

FEATURES

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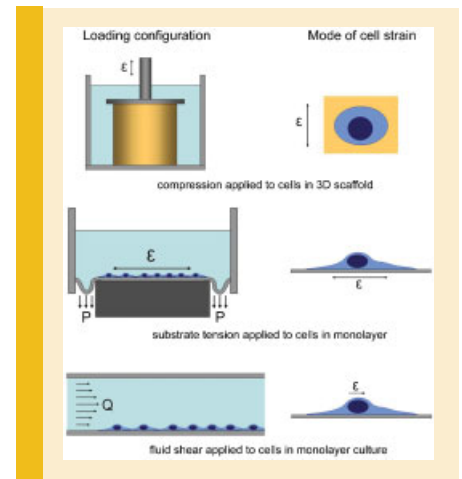
Stem Cell Mechanobiology

David A. Lee, Martin M. Knight, Jonathan J. Campbell, and Dan L. Bader

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Stem cells are undifferentiated cells that are capable of proliferation, self-maintenance and differentiation towards specific cell phenotypes. These processes are controlled by a variety of cues including physicochemical factors associated with the specific mechanical environment in which the cells reside. However the control of stem cell biology through mechanical factors remains poorly understood. While the details associated with individual studies are complex and typically associated with the stem cell type studied and model system adopted, certain key themes emerge. First, the differentiation process affects the mechanical properties of the cells and of specific sub-cellular components. Secondly stem cells are able to detect and respond to alterations in the stiffness of their surrounding microenvironment via induction of lineage specific differentiation. Finally the application of external mechanical forces to stem cells, transduced through a variety of mechanisms, can initiate and drive differentiation processes. The coalescence of these key concepts permit the introduction of a new theory for the maintenance of stem cells and alternatively their differentiation via the concept of a stem cell 'mechano-niche', defined as a specific combination of cell mechanical properties, extracellular matrix stiffness and external mechanical cues conducive to the maintenance of the stem cell population.



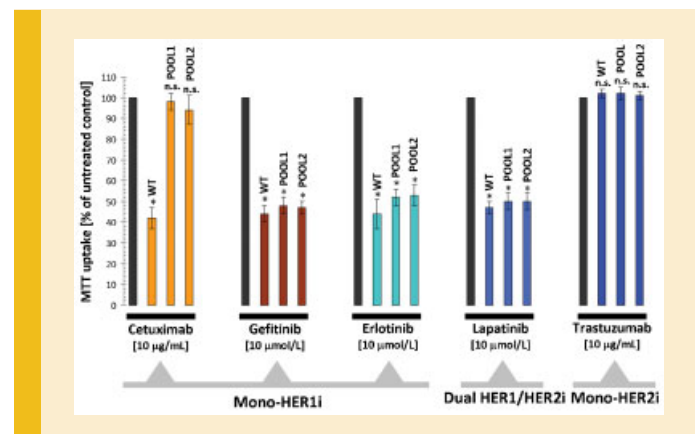
EGFR and MAPK: Linked to Cetuximab Efficacy?"

Cristina Oliveras-Ferraras, Alejandro Vazquez-Martin, Silvia Cufí, Bernardo Queralt, Luciana Báez, Raquel Guardoño, Xavier Hernández-Yagüe, Begoña Martín-Castillo, Joan Brunet, and Javier A. Menendez

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Beyond the well recognized effect of *KRAS* mutations in determining *de novo* inefficacy of cetuximab in metastatic colorectal cancer, there is a need for a biomarker signature for predicting cetuximab efficacy in *KRAS* wild-type tumors. In this paper by Oliveras-Ferraras et al, cetuximab-adapted *EGFR* gene-amplified *KRAS* WT tumor cell populations were induced by stepwise chronic exposure of A431 epidermoid cancer cells to cetuximab. Genome-wide analyses of 44 K Agilent's whole human arrays were bioinformatically evaluated by GSEA-based screening of the KEGG pathway database. Molecular functioning of cetuximab was found to depend on: 1.) the occurrence of a positive feedback loop on *EGFR* activation driven by genes coding for *EGFR* ligands; 2.) the lack of a negative feedback on *MAPK* activation regulated by dual-specificity phosphatases, and; 3.) the transcriptional status of gene pathways controlling the Epithelial-to-Mesenchymal Transition (EMT) and its reversal (MET) program. Quantitative RTPCR, high-content immunostaining and flow-cytometry analyses confirmed that cetuximab efficacy depends on its ability to promote: a) stronger cell-cell contacts by up-regulating the expression of the epithelial markers E-cadherin and occludin; b) down-regulation of the epithelial transcriptional repressors *Zeb*, *Snail* and *Slug* accompanied by restoration of cortical F-actin; and c) complete prevention of the CD44pos/CD24neg/low mesenchymal immunophenotype. The impact of *EGFR* ligands/*MAPK* phosphatases gene transcripts in predicting cetuximab efficacy in *KRAS* WT tumors may be tightly linked with the ability of cetuximab to concurrently reverse the EMT status, a pivotal property of migrating cancer stem cells.



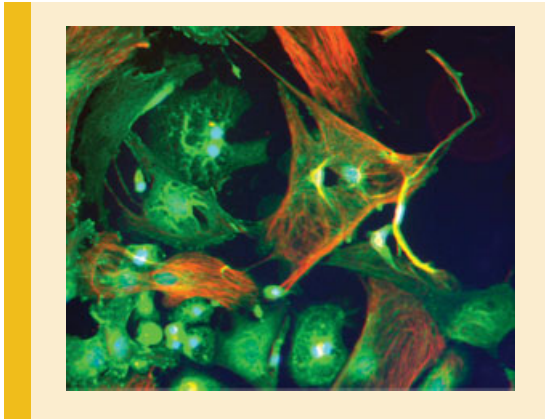
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MsRs and AMI Stem Cell Protection

Chi Zhang, Pingping Jia, Yuanyuan Jia, Yuejin Li, Keith A. Webster, Xupei Huang, Mohan Achary, Sharon L. Lemanski, and Larry F. Lemanski

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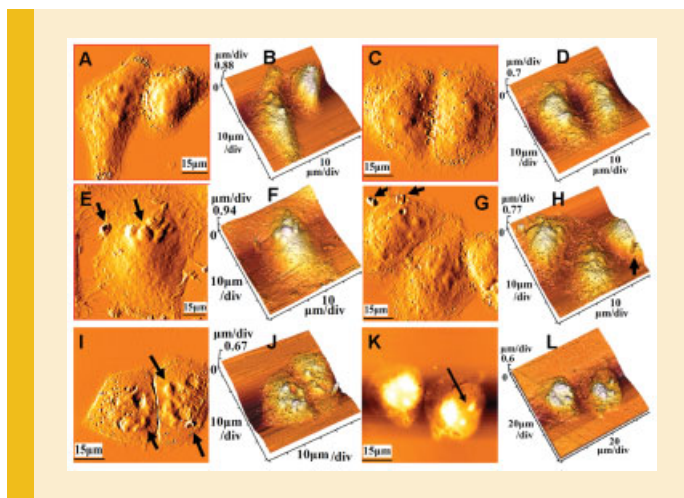
Acute myocardial infarction (AMI) leads to heart failure, the greatest cause of morbidity and mortality in western societies. AMI has become a prime target for stem cell therapy. During and after AMI endogenous stem cells are released from adjacent tissues and the bone marrow and home to the infarct where they limit damage, promote repair and initiate regeneration of the vasculature. Stem cell therapy involving direct injection of autologous cells is being developed as a way to augment the endogenous repair processes. However both the endogenous and exogenous therapy is limited because of the toxic environment of the infarct that includes hypoxia, acidosis and the oxidative stress of reperfusion. Because of this many of the cells die immediately after delivery. The methionine sulfoxide reductase (Msr) family of genes provide protection from oxidative damage by reducing the oxidized sulfide groups of methionine residues in proteins. This restores normal protein functions and neutralizes intracellular reactive oxygen species (ROS). Here, the authors provide evidence for an infarct-targeted regulation of all four Msr genes in mouse embryonic stem cells. Remarkably these genes responded individually and selectively to each component of infarct toxicity including hypoxia, acidosis and ROS. The results position msRs as environmentally responsive lifelines with the potential to protect conditionally against multiple stress stimuli.

AFM Supports Sonodynamic Therapy

Hua Jin, Xing Zhong, Zhiyong Wang, Xun Huang, Hongyan Ye, Shuyuan Ma, Yong Chen, and Jiye Cai

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Ultrasound can penetrate deeply into tissues and reach a small region of tumors to activate the cytotoxicity of sonosensitizers. Therefore, sonodynamic therapy (SDT) has been arousing wide interest. However, the effects of SDT in combination with hematoporphyrin monomethyl ether (HMME) on tumor cells are still unclear. Jin. et al. investigated the in situ sonodynamic effects of HMME on CNE-2 cells using MTT assay, flow cytometry and AFM-based technology. MTT assay results showed that HMME alone had less cytotoxicity whereas HMME-SDT could suppress cell proliferation in a dose-dependent manner. Interestingly, the annexin V-based flow cytometric data indicated that upon SDT treatment different concentrations of HMME induced different types of cell death, apoptosis (low concentration of HMME) or necrosis (high concentration). To further confirm the results and determine the mechanism, changes in mitochondrial membrane potential (MMP), cytosolic free calcium level, organization of cytoskeleton, and nuclear morphology were explored. Simultaneously, AFM morphological and biomechanical data indicated that HMME-SDT induced changes in chemical composition of the cell membrane and in actin cytoskeleton reorganization. This paper implies that HMME can be utilized as an ef-

fective sound sensitizer for nasopharyngeal carcinoma treatment and that AFM ability to detect subtle changes at the nanometer scale in structural and biomechanical properties of cells can open up the exciting prospect of using a simple nanodevice as a sensitive tool.