Development of the Novel Prolonged Progressive Osteoarthritis Model to Elucidate the Onset Mechanism of Primary Knee Osteoarthritis

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INTRODUCTION: Knee osteoarthritis (OA) is classified into primary and secondary according to the onset mechanism; each is characterized by the onset of OA with/without any specific trigger or trauma. Primary OA occurs in many people worldwide. However, most animal models used in basic research are made with periarticular tissue damage, such as ligament and meniscus. These models induced severe cartilage degeneration in a relatively short period, so general injury models imitate the secondary knee OA. This means the results of current Knee OA models apply to the secondary knee OA. The pathogenesis mechanisms of primary and secondary OA are different. Therefore, a novel model that mimics primary knee OA is needed to clarify the mechanism of primary knee OA. In this study, we made a posterior cruciate ligament ruptured (PCL-R) model as a slowly progressive knee OA model. Our objective of this study is to elucidate the mechanism of primary OA.

METHODS: This study was approved by the Ethics Committee of Saitama Prefectural University and strictly adhered to the on-campus animal experiment guidelines (approval number 2021-11). C57BL6 male mice were used (n=42). In the PCL-R model intervention, the PCL was ruptured by fixing the hip and knee joints at 90° in mice lying on their backs and pushing the tibia directly down on a self-made platform. (Fig.1A) The left hindlimb was used as the PCL-R group, and the right hindlimb was used as the INTACT group. Five mice had their knee joints harvested immediately after PCL rupture strength was measured, and the others had their knee joints harvested 8 (n=7), 16, 25, and 34 weeks (n=10 each) later. The tibial anterior and posterior deviation and extension angle were measured. Then, PCL rapture images were observed for histological analysis, and degeneration of the medial articular cartilage of the tibia was evaluated using the OARSI score. The subchondral bone structure, including bone volume/tissue volume fraction (BV/TV) and trabecular thickness (Tb.Th), were evaluated by micro-CT data. Statistical analysis was performed by the Wilcoxon rank sum test.

RESULTS SECTION: The PCL-R group ruptured at a strength of 8.56-12.7 N, and no articular cartilage damage was observed immediately after the rupture. (FIg.1B) The PCL-R group showed significantly greater posterior tibial deviation than the INTACT group (p= 0.008 all). (Fig.2A) At week 16 and 34, the PCL-R group had more limited extension (p=0.008, 0.016 each). (Fig.2B) Histologically, the PCL was ruptured at the center and did not heal until 34 weeks. (Fig.3A) All mice in the PCL-R group had significantly severe cartilage degeneration than INTACT group at week 16 and 34 (p=0.048, 0.040 each). (Fig.3B) Subchondral bone structure did not differ between groups at any time points. (Fig.3C)

DISCUSSION: In this study, we created and characterized a novel mouse model of non-invasive knee OA that progresses slowly. PCLR model showed no cartilage damage immediately after intervention and mild cartilage degeneration after 34 weeks. These results mean that the articular cartilage degeneration was not due to direct cartilage damage that occurs at the timing of PCL rupture but may have been induced by posterior instability. PCL-R model does not involve a dissection of the intra-articular tissues except the PCL. In the previous surgical model, surgical intervention including transection of the articular capsule results in unnecessary acute inflammation[1], which may affect the OA. In contrast, a non-invasive model such as the PCL-R model is without unnecessary inflammation and can more accurately reflect the process of primary OA onset and progression. Furthermore, in the previous common models, significant cartilage degeneration already occurred by 8 weeks in the Destabilization of the medial meniscus (DMM) model[2,3]. The PCL-R model is a model in which OA progresses slower with less joint instability than previous models. Rapidly progressive models such as the the DMM model risk missing the onset of OA. On the other hand, the PCL-R model shows a slower progression of OA degeneration than the other previous models. This indicates that the PCL-R model is expected to be applicable to basic research to elucidate the mechanism of primary OA.

SIGNIFICANCE/CLINICAL RELEVANCE: The PCL-R model is a novel and useful model for elucidating the onset mechanism of primary knee OA.

REFERENCES: [1] Christiansen BA +. OAC. 2015 [2] Glasson SS+. OAC. 2007 [3] Arakawa K+. OAC. 2022

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IMAGES AND TABLES

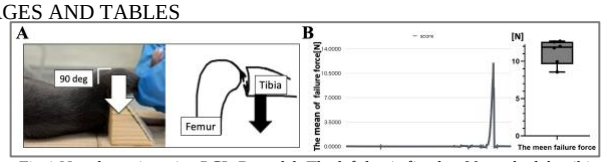

Fig.1 Novel non-invasive PCL-R model. The left leg is fixed at 90, pushed the tibia manually. [A] The PCL rapture force ranged between 8.56 and 12.7 N. [B]

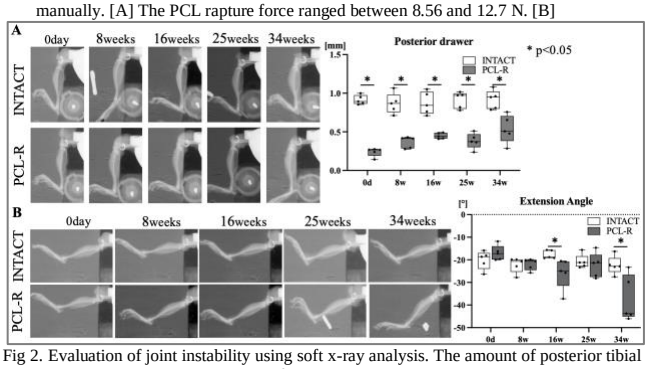

Fig 2. Evaluation of joint instability using soft x-ray analysis. The amount of posterior tibial deviation in the PCL-R group was significantly increased compared to that in the INTACT groups [A]. The extension angle was a trend to decrease in the PCL-R group at 34 weeks [B].

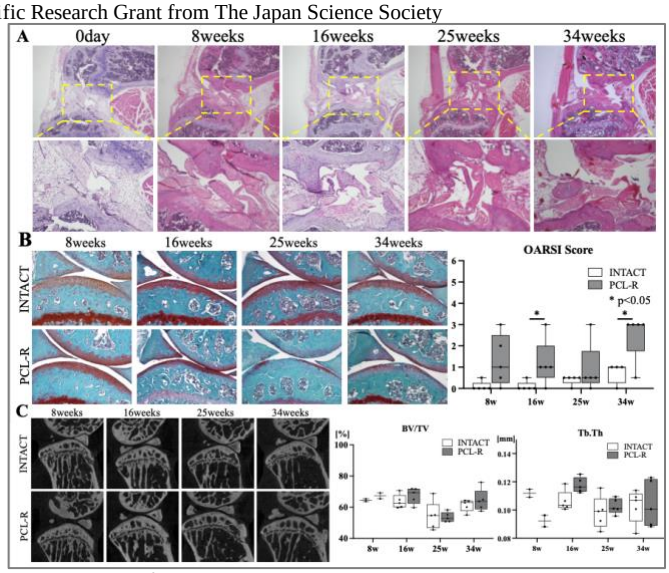

Fig 3. The results of Histological analysis and μ CT. The PCL continuity was lost until 34 weeks [A]. PCL-R group was significantly increased compared to the INTACT groups at week 16 and 34 [B]. There were no differences in BV/TV and Tb.Th between groups.