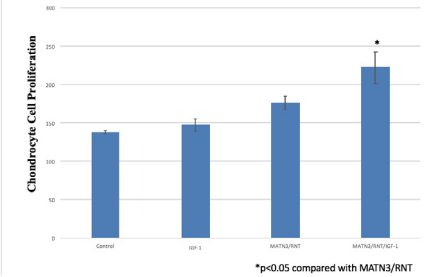

Figure 3. Promotion of chondrocyte cell proliferation

References

[1] Chen Y, Spangler T, McClure P, McAllister S, Hongchuan Y, Moore D, Ehrlich E, Chen Q. Department of Orthopaedics, Warren Alpert Medical School, Brown University, Providence, RI, 02912, USA.

[2] Trehan S, Chen Q. Matrilin-3, a Regulator of Chondrocyte Hypertrophy, Bone Mineral Density, and Osteoarthritis, Binds Bone Morphogenetic Protein-2, Vascular Endothelial Growth Factor$_{165}$ and Insulin-like Growth Factor. Department of Orthopaedics, Warren Alpert Medical School, Brown University, Providence, RI, 02912, USA.