the actin cytoskeleton to the extracellular matrix (ECM). How these proteins assemble into force sensing and transducing structures is poorly understood, due largely to a lack of methods that directly visualize the mechanical force exerted by integrins with nanometer spatial resolution. Here we use Förster resonance energy transfer (FRET)-based molecular tension sensors (MTSs) to visualize the forces exerted by integrins in living cells. Simultaneous super-resolution imaging of MTSs and GFP-tagged cellular proteins results in maps of force-producing structures within focal adhesions (FAs) with sub-diffraction spatial resolution. We find that on our Arg-Gly-Asp (RGD)-presenting surfaces αvβ3 integrin localizes to high force regions, whereas α5β1 integrin localization is more diffuse. The canonical FA proteins paxillin, vinculin, talin, and α-actinin colocalize with force production. Surprisingly, paxillin, which is not generally considered to play a direct role in force transmission, shows a higher degree of spatial correlation with force than vinculin, talin, or α-actinin, proteins with hypothesized roles in force transmission. Super-resolution imaging reveals that MTS-measured tension, paxillin, and actin form linear structures in many adhesions, suggesting that the fundamental unit of FA assembly may be an actin bundle connected to the substrate via a variety of integrin- and actin-binding complexes. The high degree of spatial correlation of both paxillin and αvβ3 integrin with mechanical tension suggests that these proteins may play direct roles in cellular mechanotransduction.

1530-Pos Board B481
Finite Element Modeling of Cell Traction
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Cell traction forces generated via the actomyosin interaction within the cell play a critical role in many biological and pathological processes including angiogenesis, wound healing, embryogenesis, metastasis, tumor invasion, and inflammation. In the case of tumor invasion, several studies have reported a correlation between cellular traction and invasion potential; however, these results are inconsistent. In their study, Kraning-Rush et al. reported a positive correlation between cellular traction as measured by total force and metastasis potential. On the other hand, Koch et al. reported a negative correlation between tumor cell invasion and cellular traction as measured by strain energy. We hypothesized that this ambiguity could be a result of overlooked effects of other parameters on measured cellular traction. Using finite element modeling of cell traction, we explored the effect of multiple morphological and mechanical parameters on the measured cellular traction using both strain energy and cellular traction forces as the model outputs. Our results demonstrate a clear dependence of strain energy on substrate stiffness, cell polarity, and contact area, whereas, total force was independent of any of the tested parameters. In addition, our results predict the ability of cells to alter the apparent stiffness of their environment by changing their focal adhesion size.

1531-Pos Board B482
Effect of Substrate Stiffness on Integrin-Ligand Binding Strength
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Tissue cells exhibit varying responses according to the stiffness of their extracellular matrix (ECM). Currently, the mechanism of this stiffness sensing is not fully understood. We believe that cells probe stiffness by applying intracellular force to the ECM via the integrin-mediated focal adhesions. In previous studies, the linkage of integrins to the cytoskeleton has been modeled as slip clutches, which are shown to affect focal adhesion formation and hence force transmission in a stiffness dependent manner. In contrast, the bonds between integrins and ECM have been characterized as ''catch bonds''. It is unclear how ECM viscoelasticity affects these catch bonds. Here we report the effects of ECM stiffness on the binding strength of integrins to ECM ligands by measuring the rupture force of individual integrin-ligand bonds of cells on collagen-coated polyacrylamide gels. Results show that the median breaking force of individual integrin-collagen bonds of 3T3 fibroblasts increases according to gel stiffness. The stronger integrin bonds on stiffer substrates can promote focal adhesion formation, suggesting that the substrate stiffness regulates the cell-ECM adhesions not only by affecting the cytoskeleton-integrin links but also by modulating the binding of integrins to the ECM.

1532-Pos Board B483
Active Elastic Dimers: Cells Moving on Rigid Tracks
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Experiments suggest that the migration of some cells in the three-dimensional extra cellular matrix bears strong resemblance to one-dimensional cell migration. Motivated by this observation, we construct and study a minimal one-dimensional model cell made of two beads and an active spring moving along a rigid track. The active spring models the stress fibers with their myosin-driven contractility and alpha-actinin-driven extendability, while the friction coefficients of the two beads describe the catch/slip bond behavior of the integrins in focal adhesions. In the absence of active noise, net motion arises from an interplay between active contractility (and passive extendability) of the stress fibers and an asymmetry between the front and back of the cell due to catch bond behavior of integrins at the front of the cell and slip bond behavior of integrins at the back. We obtain reasonable cell speeds with independently estimated parameters. We also study the effects of hysteresis in the active spring, due to catch bond behavior and the dynamics of cross-linking, and the addition of active noise on the motion of the cell. Our model highlights the role of alpha-actinin in three-dimensional cell motility and does not require Arp2/3 actin filament nucleation for net motion.

1533-Pos Board B484
Understanding the Role of Substrate Elasticity on Intracellular Stresses during Cell Spreading
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We present a two-dimensional mathematical model and finite element simulations of a cell interacting with a deformable substrate to better understand how substrate mechanical properties affect cellular mechanical response and spread areas. The cell is treated as an actively deforming hypoelastic material and the substrate is linearly elastic. The model predicts stress and displacement fields in both the cell and the substrate. This model of cell and substrate mechanics is coupled to models describing active cellular deformation due to stress fiber contraction and evolution of focal adhesions. In this work we compare cellular stresses and substrate displacements predicted by the model on substrates of increasing stiffness against two experimental works i) Hersh et. al. 2013[1] with cardiomyocytes and (ii) Marinkovic et. al. 2012[2] with hMSc's. The model predicts an increase in compressive stresses within the cell for the two cell types with increasing substrate stiffness between 1kPa-90kPa, which is in agreement with experimental results. Further model predictions of increase in substrate displacements with substrate stiffness are in good quantitative agreement with the experimental results. In addition on softer substrates we predict that increased stress fiber contraction due to a greater compliance of the substrate at the sites of attachment results in smaller spread areas.
References:
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1534-Pos Board B485
Measuring Three-Dimensional Traction Force of Mesenchymal Stem Cells on a Two-Dimensional Compliant Substrate by the Finite Element Method
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To understand cell adhesion and migration, it is crucial to have information on cellular traction stress. Most traction force microscopy only measures shear stress. Recently a few group developed develop methods to measure normal stress and mostly based on finite element method. We report our finite element-method to compute three-dimensional (3D) traction stress exerted by human mesenchymal stem cells on a two-dimensional compliant polyacrylamide substrate embedded with fluorescent nanoparticles. The images of nanoparticles are acquired by confocal microscopy. We tracked the displacement of nanoparticles and computed strain, stress and strain energy by ANSYS. We examined both experimental factors and calculation that affect the resolution of the force measurement, especially in z direction. The stress measurement of the third dimension provides complete information on traction stress.

1535-Pos Board B486
Substrate Stiffness Regulates the Behavior of Human Monocyte-Derived Macrophages
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Many studies have shown atherosclerotic plaques are heterogeneous in stiffness. What still remains unclear, however, is how this heterogeneous