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.

Micro-patterning 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 micro-patterned strings of synthetic nanoparticles, using isolated magnetosomes, the ferromagnetic organelle composed of magnetite, from Magnetospirillum magnetotacticum. Magnetic nanoparticles (MNP)s produced in magnetotactic bacteria are of extremely high crystal purity with single domain magnetic crystalline structures. MNP:s were functionalized by addition of amine groups through treatment with 3-aminopropyltriethoxysilane (APTES), and covalently linked with carboxymethyl chemistry to fluorescent avidin. These MNP:s were micropatterned on a biotinylated glass surface. MNPs with carbodiimide chemistry to fluorescent avidin. These MNPs were micropatterned on a biotinylated glass surface. MNPs with carbodiimide chemistry to fluorescent avidin. These MNPs were micropatterned on a biotinylated glass surface.