Long-term rapamycin protects against age-related osteoarthritis in adult common marmosets

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Purpose
InCREASED MECHANISTIC TARGET OF RAPAMYCIN (mTOR) ACTIVITY IS seen in cartilage from human osteoarthritis (OA) patients and is sufficient to induce OA in mice. Rapamycin, a small molecule inhibitor of mTOR, extends lifespan in multiple species and protects against experimental OA in rodent models. However, it remains unknown if rapamycin can modify features of naturally occurring OA in non-human primates. The common marmoset is a small, short-lived primate which is increasingly used to study aging and age-related disease. Therefore, we analyzed the knee joints of common marmosets receiving rapamycin during an ongoing lifespan study.

Design
Common marmosets were housed at the University of Texas Health San Antonio and were orally administered daily rapamycin (1 mg/kg/day; 13M/9F, 3.8-16.2 years) or yogurt vehicle (18M/16F; 2.6-16.5 years) until death. At necropsy, one hind limb was fixed in 10% neutral buffered formalin, scanned via micro-computed tomography (µCT), and processed for histopathology. µCT images were graded by a veterinary radiologist to assign an OA score according to the criteria in Table 1. Histopathology images were used to produce an articular cartilage structural damage (ACS) score according to the Modified Mankin guidelines. Marmosets were also classified as adult (<8 years), aged (8-12 years), and geriatric (≥12 years) for group analysis. Treatment effects (rapamycin vs. control) were determined within each age group using a Student’s t-test.

Results
µCT OA scores increase with age
Adult rapamycin-treated marmosets display lower OA scores than control

Table 1: µCT Scoring System

Presence of osteophytes: (0: none; 1: small; 3: large)
Location of osteophytes: (medial & lateral tibia: 1; patella: 2; medial & lateral femur: 3)
Subchondral bone cystic changes: (0: no; 1: yes)
Subchondral bone sclerosis: (0: no; 1: yes)
Articular cartilage lysis: (0: no; 1: yes)
Intra-articular soft tissue: (0: normal; 1: increased)

Table 2: Rapamycin treatment duration by age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Age at Rapa Start (years)</th>
<th>Rapa Treatment Duration (years)</th>
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</thead>
<tbody>
<tr>
<td>Adult (&lt;8 years)</td>
<td>5.45 ± 0.9</td>
<td>0.78 ± 0.5</td>
</tr>
<tr>
<td>Aged (8-12 years)</td>
<td>7.89 ± 3.9</td>
<td>2.63 ± 0.9</td>
</tr>
<tr>
<td>Geriatric (≥12 years)</td>
<td>11.98 ± 1.9</td>
<td>1.81 ± 1.1</td>
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Conclusions
These data are the first to demonstrate that common marmosets develop age-related OA pathology in bone and cartilage. While OA scores in marmosets receiving rapamycin are not different from control at aged or geriatric ages, adult rapamycin-treated marmosets display lower OA scores, suggesting rapamycin may modify the rate of OA progression and compress severe OA pathology to late-life.