Linking age-related joint degradation to diet by bone metabolism and SUMOylation

Supervisory team:
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Submit applications for this project to the University of Bristol

Project description:
Osteoarthritis (OA) affects a majority of people over 65 leading to loss of mobility and quality of life. OA is multifactorial with genetic, mechanical and inflammatory factors playing a role. Bone is a highly metabolic tissues and recent studies have shown that Type-2 Diabetes Mellitus (T2DM) is an independent risk factor for developing OA, though the mechanisms are not fully understood. A likely link between T2DM and OA is the regulation of metabolism in bone. In T2DM, metabolism in many different tissues is disrupted due to the lack of insulin signalling (caused either by insulin resistance or insufficient insulin secretion) and as metabolic markers in bone are altered in OA, osteoblast metabolism is likely to be a key factor linking the two conditions. This project will examine how factors associated with T2DM (termed 'diabetic stimuli'), for example saturated fatty acids and different insulin levels, affect metabolism in osteoblasts using a state-of-the-art Seahorse XFe24 metabolic analyser. We will relate these changes to changes in osteoblast function, for examine collagen production and bone mineralisation. Additionally, we will examine the role of the post-translational modification, SUMOylation in these processes. SUMOylation is protein modification analogous to ubiquitination, and is implicated in the pathology of both T2DM and OA, as well as having a demonstrated role in metabolic regulation. We will therefore examine how cellular protein SUMOylation levels response to diabetic stimuli, as well as examining the SUMOylation of several key metabolic substrates, and assay how these changes relate to the pathological changes in osteoblast function associated with T2DM. Assays will be performed in on osteoblasts in culture, and in vivo using the highly tractable zebrafish model system. The student will use CRISPR-cas9 genome editing, transgenesis and live imaging in zebrafish larvae and in adult scales and fins. This project will give the student a highly sought after skill set and the results of the project will greatly enhance our understanding of the link between T2DM and OA.