THE FAILURE OF CONNECTIVE TISSUES IS THE CAUSE OF A WIDE RANGE OF DISORDERS INCLUDING OSTEOARTHRITIS AND ABNORMALITIES OF SKELETAL DEVELOPMENT. ALTHOUGH THESE CONDITIONS ARE NOT IMMEDIATELY LIFE-THREATENING, THEY ARE CHRONIC, EXCEEDINGLY PAINFUL AND DISABLING, WITH THE COST TO THE HEALTH SERVICE SPIRALLING AS LIFE-EXPECTANCY INCREASES AND THE POPULATION AGES. WE ARE INTERESTED IN THREE RESEARCH AREAS WHERE A BASIC UNDERSTANDING OF THE ROLE OF THE CELLS (CHONDROCYTES) IN THESE DISORDERS COULD HELP TO IDENTIFY NOVEL APPROACHES AND TREATMENTS.

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1. WHAT IS THE ROLE OF ARTICULAR CHONDROCYTES IN OSTEOARTHRITIS?

Osteoarthritis (OA) is a very common and debilitating syndrome of human articular cartilage. It used to be thought that it arose from cartilage ‘wear-and-tear’, but there is increasing evidence that changes to the normal physiology of chondrocytes play a key role, although the details are unclear. Human chondrocytes are normally rounded and produce tough load-bearing cartilage throughout life. However using a special microscope [http://www.bms.ed.ac.uk/services/impact/] which enables us to see the living cells within their native cartilage environment, we have observed chondrocytes with remarkable cytoplasmic ‘processes’ extending for significant distances from the cell body (see Figure 1).

These ‘abnormal’ cells are present even in non-degenerate cartilage. Our work suggests they are producing damaging substances causing the cartilage to become weakened as occurs in OA and that their incidence increases markedly with the degree of OA. The results suggest that these changes to chondrocyte morphology might be an early and preventable step in the development of OA (see Bush & Hall, (2003)).

2. HOW DO BONES GROW?

At the end of a growing bone there is a small group of cells (chondrocytes) situated in a region called the ‘growth plate’. The regulated swelling of these cells is necessary for bone growth. However in OA, one of the causes of cartilage failure is the production of substances by abnormal chondrocytes which cause the cartilage to weaken. This weakening exposes the cells in the growth plate to their own product, leading to an inflammatory response. The result is that the growth plate cells die, and the growth plate is no longer able to swell and bone growth is halted.

Figure 1. A representation of the range of shapes of human articular chondrocytes in cartilage. The cell in the centre is ‘normal’ and has typical rounded morphology, however we have observed a significant proportion of cells which are swollen (lower left), dividing (lower right) or which have single or multiple with cytoplasmic processes (upper left, right). (Examples of the various cell morphologies are shown, with the in situ living cells labelled with a green fluorescent dye and visualised by confocal scanning laser microscopy (CLSM)).
fundamental for the orderly and rapid lengthening of the bones during skeletal development (see Fig. 2; Bush et al., 2008). This process can become disrupted during growth plate injury, and is also the basis for disorders to chronic skeletal disorders in the young. The process of cell swelling (also called hypertrophy) is poorly understood however we have evidence suggesting that a major driving force is the accumulation of osmolytes (especially ions) by cell membrane transporters which cause water to flow into the cells leading to cell swelling. To identify the role of the various transporters and to increase/decrease chondrocyte swelling in an attempt to accelerate/retard bone growth, we culture small growing bones under different conditions.

![cartilage growth plate bone](image)

Figure 2. The marked increase in the volume of growth plate chondrocytes during bone lengthening. The cartilage surface is to the left, and the bone to the right of the figures. On moving to the right, the columns of cells of increasing volume can clearly be seen. Finally the cells die and are replaced by the advancing bone (right of figure). The increase in chondrocyte volume is large (~10x) and is the main driving force for bone lengthening, although the mechanisms responsible are poorly understood (scale bar = 100μm).

We are also labelling specific membrane transporters in the growth plate to determine the changes to their activity associated with chondrocyte swelling and assess their role in bone growth. Our aim is to identify some the major factors involved in bone growth so that we can control the process more accurately in diseased or damaged growing bones.

3. HOW CAN WE PROTECT ARTICULAR CHONDROCYTES FROM MECHANICAL INJURY?

Adult human articular cartilage has a very poor capacity to repair following injury, and if damaged it can be a focal point for the development of osteoarthritis. Clearly considerable care should be taken during surgical procedures involving the joints to prevent the cartilage from being accidentally knocked, scraped or cut. We have been particularly interested in the damage to chondrocytes when cartilage is subjected to impact injury (i.e. a weight dropped on it) or when it is cut using a sharp scalpel blade. By visualising the chondrocytes during the injury, we have observed rapid cell death (see Fig. 3).

Our recent results show that by raising the osmolarity and/or reducing the Ca$^{2+}$ concentration of the medium suspending the cartilage, cell death following a scalpel injury can be almost totally eliminated (Amin et al., 2009a). In a parallel series of experiments, we have also noted that the presence of subchondral bone appears to have an important role in protecting the viability of chondrocytes within the superficial zone of cartilage (Amin et al., 2009b).

These results have direct relevance for the surgical procedures associated with trauma and orthopaedics.

**Selected References:**


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