Introduction: Local administration of therapeutic agents to joints is reasonable in osteoarthritis (OA) which is not systemic disease. However, maintenance of effective concentration of proteins is difficult because usual proteins are metabolized immediately when direct administration into joints is performed. In addition, most of growth factors are unstable and have short internal half-life period. Recently gelatin hydrogel was reported to achieve controlled release of growth factors in the condition that maintained the biological activity of growth factors (1).

We previously reported that gelatin hydrogel microspheres (GHMs) induced the controlled release of basic fibroblast growth factor (bFGF) in the rabbit knee and this system had the therapeutic effects on the rabbit experimental OA (2). In this study, we evaluated safety in administration of GHMs containing bFGF into knee joints using cynomolgus monkeys.

Materials and Methods: Six Cynomolgus monkeys (3.95-5.05 kg) were divided into three groups- very short-term group (3 days after the last injection; 101 and 102), the short-term group (7 days after the last injection; 103 and 104) and the long-term group (28 days after the last injection; 105 and 106). The injections of 100 μg bFGF-GHMs were performed twice (once three weeks for 6 weeks).

The expressions of proteoglycan core protein and type II collagen were examined using real-time PCR to confirm the anabolic effects on the treated cartilage (3, 7 and 28 days after last injection). The safety evaluations were performed generally (blood chemical findings) and locally (gross morphologic, histologic and radiographic examinations of knees).

Results: The expressions of proteoglycan core protein and type II collagen were increased 2.02- and 5.89-fold on 28 days after last injection in the cartilage from knee joints treated with 100 μg bFGF-GHMs as compared with control cartilage. The both genes expressions were not up-regulated on 3 and 7 days after last injection (Fig. 1).

Discussion: In our previous study the sustained release of bFGF in joints using the GHMs had a therapeutic effect in a rabbit model. One of the therapeutic mechanism of this system was the acceleration of anabolism in cartilage by the sustained release of bFGF in joints (2). This system induced the acceleration of cartilage matrix metabolism even in the cartilage of cynomolgus monkey. This result suggests that the intraarticular administration of bFGF-GHMs has the potential of the new conservative therapy for OA.

However, mild synovitis was observed after the intraarticular administration of bFGF-GHMs. This system could induce the sustained release of bFGF in joint for more than 7 days, but the 60 % of the administered bFGF was released to the joint cavity in one day (2). This first large amount of released bFGF might be the cause of the synovitis in treated joint. It is necessary for clinical application to examine the optimal dose of bFGF which up-regulates the anabolism of cartilage without the induction of synovitis.