Kartogenin Enhances Tendon Graft And Bone Tunnel Healing In A Rat Model

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Introduction/Purpose: The normal tendon-bone junction (TBJ) is a strong structure protected by the fibrocartilage transition zone. This allows a gradual transition of mechanical forces between tendon and bone, thus decreasing stress-concentration effects. Healing of the TBJ interface after an injury is slow and even after healing the junction often lacks the transition zone. A study on human patients showed that even years after ACL reconstruction, patients had no fibrocartilage zone regeneration. This and other studies show that surgical repair alone does not restore the unique protective fibrocartilage transition zone. We have shown that KGN injection into injured rat Achilles tendon-bone junctions enhanced wound healing with restored fibrocartilage transition zone. Here, we examined the effects of KGN treatment, along with platelet-rich plasma (PRP), on tendon-bone tunnel healing in rats.

Methods: KGN stock was prepared in DMSO and diluted to 100 μM with PRP. PRP was obtained from the blood of Sprague–Dawley rats and the platelet concentration in PRP was adjusted to 3 times over the baseline platelet concentration in whole blood. Thrombin (1 kU/mL), served as the PRP activator. 27 female rats (234~268g) were used. A 1.5 mm tunnel was drilled at the distal end of tibia. Achilles tendon was resected and sutured in the tunnel. Rats were randomly divided into 1 of 3 treatment groups: Group A: 50μl KGN + PRP; Group B: 50μl PRP solution; Group C: control. Rats were sacrificed at 4, 8, and 12 weeks for histological analysis. Whole tibia with the tendon insertion were harvested, fixed in 10% formalin and decalcified in 10% EDTA. Tissue were sectioned and stained with Safranin O + Fast green, and immunostained for collagen types 1 and 2.

Results: All animals were in good condition after surgery and complications were not present. Safranin O staining was higher in the KGN+PRP group than the other groups indicating more cartilage-like tissues regeneration in this group. Formation of the cartilage-like transitional zone was time dependent; i.e., it increased with increase in time (Fig. 1A-C). In contrast, both PRP and control groups had no cartilage-like tissues (Fig. 1D-I); in fact, some gaps in the control group were found in the tendon-bone interface after 4 and 8 weeks (Fig. 1G-I). Finally, the cartilage-like tissues in the KGN+PRP group also stained positive for both Col-1 and Col-2 indicating that these were fibrocartilage tissues (Fig. 2).

Conclusion: Here we demonstrated that KGN promotes the formation of fibrocartilage-like interface between the tendon graft and bone tunnel. This result suggests that the delivery of KGN into the tendon-bone interface could be a promising, cell-free approach to augment the tendon-bone interface healing. PRP in this study, while not effective in promoting fibrocartilage formation of the interface in its own right, it functions as an effective carrier that supplies scaffolds and growth factors necessary for the enhancement of wound healing. Future research is required to determine the optimal KGN dosage regimens and the optimal delivery method (e.g. injection vs implantation).

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