Preconditioned synovial mesenchymal stem cells (SMSCs) with basic fibroblast growth factor (bFGF) enhance meniscus regeneration via activation of the CXCL6-CXCR2 signaling pathway.

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INTRODUCTION: The meniscus plays an important role in the knee, but due to its hypocellularity and hypovascularity, the self-healing capability of the damaged meniscus is highly limited. Synovial mesenchymal stem cells (SMSCs) are gaining attention as a promising medical resource for meniscus regeneration. However several issues, such as limited cell proliferation and non-uniformity of cartilage regeneration, should be overcome. Basic fibroblast growth factor (bFGF) has diverse biological functions, such as anabolic and concomitant catabolic effects, on cartilage maintenance. A previous study reported that SMSCs cultured with bFGF promoted cartilage regeneration in vitro and in vivo. So, we hypothesized that SMSCs cultured with bFGF can promote meniscal regeneration. The current study aimed to investigate the promotion of meniscus regeneration by SMSCs cultured with bFGF and to validate the underlying mechanism.

METHODS: Human SMSCs were obtained from five patients with osteoarthritis of the knee (four women and one man; mean age: 76[range: 70-88] years) during total knee arthroplasty. 8-week-old nude rats underwent hemi-meniscectomy, and SMSCs were implanted at the site of meniscus defects in pellet form, either with or without bFGF (1.0×10^6 cells). Rats were divided into three groups: control (no transplantation), FGF (-) (pellet without bFGF), and FGF (+) (pellet with bFGF). Analysis was performed at 4 or 8 weeks post-surgery, including assessment of the regenerated meniscus area, histological scoring of the regenerated meniscus and cartilage, meniscus indentation testing, and immunohistochemistry analysis.

RESULTS: Implanted SMSCs adhered to the regenerated meniscus, with the FGF (+) group showcasing expanded areas of regenerated meniscus, elevated histological scores for both meniscus and cartilage, as well as enhanced mechanical properties of the meniscus as compared to the control group. RNA sequencing analysis of SMSCs unveiled an upregulation in the gene expression of chemokines binding to CXCR2 in response to bFGF. Moreover, conditioned media derived from bFGF-cultivated SMSCs demonstrated augmented cell migration, proliferation, and chondrogenic differentiation, processes that were specifically impeded by inhibitors targeting CXCR2 or CXCL6.

DISCUSSION: SMSCs are gaining attention as a promising medical resource for meniscus regeneration, and regenerated meniscus cells were mainly derived from the surrounding synovial tissue. However, SMSCs have several limitations. In other words, they exhibit constrained cellular proliferation and heterogeneity in cartilage regeneration. The utilization of bFGF overcomes these problems. SMSCs cultured with bFGF exhibited an augmentation in the gene expression of chemokines binding to CXCR2. Among chemokines binding to CXCR2, it has been that CXCL6, in particular, may play a crucial role in relation to chondrocytes. Our research findings also suggest the potential involvement of CXCL6, as indicated. The transplantation of SMSC pellets cultured with bFGF accelerated the secretion of CXCL6, which binds to CXCR2 and activates the downstream of the ERK and Akt pathways. Thus, cell migration from surrounding synovial tissue, cell proliferation, and chondrogenic differentiation may be promoted, thereby improving meniscus regeneration. The transplantation of SMSCs cultured with bFGF can be a simple and effective treatment option for promoting meniscus regeneration.

SIGNIFICANCE/CLINICAL RELEVANCE: (1-2 sentences): The transplantation of SMSCs cultured with bFGF can be a simple and effective treatment option for promoting meniscus regeneration.

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