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Bone cell elasticity and morphology changes during the cell cycle

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ABSTRACT

The mechanical properties of cells are reported to be regulated by a range of factors including interactions with the extracellular environment and other cells, differentiation status, the onset of pathological states, as well as the intracellular factors, for example, the cytoskeleton. The cell cycle is considered to be a well-ordered sequence of biochemical events. A number of processes reported to occur during its progression are inherently mechanical and, as such, require mechanical regulation. In spite of this, few attempts have been made to investigate the putative regulatory role of the cell cycle in mechanobiology. In the present study, Atomic Force Microscopy (AFM) was employed to investigate the elastic modulus of synchronised osteoblasts. The data obtained confirm that osteoblast elasticity is regulated by cell cycle phase; specifically, cells in S phase were found to have a modulus approximately 1.7 times that of G1 phase cells. Confocal microscopy studies revealed that aspects of osteoblast morphology, namely F-actin expression, were also modulated by the cell cycle, and tended to increase with phase progression from G0 onwards. The data obtained in this study are likely to have implications for the fields of tissue- and bio-engineering, where prior knowledge of cell mechanobiology is essential for the effective replacement and repair of tissue. Furthermore, studies focused on biomechanics and the biophysical properties of cells are important in the understanding of the onset and progression of disease states, for example cancer at the cellular level. Our study demonstrates the importance of the combined use of traditional and relatively novel microscopy techniques in understanding mechanical regulation by crucial cellular processes, such as the cell cycle.

1. Introduction

The cell cycle is a well-ordered sequence of biochemical events, occurring in eukaryotic cells between one cell division and the next (Cooper, 2000). However, a number of processes that occur during cell cycle progression, for example cytokinesis, are inherently mechanical and thus also require mechanical regulation. This has been demonstrated in a number of studies, where functionalised substrates were used to restrict cell spreading resulting in late G1 phase arrest, decreased chromatin condensation and a reduction in nuclear swelling and DNA synthesis (Huang et al., 1998; Ingber et al., 1995; Roca-Cusachs et al., 2008). These irregularities coincided with disruption of the cytoskeleton, coupled with de-regulated protein expression. Furthermore, application of mechanical loads to cells can result in initiation of specific cell cycle phases (Liao et al., 2004; Sedding et al., 2003; Sun et al., 2004). These data demonstrate the importance of mechanical forces, cell shape, as well as interplay between the extracellular matrix (ECM) and cytoskeleton in regulating cell cycle progression. However, few studies have investigated the influence of cell cycle phase on mechanical properties of cells. Progression through the cell cycle involves significant remodelling of cytoskeletal systems (Foisner, 1997; Skalli et al., 1992). Thus, changes in cytoskeletal organisation may influence mechanical properties associated with the cell, for example, cell elasticity.

In this study, we tested the hypothesis that the elasticity and morphology of bone cells change during the cell cycle. This hypothesis was tested using Atomic Force Microscopy (AFM) to measure the mean elastic modulus and height of individual phase synchronised osteoblasts. Confocal measurements were also made to investigate the effects of cell cycle progression on the nature of the actin cytoskeleton. Corroboration of this hypothesis will provide useful insights into the relationship between the cell cycle and cell mechanobiology.

2. Methods

2.1. MC3T3-E1 osteoblast cell culture and synchronisation

MC3T3-E1 osteoblasts (ATCC-LGC Standards, Middlesex, UK) were cultured in alpha minimum essential medium (α-MEM; Sigma, Dorset, UK), as described by McGarry et al. (2007). Cell synchrony was achieved via serum starvation, as described

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