Roles and regulators of autophagy during bone growth

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compromise occurs with aging, these deficits are even more pronounced in OA. A healthy neuromuscular system is pivotal in maintaining an optimal biomechanical environment for the musculoskeletal system. This presentation will discuss the role of neuromuscular deficits in the pathophysiology of OA, examine the potential relationships between these deficits, and propose directions for future research.

I-5
ROLES AND REGULATORS OF AUTOPHAGY DURING BONE GROWTH

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The main research interest of my laboratory is **to understand the regulation and the role of the lysosomal-autophagy pathway in both physiological and disease processes.** In particular, keeping in mind that the lysosomal-autophagy pathway is dynamically regulated in response to changes in the extracellular environment, my laboratory is exploring the hypothesis that the developmental regulation of this pathway is an important contributor to organismal development and growth. Using a combination of mouse genetics, cell biology and pharmacological approaches my lab has recently demonstrated that autophagy is induced in growing bones during post-natal development and regulates the intracellular trafficking of collagens, the major components of bone and cartilage ECM. The post-natal induction of autophagy is mediated by the FGF signaling, demonstrating that growth factor signalling can promote organismal growth through the activation of autophagy. More recently, we have demonstrated that enhancement of autophagy is effective in restoring bone growth retardation in mouse models of Lysosomal Storage Disorders. Our studies will have the potential to identify new pathways through which growth factors regulate cellular catabolism, to explain how catabolic processes support anabolic pathways in vivo, and to provide proof of principle that developmental disorders may be treated by modulation of cellular metabolism.

I-6
MESENCHYMAL STROMAL CELL LINEAGES IN SYNOVIUM AND THEIR CONTRIBUTION TO OSTEOARTHRITIS AND CARTILAGE REPAIR

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In recent years, landmark studies using genetic lineage tracing models in mice have identified and functionally characterised skeletal stem and progenitor cell populations in bone marrow, providing important insights in the regulation of bone homeostasis and repair, as well as the control of haematopoiesis. By comparison, the stem and progenitor cells that are resident in the synovial joint and maintain and repair joint tissues such as articular cartilage remained poorly defined, but recent work from our lab and others is starting to shed light on this. Lineage tracing of progenitor cells in cartilage has provided important new insights into the process of articular cartilage formation and maintenance. Our work has focused on characterising stem and progenitor cells in the synovial membrane, and how these cells respond to cartilage injury. Tracing of cells from the embryonic joint interzone, using Gdf5 as driver, showed that Gdf5-lineage cells persist in adult knee synovium up to at least one year of age as a mesenchymal stromal cell population with progenitor activity, which is largely distinct from the skeletal stem/progenitor cell populations identified in bone marrow. After purification, Gdf5-lineage cells display a differentiation potency in vitro that is skewed towards formation of cartilage and a synovial lining-like layer, while showing poor osteogenic ability. Cartilage injury in vivo triggers Gdf5-lineage cells in synovium to undergo proliferation leading to synovial lining hyperplasia, a process that is dependent on the activity of the transcriptional co-factor Yap in these cells. Gdf5-lineage cells also contribute to repair of traumatic joint surface defects, though they do not seem to be the sole cell population able to populate the repair tissue. We further find that in pathology, using the destabilisation of the medial meniscus model of osteoarthritis, Gdf5-lineage cells contribute to chondro-osteophyte formation and subchondral bone remodeling. In conclusion, recent findings are starting to unravel distinct mesenchymal stromal cell subsets in the adult synovium, identifying the key players in joint pathophysiology and promising therapeutic targets for cartilage repair and treatment of osteoarthritis.

I-7
FUNCTIONAL CONSEQUENCES OF TENDONITIS IN OA

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Purpose: Osteoarthritis and tendinopathy have many similarities. They are common in middle aged and older people and are both associated, to some extent, with individuals with a history of sporting activity and also with obese individuals. They are both diseases which show alterations in their extracellular matrix, and there are similarities in pathological features of these diseases. In both diseases, there is often little relationship between clinical and imaging features and clinical symptoms. In both diseases there have been recent interest in the role of inflammation in their onset and failure to resolve. Tendons play a fundamental role in locomotion, transferring the forces generated by our muscles to the skeleton, and thus facilitating movement. Fulfilling this role in an optimal and energy efficient manner requires a specialised structure. However, a close look at the functional role of our different tendons highlights that they require markedly varied mechanical characteristics. Energy storing tendons such as the Achilles must be highly extensible and able to store and release energy in an elastic manner. By contrast, positional tendons such as the digital extensor tendons of the hand require some dampening and the capacity to modulate muscle contraction into precise skeletal movement. While all tendons are composed of the same hierarchical collagen arrangement, these disparate functional requirements necessitate structural and compositional optimisation. Research in our group has focused on characterising structure-function mechanistic differences between tendons, and identifying the early changes which occur following fatigue injury.
Methods: We have performed hierarchical biomechanical testing, compositional analysis (using proteomics, immunohistochemistry, western blotting and qPCR), and defined the early failure events following fatigue loading. This work has been performed in relevant animal species (equine) as well as in human Achilles Tendon and Anterior Tibialis Tendon.
Results: With a prevalence of tendinopathy in energy storing tendons, we are particularly interested in the micromechanical specialisations facilitating more elastic, extensible behaviour in these tendons. We have shown that energy storing tendons are highly specialized, with more helically arranged fascicles that stretch less during tendon loading. Extension of energy storing tendons is also facilitated by the interfascicular matrix (IFM), which is elastin- and lubricin-rich, to facilitate sliding and recoil between fascicles during tendon loading. These specialisations lead to a less stiff, more fatigue resistant IFM in energy storing tendons, which can enable fascicle sliding and recoil during tendon loading. We have shown a loss of these structural specialisations with increasing age, leading to reduced tendon fatigue resistance, and perhaps associated with the increased risk of tendon injury with ageing. We demonstrate that fatigue loading results in specific failure within the IFM of energy-storing tendons, and is associated with upregulation of proteins associated with inflammation and matrix degradation. Subsequent to injury tendons repair by fibrochondrogenic repair and develop a tendon repair matrix which is much more cartilage like and lacks the fascicular structure which is so important for its elastic function
Conclusions: In elastic energy storing tendons, which are frequently injured, a key functional anatomical specialisation is related to the IFM, which is a proteoglycan and elastin rich compartment, which is specialised to allow both fascicular sliding, and elastic recoil. With ageing there is both a stiffening and decreased fatigue resistance in this matrix, which is likely to predispose the tendon to injury. We have evidence that early fatigue damage arises within the IFM, and results in inflammatory and proteolytic changes. Tendons heal with a loss of the IFM, and formation of fibrochondrogenic scar tissue. Whilst there are some similarities to the OA process, tendon ageing and failure is a distinct process almost certainly driven by the unique function of energy-storing tendons.

I-8
REGULATION OF MUSCULOSKELETAL INTEGRATION AND COORDINATED GROWTH

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Purpose: The musculoskeletal system is a marvel of anatomical design that underlies the exquisite range of motion in humans and other