Investigating the role of physical strain exerted by skeletal muscles on chondrocyte maturation and joint shaping

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The skeletal system is constantly remodelled to adapt to the changing demands of the organism. While we have a sense of how increased loading leads to bone deposition, we understand less about how cartilage, a key joint component, responds to the mechanical environment in vivo. This project combines experiments in zebrafish with computational modelling to establish how cartilage in developing joints responds to biomechanical strain. Using confocal microscopy to visualise jaw musculoskeletal elements, we will develop finite element (FE) models of the Meckel's cartilage, its joints and associated muscles during zebrafish development. These models will give us a 'map' of the mechanical forces acting on this cartilage. We will also map in detail how jaw joint morphology changes during development. We have evidence that muscle activity is required for normal jaw joint morphogenesis. Using FE models and in vivo experiments we will establish the extent and mechanism by which chondrocytes are influenced by muscle strain using various zebrafish musculoskeletal strains, subject to different biomechanical strains. We will assay chondrocyte proliferation and maturation using in situ hybridisation and immunohistochemistry and cartilage matrix secretion, assembly and organisation at the ultrastructural level using Electron Microscopy. Using live-imaging of transgenic-reporter lines, we will follow the dynamic expression of, and response to, ihha, a predicted 'mechanosensitive' gene. We will then test whether ihha controls the strain-response by conducting experiments in an ihha mutant line. This project will increase our understanding of how joint cartilage senses and responds to mechanical forces during development and throughout life.

Recommended reading:

Nowlan NC, et al 2008. Identification of mechanosensitive genes during embryonic bone formation. *PloS Comput Biol*. 4(12): e1000250.

Pitsillides AA and Beier F. 2011. Cartilage biology in osteoarthritis—lessons from developmental biology. *Nat Rev Rheumatol*. 7(11): 654-63.

Pitsillides AA and Ashhurst DE. A critical evaluation of specific aspects of joint development. *Dev Dyn.* 2008 Sep;237(9): 2284-94.

Rayfield EJ. 2007. Finite element analysis and understanding the biomechanics and evolution of living and fossil organisms. *Annual Review of Earth and Planetary Sciences* 35: 541-576.

This project is part of the South West Doctoral Training Partnership (SWDTP) and if funded provides broad scale training opportunities across the Universities of Bristol, Bath and Exeter, and four years of funding.

For further information about the scheme, and application criteria and process, see:-
http://www.bristol.ac.uk/science/prospective/scienceswdtp.html
http://www.bristol.ac.uk/science/prospective/bioscience.pdf

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