SES13-2013-000035

Abstract for an Invited Paper
for the SES13 Meeting of
the American Physical Society

Visualizing Molecular Forces Across Specific Proteins in Living Cells

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In vivo, cells adhere to a deformable extracellular matrix that is both a source of applied forces and a means of mechanical support. Cells detect and interpret mechanical signals, such as force and rigidity, from the extracellular environment through mechanotransduction. This process is central to cell migration, tissue organization, and many disease states. Progress has largely been limited by an inability to measure dynamic forces across proteins in living cells. Recently we developed an experimentally calibrated Forster resonance energy transfer (FRET)-based biosensor that measures forces across specific proteins in cells with pico-Newton sensitivity. While appropriate for focal adhesion proteins, such as vinculin, the previous sensor was only sensitive to 1-6 pN forces. As this sensor may not be optimal for studying vinculin in fibroblasts or appropriate for other contexts, such as use in highly contractile cells, we have designed and constructed a new class of tension sensors. These are based on unstructured polypeptides. We have developed a model, based on simple theories from polymer physics, which suggests these sensors should have force sensitivities ranging from 0.5-25 pN. This range is expected to be sufficient for many studies of mechanotransduction and mechanotransmission. Current work focuses on determining if these new linkers are well-described by this simple model, which is unlike the existing flagelliform-based sensors, and assessing the function of the new sensors. These efforts should enable the rational design of a new generation of FRET-based tension sensors appropriate for a wide range of studies in mechanobiology in many novel systems.