Project Details	
Project Code	CMD27Br Hammond
Title	How the Golgi Feels Force: Uncovering a Hidden Driver of Osteoarthritis
Research Theme	Cardiometabolic Disease
Project Type	Other
Summary	Globally, 600 million people live with osteoarthritis, a disease driven by cartilage breakdown. One major disease risk factor is abnormal mechanical loading of joints, yet how cells sense and respond to these forces remains unclear. This PhD will investigate how the Golgi, a secretory pathway organelle, responds to mechanical signals and whether disrupted extracellular matrix secretion contributes to pathology. Using bioinformatics approaches you will analyse genome wide association studies to identify osteoarthritis linked Golgi proteins, then investigate their function experimentally using 3D human cell models and tissue. This project offers the chance to uncover a novel cellular mechanism in disease.
Description	Osteoarthritis (OA) affects an estimated 10 million people in the UK and is characterised by the progressive breakdown of articular cartilage leading to joint pain, stiffness, and reduced mobility. Mechanical signals are required for the maintenance of extracellular matrix (ECM) homeostasis in the joint, however abnormal mechanical loading is a risk factor for disease. A deeper understanding of how mechanical cues regulate chondrocyte behaviour is therefore critical for developing more effective treatments and interventions for osteoarthritis. The composition and organisation of the ECM in articular cartilage is critical to its function. For example, proteoglycans like aggrecan embed within the collagen fibrillar network to provide biomechanical resilience, whilst other proteins transduce mechanical signals to chondrocytes to impact behaviour. These ECM proteins are transported through the Golgi during secretion, where they are modified to fine tune their chemistry in ways that affect how they assemble in the extracellular environment. In turn, this determines the mechanical properties of the tissue. Emerging evidence, including preliminary data from the Stevenson lab, indicates that the Golgi itself is mechanosensitive. This suggests feedback loops exist between the Golgi and ECM that regulate ECM secretion and assembly to maintain tissue health. This project aims to test the hypothesis that disruption to these pathways contributes to the progression of OA and cartilage degeneration. Aim 1: Define structural changes in the secretory pathway following mechanical injury in OA models. Working with Dr Blain and Prof Hammond, the student will characterise alterations to secretory pathway architecture in animal tissues taken from in vivo models of early onset to severe osteoarthritis. Tissue will be analysed using immunohistochemical analysis and imaging techniques. Dr Stevenson will also help the student to establish 3D culture models using human chondrocyte cell lines that can be treated with piezo-1 agonists to mimic loading, or be subjected to cyclic compressive loading with the help of Dr Blain and instrumentation located in Cardiff. These in vitro models permit tracking of changes to Golgi morphology and transport in real time using fluorescent markers.

	Aim 2: Identify OA-associated trafficking machinery from genome-wide association studies (GWAS). To find candidate mechano-sensors and effectors at the Golgi, the student will data-mine existing GWAS studies of hip and knee OA, including unpublished data from the Genetics of Osteoarthritis Consortium, to look for genetic variants in membrane trafficking genes that are associated with increased disease risk. This work will be conducted with Prof Hammond and Dr Ben Faber. Identified targets will be cross compared with large data sets of ageing and injury-induced arthritis generated by the labs of Prof Hammond and Dr Blain. This aim provides key opportunities for the student to take ownership of the project by making choices as to which candidates they wish to pursue through aim 3 and 4. Aim 3: Validate candidate trafficking components in 3D culture and OA models. A short list of candidate proteins, determined by the student, will be validated with respect to their role in the mechanical regulation of Golgi function in vitro by 1) determining their cellular localisation with and without compressive loading and/or following piezo1 stimulation to look for Golgi recruitment, and 2) investigating whether loss of the protein abrogates Golgi responses to load. The most promising candidates will then be validated in the context of osteoarthritis by performing immunohistochemistry on archived animal tissues samples as in aim 1. Aim 4: Elucidate the mechanistic role of a hit protein in disease pathology. One candidate protein, or a group of closely interacting proteins, will then be investigated in greater detail in the context of cartilage ECM homeostasis to provide insight into the mechanisms of disease. Mechano-sensitive protein function will be disrupted using either knockdown, over-expression, or Golgi mistargeting depending on the findings of aim 3, and the impact of this on ECM secretion and organisation determined using a combination of imaging, histology and biochemical assays in 3D culture and animal models. This work will focus on the trafficking and modification of proteoglycans as they are key to biomechanical integrity, are highly susceptible to Golgi dysfunction, and contribute significantly to osteoarthritis pathology. This PhD project will provide novel insights into the degree to which Golgi mechano-dysregulation contributes to OA pathology. The identification and characterisation of novel disease mechanisms are important in the development of more effective treatments and interventions for osteoarthritis.
Can be completed part time?	Yes
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