Title: Leaving the Dark Side: Shedding Light on Cell-Matrix Interactions with Molecular Force Sensors
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Project description: Increasing evidence shows that mechanical signals are equally important for regulating cellular functions than biochemical signals. Cells are constantly measuring the mechanical properties of the surrounding extracellular matrix (ECM) and respond to this mechanical information in a number of ways, with consequences on cell growth, shape, motility and differentiation. Over the last years, many proteins involved in mechanosensing processes have been identified (Fig. 1a); however, little is known about the magnitude of the forces that are transmitted through these proteins. This information is essential for understanding when these proteins become activated and how intracellular and extracellular forces are balanced.

Figure 1. Forces at the cell-matrix interface. a) Force transmission via integrins. Adaptor proteins mechanically link the integrins with the cytoskeleton. b) Molecular force sensors (MFSs) for measuring cell-generated forces.

In this project, you will use a novel approach for measuring the forces acting at the cell-matrix interface. You will develop molecular force sensors (MFSs) that convert a mechanical signal into a fluorescence readout (Fig. 1b). You will synthesize these MFSs and calibrate them with single-molecule force spectroscopy. You will then functionalize these MFSs with ECM-mimicking ligands and utilize them for studying endothelial cells and fibroblasts. The cells of interest carry mutations in the BMP (bone morphogenetic protein) signaling pathway and possess a different cytoskeleton architecture. We expect that these mutants will pull stronger on their ECM-ligands and that these altered mechanical processes are disease relevant. Mutations in the BMP pathway are known to occur in fibrodysplasia ossificans progressiva and pulmonary arterial hypertension and we expect to obtain detailed insights into the molecular mechanisms that drive disease development.

Required background: This interdisciplinary project involves a number of different methods from the areas of biophysics, biochemistry and cell biology. You should have a background in one of these areas and a strong interest in learning the methods of the others.


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