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Studying cancer cell invasion in 3D micro-structural matrices

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3795-Pos

Matrix Rigidity Mediates Growth Factor Response during 3D Endothelial Cell Sprouting

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Angiogenesis, the development of complex vascular networks from existing blood vessels, is regulated by multiple biochemical and biomechanical signals acting in concert, although few quantitative systems allow direct measurement and manipulation of these variables. In response, we designed a microfluidic device that produces stable concentration gradients of growth factors within 3D culture matrices and allows independent tuning of the matrix rigidity, soluble growth factor absolute concentration, and concentration gradient steepness within a single experimental platform. Sprout formation of human dermal microvascular endothelial cells was studied within collagen gels of varying density (shear moduli from 8-800 Pa) containing stable gradients of soluble VEGF. These experiments revealed that endothelial sprouting into multi-cellular, capillary-like structures is optimized at intermediate collagen matrix rigidities (G′~100 Pa). In more compliant gels, cells were unable to maintain coordinated motion and instead migrated as individual cells through the matrix; while at higher gel rigidities, the cells formed broad clusters that rarely elongated into a sprout. Sprout thickness directly correlated with matrix rigidity, with thicker sprouts present in gels with the highest shear moduli. Intriguingly, our 3D experiments also found that endothelial sprouts alter their sensitivity to VEGF depending on the matrix density, suggesting a complex interplay between biochemical and biomechanical factors. As matrix stiffness increases, steeper VEGF gradients and higher VEGF absolute concentrations are required to induce directional sprouting. In more compliant gels, endothelial sprouts that originally misaligned were able to turn and properly reorient parallel to the VEGF gradient; however, this turning phenomenon was only rarely observed in stiffer gels. These results demonstrate that matrix stiffness is an effective factor in stabilization and orientation of endothelial cells during sprouting and suggests new anti-angiogenic strategies for potential cancer treatments and pro-angiogenic strategies for regenerative medicine scaffolds.

3796-Pos

Micropatterning Biomanufactured Single-Domain Nanoparticles using Self-Assembly to form Artificial Magnetosome Chains

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Spatiotemporal control of motility is an important function for bacteria as they seek energy sources. Magnetotactic bacteria utilize a chain of ferromagnetic particles to form an effective compass needle that allows them to seek the oxic-anoxic border in their environment, where optimal food sources are present. The specific mechanism of synthesis and mechanical behavior of particles in vivo is not completely understood. To understand the self-assembly and mechanical behavior of these magnetic nanoparticles, we produced micropatterned strings of synthetic nanoparticles, using isolated magnetosomes, the ferromagnetic organelle composed of magnetite, from Magnetospirillum magnetotacticum. Magnetic nanoparticles (MNPs) produced in magnetotactic bacteria are of extremely high crystal purity with single domain magnetic crystal structures. MNPs were functionalized by addition of amine groups through treatment with 3-aminopropyltriethoxysilane (APTES), and covalently linked with carbodiimide chemistry to fluorescent avidin. These MNPs were micropatterned by suspension in volatile solvent on a biotinylated glass surface. MNPs self-assembled in solution in novel and unexpected ways, not completely dependent on the ambient (Earth's) magnetic field. Chains of MNPs formed successively larger ferromagnet. Chains were then used as a template for patterning f-actin filaments, using a biotinylated phalloidin, which effectively produced an in vitro artificial magnetosome chain. These chains and the observed dynamics of the assembly process provide new insight into the relevant forces governing magnetosome assembly.

3797-Pos

On the Mechanics of Cell Adhesion and Proliferation on Fractal Surfaces

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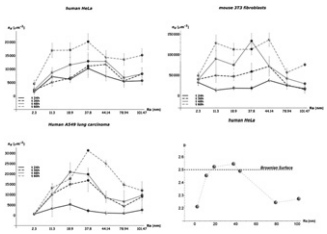
The effect of nano/micro-topography on cell adhesion, proliferation and differentiation is recognized as fundamental in the rational design of bio-inspired materials. Controversial is the literature on cell adhesion over randomly rough substrates: some studies documented a decrease in adhesion as the surface roughness (R_a) increased; others showed the opposite; few papers demonstrated a minor influence of R_a. More interestingly, it was also shown the existence of an 'optimal'roughness for maximizing adhesion and proliferation.
In this work, three cell lines of two different species were cultured over etched silicon substrates with R_a ranging from 2 to 100 nm. The rate of proliferation and surface density n_d of adhering cells was monitored over three days using confocal and atomic force microscopy. Surface roughness was characterized within the realm of fractal surfaces.
For all three cell lines, adhesion and proliferation were enhanced as D increased from a flat surface (D=2) to a Brownian surface (D=2.5). No correlation was observed with R_a. The observed behavior was interpreted within the theory of adhesion of soft solids on randomly rough substrates and the preferential formation of stable focal adhesions at the surface peaks.



3798-Pos

Studying Cancer Cell Invasion in 3D Micro-Structural Matrices

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Cellular mechanisms and external factors interact with each other during cell migration. To study cell-extracellular matrix interactions involved in cancer invasion, a collagen hydrogel-based three-dimensional (3D) model was adapted for cell culture and migration assays, in an attempt to recapitulate the mesenchymal stroma invasion. When different breast cancer cell lines were seeded inside the 3D gel, the fibrous collagen matrix only allowed the migration of highly metastatic cells.
Controlling the polymerization of collagen monomer solution through concentration and ionic conditions yielded differences in the resulting fiber thickness and network structure, and, at the same time, variance of mechanical properties of the gel. Cells in the live state and the surrounding collagen fiber networks were monitored using confocal imaging techniques, followed by 3D cell tracking. Quantitative analysis revealed that cell movement speed and directionality had certain dependence on the matrix micro-structure and mechanical strength. Cells moved faster and more directionally as a group in a gel formed with lower collagen concentration or under lower PH value during polymerization. Stream-like cell aggregates were observed in matrices with thicker collagen fibers, while individual cell movement prevailed in other matrices. Pharmacological interventions targeting at various cell migration mechanisms, including cell-activated collagen matrix degradation and cytoskeletal dynamics, showed different drug effectiveness, depending on the matrix micro-structure. The findings indicate that the multimodality of cancer cell migration is related to the characteristics of the micro-environment.

3799-Pos

A Genetic Strategy for Graded and Dynamic Control of Cell-Matrix Mechanobiology

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Mechanical interactions between cells and the surrounding extracellular matrix, such as adhesion, contraction, and force transduction, play a central role in many fundamental cell behaviors, including proliferation, cell death, and motility. The ability to precisely manipulate the intracellular machinery that regulates these interactions could therefore provide a powerful tool for controlling the mechanical properties of living cells and could also allow us to re-engineer how cells sense and respond to mechanical stimuli in their microenvironment, which would be particularly useful for tissue engineering and cellular technologies where cells are interfaced with synthetic microenvironments. Towards this goal, we have genetically engineered stable cell lines in which we can precisely and dynamically alter the mechanobiological behavior of living cells by varying the activity of signal transduction proteins, such as RhoA GTPase, using constitutively active and dominant negative mutants under the control of a tetracycline-repressible promoter. Through a variety of imaging and biophysical techniques, including atomic force microscopy and traction force microscopy, we have demonstrated graded and dynamic control over cytoskeletal architecture, cell shape and spreading, contractility, and cellular stiffness. In addition, using glioblastoma multiforme as a model system, we show how these cell lines can be used to study the effects of altered cellular mechanical properties on cancer cell motility and invasion.