Postgraduate Research Day- 15th May, 2019

First Name: Soraia

Last Name: Caetano-Silva

Department: Comparative Biomedical Sciences, Camden

Abstract Title:

The role of *ex vivo* modulation of mechanical signals in endochondral ossification

Authors and Affiliations:

Caetano-Silva, Soraia P[1], Allen, Steven[2], Pitsillides, Andrew A[1]

[1]Skeletal Biology Group, Comparative Biomedical Sciences

[2]Musculoskeletal Biology Group, Immune Regulation and Cancer, Comparative Biomedical Sciences

Abstract

Osteoarthritis (OA), a chronic disease characterised by articular cartilage degradation, osteophyte formation and subchondral sclerosis, is the most common cause of pain and disability in adults. Whilst genetic and mechanical factors are known to be the most significant determinants of such cartilage-to-bone transition involved in OA development, its pathophysiology remains unresolved. Recent data indicate that the mTOR and NF-κB pathways can regulate cartilage-to-bone transition recapitulated in OA. The aim of the study is to determine whether regulators of these pathways interact with mechanical factors to control endochondral ossification (EO) underpinning cartilage-to-bone transition.

mTOR is composed of two protein complexes mTORC1 and mTORC2. Activation of mTORC1 is achieved in response to nutrients, amino acids and growth factor levels, whereas mTORC2 is related with cytoskeletal organisation and cell survival. NF-κB is an important pathway for drug discovery in inflammation, autoimmune diseases and cancer, which is a novel activator of mTOR signalling. Selective activators/inhibitors can pharmacologically modulate both pathways. To explore whether regulators of these pathways interact with mechanical factors to control EO, we

have used mouse embryonic metatarsal cultures maintained in aqueous conditions or in the presence of quasi-static mechanical loading conferred by their maintenance within a stiff hydrogel matrix.

Metatarsi grown under control conditions expanded ~2.5 fold during the 14 days of culture. Treatment with inhibitors/activators of mTOR, namely rapamycin/leucine and NF-κB using BA/SC-514 failed to modify length. When metatarsi were cultured in the presence of hydrogel, longitudinal growth was almost completely arrested. However, it revealed a growth-promoting influence for both activators and inhibitors of the mTOR pathway, which reverses the growth-restricting effects of culture in the presence of loading.

These data show the potential to modify loading conditions in embryonic metatarsals that will allow the mechanical control of EO to be studied in isolation of systemic influences *in vitro*.