

FEATURES

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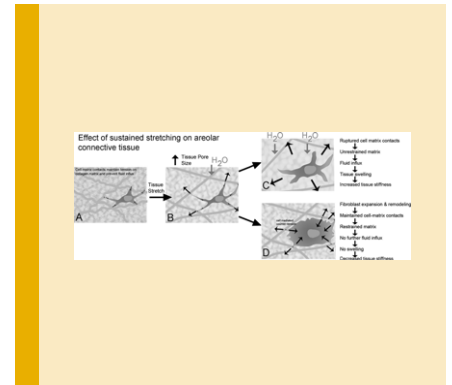
Cellular Control of Connective Tissue Matrix Tension

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1714

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The biomechanical behavior of connective tissue in response to stretching is generally attributed to the molecular composition and organization of its extracellular matrix. It also is becoming apparent that fibroblasts play an active role in regulating connective tissue tension. In response to static stretching of the tissue, fibroblasts expand within minutes by actively remodeling their cytoskeleton. This dynamic change in fibroblast shape contributes to the drop in tissue tension that occurs during viscoelastic relaxation. It is proposed that this response of fibroblasts plays a role in regulating extracellular fluid flow into the tissue, and protects against swelling when the matrix is stretched. This article reviews the evidence supporting possible mechanisms underlying this response including autocrine purinergic signaling. Also discussed is fibroblast regulation of connective tissue tension with respect to lymphatic flow, immune function and cancer.



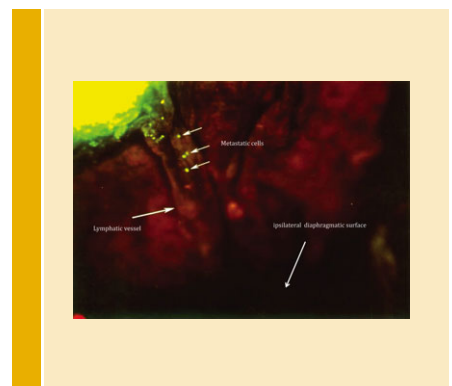
Specific Route Mapping Visualized With GFP of Single-File Streaming Contralateral and Systemic Metastasis of Lewis Lung Carcinoma Cells Beginning Within Hours of Orthotopic Implantation

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1738

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In this study, the origin of lung cancer metastasis after transducing tumor cells with green fluorescent protein (GFP) is visualized and transplanting them orthotopically in the middle lobe of the right lung of nude mice. Metastasis was visualized in live tissue at single cell resolution by GFP-expression as early as 18 hours post-tumor transplant. At this time, cells already had invaded inferiorly via a tubular lymphatic structure crossing the lower lobes of the lung to the ipsilateral diaphragmatic surface. By post-implantation day-2, the ipsilateral lower lobes of the lung were involved with metastatic cells. By post-implantation day-3, the ipsilateral lower lobes of the lung and the ipsilateral diaphragmatic surface were highly involved with streaming metastatic cells trafficking in single file. By day-4 post-implantation, cancer cells invaded across the diaphragm to the contralateral diaphragmatic surface. Metastatic cells then invaded superiorly through a lymphatic vessel to involve the contralateral mediastinal lymph nodes. In this model of lung cancer, the origin of metastasis was an inferior invasion from the implanted tumor via a lymphatic duct to the ipsilateral diaphragmatic surface. The cancer cells from this site invaded on the surface of the diaphragm to the contralateral diaphragmatic surface and proceeded superiorly through a lymphatic duct to contralateral lymph nodes. The use of GFP and the highly metastatic orthotopic lung cancer model allowed the visualization of the origin of metastasis at the single-cell level and demonstrated the critical role of lymphatic ducts and the diaphragmatic surface as the path to the contralateral side.

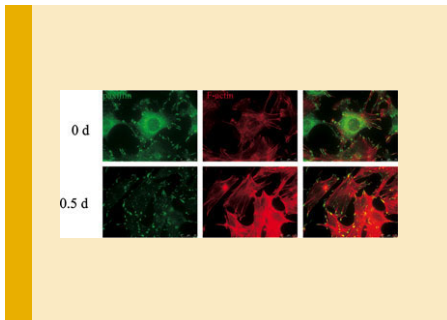


Dynamics of Focal Adhesions and Reorganization of F-Actin in VEGF-Stimulated NSCs Under Varying Differentiation States

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1744

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Precise migration of neural stem/progenitor cells (NSCs) is crucially important for neurogenesis and repair in the nervous system. However, the detailed mechanisms are not clear. Our previous results showed that NSCs in varying differentiation states possess different migratory ability to vascular endothelial growth factor (VEGF). In this study, the different dynamics of focal adhesions (FAs) and reorganization of F-actin in NSCs during spreading and migration stimulated by VEGF. VEGF is demonstrated. It is found that the migrating NSCs of 0.5 d and 1 d differentiation possess more FAs at leading edge than cells of other states. Moreover, the phosphorylation of focal adhesion kinase (FAK) and paxillin in NSCs correlates closely with their differentiation states. VEGF promotes FA formation with broad lamellipodium generation at the leading edge in chemotaxing cells of 0 d, 0.5 d and 1 d differentiation, but not in cells of 3 d differentiation. Furthermore, cells of 1 d differentiation show a maximal asymmetry of FAs between lamella and cell rear, orchestrating cell polarization and directional migration. Time-lapse video analysis shows that the disassembly of FAs and the cell tail detachment

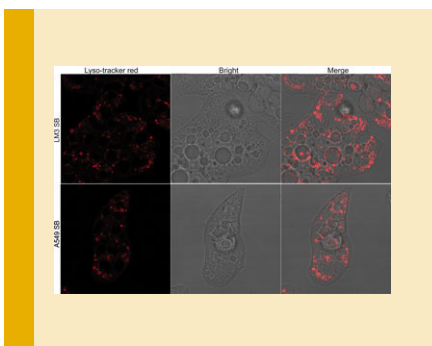
in NSCs of 1 d differentiation are more rapid, along with the concurrent enlarged size of FAs at the leading edge, leading to the most effective chemotactic response to VEGF. Collectively, these results indicate that the dynamics of FAs and reorganization of F-actin in NSCs that undergo directional migration correlate closely with their differentiation states, contributing to the different chemotactic responses of these cells to VEGF.

The Suppressive Role of p38 MAPK in Cellular Vacuole Formation

Run Chen, Chun-Yan Duan, Shao-Kun Chen, Chun-Yan Zhang, Tao He, Hong Li, You-Ping Liu, and Rong-Yang Dai

1789

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Vacuolization of the cytoplasm is one of the dramatic and frequently observed phenomena in various cell types. Cellular vacuoles occur spontaneously or via a wide range of inductive stimuli, but the molecular mechanism involved in this process remains largely unknown. In this study, the role of the p38 and JNK pathways in the formation of cytoplasmic vacuoles is investigated. It is found that p38 and JNK agonist anisomycin abolishes spontaneous cytoplasmic vacuolization of HepG2 cells through p38 activation, but not through JNK activation. Importantly, blocking the activity of p38 or suppression the expression of p38 elicits cytoplasmic vacuoles formation in various cancer cells. Furthermore, cytoplasmic vacuoles induced by p38 blocking are derived from the perinuclear region. These observations provide direct evidence for a role of p38 signaling in regulating the formation of cytoplasmic vacuoles.