Modelling the Interactions of Cells with the Environment

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How do cells interact mechanically with the environment?
Why is it important?
What has been done from the modeling point of view?
How do cells interact mechanically with the environment?

Why is it important?

What has been done from the modeling point of view?
Biological background

The cytoskeleton is an intricate network of protein filaments that extends throughout the cytoplasm.
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Functions of the cytoskeleton

- Structural support for the cytoplasm
- Causes changes in cell shape
- Drives cell division
- Causes cell movements
- Causes muscle contraction
- Controls location of organelles
- Provides transport between organelles
The actin cytoskeleton

- Keratocyte
- Keratocyte fragment

A. Verkhovsky

www.youtube.com/watch?v=saYK4Xseg2g
Actin polymerisation
(Pantaloni and Carlier, 2002)
Actin filaments

- Actin filaments are concentrated beneath the plasma membrane (cell cortex) and give the cell mechanical strength.
- Assembly of actin filaments can determine cell shape and cause cell movement.
- Association of actin filaments with myosin can form contractile structures.

www.sci.sdsu.edu/movies/actin_myosin_gif.html
Motor proteins bind to actin filaments and microtubules and move by cycles of conformational changes using energy from ATP.

One end of the protein can bind to specific cellular components.

myosin

Original at: www.youtube.com/watch?v=vJ9ffKeUCvE&hl=it
Cell crawling

- Motion of a melanoma cell
- Motion of a fibroblast

Original at: cellix.imba.oeaw.ac.at/fileadmin/conferences/Videotour_CellMotility/fig3.mov
(Burridge & Chrzanowska-Wodnick)
Cell crawling

- **Actin cortex**
- **Lamellipodium**
- **Substratum**

- **Cortex under tension**
- **Actin polymerization at plus end extends lamellipodium**
- **Movement of unpolymerized actin**
- **Retraction**
- **Anchorage points**
Focal contacts

• Focal contacts and microtubulin
• Animation focal contact and cytoskeleton
• Making a focal contact

(cellix.imba.oeaw.ac.at/fileadmin/conferences/Videotour_CellMotility/fig40.mov
fig26.mov fig15.mov)
Extra-cellular matrix
Extra-cellular matrix
How do cells interact mechanically with the environment?

Why is it important?

What has been done from the modeling point of view?
Mechanosensing = How cells sense mechanical forces
Mechano-transduction = How cells respond to mechanical signals, either directly or via the activation of signalling pathways
Mechanosensing = How cell cease mechanical forces
Mechano-transduction = How cell respond to mechanical signals, either directly or via the activation of pathways


Guilak, … & Chen, Control of stem cells by physical interaction with the ECM, *Cell Stem Cell* **5**, 17-26 (2009)
Diseases of mechanotransduction

Cardiology
- Angina (vasospasm)
- Atherosclerosis
- Atrial fibrillation
- Heart failure
- Hypertension
- Intimal hyperplasia
- Valve disease

Dermatology
- Scleroderma
- Achalasia
- Irritable bowel syndrome
- Volvulus

Gastroenterology
- Diabetic nephropathy
- Glomerulosclerosis

Nephrology
- Cerebral edema
- Facial tics
- Hydrocephalus
- Migraine
- Stroke
- Stuttering
- Dementia

Abnormal conversion of mechanical stress into intracellular gradients of electrical activity

Stretch activated signalling cascades due to stents and grafts

Abnormal ECM accumulation

Stretching of mesangial cells through ECM and integrins due to glomerular hypertension

Vasculature feels and adapt to shear and pressure

Ingber, Mechanobiology and diseases of mechanotransduction
Diseases of mechanotransduction

**Oncology**
- Cancer
- Metastasis
- Glaucoma
- Ankylosing spondylitis
- Carpal tunnel syndrome
- Chronic back pain
- Dupytren's contracture
- Osteoporosis
- Osteoarthritis
- Rheumatoid arthritis
- Collagenopathies
- Congenital deafness
- Mucopolysaccharidoses
- Musculodystrophies
- Osteochondroplasias
- Polycystic kidney disease
- Pulmonary hypertension of newborn

**Opthalmology**
- ARDS
- Asthma
- Emphysema
- Pulmonary fibrosis
- Pulmonary hypertension
- Ventilator Injury

**Orthopedics**
- Pre-eclampsia
- Sexual dysfunction (male & female)
- Urinary frequency/incontinence

**Pediatrics**
- Insufficient mechanosensing

**Pulmonary medicine**
- Excessive ECM

**Reproductive medicine**
- Enhanced ECM breakdown

**Urology**
- Loss of contact inhibition

**Matrix Metallo Proteinases**
- Excessive production of ECM

**Insufficient mechanosensing**

**Enhanced ECM breakdown**

**Cell hypercontractility**
Tumour-stroma interaction

Relations between ECM stiffness and cell tensile stress influences

- Proliferation
- Apoptosis
- Migration

Kass, Erler, Dembo & Weaver, Mammary epithelial cell
Influence of ECM composition and organization during development and tumorigenesis
Tumour-stroma interaction

Butcher, Alliston & Weaver,
A tense situation: forcing tumour progression
Tissue engineering: Controlling stem cell fate

Control of stem cell fate:
- Genetic and molecular mediators (growth factors, transcription factors, …)
- ECM interaction
  - ECM elasticity
  - ECM morphology
  - ECM mediated stress

Jones & Wagers, No place like home: Anatomy and function of the stem cell niche
Mechano-reciprocity

- It maintains tensional homeostasis in the tissue
- Is necessary for development and tissue-specific differentiation
- Its loss promotes disease progression, including liver fibrosis, atherosclerosis and cancer

**Figure 1.** Cells are tuned to the materials properties of their matrix

All cells, including those in traditionally mechanically static tissues, such as the breast or the brain, are exposed to isometric force or tension that is generated locally at the nanoscale level by cell–cell or cell–extracellular matrix interactions and that influences cell function through actomyosin contractility and actin dynamics. Moreover, each cell type is specifically tuned to the specific tissue in which it resides. The brain, for instance, is infinitely softer than bone tissue. Consequently, neural cell growth, survival and differentiation are favoured by a highly compliant matrix. By contrast, osteoblast differentiation and survival occurs optimally on stiffer extracellular matrices with material properties more similar to newly formed bone. Normal mammary epithelial cell growth, survival, differentiation and morphogenesis are optimally supported by interaction with a soft matrix. Following transformation, however, breast tissue becomes progressively stiffer and tumour cells become significantly more contractile and hyper-responsive to matrix compliance cues. Normalizing the tensional homeostasis of tumour cells, however, can revert them towards a non-malignant phenotype.
Mechano-reciprocity
Mechano-reciprocity
Mechano-reciprocity

(C) When primary glial cells (astrocytes) are cultured on substrates with a stiffness comparable to that of muscle tissue (‘stiff’), they spread and assume a morphology similar to that observed when they are cultured on tissue culture plastics. (D) However, when the same cells in the same chemical environment are cultured on softer substrates with a compliance similar to that of brain tissue (‘soft’), their cellular morphology changes drastically, and they extend star-like processes and resemble their in vivo appearance. Images in C,D courtesy of Pouria Moshayedi. Scale bars: in A, 5 µm for A,B; in C, 10 µm for C,D.

Franzè, The mechanical control of nervous system development

*Development* **140**, 3069-3077 (2013)
Building stem cell niches

Fibroblasts → Stem Cells

Optimal Microenvironmental Niche

Cardiac Patch

Endothelial Cells → Cardiomyocytes

Smooth Muscle Cells

Vascular Graft
Figure 3 | Targeting the niche for therapy. Stem cell deficiency or deregulation contributes to multiple human pathologies, and accumulating evidence suggests that therapeutic targeting of the stem cell niche may provide a novel and effective strategy for improving treatment of these disorders. a | For example, correction of ageing- or disease-associated alterations in the niche could be used to boost endogenous stem cell number or function, and thereby improve tissue function\(^{17,19,115}\). b | Likewise, enhancing supportive niche function during transplantation could improve the efficiency of engraftment or accelerate stem cell reconstitution, perhaps reducing the number of stem cells needed for effective tissue reconstitution\(^{115}\). c | In addition, because the niche can have an important role in influencing stem cell fate decisions\(^{19,70}\), as well as promoting stem cell self-renewal, appropriate modification of signals from the niche could be used to alter the outcomes of stem cell differentiation to favour production of a needed cell type or inhibit production of a detrimental one. d | Finally, in light of accumulating evidence suggesting that tumour-propagating cancer stem cells are dependent on signals from their niche\(^{22,23,114}\), just like their non-malignant counterparts, therapeutic ablation of components of the cancer stem cell niche could provide a novel strategy to remove tumour support factors, and thus achieve cancer remission.

Figure 1
Stem cell–based therapies for PD. PD leads to the progressive death of DA neurons in the substantia nigra and decreased DA innervation of the striatum, primarily the putamen. Stem cell–based approaches could be used to provide therapeutic benefits in two ways: first, by implanting stem cells modified to release growth factors, which would protect existing neurons and/or neurons derived from other stem cell treatments; and second, by transplanting stem cell–derived DA neuron precursors/neuroblasts into the putamen, where they would generate new neurons to ameliorate disease-induced motor impairments.

Figure 2
Stem cell–based therapies for ALS. ALS leads to degeneration of motor neurons in the cerebral cortex, brainstem, and spinal cord. Stem cell–based therapy could be used to induce neuroprotection or dampen detrimental inflammation by implanting stem cells releasing growth factors. Alternatively, stem cell–derived spinal motor neuron precursors/neuroblasts could be transplanted into damaged areas to replace damaged or dead neurons.

Figure 3
Stem cell–based therapies for AD. AD leads to neuronal loss in the basal forebrain cholinergic system, amygdala, hippocampus, and cortical areas of the brain; formation of neurofibrillary tangles; and β-amyloid protein accumulation in senile plaques. Stem cell–based therapy could be used to prevent progression of the disease by transplanting stem cells modified to release growth factors. Alternatively, compounds and/or antibodies could be infused to restore impaired hippocampal neurogenesis.

Cell-ECM contact are regulators of cell function.

Guilak, … & Chen, Control of stem cell fate by physical interaction with the ECM. *Cell Stem Cell* 5, 17-26 (2009)
Interaction with ECM micropatterns

a) 
- MSCs: Mesenchymal Stem Cells
- PDMS: Polydimethylsiloxane
- PA: Protein Adsorption
- circular patterns
- without patterns
- adipogenesis
- neurogenesis

b) 
- Bar charts showing percentage differentiation:
  - Fn, Ln, Cn
  - circle, spread

h) 
- Ligands: Fn, Ln, Cn
- Shapes: 1000 circle, spread
- Adipogenic vs Neurogenic differentiation

Legend:
- adiogenic
- neurogenic

- Significant differences indicated by asterisks:
  - * p < 0.05
  - ** p < 0.01
  - *** p < 0.001
Interaction with ECM micropatterns

Théry, ... & Julicher
Experimental and theoretical study of mitotic spindle orientation
Building a proper artificial ECM
Building a proper artificial ECM

Fig. 2. Scaffold architecture affects cell binding and spreading. (A and B) Cells binding to scaffolds with microscale architectures flatten and spread as if cultured on flat surfaces. (C) Scaffolds with nanoscale architectures have larger surface areas to adsorb proteins, presenting many more binding sites to cell membrane receptors. The adsorbed proteins may also change conformation, exposing additional cryptic binding sites.

Tissue engineering: building the stem cell niche

**Figure 6**

Microtechnology/nanotechnology for constructing synthetic in vitro stem cell niche to regulate stem cell fate. (a) SEM of single hMSCs plated on top of microfabricated PDMS microposts. The bending spring conic of the PDMS micropost could switch the differentiation potential of hMSCs between osteogenic and adipogenic fates. Adapted from Reference 40, Copyright © 2010, with permission from Nature Publishing Group. (b) SEM image showing single cells spreading on an array of nanodots fabricated using advanced sub-100-nm NIL. These nanostructured surfaces were used to explore how the geometric organization of the binding ligand RGD affects cell adhesion and spreading. Adapted with permission from Reference 115, Copyright © 2011, American Chemical Society. (c) Microfluidic arrays for logarithmically perfused mouse ESC culture. The top photograph shows a microfluidic device fabricated using soft lithography with multiple chambers for long-term culture of mouse ESCs. The bottom two brightfield images show colonies of mouse ESCs after 4 days of perfusion at different culture flow rates. Adapted from Reference 67 by permission of the Royal Society of Chemistry. (d) Microfabricated cell traps for cell pairing and fusion, by using a three-step cell-loading protocol, as indicated. Adapted from Reference 118, Copyright © 2009, with permission from Nature Publishing Group. Abbreviations: SEM, scanning electron micrograph; hMSC, human mesenchymal stem cell; PDMS, polydimethylsiloxane; RGD, arginine-glycine-aspartic acid; ESC, embryonic stem cell; NIL, nanoimprint lithography.
Tactile sensors
Flow sensors