Validation of anterior cruciate ligament rupture after compressive load in a clinically relevant in vivo rat model of post traumatic osteoarthritis

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Introduction

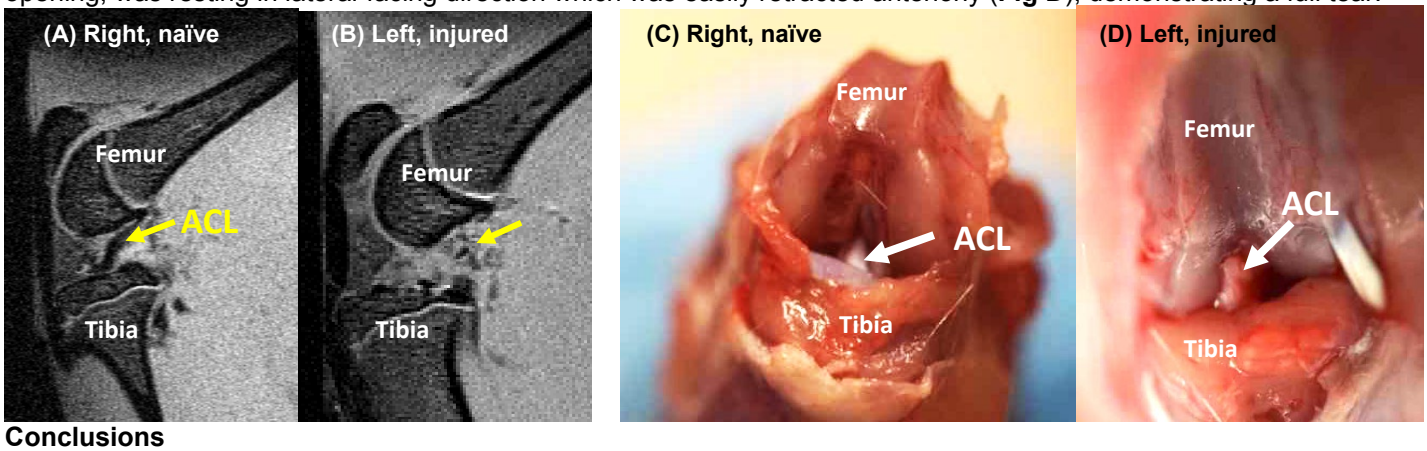
Osteoarthritis (OA), a degenerative disease of the joint, is one of the most common diseases worldwide and has numerous etiologies. Current treatment options in the clinic are limited to palliative drugs, and no cure exists. There exist promising opportunities to improve pharmaceutical efficiency of OA drugs by advancing intra-articular drug delivery systems. However, the study of intra-articular fate of therapeutics in OA joints is limited by readily available in vivo models. Common models include chemical ablation of cellular activity in the joint, which poorly resembles the human condition, and surgical destabilization, which disrupts the integrity of the joint capsule, thereby impacting joint clearance and biodistribution of therapeutics. Here we present the development of a Non-Invasive Knee Injury (NIKI) device that delivers an external force in skeletally mature rats to rupture the anterior cruciate ligament (ACL), an injury that commonly leads to OA in humans. Non-invasive ACL ruptures have been successful in mice, but few studies have involved rats. In cadaveric testing, ACL condition post injury was analyzed by gross dissection, but a reliable, non-invasive assessment technique is needed for in vivo studies to predict if the ACL occurred as expected. This study evaluated the success of ACL rupture in three live animals immediately post injury via MRI and correlated those results to blunt dissection and force response curves. Future work will evaluate the biological, behavioral, and structural consequences of the injury. Ultimately, we aim to develop a biologically and clinically relevant model of OA with an undisrupted synovial capsule.

Experimental

Three adult Lewis rats were anesthetized with isoflurane, and underwent compressive load by the NIKI device until an ACL rupture was observed. Injury was only induced in the left limb; the ipsilateral knee served as a naïve control. Live recordings of force sensor data and system voltage were collected during the loading. Rats were immediately euthanized without waking from anesthesia, and the legs were isolated by dissection without disrupting the knee capsule. The legs were imaged fresh via the Avance III HD 750 MHz system to visualize the ACL condition.

Results and Discussion

By MRI (**Fig A-B**), the rat ACL appeared intact in the naïve (right) leg. No ACL was visualized in the same plane of view in the left, injured knees. The left knees had debris in the joint space that was not as pronounced in the right knees. The MRI images were corroborated by visualization by gross dissection (**Fig C-D**), whereby the naïve knee (**Fig C**) had an intact ACL that tightly held the femur and tibia together. The injured knee had a loose ACL that, immediately upon opening, was resting in lateral-facing direction which was easily retracted anteriorly (**Fig D**), demonstrating a full tear.



Conclusions

MRI confirmed the full rupture of the ACL after injury via the NIKI device in all three non-survival animals. MRI was confirmed by gross dissection. Debris in the joint space may be boney pieces, suggesting that the tear type may be an avulsion tear, whereby the ACL is torn out of the bone insertion point on the lateral femur.

Acknowledgements

The National High Magnetic Field Laboratory is supported by the National Science Foundation through NSF/DMR-1157490/1644779 and the State of Florida.

Research reported in this publication was supported by the Longenbaugh Foundation Faculty Support Funds (# F023099).