A14/C4–MOLECULES AND CELLS IN MOTION

Organised by M. Riehle for the Cell Section and A. El Haj for the Biomechanics Group

A14/C4.1–Measuring forces exerted by cells

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Various methods of measuring the mechanical force that can be exerted by a single cell in tension or compression upon its surroundings will be described. The methods require measurement of the deformation of a sensing element usually an electrical or optical device. There are appreciable advantages in using microfabrication methods to make the device. Especial attention will be given to novel lnterferometric methods and to optical polarisation methods using the Polscope microscope.
The effects of the interaction of the cell with the measuring device will be considered. By using microfabrication methods the environment of the cell while being measured can be brought close to that of a variety of natural environments.

A14/C4.2–Modulation of actin polymerisation and mechanics with conventional and unconventional binding proteins

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Actin polymerisation and depolymerisation is a key process for the motile behaviour of cells including locomotion, generation of cell shape, volume regulation or responses to local stimulations. In addition to actin a variety of actin binding proteins is involved in these processes. Besides the 'classical' binding proteins (e.g. thymosin ß4, profilin, arp etc.) glycolytic enzymes may play a major role in the control of polymerisation, bundling and stiffness of actin fibrils. These actions are in addition to their role in energy metabolism which also is strongly related to their association with cytoskeletal elements providing the ATP driving cytoplasmic contractions. Using an oscillating rod rheometer based on a phase – sensitive acoustic microscope operated at 1 GHz, polymerisation kinetics of alpha- and of beta-actin in the presence of profilin, aldolase and LDH have been investigated. Mutual alterations of enzyme activity and polymerisation kinetics underline the specificity of the interaction and the functional significance. E.g. aldolase stimulates polymerisation in presence of its substrate while it inhibits filament formation without fructose-bisphosphate. Some structural consequences of these interactions were analysed by electron microscopy. The functional significance of the associations of the glycolytic enzymes with the actin fibrils for cell motility was revealed by induction of movement or of contraction in permeabilised cells fed with fructose-bisphosphate and by reduction of lamella propagation and amount of polymerised actin at the leading edge after inhibition of LDH using oxamic acid.

A14/C4.3–Microtubule Depolymerization by the Kinesin-related Protein MCAK

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MCAK belongs to the Kin I subfamily of kinesin-related proteins, a unique group of motor proteins that are not motile but instead catalyze microtubule depolymerization. We have used a combination of stopped-flow, ATPase and single-molecule assays to probe the kinetics of the MCAK-microtubule interaction and to understand how this interaction is coupled to ATP hydrolysis. In the presence of ATP, MCAK depolymerizes microtubules from both ends with a maximum rate corresponding to the dissociation of 30 tubulin dimers per second per microtubule. For the stable GMP-CPP microtubules used in these experiments, this corresponds to a 100-fold acceleration of the basal depolymerization rate. There is one high affinity site (Kd = 1 nM) per protofilament end. The short delay between the mixing of MCAK with microtubules and the initiation of depolymerization indicates that MCAK targets these binding sites very quickly: the second-order association rate constant is 0.05 $nM-1\ s-1$, more than 10-times greater than the fastest, diffusion-limited protein–protein association rates. Several lines of evidence support a model in which MCAK first binds to the microtubule lattice, then diffuses along the lattice until it finds its binding site at the microtubule end. Once there MCAK acts processively, removing on average 20 tubulin dimers from the protofilament before dissociating. MCAK has a low basal ATPase activity which is stimulated 10-fold by free tubulin and 350-fold by microtubule ends. Our results show how an ATP hydrolysis cycle has evolved from one that powers a motor to one that powers a depolymerase.

A14/C4.4–Mechanotransduction and the role of the osteocyte

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The osteogenic effects of load engendered strains have been evident for some time, as has the resorption inducing effect of under-loading our skeletons, but the cell types responsible for orchestrating the targeted function of the effector cells is still in question. It is generally considered that the osteocyte is the most likely candidate for this role due to their distribution throughout the bone matrix, their responsiveness to strain and their existence as part of a syncitial network. However, until recently, it has not possible to identify osteocyte-specific behaviour that is related spatially to the damage/strain environment and is associated with localised remodelling activity.

We noted earlier, that osteocytes death by apoptosis is over represented in bone tissue which is undergoing rapid remodelling. We proposed that the marked apoptosis of osteocytes observed in women and female rats subjected to acute estrogen withdrawal provides a targeting mechanism for inducing the removal of bone by osteoclasts under osteoporotic conditions. Since then a number of reports have confirmed and extended our findings and we have identified a relationship between load engendered, targeted osteoclast activity and osteocyte apoptosis.

These observations raised the possibility that the targeted removal of bone that is underloaded or damaged during overloading might involve the apoptosis of the osteocyte. We will consider the possible mechanisms by which controlled cell death might contribute to the signals for removal/repair of bone in the light of work involving cells in other tissue systems. We will also examine the potential reasons for the loss of the effector cell targeting system associated with ageing and a number of disease states.

A14/C4.5–Manipulation of ion channels using magnetic micro- and nanoparticle cytometry

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Magnetic bead cytometry has been used to define the mechanical properties of cells. Beads have been tagged with antibodies or protein motifs such as RGD. Directional forces can be applied to the beads and a stretch imposed upon the cell. These procedures have begun to define the potential roles of mechanotransducers within a cell and facilitating experimental manipulation of these pathways. Our group has conducted previous studies in biocompatible magnetic nanoparticle synthesis, theoretical analysis of magnetic methods of ion channel activation and into defining the role of MS and voltage-gated ion channel activation in response to mechanical loading. Mechanosensitive ion channels have been identified in many cell types. One such channel is the TREK − 1, part of the 2P K^+ channel family. We have recently demonstrated the presence of TREK-1 in connective tissue although the function is not yet known. In this study, we aim to define how these channels are activated and if there is a mechanical magnetic method for selectively targeting these channels. We present the early results from our efforts to specifically target TREK − 1 using magnetic particles. The TREK-1 gene with the extracellular loop region modified to contain a 12 mer histidine has been transfected and functionally expressed in HEK29 and COS cells allowing us to tag this region with anti-histidine coated magnetic nanoparticles. We propose to alter additional regions of the molecule in a similar fashion for tagging and to make comparisons with responses to a general membrane stretch using RGD or collagen-coated micro beads.

A14/C4.6–Mechanical conditioning of 3-D skeletal muscle constructs: IGF-1 and MGF Regulation in Skeletal Muscle Organoids following Mechanical Loading

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To understand the role mechanics plays in growth and development of skeletal muscle, it is necessary to model this tissue. It then becomes possible to control other variables, and examine the detailed effects of mechanical load (strain) on gene regulation. We have developed a 3D tissue engineered skeletal muscle construct (muscle organoids), by seeding c2c12 mouse myoblasts into collagen (type I) gels. Using a bioreactor, the t-CFM (tensioning-Culture Force Monitor), mechanical loads were applied to the organoids, and changes of IGF-1 Ea (Insulin-like Growth Factor-1), and MGF (Mechano-Growth Factor) mRNA expression were measured by real-time PCR. Uni-axial ramp loads of 10% strain (with strain rates from 3 to 37 dynes/minute), and 1–10 cycles/hour were applied.

Application of ramp load (10% strain) over 1 hour up-regulated both MGF (6060 fold increase), and IGF-1 Ea mRNA expression (1800 fold increase). This regime gave the highest up-regulation of both growth factors in the study. IGF-1 mRNA expression was higher for most loading regimes, with the exception of the 1 cycle/hour loading regime (1% strain), where the MGF/IGF-1 ratio was 80/20.

In conclusion, using the muscle organoid model in the t-CFM, we have identified a relationship between distinct patterns of mechanical load, important in muscle development, and the regulation of particular growth factors.

A14/C4.7–The Influence of tensile strain on fibroblasts in culture

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This study investigates the influence of cyclic tensile strain, applied to a fully contracted fibroblast-seeded collagen constructs. The constructs were preloaded to either 2 mN or 10 mN. The preloaded constructs were subsequently subjected to a further 10% cyclic strain (0–10%) at 1Hz using a triangular waveform, or were cultured in the preloaded state. In all cases cellular viability was maintained during the conditioning period. Cell proliferation was enhanced by the application of cyclic strain for constructs preloaded to both 2 mN or 10 mN. Collagen synthesis was enhanced by cyclic strain within constructs preloaded at 2 mN only. The profile of matrix metalloproteinase (MMP) expression, determined using zymography, was broadly similar in constructs preloaded at 2 mN with or without the application of cyclic strain. By contrast, constructs preloaded at 10 mN and subjected to cyclic strain expressed enhanced levels of staining for latent MMP-1, latent MMP-9 and both latent and active MMP-2, when compared to the other conditioning regimens. The structural stiffness of constructs preloaded at 2 mN and subjected to cyclic strain was enhanced compared to control specimens, reflecting the increase in collagen synthesis. By contrast the initial failure loads for cyclically strained constructs preloaded at 10 mN was reduced, potentially due to enhanced catabolic activity.

A14/C4.8–Cytomechanics and engineering of 3D structures in culture

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Cytomechanics is crucial to engineering 3D (connective) tissues in vitro, in that it focuses on the role of mechanical forces *at the cell level* on cell responses. At this scale, the material properties of the pericellular matrix are key. Our previous studies have indicated that control at this level is particularly important at the earliest stage of organization[1], when the cell-substrate material can best be described as an ultra soft material (eg. weak collagen gels). The aim of this work is to identify the cytomechanical control mechanisms to optimise collagen deposition into a dense, organised 'tissue'. Part of this is the need to promote cell remodeling of collagen (to shorter, denser structures[1]). Monitoring of cell force generation (in a culture force monitor) under the influence of TGF-beta, has identified a rapid onset stimulation of force generation[2]. This preceded an alteration in integrin expression, suggesting that it was due to stimulation of the cytoskeletal motor element. At the same time, it was possible to identify a new effect, of permanent matrix shortening in rat tendon fibroblasts (i.e. not due to cell contraction) corresponding to matrix remodeling, by blocking cell contraction with cytochalasin. This shortening of matrix structure (the key remodeling objective) was dependent on the culture period and addition of TGF-beta and can be used as the basis for rapid production of dense, 3D, aligned collagen neo-tissues. [EU. Framework 6 supported, QLK-1999–00559].

1. Tomasek et al. Nature Reviews Molec. Cell. 2002:3;349–363.
2. Brown et al. Exp.Cell Res. 2002:274;310–322.

A14/C4.9–Cortical tension in adherent cells is involved in volume regulation

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Cell volume is an important parameter in many physiological and pathological processes. Hence cell volume is closely regulated in many cells. A decrease in extracellular osmolarity leads to an initial increase in cell volume, which is often counteracted by a process termed regulatory volume decrease (RVD). We investigated the changes in mechanical parameters of a human keratinocyte cell line (HaCaT) during cell swelling and RVD with scanning acoustic microscopy (SAM, f 1.0 GHz). After a fast phase of swelling ($t<60$ s) accompanied by a loss of elasticity, in 70% of all observed cells an immediate RVD re-establishes approximately the previous volume in less than 5 min and cellular elasticity as well. After this first swelling and RVD phase a second swelling phase lasting about 10 min occurs in 55% of the cells. The swelling processes primarily take place in the cell body and the transition region between the central cell body and the thin peripheral cytoplasm corresponding to locally different mechanical properties. RVD is totally inhibited in the presence 1 μg/mL cytochalasin D. Altering cortical tension with lower doses of cytochalasin D before onset of hypotonicity showed not only the requirement for an intact actin cytoskeleton but also a possible involvement of cortical tension in the sensing mechanism for volume changes, most likely by interactions between the actin cytoskeleton and mechanosensitive ion channels like the recently characterised TRPV4 (see C4/A14.19 – Expression and Characterisation of TRPV4 in Volume-Regulating Cells).

A14/C4.10–Dynamic Changes in Traction Forces with DC Electric Field in Osteoblast-like Cells

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Primary bovine osteoblasts and human osteosarcoma cells exposed to direct current electric fields undergo a cellular alignment process with retraction, elongation, alignment or movement according to the field strength and time of exposure. The time needed for the orientation process seems to be correlated inversely to field strength in a certain range. Cellular orientation was analyzed using traction force microscopy and measurement of cytosolic calcium with the fluorescent dye Fura 2 AM. Analysis of traction force vector changes showed that the first detectable reaction to electric fields was an increasing traction force between 10 and 30 seconds. Intracellular free calcium (IFC) levels however were first detectable at 35 seconds (mean 85 seconds) and there was no correlation between the initial contraction and IFC. The IFC increase lasted at least 60 seconds. In the following 2 to 15 minutes, tractions at margins not normal to the electric field decreased to values below initial tractions and reflect the earliest point at which the cells demonstrate a galvanotaxis. At these margins phase contrast microscopy revealed elongating protrusions several minutes later and was associated also with significant IFC changes.

A14/C4.11–Mechanotransduction pathways in chondrocytes

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Mechanical stimulation is critically important for the maintenance of normal articular cartilage integrity. Molecular events regulating responses of chondrocytes to mechanical forces are beginning to be defined. Chondrocytes from normal human articular knee joint cartilage show increased levels of aggrecan mRNA and decreased levels of MMP3 mRNA within 1 hour of mechanical stimulation at 0.33 Hz. This anabolic response, associated with membrane hyperpolarisation, is activated via a novel integrin-mediated signalling pathway that involves substance P and an interleukin-4 autocrine/paracrine loop. Work in our laboratory suggests that this chondroprotective response may be aberrant in osteoarthritis (OA). In both normal and OA chondrocytes the response to mechanical stimulation is mediated via $\alpha5\beta1$ integrins, but the downstream signalling differs. Stimulation of chondrocytes from OA cartilage induces a membrane depolarisation following activation of an IL1β autocrine/paracrine loop, and shows no changes in aggrecan or MMP3 mRNA. Altered mechanotransduction and signalling in OA may contribute to changes in chondrocyte behaviour leading to increased cartilage breakdown and disease progression.

A14/C4.12–Cell guidance by mechanical surface structuring

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The capacity of cells either in situ or isolated in culture to interact intimately with natural and fabricated surfaces has been the subject of sustained research efforts. *Tactile* sensing, *taste and smell* by cells have been investigated using microfabricated surfaces and devices. Mechanosensing of *tension, shear* and *pressure* has been investigated using a variety of methods, but the molecular mechanism of mechanosensation of cells is still a field of ongoing research. However we still do not know how many *senses* a cell has and how the information is integrated. The use of a surface with graded mechanical stiffness has allowed Lo et al. (Biophys. J. 79: 144, 2000) to show that cells sense gradients in surface rigidity, they termed this orienting reaction of the cells *durotaxis*. To explore *durotaxis* we use microfabricated rigidity landscapes and investigate the cellular sensing mechanisms involved at a single cell level. Rat calvaria bone cells oriented along step gradients of surface rigidity 25 μm repeat (collagen coated surface). From our results follows, that the cells are aligned if the repeat frequency is higher than 10 μm. The spreading area does not vary whereas the cells become more elongated when aligned (significance tested at $p<0.05$ using t-test).

A14/C4.13–Mechanical loading modulates cytoskeletal organisation in living chondrocytes

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Mechanical loading is essential for the health of articular cartilage and may be used to enhance tissue engineered repair. The cytoskeleton is involved in mechanotransduction although the influence of compressive strain on chondrocyte cytoskeleton is unclear. The overall test hypothesis is that chondrocyte deformation induces cytoskeletal distortion and subsequent remodeling via a Ca^{2+}-dependent pathway. A feedback system is pro-

posed, whereby loading modulates cytoskeletal organisation and hence changes cellular mechanosensitivity.
Isolated bovine articular chondrocytes were seeded in agarose constructs and maintained at either static compression or 1Hz cyclic compression for a period of 3 hours. Cells were then fixed, stained for actin microfilaments and visualised using confocal microscopy. Using a novel image analysis technique, it was shown that both static and cyclic compression resulted in significant difference in cytoskeletal organisation compared to unstrained cells.
To further investigate the nature of the cytoskeletal remodeling mitochondrial staining (JC-1) was used to indirectly label microtubules in living chondrocytes. A quantitative computer modeling technique was developed to determine the localised displacement and deformation of mitochondrial/cytoskeletal structures. However to effectively visualise all three cytoskeletal components viable cells were transfected with expression plasmids for EGFP-tagged actin, tubulin and vimentin. New plasmids were produced for tubulin and vimentin whilst a commercially available plasmid (Clontech) was used for actin. Studies using an osteoblastic cell line, demonstrated that EGFP transfection and confocal microscopy can be used to visualise cytoskeletal dynamics in living cells. However the transfection techniques needs to be further optimised for use with primary chondrocytes.

A14/C4.14–Alignment and fusion of cultured mouse myoblasts

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Cultured mouse myoblasts aggregate into groups of aligned cells before they fuse into multinucleated myotubes. How myoblasts recognise each other, become committed to fusion, and fuse is not very well understood. We have found that myotubes formed on laminin coated tracks that varied in width from 5 to 100 microns in diameter, had a constant diameter of approximately 12 μm, suggesting that lateral (side-to-side) fusion is inhibited (Clark, Coles & Peckham, 1987, Exp. Cell. Res **230**, 275–283). We also found that fusion is inhibited when myoblasts align along ultrafine gratings that inhibit lateral movement (Clark, Knibbs & Peckham, 2002, Int. J Biochem. Cell. **34**, 816–25). This supports the idea that myoblasts do not fuse laterally, but must move laterally to make end-to-end contact if the initially make contact laterally. The elongated, 'rounded-up' shape of myoblasts in pre-fusion aggregates is also likely to favour end-to-end fusion. Most of the actin is organised into actin filament bundles just underneath the plasma membrane, together with non-muscle myosin II, in aligned cells and the stress fibre like bundles of isolated myoblasts are absent (Wells Coles, D., Entwistle, A., & Peckham, M 1997, J.M.R.C.M. 18, 501–15). From serial EMs we found that cell–cell contact in aligned groups was mostly end-to-end and filopodia were involved. We also found that the sub plasma membrane actin bundles had mixed polarity. Together with non-muscle myosin II, this cytoskeletal arrangement would generate a strong sub-cortical tension, which would make an important contribution to the observed shape of aligned cells.

A14/C4.15–Analysis of mechanical interactions between distinct intraneural regions of the rat sciatic nerve, and their restoration after damage and repair

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Peripheral nerves retain functionality whilst bending and stretching to accommodate the movement of limbs. The nerve trunk contains a selection of anatomical structures that have been defined in terms of composition and biological function, but little is known about how these parts interact mechanically. The aim of this work was to develop a model for use alongside existing experimental assays of nerve function to explore the restoration of mechanical features in the regenerating rat sciatic nerve. Manipulation of excised rat sciatic nerves revealed the presence of a mechanically distinct core and sheath which could be pulled apart experimentally using a purpose-built tensile testing machine rig with a force of 0.41 ± 0.04 N ($n = 9$). Pre-loading by application of 2% and 10% strain prior to complete separation had no effect on the maximum force required whereas an initial application of 25% strain reduced the subsequent pullout force by seven-fold. The location of the interface between the mechanically distinct regions was shown, using transmission electron microscopy, to be at the level of the inner perineurial cell layer. The data obtained using this quantifiable approach establish a consistent baseline for assessing the interaction of the core/sheath interface in models of peripheral nerve repair. An understanding of the mechanical aspects of nerve anatomy is important when designing tissue engineering approaches to surgical nerve repair where restoration of mechanical integrity would be desirable.

A14/C4.16–Integrative biology of a host-parasite interaction: parasite-associated changes in the performance of dragonfly flight muscle

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Effects of parasites on the integrated physiology of free-living animal hosts are poorly understood. Here we demonstrate how parasitic infections can induce systemic effects on host protein expression, metabolism and locomotory performance. We have analyzed the effects of a protozoan (gregarine) gut parasite on the contractile performance of the flight muscles of *Libellula pulchella* dragonflies. Parasitized individuals showed a significant decrease in the muscle contraction frequency at which they produce maximum power during work loop experiments, and need significantly more time to achieve maximum power during continuous oscillatory contraction. We propose that these changes are induced by an immune-response driven impairment of the function of insulin, which has been shown to regulate expression of both pyruvate kinase (PK), an important regulator of glycolysis, and myosin heavy chain (MyHC) isoforms. Western blot analyses of p38-MAPK, an important immune-response signaling protein, show that p38-MAPK is chronically phosphorylated in muscle tissue of parasitized individuals. Chronic activation of p38-MAPK has been shown to negatively affect insulin function in vertebrate skeletal muscle. Although we have not yet analyzed insulin function, muscle glucose levels are elevated in parasitized individuals. 2-D gel electrophoresis of muscle samples indicates that PK expression is downregulated, and a different mix of MyHC isoforms are expressed in parasitized vs. unparasitized individuals. Our working hypothesis is that the inability to process glucose intracellularly is the reason why parasitized individuals need more time to reach maximum power, whereas differential expression of MyHC isoforms causes the decrease in optimal contraction frequency.

A14/C4.17–Motion and adhesion: biomechanics of tarsal adhesive pads in ants

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Organisms would not be able to manoeuvre if they didn't have sufficient contact to the surface. However, friction and adhesion can be a major obstacle to locomotion. The conflict between energy-efficient motion and manoeuvrability is most crucial in animals that possess adhesive pads on their legs.

Many ants combine fast running performance with strong resistance to detachment forces. Regulation of attachment during walking and running includes purely mechanical control inherent in the design of the claw flexor system. The smooth adhesive pad (arolium) can be actively deployed by contraction of the claw flexor muscle. Moreover, arolia partly in contact are passively unfolded when the leg is pulled toward the body.

The passive extension of the pad enables ants to reject strong perturbations without having to deal with excessive attachment forces during normal locomotion. Investigation of the pad contact in running ants showed that most ants use only a fraction of their maximum possible contact area. This effect is most conspicuous in insects with a large detachment 'safety factor'.

Rejection of perturbations is further enhanced by the physical properties of the adhesive system. Friction force per unit contact area strongly increases with sliding velocity. We studied the adhesive contact using Interference Reflection Microscopy (IRM). Adhesion is mediated by a thin film of secretion. Estimation of the fluid's viscosity using IRM, however, indicates that the liquid film alone cannot explain the observed forces and that direct interaction of the cuticle with the surface is involved.

A14/C4.18–The role of titin and titin kinase in myofibrillogenesis

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Titin is the largest protein known and is essential for organising muscle sarcomeres. It has many domains with a variety of functions and stretches from the Z-line to the M-line, in the muscle sarcomere. Both antisense experiments and a deletion in the titin gene close to the 5′ end have been shown to affect myofibrillogenesis dramatically (Person et al., 2000; Van der Ven et al., 2000; Zhang et al., 2000). The titin kinase domain is found close to the M-line, but phosphorylates telethonin (t-cap) at the Z-line, in developing muscle (Mayans et al., 1998). This phosphorylation is thought to be important for initiating or regulating early myofibrillogenesis. Here we used a gene targeting approach in cultured myoblasts to truncate the titin gene so that the kinase domain and other domains downstream of the kinase are not expressed. We recovered cells in which one allele was targeted. We found that these cells expressed full length and a truncated titin as well as an additional band that is approximately 0.5 kDa smaller in size and not present in the wild type clones. Myofibrillogenesis in these cells was impaired. Myotubes were generally smaller and the organisation of the muscle sarcomeres, M and Z-line bands was poorer than in wild type cells. These results suggest that the activity of the titin kinase domain, as well as the M-line binding domain, are important in organising myofibrils early in myofibrillogenesis.

A14/C4.19–Expression and Characterisation of TRPV4 in Volume-Regulating Cells

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The ability to regulate the cell volume is important for the maintenance of cellular homeostasis. In a hypotonic environment many vertebrate cells react by swelling. This is followed by an active reduction of their volume a process called regulatory volume decrease (RVD). We used a human keratinocyte cell line (HaCaT) as an in vivo model for volume regulation. When HaCaT cells were exposed to a hypotonic solution (200 mOsm) swelling reached its maximum within 1 min followed by RVD (detailed in C14/A14). During the volume regulation a strong calcium influx was measured. A recently discovered receptor TRPV4 is supposed to be connected to volume regulation and increase of free cytosolic calcium (Liedtke et al. Cell. 2000 103(3):525–35). HaCaT cells express TRPV4 strongly as we have demonstrated on mRNA level by RT-PCR. Renal tubule cells represent another cell type that needs a tight volume regulation. Proximal and distal tubule renal cells also expressed TRPV4 mRNA at a high level. Using a semiquantitative RT-PCR approach we found no difference in the levels of TRPV4 mRNA between proximal and distal cells. On the other hand there was no expression of TRPV4 in human umbilical vein endothelial cells (HUVEC) or human embryonic kidney cells (293) indicating that expression of TRPV4 is not ubiquitous. Taken together these results are stressing a potential involvement of TRPV4 in volume regulation.

A14/C4.20–Simulation of Collagen Deformation due to Fibroblast Traction Forces using the Immersed Boundary Method

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Computer modelling of the deformation that occurs in the collagen matrix due to the traction forces exerted by clusters of fibroblast cells can increase our understanding of diverse problems such as the non-linear mechanical stress–strain response of skin, the process of wound healing, scar-tissue formation and ligament growth. An implementation of the immersed boundary method (IBM) [1] is used in this work to analyse and simulate deformations observed in collagen networks that contain single and multiple fibroblast explants. Experimental data is obtained in the form of deformation fields resulting from the action of traction forces by the fibroblasts on the collagen matrix over a sufficient period of time. Parameters specific to the fibroblast system and the microscopic collagen network properties, are used as input to the simulation, and are fitted using a Monte-Carlo version of the downhill simplex method, followed by an adaptive full-Newton type minimization based on NL2SOL/NL2SNO. IBM calculations are shown to predict the behaviour of such a system to sufficient accuracy.

[1] Peskin, C.S., Numerical analysis of blood flow in the heart, J.Comput. Phys. 25(3), 220 (1977).